



XIX
CONGRESSO
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Farmaci generici: falsi miti e problemi reali

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Disclosure

I have received consultant and speaker fees from:

- AstraZeneca, Bayer, BMS, Chiesi, DOC-generici, Eli Lilly, GFK, Grunenthal, MSD, NovoNordisk, Otsuka, Pfizer, Rathiopharm, Rottapharm, Sanofi-Aventis, Schering-Plough, Servier, Theva.
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Farmaco generico: definizioni

EQUIVALENTI “BRANDED”

Specialità medicinali con brevetto scaduto in possesso di un proprio marchio distintivo (Ex originator compresi i co-marketing)

EQUIVALENTI GENERICI “UNBRANDED”

Commercializzati con la denominazione comune internazionale (DCI) del principio attivo o la denominazione scientifica dello stesso

EQUIVALENTI GENERICI “SEMIBRANDED”

Commercializzati con la denominazione comune internazionale (DCI) seguita dal nome del produttore (titolare AIC)

Es. Nimesulide

Originator
AULIN
MESULID

Originator= 2

Farmaco Copia	Farmaco Copia
LEDOREN	NIDE
ERREFLOG	EFRIDOL
NIMEDEX	NIMESULENE
NIMESULIDE ATE	SOLVING
NIMS	DOMES
SULIDE	NIMENOL
ALGIMESIL	FLOLID
MIGRALESS	REMOV
ANTALGO	ISODOL
DOLOXTREN	EUDOLENE
EDEMAX	ALGOLIDER
FANSIDOL	NIMESULIDE UCB
FANSULIDE	NERELID
SULIDAMOR	DELFO
NIMESIL	AREUMA
NOXALIDE	DIMESUL
RESULIN	NOALGOS
PANTAMES	

Copia = 35

Farmaco Generico	Farmaco Generico
NIMESULIDE EG	NIMESULIDE MIP
NIMESULIDE RAT	NIMESULIDE ALM
NIMESULIDE DOC	NIMESULIDE PLI
NIMESULIDE MGI	NIMESULIDE ALN
NIMESULIDE DRM	NIMESULIDE TEV
NIMESULIDE SAN	NIMESULIDE AGE
NIMESULIDE HEX	NIMESULIDE JET
NIMESULIDE BIG	NIMESULIDE UNH

Generici = 16

al 29.11.2012

Farmaci a brevetto scaduto

Spesa e consumo – gennaio - settembre 2012

	Consumi totali		Consumi farmaci a brevetto scaduto			Spesa lorda farmaci a brevetto scaduto			%Spesa equivalenti
	DDD/1000 ab die	Δ% 12/11	DDD/1000 ab die	% sul totale DDD	Δ% 12/11	€ pro capite	% sul totale spesa	Δ% 12/11	
Piemonte	909,4	1,5	505,5	55,6	10,7	49,4	38,7	6,9	29,8
Valle d'Aosta	889,0	-0,6	473,3	53,2	8,8	44,9	35,9	6,7	29,3
Lombardia	883,5	1,7	497,3	56,3	11,4	48,1	35,3	8,7	34,0
P.A. Bolzano	720,0	-0,7	387,0	53,7	11,4	36,6	37,6	7,4	31,4
P.A. Trento	838,3	1,4	456,8	54,5	11,8	42,7	37,8	7,1	39,7
Veneto	914,2	0,8	517,4	56,6	9,8	49,1	39,5	6,1	30,2
Friuli V.G.	938,7	0,7	511,5	54,5	11,5	48,3	37,2	8,5	29,6
Liguria	896,1	-4,1	486,5	54,3	6,9	49,8	38,9	2,2	27,1
Emilia R.	936,7	-1,6	530,7	56,7	8,3	48,5	42,1	2,1	31,5
Toscana	949,5	-0,4	539,7	56,8	7,6	50,3	43,4	2,1	29,2
Umbria	1.048,5	1,7	605,5	57,7	9,7	54,9	42,5	5,5	24,0
Marche	957,7	-0,1	517,3	54,0	10,0	54,0	40,8	6,0	21,8
Lazio	1.050,2	-0,7	576,4	54,9	10,0	62,5	39,4	5,8	20,3
Abruzzo	964,1	-0,8	507,3	52,6	10,6	55,8	36,3	9,2	23,9
Molise	941,5	-2,0	485,5	51,6	9,7	53,7	37,6	5,5	18,2
Campania	985,6	-0,4	547,0	55,5	10,0	62,3	37,7	6,5	16,8
Puglia	1.056,2	-0,2	567,8	53,8	11,2	63,2	39,0	7,5	21,3
Basilicata	943,0	-4,2	486,6	51,6	7,4	52,6	39,2	3,3	17,1
Calabria	1.040,2	0,9	553,6	53,2	13,4	62,7	38,4	9,7	16,2
Sicilia	1.083,7	-0,6	597,0	55,1	10,4	67,6	37,4	6,4	18,5
Sardegna	1.059,0	1,3	543,9	51,4	12,4	58,4	34,2	11,0	24,9
Italia	965,2	0,03	533,3	55,3	10,2	54,8	38,4	6,4	25,2



History of the bioequivalence concept

In early 1970s, generic digoxin formulations were increasingly prescribed in the United States, and a change in the manufacturing process of a company in Great Britain led to an unintentional increase in the bioavailability of one brand of digoxin tablets (1,2)

Public concern and ongoing discussion about bioequivalence started with those reports about digoxin intoxications.

It became clear that drug products that are pharmaceutically equivalent, that is, products that contain the same drug in the same dose, are not necessarily bioequivalent (3)

1. Lindenbaum J et al., Variation in biologic availability of digoxin from four preparations. *N Engl J Med* 1971; 285: 1244–47.
2. Schulz H-U, Steinijans VW. Striving for standards in bioequivalence assessment: a review. *Int J Clin Pharm Ther Toxicol* 1991; 29: 293–8.
3. Skelly KP, Knapp G. Biologic activity of digoxin tablets. *J Am Med Ass* 1973; 224: 243.

Hatch-Waxman Act: 1984

Authorizes the FDA to approve generic drugs that were demonstrated by the manufacturer to be bioequivalent.

The initial test-to reference ratio was 75% to 125% but was subsequently modified to 80% to 125%.

The components of this metric vary on dose administered, gut wall absorption, site of activity, therapeutic effect, the width of the narrow therapeutic window, and the ratio of treatment effect to drug side effects.

The definition of *biologically equivalent* is therefore of crucial importance and can vary based on inert binders, manufacturer curves, area under the curve, as well as the function of time.

A prespecified equivalence of 80% to 125% might be satisfactory to meet the criteria of equivalence if the risk– benefit ratio is wide.

For drugs with a more narrow risk– benefit ratio, that wide confidence interval would have important implications for risk or benefit.

U.S. Food and Drug Administration. Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations. 2011. Available at: <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed February 6, 2011.

Falsi miti: Generici e prescrizione

- I dubbi, a volte i pregiudizi, che hanno accompagnato la loro introduzione in Italia dal 2001, fra i quali:
 - « ... i generici sono meno efficaci ... »
 - « ... i generici sono meno sicuri ... »
 - « ... i generici causano più effetti secondari ... »
 - « ... i generici impiegano più tempo ad agire ... »
 - « ... i fabbricanti di generici non sono sottomessi agli stessi standard di qualità ... ».

