Generics of antibiotics: are you sure of what you get …
and of what you pay ?

Paul M. Tulkens, Dr Med., Sp. Biol. Clin.
Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Secteur des Sciences de la Santé
Université catholique de Louvain
Brussels, Belgium

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  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, AstraZeneca
- Decision-making and consultation bodies
  - General Assembly (current) and steering committee (part) of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

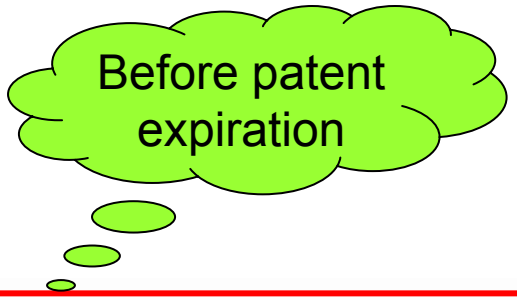
Slides: http://www.facm.ucl.ac.be → Lectures

Whay are generics knocking at your doors ?

Generics are cheaper !

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 legal framework
2. What is bioequivalence (for a generic) ?
3. Microbiological equivalence ?
   - potency, heteroresistance, selection of resistance …
4. Pharmacodynamic equivalence ?
   - PK/PD animal models, clinical alerts …
5. Dissolution, impurities/instability, true content, "substandard drugs"…
6. Over-consumption of "low cost" antibiotics ?
7. Economic considerations in antibiotic discovery, development and use

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The EU Directive

►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

The EU Directive

- 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 rules: 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

The US Law

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

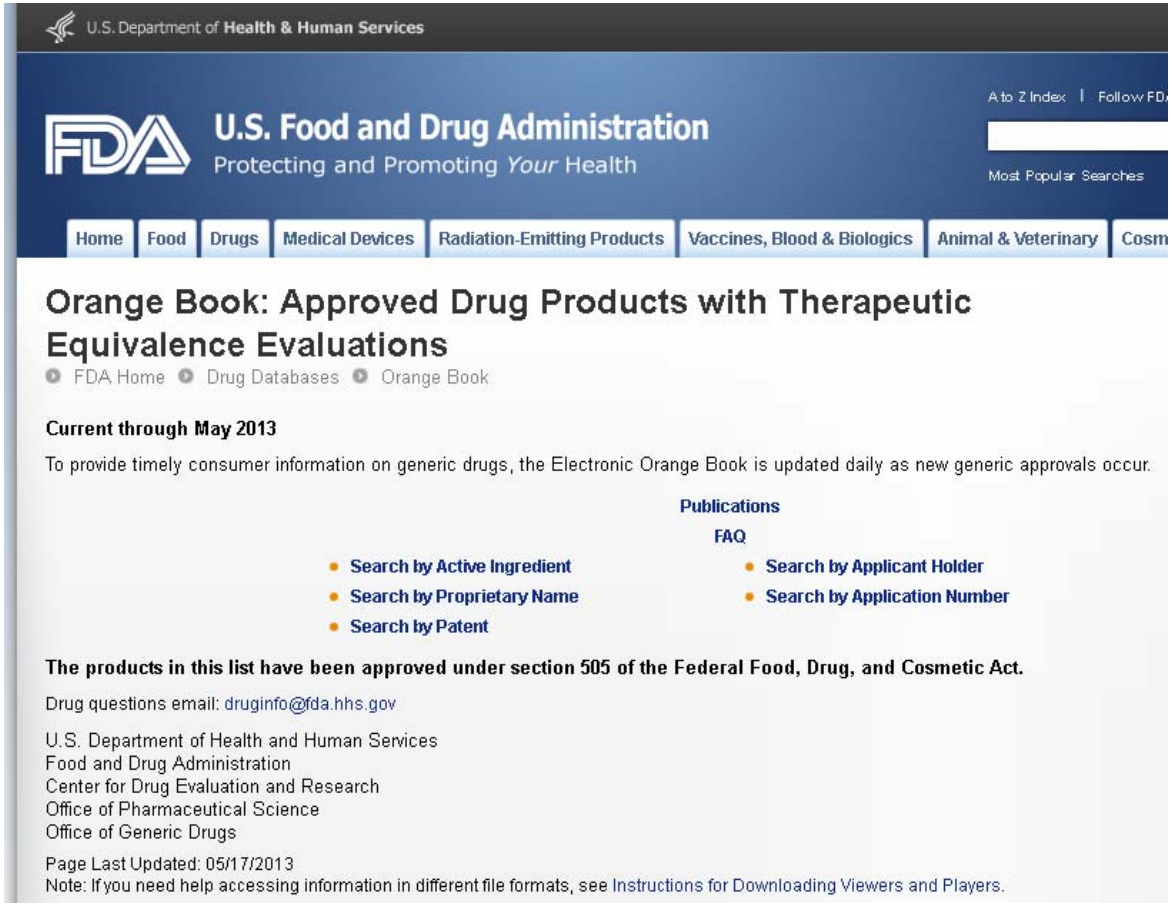
FDA requirements in a nutshell *

- 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.

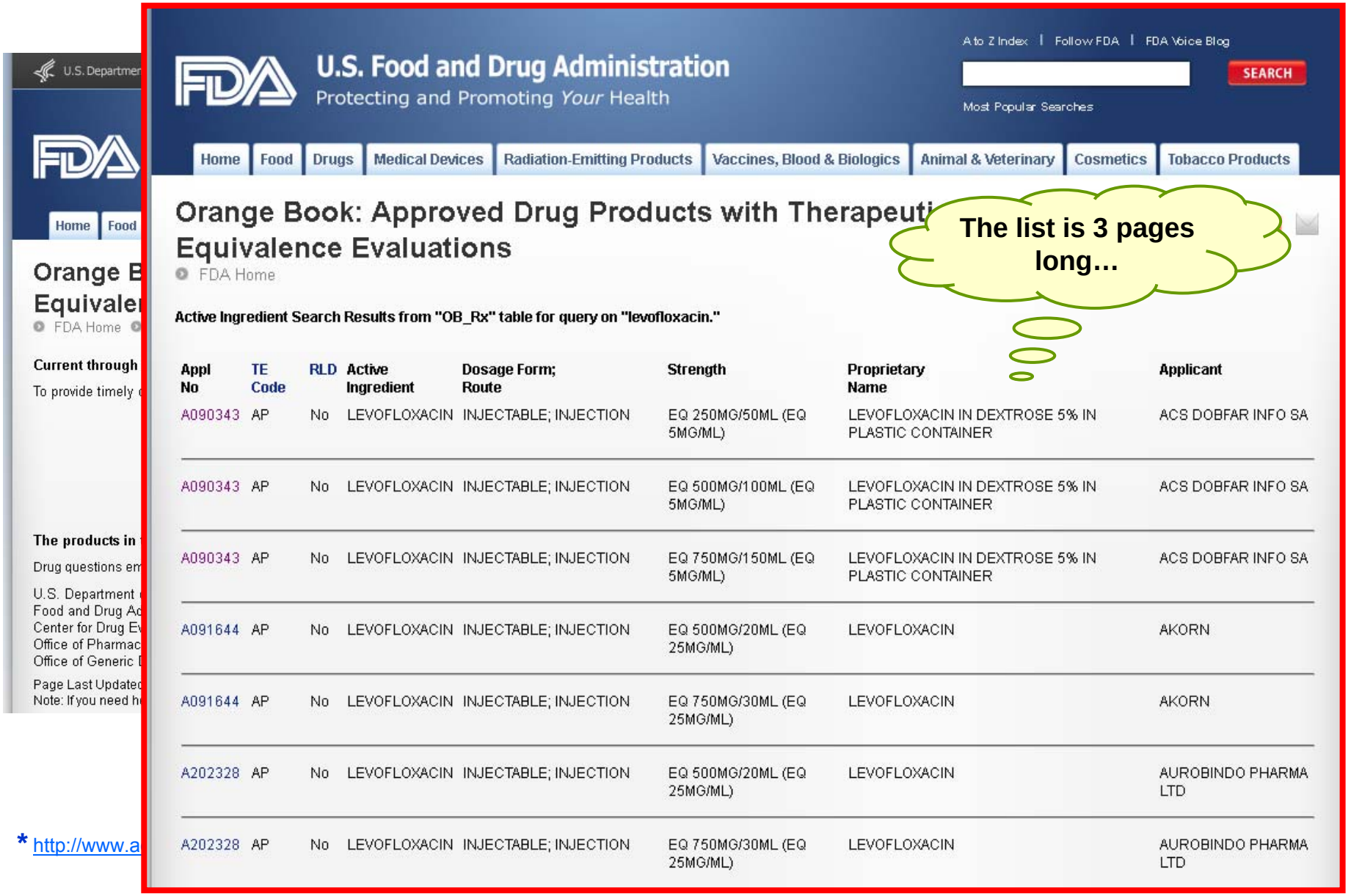
* 505 (B) (2) Application (Guidance to Industry)
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf

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 Therapeuti
Equivalence Evaluations

FDA Home

The list is 3 pages long…

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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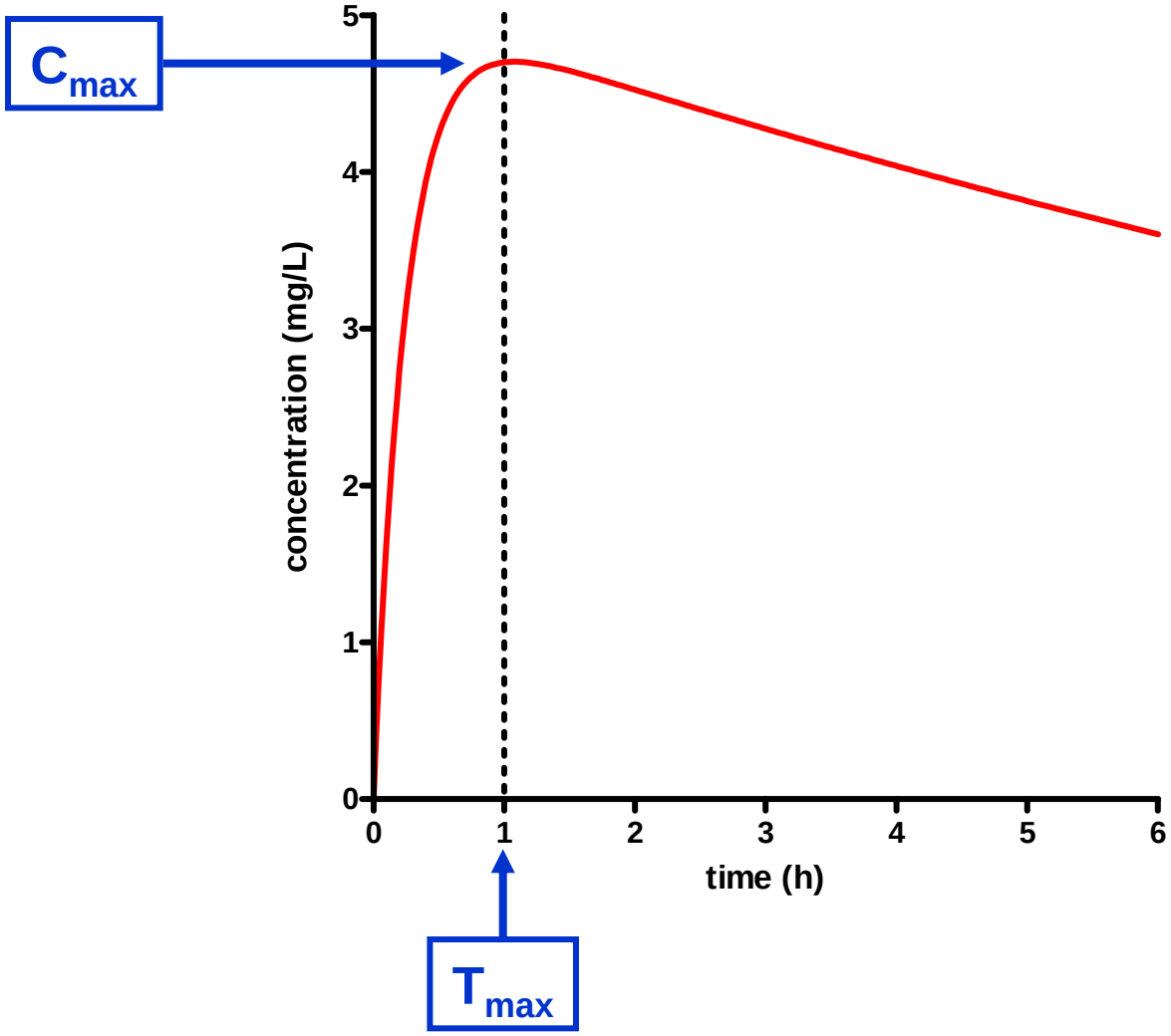
Bioequivalence: principles

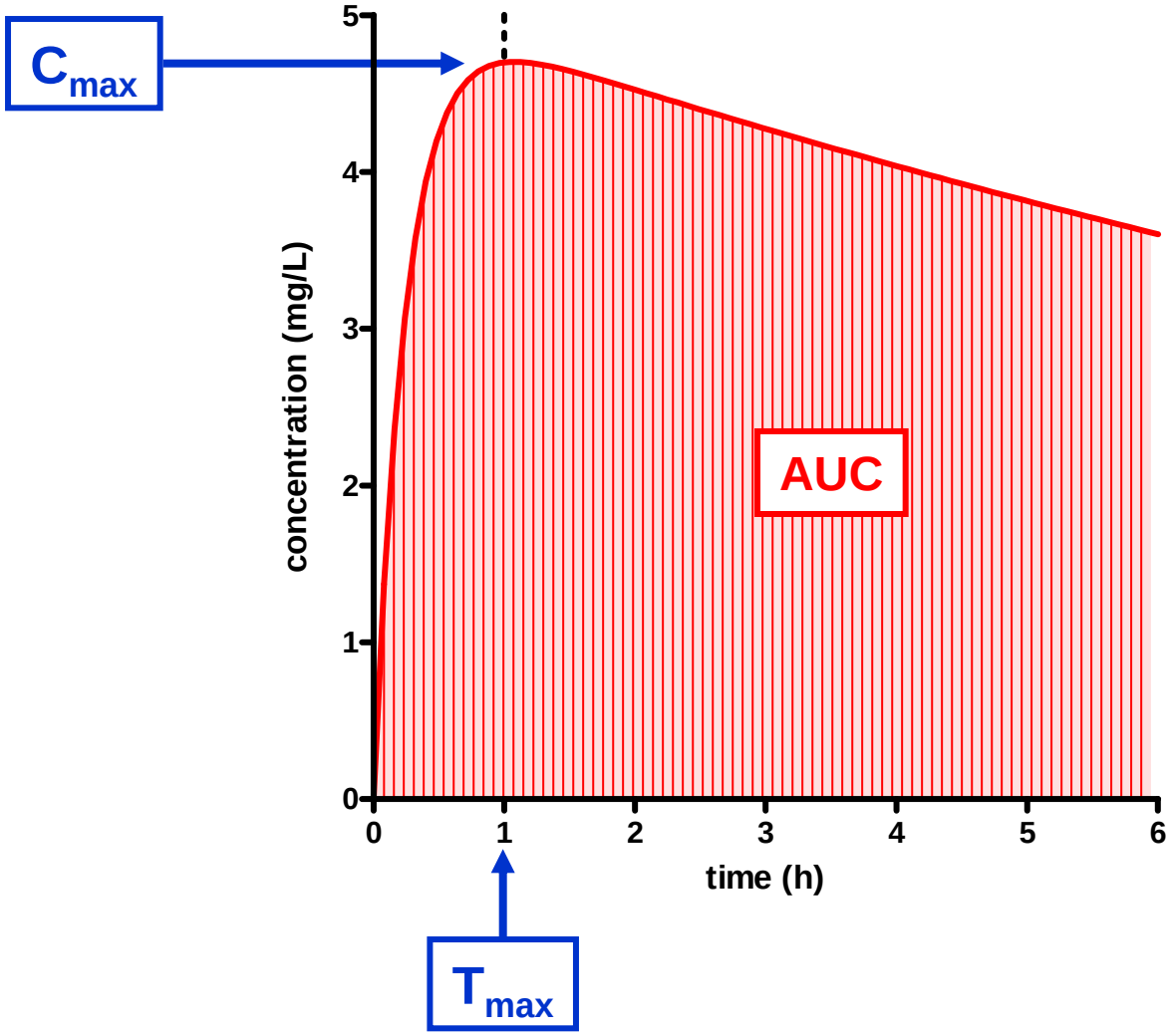
- Bioequivalence is an **accepted surrogate for therapeutic equivalence** [1] (including for branded drugs when the mareketed form differs from the form used in development…) [2]
- Primary metrics are [1,3]
  - **AUC** (area under the plasma concentration-time profile of the active substance)
    → **extent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

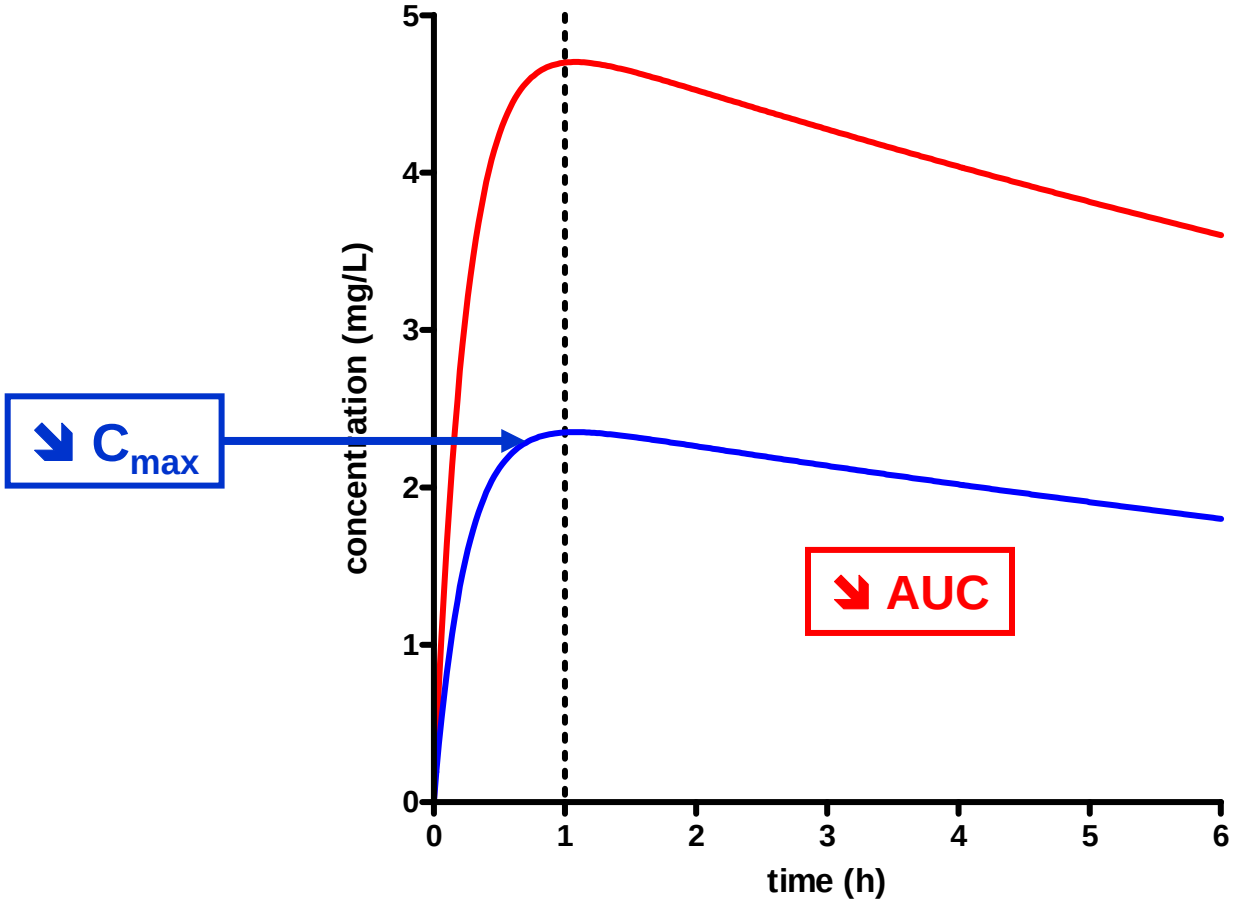
C_{max} – T_{max}



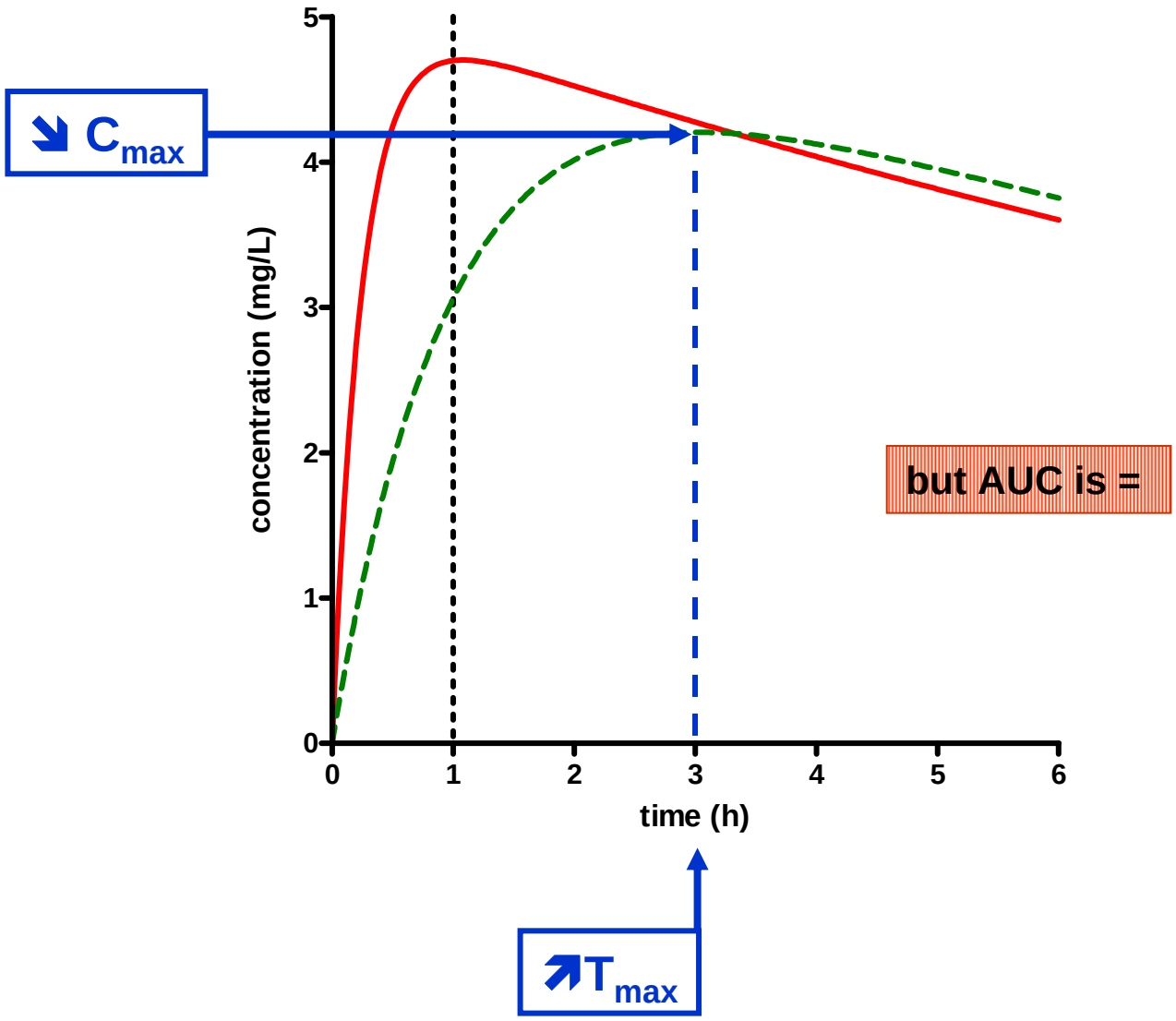
AUC



What if the absorption is decreased ?

