Thoughts on generic product properties that might impact the clinical effect: what are the downsides ?

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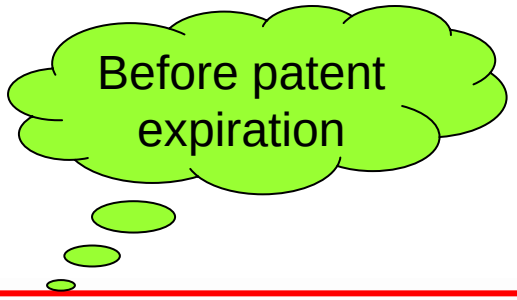
With approval from the Belgian Common Ethical Platform - visa n° 13/V1/4806/052924

Are they equal ?

Lead generic companies resort to multiple strategies for growth - these include applying for generic approvals with Food and Drug Administration (FDA) and European Medicines Agency (EMA); merger and acquisitions; developing a strong and innovative generic drug pipeline; improving infrastructure to enhance manufacturing and R&D capabilities; new product launches, and geographic expansion.

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

A well known antibiotic in Belgium…



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

A well known antibiotic in Belgium…

After …

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

What shall we discuss ?

1. The EU and US regulations
2. Approach to PK bioequivalence
3. Approach to microbiological equivalence
   - MIC, MPC, heteroresistance …
4. Approach to pharmacodynamic equivalence
   - PK/PD animal models and clinical data
5. Problems related to dissolution and stability
6. True content and impurities
7. The hidden risk of "low cost" antibiotics

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EU regulations

►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

EU regulations

- By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, **the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product** which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

- '**generic medicinal product**' shall mean a medicinal product which has the **same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product**, and whose **bioequivalence** with the reference medicinal product has been demonstrated by **appropriate bioavailability studies**. …

  Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

EU regulations: what needs to be supplied for non-biological product

- Data for Modules 1, 2 and 3 *
- **together** with data showing **bioavailability and bio-equivalence** with the original medicinal product

Special attention needs to be paid to:

- the grounds for claiming essential similarity;
- a summary of **impurities** (with an evaluation of these);
- an evaluation of the **bio-equivalence studies** or a justification why studies were not performed;
- an **update of published literature** relevant to the substance and the present application;
- every claim not known from or inferred from the properties of the medicinal product should be discussed and substantiated by published literature and/or additional studies.
- **equivalence of safety and efficacy properties of different salts, esters or derivatives** of an authorised active when he claiming essential similarity.

* 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".

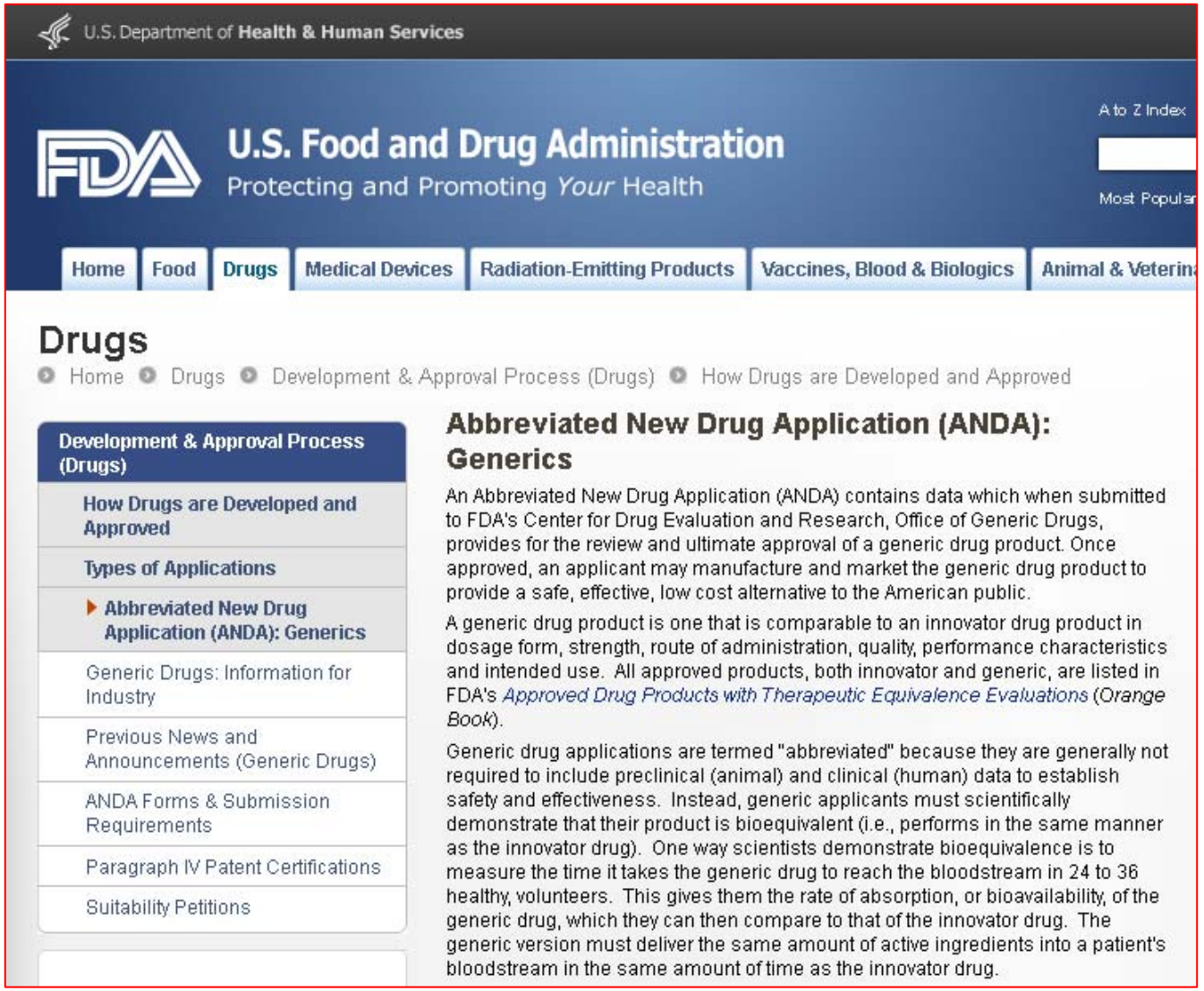
Drug Price Competition and Patent Term Restoration Act of 1984.
21 USC 301 note.

TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

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

- FDA works along the provisions of the **Drug Price Competition and Patent Term Restoration Act** ("Hatch-Waxman Act" [Public Law 98-417]), which encouraged the manufacture of generic drugs
- Marketers of generic drugs can file an **Abbreviated New Drug Application** (ANDAs) to seek FDA approval

US "Abbreviated New Drug Application"



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

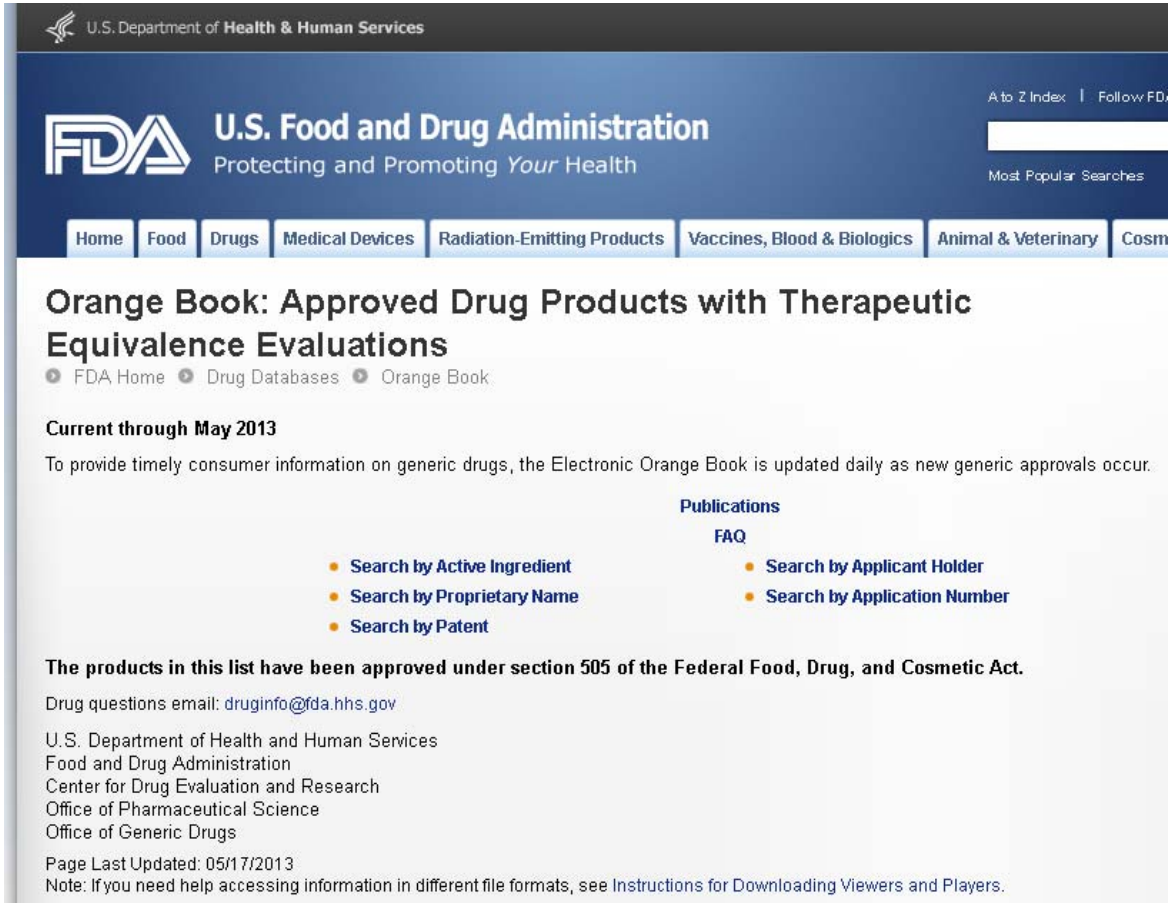
FDA requirements in a nutshell *

- Published literature (for data for which the applicant has no right of reference to the original raw data supporting the application)
- FDA's findings (safety and effectiveness of the already approved drug)
- Comparison with the original NCE/NME (New Chemical Entity/New Molecular Entity) application for
  - dosage form, strength, route of administration
  - substitution of an active ingredient in a combination product or change such as different salt, ester, complex, …
- Bioequivalence study

The proposed product does not need to be shown to be clinically *better* than the previously approved product; however, the application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the standards for bioequivalence.

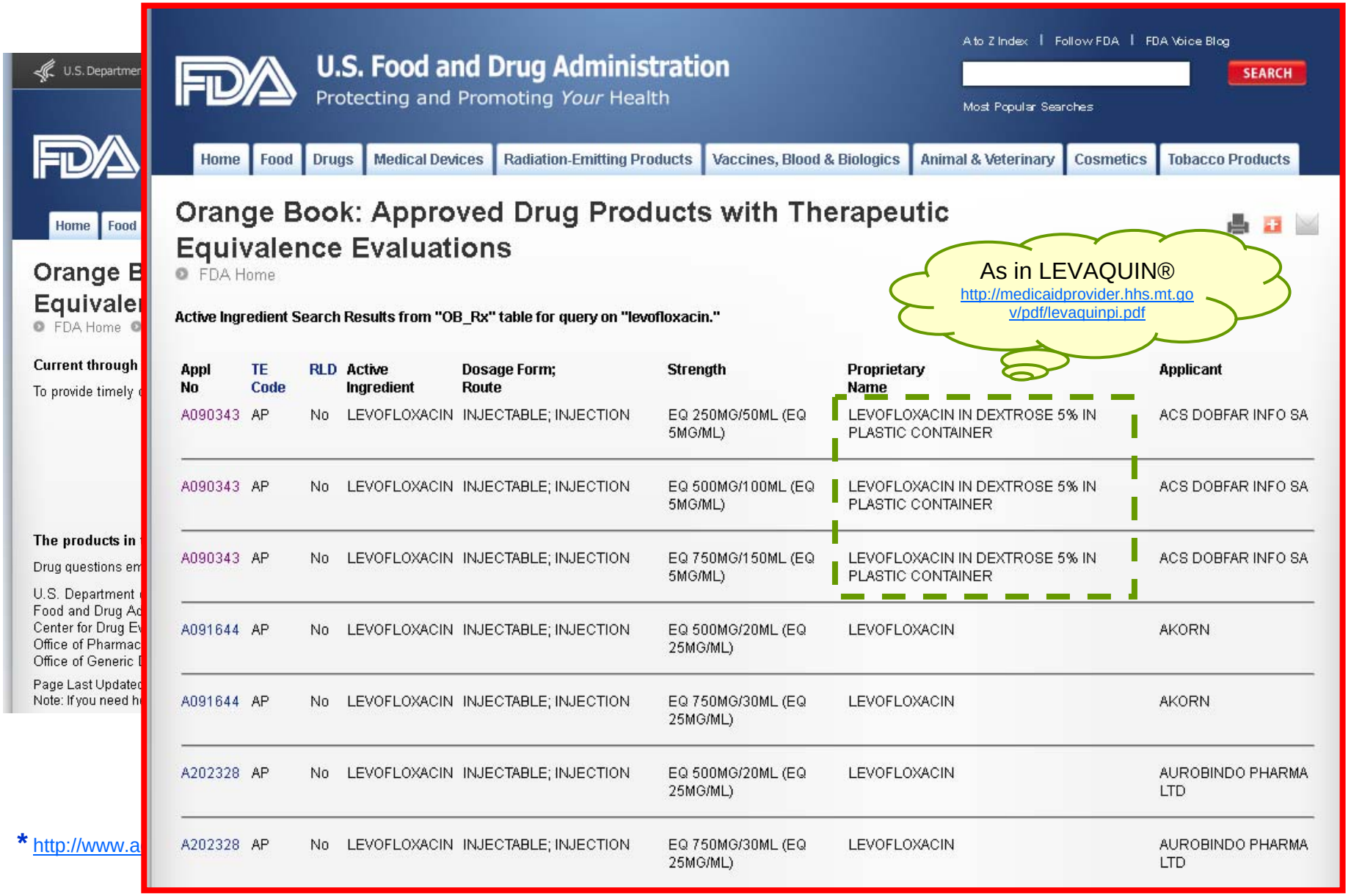
* 505 (B) (2) Application (Guidance to Industry)
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf

FDA approved generic drugs: "Orange book" *



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

FDA approved generic drugs: "Orange book" *



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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

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Bioequivalence: principles

- Bioequivalence is an **accepted surrogate for therapeutic equivalence** [1] (including for branded drugs when the mareketed form differs from the form used in development…) [2]
- Primary metrics are [1,3]
  - **AUC** (area under the plasma concentration-time profile of the active substance)