My talk today

Equivalenza dei farmaci

Controlli sui farmaci e qualità dei generici

Compliance del generico verso il griffato

Sostituibilità

Indicazioni diverse fra generico e griffato

Effetto nocebo

Il Concetto di Equivalenza

Equivalenza farmaceutica

Bioequivalenza

Equivalenza terapeutica

FDA: Drug products are considered pharmaceutical equivalents

If they contain the identical amounts of the same active ingredient in the same dosage form and route of administration, as well as meet compendia or other applicable standards of strength, quality, purity, and identity.

However, they may differ from the innovator product in shape, drug release mechanisms, scoring configurations, and shelf lives/expiration times.

Standards of pharmaceutical equivalence do not require that additives such as fillers, coatings, flavoring, coloring, and binders utilized in generic formulations be similar or identical to the innovator counterparts.

It is important to note that some additives traditionally thought to be inert, such as alcohol sugars, cyclodextrans, and polysorbate-80, may alter a drug's dissolution, thereby impacting its bioavailability.

Chen ML et al. A modern view of excipient effects on bioequivalence: case study of sorbitol. *Pharm Res.* 2007;24: 73–80.
Dannenfelser RM et al. Development of clinical dosage forms for a poorly water soluble drug I: application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. *J Pharm Sci.* 2004; 93:1165–75.
Jackson K et al. Drug-excipient interactions and their affect on absorption. *Pharm Sci Technolo Today.* 2000;3:336–45.

Key Terms and Definitions Related to Therapeutic Interchange/Substitution

Pharmaceutical equivalence

Drug products that:

- ✓ contain the same active ingredient(s).
- ✓ are of the same dosage form and route of administration.
- ✓ are identical in strength or concentration.

Bioavailability

The rate and extent to which a **drug's active ingredient** is absorbed from the drug product and becomes available at its site of action

Bioequivalence

The **absence of a significant difference** in bioavailability between a drug product and its innovator when administered at the same molar dose under similar conditions in an appropriately designed study.


Therapeutic equivalent

Drug products that are approved as safe and efficacious; are pharmaceutical equivalents; are bioequivalent; and are manufactured in compliance with current Good Manufacturing Practice regulations.

Peters JR et al., *Generic drugs - safe, effective and affordable.*
Dermatologic Therapy 2009; 22: 229-40

Summary of Bioequivalence Methods

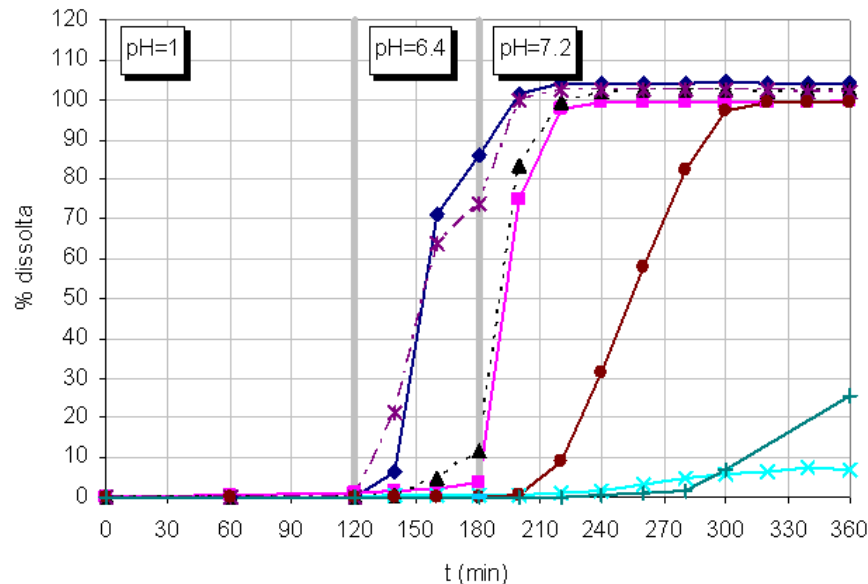
[Code of Federal Regulations, Title 21 Volume 5 Sec. 320.24]

- 
1. Comparative in vivo pharmacokinetics.
 2. Comparative in vitro test for which an IVIVC is established.
 3. Comparative In vivo pharmacodynamics.
 4. Comparative clinical trials.
 5. Comparative vitro test acceptable to FDA
 6. Other approach deemed adequate by FDA

Farmaci generici che possono essere approvati solo sulla base di studi di dissoluzione in vitro

- Studi di dissoluzione in vitro: informazioni su solubilità in mezzi acquosi e permeabilità intestinale del farmaco
- Parametri valutati:
 - solubilità e permeabilità del principio attivo
 - similarità del profilo di dissoluzione a diversi valori di pH (generico vs prodotto di marca)
 - eccipienti
 - rischi connessi al principio attivo (indice terapeutico, indicazioni terapeutiche)
- Quali prodotti medicinali?: formulazioni solide per uso orale, a cessione non modificata e modificata (es. ad azione topica intestinale)