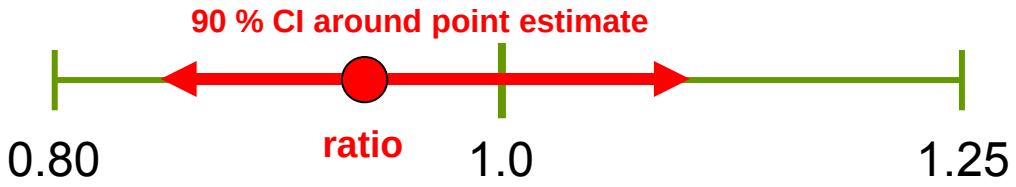


What if absorption is delayed ?



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**.



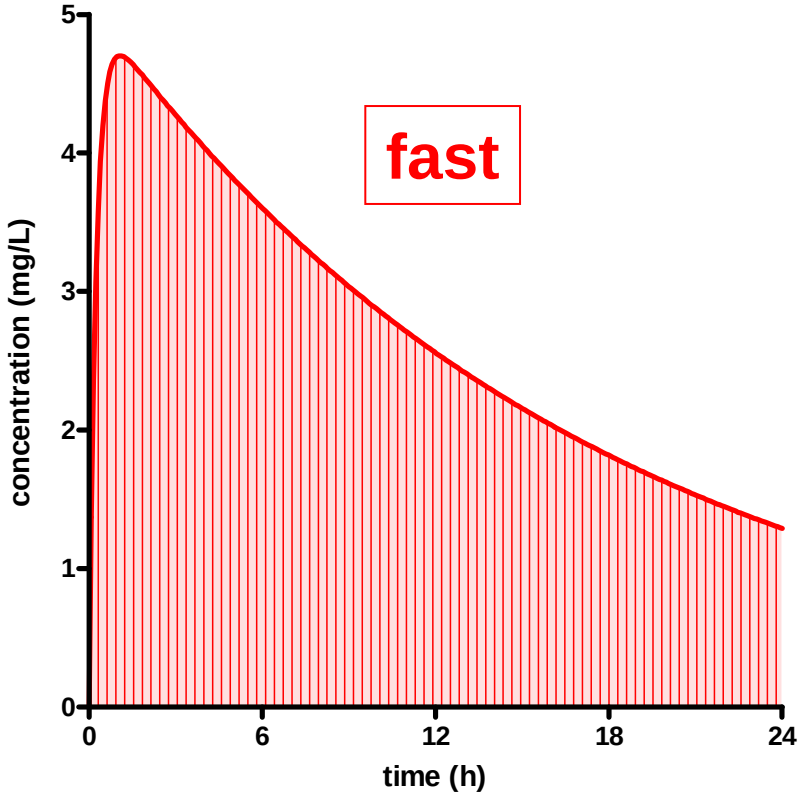
Notes:

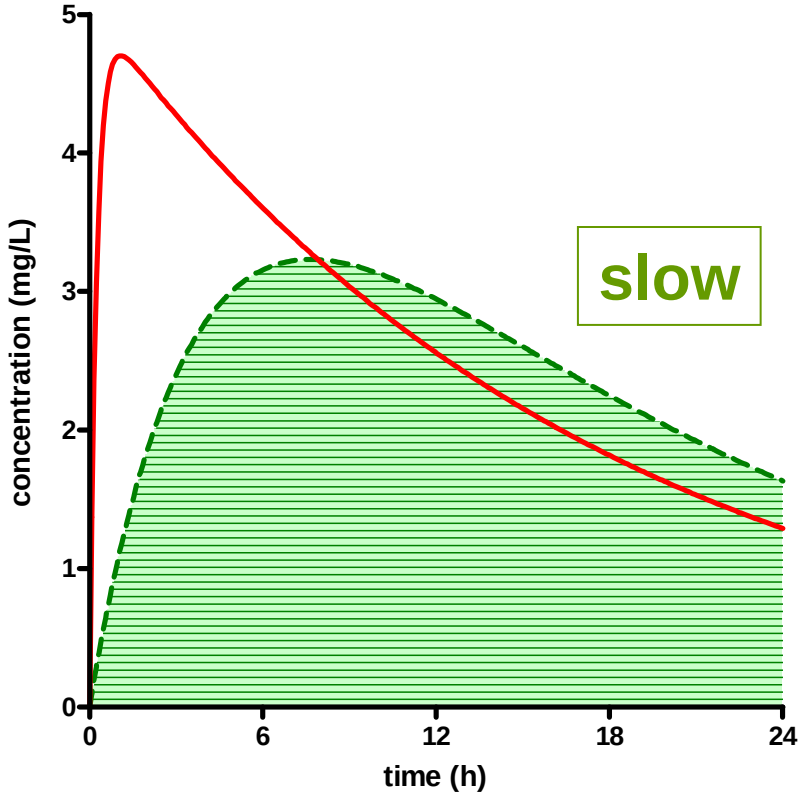
1. *if both **AUC** and C_{max} are within range, the generic should have the same bioavailability than the reference*
2. *statistical evaluation of T_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects (see next slide)*
3. *For 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

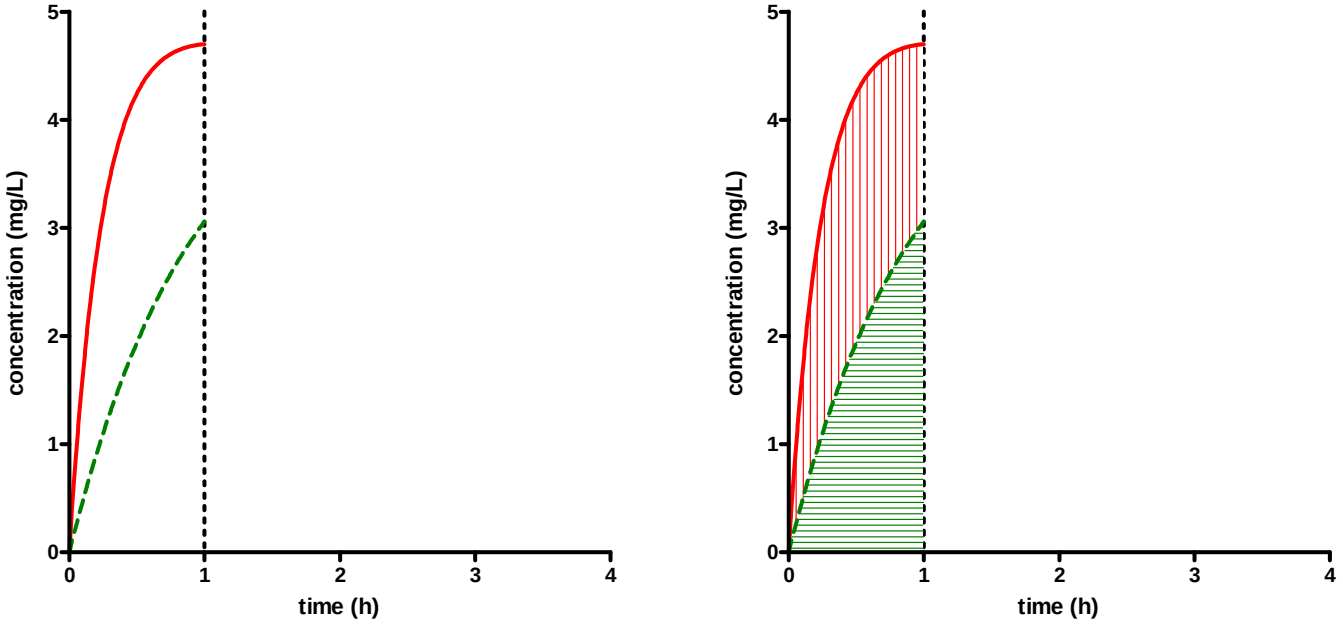
** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/Guidance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

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





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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MIC determinations (piperacillin)

Using the incremental MIC assay (Jones *et al.* Diagn Microbiol Infect Dis 2008; 61:76–79).

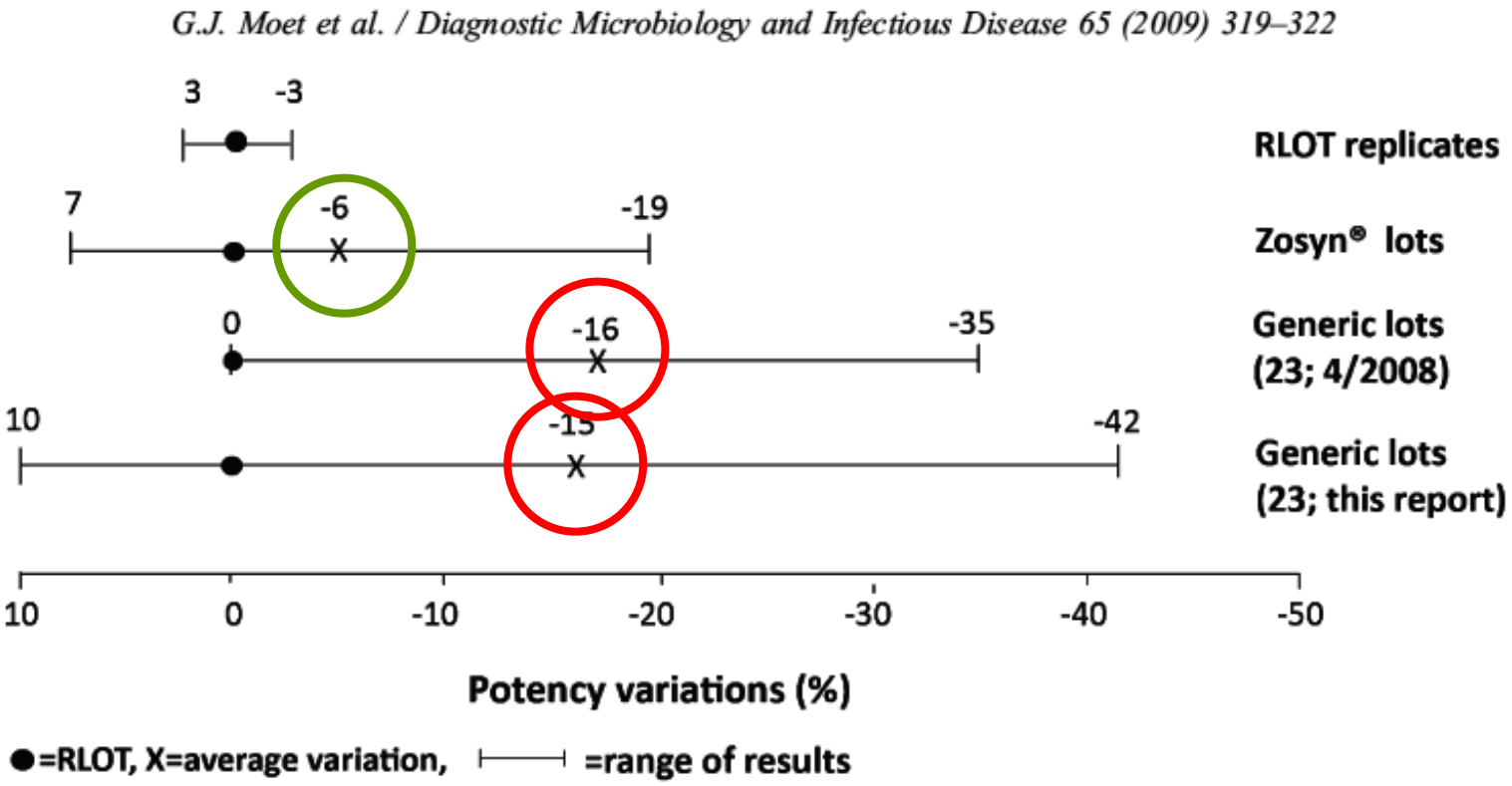
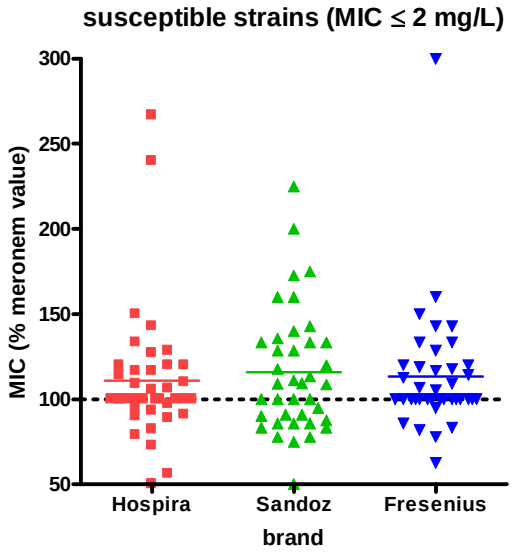


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

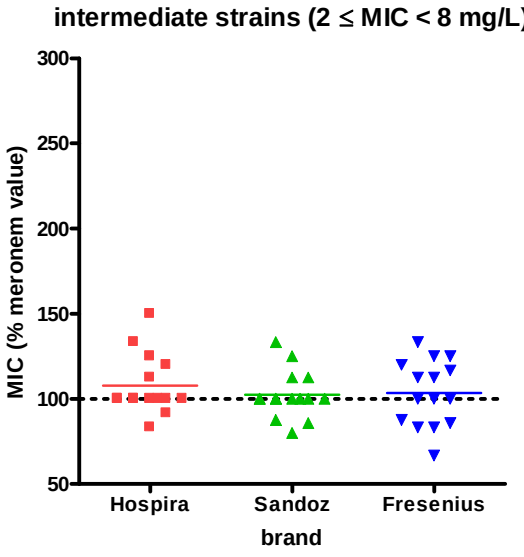
Moet *et al.* Diagnostic Microbiology and Infectious Disease 2009;65: 319–322

MIC determinations (meropenem)

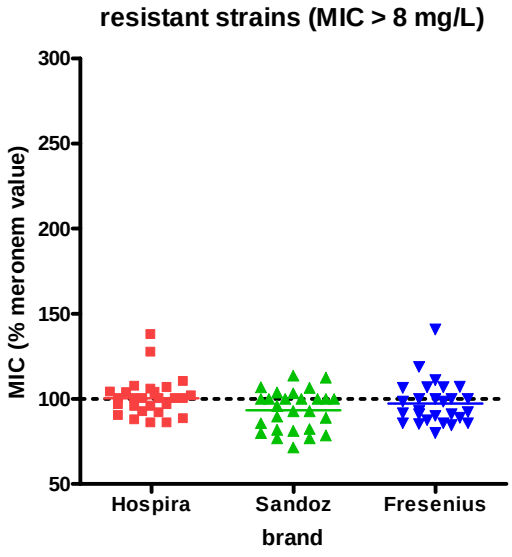
MICs determined by arithmetic dilutions for strains displaying MICs ranging from 0.125 to 128 mg/L (geometric values)



	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

MIC determinations (vancomycin)

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

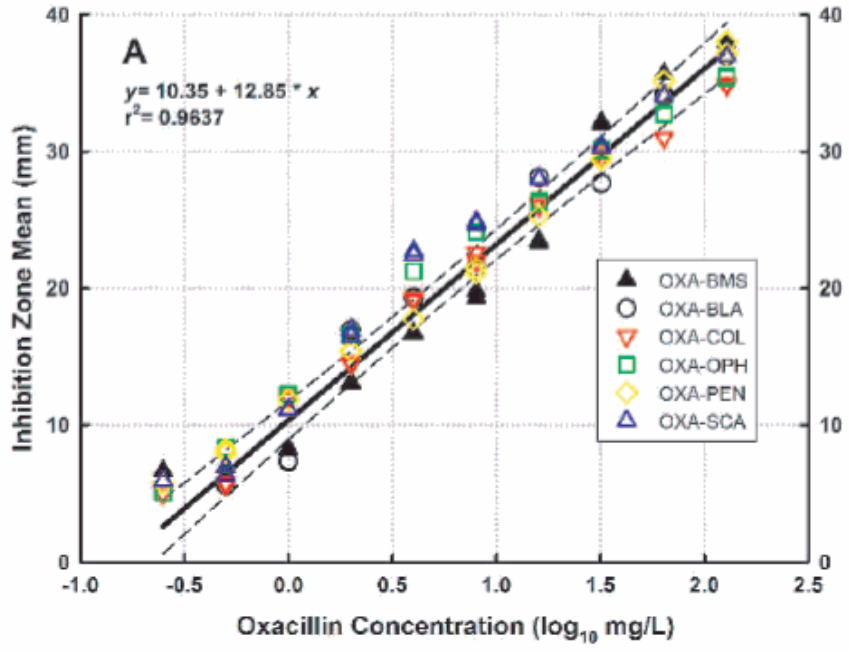
Antibiotic	Pathogen (no.)	No. of generic markers	Nonidentical rate of the MIC value of all generics (mean ± SD)	MIC distribution (%) of the most different generic versus brand name drug						
				1/8	1/4	1/2	1[a]	2	4	8
Vancomycin	MRSA (90)	5	25.00 ± 15.52	–	–	–	54.4	45.6	–	–
Teicoplanin	MRSA (147)	7	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…

Zone diameters (oxacillin)



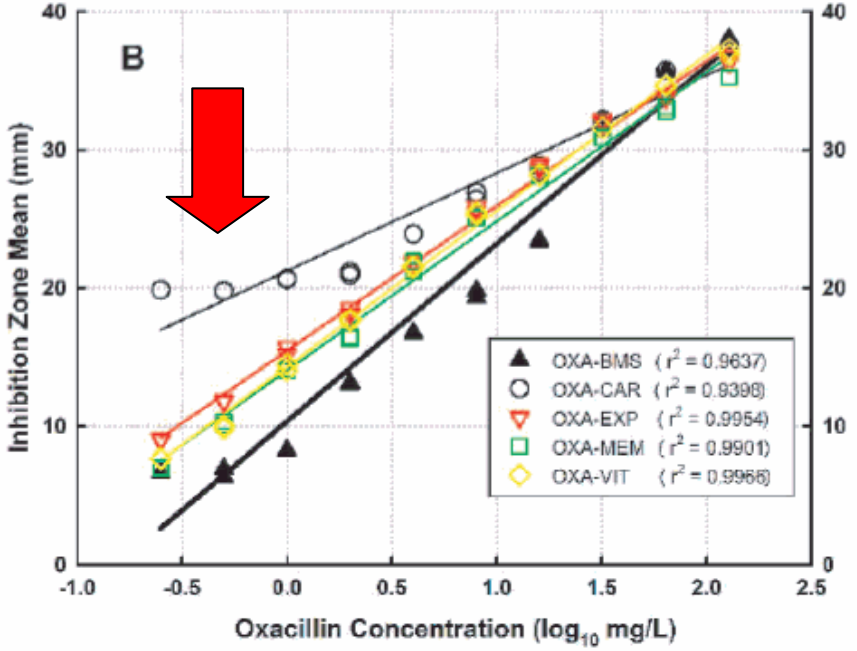


Figure 1 Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay. **A**. The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical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

Post-exposure hetero-resistance (vancomycin)

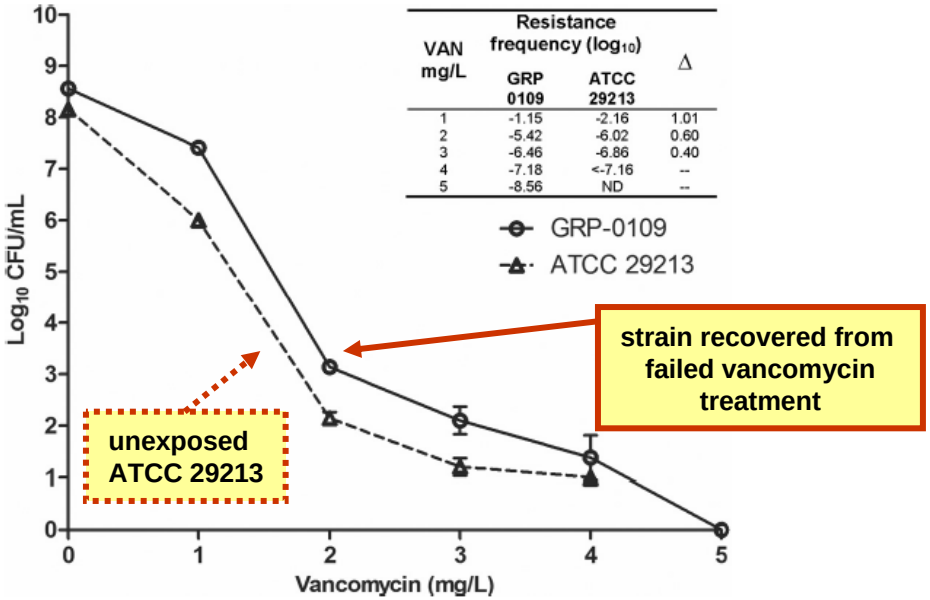
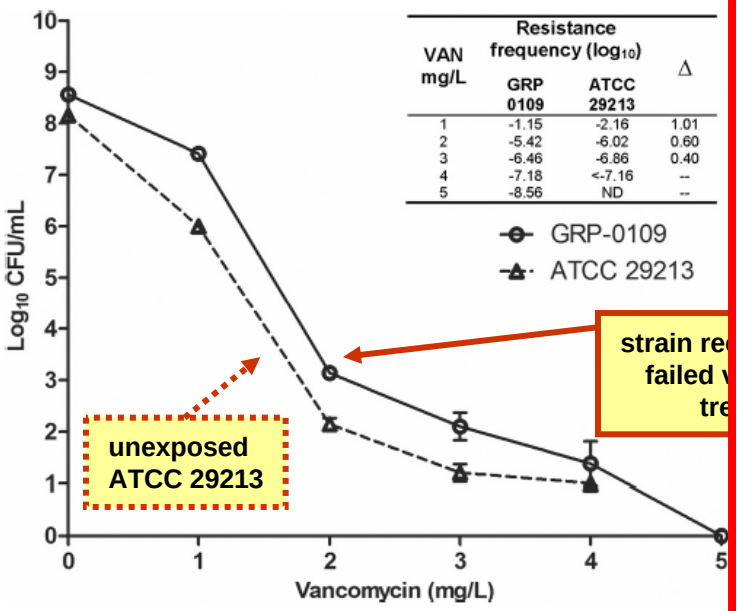


FIG 1 Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin,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

Post-exposure 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 afte being isolated from a patient with persistent bacteremia and unsuccessful ge neric treatment, indicating altered susceptibility in comparison with strai ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomy cin, 4 times more grew at 2 mg/liter, and 2.5 times more grew at 3 mg/lite (resistance frequency data at right).