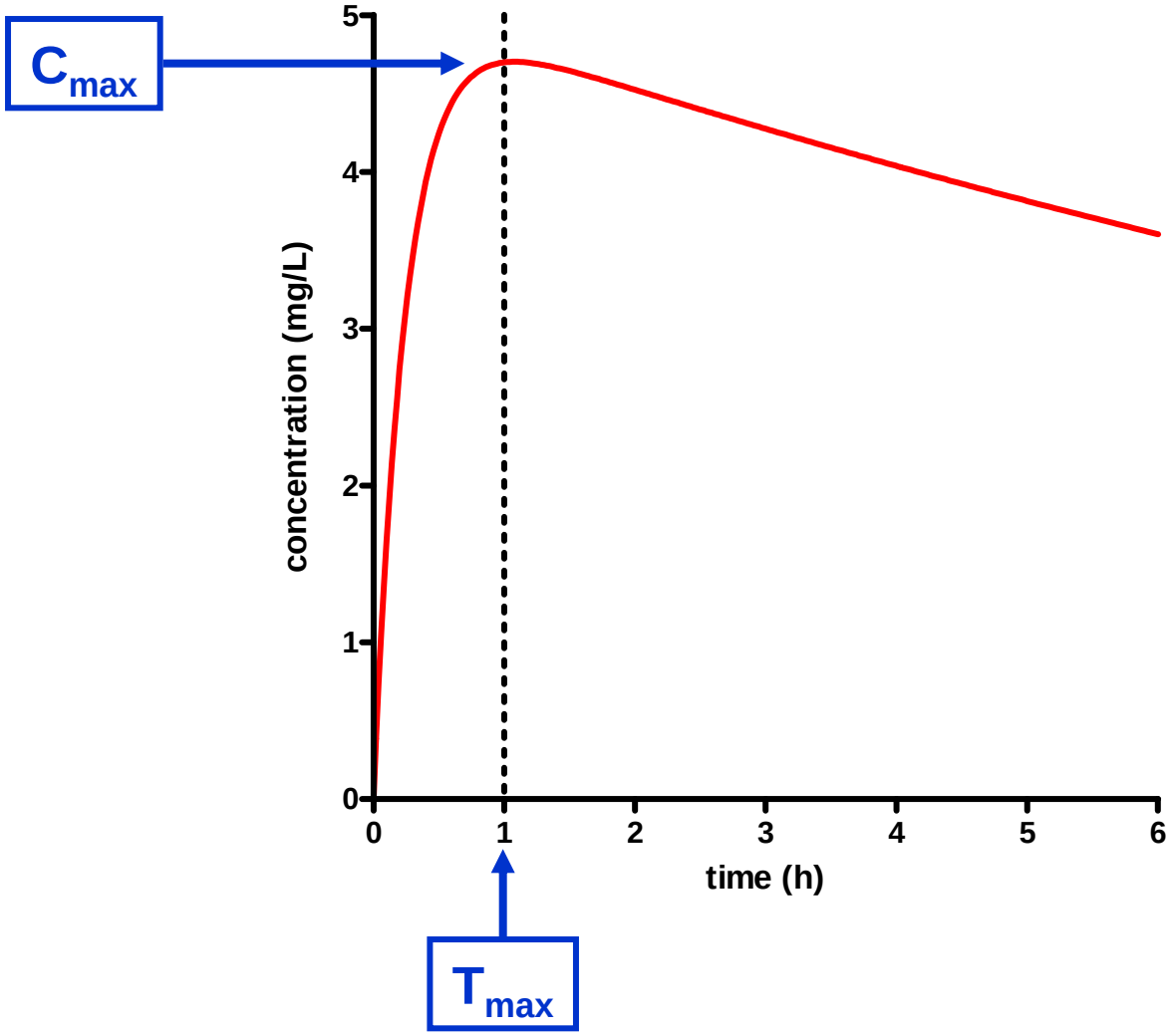
    → **extent of absorption**
  - **C_{max}** (the maximum plasma concentration of the active substance)

    → **extent and rate of absorption**
  - **T_{max}** (the time at which C_{max} is reached)

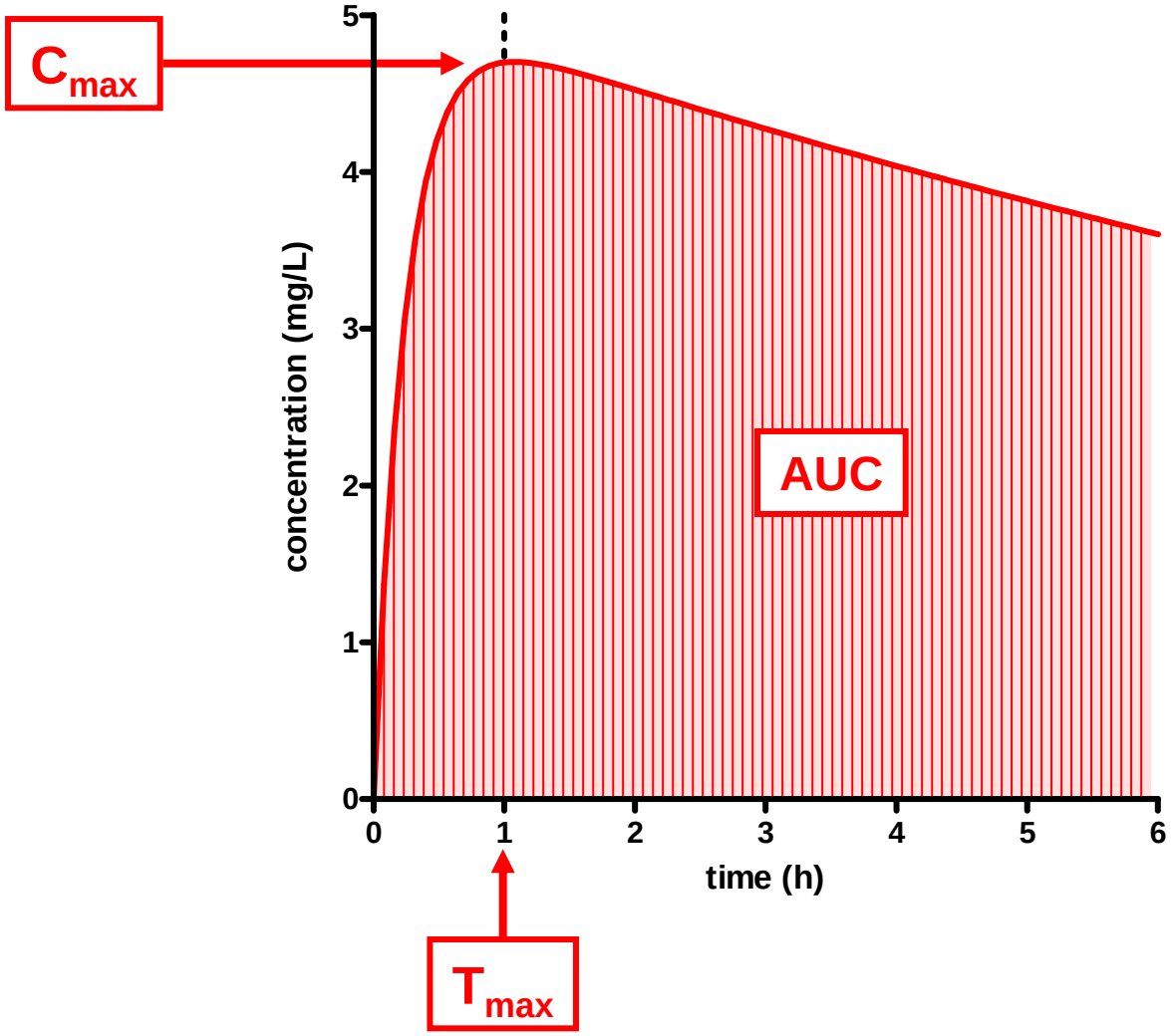
    → **rate of absorption**

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.

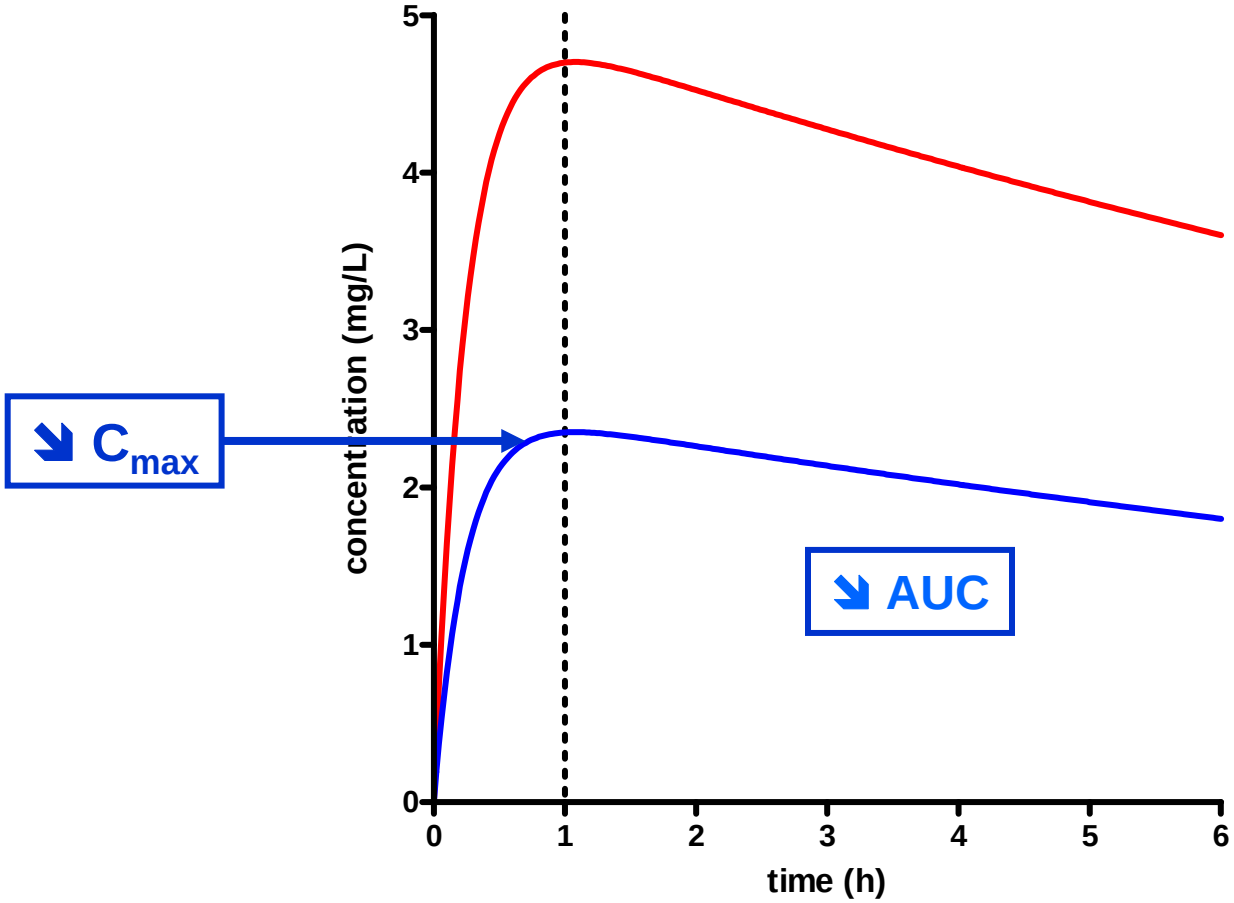
AUC – C_{max} – T_{max}



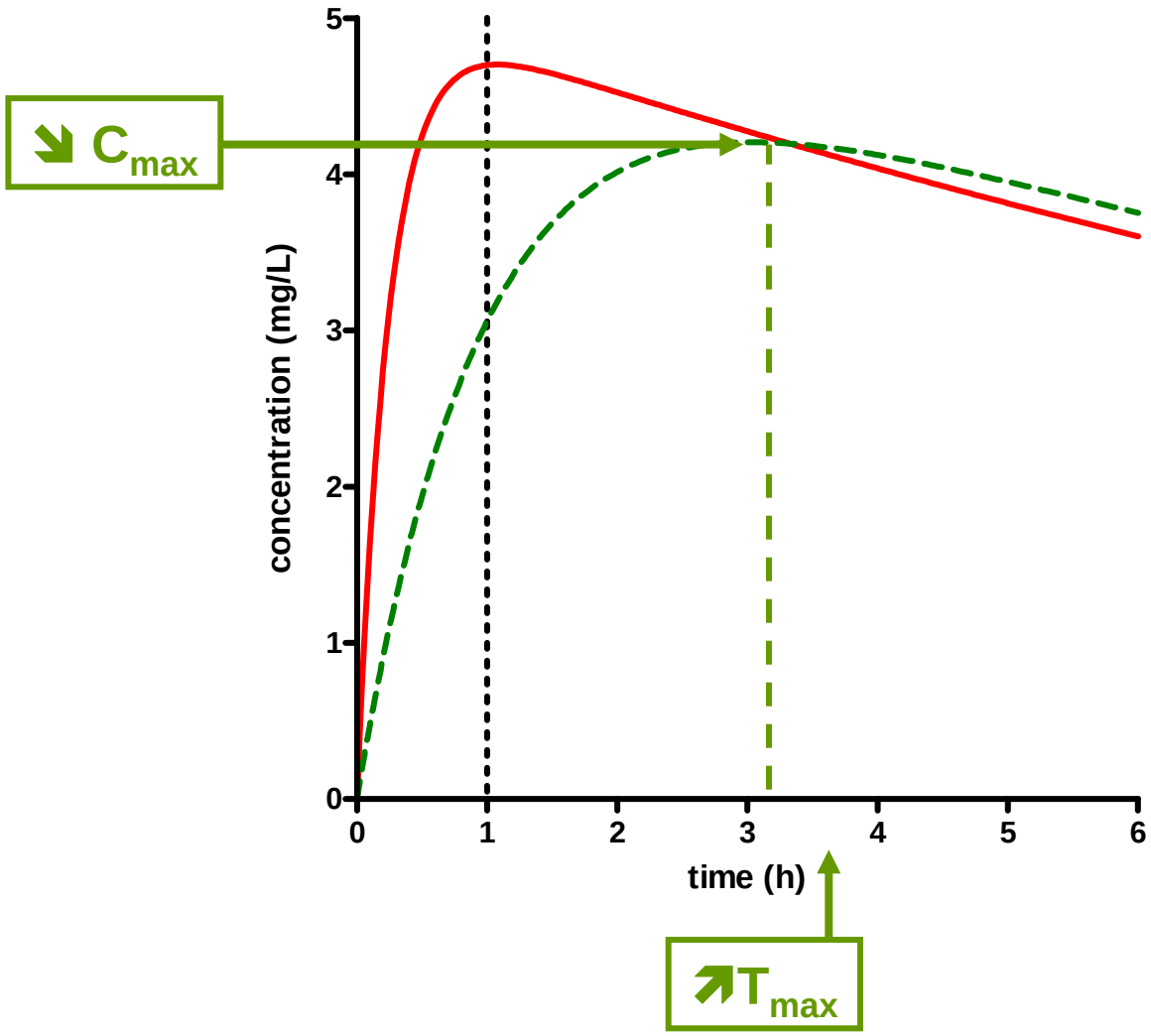
AUC – C_{max} – T_{max}



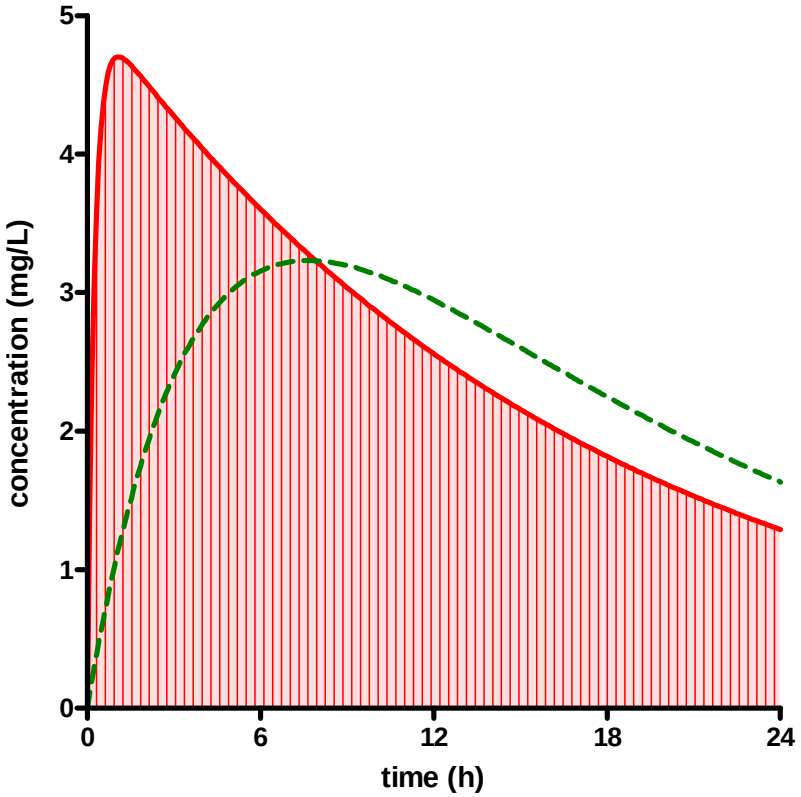
What if the absorption is decreased ?

