思考：仿制药的产品质量对临床疗效的影响，有哪些缺点？

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比利时，布鲁塞尔

专家顾问会议
2013年6月26日
北京首都机场希尔顿酒店，北京，中国

With approval from the Belgian Common Ethical Platform - visa n° 13/V1/4806/052924

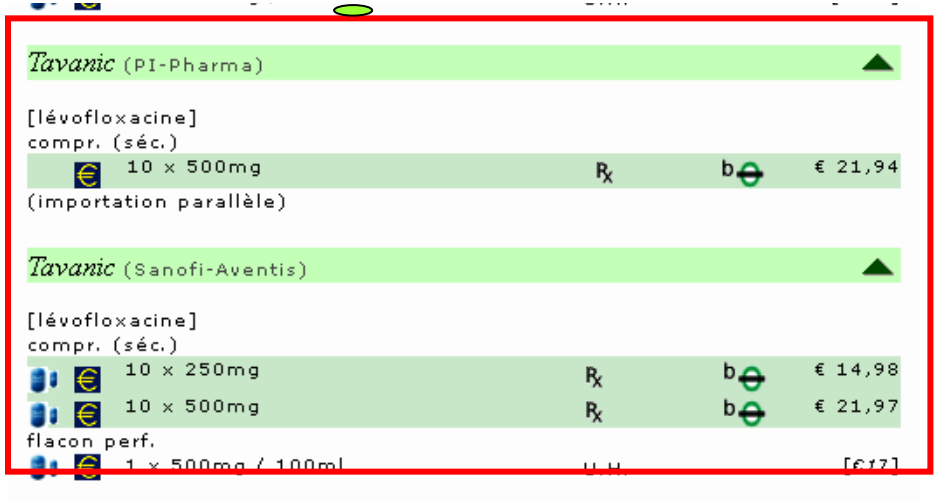
原研药物和仿制药一样吗？

FDA和欧洲药品管理局(EMA)批准通过相关仿制药企业采取多种增长策略。包括批准相关生产许可，并购方案，用以发展一个强大、创新的仿制药的渠道，并通过改善基础设施以提高仿制品的制造和研发能力，最终以便推出新产品和相关产品在各区域业绩的增长。

http://www.computescotland.com/generic-drug-strategies-5795.php

比利时，一种众所周知的抗菌药物...

专利到期之前



Tavanic (PI-Pharma)

[lévofloxacine]
compr. (séc.)
10 x 500mg Rx b € 21,94
(importation parallèle)

Tavanic (Sanofi-Aventis)

[lévofloxacine]
compr. (séc.)
10 x 250mg Rx b € 14,98
10 x 500mg Rx b € 21,97
flacon perf.
1 x 500mg / 100ml [€17]

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm

比利时，一种众所周知的抗菌药物...

之后...

1

Levofloxacine Actavis (Actavis)

[lévofloxacine]
sac perf.

5 x 500mg / 100ml	U.H.			[€85]

2

Levofloxacine EG (Eurogenerics)

[lévofloxacine]
compr. (séc.)

10 x 500mg	Rx	b	€ 21,42
30 x 500mg	Rx	b	€ 57,66

sac perf.

1 x 500mg / 100ml	U.H.	[€17]

3

Levofloxacine Fresenius Kabi (Fresenius Kabi)

[lévofloxacine]
flacon perf.

1 x 500mg / 100ml	U.H.	[€17]

4

Levofloxacin Hospira (Hospira)

[lévofloxacine]
sac perf.

1 x 500mg / 100ml	U.H.	[€17]

5

Levofloxacine Mylan (Mylan)

[lévofloxacine]
compr. (séc.)

10 x 250mg	Rx	b	€ 14,98
14 x 250mg	Rx	b	€ 24,43
10 x 500mg	Rx	b	€ 21,98
14 x 500mg	Rx	b	€ 35,13

flacon perf.

10 x 500mg / 100ml	U.H.	[€170]

6

Levofloxacine Sandoz (Sandoz)

[lévofloxacine]
compr. (séc.)

10 x 250mg	Rx	b	€ 14,42
10 x 500mg	Rx	b	€ 21,09
30 x 500mg	Rx	b	€ 58,15

7

Levofloxacine Teva (Teva)

[lévofloxacine]
compr. (séc.)

10 x 250mg	Rx	b	€ 14,42
10 x 500mg	Rx	b	€ 21,09
30 x 500mg	Rx	b	€ 56,66

sac perf.

10 x 250mg / 50ml	U.H.	[€85]
10 x 500mg / 100ml	U.H.	[€170]

Tavanic (PI-Pharma)

[lévofloxacine]
compr. (séc.)

10 x 500mg	Rx	b	€ 21,94

(importation parallèle)

Tavanic (Sanofi-Aventis)

[lévofloxacine]
compr. (séc.)

10 x 250mg	Rx	b	€ 14,98
10 x 500mg	Rx	b	€ 21,97

flacon perf.

1 x 500mg / 100ml	U.H.	[€17]

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm

我们接下来讨论的话题？

1. 欧盟和美国的法规
2. 支持进行药效学的生物等效性研究
3. 支持微生物学的等效性研究
   - 最小抑菌浓度，防突变浓度，异质耐药性…
4. 药动学等价方法
   - PK / PD动物模型和临床数据
5. 相关溶解和稳定性的问题
6. 真正的含量与杂质
7. “低成本”抗菌药物潜在的风险

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欧盟质量管理规范

►B **DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL***

of 6 November 2001

on the Community code relating to medicinal products for human use

(OJ L 311, 28.11.2001, p. 67)

Amended by:

		Official Journal		
		No	page	date
►M1	Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003	L 33	30	8.2.2003
►M2	Commission directive 2003/63/EC of 25 June 2003	L 159	46	27.6.2003
►M3	Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004	L 136	85	30.4.2004
►M4	Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004	L 136	34	30.4.2004
►M5	Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006	L 378	1	27.12.2006
►M6	Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007	L 324	121	10.12.2007
►M7	Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008	L 81	51	20.3.2008
►M8	Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009	L 168	33	30.6.2009
►M9	Commission Directive 2009/120/EC of 14 September 2009	L 242	3	15.9.2009
►M10	Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010	L 348	74	31.12.2010
►M11	Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011	L 174	74	1.7.2011

* Legislative act of the European Union that is then translated into country-specific laws for actual implementation, which may vary (in details) between countries (*vs* regulations that are self-executing and do not require local adaptations)

http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_en.htm

欧盟质量管理规范

- 如果申请者是会员国成员，在不超过8年的时间内，能提供在欧盟规定的第6条法案中的相关内容，并通过药物相关资料审批，那么依据第8条(3)(i)中和有关保护性工商业产权无偏见的法律——申请者则不需要提供相关的临床前试验和临床试验的结果。

- 仿制药是指一种与参考药物具有相同的定性和定量活性成分及相同配药形式的药物，作为仿制药，其生物等效性需与参考药物进行相关生物利用度研究…

如果申请人能证明仿制药符合指南中的相关标准，则不要求申请者提供生物利用度研究。

欧盟规定：非生物制剂申请需提供何种资料？

- 模块1，模块2和模块3*的数据
- 总体提供原研药物的生物利用度和生物等效性的研究

需特别关注：

- 药物组成需类似
- 杂质的评估(关于这些评估的证据)
- 生物等效研究的评估或不实施研究的理由
- 与药物本身和临床应用现状的最新文献
- 当药物特性未被证实或验证时，应根据出版发行的相关文献和/或其他研究进行讨论
- 针对药物中的盐类，脂类及其衍生物的安全性或有效性进行相关生物等效性研究以证实其主要成分的类似性

* Module 1 = administrative information: Module 2 = Summaries: Module 3 = Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances; Module 4 = non-clinical reports; Module 5 = clinical reports

US regulations

PUBLIC LAW 98-417—SEPT. 24, 1984 98 STAT. 1585

Public Law 98-417
98th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise the procedures for new drug applications, to amend title 35, United States Code, to authorize the extension of the patents for certain regulated products, and for other purposes.

Sept. 24, 1984
[S. 1538]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Drug Price Competition and Patent Term Restoration Act of 1984".

Drug Price Competition and Patent Term Restoration Act of 1984.
21 USC 301 note.

TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf

- 依据药品价格竞争和专利术语恢复法案的规定(“Hatch-Waxman法案”[法98 - 417])，FDA鼓励具有相同化学名药物的生产
- 为获得美国食品及药物管理局的批准，具有相同化学名药物营销人员可以提出一个简略新药申请(ANDAs)

US “缩减版的新要申请"

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm

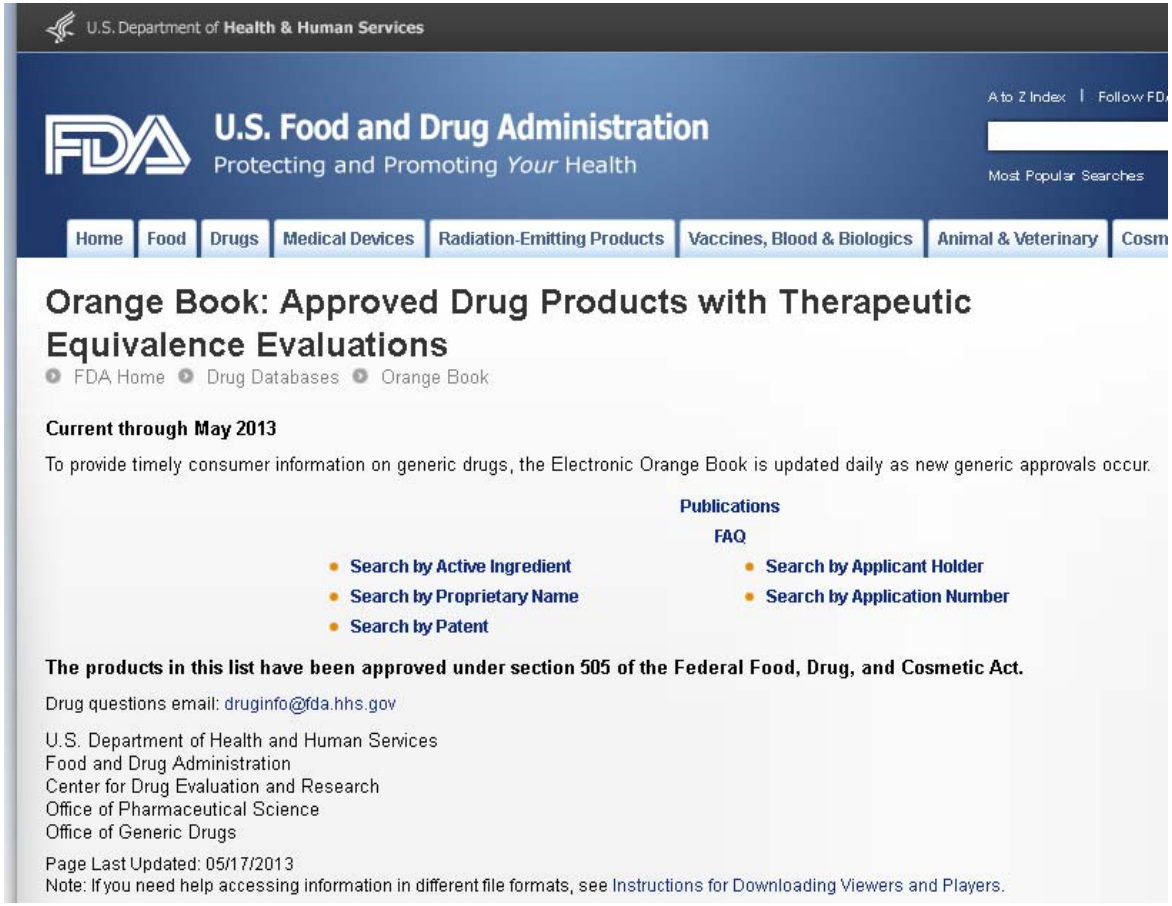
FDA的规定提要*

- **出版的文献**(可以作为没有参考最初原始数据权利的申请人的申请支持文件)
- **FDA的调查结果**(获批药物的安全性和有效性)
- 与原NCE/NME(新化学实体/新分子实体)申请的比较
  - 剂型、强度、用药途径
  - 替换组合产品的一种活性成分或改变诸如不同的盐、酯、复合体,…
- 生物等效性研究

相关药物的提案不需要证明在临床上比先前批准的产品更好；然而，对于无法满足生物等效性的标准或生物有效性差的仿制药物，FDA不予批准通过。

* 505 (B) (2) Application (Guidance to Industry)
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf

美国食品药物管理局批准的非专利药：“橙皮书”*



U.S. Department of Health & Human Services

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home ▸ Drug Databases ▸ Orange Book

Current through May 2013

To provide timely consumer information on generic drugs, the Electronic Orange Book is updated daily as new generic approvals occur.

Publications

FAQ

- **Search by Active Ingredient**
- **Search by Proprietary Name**
- **Search by Patent**
- **Search by Applicant Holder**
- **Search by Application Number**

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: druginfo@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Generic Drugs

Page Last Updated: 05/17/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

美国食品药物管理局批准的非专利药："橙皮书"*

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home

As in LEVAQUIN®
http://medicaidprovider.hhs.mt.gov/pdf/levaquinpi.pdf

Active Ingredient Search Results from "OB_Rx" table for query on "levofloxacin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
A090343	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 250MG/50ML (EQ 5MG/ML)	LEVOFLOXACIN IN DEXTROSE 5% IN PLASTIC CONTAINER	ACS DOBFAR INFO SA
A090343	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 500MG/100ML (EQ 5MG/ML)	LEVOFLOXACIN IN DEXTROSE 5% IN PLASTIC CONTAINER	ACS DOBFAR INFO SA
A090343	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 750MG/150ML (EQ 5MG/ML)	LEVOFLOXACIN IN DEXTROSE 5% IN PLASTIC CONTAINER	ACS DOBFAR INFO SA
A091644	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 500MG/20ML (EQ 25MG/ML)	LEVOFLOXACIN	AKORN
A091644	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 750MG/30ML (EQ 25MG/ML)	LEVOFLOXACIN	AKORN
A202328	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 500MG/20ML (EQ 25MG/ML)	LEVOFLOXACIN	AUROBINDO PHARMA LTD
A202328	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 750MG/30ML (EQ 25MG/ML)	LEVOFLOXACIN	AUROBINDO PHARMA LTD

* http://www.a

我们接下来讨论的话题？

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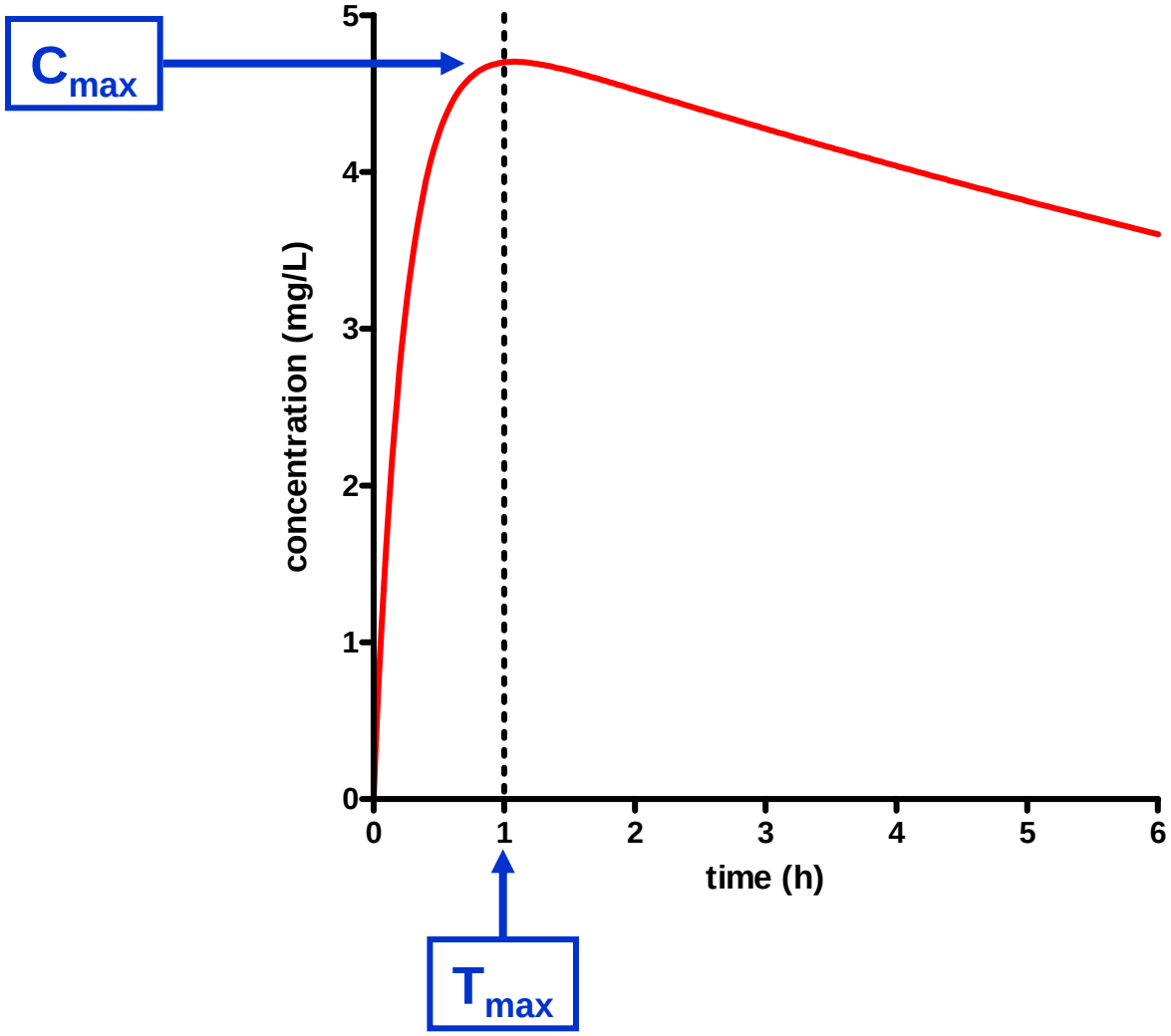
生物等效性:原则