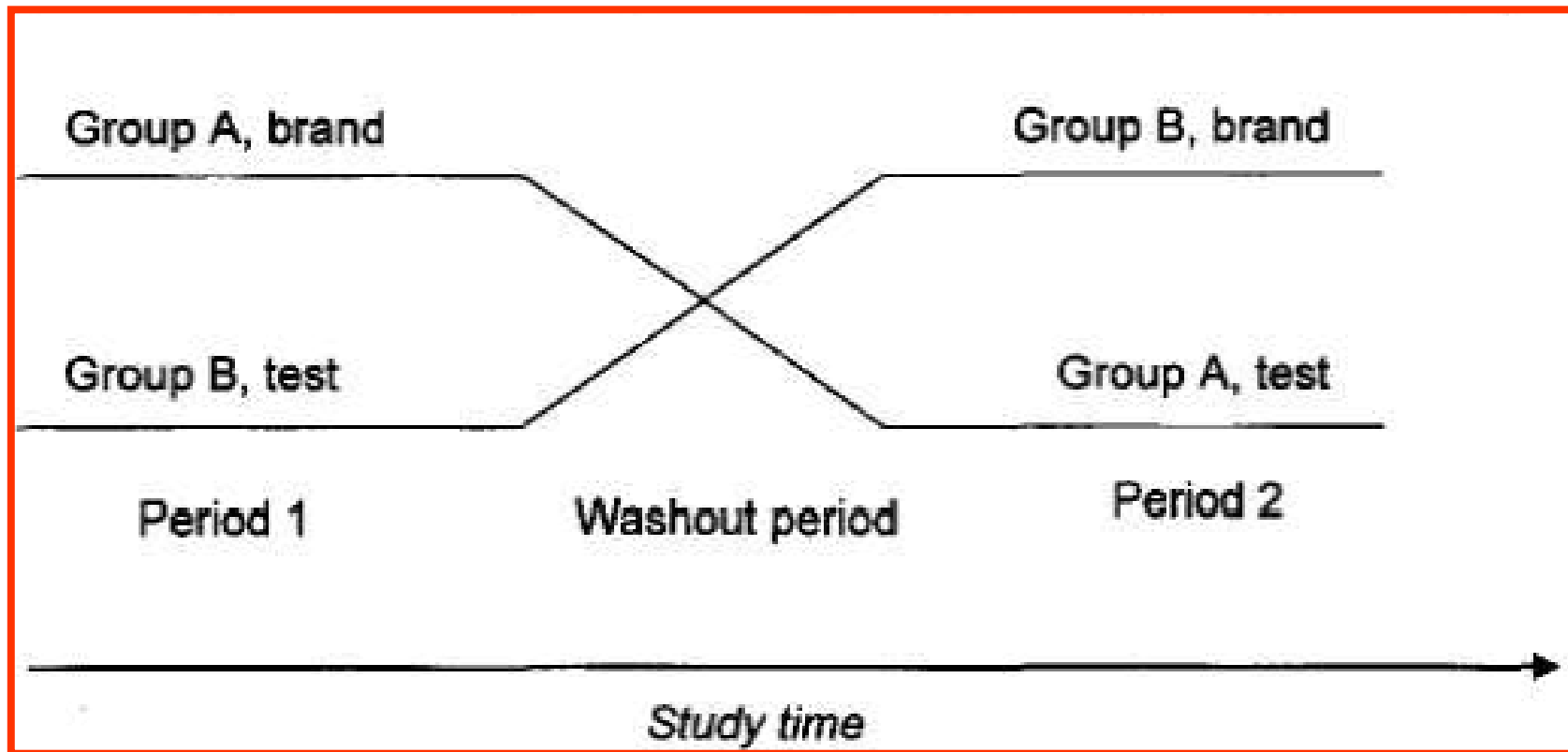
Linea guida OMS



Mesalazina (800 mg, compresse)
Confronto di profili di dissoluzione

Bioequivalenza (farmacocinetica)

Sono definiti *bioequivalenti* due *equivalenti farmaceutici* le cui *velocità ed entità di assorbimento* non differiscono statisticamente quando essi sono somministrati alla stessa dose e in condizioni sperimentali simili.



Come si dimostra la bioequivalenza di 2 farmaci?

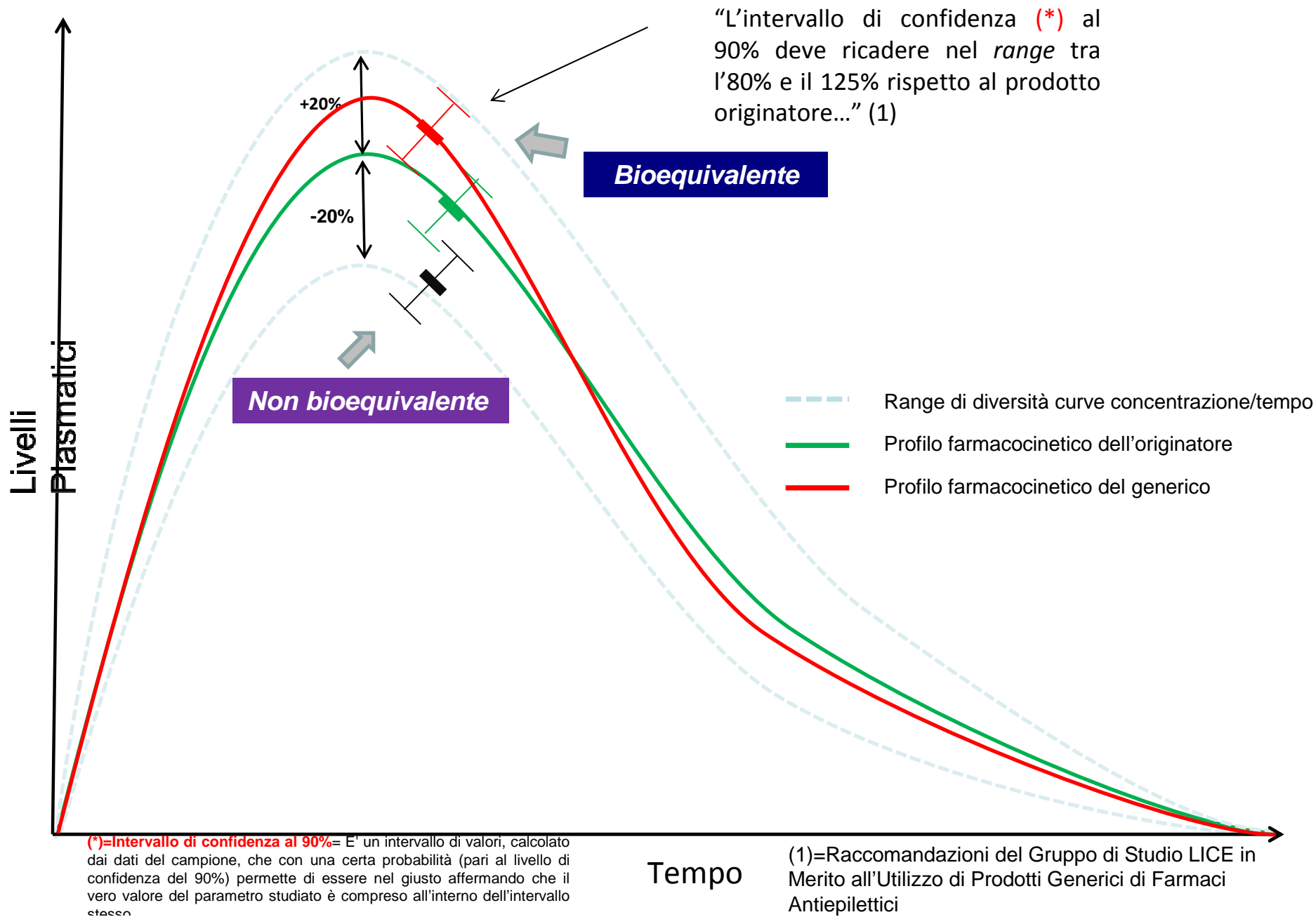
Si confronta il valore medio di alcuni parametri ottenuti dalla misurazione delle concentrazioni ematiche del farmaco in un gruppo di volontari sani (24-36) ai quali viene somministrata in due periodi successivi (studio cross-over) una singola dose a digiuno dei due prodotti a confronto.

Non esistendo alcun metodo statistico per dimostrare l'uguaglianza di due prodotti, gli studi di bioequivalenza si propongono di verificare l'assenza di una differenza clinicamente rilevante attraverso la stima di una differenza minima ammissibile.

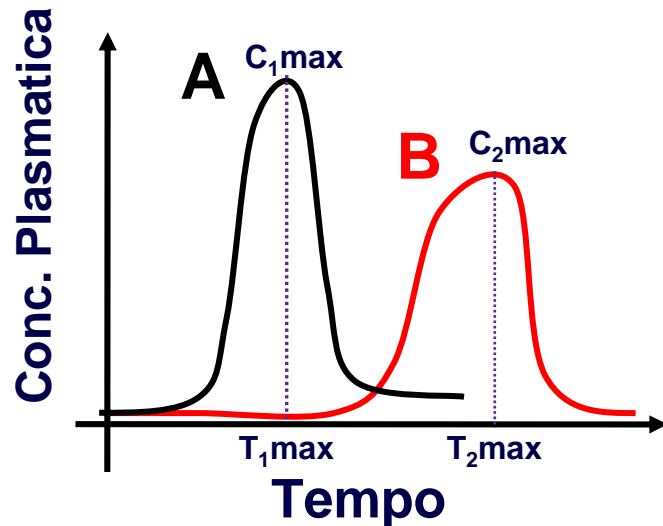
“essential similarity”