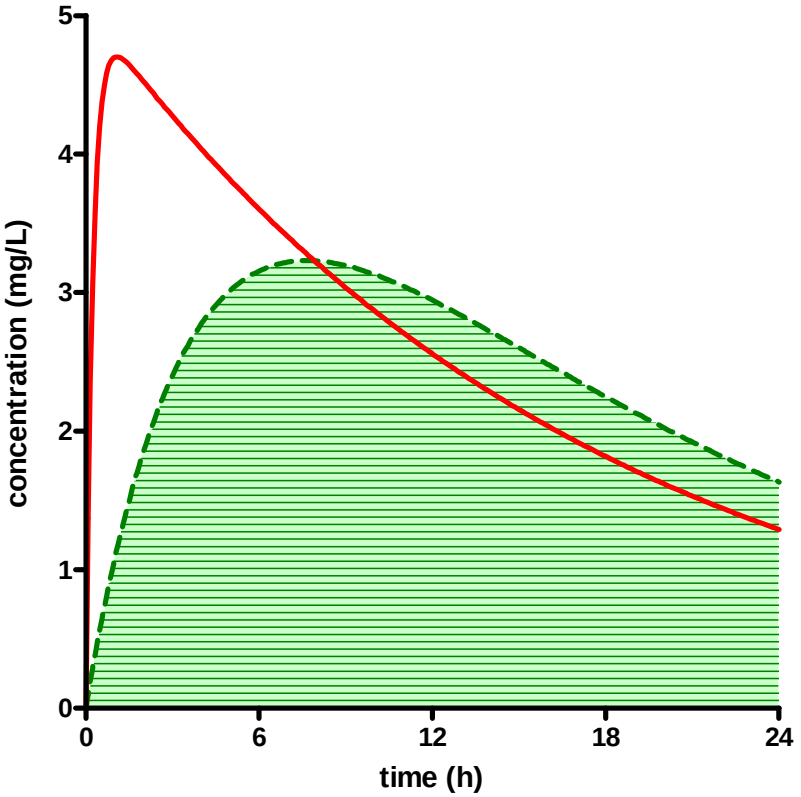


What if absorption is delayed ?



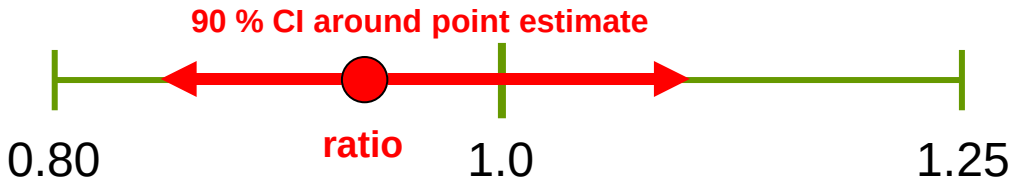
If absorption is markedly delayed, you also have a lower initial AUC





Criteria of bioequivalence (EMA* / FDA**)

- Calculate the **90% confidence interval** around the **geometric mean ratios** of **both AUC** and C_{max} for Test (generic) and Reference (innovator).
- The 90% confidence intervals should, in most cases, be **within the 0.80 – 1.25 acceptance limits**.



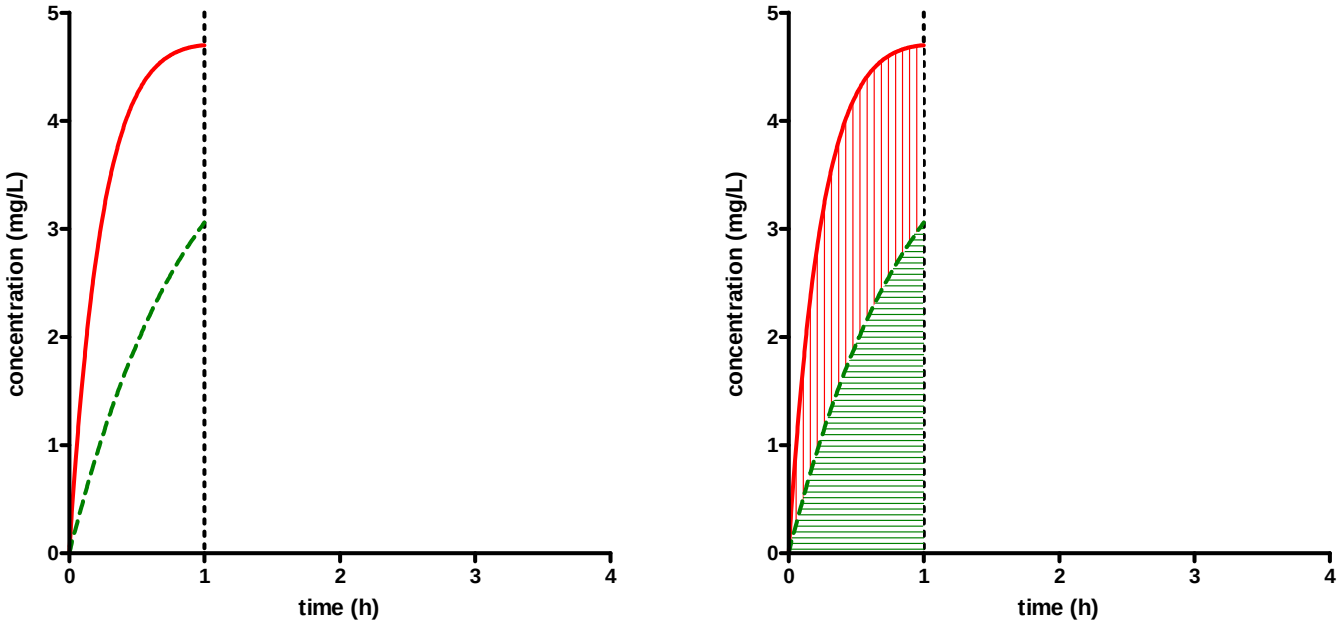
Notes:

1. *if both **AUC** and C_{max} are within range, the generic should have the same bioavailability than the reference*
2. *statistical evaluation of T_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects (see next slide)*
3. *For drugs with narrow therapeutic index, EMA recommends "tightened acceptance inervals, Health Canada requires 0.9 – 1.12, but FDA accepts 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

Additional criteria for early AUC (EMA) *



- Use the partial **AUC truncated** at the population median of T_{max} for the reference formulation for for products where rapid absorption is of importance

* 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

Unsolved problems with PK-based bioequivalence … (application to antibiotics)

- Is **PK equivalence** leading to **pharmacological equivalence** ?
  - *in vitro* testing (MIC, MPC, impact on hetero-resistance) …
  - PK/PD models (animals)
  - Clinical studies (?)
- What about **intravenous forms** ?
  (that, by definition, are not amenable to conventional bioequivalence studies)
- What about
  - dissolution times (critical in a nursing environment)
  - stablility (penems, e.g.)
  - impurities (do you like them ?)
  - …

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Potency (piperacillin)

Using the incremental MIC assay (Jones et al. Diagn Microbiol Infect Dis 61:76–79).

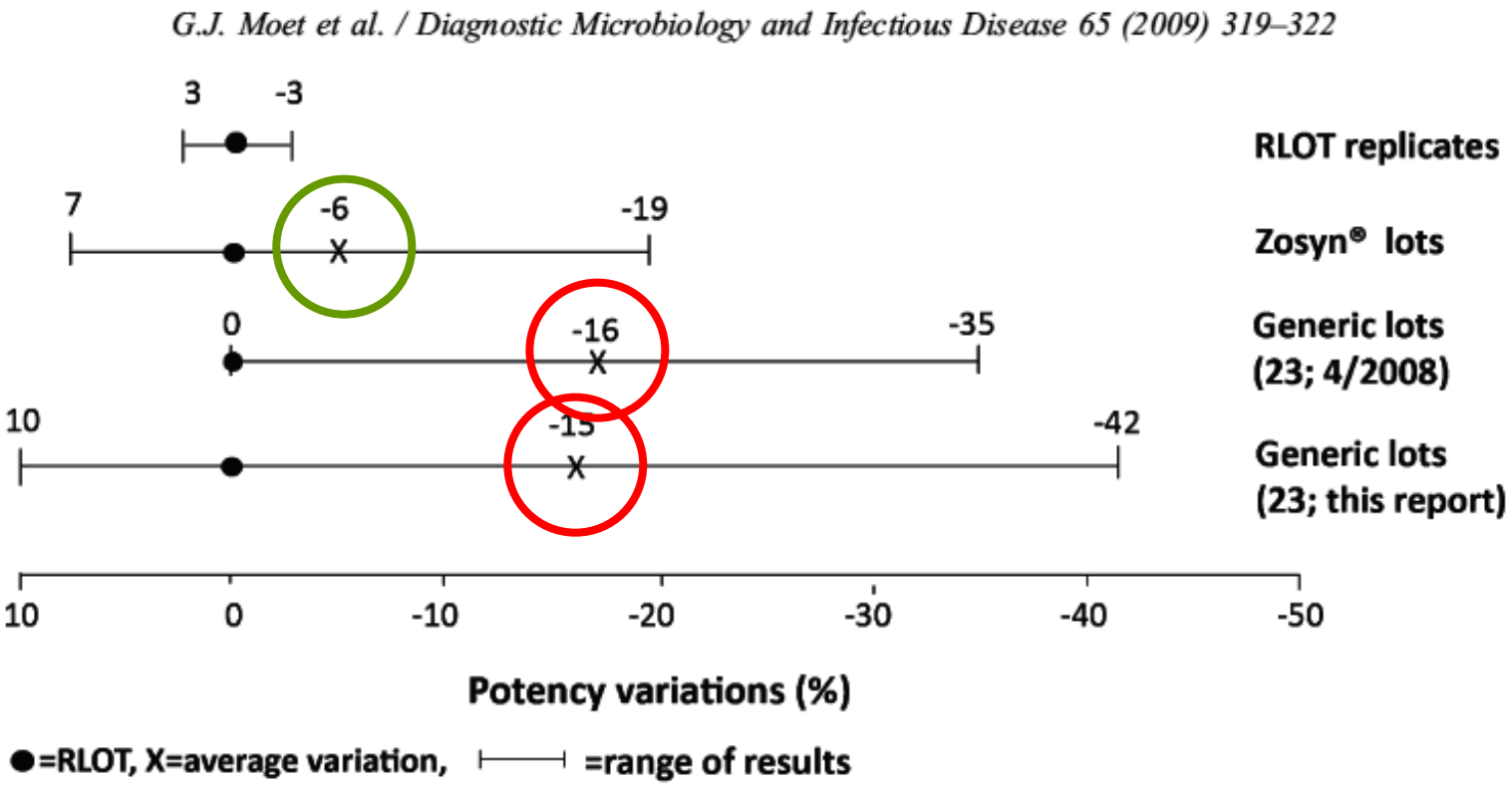
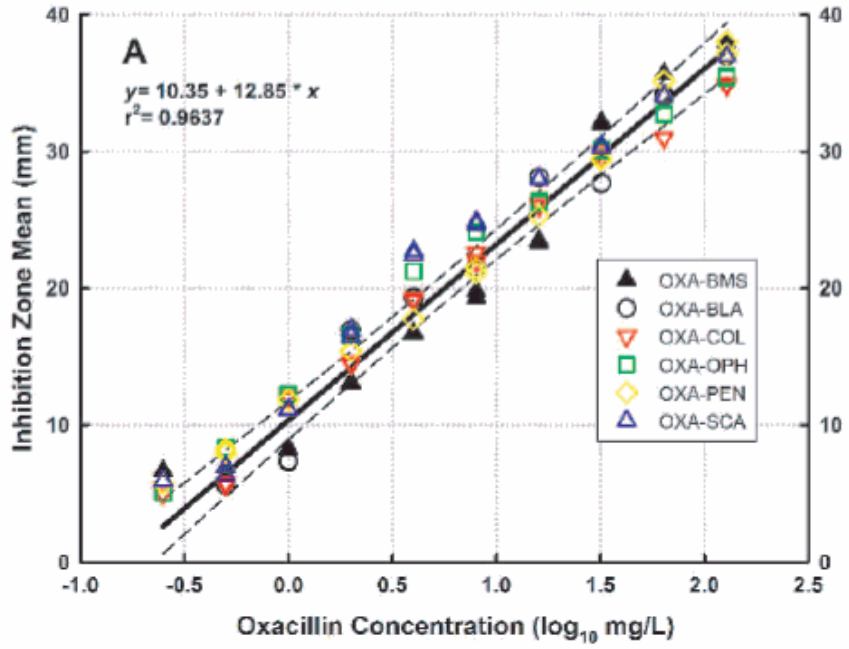


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

Potency (oxacillin)



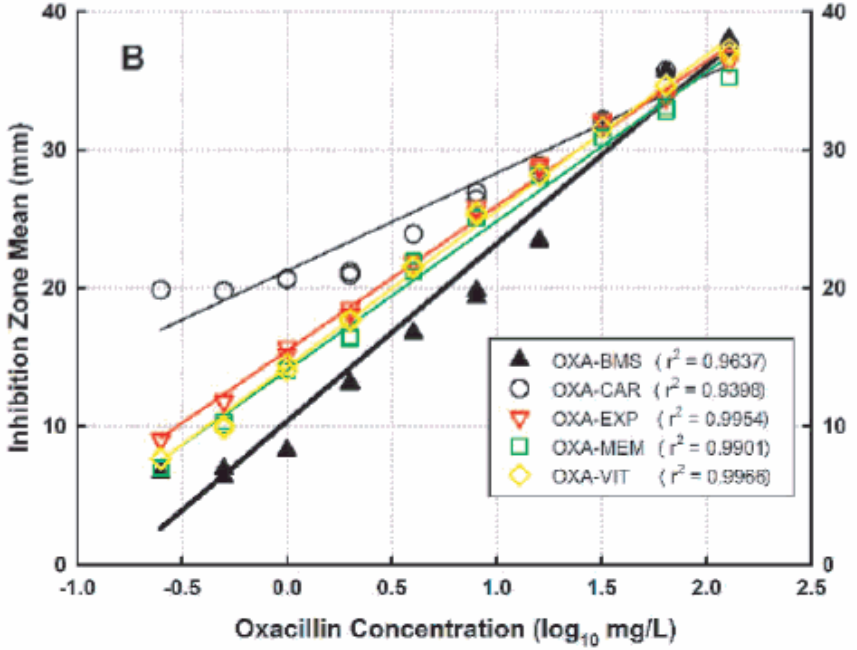


Figure 1 Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay. **A**. The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical 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