- 生物等效性是公认的可替代治疗评价[1] (包括原研药改变剂型 …) [2]

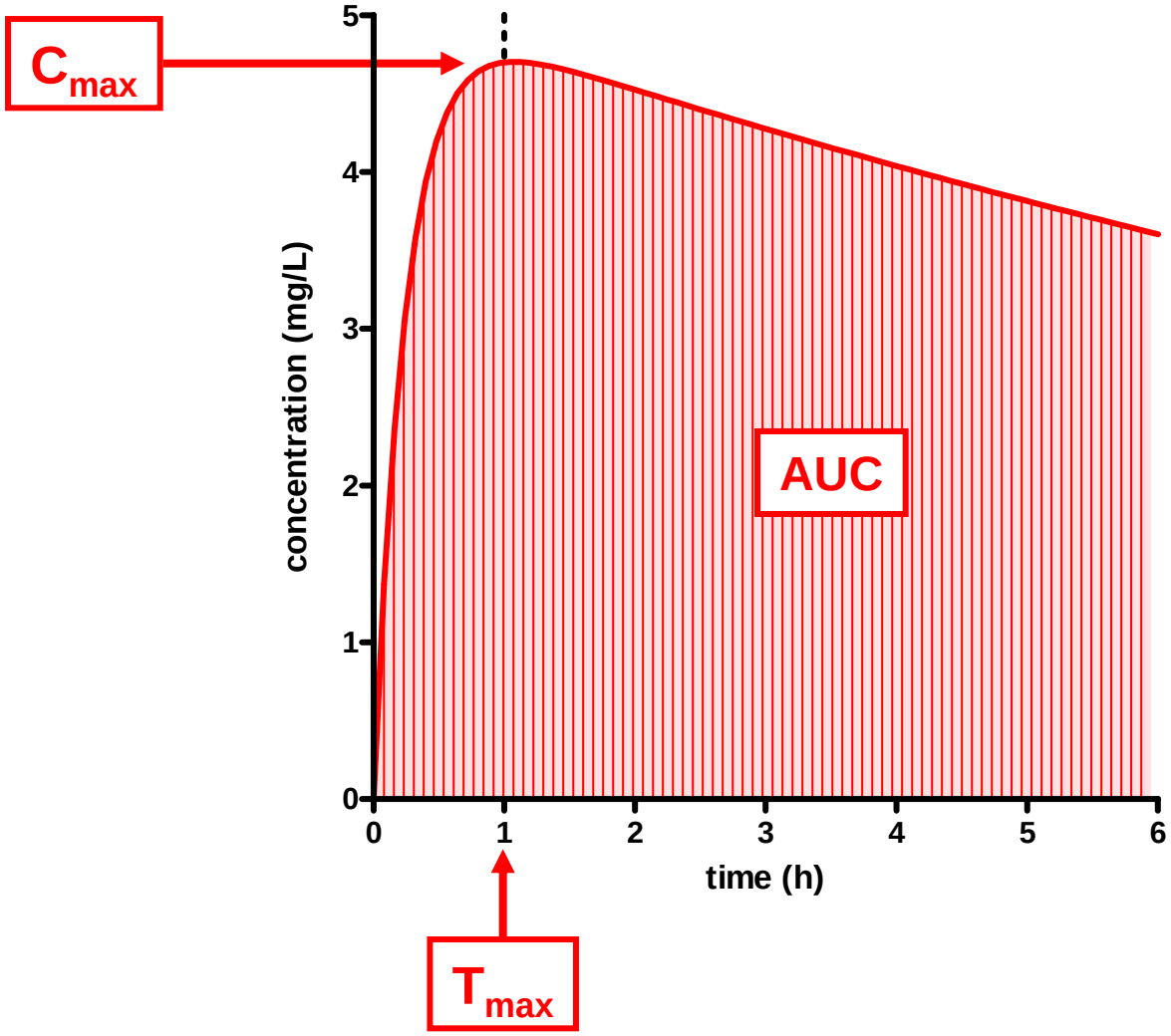
- 主要指标[1,3]
  - **药时曲线下面积**（血液浓度时间活性物质的剖面面积）
    → 吸收度
  - **峰浓度**(活性物质的最大血浆的浓度)
    → 吸收速率和吸收程度
  - **达峰时间**（达峰浓度的时间）
    → 吸收速率

1. Hauschke et al. Bioequivalence Studies in Drug Development – Methods and Applications, John Wiley & Sons Ltd. (UK), 2007.
2. Benet LZ: Understanding bioequivalence testing. Transplant.Proc. 31 (Suppl 3A): 7S-9S, 1999.
3. Niazi SK: Handbook of Bioequivalence Testing, “Drugs and the Pharmaceutical Sciences”, vol. 171, Informa Healthcare (New York), 2007.

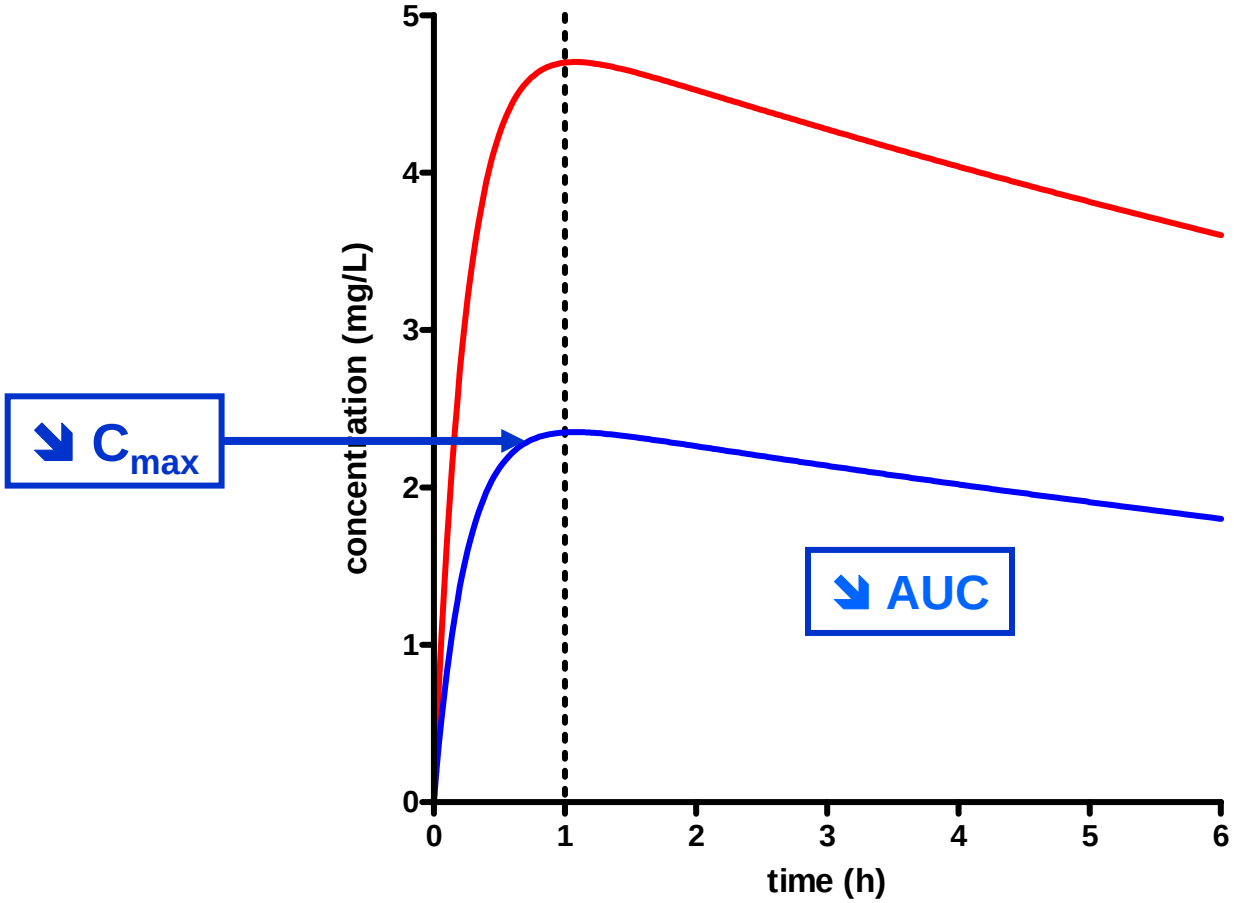
药时曲线下面积-峰浓度-达峰时间



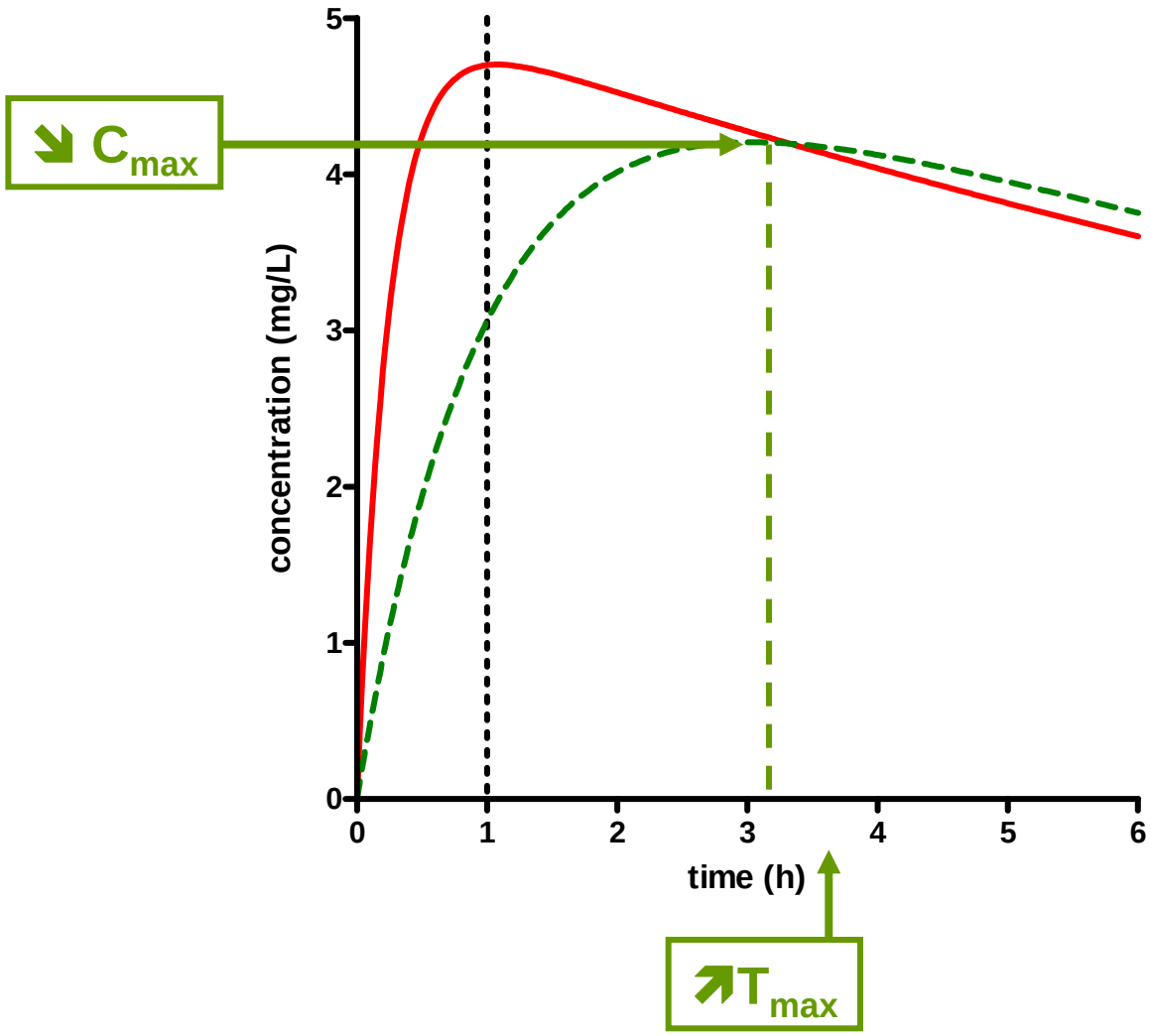
药时曲线下面积-峰浓度-达峰时间



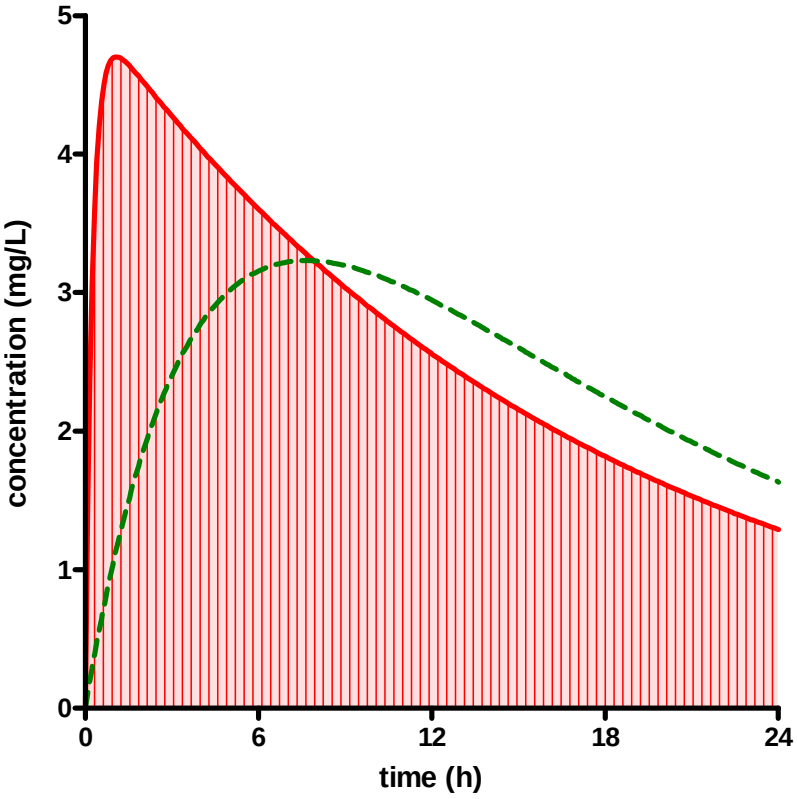
如果吸收减少会发生什么呢？

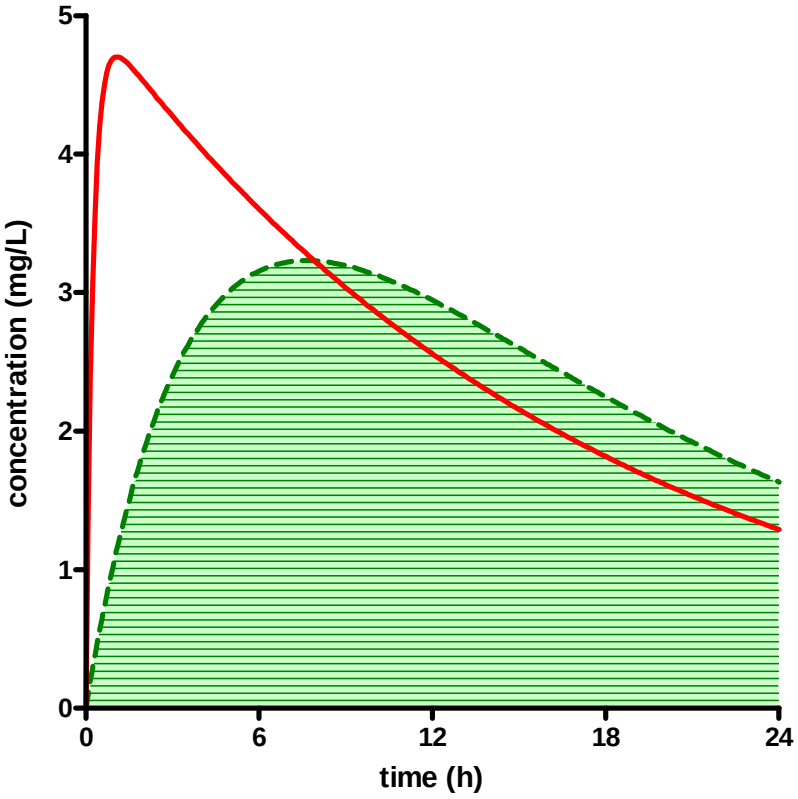


如果吸收延迟会发生什么呢？



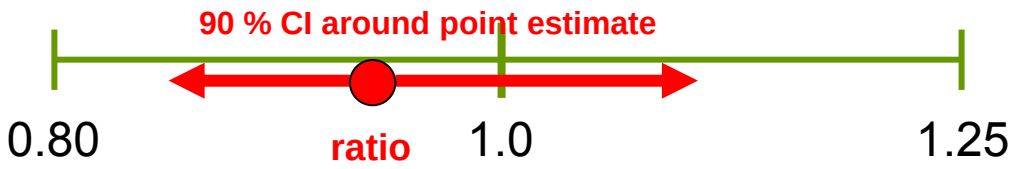
如果吸收显著减少，
你将获得一个相对较低的初始AUC值





生物等效性的标准(EMA * / FDA * *)

- 可通过参考药物(原研药)或测试药物(仿制品)的**AUC和Cmax的几何平均比率**计算**90%的置信区间**
- 大多数情况下，90%的置信区间应是**在0.80 - 1.25的可接受范围。**



* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052363.pdf

基于PK的生物等效性尚未解决的问题（抗生素的申请）

- PK生物等效性等于药效学等价吗？
  - -体外实验（最小抑菌浓度，防突变浓度，异质耐药性）……
  - -PK/PD模型（动物）
  - -临床研究(?)
- 静脉注射剂型会怎样？

（从定义上讲，就是不接受传统的生物等效性研究）

- 其他相关讨论？

–溶解时间 （在护理时很关键）

–稳定性（如青霉烯类抗生素）

–杂质(你喜欢它们?)

–……

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抗菌活性(哌拉西林)

使用补充的MIC相关评价 (Jones et al. Diagn Microbiol Infect Dis 61:76–79).