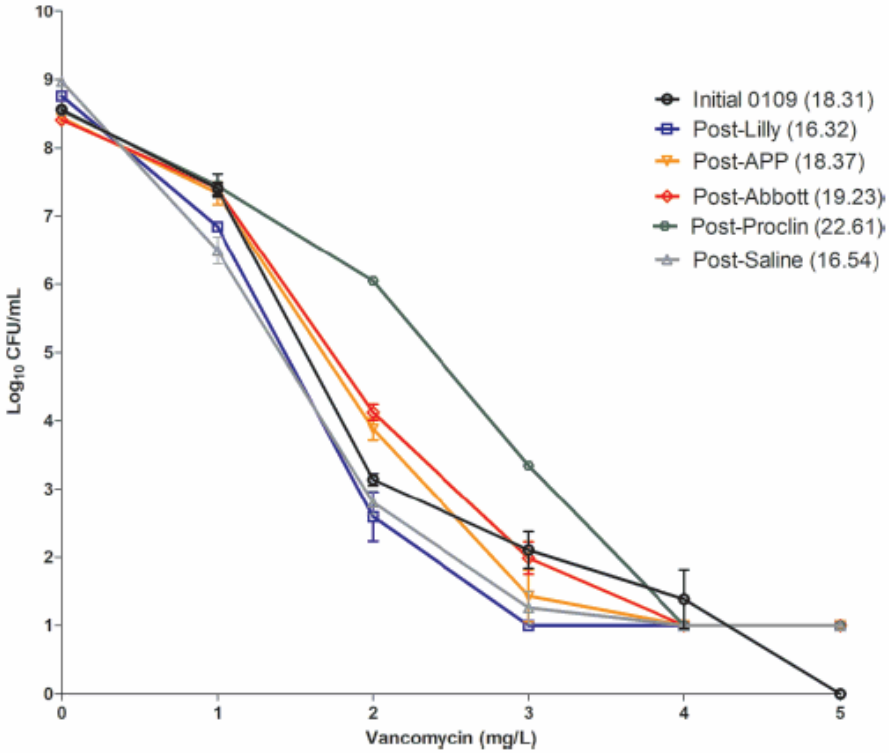


FIG 3 Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction of the less susceptible subpopulations, which is sharply different from three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

Resistance frequencies after *in vivo* exposure (vancomycin)

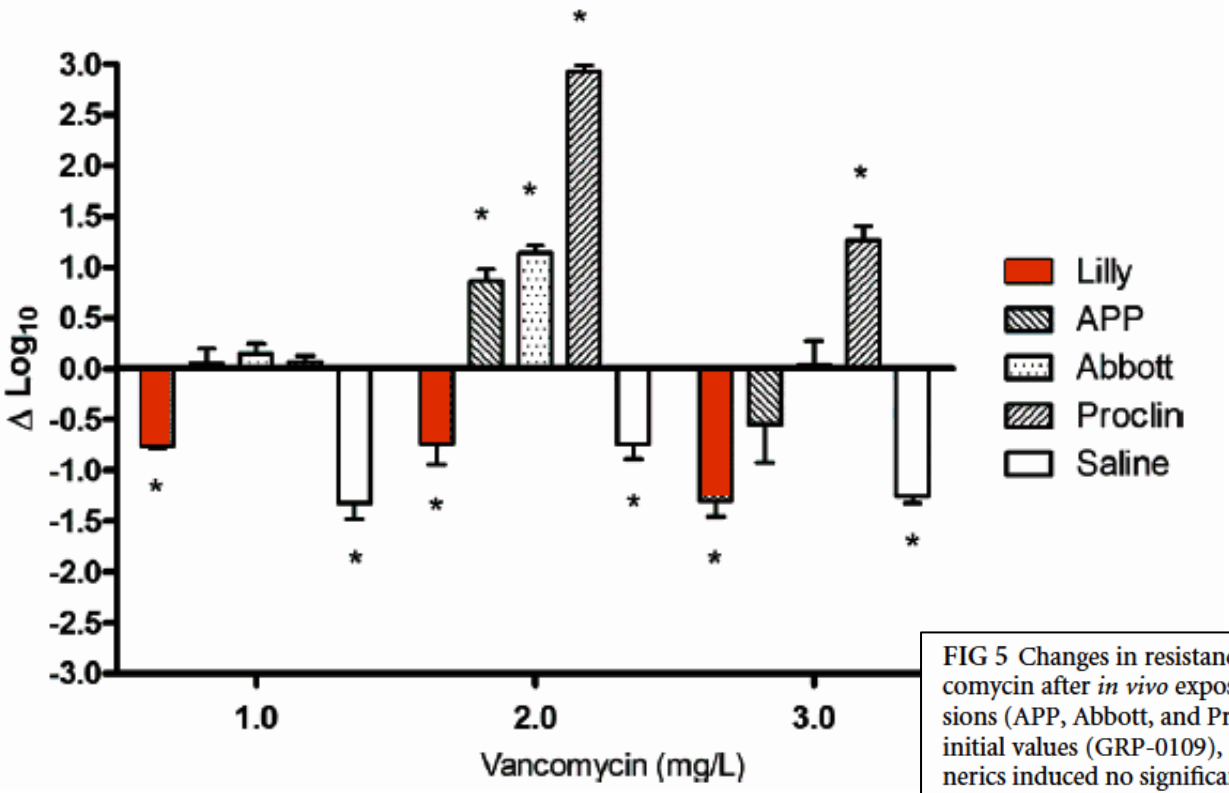


FIG 5 Changes in resistance frequencies (RFs) to 1, 2, and 3 mg/liter of vancomycin after *in vivo* exposure to innovator vancomycin (Lilly), generic versions (APP, Abbott, and Proclin), or sterile saline. At 1 mg/liter, compared to initial values (GRP-0109), Lilly reduced the RFs by almost 10-fold,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

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

What shall we discuss ?

1. The EU and US legal framework
2. What is bioequivalence (for a generic) ?
3. **Microbiological equivalence ?**
   - **potency, heteroresistance, selection of resistance …**
4. **Pharmacodynamic equivalence ?**
   - **PK/PD animal models, clinical alerts …**
5. Dissolution, impurities/instability, true content, "substandard drugs"…
6. Over-consumption of "low cost" antibiotics ?
7. Economic considerations in antibiotic discovery, development and use

Vancomycin: evidence of non-equivalence in a dose-response mouse tight model (*f*AUC/MIC)

Neutropenic tight mouse model

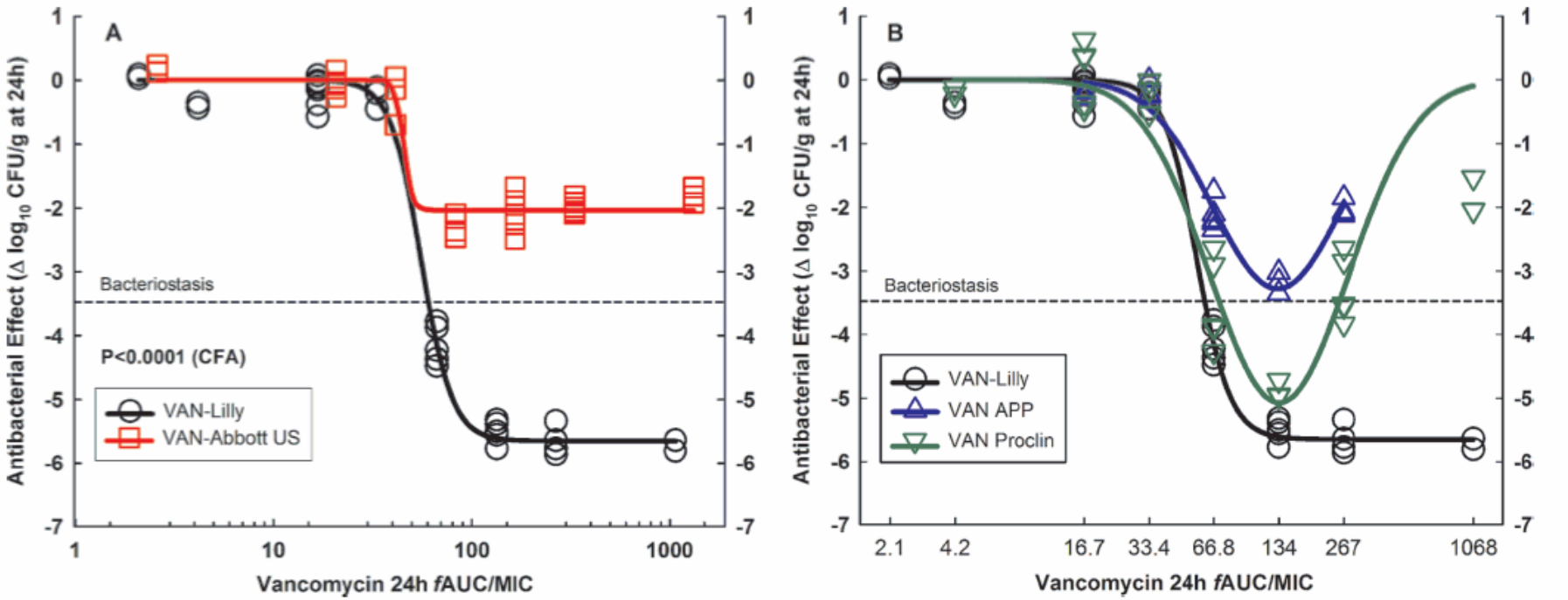


FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per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

Neutropenic tight mouse model

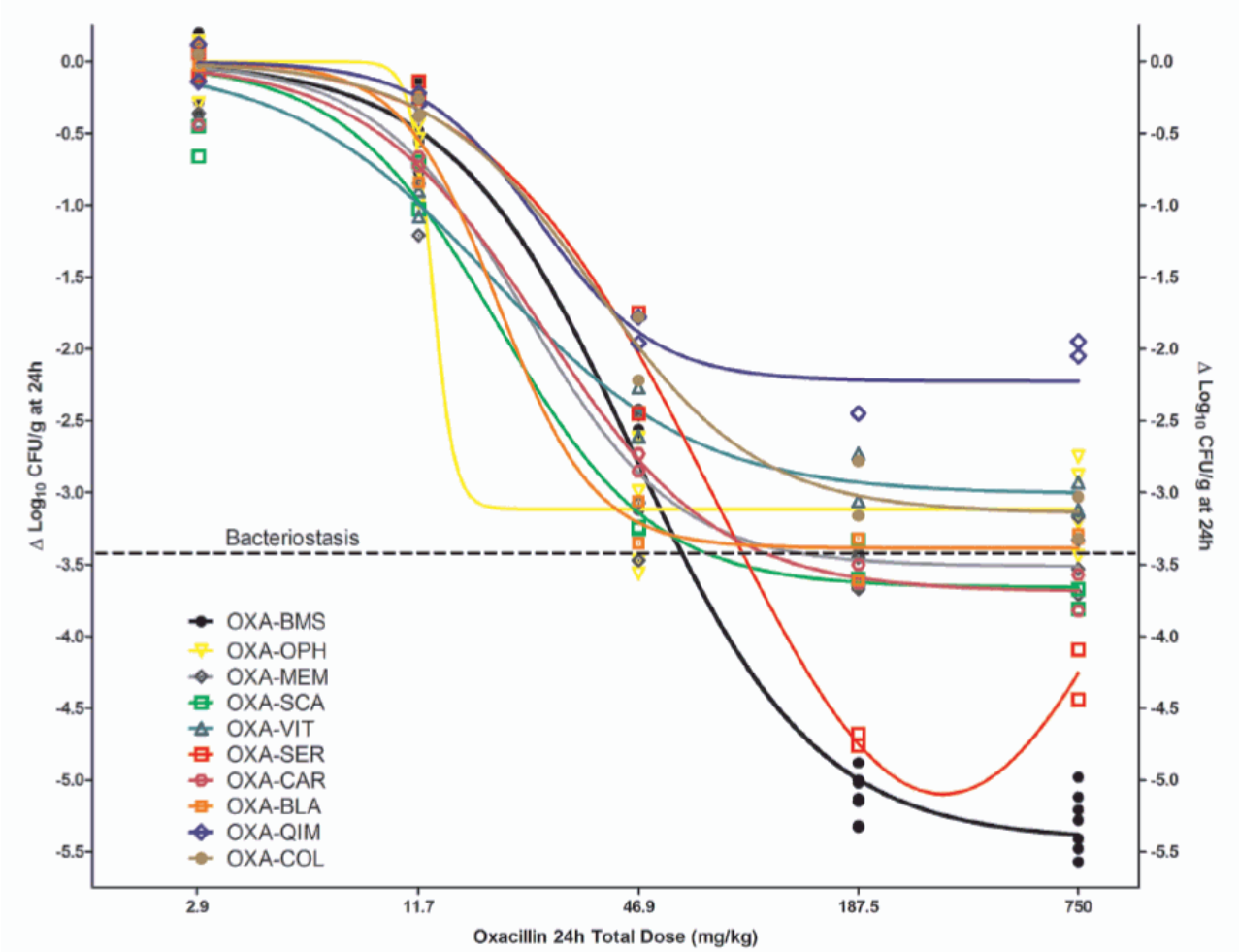


Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless 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 a dose-response mouse thight model (total dose)

Neutropenic tight mouse model

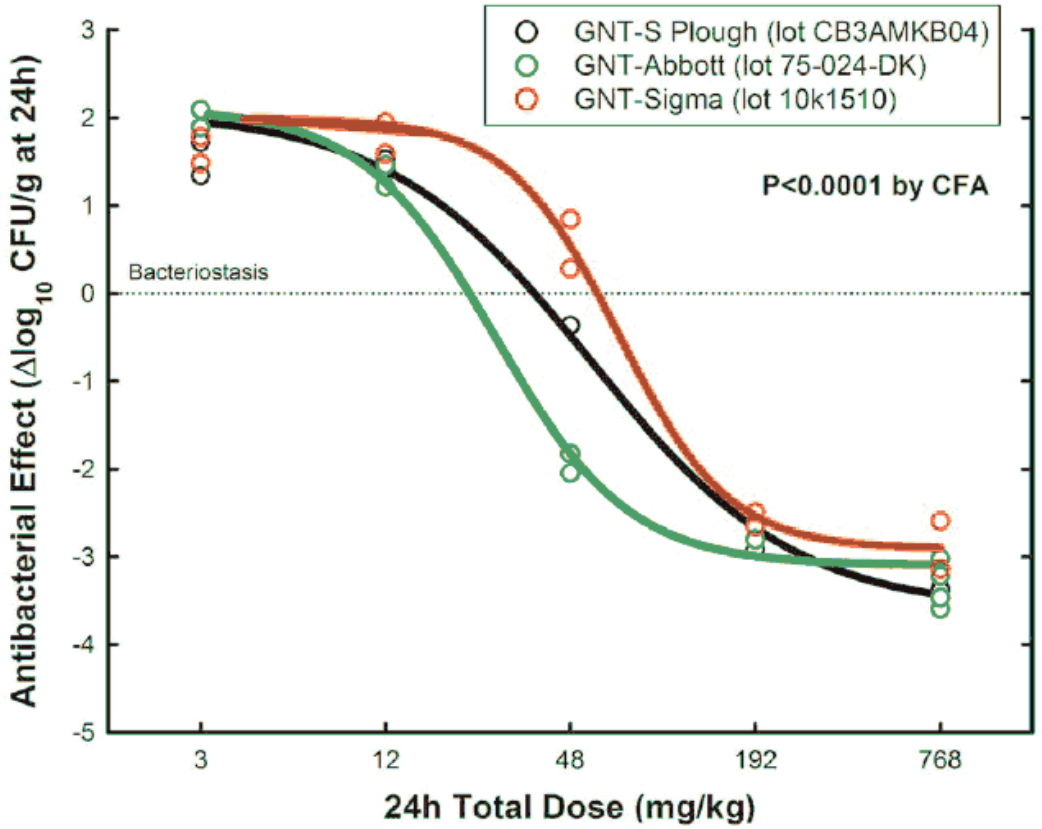


Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence. The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency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

Neutropenic tight mouse model

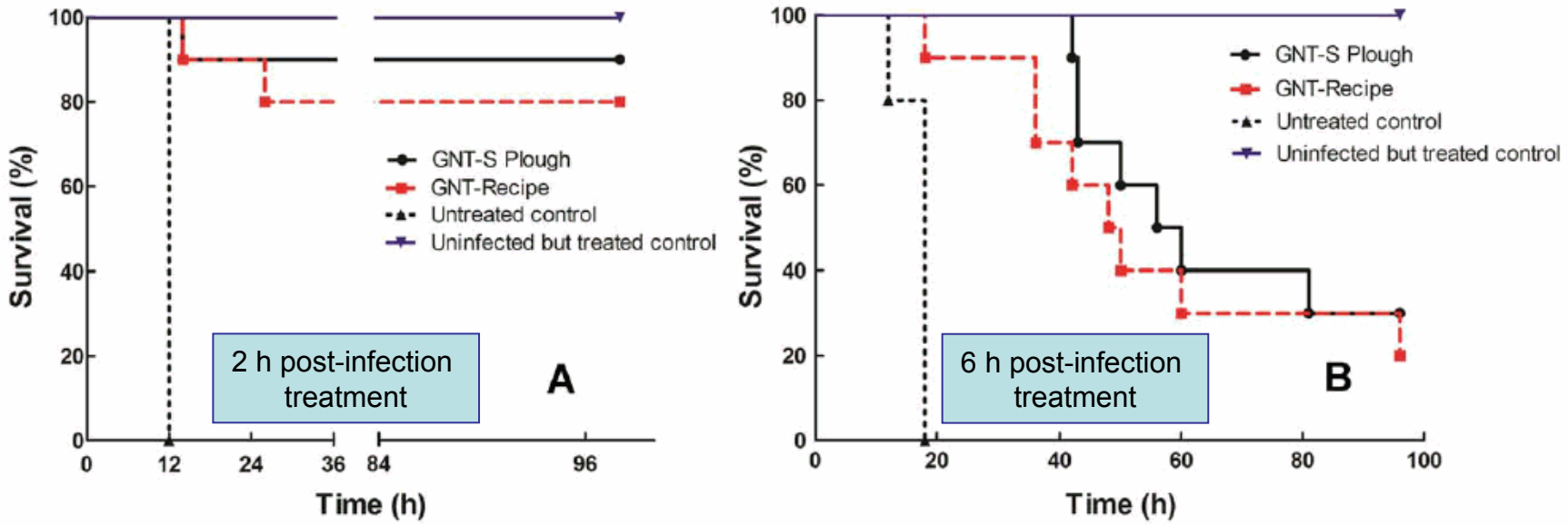


Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect (768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

Vancomycin: complete equivalence in the rabbit endocarditis model

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Comparison of Six Generic Vancomycin Products for Treatment of Methicillin-Resistant *Staphylococcus aureus* Experimental Endocarditis in Rabbits

P. Tattevin,[a,b] A. Saleh-Mghir,[c,d] B. Davido,[c] I. Ghout,[e] L. Massias,[f] C. Garcia de la Maria,[g] J. M. Miró,[g] C. Perronne,[c,d] F. Laurent,[h] A. C. Crémieux[c,d]

Pontchaillou University Hospital, Rennes, France[a]; INSERM U835, Université Rennes 1, Rennes, France[b]; EA 3647, Versailles Saint-Quentin University, Versailles, France[c]; Raymond Poincaré University Hospital, Garches, France[d]; Ambroise Paré University Hospital, Boulogne, France[e]; Bichat-Claude Bernard University Hospital, Paris, France[f]; Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain[g]; National Reference Center for Staphylococci, Hôpital de la Croix Rousse, Lyon, France[h]

Antimicrob Agents Chemother. 2013 Mar;57(3):1157-62. PMID: 23254435; PMCID: PMC3591878.