MIC values (vancomycin)

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	–

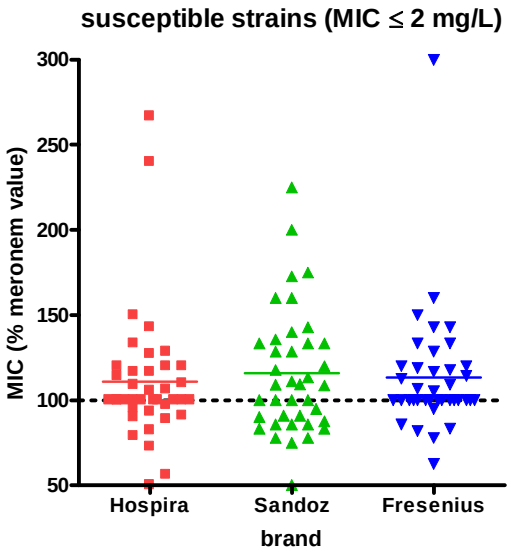
MRSA methicillin-resistant *Staphylococcus aureus*[a]Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug: MIC was determined by broth micro-dilution method using powder in each drug vial

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

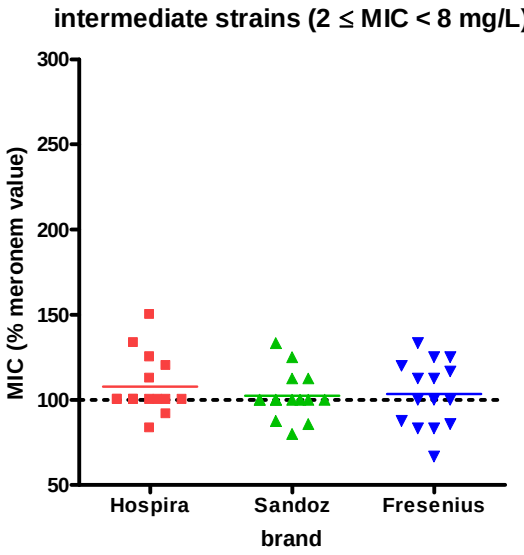
MICs were often higher than for the reference product…

MIC values (meropenem)

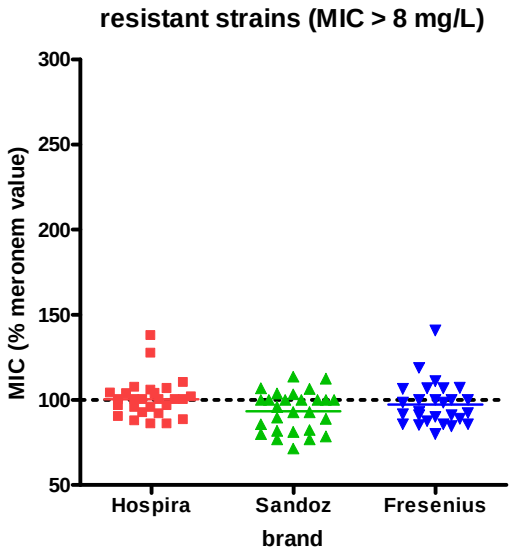
MICs determined by arithmetic dilutions for strains displaying MICs ranging from 0.125 to 128 mg/L (geometric values)



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



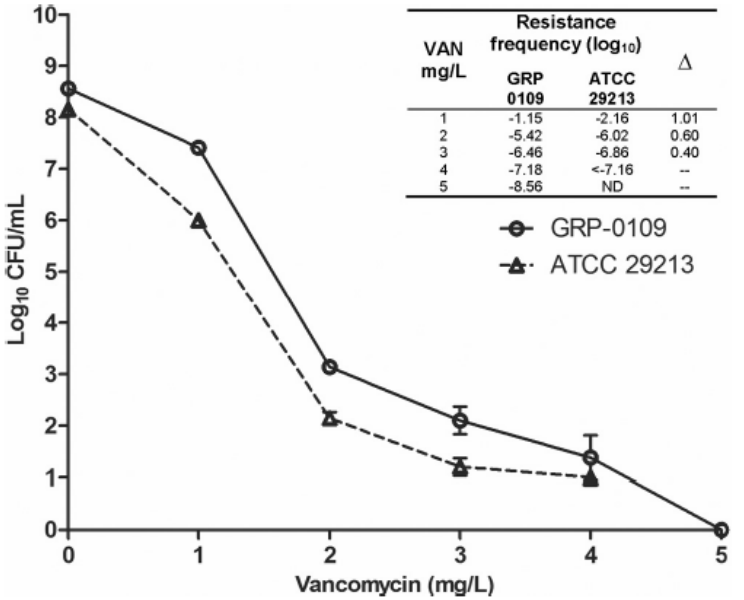
	Hospira	Sandoz	Fresenius
mean=	107.7	102.7	103.4
SD=	17.41	13.9	19.3



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

Van Bambeke *et al*., in preparation

Killing curves and hetero-resistance (vancomycin)

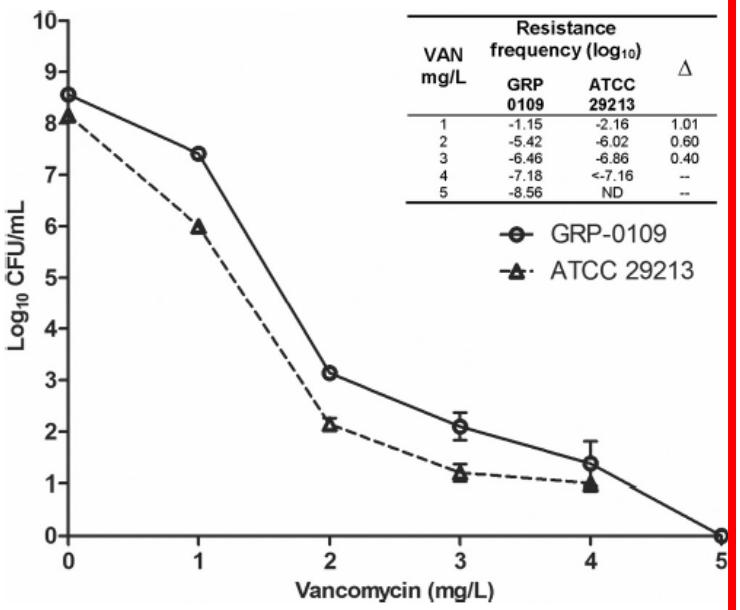


VAN mg/L	Resistance frequency (log_{10}) GRP 0109	ATCC 29213	Δ
1	-1.15	-2.16	1.01
2	-5.42	-6.02	0.60
3	-6.46	-6.86	0.40
4	-7.18	<-7.16	--
5	-8.56	ND	--

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

Killing curves and hetero-resistance (vancomycin)



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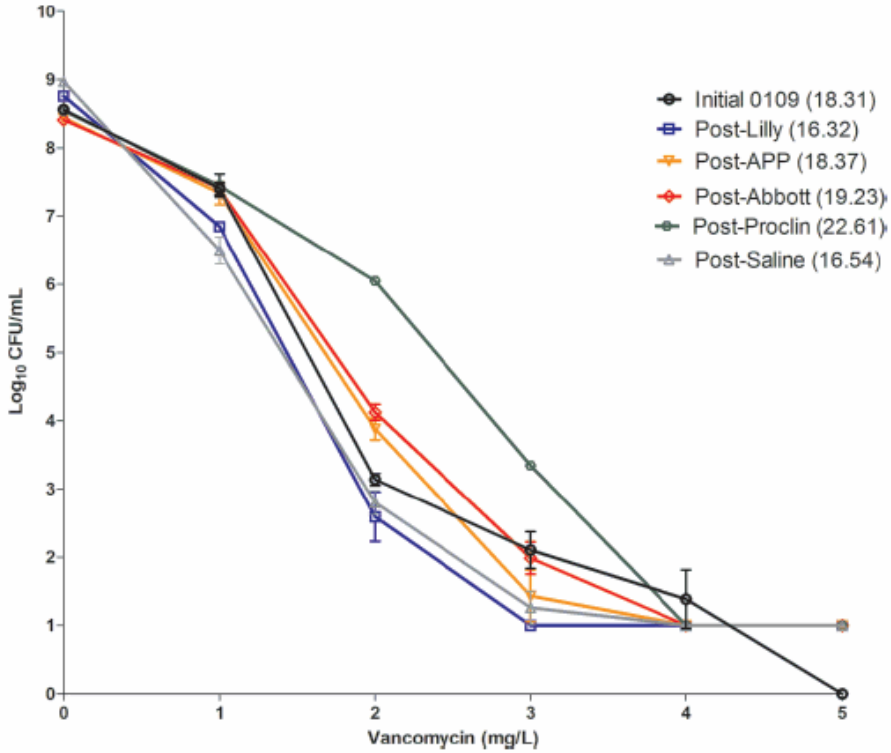

FIG 3 Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction of the less susceptible subpopulations, which is sharply different from three 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

Killing curves and hetero-resistance (vancomycin)

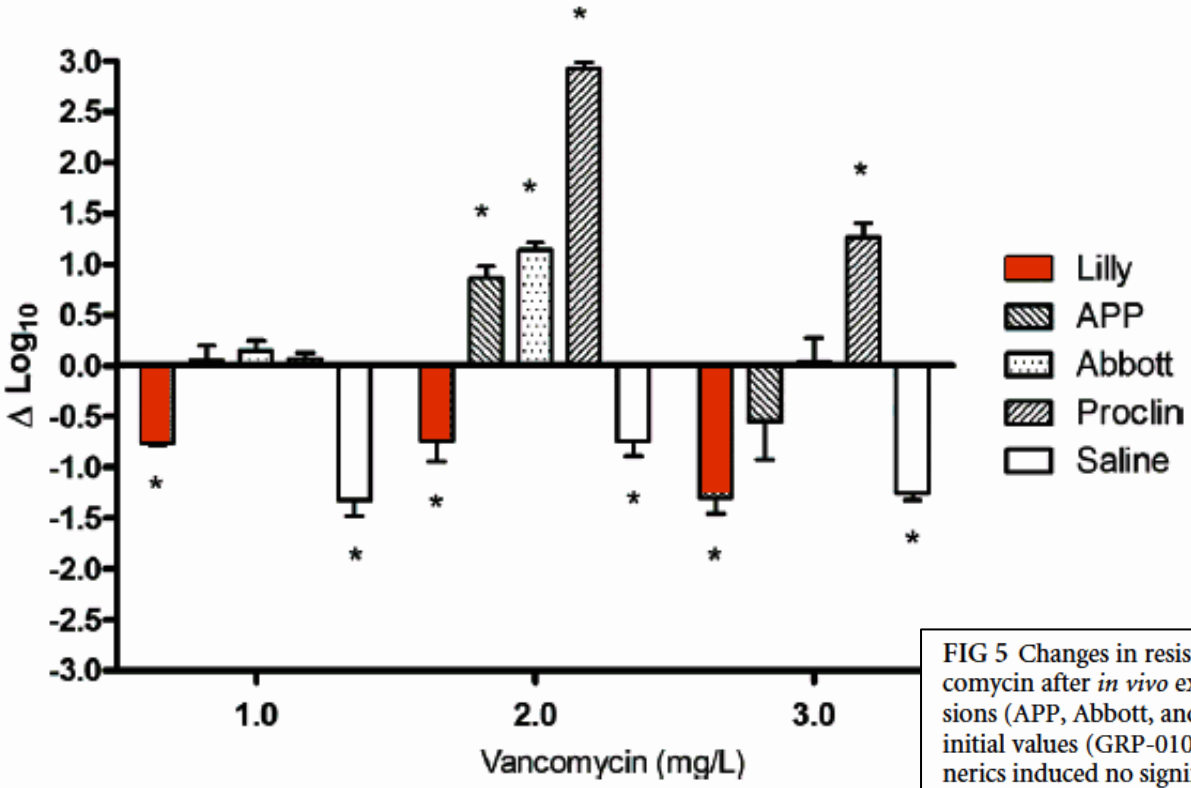

FIG 5 Changes in resistance frequencies (RFs) to 1, 2, and 3 mg/liter of vancomycin after *in vivo* exposure to innovator vancomycin (Lilly), generic versions (APP, Abbott, and Proclin), or sterile saline. At 1 mg/liter, compared to initial values (GRP-0109), Lilly reduced the RFs by almost 10-fold, 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.

Production of mutant (piperacillin/tezobactam)

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	

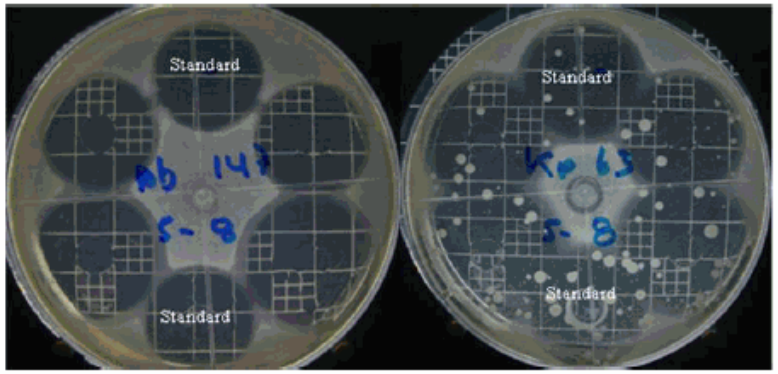

Figure 8 Diffusion gel assay testing the production of spontaneous Meropenem-resistant mutants, with *A. baumanii* 147 as a control strain and *K. pneumoniae* 63 as a mutant-producing strain.

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

What shall we discuss ?