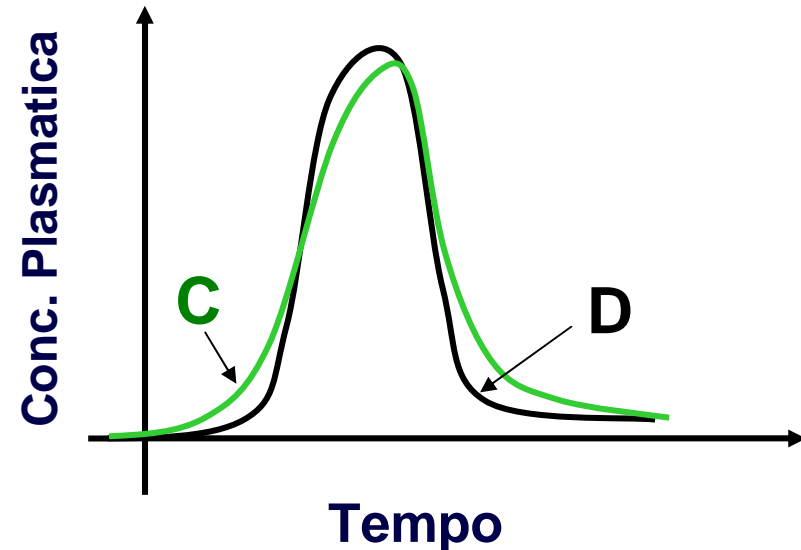
Requisiti per la bioequivalenza imposti dalla FDA



Giudizio di bioequivalenza

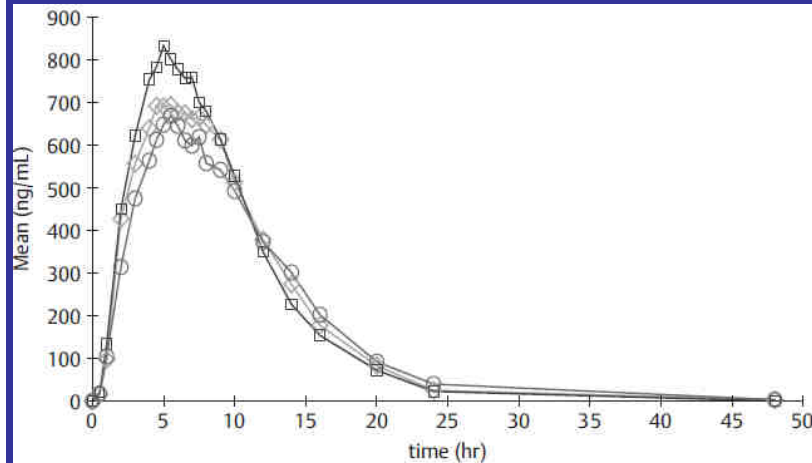


Forme farmaceutiche non-bioequivalenti



Forme farmaceutiche bioequivalenti

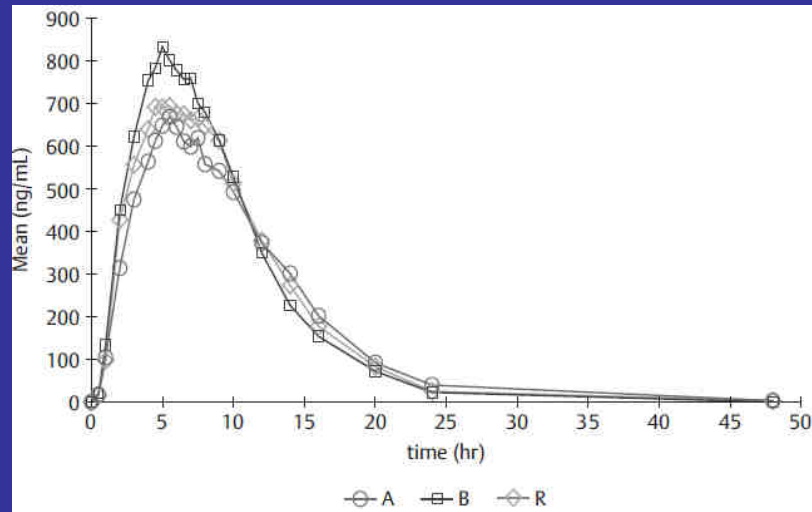
- I valori di AUC, C_{max} e T_{max} devono essere simili
- E' ammessa una variazione compresa tra 80% e 125% (ovvero: da -20% a +25%) rispetto alla forma farmaceutica di riferimento



Pharmacokinetic parameters of test A, B and reference R after single dose administration of metformin XR/SR 500 mg tablet in healthy male volunteers (n = 17).

Batolar LS et al., Arzneimittelforschung 2012; 62: 22–6

Parameters	Test A	Test B	Reference R
C_{max} (ng/mL)			
Mean (SD)	729.11 (177.23)	923.65 (215.40)	810.50 (209.58)
%CV	24.23	23.30	25.90
AUC_{0-t} (ng.h/mL)			
Mean (SD)	7637.65 (2116.35)	8247.54 (1471.29)	8018.51 (1704.86)
%CV	27.70	17.80	21.30
$AUC_{0-\infty}$ (ng.h/mL)			
Mean (SD)	8116.68 (2328.11)	8557.29 (1500.95)	8464.55 (1712.12)
%CV	28.70	17.50	20.20
% $AUC_{0-t}/AUC_{0-\infty}$			
Mean (SD)	94.37 (2.89)	96.35 (1.28)	93.60 (3.90)
%CV	3.06	1.33	4.13
T_{max} (h)			
Mean (SD)	6.27 (1.1)	5.53 (1.19)	5.88 (2.05)
%CV	17.60	21.60	34.90
$t_{1/2}$ (h)			
Mean (SD)	4.41 (1.95)	3.64 (0.65)	4.15 (1.87)
%CV	44.30	17.80	45.10



Summary statistics of different pharmacokinetic parameters of single dose Metformin XR/SR 500 mg for different product in healthy human male volunteers (n = 17).

Batolar LS et al., Arzneimittelforschung 2012; 62: 22–6

Parameter	$\ln C_{\max}$	$\ln AUC_{0-t}$	$\ln AUC_{0-\infty}$
%LSM (A/R)	90.12	93.89	94.12
%LSM (B/R)	114.58	103.13	101.22
90% CI (A/R)	82.11–98.91	86.29–102.17	86.34–102.59
90% CI (B/R)	104.39–125.76*	94.78–112.22	92.85–110.33

Values are ratio (%) of test A vs. reference R and test B vs. reference R [log transformed least-squares means (LSM) (90%CI)]

*Values lies outside the normal range (80–125%)

Bioequivalence (BE) testing of an **acarbose formulation** in healthy volunteers through the use of recommended and innovative pharmacodynamic (PD) parameters

FDA: 2 parameters

Δ CSG,max (maximum reduction in serum glucose concentration)

AUEC (0-4h) (reduction in the AUC(0-4h) of glucose between baseline and acarbose formulation)

4 newly defined PD measures of glucose fluctuation (glucose excursion (GE), GE' (glucose excursion without the effect of the homeostatic glucose control), fAUC (degree of fluctuation of serum glucose based on AUC)), Plateau glucose concentration (C_{ss}), Time of maximum reduction in glucose concentration (T_{max})

AAPS Journal, 2012; 14: 345-51

Values of Parameters Used in Expanded BE Evaluation of Acarbose Formulations in 40 Subjects with Calculated 90% CIs for T/R Values and P Value for Tmax