Vancomycin: complete equivalence in the rabbit endocarditis model

AAC Journals.ASM.org

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Raymond Poincaré University Hospital, Garches, France[d]; Ambroise Paré University Hospital, Boulogne, Franc
Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain[g]; National Reference Center for Staphyloco

Antimicrob Agents Chemother. 2013 Mar;57(3):1157-62. PM

T0: no antibiotic
T1 – T6: generics of vancomycin

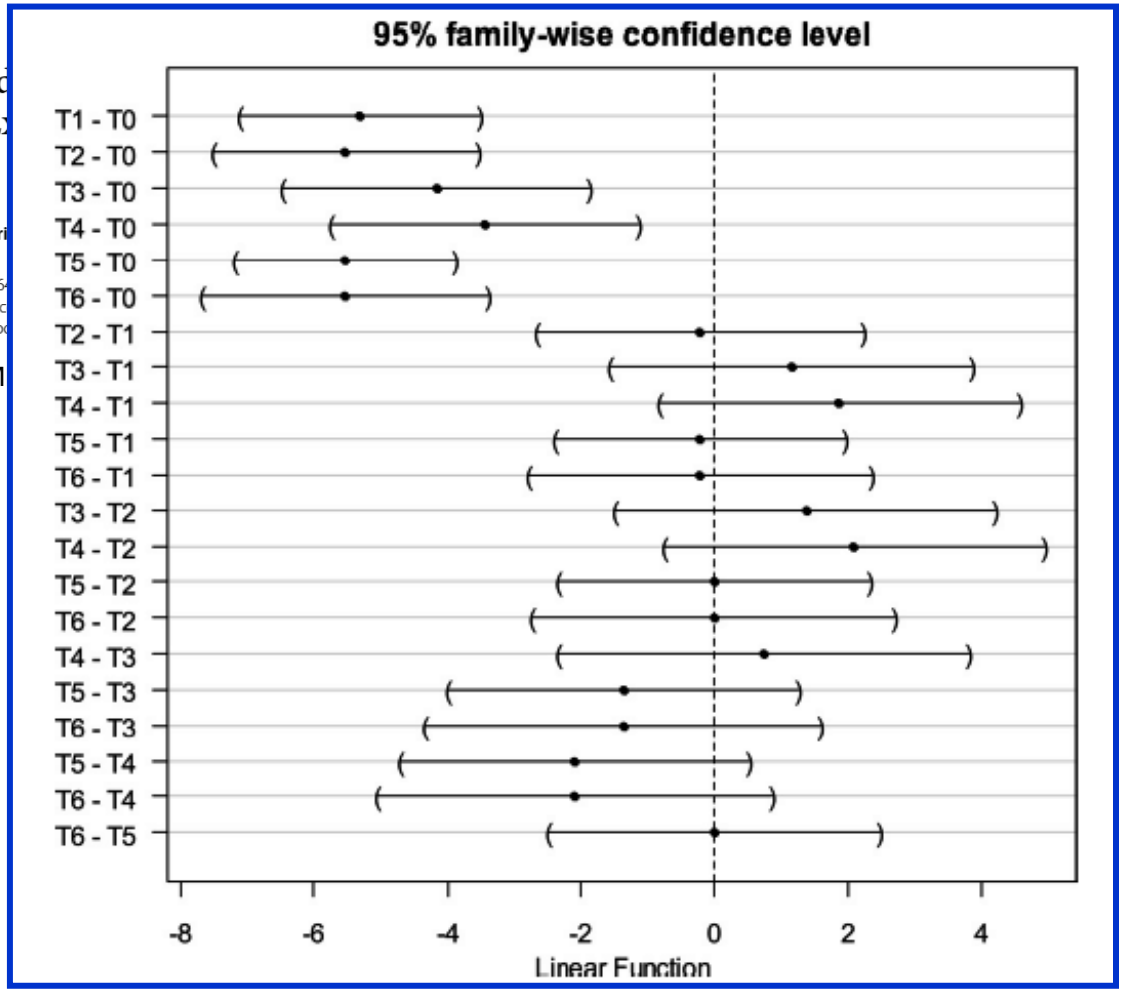

FIG 3 Differences between treatment groups in terms of organism titers in vegetations (log_{10} CFU/g). Dots are mean differences between treatment groups, and parentheses are the upper and lower bounds of their 95% confidence interval. Analysis was performed using the Tukey method, taking into account multiple comparisons, with corrected α risk. Differences between two groups are statistically significant if the confidence interval does not include the zero value. T0, untreated rabbits; T1, vancomycin generic, Mylan; T2, vancomycin generic, Sandoz; T3, vancomycin generic, Teva; T4, vancomycin generic, APP; T5, vancomycin generic, Akorn Strides; T6, vancomycin generic, Hospira.

Differences in terms of no. of organisms in vegetations

Metronidazole: complete equivalence in a dose-response animal model (AUC/MIC)

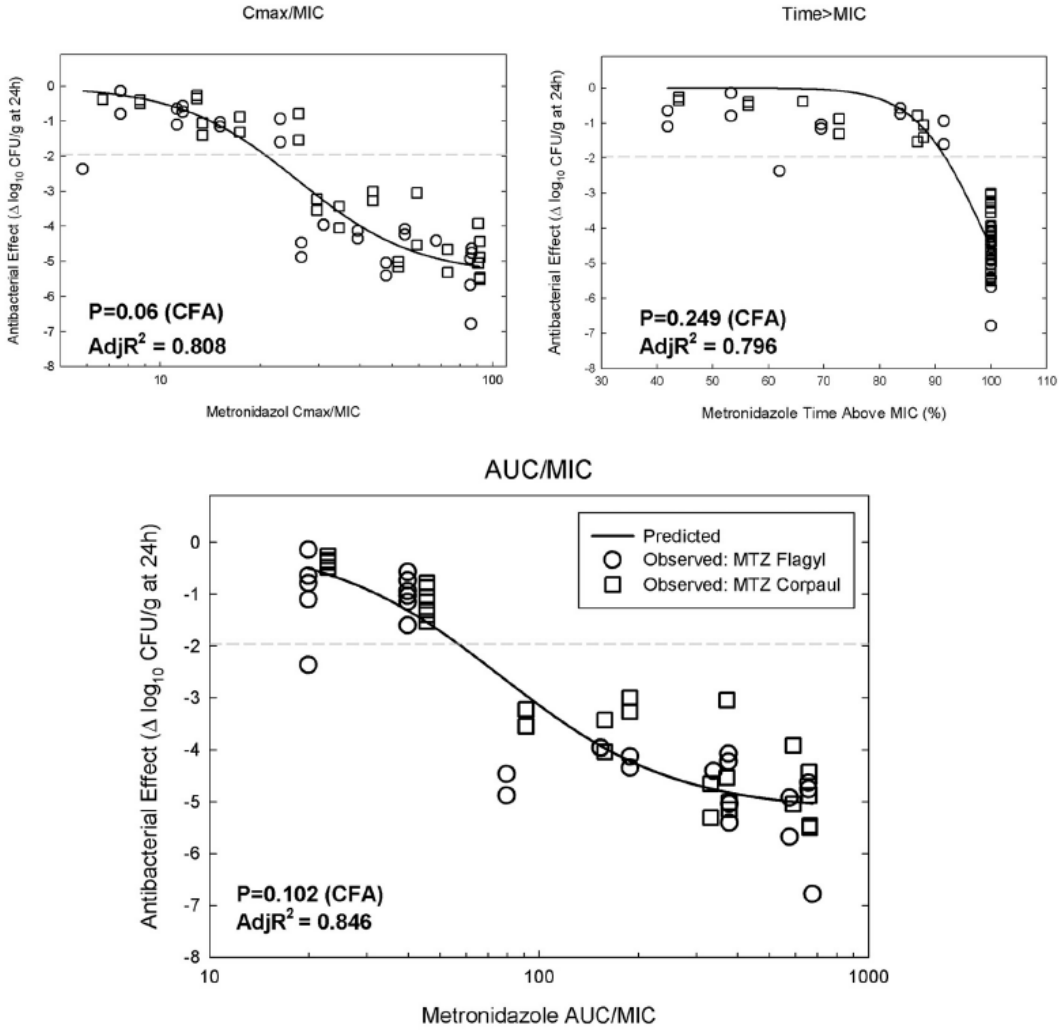

FIG 5 Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *B. fragilis* in a neutropenic mouse thigh anaerobic infection model. Only one curve is depicted because the data belong to a single population despite the fact that they were obtained after treatments of different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

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generic drugs with respect to brand formulation

Luca Gallelli[1], Caterina Palleria[1], Antonio De Vuono[2], Laura Mumoli[1], Piero Vasapollo[2], Brunella Piro[3], Emilio Russo[1]

[1]Department of Health Science, Regional Center on drug information, Mater Domini University Hospital, Italy and Chair of Pharmacology, School of Medicine, University of Catanzaro, [2]Department of General Medicine, ASP Cosenza, [3]Department of Pharmacovigilance, ASP Cosenza, Italy

J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S110-4.

In this case-review, we report the lack of efficacy during treatment with generic formulations of fluoroquinolones and discuss the relative reasons also considering the limitations of this legal approach.

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generi to brand formulation

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[1]Department of Health Science, Regional Center on drug information, Ma School of Medicine, University of Catanzaro, [2]Department of General Mec Cosenza, Italy

J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1)

In this case-review treatment with gene discuss the relative r this legal approach.

CONCLUSION

In conclusion, the use of generic drugs could be related with an increased days of disease (time to relapse) or might lead to a therapeutic failure; on the other hand, a higher drug concentration might expose patients to an increased risk of dose-dependent side-effects. Overall, it is advisable to well evaluate the effects of generic formulations during the therapeutic treatment.

In agreement with Manning and Smith,[41] it is necessary to underline the importance that clinician's change their attitude toward pharmacovigilance and post-marketing surveillance systems, which can help to identify the lack of efficacy during the treatment with generic formulations.

ACKNOWLEDGMENTS

The Italian Drug Agency (Agenzia Italiana del Farmaco) is kindly acknowledged for its financial and technical support.

What shall we discuss ?

1. The EU and US legal framework
2. What is bioequivalence (for a generic) ?
3. **Microbiological equivalence ?**
   - **potency, heteroresistance, selection of resistance …**
4. Pharmacodynamic equivalence ?
   - PK/PD animal models, clinical alerts …
5. **Dissolution, impurities/instability, true content, "substandard drugs"…**
6. Over-consumption of "low cost" antibiotics ?
7. Economic considerations in antibiotic discovery, development and use

Dissolution of amoxicillin

Evaluation and comparison of in-vitro dissolution profiles for different brands of amoxicillin capsules

*Kassaye L, Genete G

Food and Medicine quality Control Laboratory, Food, Medicine and Healthcare Administration and Control Authority, Ethiopia, Addis Ababa

Afr Health Sci. 2013 Jun;13(2):369-75. doi: 10.4314/ahs.v13i2.25. PMID: 24235938; PMCID: PMC3824474.

Table 1: Samples of amoxicillin capsules

Samples code	Country of origin	Mfg date	Exp date
Amoxil™	United Kingdom	06/2009	06/2014
A	India	09/2009	08/2012
B	India	10/2009	09/2012
C	Cyprus	07/2009	07/2014
D	Ethiopia	03/2010	03/2014
E	India	08/2009	07/2012
F	Ethiopia	11/2009	11/2014
G	India	03/2009	02/2013
H	India	12/2009	11/2011

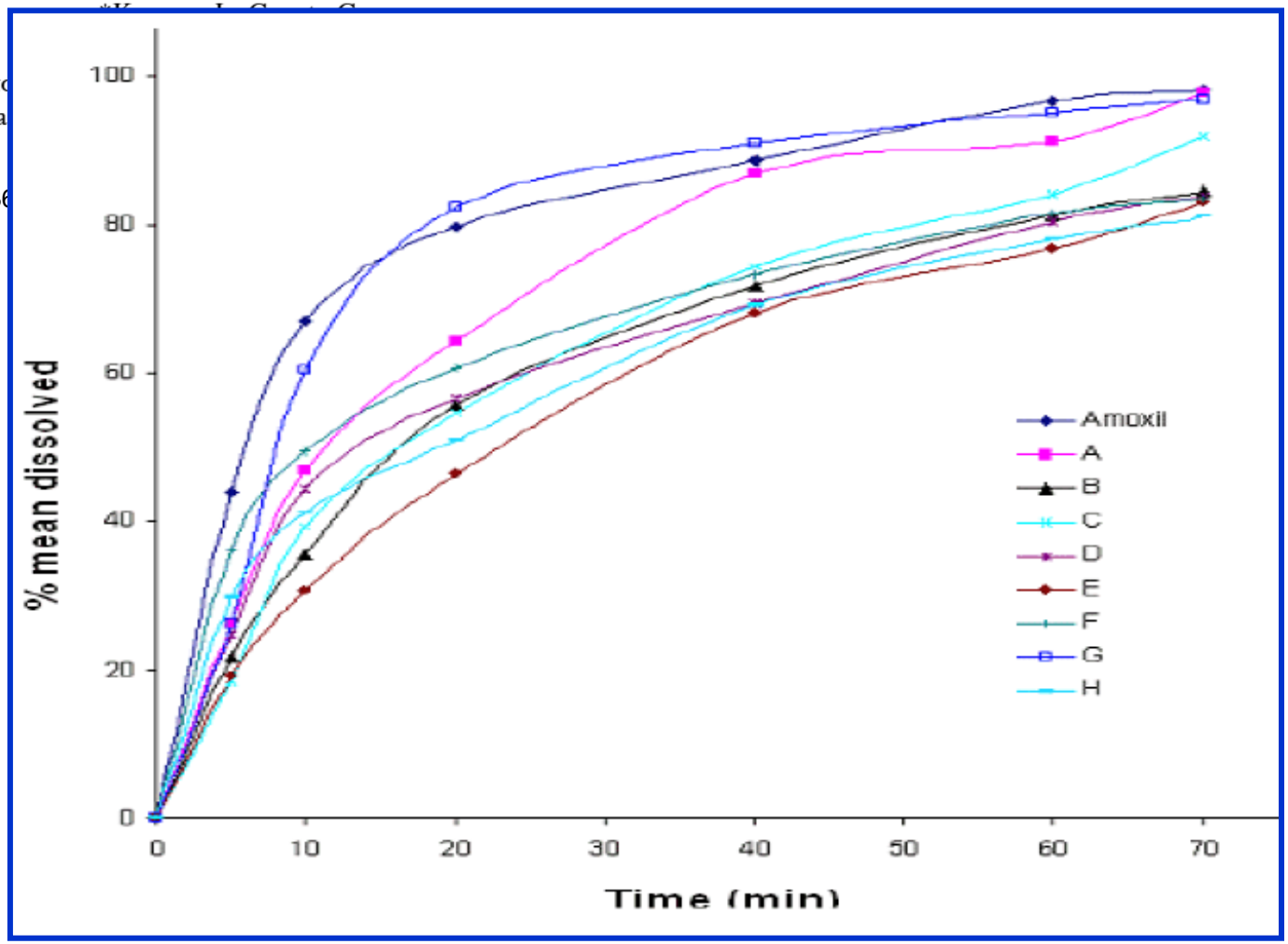
The label claim for all samples is amoxicillin 500 mg

Dissolution of amoxicillin

Evaluation and comparison of in-vitro dissolution profiles for different brands of amoxicillin capsules

Food and Medicine quality Contro
Authority, Ethiopia, Addis Ababa

Afr Health Sci. 2013 Jun;13(2):36



Dissolution of meropenem (Japan)

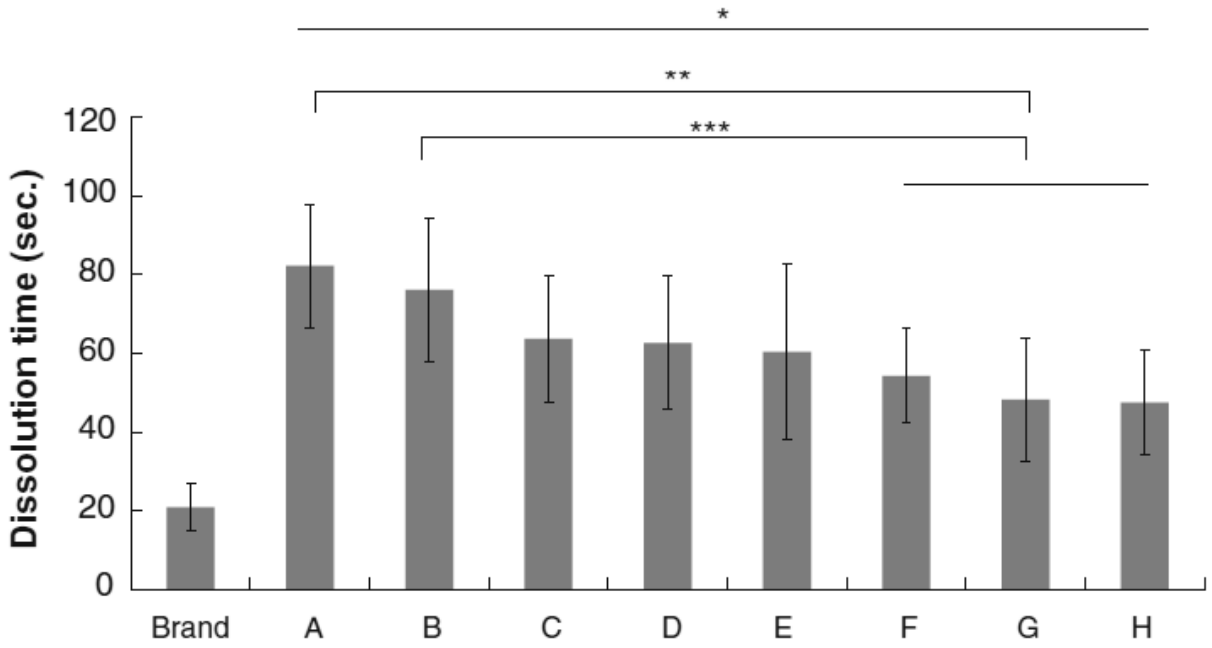


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

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

Crystals size of meropenem (Japan)

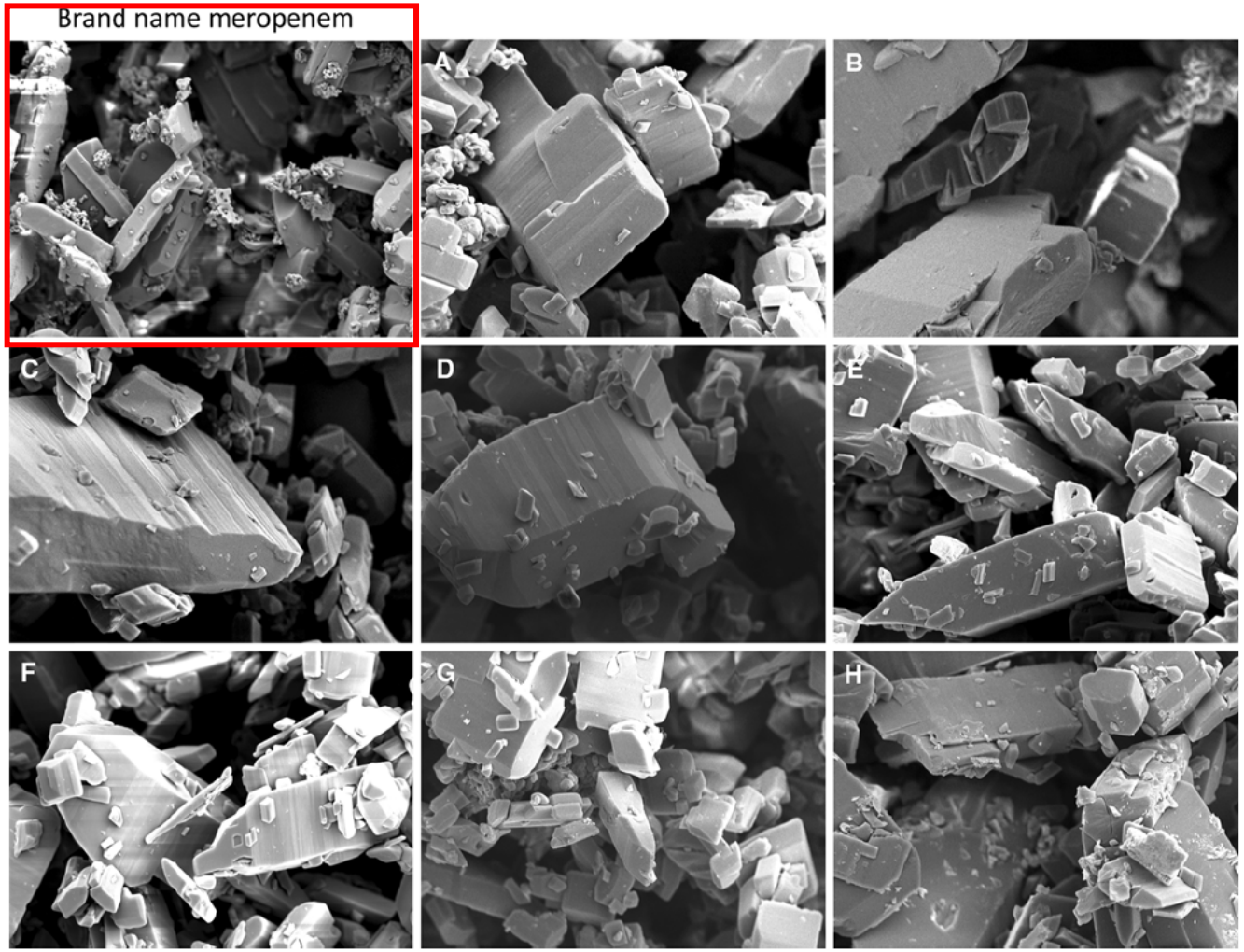
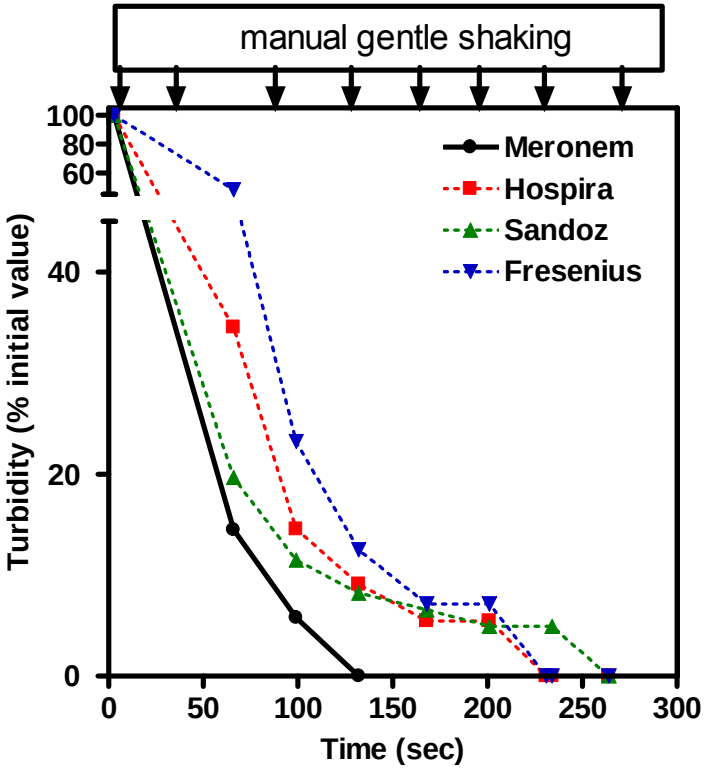