1. The EU and US regulations (6 slides)
2. Approach to PK bioequivalence (6 slides)
3. Approach to microbiological equivalence
   - MIC, MPC, killing curves … (8 slides)
4. **Approach to pharmacodynamic equivalence**
   - **PK/PD (animal models) and clinical data … (8 slides)**
5. Dissolution and stability
6. True content and impurities
7. The hidden risk of "low cost" antibiotics

Vancomycin: evidence of non-equivalence

Neutropenic tight mouse model

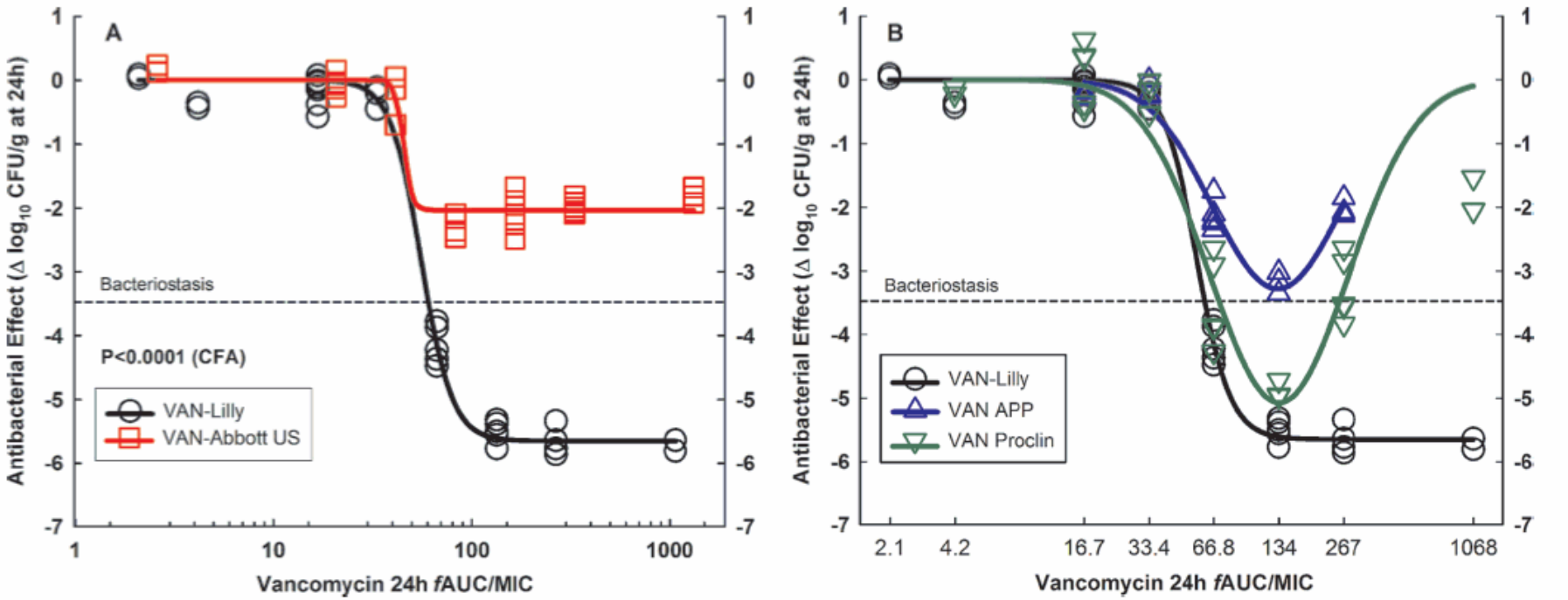

FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per 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.

Oxacillin: evidence of non-equivalence

Neutropenic tight mouse model

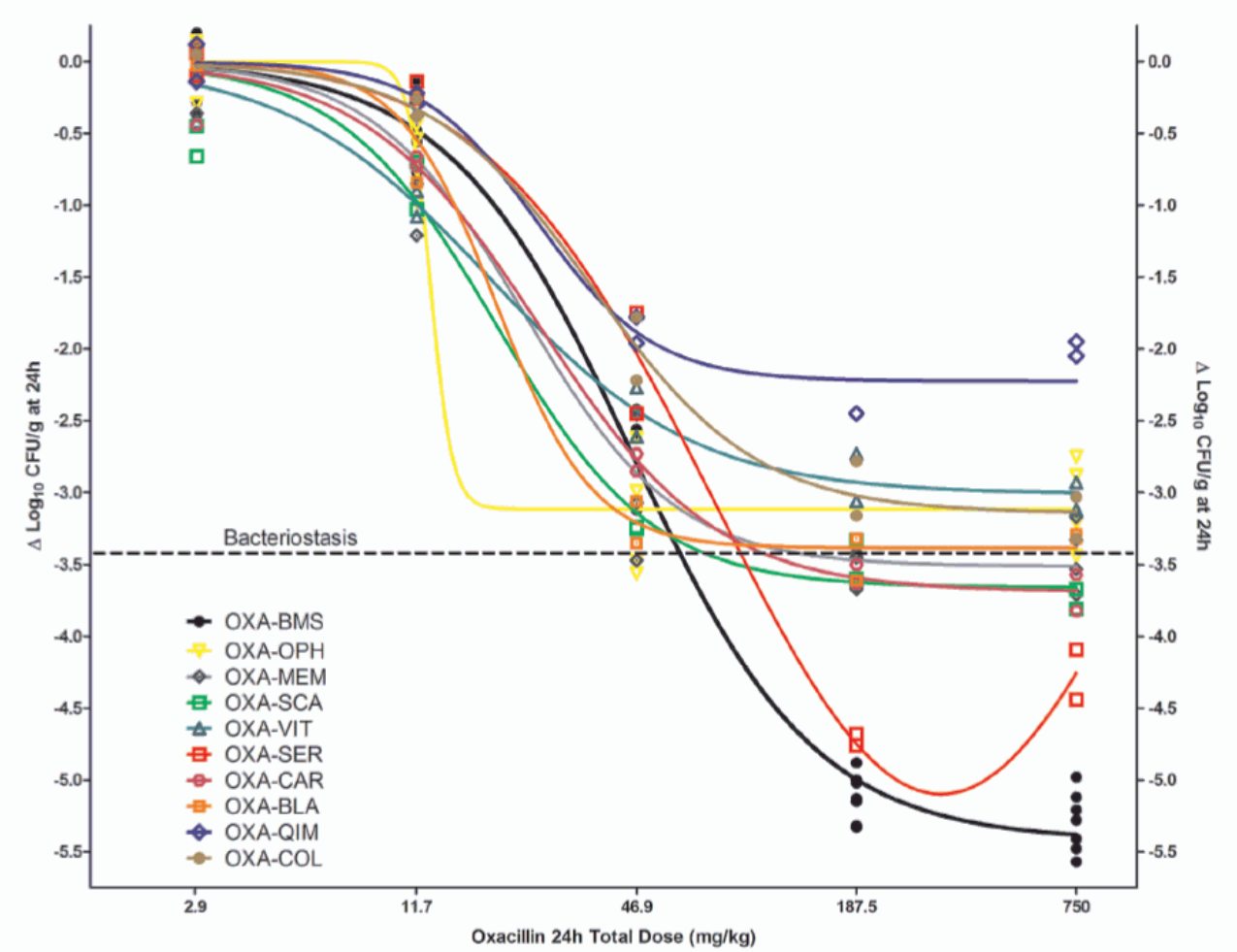

Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless of pharmaceutical equivalence and in vitro activity, all generics displayed significantly inferior bactericidal efficacy ($P < 0.0001$) or different pharmacodynamic behavior (Gaussian instead of sigmoid) compared with the innovator, thus lacking therapeutic equivalence.

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

Gentamicin: evidence of non-equivalence in vivo

Neutropenic tight mouse model

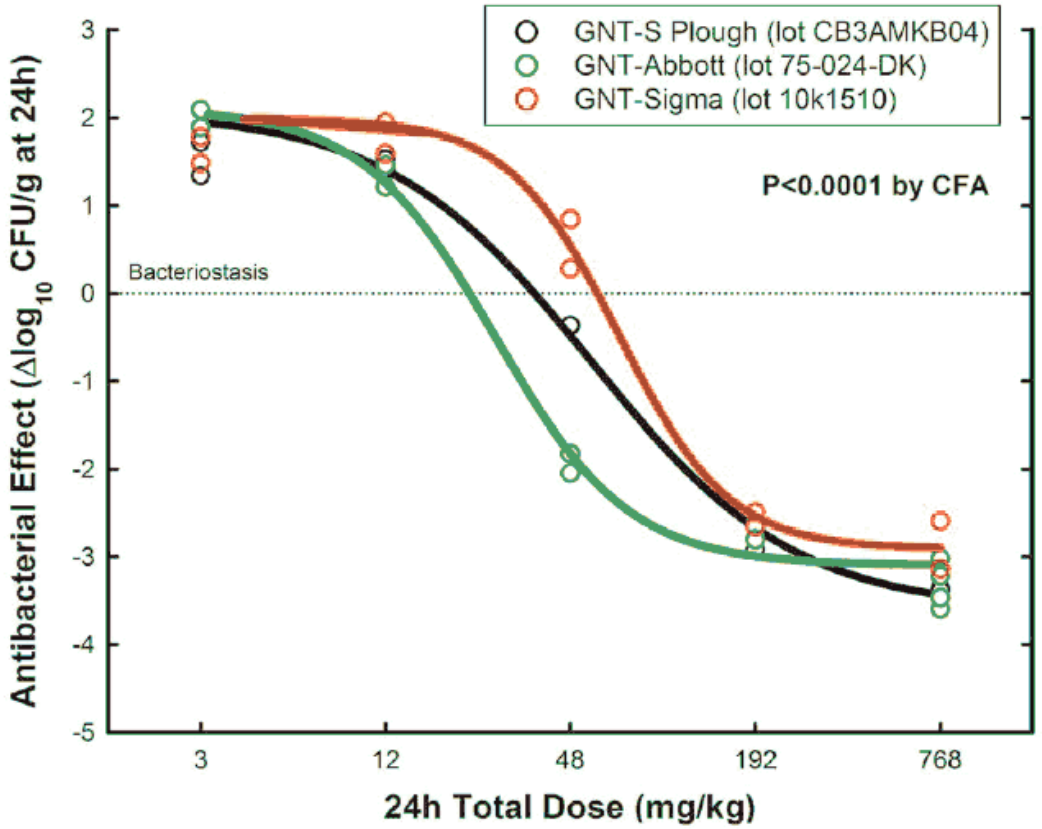

Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence. The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency 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

Gentamicin: evidence of non-equivalence in vivo

Neutropenic tight mouse model

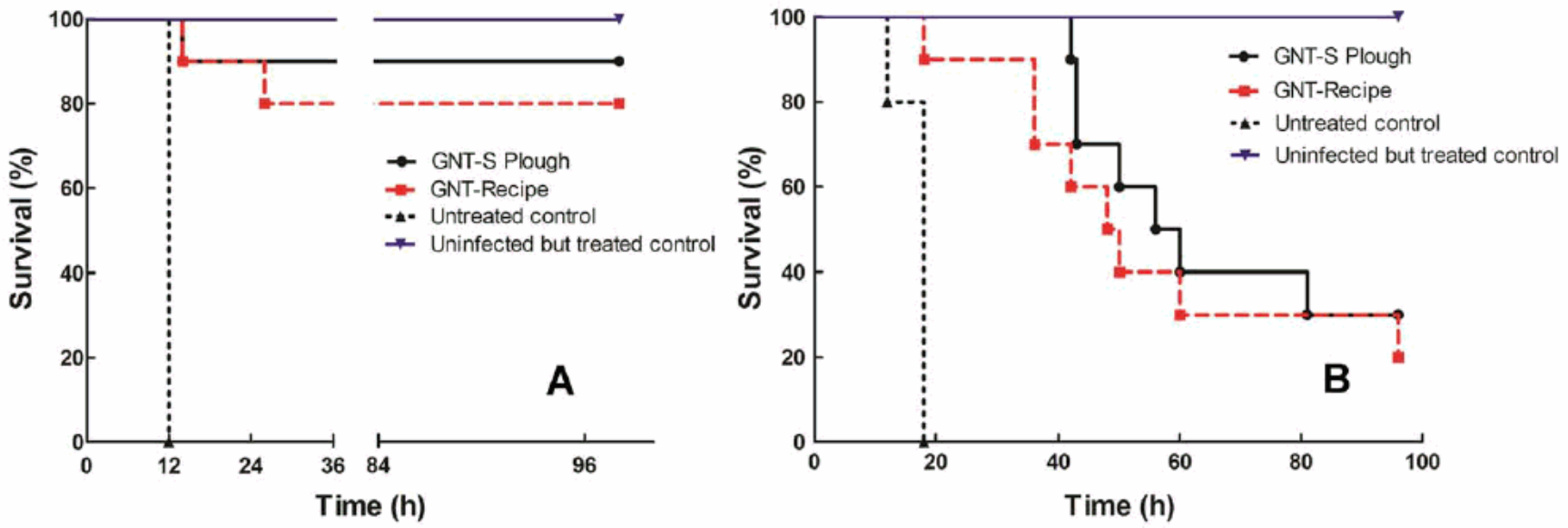

Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect (768 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

Metronidazole: complete equivalence

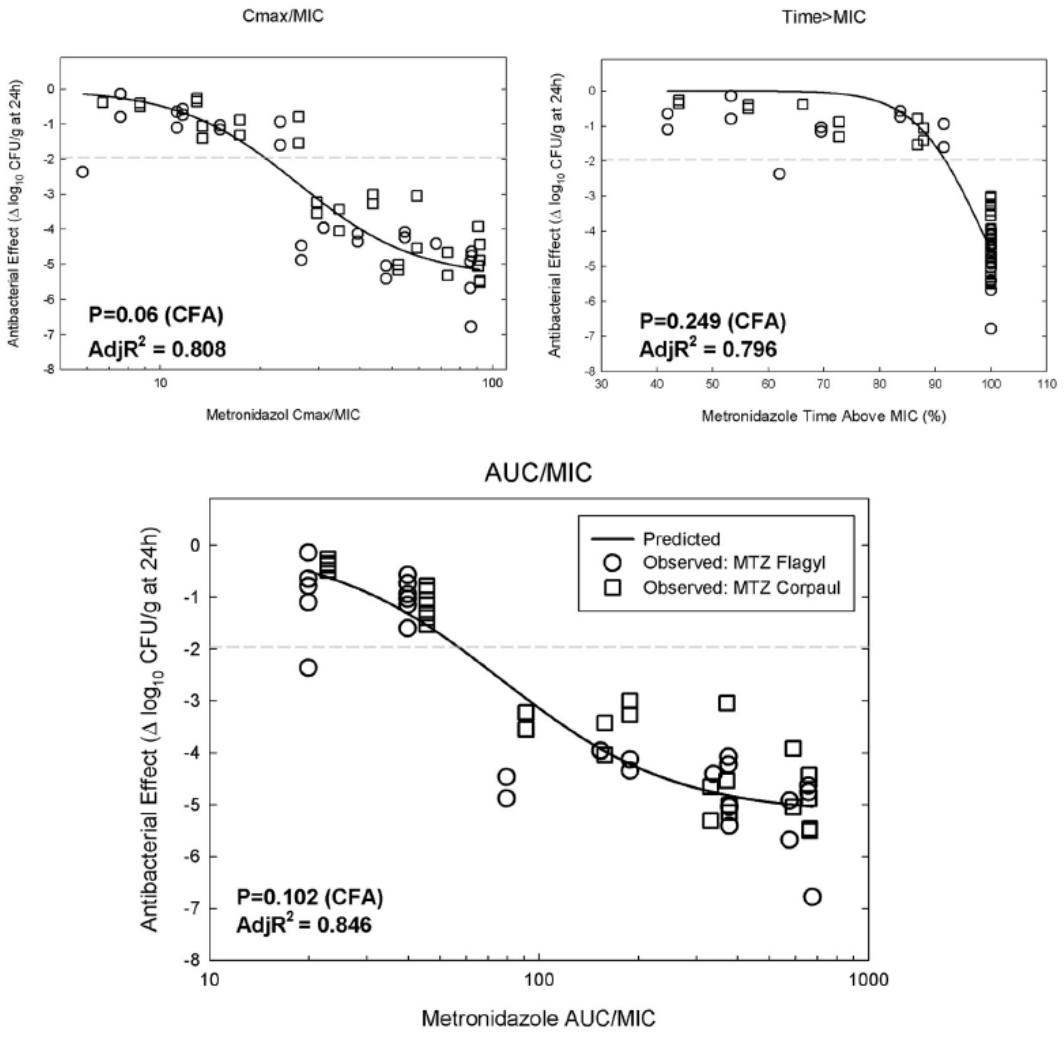

FIG 5 Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *B. fragilis* in a neutropenic mouse thigh anaerobic infection model. Only one curve is depicted because the data belong to a single population despite the fact that they were obtained after treatments of different 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

But what about clinical effectiveness ?