Parameter	Treatment	Mean	SD	GeoM	Minimum	Median	Maximum	90% CI for T/R (or P value)	Sequence difference		
$\Delta C_{SG,max}$ (mmol/L)	T	2.27	0.84	2.09	0.53	2.27	4.07	89.9–113.9%	0.13		
	R	2.22	0.89	2.06	0.73	1.97	4.64				
C_m (mmol/L)	Baseline of T	5.00	0.48	4.98	4.03	4.98	6.00	97.7–101.8%	0.17		
	Baseline of R	5.01	0.39	4.99	4.21	5.05	5.70				
GE (mmol/L)	T	4.88	0.34	4.87	4.19	4.93	5.71	99.3–102.1%	0.57		
	R	4.85	0.34	4.84	4.23	4.80	5.73				
	Baseline of T	4.07	1.10	3.92	1.79	4.05	6.33				
	Baseline of R	3.84	1.07	3.69	1.49	3.76	6.57				
GE' (mmol/L) ^a	T	1.46	0.65	1.33	0.56	1.32	3.31	89.3–117.9%	0.31		
	R	1.45	0.78	1.30	0.64	1.26	4.19				
	Baseline of T	3.08	0.91	2.93	1.12	3.17	4.84				
	Baseline of R	2.76	0.98	2.60	1.15	2.61	5.78				
fAUC (mmol h/L)	T	1.03	0.59	0.89	0.19	0.82	2.55	78.6–120.4%	0.95		
	R	1.08	0.68	0.91	0.30	0.83	2.85				
	Baseline of T	3.87	1.56	3.55	1.18	3.66	7.90				
	Baseline of R	3.68	1.56	3.39	1.30	3.15	9.30				
T_{max} (h)	T	1.38	0.66	1.25	0.51	1.21	3.37	93.7–122.0%	0.61		
	R	1.27	0.55	1.17	0.56	1.06	2.92				
	T	0.61	0.32	^b	0.00	0.50	2.00			P=0.64	^b
	R	0.62	0.23	^b	0.25	0.50	1.00				

BE bioequivalence, CI confidence interval, T/R test/reference ratio, GE glucose excursion, fAUC degree of fluctuation of serum glucose based on AUC

^aData for subjects 5, 6, and 17 were excluded from analysis

^bData were not computed

Qual è l'intervallo accettabile per definire 2 prodotti bioequivalenti?

Il range di diversità che si può avere nelle curve concentrazione/tempo in seguito all'assunzione di due unità posologiche dello stesso farmaco, somministrate a due differenti soggetti è del $\pm 20\%$, ossia compreso tra **80-125%***

** questi limiti sono asimmetrici a causa della trasformazione logaritmica dei dati impiegati per la comparazione.*

Qual è quindi la massima differenza ammessa?

Teoricamente la variazione fra un prodotto e l'altro potrebbe raggiungere il **45%**, in realtà l'obbligo di presentare un intervallo di confidenza entro i limiti stabiliti spinge i produttori a mantenersi abbastanza vicini al 100%.

Ma è vero ?

Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration
(David BM et al., *Ann Pharmacother* 2009; 43:1583-97)

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 **FDA** from 1996 to 2007 (**12 y**).

Bioequivalence measures evaluated were **C_{max}** and **AUC**, representing drug rate and extent of absorption, respectively.

Table 3. Distribution of Percent Absolute Differences Between Generic and Innovator Bioequivalence Parameter Geometric Means

Range of Percent Differences	Percent of Total BE Studies (Studies, n)					
	All Drug Products (n = 2070) ^a		IR Drug Products (n = 1788)		MR Drug Products (n = 282)	
	C _{max}	AUC _{0-t}	C _{max}	AUC _{0-t}	C _{max}	AUC _{0-t}
0-5	64.1 (1327)	80.8 (1673)	66.1 (1182)	81.5 (1457)	51.4 (145)	76.3 (215)
6-10	27.5 (569)	16.8 (348)	26.2 (468)	16.3 (291)	36.2 (102)	19.8 (56)
11-15	5.0 (104)	2.2 (47)	7.3 (131)	2.1 (38)	12.1 (34)	3.5 (10)
>15	0.4 (8)	0.1 (2)	0.4 (7)	0.1 (2)	0.3 (1)	0.4 (1)

AUC = area under the concentration-time curve; BE = bioequivalence; C_{max} = peak drug plasma concentration; IR = immediate release; MR = modified release.
^aTotal number of studies in which the bioequivalence parameter was measured.

Solo nel 2.4% (49) degli studi (2070) l'AUC del generico varia rispetto al reference di più del 10%.

Nessuno degli studi con tale variazione riguarda farmaci con stretto indice terapeutico (antiepilettico, immunoppressore, ecc.)

Nell'analisi dei farmaci generici approvati in un periodo di 18 anni:

Differenza media nel fra generico e griffato:

C_{max} = 4.35%

AUC = 3.56%

Differenza molto di sotto del 10% nel 98% dei casi



My talk today

Equivalenza dei farmaci

Controlli sui farmaci e qualità dei generici

Compliance del generico verso il griffato

Sostituibilità

Indicazioni diverse fra generico e griffato

Effetto nocebo

Qualità dei farmaci griffati e generici

Controlli della F.U. previsti per evitare difetti durante la produzione di formulazioni farmaceutiche

- uniformità di massa;
- tempo di disaggregazione;
- velocità di dissoluzione.

massa media	deviazione %
250 mg o maggiore	5
oltre 80 e meno di 250 mg	7.5
80 mg o inferiore	10

Una domanda.....

L'AIFA controlla la qualità dei farmaci sia griffati che generici.

Se si sospetta che l'AIFA non esegua i controlli, perché non si dubita anche che l'AIFA controlli realmente i farmaci griffati e/o quelli innovativi?

My talk today

Equivalenza dei farmaci

Controlli sui farmaci e qualità dei generici

Compliance del generico verso il griffato

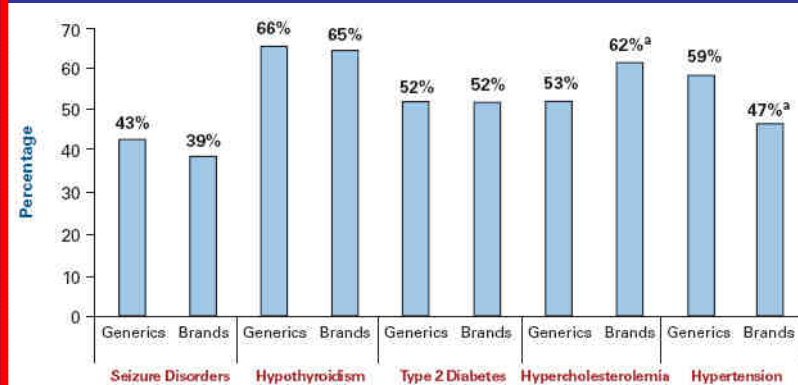
Sostituibilità

Indicazioni diverse fra generico e griffato

Effetto nocebo

Farmaci generici e compliance

Proportion of Individuals With a Medication Possession Ratio of >80%



Discontinuation rates and health care costs in adult patients starting generic versus brand SSRI or SNRI antidepressants in commercial health plans

Vlahiotis A et al. J Manag Care Pharm. 2011;17:123-32

MarketScan database fra il 1 luglio 2005 ed il 30 giugno 2007

Identificati tutti gli utilizzatori di antidepressivi (fra 18 e 64 anni) senza prescrizione per un SSRI/SNRI nei 180 giorni antecedenti l'inizio di una terapia SSRI/SNRI (baseline) e seguiti per i successivi 180 giorni (follow.up)

16,659 new SSRI/SNRI users,

- 47.8% (n = 7,955) initiated a brand-name medication
- 52.2% (n = 8,704) initiated a generic product.

Discontinued drug within 180 days of people who initiate with

- 46.8% (n = 3,723/7955) brand-name AD
- 44.2% (n = 3,843/8704) generic AD .