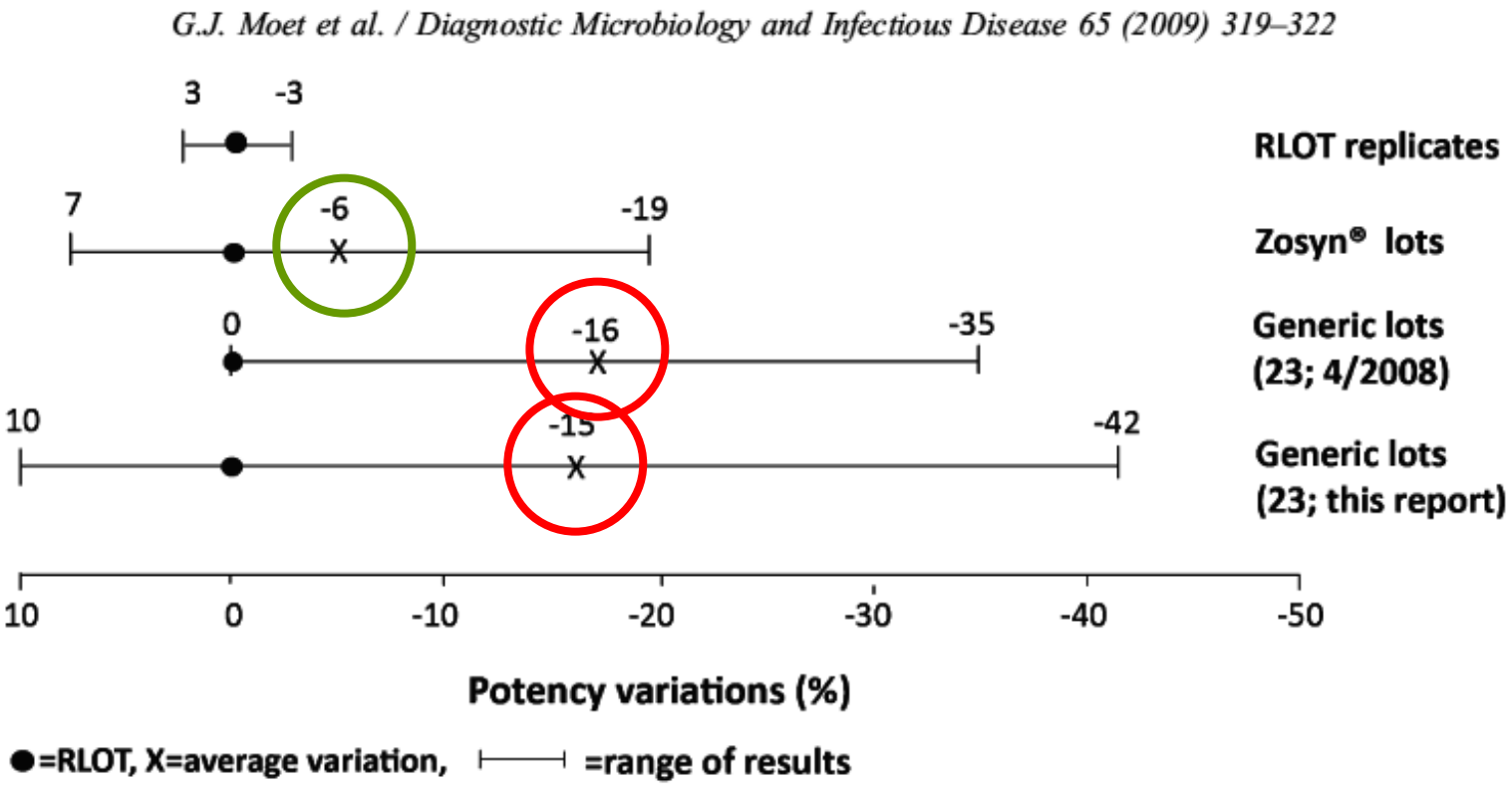


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

Moet *et al.* Diagnostic Microbiology and Infectious Disease 2009;65: 319–322

抗菌活性（苯唑西林）

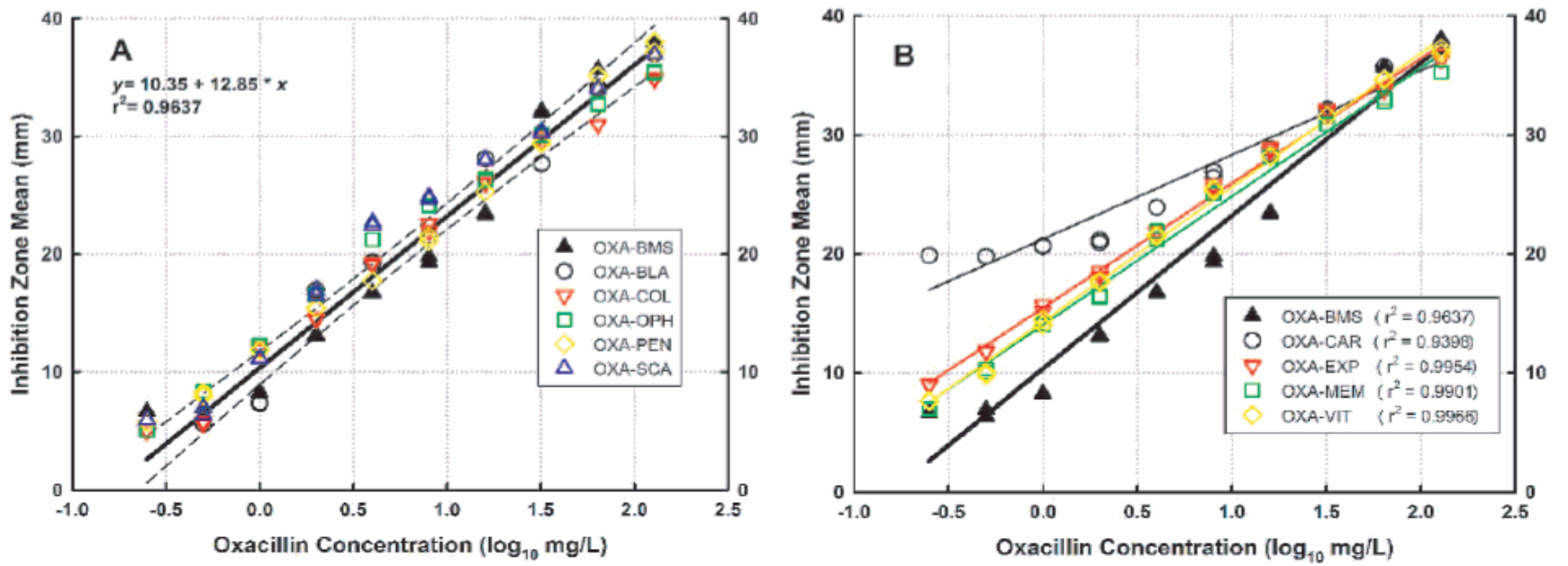


Figure 1 Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay. **A**. The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical equivalence (P = 0.1165). The standard curves of all products are better described by a single linear regression, shown here with the 95% confidence interval. **B**. The slopes and intercepts of OXA-CAR, OXA-EXP, OXA-MEM and OXA-VIT were significantly different to the innovator's (P < 0.03458), thus failing pharmaceutical equivalence. As generic products belong to populations different to that of the innovator, each is described by an independent linear regression with their respective coefficient of determination (r^2).

Rodriguez *et al. BMC Infectious Diseases* 2010, **10**:153
http://www.biomedcentral.com/1471-2334/10/153

最小抑菌浓度的价值（万古霉素）

Table 1 Comparison of antimicrobial activity against various clinical isolates in a brand name and generic antibiotics

Antibiotic	Pathogen (no.)	No. of generic markers	Nonidentical rate of the MIC value of all generics (mean ± SD)	MIC distribution (%) of the most different generic versus brand name drug						
				1/8	1/4	1/2	1[a]	2	4	8
Vancomycin	MRSA (90)	5	25.00 ± 15.52	–	–	–	54.4	45.6	–	–
Teicoplanin	MRSA (147)	7	28.09 ± 10.29	–	–	–	59.2	40.1	0.7	–
Cefotiam	*Staphylococcus aureus* (100)	7	8.71 ± 3.04	–	–	–	87.0	13.0	–	–
	Escherichia coli (100)	7	12.00 ± 5.89	–	–	–	77.0	22.0	1.0	–
Ceftriaxone	*Streptococcus pneumoniae* (126)	6	12.70 ± 4.77	–	–	–	81.7	18.3	–	–
Ceftazidime	*Pseudomonas aeruginosa* (100)	2	3.00 ± 2.83	–	–	–	95.0	5.0	–	–
Meropenem	*P. aeruginosa* (100)	7	18.57 ± 3.46	–	–	–	78.0	19.0	2.0	1.0
Imipenem	*P. aeruginosa* (100)	4	9.00 ± 2.58	–	–	–	88.0	11.0	1.0	–

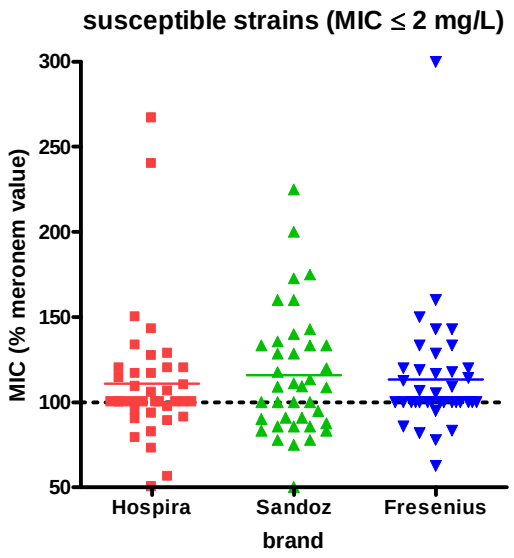
MRSA methicillin-resistant *Staphylococcus aureus*[a]Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug: MIC was determined by broth micro-dilution method using powder in each drug vial

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427

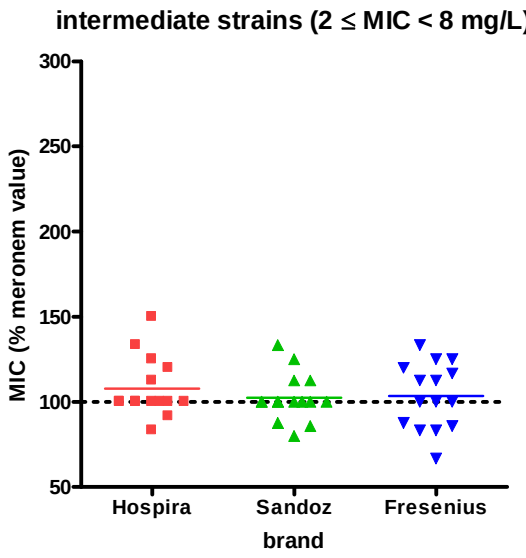
MICs 常常比参考药物高

最小抑菌浓度的价值（美罗培南）

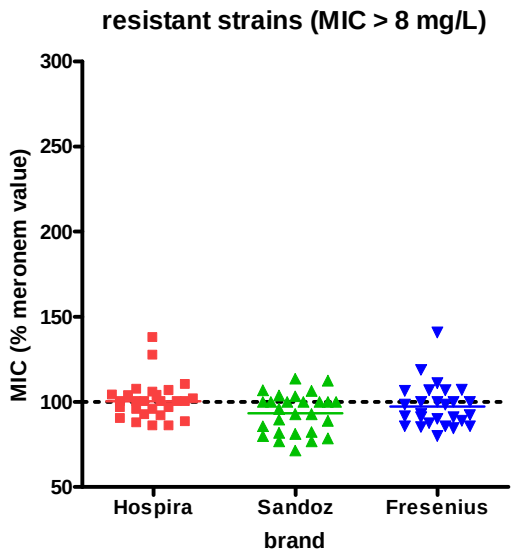
最小抑菌浓度是由显示了从0.125到128 mg / L（几何值）的最小抑菌浓度菌株的稀释值决定。



	Hospira	Sandoz	Fresenius
mean =	110.8	115.8	113.3
SD=	39.2	36.5	36.6



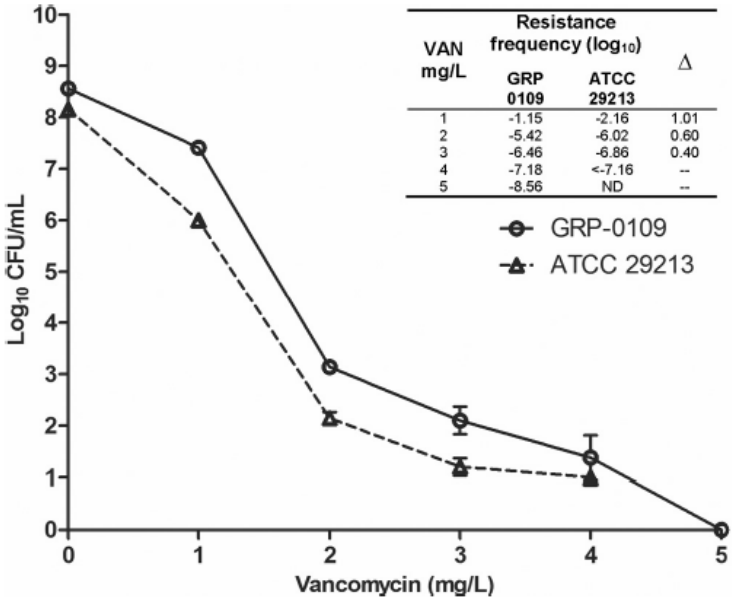
	Hospira	Sandoz	Fresenius
mean=	107.7	102.7	103.4
SD=	17.41	13.9	19.3



	Hospira	Sandoz	Fresenius
mean =	100.4	93.4	97.3
SD=	11.5	11.7	12.9

Van Bambeke *et al*., in preparation

杀菌曲线和异质性耐药(万古霉素)

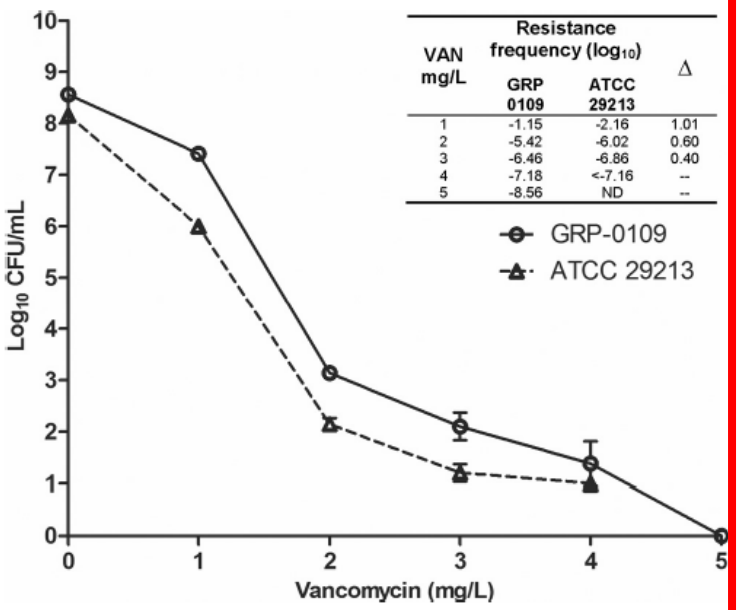


VAN mg/L	Resistance frequency (log_{10}) GRP 0109	ATCC 29213	Δ
1	-1.15	-2.16	1.01
2	-5.42	-6.02	0.60
3	-6.46	-6.86	0.40
4	-7.18	<-7.16	--
5	-8.56	ND	--

FIG 1 Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin, 4 times more grew at 2 mg/liter, and 2.5 times more grew at 3 mg/liter (resistance frequency data at right).

Rodriguez *et al.* Antimicrob Agents Chemother. 2012; 56:243–247

杀菌曲线和异质性耐药(万古霉素)



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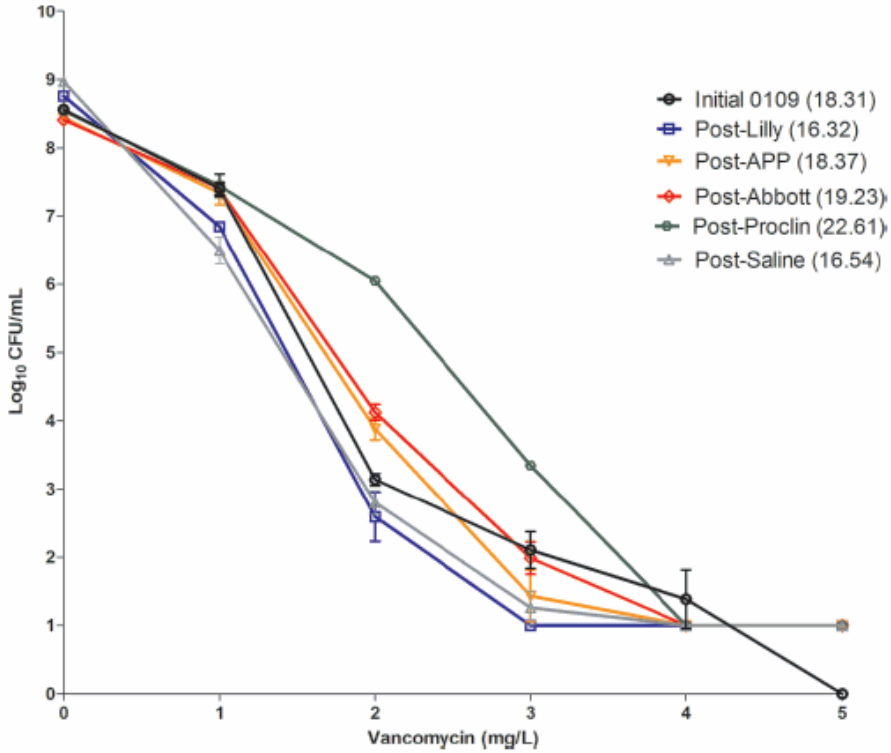

FIG 3 Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction of the less susceptible subpopulations, which is sharply different from three generics, which had higher AUCs and up and/or right displacement of the curve, (especially Proclin), due to resistant subpopulation enrichment. The control saline group exhibited a down and left displacement, consistent with reversion of unstable resistance associated with reduced fitness. The limit of detection for all of the postexposure isolates was 10 CFU/ml, and for the GRP-0109 initial strain the limit was 0 CFU/ml.