Cost-effectiveness of empirical prescribing of antimicrobials in community-acquired pneumonia in three countries in the presence of resistance.

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

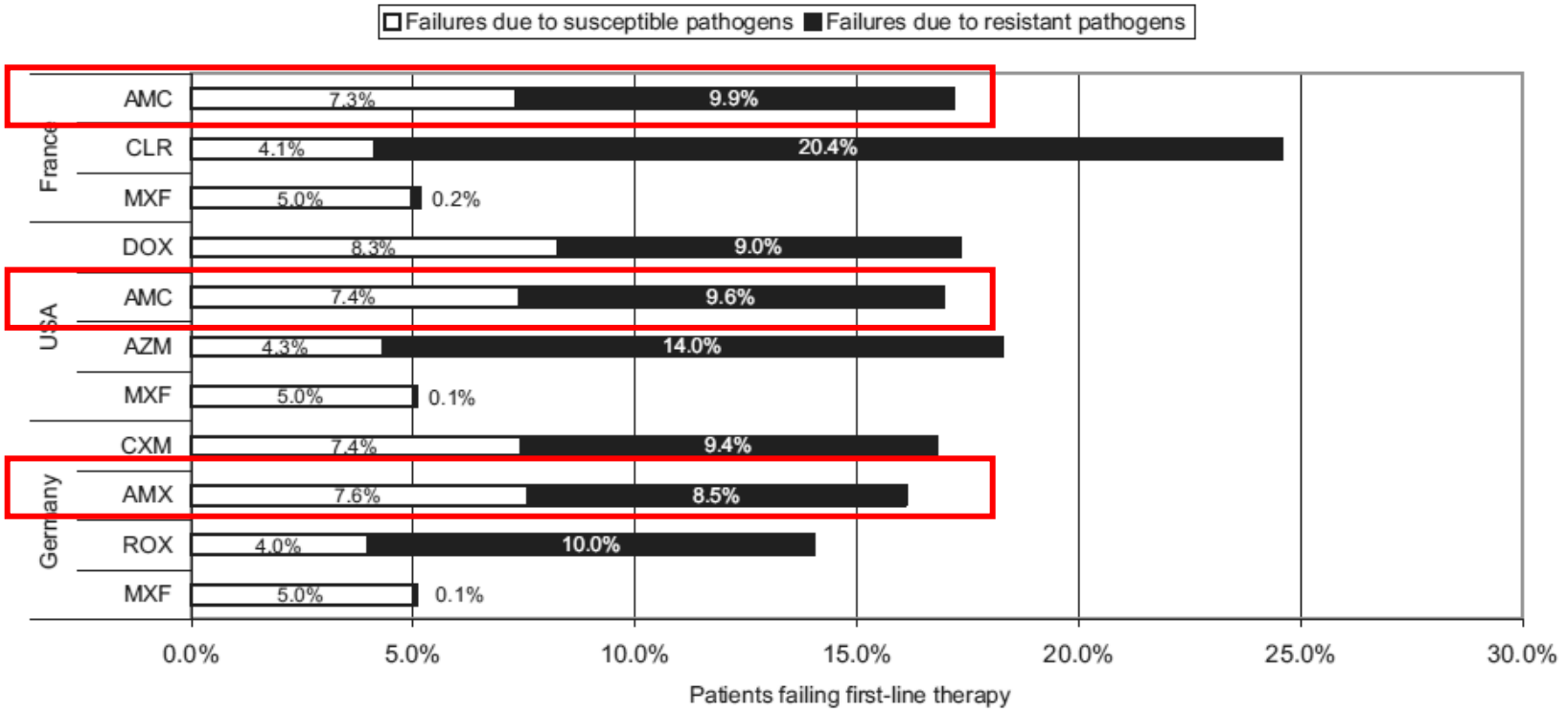

Figure 2. Calculated clinical failure rates with first-line therapy in CAP due to susceptible pathogens and antimicrobial-resistant pathogens (rounded). MXF, moxifloxacin; CLR, clarithromycin; AMX, amoxicillin; AMC, co-amoxiclav; AZM, azithromycin; DOX, doxycycline; ROX, roxithromycin; CXM, cefuroxime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

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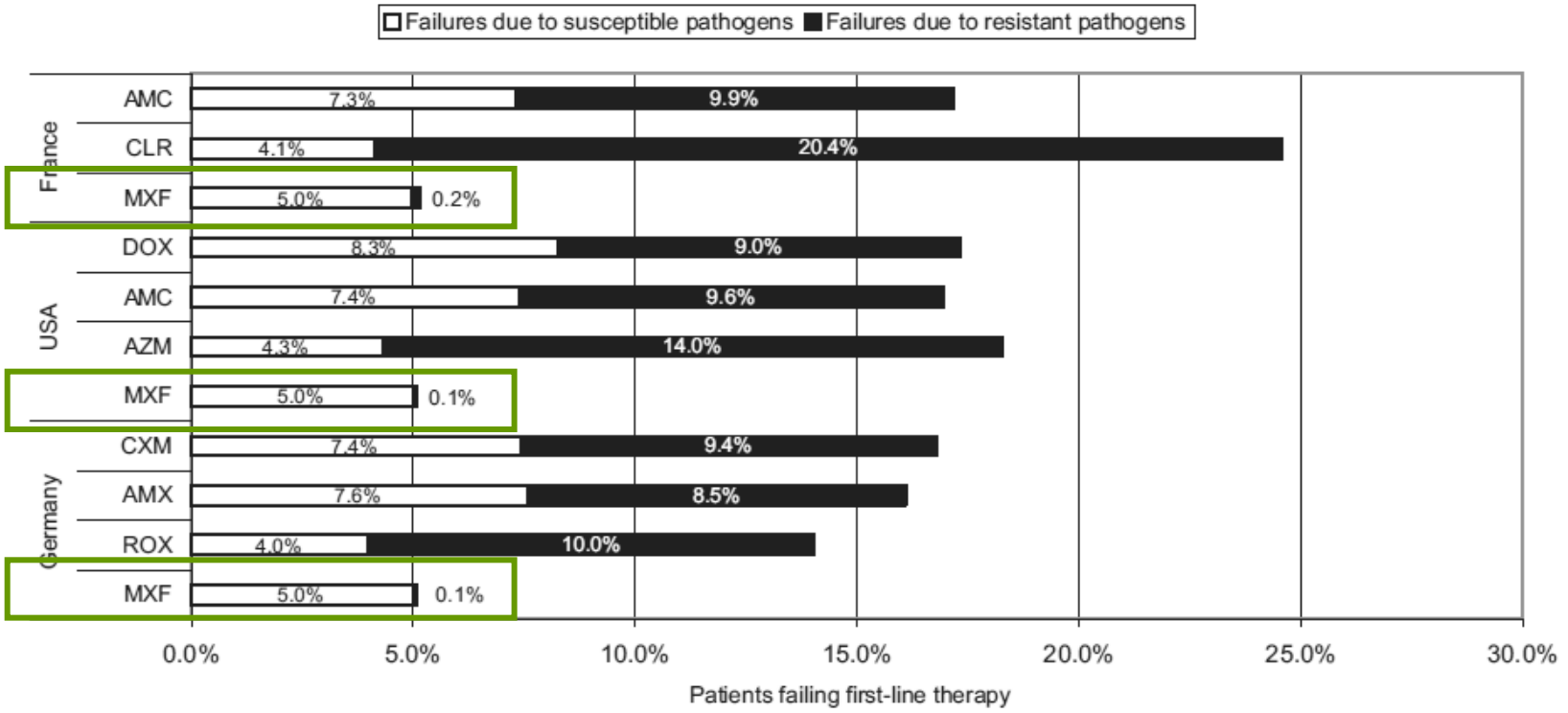

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What shall we discuss ?

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3. Approach to microbiological equivalence
   - MIC, MPC, killing curves … (8 slides)
4. Approach to pharmacodynamic equivalence
   - PK/PD animal models … (8 slides)
5. **Dissolution and stability** (5 slides)
6. True content and impurities
7. The hidden risk of "low cost" antibiotics

Dissolution in Japan (meropenem)…

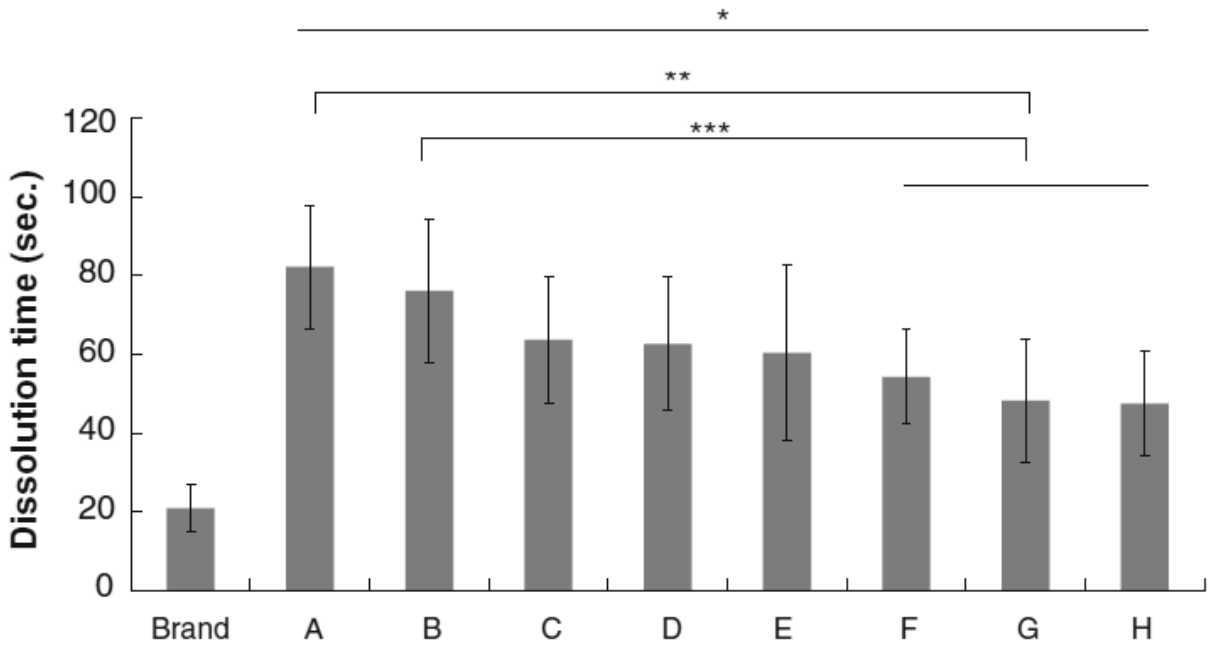


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

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

Crystals size in merpenem

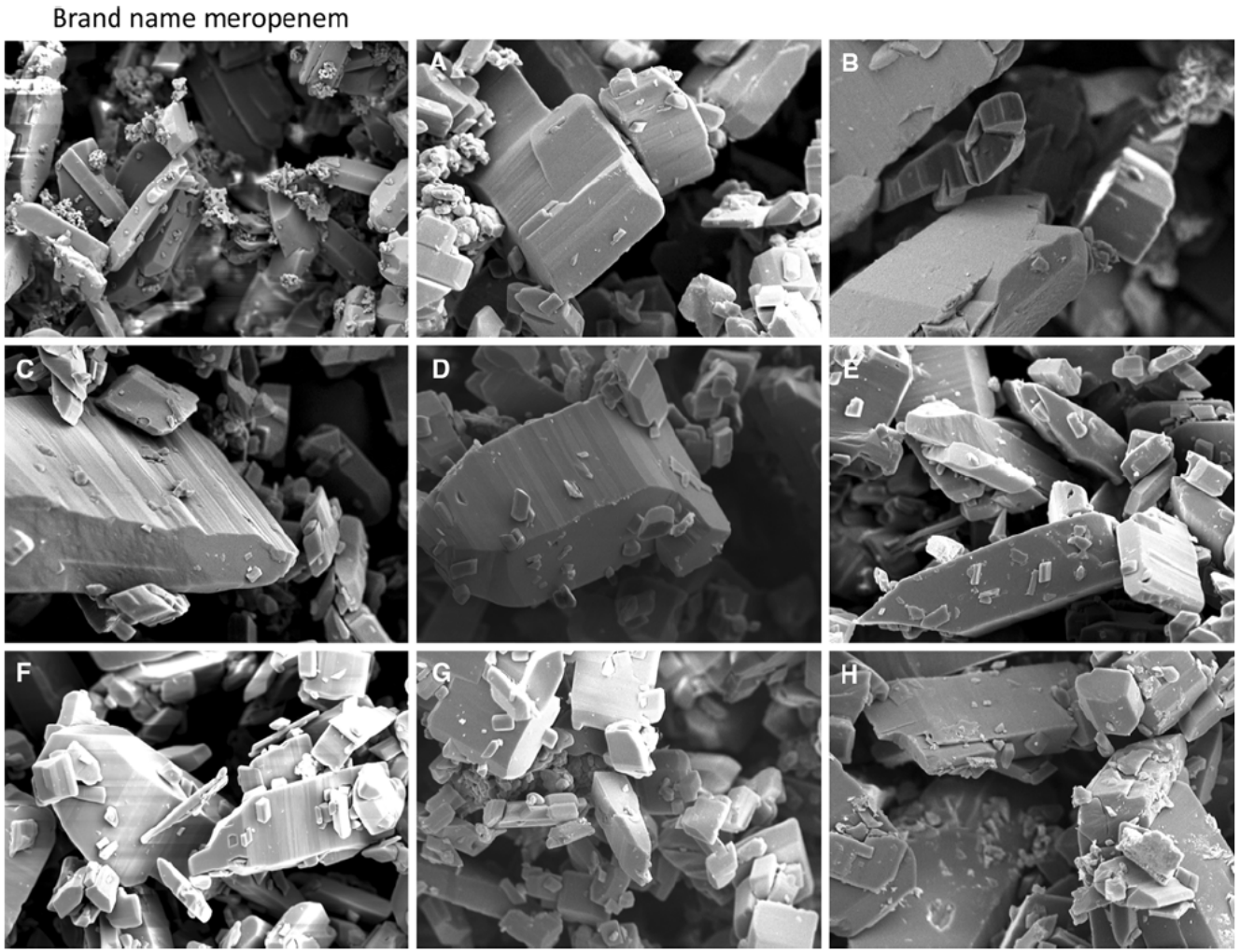
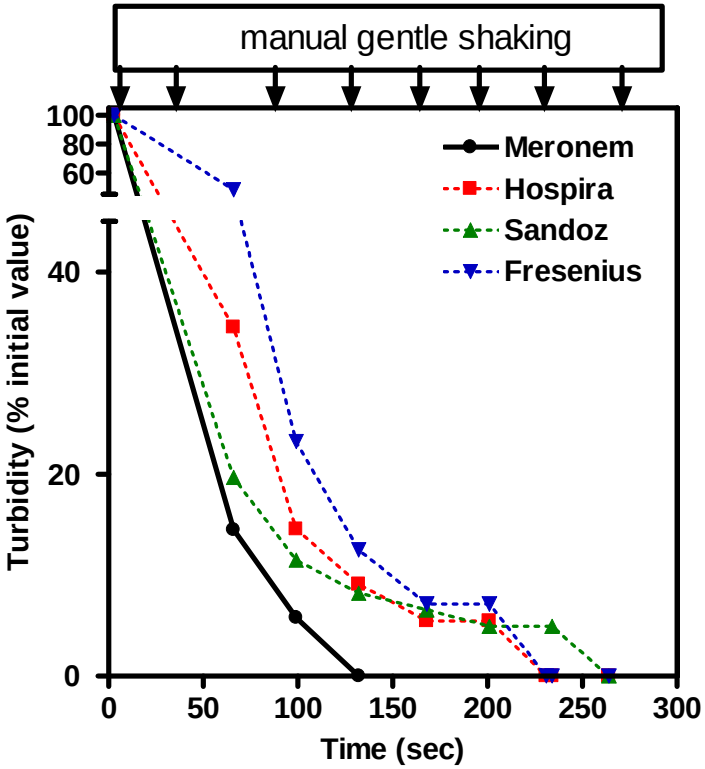