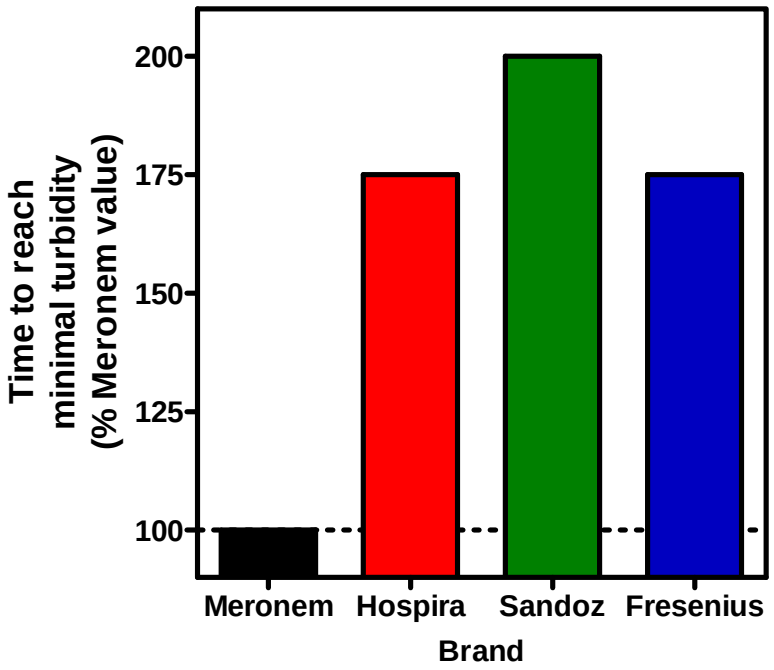
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

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

Dissolution of meropenem in Belgium

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





Van Bambeke *et al*., in preparation

Dissolution of meropenem in Belgium

Drug concentration : 50 mg/mL (~ solution used for infusion)
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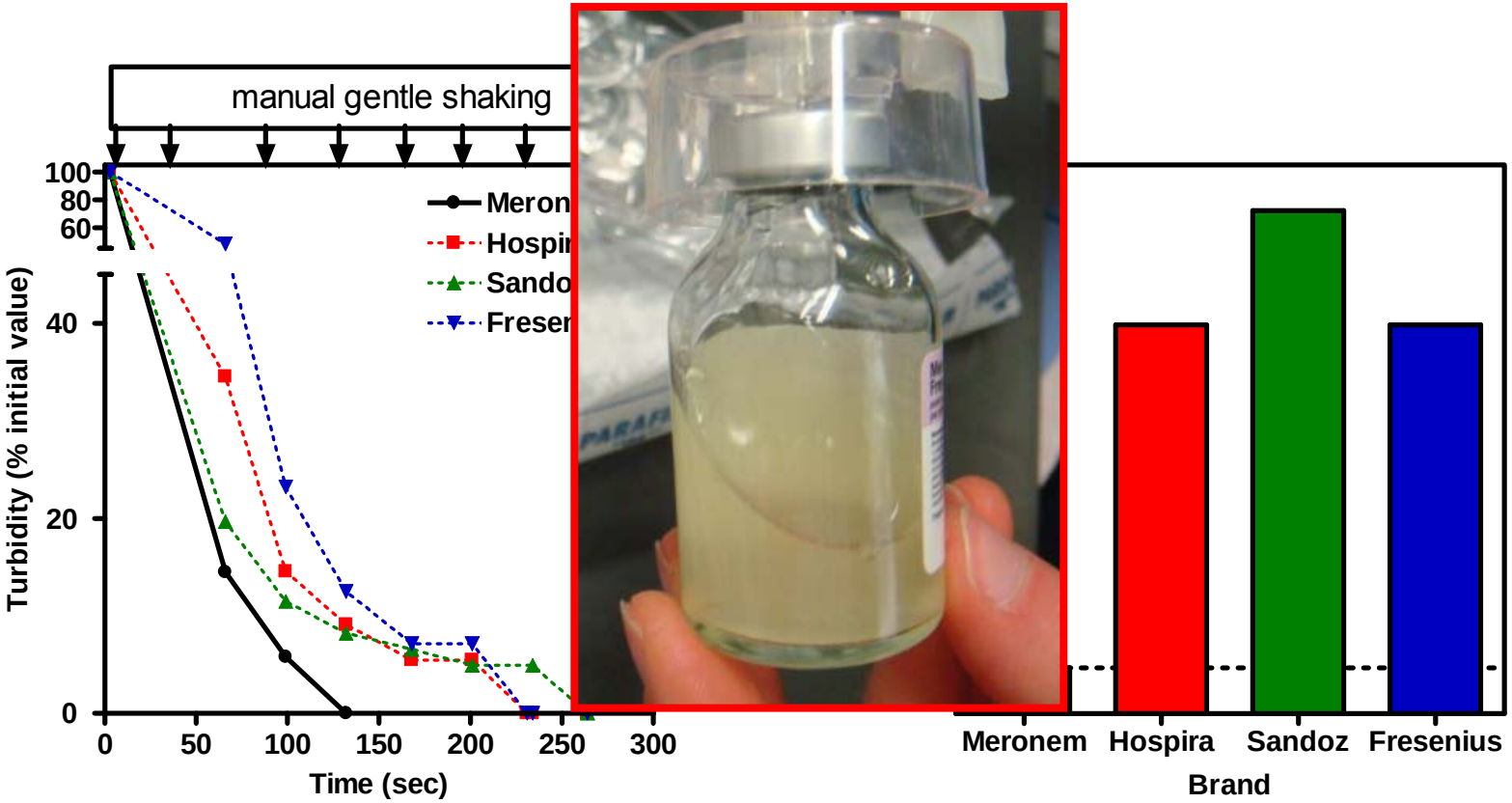
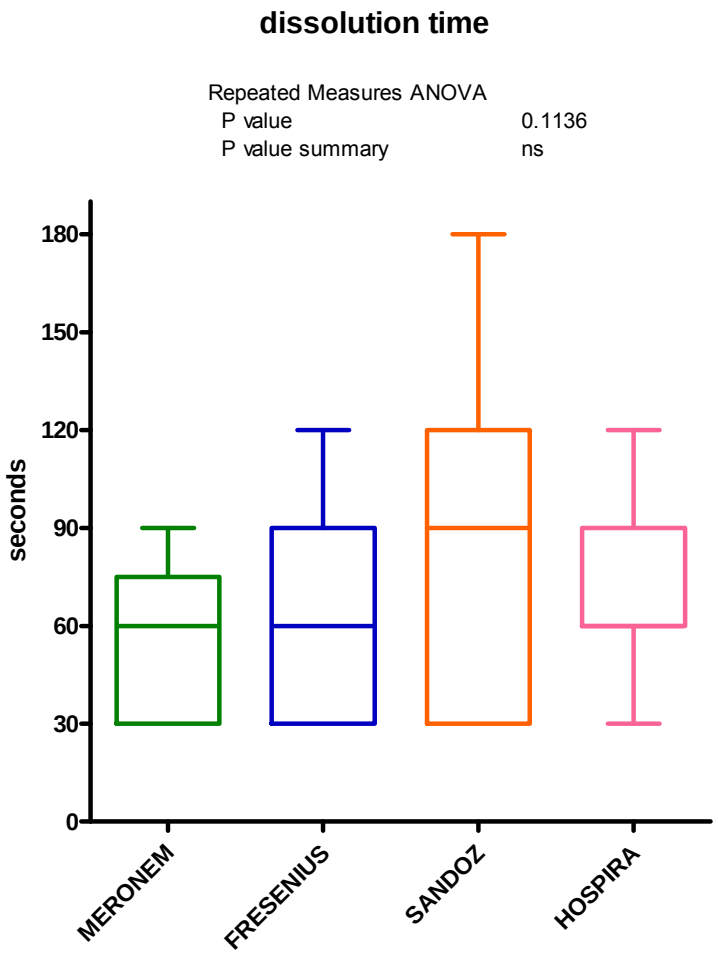
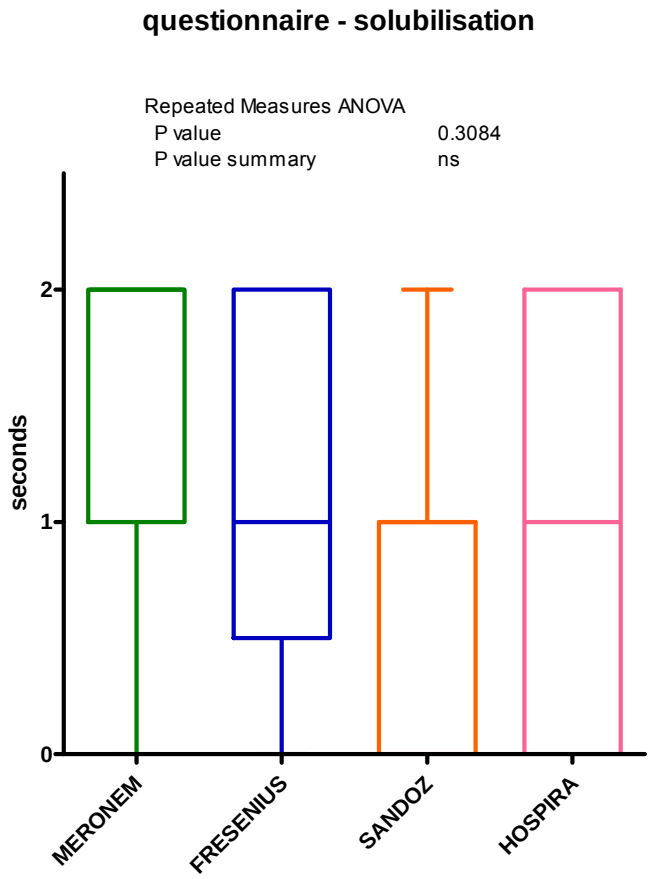


Van Bambeke *et al*., in preparation

Are nurses happy with generic meropenem (in Belgium) ?





Van Bambeke *et al*., in preparation

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

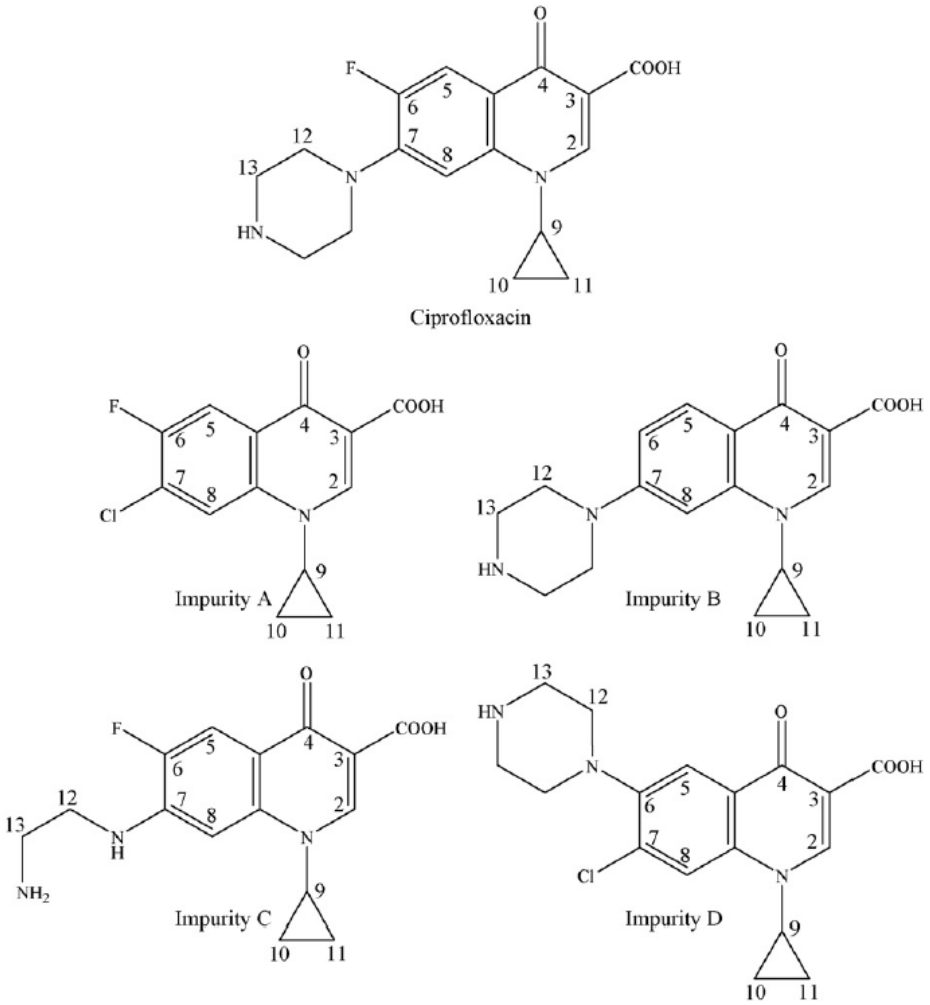
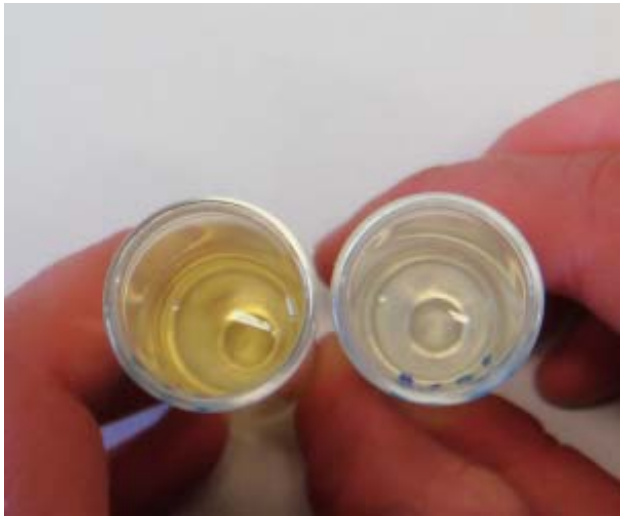
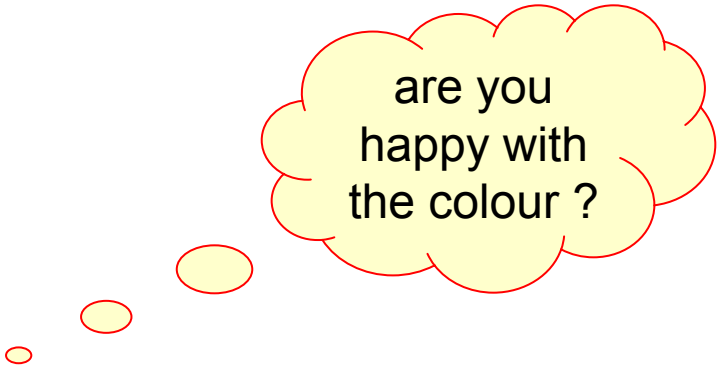


Fig. 1. Structure of ciprofloxacin and its main impurities.

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

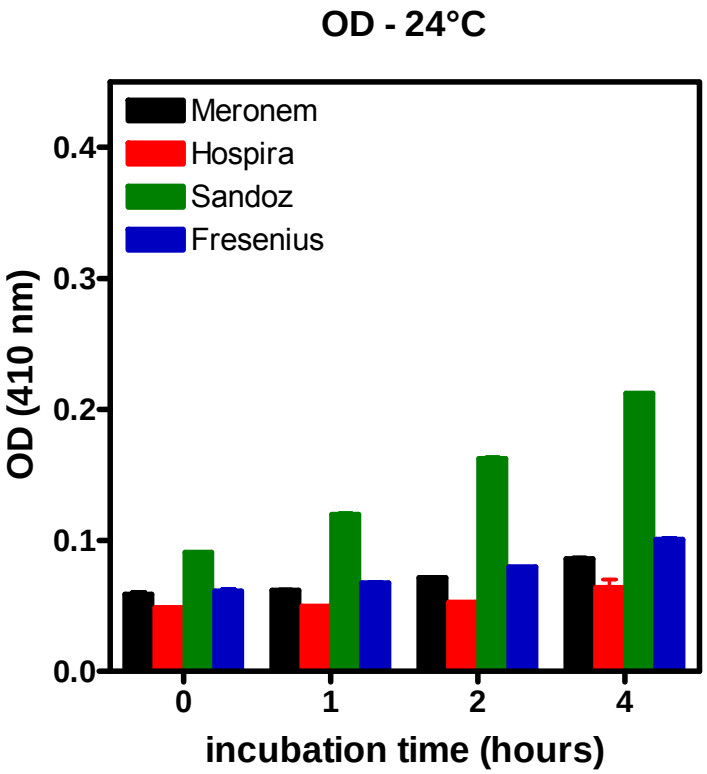
Instability and release of coloured compounds with meropenem

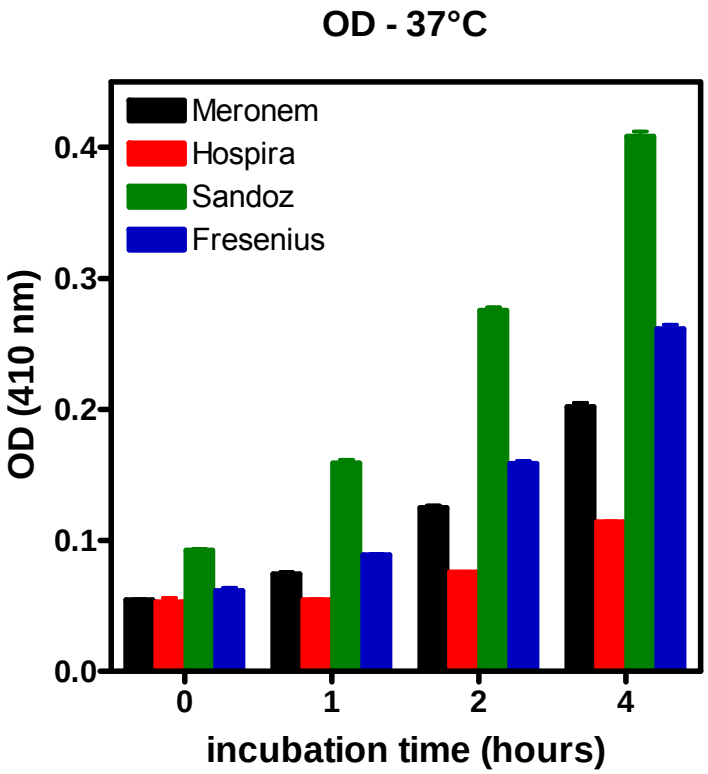




Van Bambeke *et al*., in preparation

Impurities in meropenem: coloured compounds





Van Bambeke *et al*., in preparation

Substandard drugs in the world ?

Figure 1.