Rodriguez *et al.* Antimicrob Agents Chemother. 2012; 56:243–247

我们接下来讨论的话题？

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2. 支持进行药效学的生物等效性研究
3. 支持微生物学的等效性研究
   - 最小抑菌浓度，防突变浓度，异质耐药性…
4. **药动学等价方法**
   - **PK / PD动物模型和临床数据**
5. 相关溶解和稳定性的问题
6. 真正的含量与杂质
7. “低成本”抗菌药物的潜在的治疗风险

万古霉素:非等价的证据

粒缺的小鼠模型

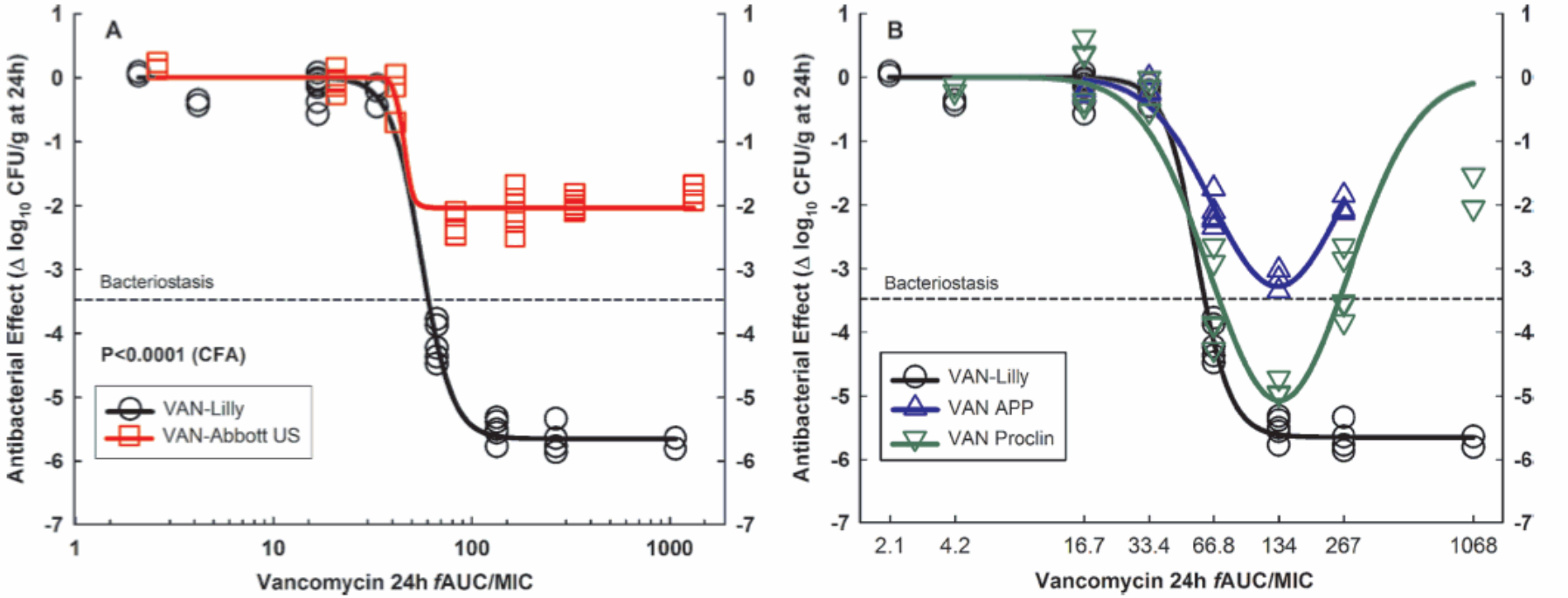

FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per day) using the neutropenic mouse thigh infection model (each data point represents the mean CFU/g of both thighs from a single mouse). (A) Pharmacodynamic patterns of VAN-Abbott US and VAN-Lilly fitted to the Hill model. Despite containing a significantly greater concentration of API (125%), VAN-Abbott US was completely ineffective *in vivo*. VAN-Abbott US is shown in a separate graph because of its greater AUC/MIC ratio than that of VAN-Lilly (123%; their dosing regimens were identical). (B) VAN-APP and VAN-Proclin were both pharmaceutically equivalent to VAN-Lilly, but neither was therapeutically equivalent due to their marked Eagle effect. The curve for VAN-APP ends at 300 mg/kg (*f*AUC/MIC, 267 h) because this product was discontinued and the remaining amount was insufficient for the highest doses.

Vesga et al. Antimicrob Agents Chemother. 2010; 54:3271–3279.

苯唑西林:非等价的证据

粒缺的小鼠模型

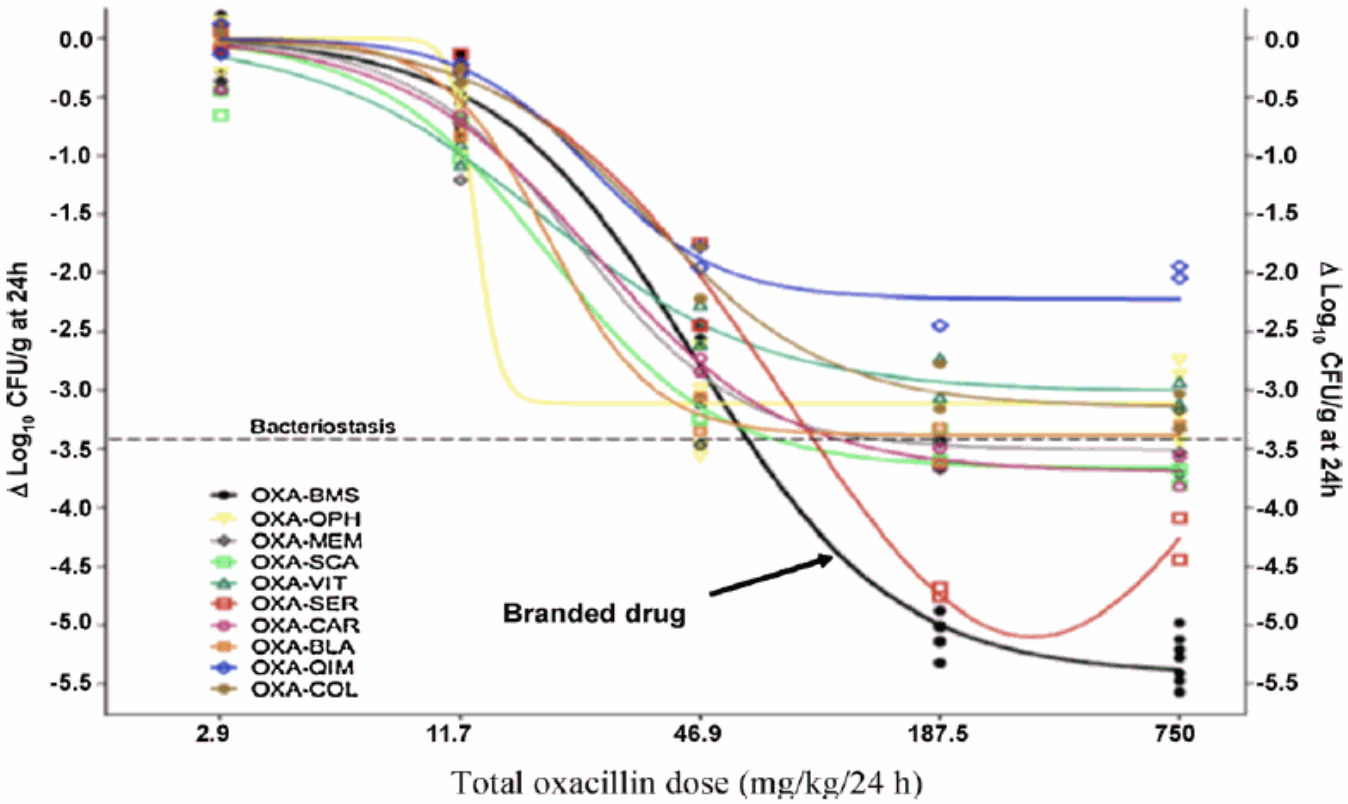

Fig. 1. Dose/response relationship for branded drugs and nine generic oxacillin drugs in a model of thigh infection in neutropenic mice [17]. For eight generic drugs: bactericidal effectiveness inferior to branded drugs ($P < 0.0001$). For one generic drug (red curve): presence of an "Eagle" effect.
Relation dose/réponse du princeps et de neuf génériques d'oxacilline dans le modèle d'infection de la cuisse de souris neutropénique [17].

Gauzit & Lakdhari Médecine et maladies infectieuses 2012;42:141–148

庆大霉素:活体非等价的证据

粒缺的小鼠模型

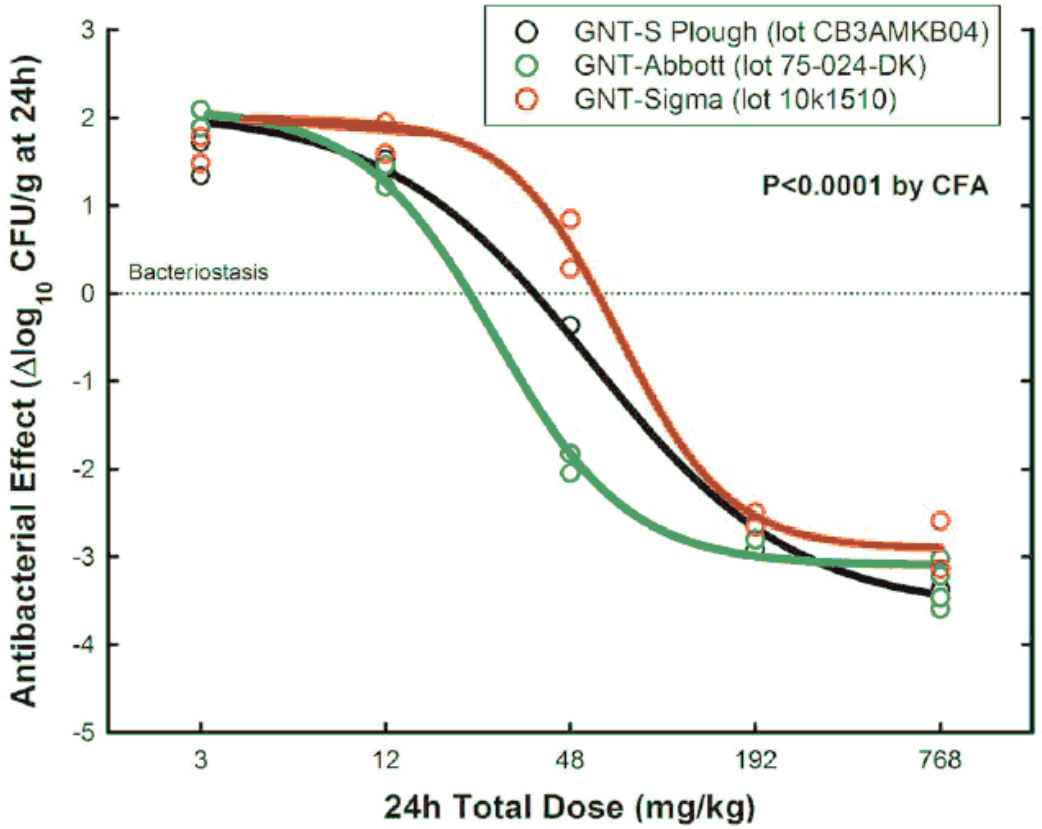

Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence. The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency of the active pharmaceutical ingredient, MIC, MBC, MBC/MIC ratios but significantly different in terms of therapeutic efficacy, although the same batch of each product was tested in vitro and in vivo.
doi:10.1371/journal.pone.0010744.g003

Zuluaga et al. PLoS ONE 2010; 5: e10744. doi:10.1371/journal.pone.0010744

庆大霉素:活体非等价的证据

粒缺的小鼠模型

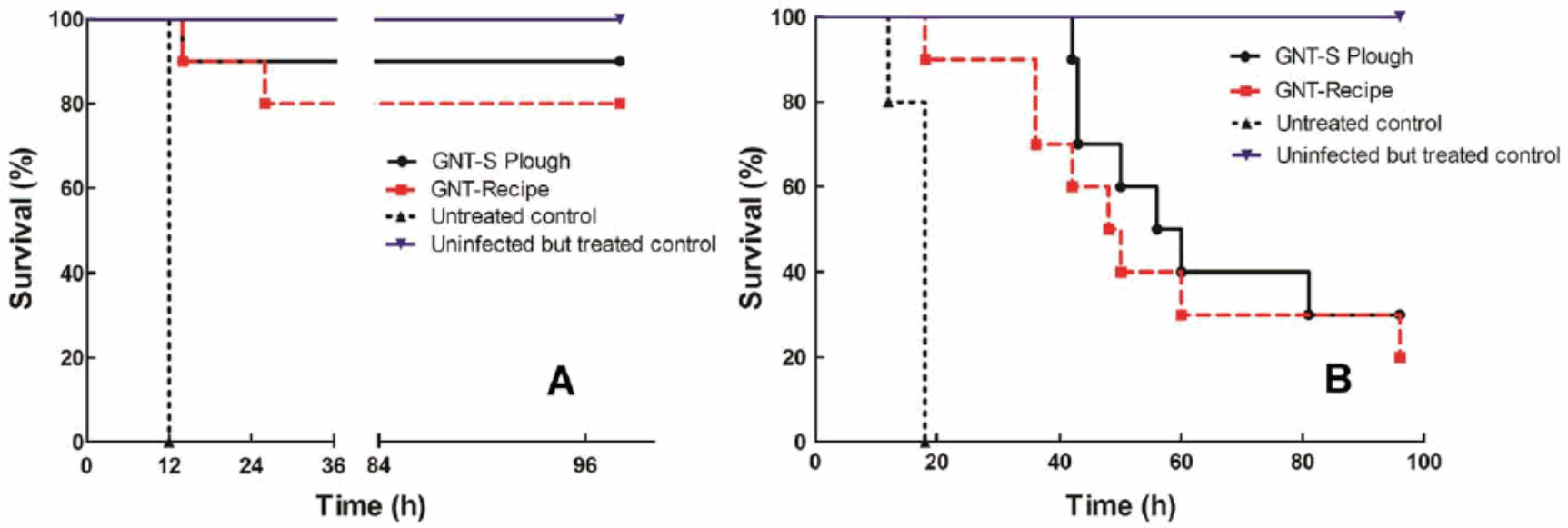

Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect (768 mg/kg per day divided q6h), starting 2 h (panel A) or 6 h (panel B) post-infection. Uninfected neutropenic mice serving as toxicity controls received the same treatment and were identical to the other animals but, instead of *P. aeruginosa*, were mock-inoculated in the thighs with sterile saline (n = 5 mice per gentamicin product). No significant impact on survival was detected between both gentamicin products. doi:10.1371/journal.pone.0010744.g004

Zuluaga et al. PLoS ONE 2010; 5: e10744. doi:10.1371/journal.pone.0010744

甲硝唑:完全等价

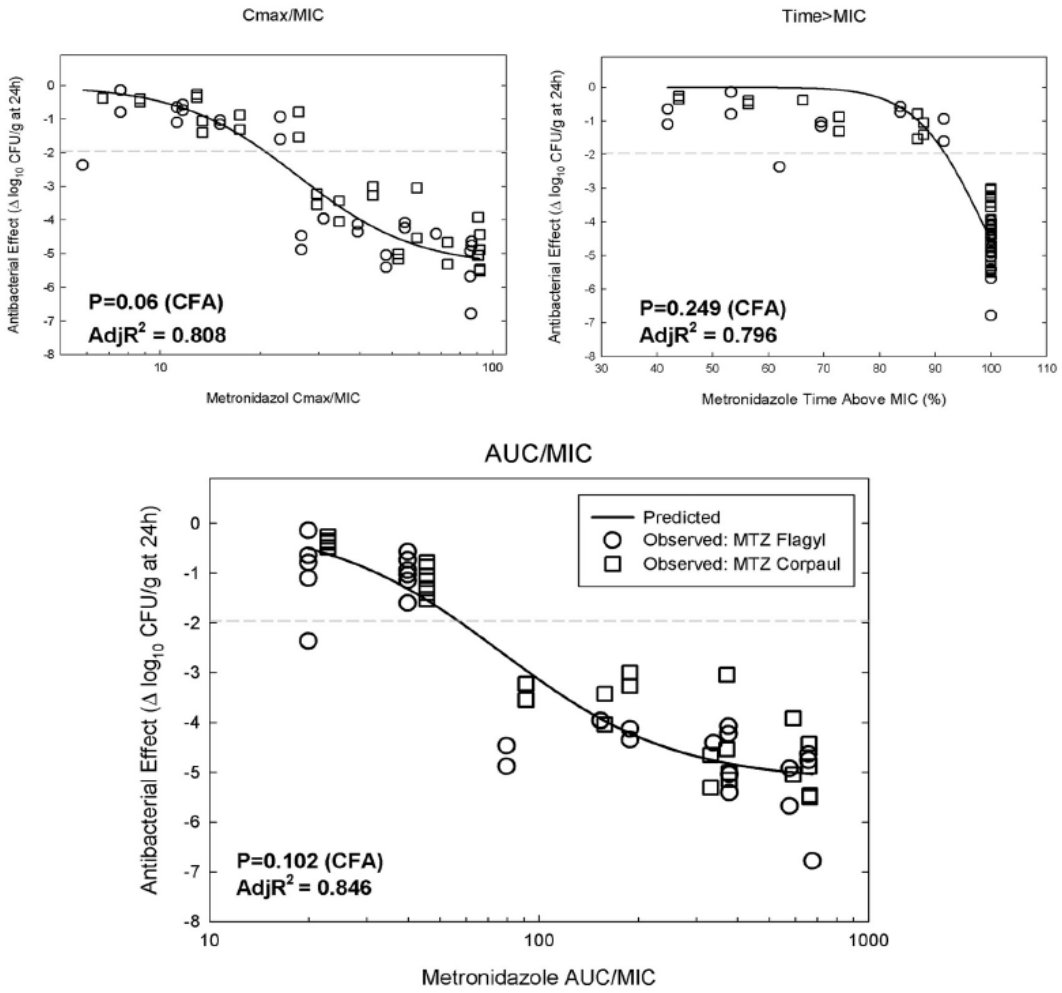

FIG 5 Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *B. fragilis* in a neutropenic mouse thigh anaerobic infection model. Only one curve is depicted because the data belong to a single population despite the fact that they were obtained after treatments of different groups of animals with a generic product or the innovator. The AUC/MIC ratio drives the antibacterial efficacy of metronidazole.