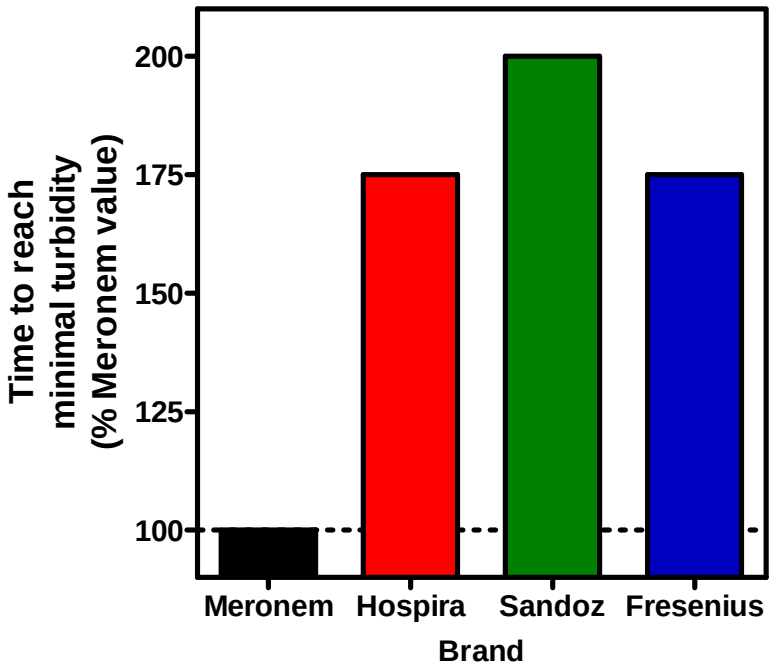
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

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

Dissolution in Belgium (meropenem)…

Drug concentration : 50 mg/mL (~ solution used for infusion)
gentle manual shaking followed by turbidity measures;
room temperature





Van Bambeke *et al*., in preparation

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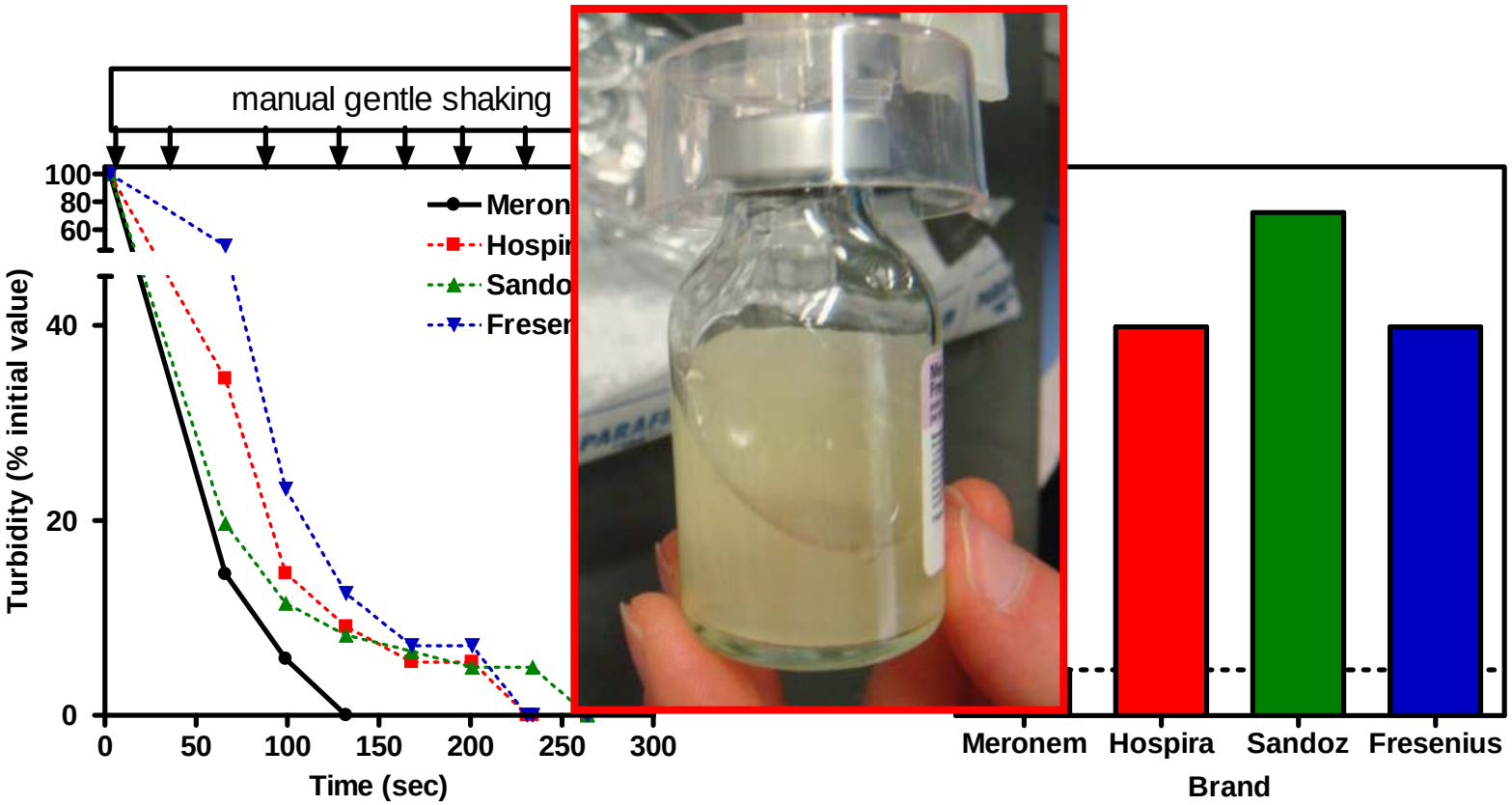
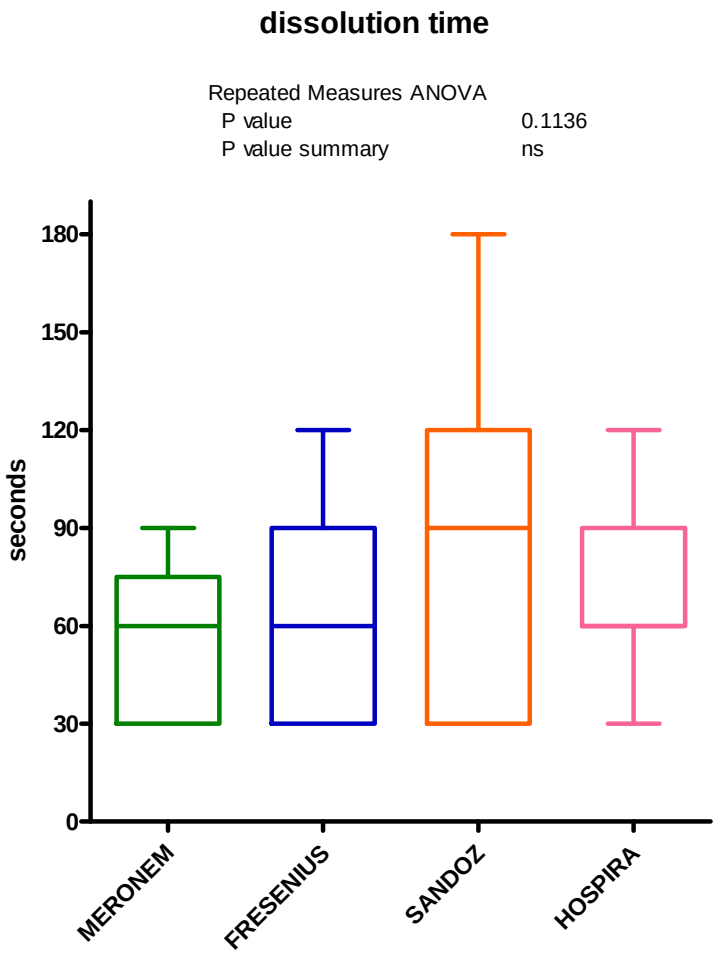
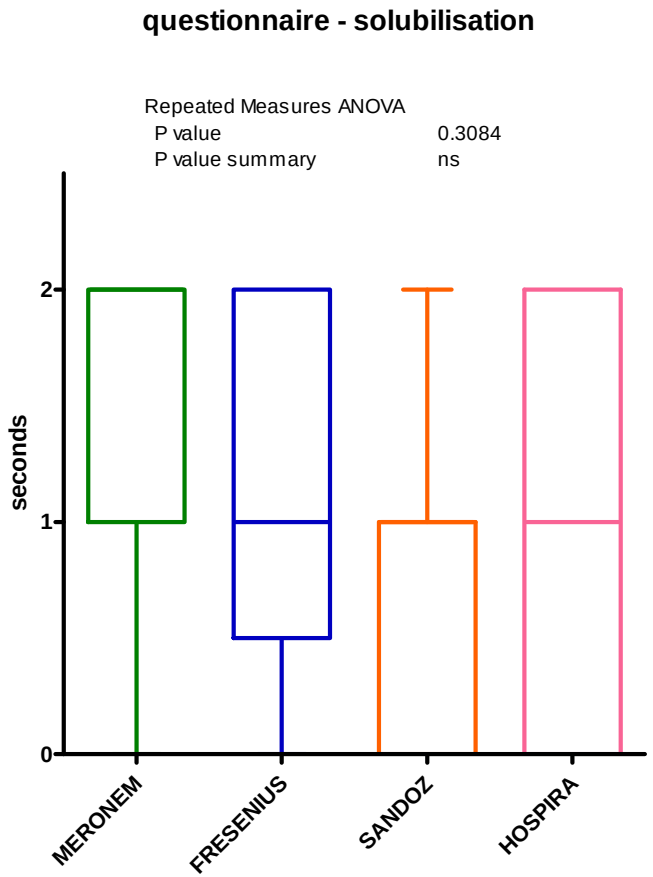


Van Bambeke *et al*., in preparation

Are Primary Health Care Professionals (nurses) happy ? (meropenem)





Van Bambeke *et al*., in preparation

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4. Approach to pharmacodynamic equivalence
   - PK/PD animal models … (8 slides)
5. Dissolution and stability (6 slides)
6. **True content and impurities** (4 slides)
7. The hidden risk of "low cost" antibiotics

Impurities

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

Groupe de RMN Biomédicale, Laboratoire SPCMIB (UMR CNRS 5068), Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse cedex, France

Received 29 November 2006; received in revised form 19 February 2007; accepted 19 February 2007
Available online 1 March 2007

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

Impurities in ciprofloxacin

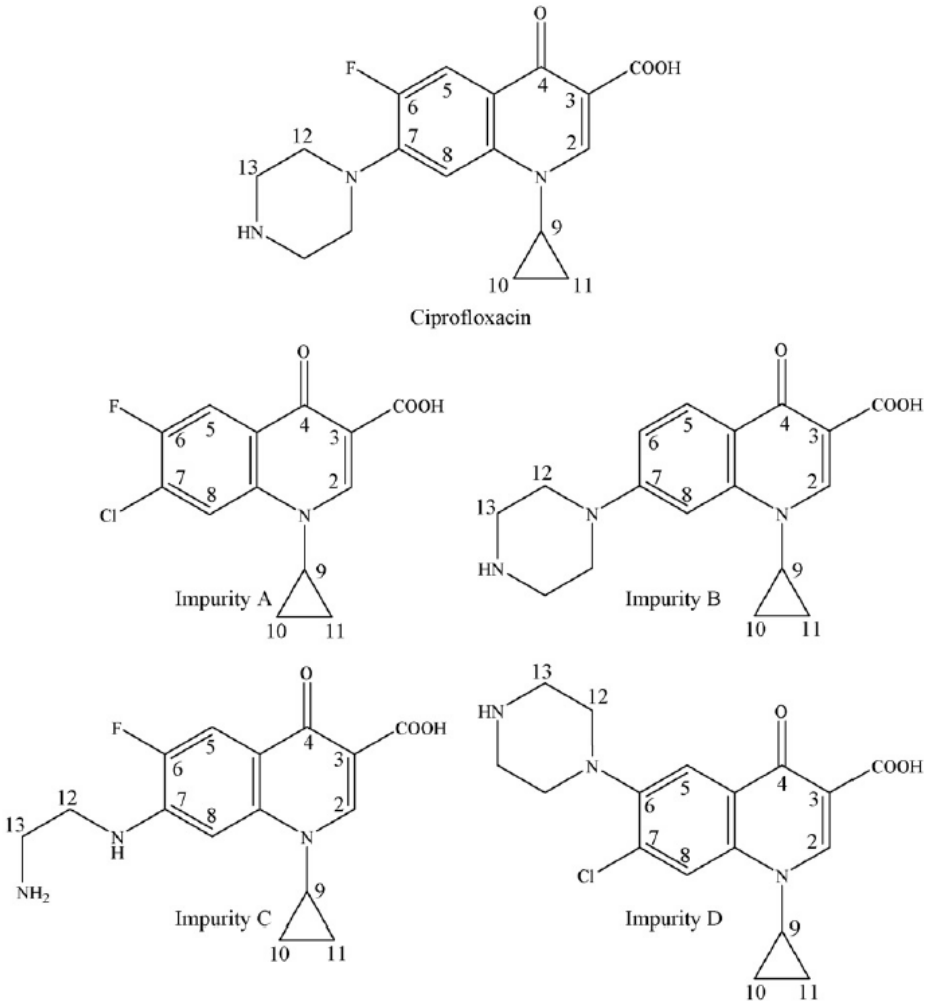
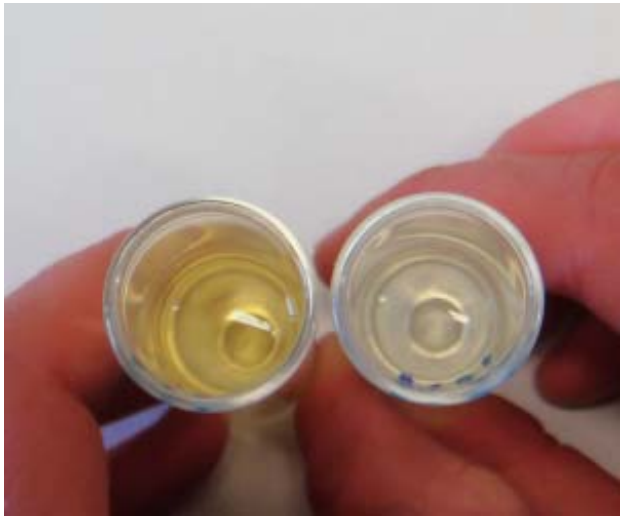


Fig. 1. Structure of ciprofloxacin and its main impurities.