Adjusted OR of discontinuation among generic and brand drug users = 1.09 (95% CI = 0.98-1.22)

Not significantly differ!!!!

My talk today

Equivalenza dei farmaci

Controlli sui farmaci e qualità dei generici

Compliance del generico verso il griffato

Sostituibilità

Indicazioni diverse fra generico e griffato

Effetto nocebo

Sostituibilità ed equivalenza terapeutica

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart
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**ACCF/AHA 2011 Health Policy Statement on Therapeutic Interchange and
Substitution : A Report of the American College of Cardiology Foundation
Clinical Quality Committee**

Writing Committee Members, David R. Holmes, Jr, Jeffrey A. Becker, Christopher B.
Granger, Marian C. Limacher, Robert Lee Page II and Cathy Sila

Circulation 2011, 124:1290-1310: originally published online August 15, 2011
doi: 10.1161/CIR.0b013e31822d97d5

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX
72514

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ISSN: 1524-4539

Warfarin

Only a few, small prospective RCT including clinical endpoints compared generic and brand-name warfarin.

1. Alterations in INR occur after a switch in medications,

Halkin H et al. Increased warfarin doses and decreased international normalized ratio response after nationwide generic switching. Clin Pharmacol Ther. 2003;74:215–21.

2. No consistent impact on INR after switching from brand name to generic

Lee HL et al. Efficacy and tolerability of the switch from a branded to a generic warfarin sodium product: an observer-blinded, randomized, crossover study. Clin Ther. 2005;27:309–19.

Pereira JA, Holbrook AM, Dolovich L, et al. Are brand-name and generic warfarin interchangeable? Multiple n-of-1 randomized, crossover trials. Ann Pharmacother. 2005;39:1188–93.

3. Conversion of 87% of prescriptions to generic medication with no changes in rates of INR testing, hospitalization for major hemorrhage, or cerebral thromboembolism (a large large-scale study of older individuals in Canada)

Paterson JM, Mamdani M, Juurlink DN, et al. Clinical consequences of generic warfarin substitution: an ecological study. JAMA. 2006;296: 1969–72

**Hemorrhagic and Thrombotic Events Associated with Generic Substitution of Warfarin in Patients with Atrial Fibrillation:
A Retrospective Analysis**
Ghate SR et al., Ann Pharmacother 2011;45:701-12.

OBJECTIVE:

To assess risk of thrombotic and hemorrhagic events following substitution of warfarin formulations in patients AF.

METHODS:

- Historical cohort analysis using a commercial insurance claims database.
- Adults with a diagnosis of AF (January 2003- December 2007), with 16 or more months of continuous eligibility, a warfarin prescription within 30 days after index AF diagnosis, and at least 3 warfarin prescription fills during the follow-up period were included.

PATIENTS

37,756 subjects included in the analysis
(mean age 70.96 years, 42.3% females),

- **12,996 (34.4%) switched warfarin formulations,**
- **20,292 (53.7%) used only 1 generic product,**
- **4468 (11.8%) used only Coumadin during**

Hazard Ratios for Adverse Events in Patients Who Switch or Remain on Generic, Compared to Those Who Remain on Brand Warfarin

Warfarin Formulation Utilization	Hazard Ratios for Hemorrhagic Adverse Event (N = 1,614)			Hazard Ratios for Thrombotic Adverse Event (N = 1,689)		
	Hazard Ratio	95% Confidence Limit	p Value	Hazard Ratio	95% Confidence Limit	p Value
Warfarin (Dupont/BMS) (brand) only	ref			ref		
Switched from brand to generic	1.51	1.17 to 1.93	0.001	1.81	1.42 to 2.31	<0.001
Switched from generic to brand	1.60	1.23 to 2.1	0.001	1.76	1.35 to 2.3	<0.001
Switched from 1 generic to another generic	1.74	1.45 to 2.11	<0.001	1.89	1.57 to 2.29	<0.001
1 Generic only	1.04	0.88 to 1.22	0.649	1.23	1.04 to 1.44	0.015

Ghate SR et al., Ann Pharmacother 2011;45:701-12

Hemorrhagic and Thrombotic Events Associated with Generic Substitution of Warfarin in Patients with Atrial Fibrillation: A Retrospective Analysis

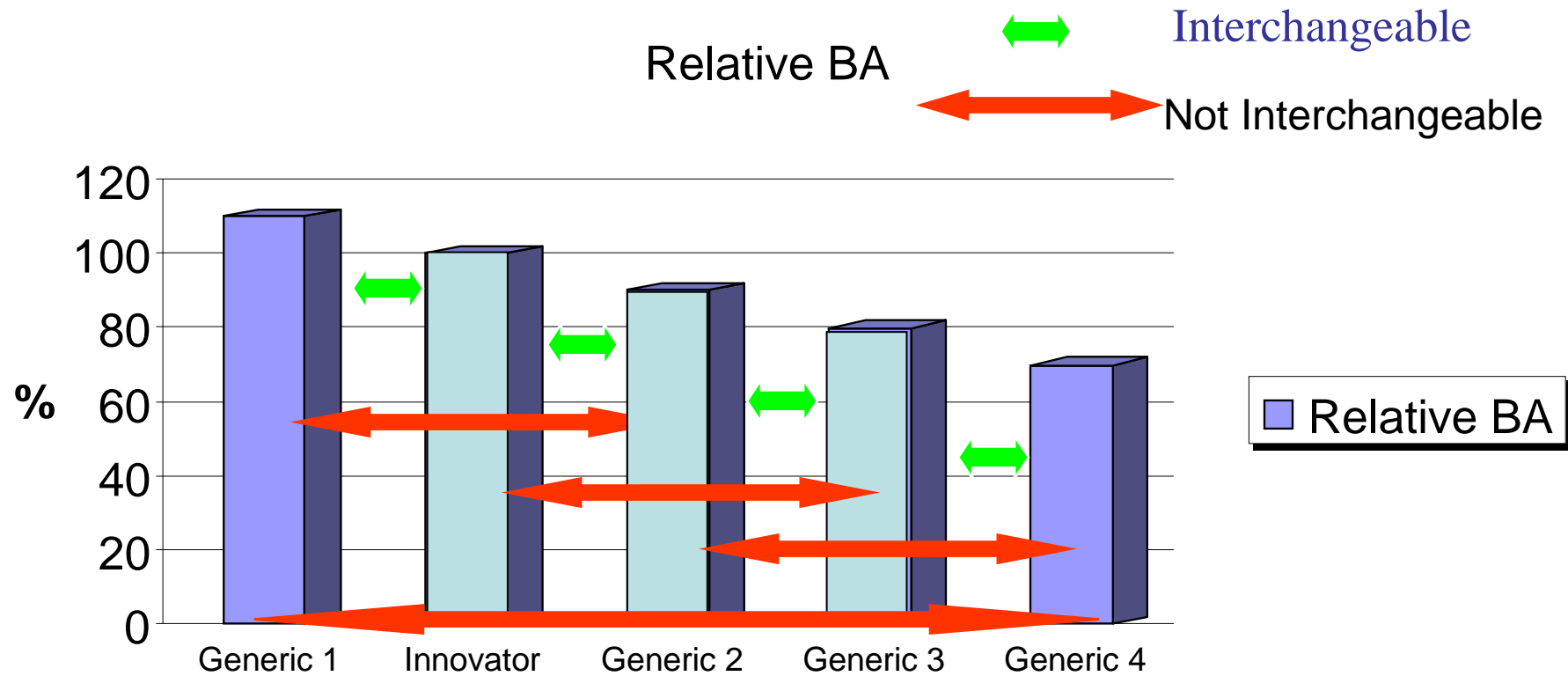
Ghate SR et al., Ann Pharmacother 2011;45:701-12.