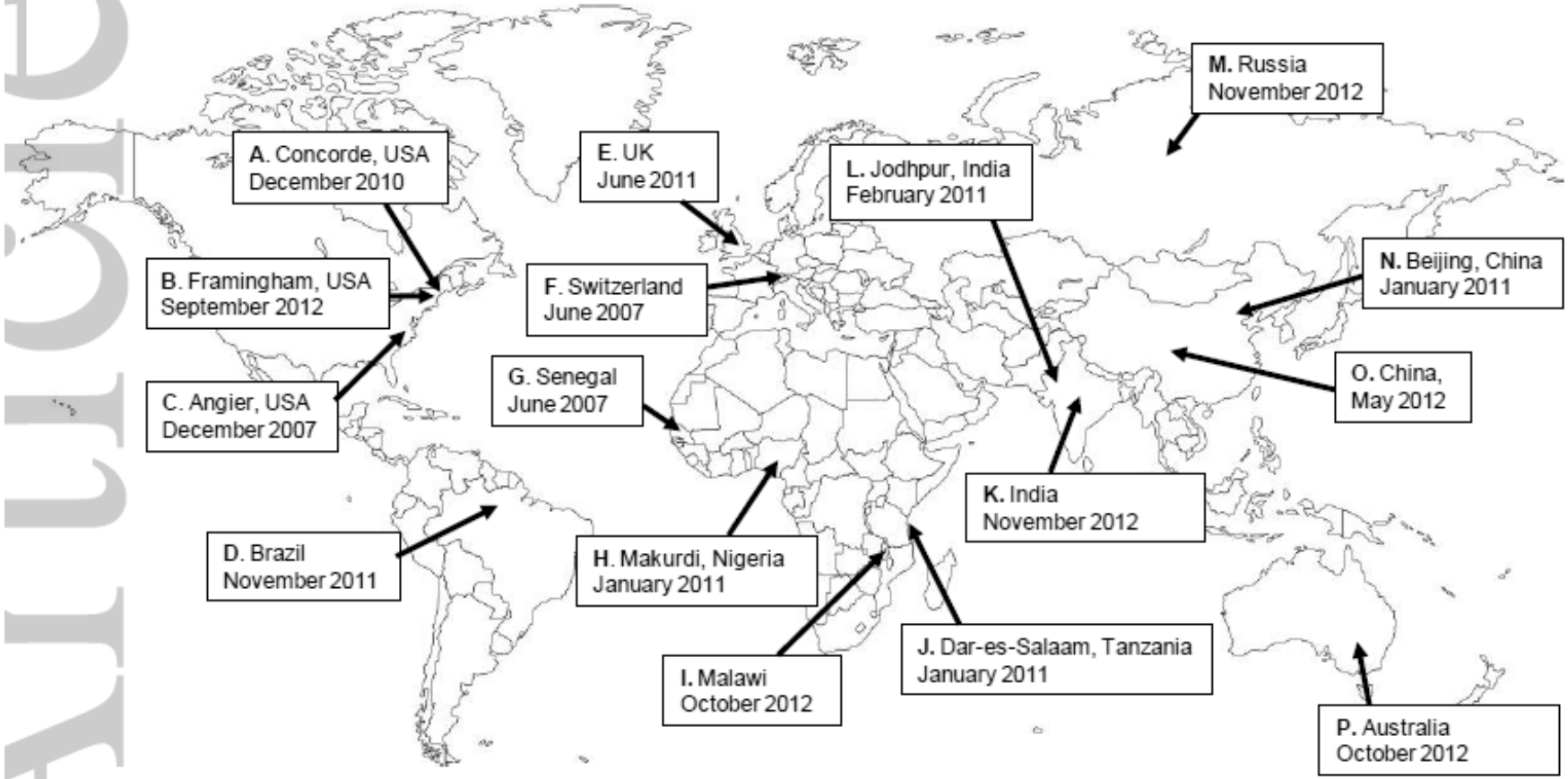


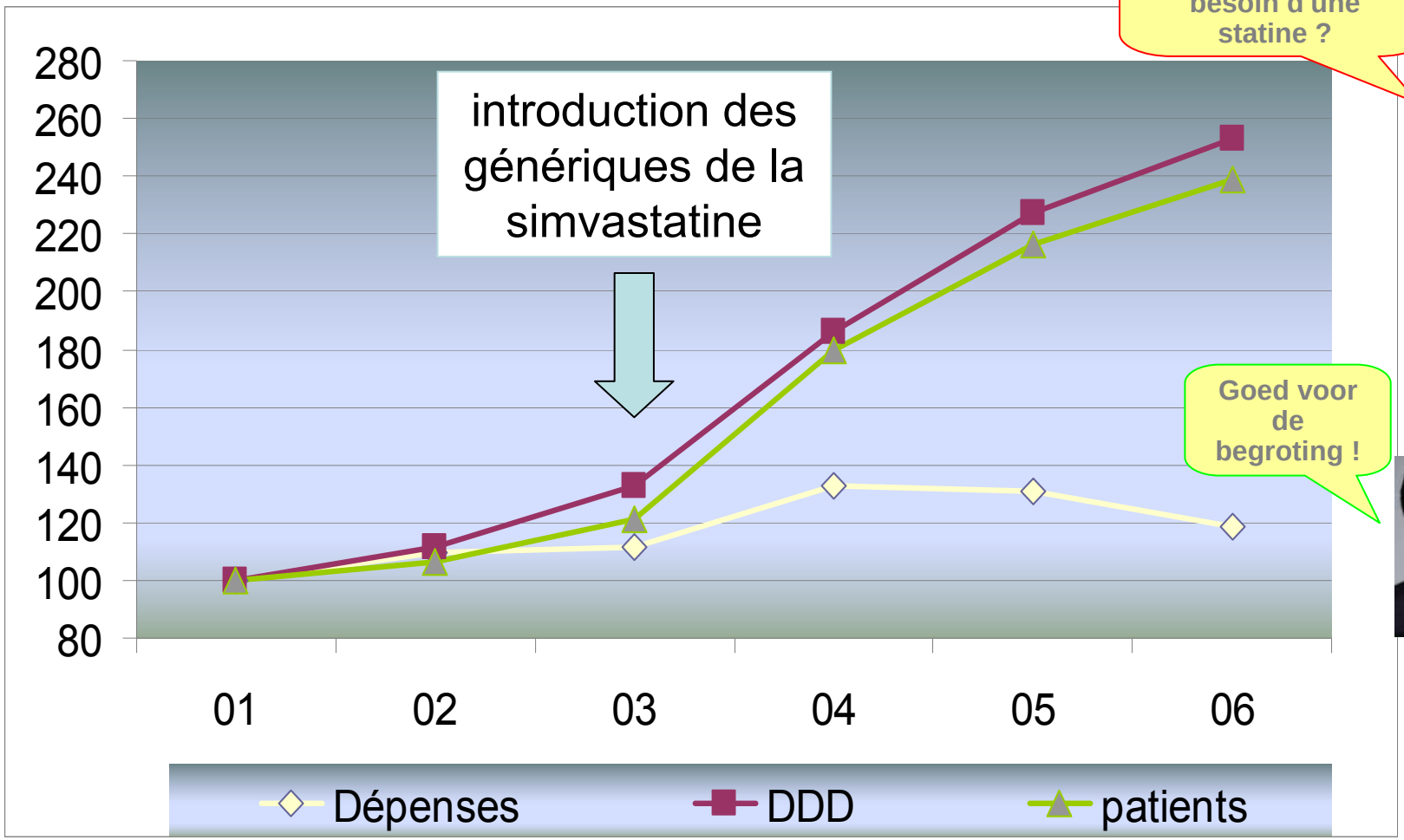
Figure 1. Examples of recent accounts of substandard drugs around the world

Johnston & Holt. Substandard drugs: a potential crisis for public health.
Br J Clin Pharmacol. 2013 Nov 29. doi: 10.1111/bcp.12298. [Epub ahead of print] PubMed PMID: 24286459.

What shall we discuss ?

1. The EU and US legal framework
2. What is bioequivalence (for a generic) ?
3. **Microbiological equivalence ?**
   - **potency, heteroresistance, selection of resistance …**
4. Pharmacodynamic equivalence ?
   - PK/PD animal models, clinical alerts …
5. Dissolution, impurities/instability, true content, "substandard drugs"…
6. **Over-consumption of "low cost" antibiotics ?**
7. Economic considerations in antibiotic discovery, development and use

A Journey to the statins in Belgium ….



Source: INAMI / RIZIV (Balgian National Institute for Sickness and Invalidity Insurance)

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

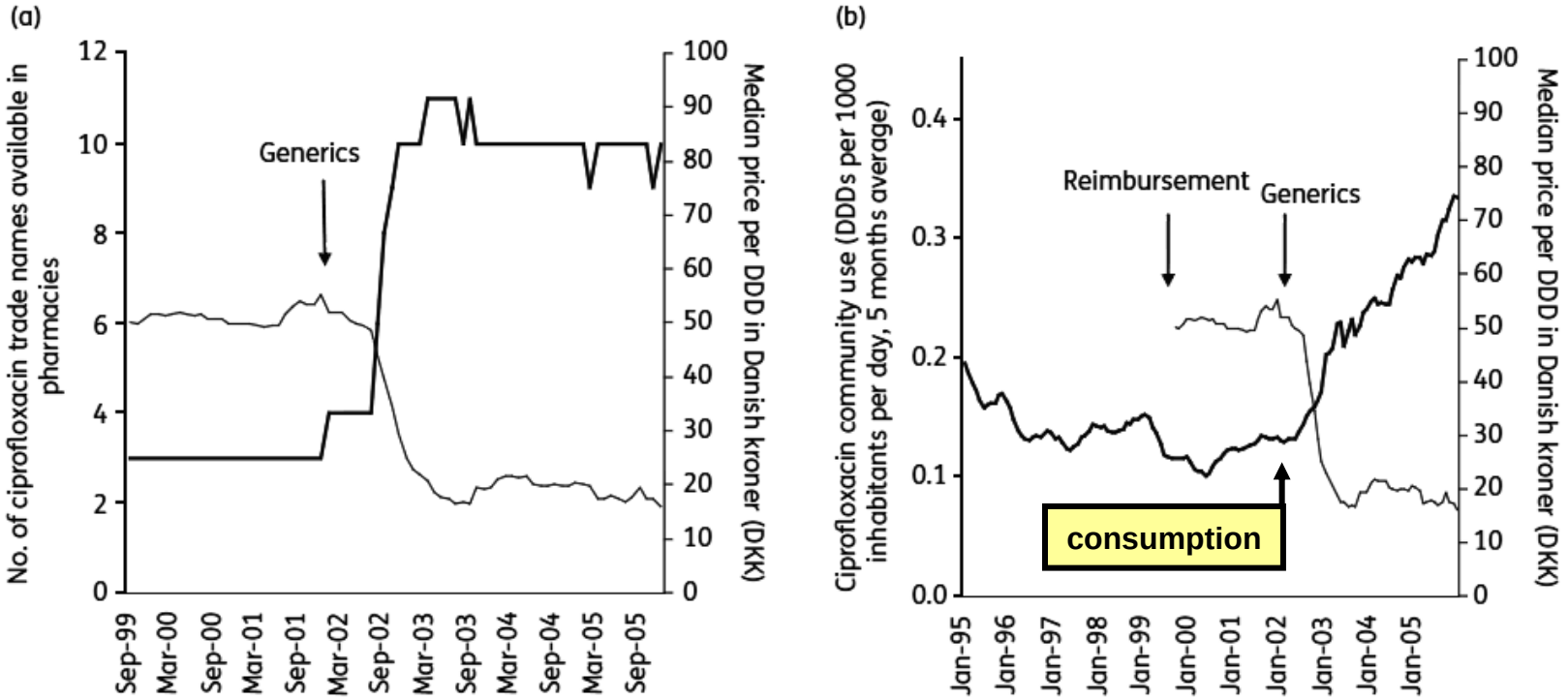
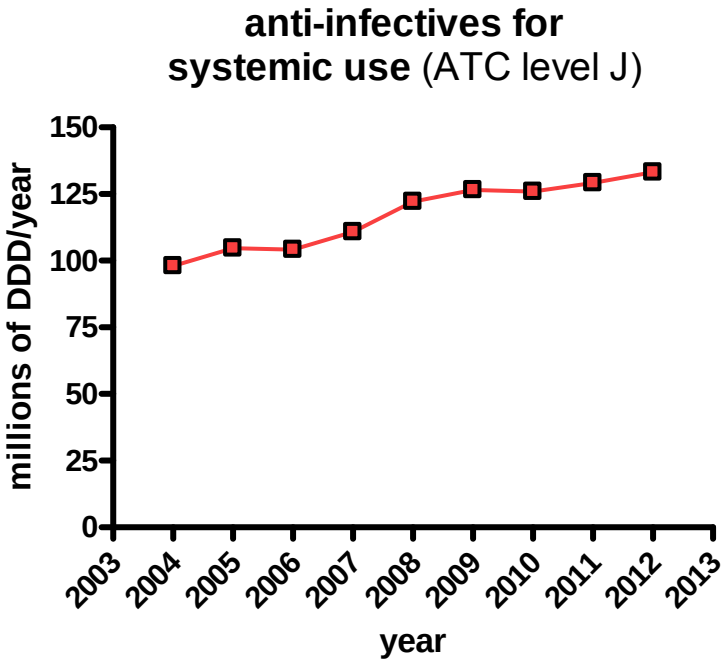


Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin.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

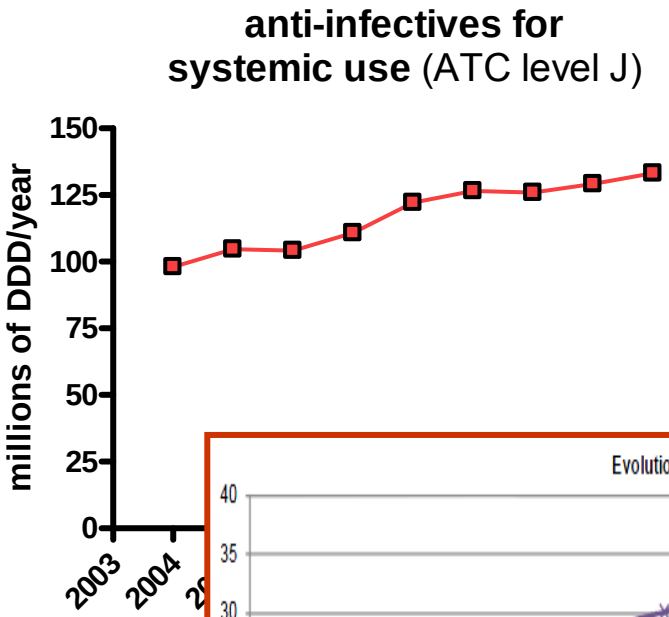
Antibiotic reimbursements in Belgium



Source:
Belgian National Institute for Sickness and Invalidity Insurance
"*Tableaux de bord pharmaceutiques: Délivrances pharmaceutiques dans le secteur ambulant – année 2012*"

http://www.inami.be/drug/fr/statistics-scientific-information/pharmanet/pharmaceutical-tables/pdf/2012/tables2012.pdf
Last accessed: 20/01/2014

Antibiotic reimbursements in Belgium



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Belgian National Institute for Sickness and Invalidity Insurance
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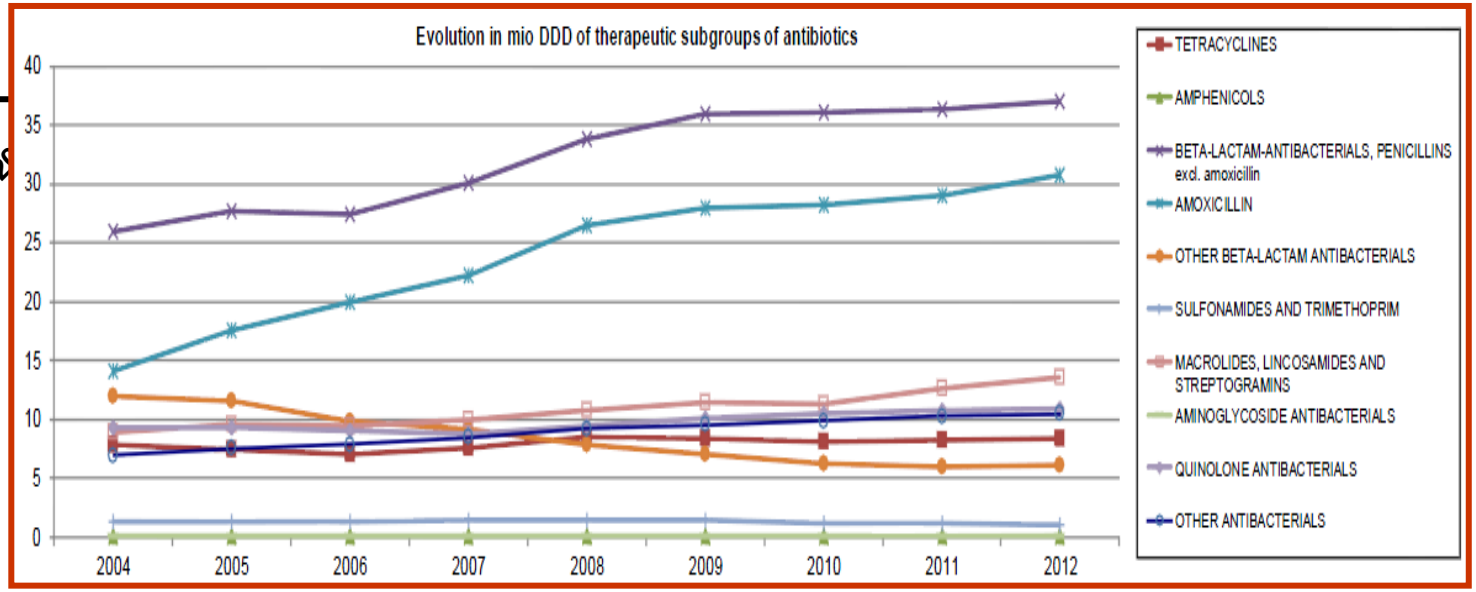
http://www.inami.be/drug/fr/statistics-scientific-information/pharmanet/pharmaceutical-tables/pdf/2012/tables2012.pdf
Last accessed: 20/01/2014



A recent economic US study about "free of charge antibiotics"

HEALTH ECONOMICS
Health Econ. (2013)
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.3008

ARE PHYSICIANS' PRESCRIBING DECISIONS SENSITIVE TO DRUG PRICES? EVIDENCE FROM A FREE-ANTIBIOTICS PROGRAM†

SHANJUN LI[a,*] and RAMANAN LAXMINARAYAN[b,c]

[a]*Dyson School of Applied Economics and Management, Cornell University, Ithaca, NY, USA*
[b]*Center for Disease Dynamics, Economics & Policy, Washington DC, USA*
[c]*Princeton University, Princeton, NJ, USA*

A "natural experiment" in which Meijer, a popular Midwestern retail chain, offered 14-day supplies of certain generic oral antibiotics **free of charge to customers with prescriptions** from October 2006 (about 2 millions prescriptoins analayzed from 2004 trough 2008)

- We find that the program increased the filled prescriptions of covered (free) antibiotics while reducing those of not-covered (paid) antibiotics, **with an increase in overall antibiotic prescriptions.**

The situation may be worse in veterinary medicine

JOURNAL OF
Veterinary Pharmacology and Therapeutics

J. vet. Pharmacol. Therap. **36**, 420–424. doi: 10.1111/jvp.12061. REVIEW ARTICLE

The consequences of generic marketing on antibiotic consumption and the spread of microbial resistance: the need for new antibiotics

P.-L. TOUTAIN &
A. BOUSQUET-MELOU

UMR 1331 Toxalim INRA, INPT– Ecole Nationale Veterinaire de Toulouse, Toulouse Cedex, France

The situation may be worse in veterinary medicine

JOURNAL OF
Veterinary Pharmacology and Therapeutics

J. vet. Pharmacol. Therap. **36**, 420–424. doi: 10.1111/jvp.12061. REVIEW ARTICLE

The consequences of generic marketing on antibiotic consumption and the spread

P.-L. TOUTAIN
A. BOUSQUET

- In France, introduction of generics of fluoroquinolones increased their use by 30% in turkey (n=5500) production and 50% in chicken broiler (n=7000) production.
- The level of resistance in Spain where cheap generics are available is associated with a higher use of fluoroquinolones in poultry and pigs *vs* Germany, UK, or Denmark where prices are higher and practice better controlled

➔ Generic drug promotion in veterinary medicine is not consistent with the general objective of Public Health authorities to restrict the use of antibiotics in veterinary medicine…

A spiral to death (in Belgium) ?

- For **antibiotics** and **antifungals**, if a medical doctor or a dentist prescribes for an **acute treatment**:
  - under the name of the active compound: the rules of prescription under INN (*) are of application (delivery of the cheapest preparation available)
  - under a trade name: as from **1st Mai 2012**, the pharmacist must deliver the product available in the group of « **the cheapest drugs** ».

Official text in French available at: http://www.inami.fgov.be/drug/fr/drugs/general-information/antibiotic/index.htm (last accessed: 7 November 2013)

- The drug acquisition cost for the treatment of a **community acquired pneumonia** following the **recommandations of BAPCOC** (**) (amoxicillin [3 g per day in 3 administrations for 5 to7 days] is only **13-14 €** … (ex-factory price: ~7 €)

Source: Belgian "Répertoire commenté des médicaments" available at http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_A.cfm (last accessed: 7 November 2013)

* INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee

A spiral to death (in Belgium) ?