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

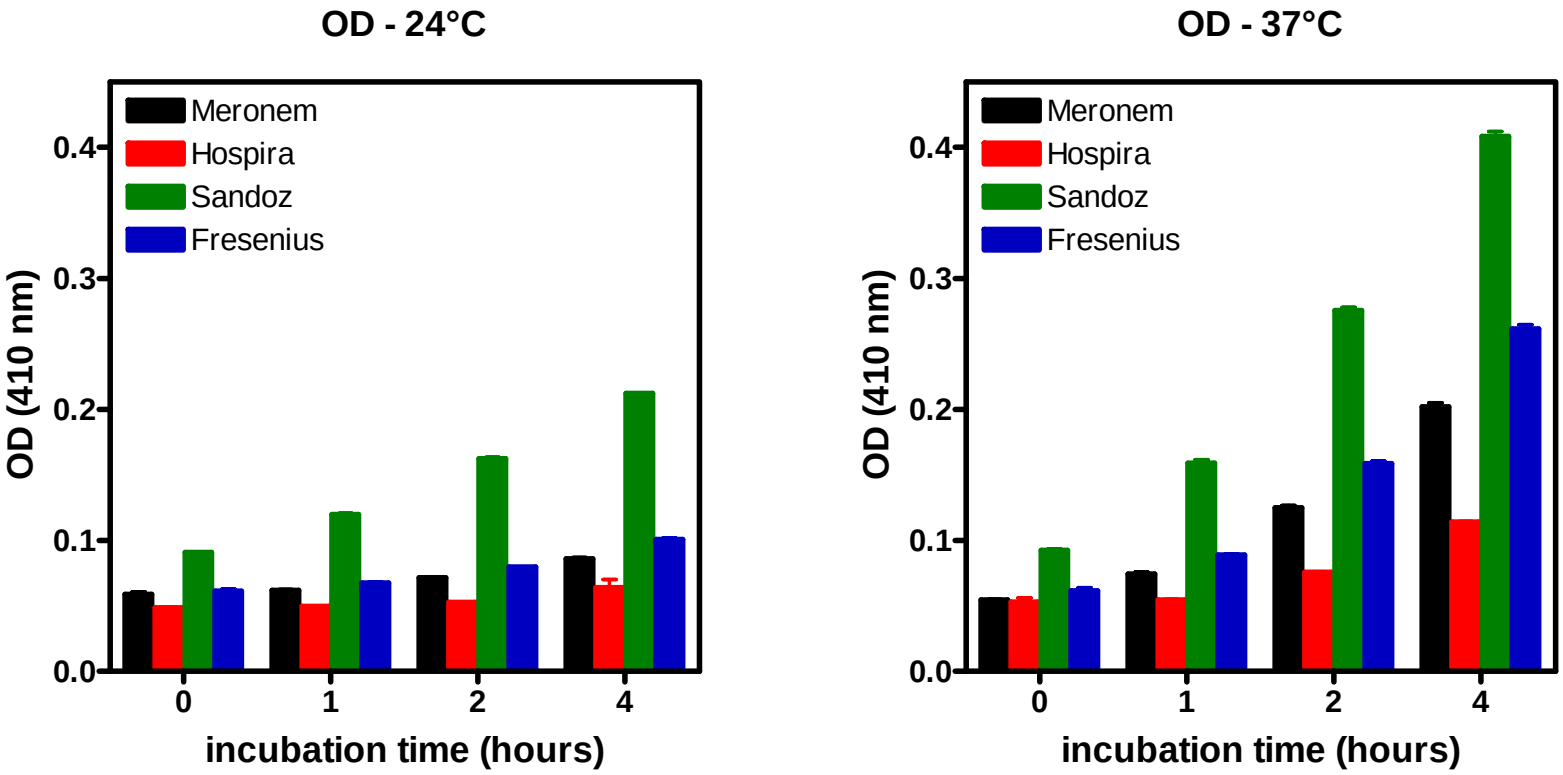
Impurities in meropenem: coloured compounds



are you happy with the colour ?

Van Bambeke *et al*., in preparation

Impurities in meropenem: coloured compounds



Van Bambeke *et al*., in preparation

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3. Approach to microbiological equivalence
   - MIC, MPC, killing curves … (8 slides)
4. Approach to pharmacodynamic equivalence
   - PK/PD animal models … (8 slides)
5. Dissolution and stability (6 slides)
6. True content and impurities (6 slides)
7. **The hidden risk of "low cost" antibiotics** (1 slide)

"Low cost antibiotics" and "prudent use" … The sour Danish experience

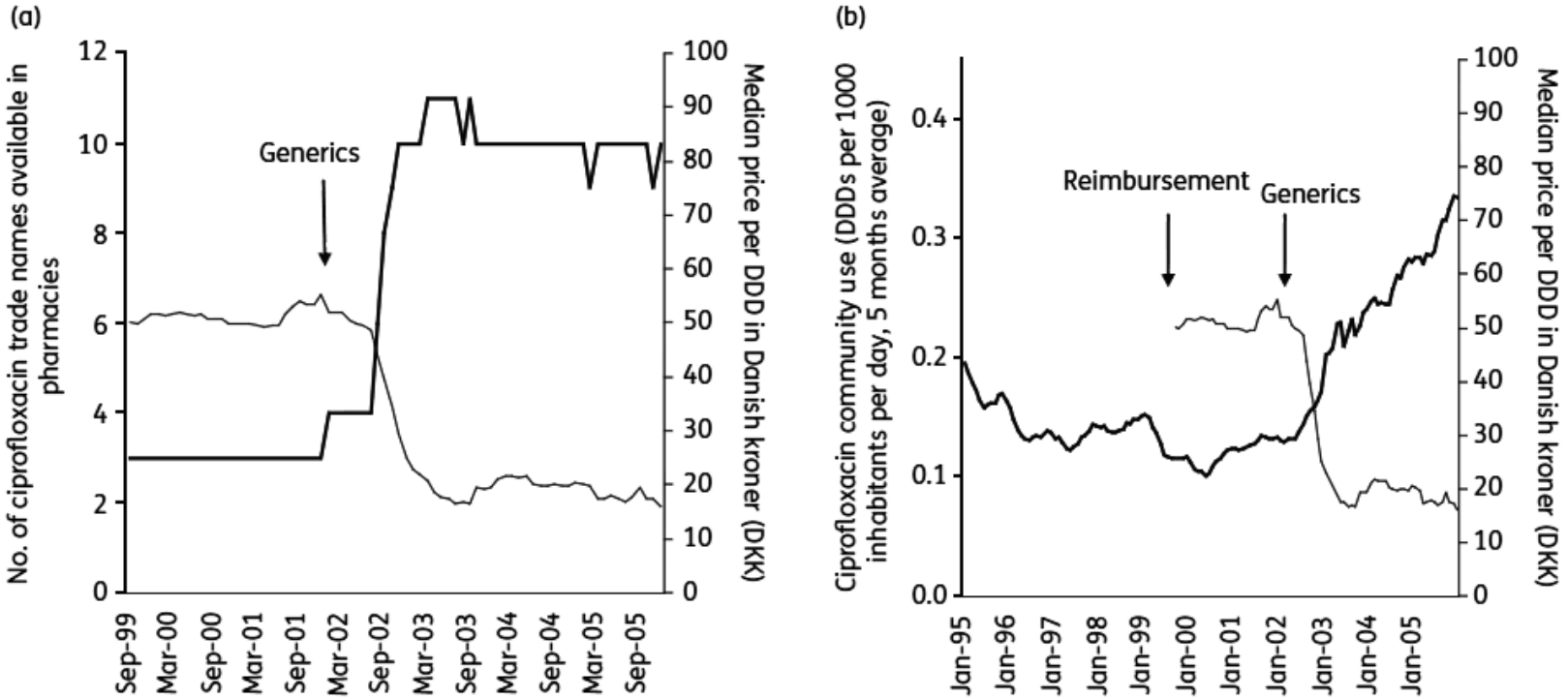


Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin. (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.

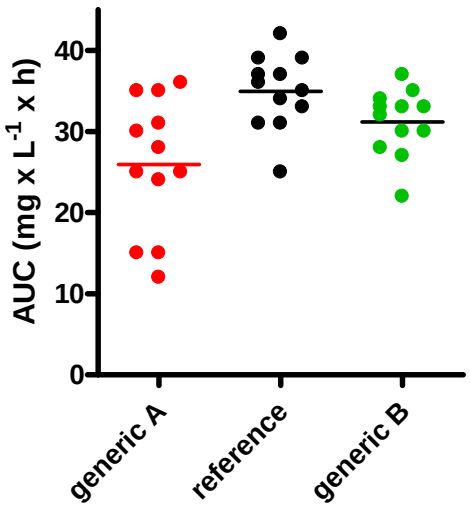
Jensen *et al.* J Antimicrob Chemother 2010; 65:1286–1291

Summary / Discussion

- The decision to "**go for generics**" is a political one that may need revision (at political level) to avoid over-use of antibiotics
- **Pharmacokinetic criteria** are, so far, the (nearly) only ones adopted and accepted by the Regulatory Authorities (EMA/FDA)
- **Improved criteria** for **anti-infective drugs** (MIC, MPC, animal PK/PD, … are probably necessary (but are not yet implemented)
- **Antibiotics are cheap** (compared to other chemotherapeutic agents), making discussion about costs largely irrelevant
- Antibiotics might be a good starting point to **modify the current legislative framework** concerning generics at the level of the EU-Parliament and the US Congress … or another "World Power"…

Back-up

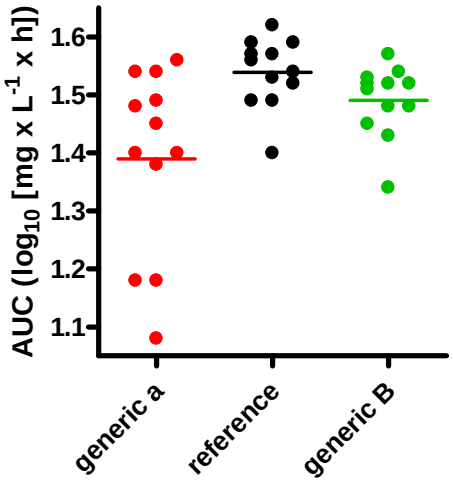
Are generic really comparable ?



	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



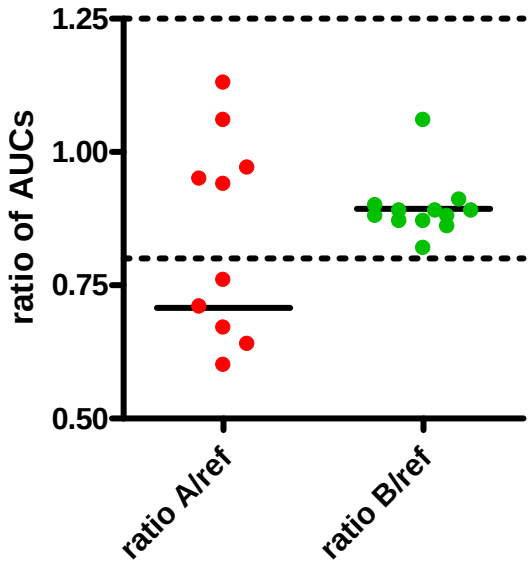
	generic a	reference	generic B
Number of values	12	12	12
Minimum	1.080	1.400	1.340
25% Percentile	1.280	1.505	1.465
Median	1.425	1.550	1.515
75% Percentile	1.515	1.580	1.525
Maximum	1.560	1.620	1.570
Mean	1.390	1.539	1.491
Std. Deviation	0.1596	0.05931	0.06142
Std. Error	0.04607	0.01712	0.01773
Lower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

Are generic really comparable ?

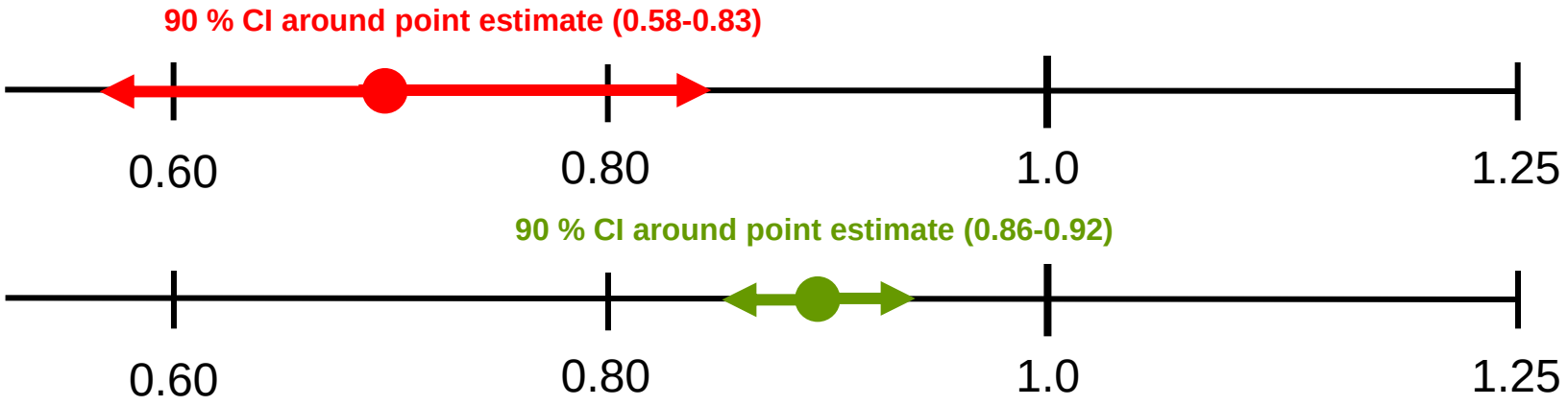
subject#	AUC generic A	AUC reference	AUC generic B	A/reference	B/reference
1	30.00	31.00	33.00	0.97	1.06
1	31.00	33.00	30.00	0.94	0.91
1	24.00	36.00	32.00	0.67	0.89
1	28.00	37.00	33.00	0.76	0.89
1	36.00	34.00	28.00	1.06	0.82
1	35.00	31.00	27.00	1.13	0.87
1	15.00	25.00	22.00	0.60	0.88
1	35.00	37.00	33.00	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**

Are generic really comparable ?

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**



Special situations (EU)

Narrow therapeutic index drugs

- In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to **90.00-111.11%**. Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.

Highly variable drugs or drug products

- The extent of the **widening** is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to [U, L] = exp [±k·sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the within-subject standard deviation of the log-transformed values of Cmax of the reference product (Important: this applies to C_{max} only, NOT to 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

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