Conclusions

Staying in therapy with a single generic is not associated with a different risk of thrombotic or bleeding events compared with staying on Coumadin,

Switching warfarin formulations, including the substitution of one generic for another, may expose patients with AF to a higher risk of thrombotic and bleeding events compared to remaining on therapy with the same formulation

„Bio-Creep“



Examples of Narrow Therapeutic Index Drugs

Therapeutic Class	Examples
Antiarrhythmic drugs	Digoxin, disopyramide, flecainide, procainamide, quinidine
Anticoagulant drugs	Warfarin
Antiepileptic drugs	Carbamazepine, oxcarbazepine, phenytoin, valproic acid
Antirejection drugs	Cyclosporine, everolimus (Afinitor), sirolimus (Rapamune), tacrolimus
Bronchodilators	Theophylline
Mood stabilizers	Lithium
Synthetic hormones	Ethinyl estradiol, levothyroxine

ACCF/AHA 2011 Health Policy Statement on Therapeutic Interchange and Substitution
A Report of the American College of Cardiology Foundation Clinical Quality Committee
Circulation 2011, 124:1290-1310.

My talk today

Equivalenza dei farmaci

Controlli sui farmaci e qualità dei generici

Efficacia clinica dei farmaci generici

Compliance del generico verso il griffato

Sostituibilità

Indicazioni diverse fra generico e griffato

Effetto nocebo

Indicazioni

Clopidogrel

N° equivalenti in commercio: 13	
ORIGINATORE	EQUIVALENTI
Prevenzione di eventi di origine aterotrombotica in pazienti affetti da infarto miocardico, ictus ischemico o arteriopatia obliterante periferica comprovata	Tutti gli equivalenti presentano la stessa indicazione dell'originatore
Prevenzione di eventi di origine aterotrombotica in associazione con ASA in pazienti affetti da sindrome coronarica acuta con o senza innalzamento del tratto ST	Indicazione mancante (12 equivalenti)

Ramipril.

N° equivalenti in commercio: 17	
DELL'ORIGINATORE	EQUIVALENTI
Trattamento dell'ipertensione	Specificato "lieve o moderata" (9 equivalenti)
Prevenzione cardiovascolare	Indicazione mancante (11 equivalenti)
Trattamento delle patologie renali	Indicazione mancante (13 equivalenti)
Trattamento dell'insufficienza cardiaca sintomatica	Indicazione mancante (10 equivalenti)
Prevenzione secondaria dopo infarto miocardico acuto	Indicazione mancante (8 equivalenti)

Le indicazioni terapeutiche dei generici sono spesso sottodimensionate rispetto a quelle del farmaco originatore branded

- Per ciascuna indicazione le aziende devono avviare una pratica formale piuttosto costosa.
- Per risparmiare ne riducono il numero. E così un generico con dieci potenziali indicazioni terapeutiche finisce per riportarne solo due sul foglietto illustrativo.
- Ciò naturalmente confonde i medici, già portati a preferire il farmaco di marca, ed i pazienti.
- Penalizza il mercato dei generici

Le liste di trasparenza dell'AIFA

1- Registrativa

In passato, la domanda di autorizzazione alla commercializzazione (AIC) di un farmaco veniva presentata a livello nazionale. Per farmaci approvati da tempo è quindi possibile un disallineamento delle indicazioni, in quanto ogni Paese era libero di accettare o meno la dimostrazione clinica dell'efficacia di un medicinale in una data indicazione.

Se quindi nel paese (es. Germania, Olanda, UK, ecc.), usato come riferimento per la procedura di ottenimento dell'AIC in Italia, l'originatore non aveva le stesse indicazioni dell'Italia, il prodotto equivalente autorizzato in Italia veniva autorizzato per le sole indicazioni comuni ai due paesi.

Questa situazione è comunque transitoria per due motivi:

- 1 l'EMA ha riconosciuto che le difformità nei testi degli stampati approvati costituiscono un'anomalia e la direttiva 2001/83 esplicitamente prevede un programma di armonizzazione dei testi che è già in corso e verrà completato nei prossimi anni;**
- 2 le richieste di AIC da parte degli originatori sono attualmente presentate quasi esclusivamente con procedure europee (quindi con le stesse indicazioni), pertanto i prossimi prodotti equivalenti avranno indicazioni armonizzate.**

2- Brevettuale

L'originatore ha la possibilità di ottenere la copertura brevettuale non soltanto per la molecola ma anche per indicazioni terapeutiche specifiche. Questo fa sì che ci possano essere indicazioni con scadenze brevettuali successive a quella associata al primo brevetto sulla molecola.

Al produttore del farmaco equivalente sarà quindi preclusa la possibilità di menzionare nel riassunto delle caratteristiche del prodotto e nel foglio illustrativo tutte le indicazioni che hanno una copertura brevettuale successiva a quella del primo brevetto.

Si tratta anche in questo caso di una situazione transitoria in quanto alla scadenza della copertura brevettuale dell'indicazione, il produttore del farmaco equivalente avrà il diritto di inserirla nel riassunto delle caratteristiche del prodotto e nel foglio illustrativo.

My talk today

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La "percezione" del generico

- There is an extensive publicity suggesting that generic prescribing is potentially problematic.
- A patient knowing that a generic is being prescribed might view this in a very negative way and might have an increased tendency to attribute any adverse event to the change.
- This is the "negative placebo" or "nocebo" effect, the opposite of a placebo effect

Generic antiepileptic drugs and increased health care utilization. Fact or myth?

Besag FMC. Neurology 2010; 74: 1562-3

E per concludere.....

..... il ticket!

Copayment (ticket)

Are prescription copayments compromising patient care?

Ortiz M. Aust Prescr 2013;36:2–3

The copayment is the price paid by a patient for a prescription.

Tatchell M. Prescription pricing demystified. *Aust Prescr* 2009;32:6-8.

Increases in copayments primarily affect vulnerable populations such as those on low incomes and patients with chronic medical conditions taking multiple medications. Patients often reduce or stop taking their medicines and this can have potentially serious health consequences.

Hynd A, Roughead EE, Preen DB, Glover J, Bulsara M, Semmens J. The impact of co-payment increases on dispensings of government-subsidised medicines in Australia. *Pharmacoepidemiol Drug Saf* 2008;17:1091-9

This failure to take medicines can also lead to increased visits to the doctor and hospitalisations.

Hsu J, Price M, Huang J, Brand R, Fung V, Hui R, et al. Unintended consequences of caps on Medicare drug benefits. *N Engl J Med* 2006;354:2349-59.

There is a relationship between patient cost sharing, medication adherence and clinical and economic outcomes. Increasing the patient's share of medication costs is associated with a decrease in adherence, which in turn is associated with poorer health outcomes.

Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How patient cost-sharing trends affect adherence and outcomes: a literature review. *P T* 2012;37:45-55.