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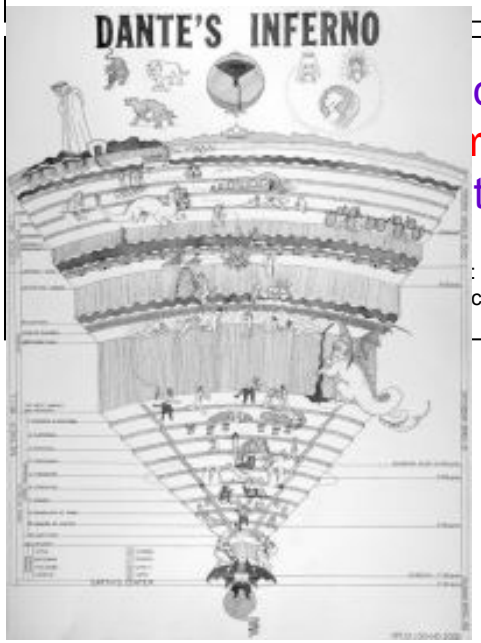

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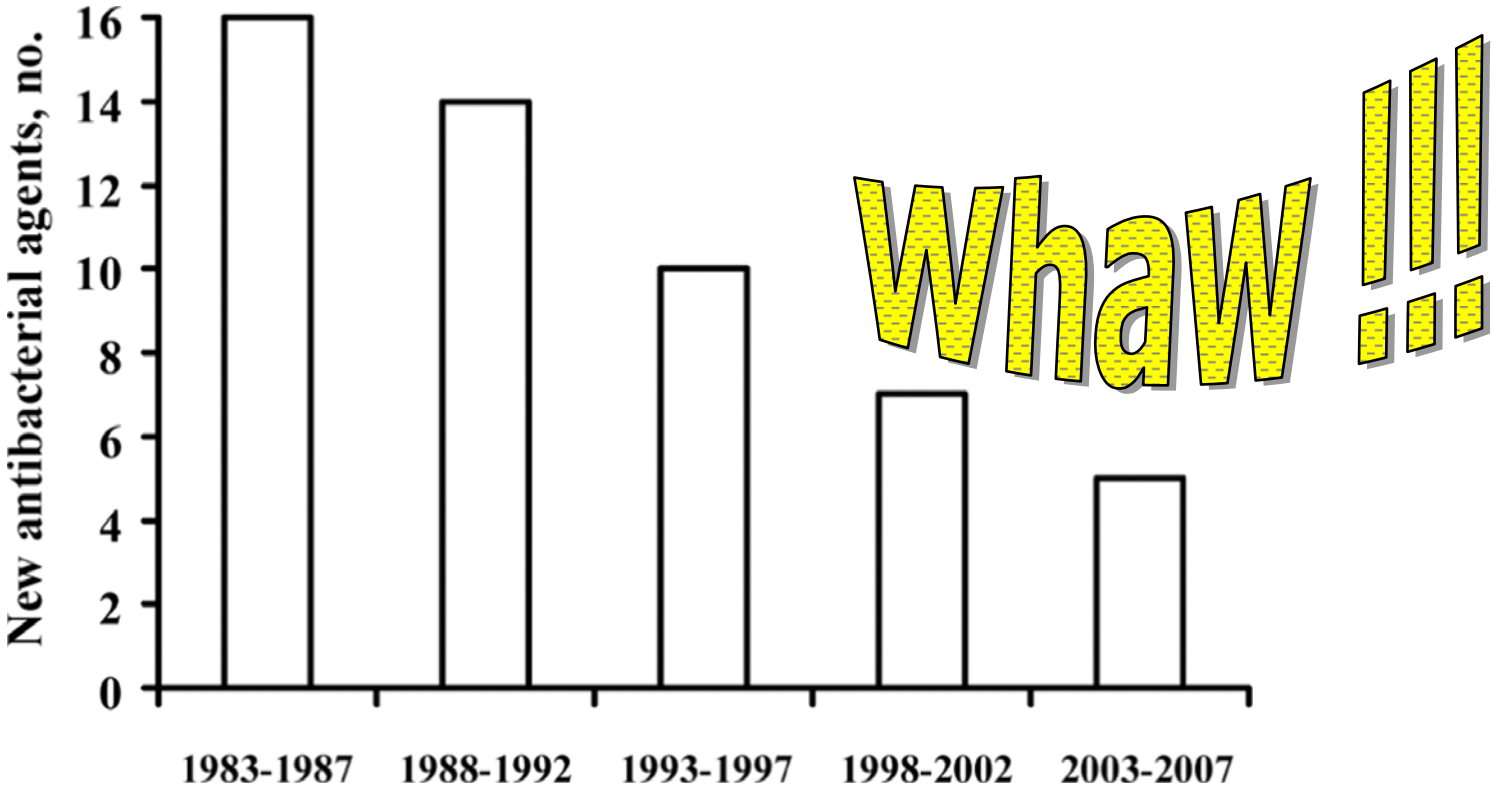
: Belgian "Répertoire commenté des médicaments" available at http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_A.cfm
cessed: 7 November 2013)

This infernal spiral (to low prices)
explains why innovators leave the field

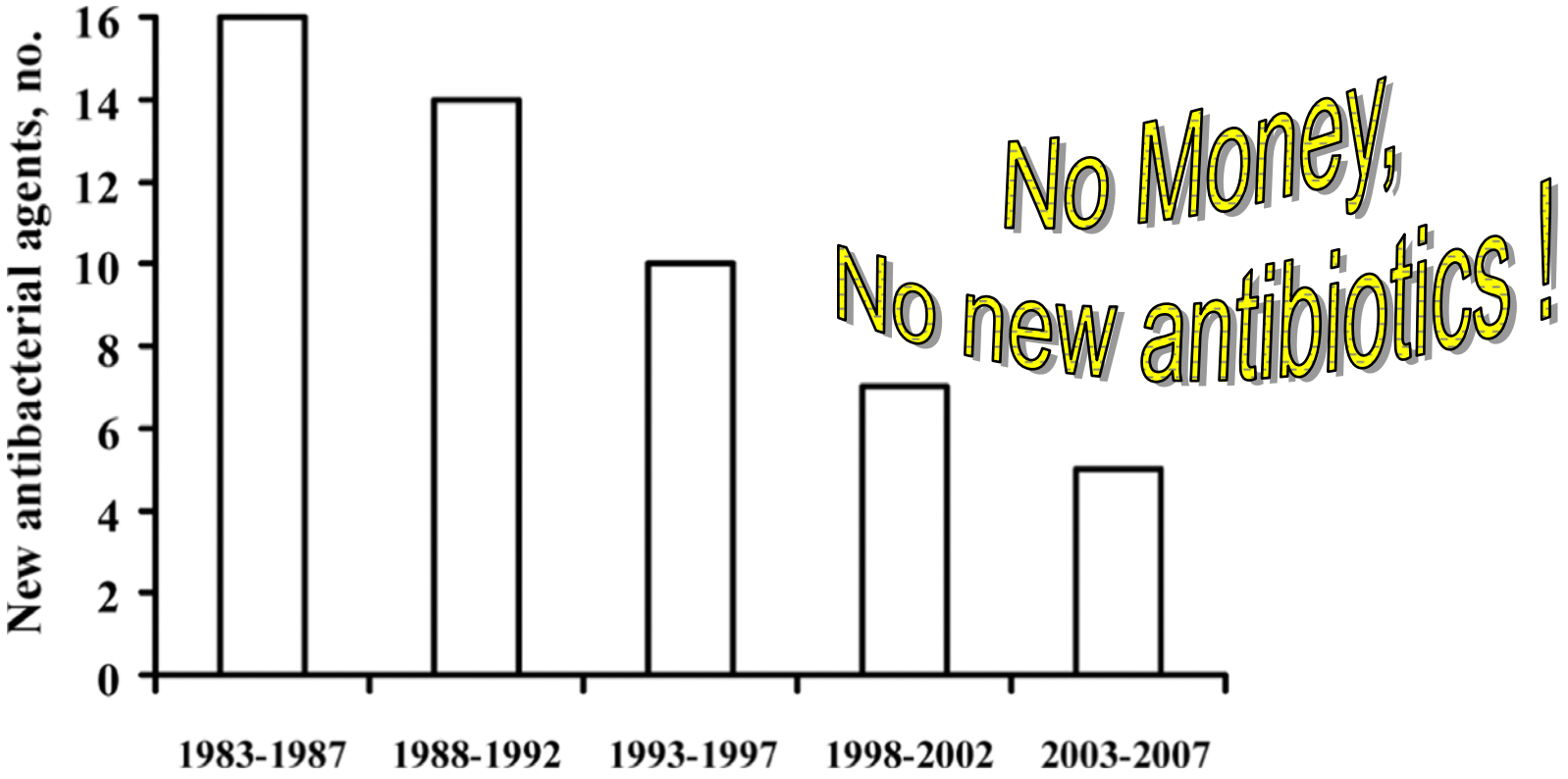
* INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee

The spiral to death in the US…



Boucher H W et al. Clin Infect Dis. 2009;48:1-12

The spiral to death in the US…



Boucher H W et al. Clin Infect Dis. 2009;48:1-12

The "Qualy" of antibiotics (*)

- The **quality-adjusted life year** or **quality-adjusted life-year** (**QALY**) is a measure of **disease burden**, including both the quality and the quantity of life lived. It is used in assessing the **value for money of a medical intervention**.
- If antibiotics **prolong your life of 2 to 10 years**, and the cost of one year of **your life is 20,000 euros**, then the value of the **"Qualy" of an antibiotic treatment is 40,000 to 200,000 euros**
- But the real cost of an antibiotic treatment is usually <<< 40,000 euros for a treatment that gives you 2-10 years survival…
- The cost of an anticancer treatment for 1 year survival is…. up to 20,000 to 70,000 euros… (and the accepted "Qualy" is close to that)
- Find where is the problem…

---

* inspired by Hollis & Ahmed, Preserving Antibiotics Rationally, New Engl. J. Med. 2013; 369,26:2474-2476

But Big Brother comes to your help…

U.S. Department of Health & Human Services

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Public Health and Medical Emergency Support for a Nation Prepared

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MCM Procurements and Grants

About BARDA

- BARDA Strategic Plan
- Procurement and Grant Awards
- Program Divisions
- Making Progress, End to End, in Medical Countermeasures
- Project BioShield Annual Reports
- Leadership Biographies

Medical Countermeasures Advanced Research, Development and Acquisition Contract and Grant Awards

October 21, 2013: New blood test would provide fast results for medical care after anthrax attack

September 26, 2013: BARDA boosts global ability to respond to pandemics

September 20, 2013: HHS funds development of freeze-dried platelets for disaster response

September 19, 2013: BARDA funds development of device to aid burn patients in disasters

September 19, 2013: HHS replenishes nation's supply of anthrax antitoxin

September 18, 2013: HHS explores new emergency response use for approved steroid

September 17, 2013: BARDA funds study of therapy for thermal burns

September 16, 2013: BARDA evaluates burn dressing for radiation, sulfur mustard burns

August 23, 2013: BARDA Contract Supports Evaluation of Therapy for Severe Thermal Burns

August 22, 2013: BARDA Supports Proof-Of-Concept Studies for Small Molecule Development

July 30, 2013: BARDA contract supports the development of a more effective skin graft to help burn patients after a rad/nuke event

June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis

May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tularemia

May 22, 2013: HHS forms strategic alliance to develop new antibiotics

April 3, 2013: HHS awards contract to create test to identify resistant influenza viruses

This page last reviewed: January 03, 2014

http://www.phe.gov/newsroom/Pages/mcm-procurements.aspx

When Big Brother helps Big Pharma…

May 22, 2013: HHS forms strategic alliance to develop new antibiotics

Date: May 22, 2013

Company: GlaxoSmithKline of North Carolina

GlaxoSmithKline US

40 to 200 x 10^6 US$

Contract amount: This agreement is not a contract; other transactional authority was used to create a strategic alliance. BARDA will contribute $40 million over 18-months. The agreement can be extended up to five years and up to a total of $200 million

About the contract: The agreement is the first in which BARDA has taken a portfolio approach with a private sector company instead of contracting to develop a single medical countermeasure. The agreement is flexible, allowing drug candidates to be moved in or out of the portfolio, based on advanced development stage and technical considerations, during joint semi-annual portfolio reviews. Under the agreement, GSK researchers will conduct safety and toxicology testing, clinical pharmacology studies, clinical studies, and non-clinical studies to support approval to treat illnesses caused by bioterrorism agents like anthrax, plague and tularemia, as well as address antibiotic resistance. One of the antibiotics to be further developed under this agreement is GSK'944, the first in class of drugs that targets bacterial DNA replication in a unique fashion. GSK has conducted studies in which GSK'944 protected or successfully treated animals suffering from anthrax, plague, or tularemia.

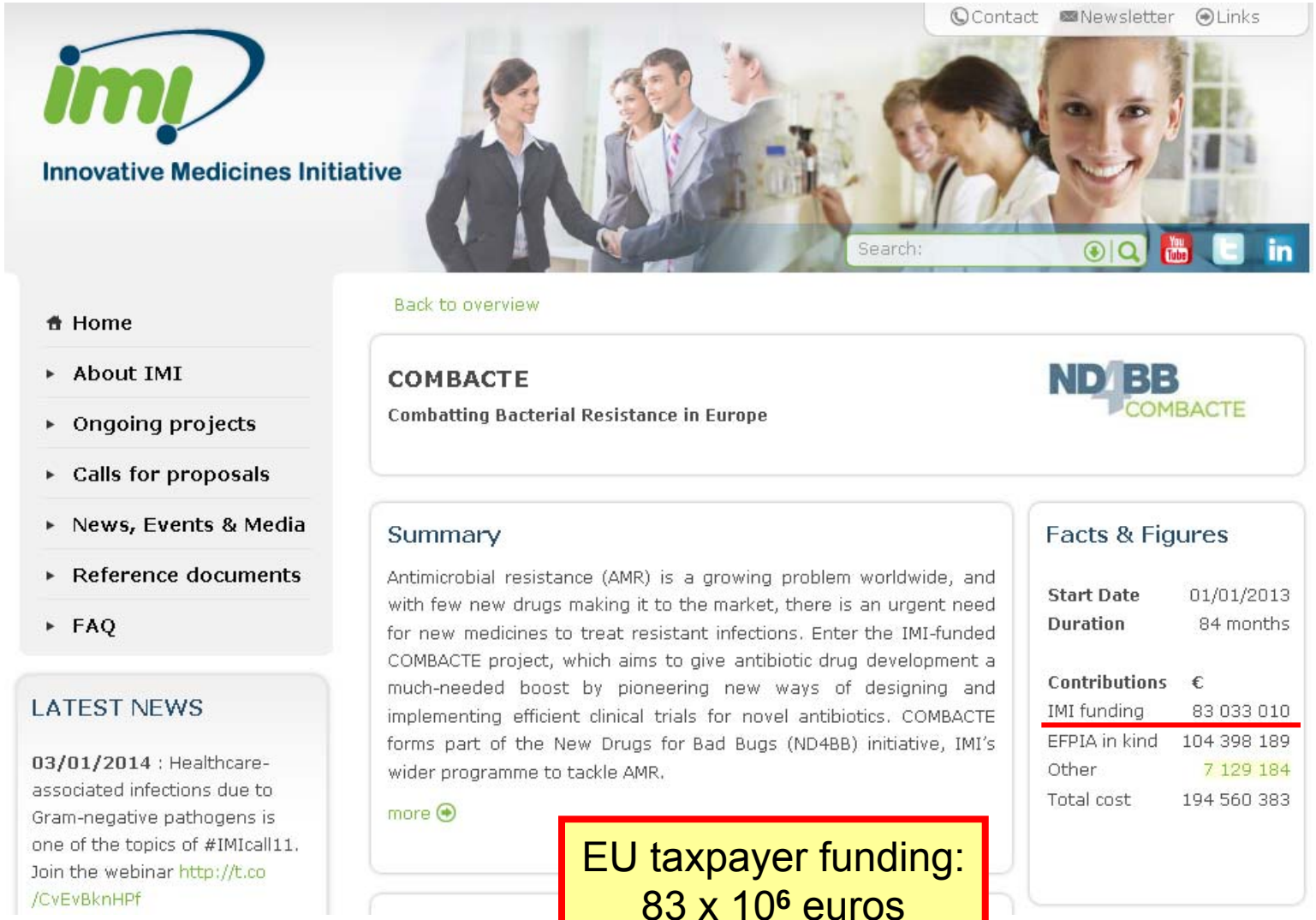
Additional information: The partnership with GSK is funded by BARDA's Broad Spectrum Antimicrobials Program. BARDA is seeking additional proposals for broad-spectrum antimicrobials that could potentially treat or prevent illness due to biological threat agents. Proposals are accepted through the Broad Agency Announcement BARDA-BAA-12-100-SOL-00011 at www.fbo.gov.

Anthrax, plague, tularemia … and resistance

Press Release: HHS forms strategic alliance to develop new antibiotics

http://www.piersystem.com/go/doc/3803/1863406/

But EU is not too bad either



http://www.imi.europa.eu/

How can you COMBACTE ?

CLIN-Net Network Participants

As of April 2013, 261 clinical sites in 32 countries have expressed an interest in joining CLIN-Net. In the third quarter of 2013, these sites will be approached with an explorative questionnaire to establish their current experience with clinical trials, their facilities to conduct trials and their need for (additional) GCP training.

Further auditing, site visits and certification will start in 2014.

https://www.combacte.com/?q=node/32

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, triggering of resistance, animal efficacy studies, dissolution, impurities…) are probably necessary (but are not yet really implemented)
- **Antibiotics are cheap** (compared to other chemotherapeutic agents), making **discussion about still reducing costs somewhat surprising** …
- Savings in this area may cause **HUGE expenses soon and later because of lack of proactive developments of new compounds or new approaches**
- 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…

Back-up

Whay are generics knocking at your doors ?

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

True content and release: the colistimethate/colistin problem

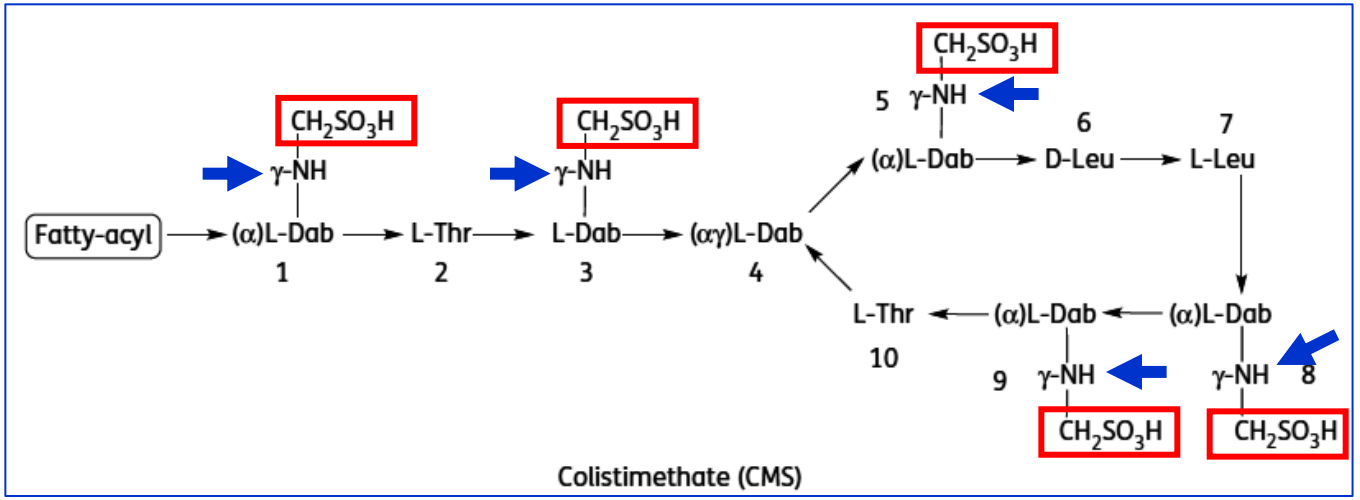
J Antimicrob Chemother 2013; **68**: 2311 – 2317
doi:10.1093/jac/dkt207 Advance Access publication 7 June 2013

Journal of Antimicrobial Chemotherapy

Pharmacokinetics of four different brands of colistimethate and formed colistin in rats

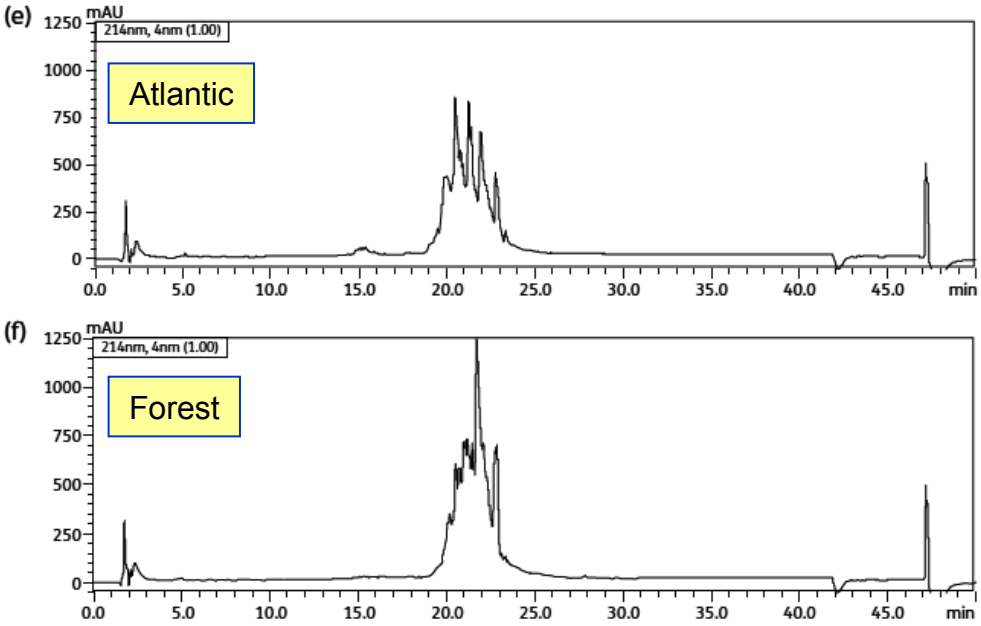
Hui He[1]†‡, Ji-Chang Li[1,2]†, Roger L. Nation[1], Jovan Jacob[1], Gong Chen[1], Hee Ji Lee[1], Brian T. Tsuji[3], Philip E. Thompson[4], Kade Roberts[1,4], Tony Velkov[1] and Jian Li[1]*

[1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; [2]College of Veterinary Medicine, Northeast Agricultural University, Harbin 150030, P. R. China; [3]School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA; [4]Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia



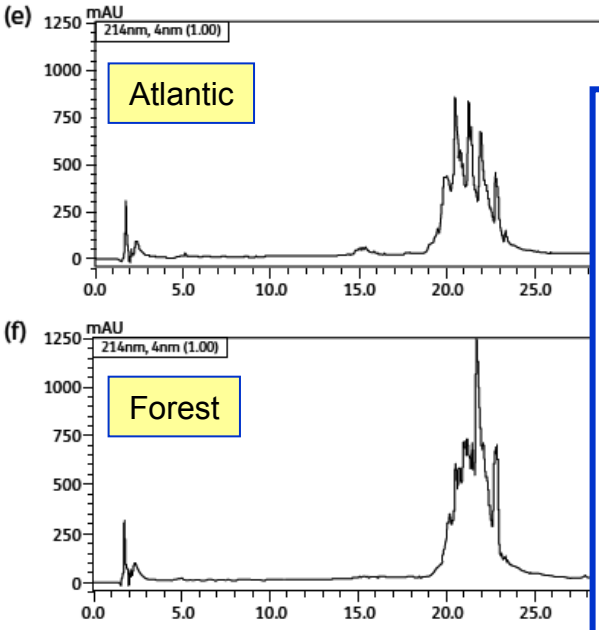
True content and release
1. colistimethate diversity

1. HPLC

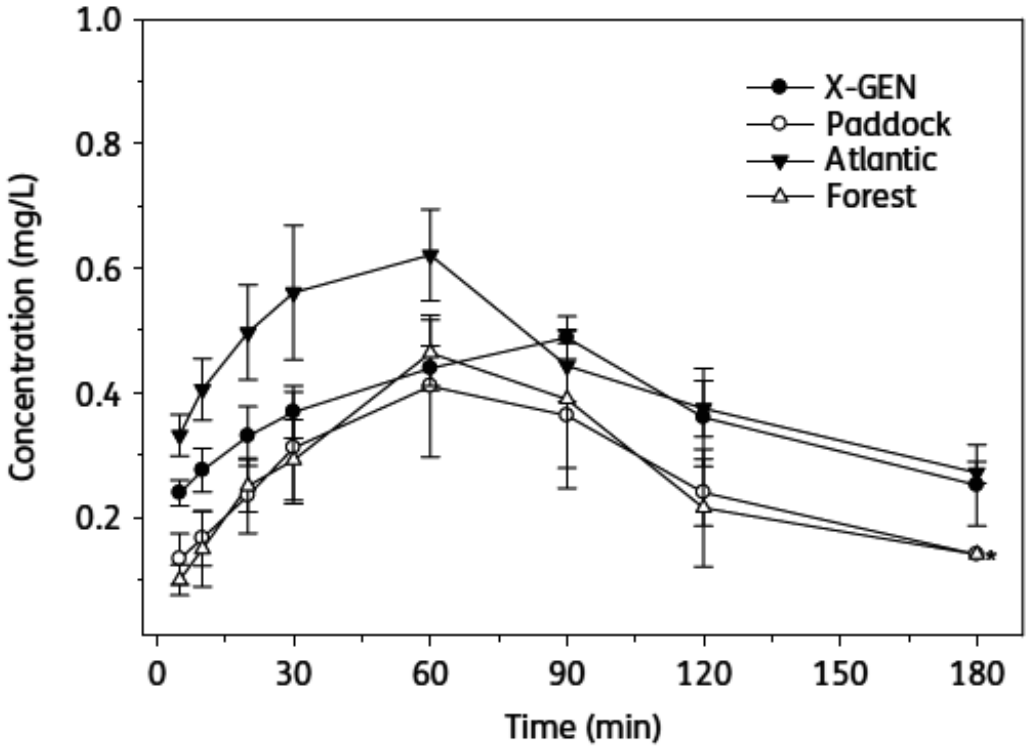


True content and release
2. colistine release

1. HPLC of colistimethate



2. Release of colistin



formed colistin in rats (n=4) following an intravenous dose of CMS (28.1 mg/kg).

and also helps small pharma for a new ketolide …

May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tulermia

Date: May 24, 2013

Company: Cempra Pharmaceuticals of Chapel Hill, N.C.