Agudelo & Vesga, Antimicrob Agents Chemother. 2013; 56:2659–2665

临床疗效如何呢？

经验性处方抗菌药物的三个国家中社区获得性肺炎抗菌素经验处方的成本效益

Martin *et al.* J Antimicrob Chemother. 2007; 59:977-989

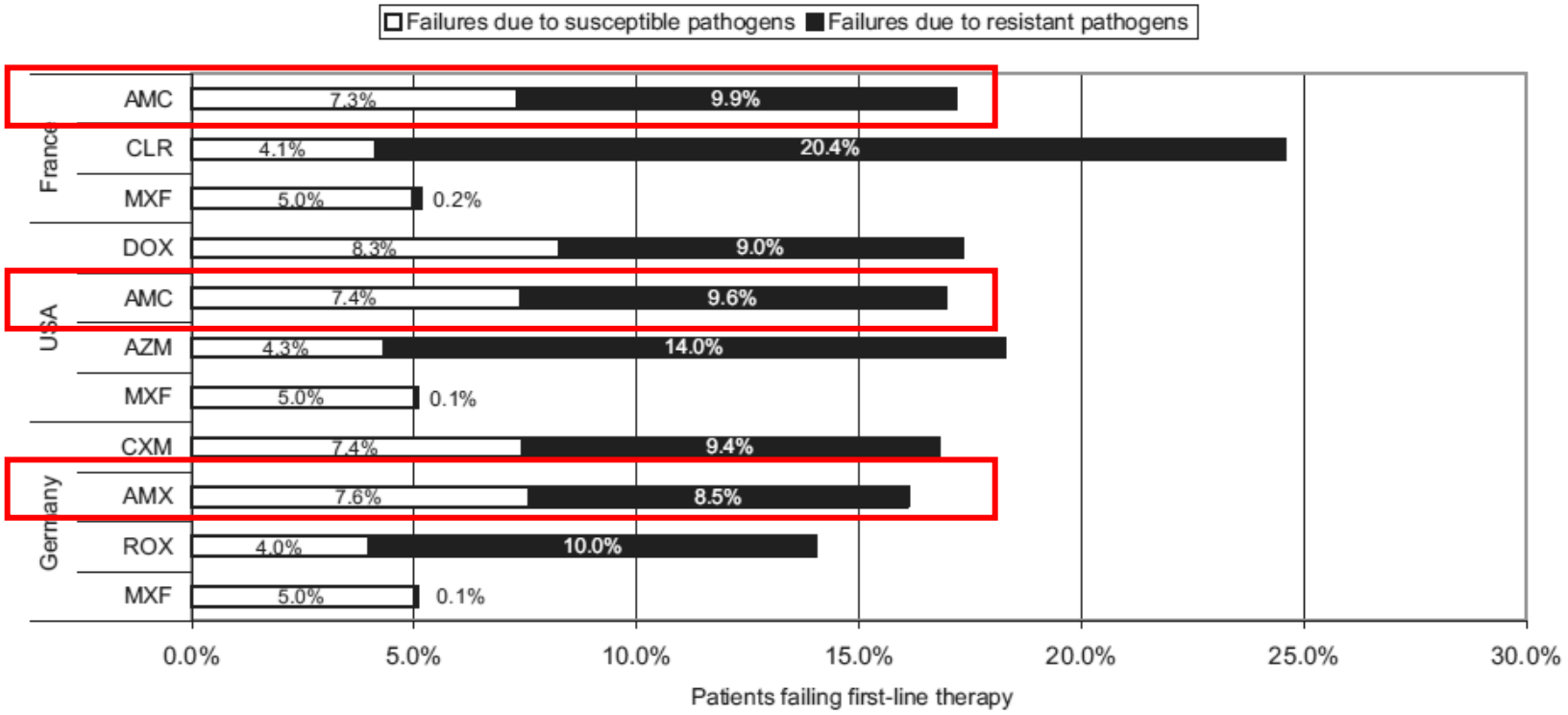

Figure 2. Calculated clinical failure rates with first-line therapy in CAP due to susceptible pathogens and antimicrobial-resistant pathogens (rounded). MXF, moxifloxacin; CLR, clarithromycin; AMX, amoxicillin; AMC, co-amoxiclav; AZM, azithromycin; DOX, doxycycline; ROX, roxithromycin; CXM, cefuroxime axetil.

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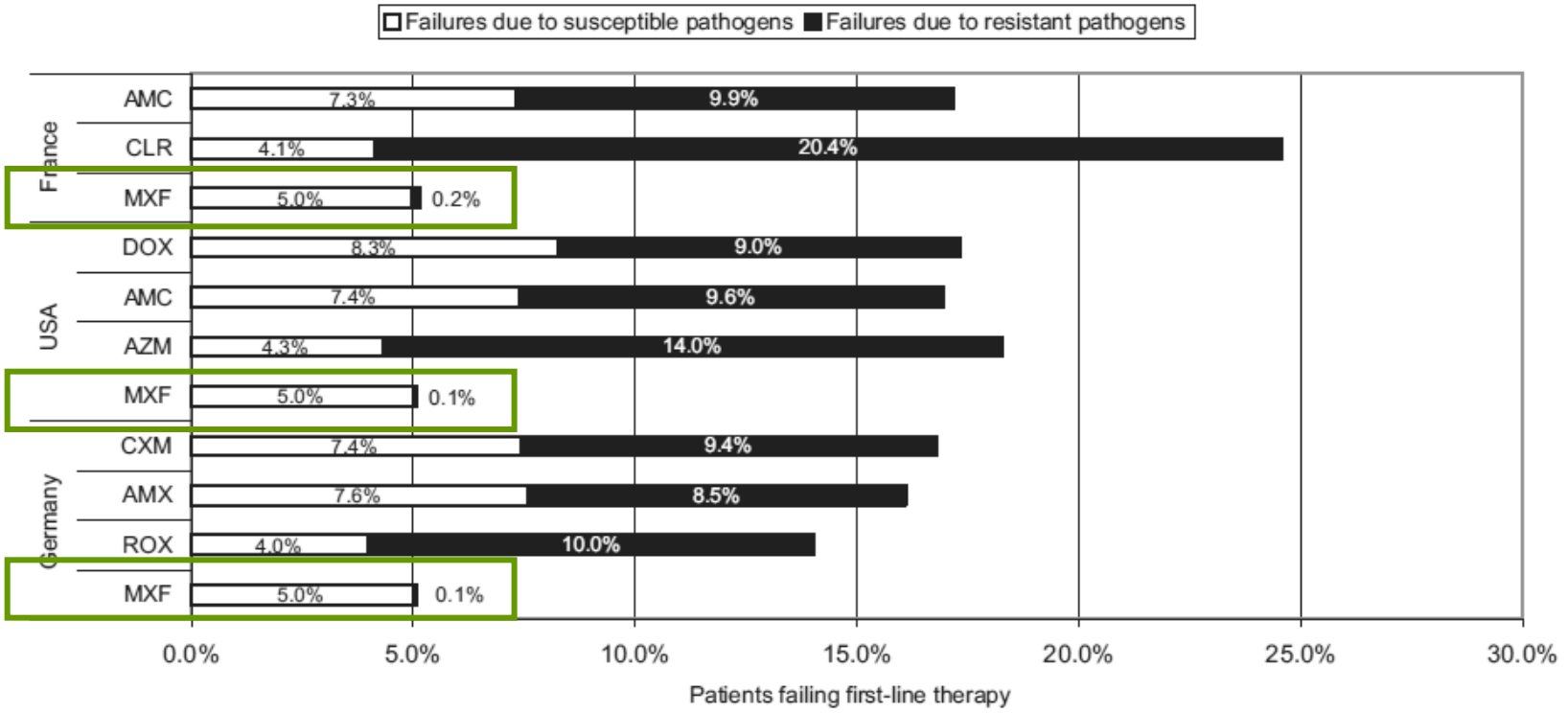

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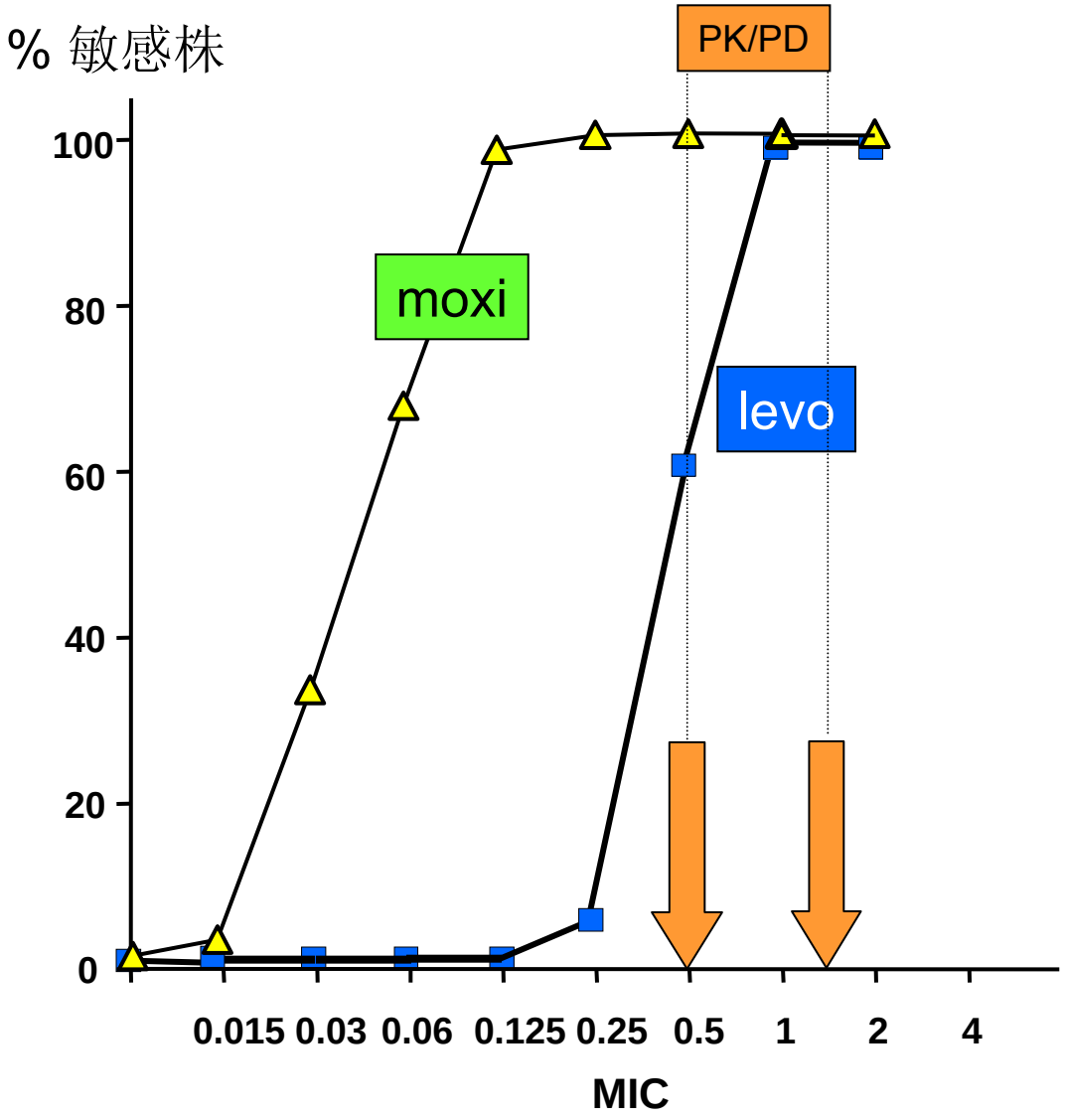
为什么莫西沙星 400mg 如此有效 (与左氧氟沙星500 mg比较)



莫西沙星 400 mg 1x/d

- AUC [(mg/l)xh]: 48
  - MIC max: 0.5-1.5
- peak [mg/l]: 4.5
  - MIC_{max} : ~ 0.5

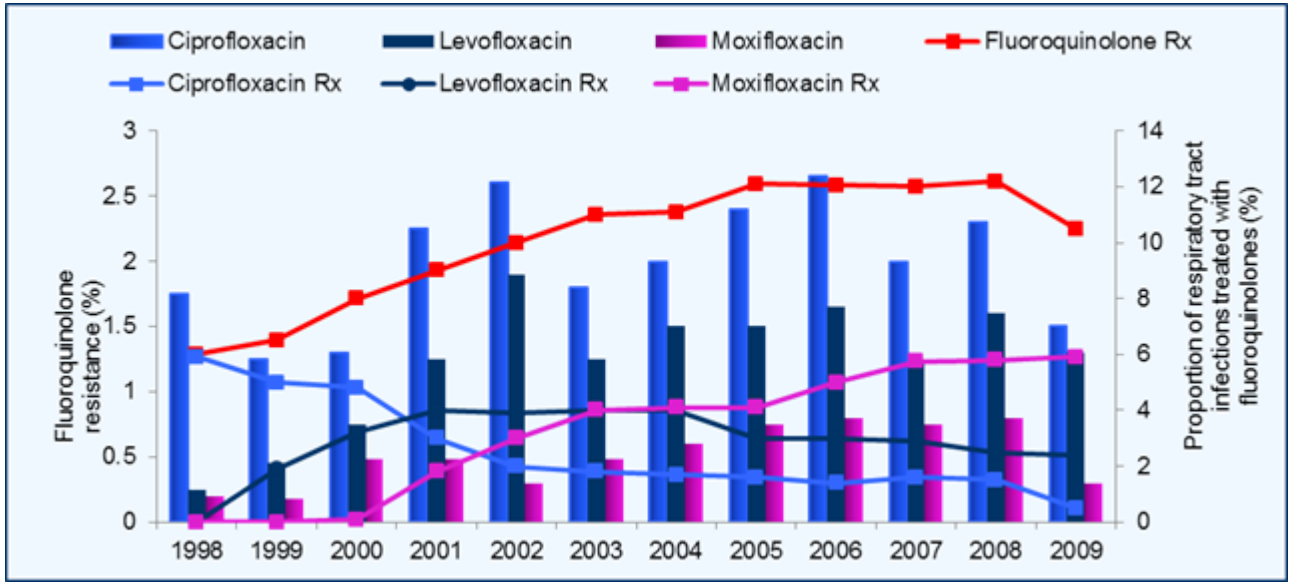
左氧氟沙星 500 mg 1x/d

- AUC [(mg/l)xh] 47
  - MIC max: 0.5-1.5
- peak [mg/l] 5
  - MIC_{max}: ~ 0.5

MIC data: J. Verhaegen et al., ECCMID 2003
Similar values in 2009 (Vanhoof, ECCMID 2009)

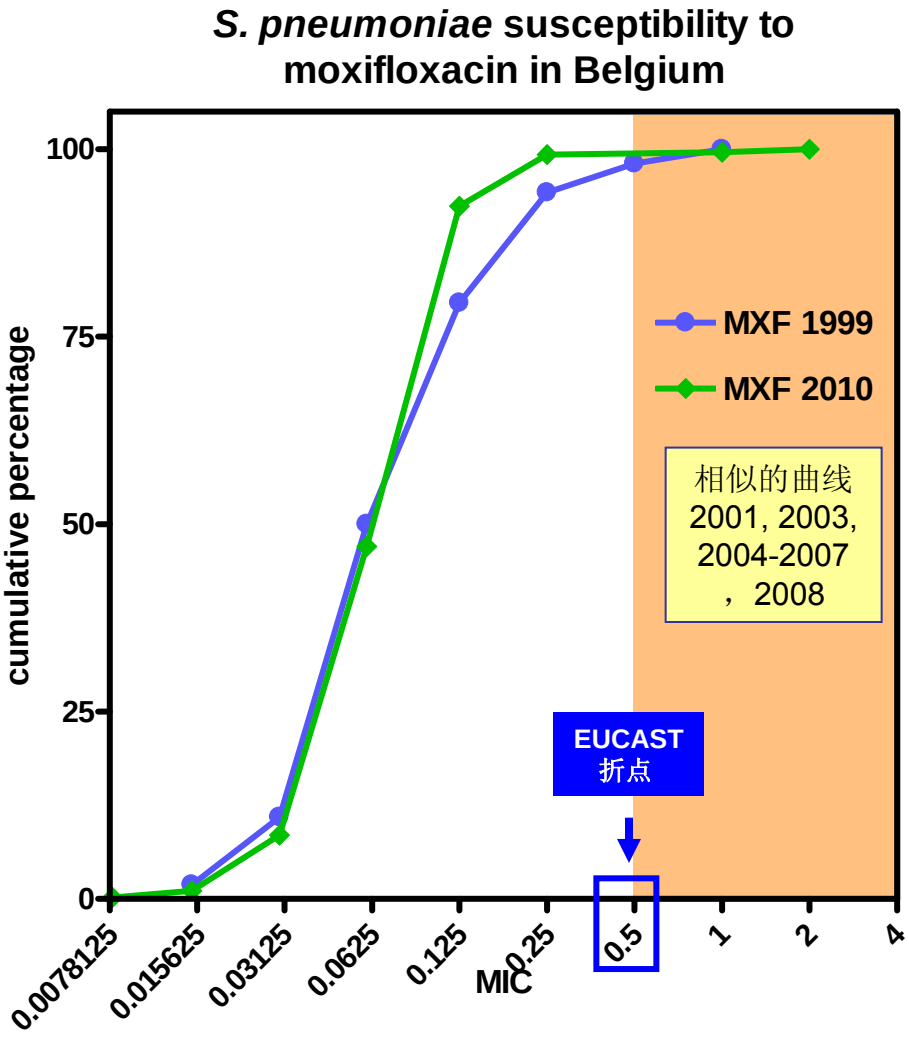
在加拿大，将环丙沙星／左氧氟沙星变为莫西沙星时，氟喹诺酮的耐药方式向好的方向转变

- 加拿大细菌调研网分析了1999到2009年间分离的菌株(n=26,081)，发现：
  - 1999到2009年，氟喹诺酮的处方从64/1000人/年增加到96/1000人/年
  - 呼吸道感染的处方从5.9%增加到10.7%
    - 环丙沙星的处方从5.3% 减少到 0.5%
    - 左氧氟沙星和莫西沙星的处方从1.5% 增加到5.9%
  - 尽管如此，左氧氟沙星和莫西沙星的耐药仍维持在低于<2% (MIC ≥ 4μg/mL)



Patel *et al. Antimicrob Agents Chemother* 2011; 55:3703–8

1999-2010，莫西沙星对肺炎链球菌的MIC值在比利时没有升高



事实：

数据来源于全国的数据收集 * 独立于我们自己收集的数据（如前张幻灯所示）

- 1999（预商业化）-2008（上市后7年），莫西沙星对肺炎链球菌的敏感度没有变化（甚至也没有进展）
- 在 2010年, 99.3 % 分离株始终低于 EUCAST 折点 (0.5 mg/L)， **MIC 值 > 10倍低于$C_{max.}$**

* 非侵入性呼吸道感染
** 在比利时上市的第一个呼吸喹诺酮类药物

Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates
(n=156 in 1999 and 448 in 2008)
http://www.iph. fgov.be
Data available yearly for 1999 through 2008.
Presented at 19th ECCMID, May 2009, Helsinki, Finland (Vanhoof et al.)
Data up to 2010 are from Lismond et al. 2012 (IJAA)

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   - 最小抑菌浓度，防突变浓度，异质耐药性…
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   - PK / PD动物模型和临床数据
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在日本的溶解度（美罗培南）...