Pharmacy benefits and the use of drugs by the chronically ill patients

JAMA 2004; 291: 2344-50

Politiche di contenimento del costo dei farmaci:

- aumento del ticket
- obbligo di usare i generici

Raddoppio del ticket (Studio condotto sui farmaci di 25 industrie farmaceutiche)

- Riduzione delle spese per farmaci dal 19 al 33%
- Riduzione spese farmaci per patologie croniche in pazienti ad alto rischio



Doubling co-payment: results

NSAIDs 45%
antihistamines 44%
antihyperlipidemics 34%,
antiulcerants 33%,
antiasthmatics 32%,
antihypertensives 26%,
antidepressants 26%,
antidiabetics 25%

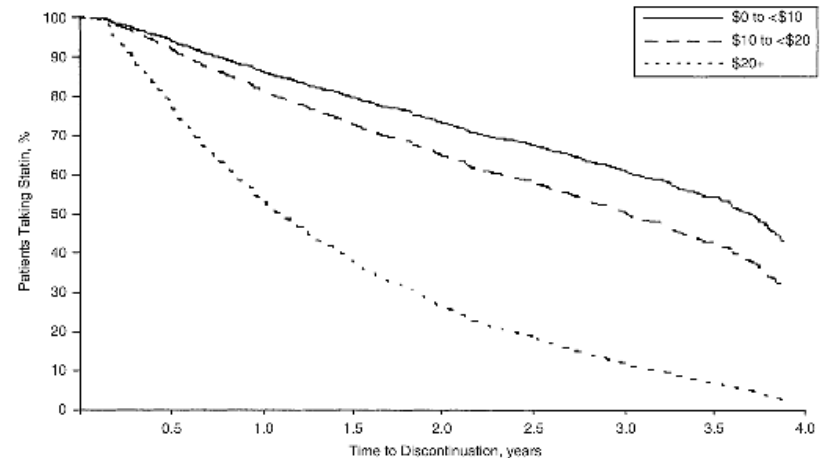
} in overall days supplied

Use of, and decrease by

antidepressants by depressed patients = 8%.
antihypertensives by hypertensive = 10%.
NSAIDs in arthritis patients = 27%.
antihistamines in allergy patients = 31%.
antidiabetic = 23%.

Molti studi indicano che la sensibilità del consumatore al cost-sharing (ticket) dipende dalla classe terapeutica e che l'aumento del cost sharing può ridurre l'uso di farmaci "non essenziali" più di quello dei farmaci essenziali"

Suboptimal statin adherence and discontinuation in secondary prevention populations. Should we target patients with the most to gain (J Gen Inter Med 2004;19: 638-45)



MEDICARE and drug prescription

- The “standard” Medicare Part D prescription drug benefit has a gap in coverage after total drug costs exceed an annually adjusted threshold, e.g., \$2,510 in 2008 (1).
- During the coverage gap, beneficiaries with the standard benefit are responsible for 100% of the cost of their medications (2).
- Studies have found that many Part D beneficiaries with a coverage gap use less medication than prescribed due to cost and go without necessities such as food or rent in order to afford medications (3).

1. The Medicare Prescription Drug Benefit Fact Sheet. The Henry J. Kaiser Family Foundation (online); Available at:http://www.kff.org/medicare/upload/7044_08.pdf
2. Hsu Jet al. Unintended consequences of caps on Medicare drug benefits. *N Engl J Med.* 2006; 354:2349–59.
3. Piette JD, Heisler M, Wagner TH. Problems paying out-of-pocket medication costs among older adults with diabetes. *Diabetes Care.* 2004; 27:384–91.

Medicare Part D: entering the coverage gap in diabetes and drug utilization

Beneficiaries with diabetes and other chronic diseases may be at particular risk, given a high likelihood of entering the coverage gap due to their multi-drug regimens.

High cost sharing among chronically ill beneficiaries has also been associated in pre-Part D studies with a decline in health and an increase in emergency department visits and hospitalizations.

While the majority of Part D plans provide no drug coverage during the gap, several plans have tried **to bridge the gap with coverage for generic medications only (generic-only gap coverage)**.

These plans discontinue coverage for brand name medications, such as insulin, once patients enter the gap.

Schmittziel JA et al. Medicare Part D coverage gap and diabetes beneficiaries. *Am J Manag Care*. 2009; 15:189-93.

Cole JA et al. Drug copayment and adherence in chronic heart failure: effect on cost and outcomes.

Pharmacotherapy. 2006; 26:1157-64.

Heisler M et al. The health effects of restricting prescription medication use because of cost. *Med Care*. 2004;

42:626-34. Piette JD et al. Health insurance status, cost-related medication underuse, and outcomes among

diabetes patients in three systems of care. *Med Care*. 2004; 42:102-109.

Generic-only Drug Coverage in the Medicare Part D Gap and Effect on Medication Cost-Cutting Behaviors for Patients with Diabetes: The Translating Research into Action for Diabetes (TRIAD) Study

Duru OK et al, J Am Geriatr Soc. 2010; 58: 822–8.

Objective

To examine the association between drug coverage during the gap and medication cost-cutting behaviors among insulin users and non-users.

Participants and Setting

2007 survey of Medicare Advantage Part D (MAPD) and Prescription Drug Plan (PDP) beneficiaries within a network-model health system who entered the gap by October 2006 (N=1,468, 57% response rate).

Design

The study was cross-sectional.

Measurements

The primary predictor variable was no gap coverage versus generic-only gap coverage.

Seven cost-cutting behaviors as dependent variables, including cost-related non-adherence (CRN) to any medication were examined.

Covariates included race/ethnicity, education, health status, income, and comorbidities, as well as generic medication use in the first quarter.

Adjusted Predicted Percentages of Medication Cost-Cutting Behaviors by Type of Gap Coverage, among Beneficiaries using Insulin

	No gap coverage (n=614)	Generic-only gap coverage (n=388)	P value
<i>Cost-related nonadherence (CRN)</i>			
During 2006, because of the amount you had to pay, did you <u>use any medication less often than the doctor prescribed</u> , either by skipping doses, stopping the medication altogether, or deciding not to fill a new prescription?	18%	14%	0.24
<i>Forgoing necessities due to financial hardship</i>			
During 2006, did you <u>go without some necessity</u> (such as food, rent or other basics) because of the amount that you would have to pay for a prescription medication?	8%	8%	0.91
<i>Substitution</i>			
During 2006, because of the amount you had to pay for prescription medications, did you <u>use an over-the-counter medication instead</u> ?	9%	6%	0.14
During 2006, because of the amount you had to pay ... did you <u>split pills</u> (for example, break them in half) according to your doctor's advice?	22%	18%	0.31
During 2006, because of the amount you had to pay ... did you <u>switch to a cheaper medication</u> , such as a generic one?	46%	36%	0.01
During 2006, because of the amount you had to pay ... did you <u>use a mail-order pharmacy</u> to fill your prescriptions?	51%	53%	0.67
During 2006, because of the amount you had to pay ... did you <u>call different pharmacies to find the lowest price</u> for your medications?	36%	22%	<0.001

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Duru OK et al, J Am Geriatr Soc. 2010; 58: 822–8.

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Results

In multivariate analyses, beneficiaries taking insulin were less likely to report CRN if they had generic-only gap coverage compared to no gap coverage (16% vs. 29%, $p=0.03$).

No differences in CRN by type of gap coverage were seen among beneficiaries not taking insulin.

Conclusions

Medicare beneficiaries using insulin are at high risk of CRN.

Generic-only coverage during the gap is associated with an attenuated risk of CRN among insulin users, possibly due to savings on other, generic medications.

Il problema generale dei generici

“Poichè di solito i farmaci generici costano meno dei farmaci branded, molte persone credono erroneamente che i generici siano inferiori rispetto ai branded”

Doug Sporn

Director of FDA's Office of Generic Drugs



Grazie per l'attenzione