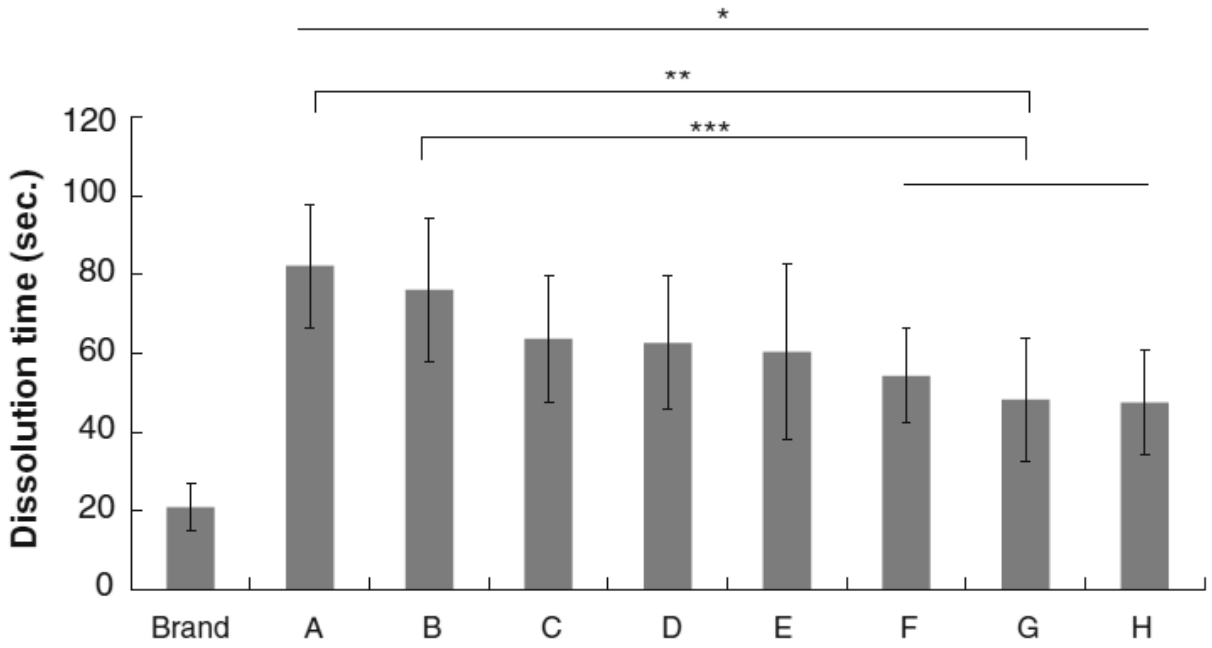


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427

美罗培南的晶体尺寸

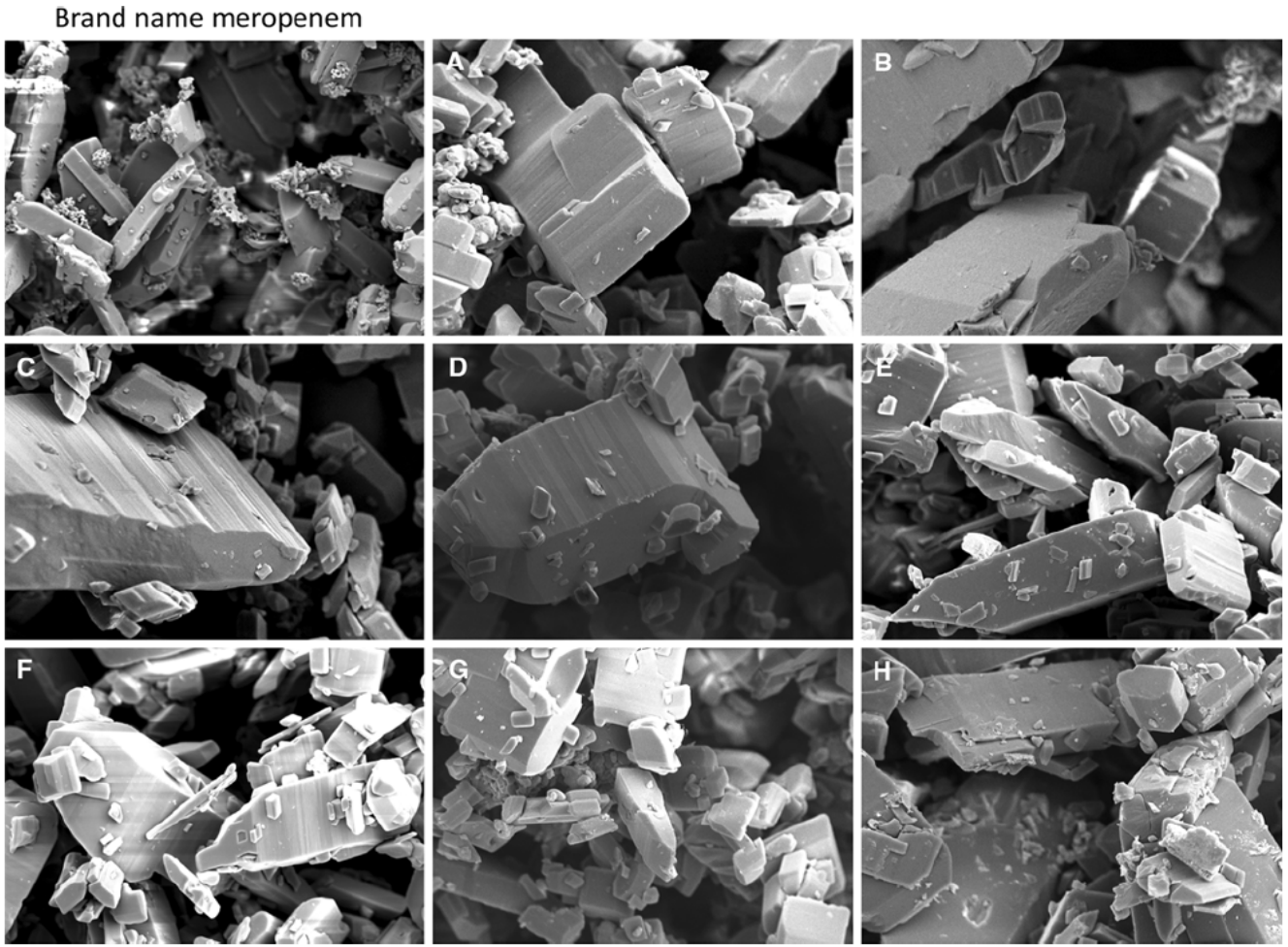


Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

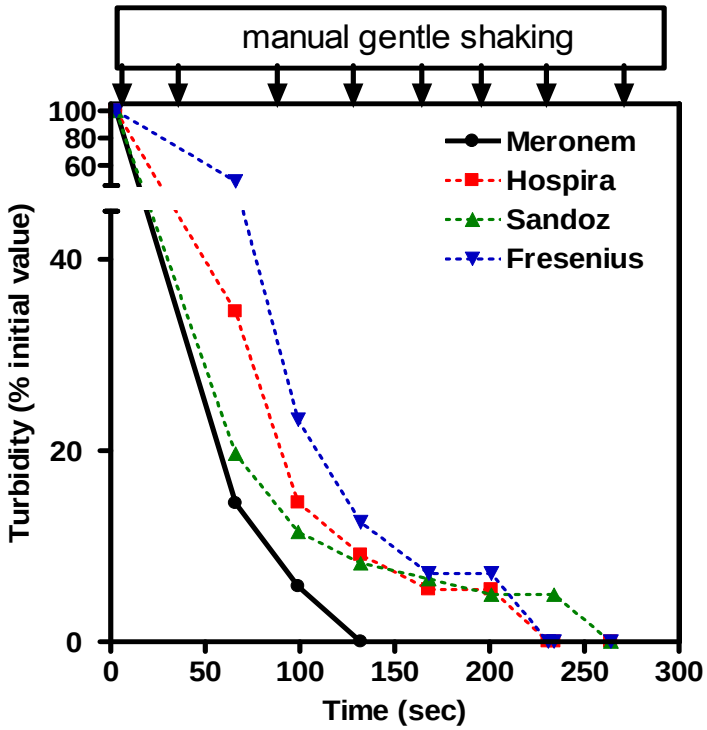
Fujimura & Watanabe J Infect Chemother (2012) 18:421–427

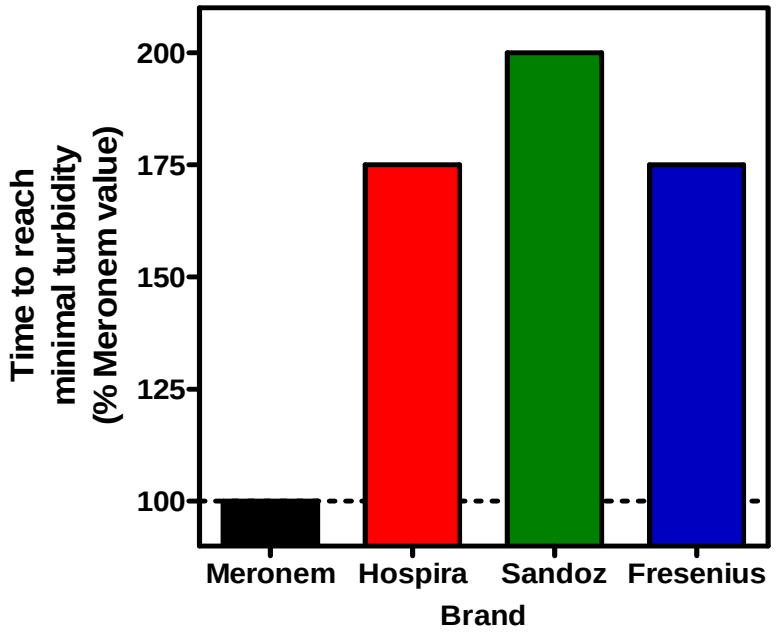
在比利时的溶解度（美罗培南） ...

药物浓度:50毫克/毫升(~用于输液的溶液)

轻柔地手动摇晃后采取浊度措施；

室温

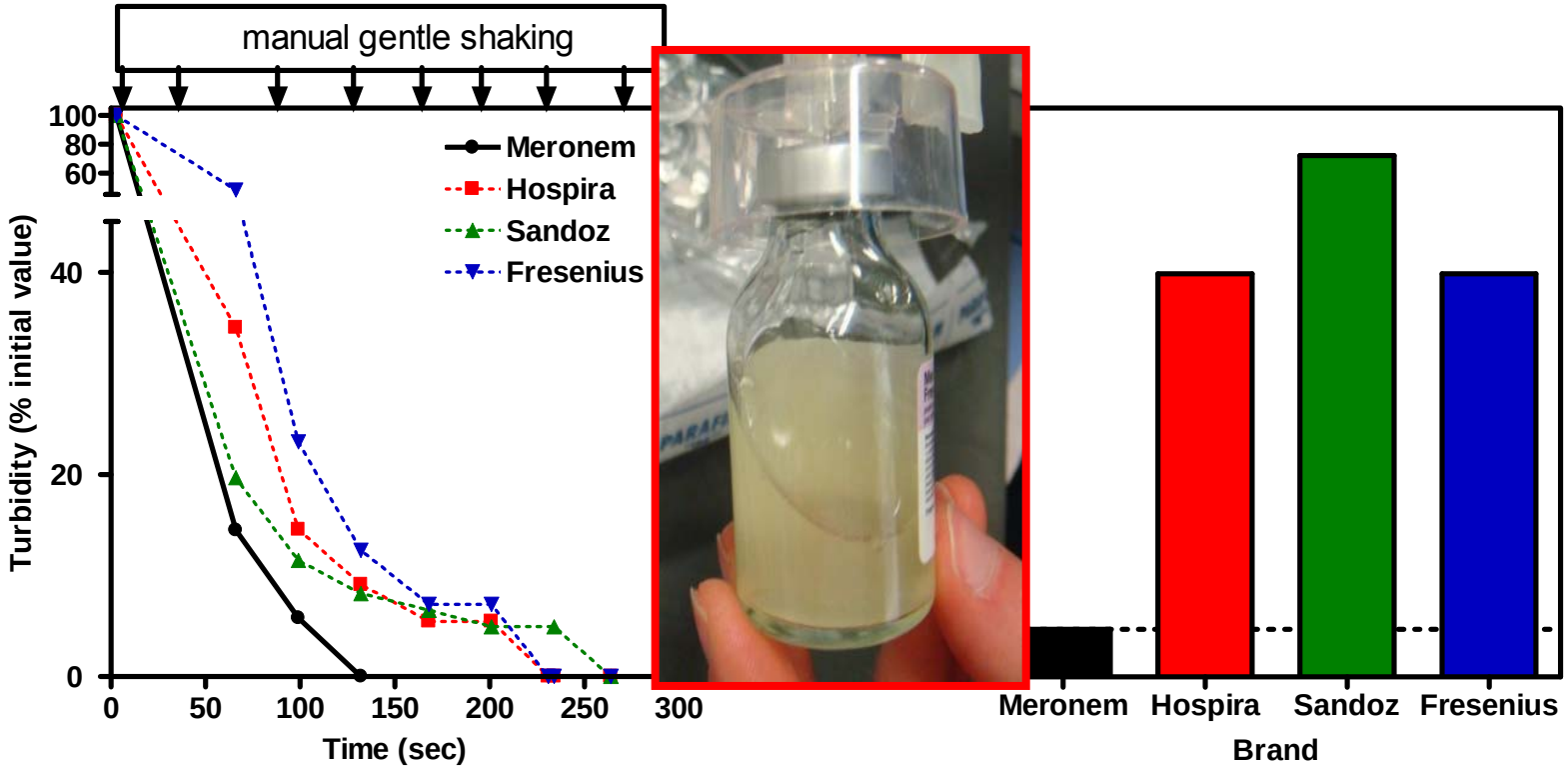




Van Bambeke *et al*., in preparation

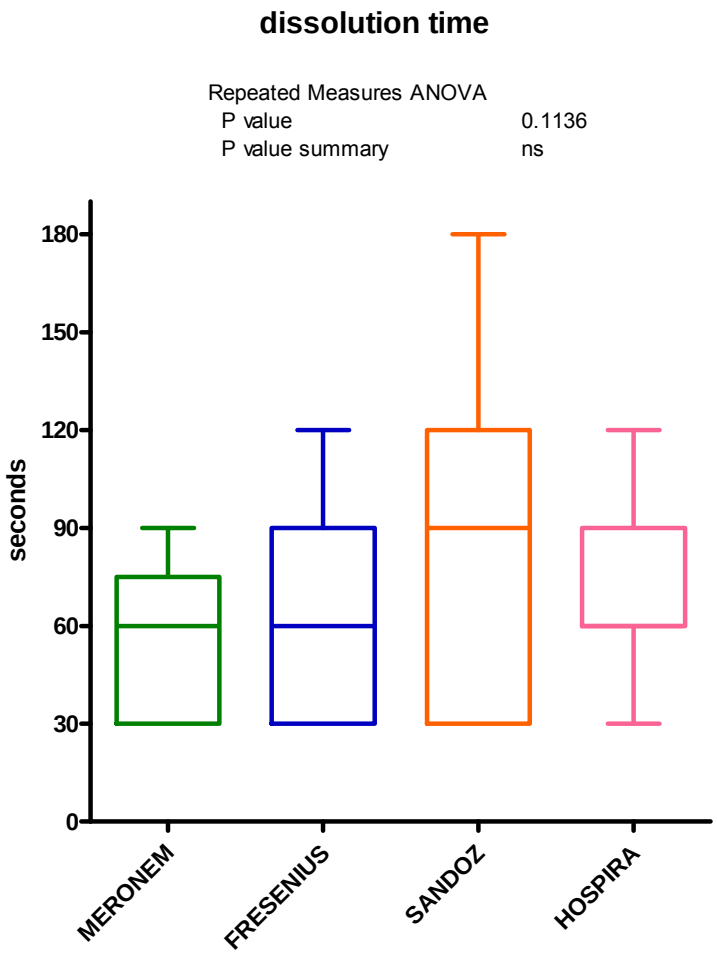
在比利时的溶解度（美罗培南） ...

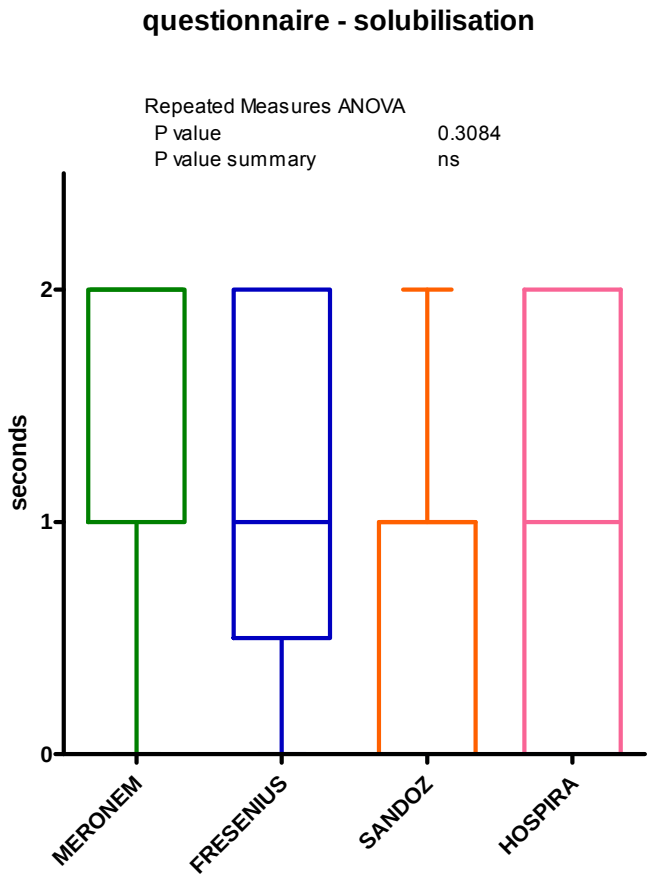
药物浓度:50毫克/毫升(~用于输液的溶液)
;
轻柔地手动摇晃后采取浊度措施;
室温



Van Bambeke *et al*., in preparation

初级卫生保健专业人员(护士)使用方便吗?（美罗培南）





Van Bambeke *et al*., in preparation

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4. 药动学等价方法
   - PK / PD动物模型和临床数据
5. 相关溶解和稳定性的问题
6. **真正的含量与杂质**
7. “低成本”抗菌药物的潜在的治疗风险

杂质

Available online at www.sciencedirect.com
ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Generic ciprofloxacin tablets contain the stated amount of drug and different impurity profiles: A ^{19}F, ^{1}H and DOSY NMR analysis

Saleh Trefi, Véronique Gilard, Myriam Malet-Martino*, Robert Martino

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Abstract

The objective of this study was to control the purity of 16 commercial formulations of ciprofloxacin tablets purchased in different countries or via the Internet using ^{19}F and ^{1}H nuclear magnetic resonance (NMR). Twelve out of the sixteen commercial formulations of ciprofloxacin measured by ^{19}F NMR contain the active ingredient within $100 \pm 5\%$ of stated concentration. Three formulations have a lower ciprofloxacin content between 90 and 95% and one shows a higher concentration superior to 105%. The impurity profile was characterised using ^{19}F and ^{1}H NMR, and is characteristic of the manufacturer. Four to twelve fluorinated impurities among them fluoride ion and two already known compounds were detected and quantified in the sixteen formulations analysed by ^{19}F NMR. Two other non-fluorinated impurities were observed in the seven formulations analysed with ^{1}H NMR. The total content of impurities as well as their individual levels are in agreement with those reported previously in the few studies devoted to ciprofloxacin purity. However, all the formulations do not comply with the limits for impurities given in the ciprofloxacin monograph of the European Pharmacopeia. Finally, a "signature" of the formulations was obtained with Diffusion-Ordered SpectroscopY (DOSY) ^{1}H NMR which allowed the characterisation of some excipients present in the formulations studied.

Keywords: ^{19}F NMR; ^{1}H NMR; DOSY ^{1}H NMR; Ciprofloxacin; Impurities

环丙沙星的杂质

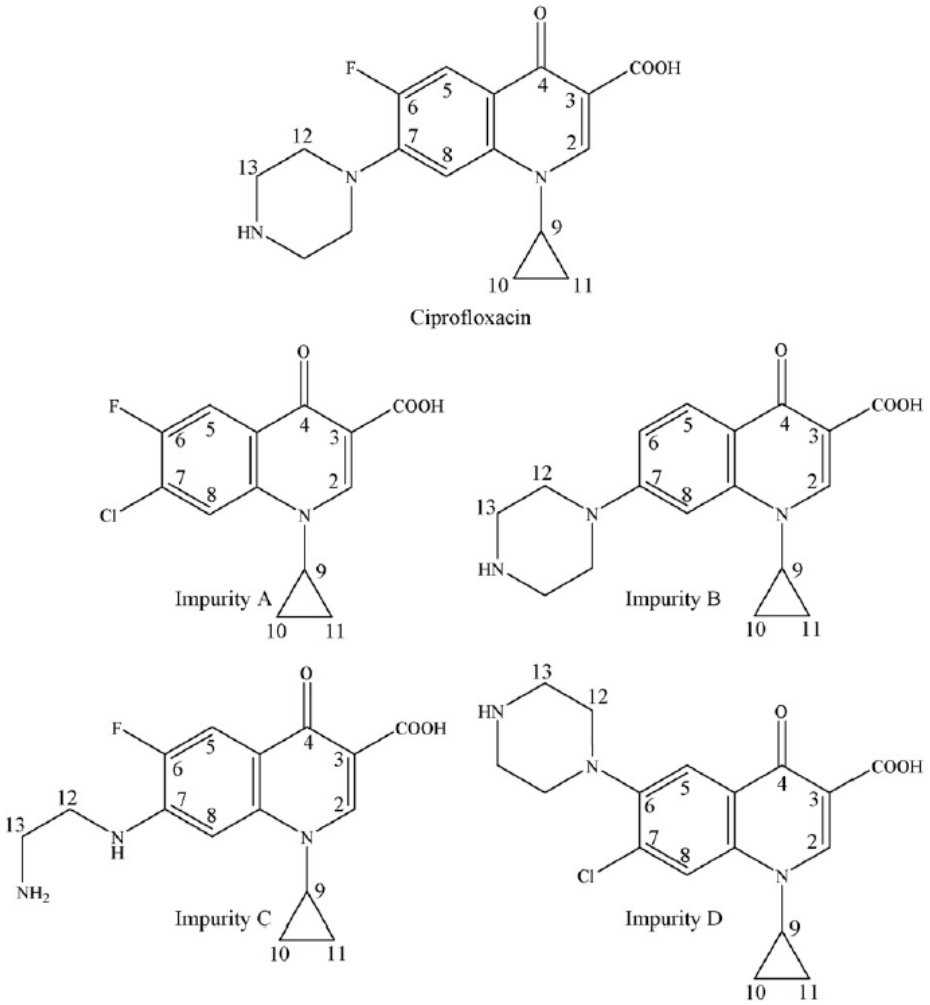
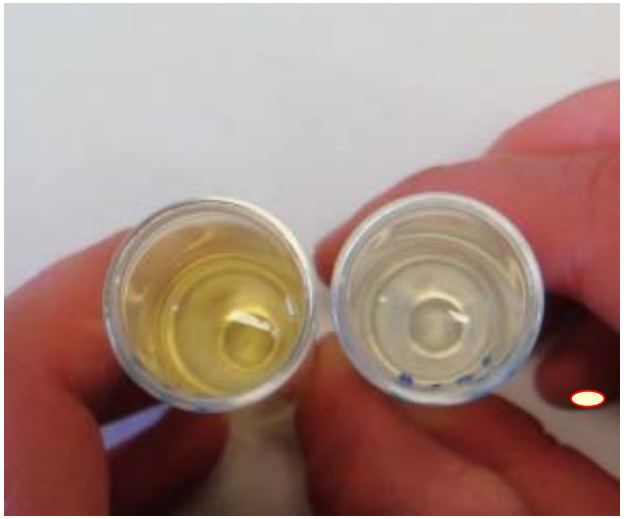


Fig. 1. Structure of ciprofloxacin and its main impurities.

Trefi et al. Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754

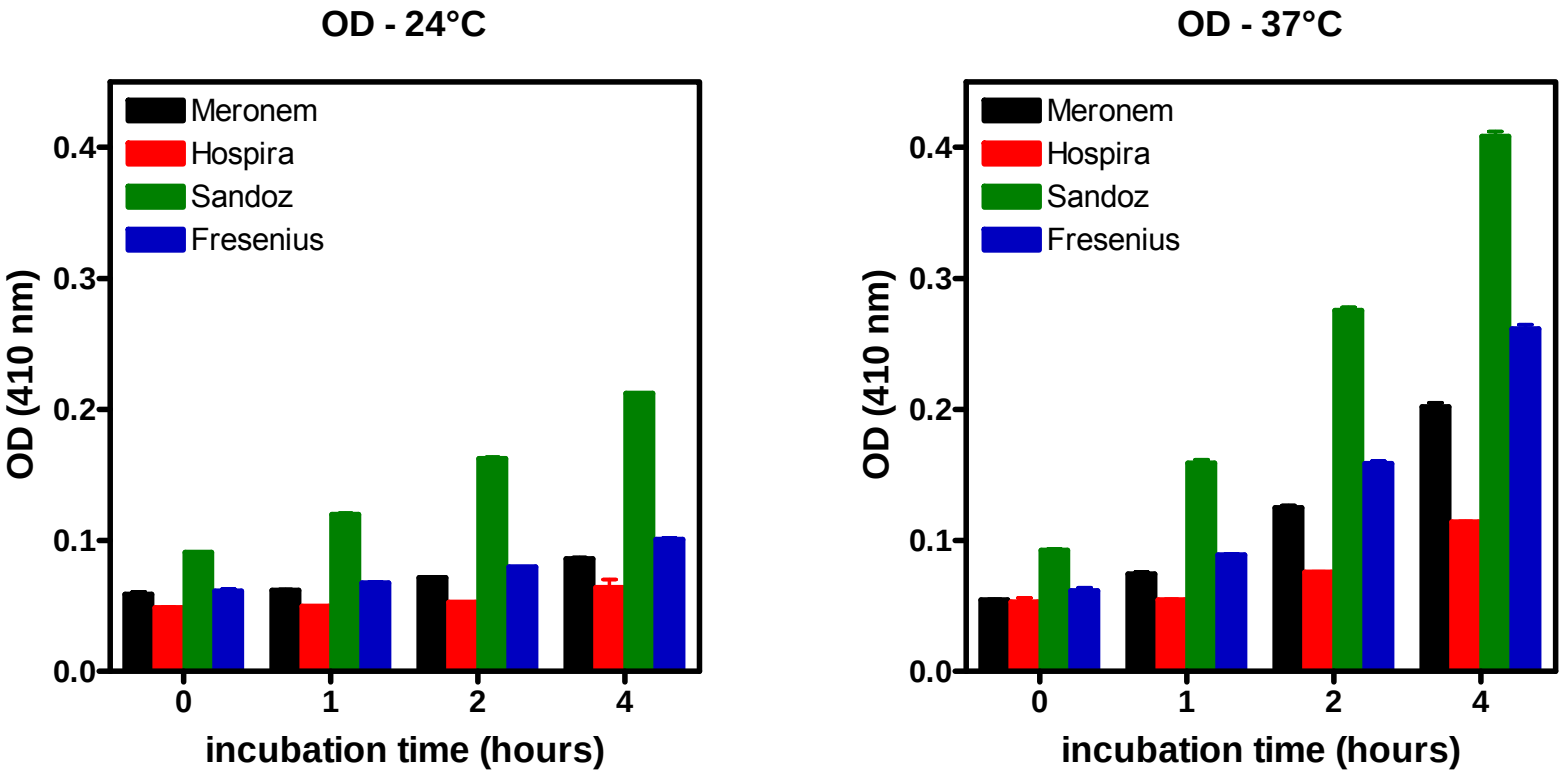
美罗培南的杂质：有色化合物



你对这颜色满意吗？

Van Bambeke *et al*., in preparation

美罗培南的杂质：有色化合物



Van Bambeke *et al*., in preparation

我们接下来讨论的话题？

1. 欧盟和美国食品药品管理局规定
2. 支持进行药效学的生物等效性研究
3. 支持微生物学的等效性研究
   - 最小抑菌浓度，防突变浓度，异质耐药性…
4. 药动学等价方法
   - PK / PD动物模型和临床数据
5. 相关溶解和稳定性的问题
6. 真正的含量与杂质
7. **“低成本”抗菌药物的潜在的治疗风险**

“低成本抗菌药物”和“谨慎使用”…源于的丹麦经验

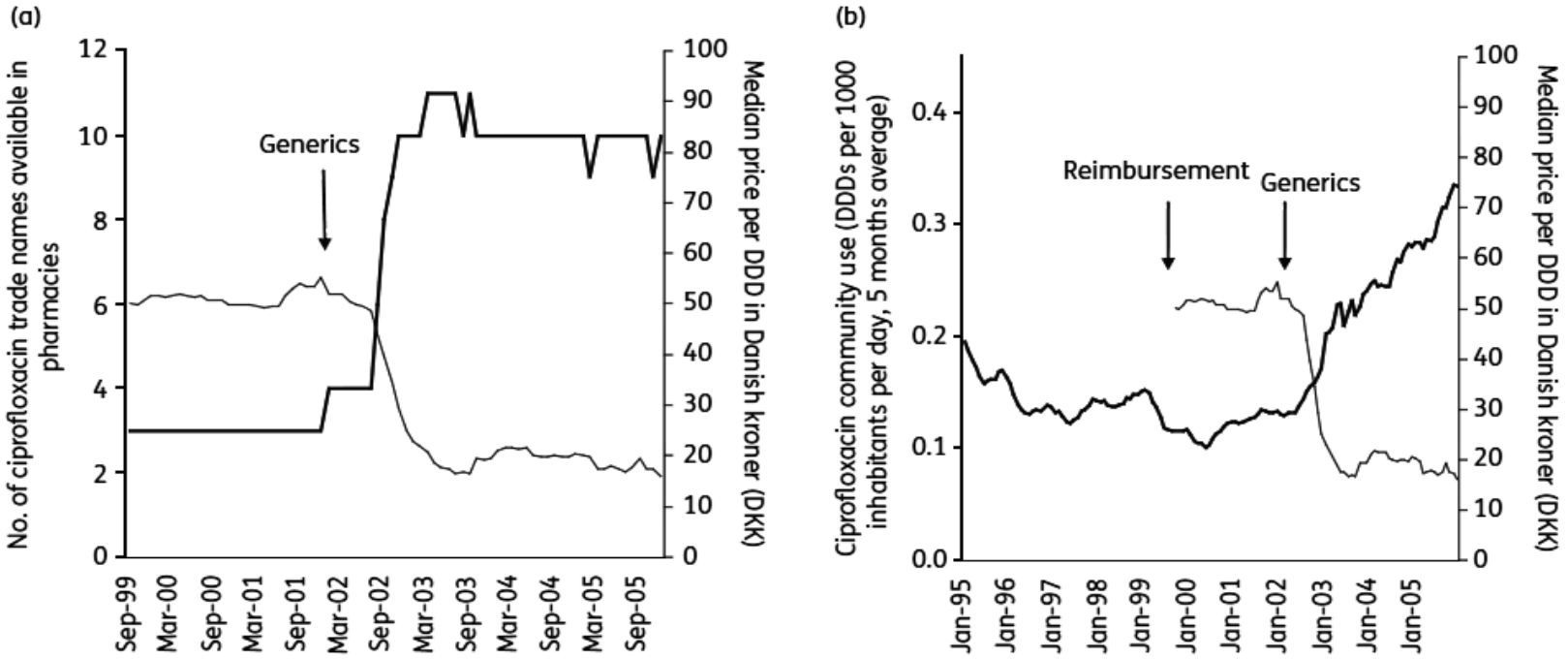


Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin. (b) The influence of removal of 50% reimbursement and of the introduction of generics on the total use of ciprofloxacin and median price per DDD registered monthly in PHC in Denmark (thin line). Consumption (thick line) is expressed in terms of DDDs per 1000 inhabitants per day. The arrows mark the times of removal of reimbursement of ciprofloxacin and the introduction of generic versions, respectively. 100 DDK≈13 EUR.

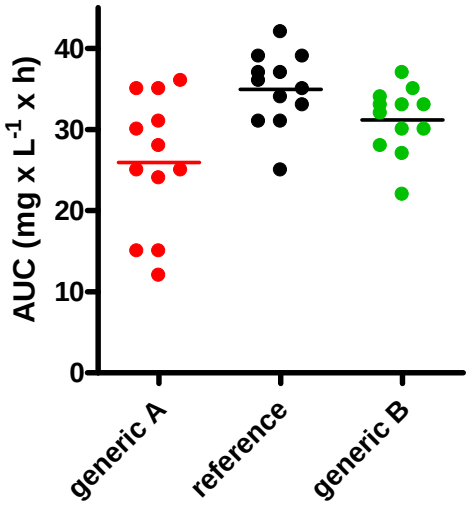
Jensen *et al.* J Antimicrob Chemother 2010; 65:1286–1291

总结与讨论

- 决定“努力保护仿制药”是可能需要修改(在政治层面)，以避免抗菌药物的过度使用
- 目前为止，药动学标准是监管当局(EMA / FDA)唯一采用和接受的标准
- 抗感染药物改善标准(最小抑菌浓度,职业医师委员会,动物PK/PD,…可能是必要的(但尚未实现)
- 抗菌药物更便宜(相比其他化疗药物)，其成本讨论很大程度上显得无关紧要
- 欧盟国会和美国国会中(或其他国家)修订相关的当前立法框架，可能对于抗菌药物的使用是一个更好的起点.....

备份资料

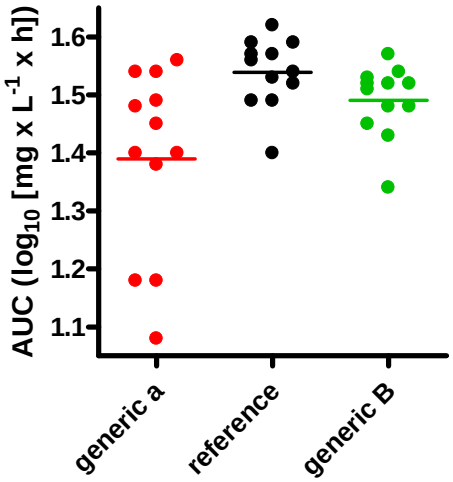
仿制品真正的具有可比性吗？



	generic A	reference	generic B
Number of values	12	12	12
Minimum	12.00	25.00	22.00
25% Percentile	19.50	32.00	29.00
Median	26.50	35.50	32.50
75% Percentile	33.00	38.00	33.50
Maximum	36.00	42.00	37.00
Mean	25.92	34.92	31.17
Std. Deviation	8.262	4.542	4.064
Std. Error	2.385	1.311	1.173
Lower 90% CI	21.63	32.56	29.06
Upper 90% CI	30.20	37.27	33.27

arithmetic comparison

geometric comparison



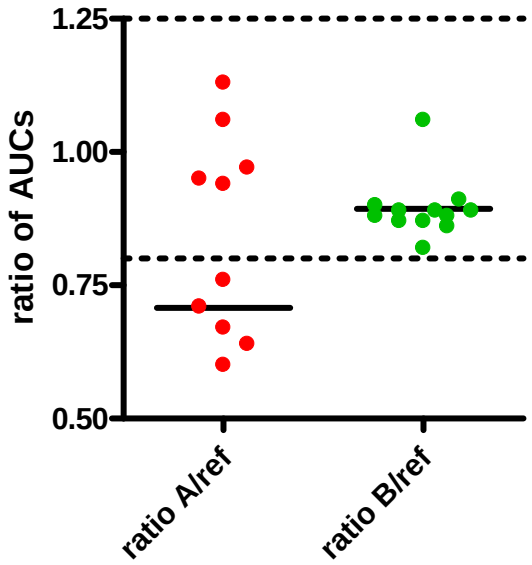
	generic a	reference	generic B
Number of values	12	12	12
Minimum	1.080	1.400	1.340
25% Percentile	1.280	1.505	1.465
Median	1.425	1.550	1.515
75% Percentile	1.515	1.580	1.525
Maximum	1.560	1.620	1.570
Mean	1.390	1.539	1.491
Std. Deviation	0.1596	0.05931	0.06142
Std. Error	0.04607	0.01712	0.01773
Lower 90% CI	1.307	1.508	1.459
Upper 90% CI	1.473	1.570	1.523

仿制品真的具有可比性吗？

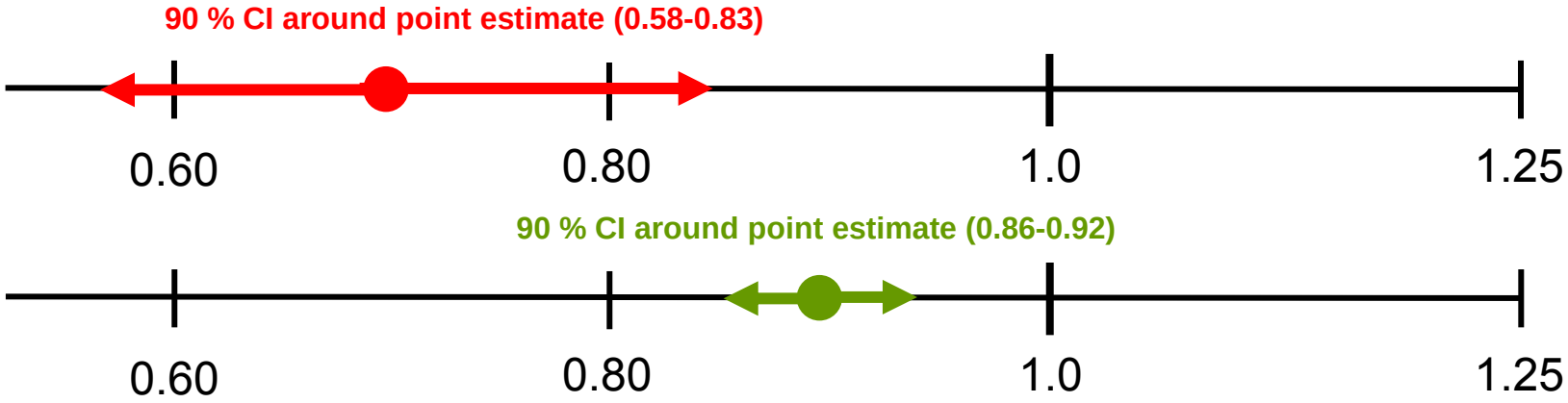
subject#	AUC generic A	AUC reference	AUC generic B	A/reference	B/reference
1	30.00	31.00	33.00	0.97	1.06
1	31.00	33.00	30.00	0.94	0.91
1	24.00	36.00	32.00	0.67	0.89
1	28.00	37.00	33.00	0.76	0.89
1	36.00	34.00	28.00	1.06	0.82
1	35.00	31.00	27.00	1.13	0.87
1	15.00	25.00	22.00	0.60	0.88
1	35.00	37.00	33.00	0.95	0.89
1	25.00	39.00	34.00	0.64	0.87
1	12.00	42.00	37.00	0.29	0.88
1	25.00	35.00	30.00	0.71	0.86
1	15.00	39.00	35.00	0.38	0.90
arithmetic mean	25.92	34.92	31.17	0.76	0.89
SD	8.26	4.54	4.06	0.26	0.06
geometric mean	24.49	34.63	30.90	**0.71**	**0.89**
CI 90				0.12	0.03
lower 90				**0.58**	**0.86**
higher 110				**0.83**	**0.92**

仿制品真正的具有可比性吗？

Ratio of AUCs with calculation of the geometric means (point estimates)

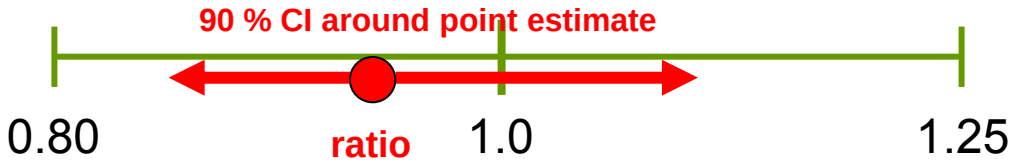


	ratio A/ref	ratio B/ref
Number of values	12	12
Minimum	0.2900	0.8200
25% Percentile	0.6200	0.8700
Median	0.7350	0.8850
75% Percentile	0.9600	0.8950
Maximum	1.130	1.060
Mean	0.7583	0.8933
Std. Deviation	0.2620	0.05726
Std. Error	0.07565	0.01653
Geomean	**0.7072**	**0.8924**



生物等效性的标准(EMA * / FDA * *)

- 可同过相关文献(研究者)或药物研究实验(仿制品)，依**AUC和Cmax的几何平均比率**可计算**90%的置信区间**
- 大多数情况下，90%的置信区间应是**在0.80 - 1.25的验收范围。**



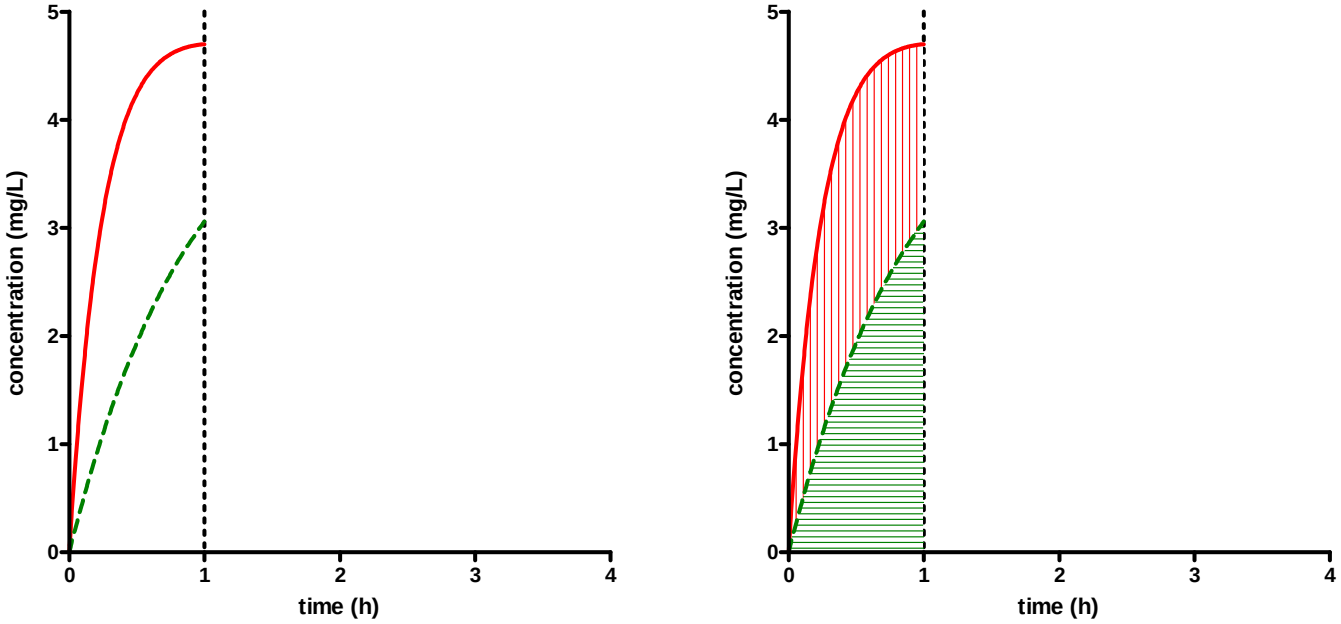
Notes:

1. *如果两个AUC和Cmax都在范围内,仿制药应有相同的生物利用度*
2. *达峰时间的数据评估仅在需要验证临床快速缓解临床症状或相关不良反应的中有意义(见下一张幻灯)*
3. *对于治疗指数狭窄的药物,EMA建议"缩紧验证的范围",加拿大卫生部要求为0.9 - 1.12,但FDA要求为0.8 - 1.25*

* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052363.pdf

早期AUC(EMA) *的额外标准



- 从中位数中的Tmax中截取相关的AUC值，作为快速吸收的重要相关参数

* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

特殊情况(EU)

狭窄治疗指数的药物

- 对于一个治疗指数狭窄的特殊药物，AUC可接受区间应缩紧于90.00-111.11 %。因为Cmax此时对于安全性，疗效或药物浓度尤其重要，90.00-111.11 %的可接受区间也应适用于该参数。通过定义一套标准来对治疗指数狭窄的药物分类不太可能，因此对于活性成分是治疗指数狭窄的药物一定要充分考虑临床的情况。

可变指数较高的药物

- 扩展的程度依赖于生物等效性研究中组内的可变度，常根据[U, L] = exp [±k·sWR]来计算平均生物等效性。U是指可接受范围的上限，L指下限，k指调节常数0.760，sWR 是指Cmax值的log值的组内均方差（提示：只应用于C_{max}，不用于AUC)

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$* CV(\%) = 100\sqrt{e^{s_{WR}^2} - 1}$$

杀菌曲线和异质性耐药(万古霉素)

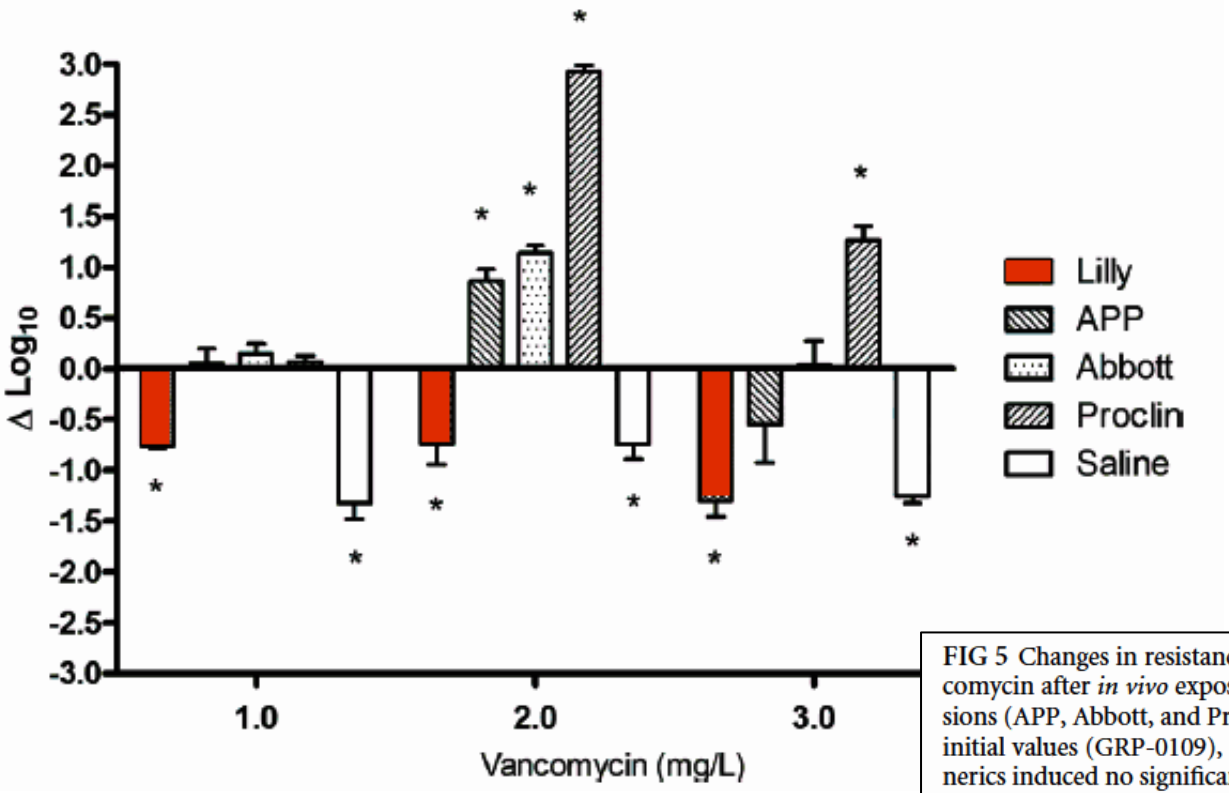


FIG 5 Changes in resistance frequencies (RFs) to 1, 2, and 3 mg/liter of vancomycin after *in vivo* exposure to innovator vancomycin (Lilly), generic versions (APP, Abbott, and Proclin), or sterile saline. At 1 mg/liter, compared to initial values (GRP-0109), Lilly reduced the RFs by almost 10-fold, while generics induced no significant change. At 2 mg/liter Lilly also reduced the RFs, but generic products significantly increased them 10- to 1,000-fold. At 3 mg/liter, again Lilly reduced the RFs, APP and Abbott did not change the baseline RF, and Proclin significantly increased it by 1 order of magnitude. In the saline group RFs were reduced about 1 $\log_{10}$ at all concentrations. The asterisk indicates that the postexposure value is significantly different from the preexposure value (Student's *t* test): *P* values of 0.0002 and 0.0005 for Lilly and saline at 1 mg/liter, respectively; *P* values of 0.0258, 0.0012, 0.0002, <0.0001, and 0.0029 for Lilly, APP, Abbott, Proclin, and saline at 2 mg/liter, respectively; *P* values of 0.0140, 0.0152, and 0.0094 for Lilly, Proclin, and saline at 3 mg/liter, respectively. CFU counts at 4 mg/liter and higher were below the limit of detection.

Rodriguez *et al.* Antimicrob Agents Chemother. 2012; 56:243–247

突变菌株的产生（哌拉西林-三唑巴坦)

Table 17 Spontaneous mutant production in the diffusion gel assay for Piperacillin/Tazobactam

Sample	*A. b.* 189		*P. a.* 54	
	Median	δ	Median	δ
Standard	125.17	1.472	110.00	9.381
M1	127.00	1.000	109.33	1.528
M9	123.67	2.517	104.67	1.528
M18	124.33	1.528	105.00	1.000
M6	125.67	1.528	109.67	1.155
M10	127.67	3.055	102.33	2.517
M16	128.33	1.528	109.67	0.577
M5	128.00	1.000	105.00	2.000
M14	124.33	1.155	101.67	2.082
M4	122.67	0.577	108.00	2.000
M3	125.67	2.082	111.00	1.732
M15	123.33	2.082	105.00	1.000
M7	127.67	1.528	107.67	1.155
M8	123.00	1.732	107.67	1.155
M17	129.33	5.859	108.67	1.528
M13	126.67	1.155	107.00	2.000
M2	123.33	1.528	107.33	1.528
M11	125.33	1.528	103.00	3.000
M12	125.67	2.517	110.00	1.000
F	2.657		1.898	
prob.	0.005		0.045	

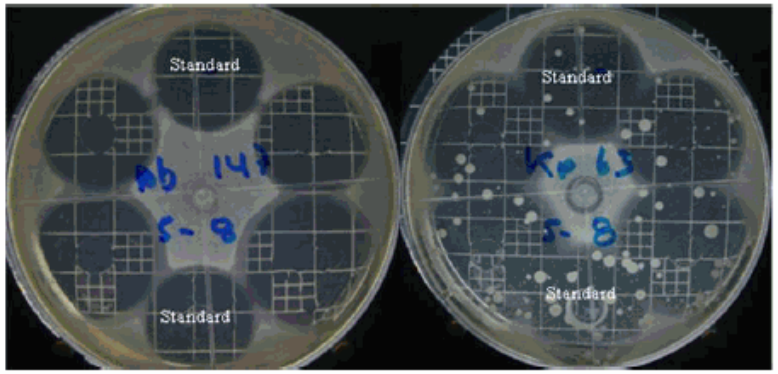


Figure 8 Diffusion gel assay testing the production of spontaneous Meropenem-resistant mutants, with *A. baumanii* 147 as a control strain and *K. pneumoniae* 63 as a mutant-producing strain.

Conclusions

All the samples analyzed by standardized microbiological methods fulfill the requirements for content according to USP XXVII. They all show the same antimicrobial behavior because they have similar MIC, MLC and CC values and produce similar numbers of mutants.

Silva et al. BMC Clinical Pharmacology 2010, 10:3
http://www.biomedcentral.com/1472-6904/10/3