Contract amount: $17.7 million for two years

About the contract: The contract supports studies needed to request FDA approval of a drug called solithromycin to treat adults and children infected with anthrax, tularemia or community-acquired bacterial pneumonia. If approved, the drug would be the first orally administrated antibiotic approved in decades to treat children who develop community acquired bacterial pneumonia. Studies of the drug's use in treating anthrax or tularemia will be conducted under the FDA's Animal Efficacy Rule.

Additional information: BARDA is seeking additional proposals for broad-spectrum antimicrobials that could potentially treat or prevent illness due to biological threat agents. Proposals are accepted through a Broad Agency Announcement BARDA-BAA-12-100-SOL-00011 at www.fbo.gov

Press Release: HHS funds drug development for bioterror infections

http://www.piersystem.com/go/doc/3803/1863410/

And even for an aminoglycoside ...

Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin — Achaogen - Mozilla Firefox

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www.achaogen.com/media-all/2013/4/24/achaogen-awarded-60m-contract-option-by

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Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin — Achaogen

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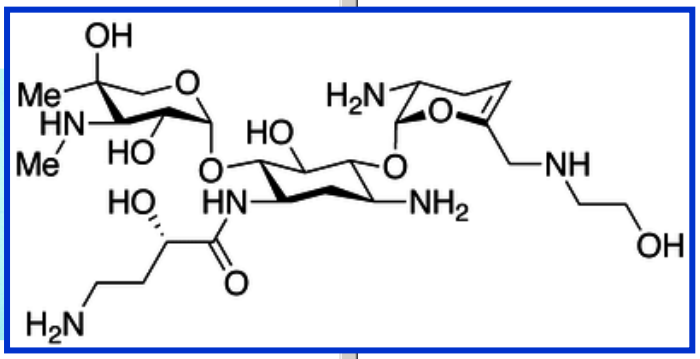

Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin

April 24, 2013

- Contract to fund Phase 3 superiority study of plazomicin in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections -

South San Francisco, CA, April 24, 2013 – Achaogen, Inc. today announced the award of a $60M contract option from the Biomedical Advanced Research and Development Authority (BARDA). The option supports the conduct of a global Phase 3 superiority study that will evaluate the efficacy and safety of plazomicin in treating patients with serious gram-negative bacterial infections due to CRE. This pathogen-specific clinical study represents a new development approach to address unmet medical needs for multi-drug resistant bacterial infections. The study is expected to start in fourth quarter of 2013.

"We are excited and honored to continue the development of plazomicin in partnership with BARDA," said Kenneth J. Hillan, M.B. Ch.B., Chief Executive Officer and Chief Medical Officer of Achaogen. "The growing prevalence of CRE infections poses a substantial public health threat, given the high mortality rates associated with CRE infections. Plazomicin's strong potential to address this public health issue and to contribute to the global effort to guard against bacterial biothreats makes it a critically important agent in the antibacterial pipeline."

Plazomicin is a next-generation aminoglycoside antibiotic that Achaogen engineered to overcome key aminoglycoside resistance mechanisms. It has potent bactericidal activity against

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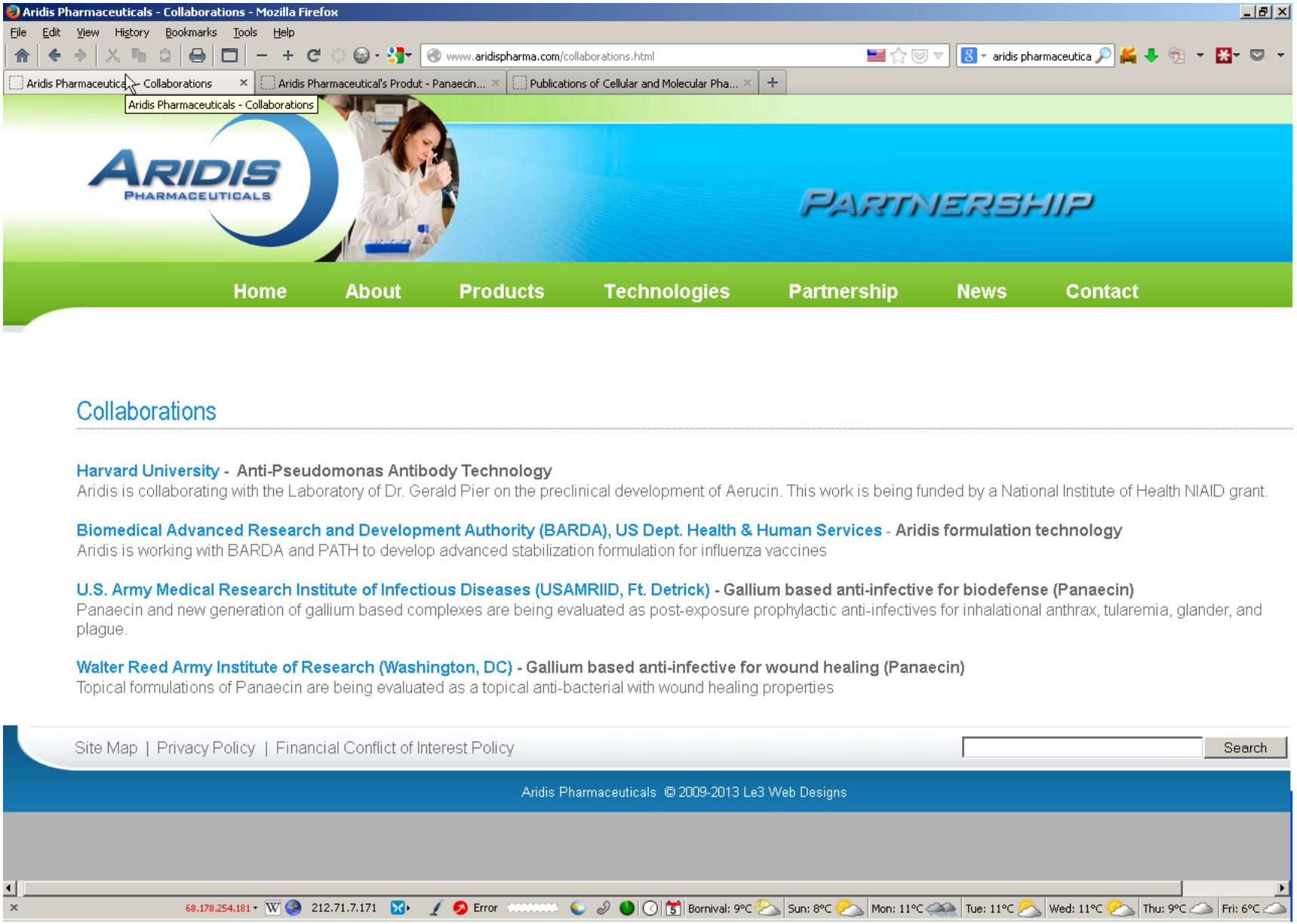
Unless Big Brother comes to your help…



Big Brother in Switzerland…

June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis

Date: June 25, 2013

Company: Basilea Pharmaceutica International Ltd., Basel, Switzerland

Contract amount: BARDA will provide $16.8 million in the first phase of the contract. The contract can be extended up to a total of six years with BARDA contributing up to a total of $89 million

About the contract: This contract is a cost-sharing public-private partnership. The partnership supports Basilea in conducting studies to evaluate the safety and efficacy of the antibiotic BAL30072 to treat Gram-negative infections including melioidosis, glanders, hospital-acquired pneumonia, and complicated urinary tract infections. Results from these studies will support the eventual filing of a new drug application with the FDA. In addition to showing promise in treating melioidosis and glanders, early studies of BAL30072 have demonstrated the drug's potential in treating a broad range of multidrug-resistant Gram-negative bacteria commonly found in hospitals.

Additional information: BARDA is seeking additional proposals for broad-spectrum antimicrobials that potentially could treat or prevent diseases caused by bacterial and viral threat agents, and clinically relevant emerging and drug resistant pathogens that through the Broad Agency Announcement BARDA CBRN BAA-12-100-SOL-00011 at www.fbo.gov.

Press Release: BARDA supports new broad-spectrum antibiotic

http://www.piersystem.com/go/doc/3803/1863402/

Unless Big Brother comes to your help… even in Switzerland

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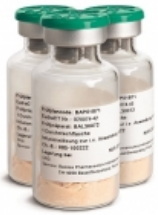
BAL30072



BAL30072 is a novel monosulfactam antibiotic in phase 1 with bactericidal activity against multidrug-resistant Gram-negative bacteria. It has demonstrated *in-vitro* and *in-vivo* coverage of Gram-negative pathogens including multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. It has robust activity against common strains of resistant pathogens including those that produce antibiotic-inactivating enzymes such as carbapenemases and metallo-beta-lactamases. BAL30072 has shown additive or synergistic activity with antibiotics from the carbapenem class.

Due to its potent antimicrobial activity against a broad range of clinically relevant Gram-negative bacteria, BAL30072 has the potential to be used for patients with serious and life-threatening infections such as hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infections or complicated urinary tract infections.

Basilea entered a contract with U.S. Biomedical Advanced Research and Development Authority (BARDA), a division within the U.S. Department of Health and Human Services, for up to USD 89 million in funding for the development of BAL30072.

Ongoing phase 1 program

To date, Basilea has conducted a single ascending dose, double-blind, randomized, placebo-controlled trial and double-blind, randomized, placebo-controlled dose-ranging studies with multiple ascending doses in healthy volunteers assessing the pharmacokinetics, safety and tolerability of BAL30072.

The need for new Gram-negative antibiotics

Antibiotic-resistance is a recurring issue in the infectious disease field. Many pathogens will eventually develop mechanisms that enable them to deactivate even the most potent antibiotics in the medical arsenal.

In hospitals, beta-lactam antibiotics form the main-stay antimicrobial therapy but their use is increasingly compromised by acquired beta-lactam resistance, especially in Gram-negative bacteria such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*. In a recent survey involving thousands of patients from hospitals around the world, Gram-negative bacteria have been found in sixty percent of clinical isolates in intensive care units. The need for novel Gram-negative antibiotics with a broad coverage of clinically relevant pathogens is therefore undeniable.

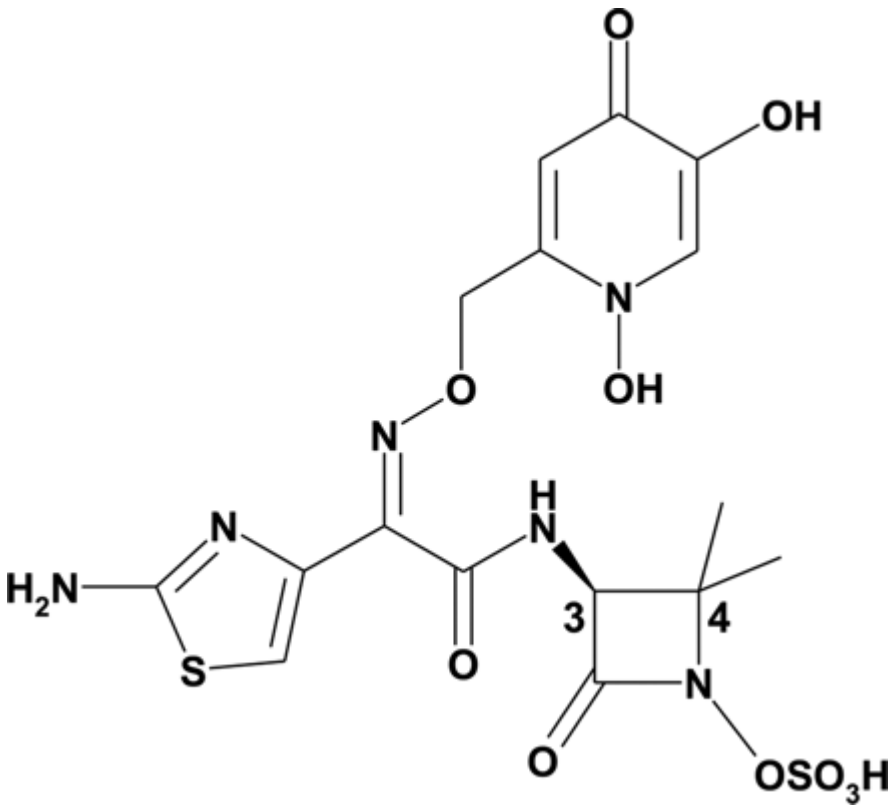
Info

Printable Version

IDSA
Infectious Diseases
Society of America
idsociety.org

http://www.basilea.com/Development/BAL30072/

A good (old) friend described about 4 years ago …

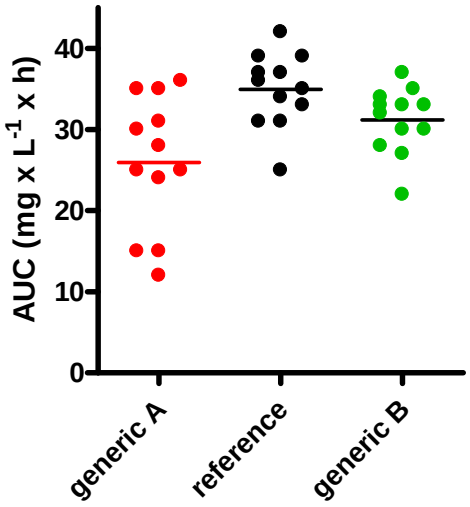


Structure of BAL30072

Numerous attempts have been made to introduce iron-binding functional groups into β-lactams since the 1980s, in order to circumvent the limitations imposed by porin mutation or deletion. BAL30072 is a sulfactam, analogous to tigemonam, with a dihydropyridone iron-chelating group.

http://aac.asm.org/content/54/6/2291.full
AAC *June 2010 vol. 54 no. 6 2291-2302*

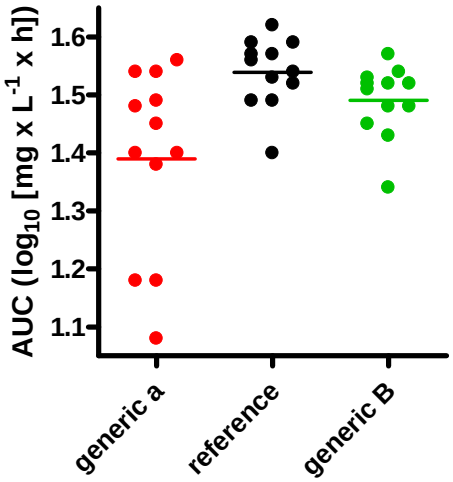
Are generic really comparable ?



	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



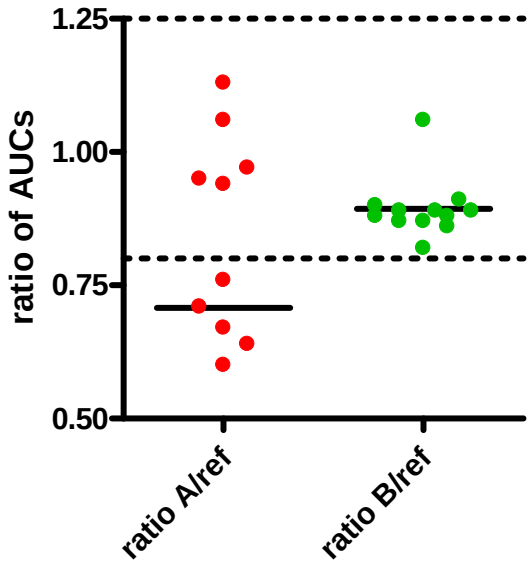
	generic a	reference	generic B
Number of values	12	12	12
Minimum	1.080	1.400	1.340
25% Percentile	1.280	1.505	1.465
Median	1.425	1.550	1.515
75% Percentile	1.515	1.580	1.525
Maximum	1.560	1.620	1.570
Mean	1.390	1.539	1.491
Std. Deviation	0.1596	0.05931	0.06142
Std. Error	0.04607	0.01712	0.01773
Lower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

Are generic really comparable ?

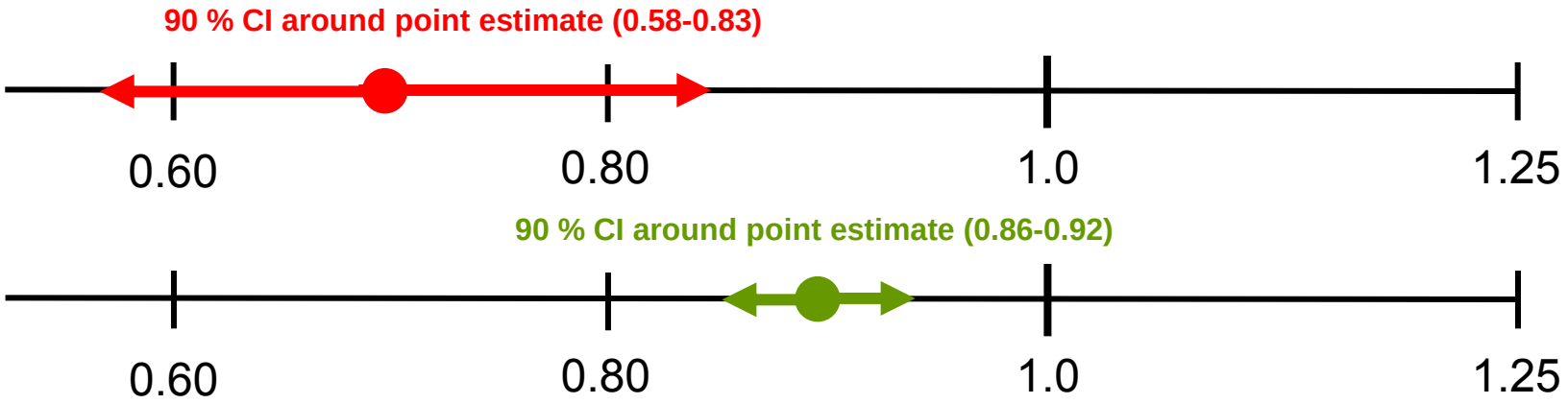
subject#	AUC generic A	AUC reference	AUC generic B	A/reference	B/reference
1	30.00	31.00	33.00	0.97	1.06
1	31.00	33.00	30.00	0.94	0.91
1	24.00	36.00	32.00	0.67	0.89
1	28.00	37.00	33.00	0.76	0.89
1	36.00	34.00	28.00	1.06	0.82
1	35.00	31.00	27.00	1.13	0.87
1	15.00	25.00	22.00	0.60	0.88
1	35.00	37.00	33.00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

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

True content: the Liège approach…

Journal of Pharmaceutical and Biomedical Analysis 85 (2013) 83–92

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Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Application of an innovative design space optimization strategy to the development of LC methods for the simultaneous screening of antibiotics to combat poor quality medicines

J.K. Mbinze[a,b], A. Dispas[a], P. Lebrun[a], J. Mavar Tayey Mbay[b], V. Habyalimana[a,c], N. Kalenda[a,b], E. Rozet[a], Ph. Hubert[a], R.D. Marini[a,*]

[a] University of Liege (ULg), Department of Pharmacy, CIRM, Laboratory of Analytical Chemistry, 1 Avenue de l'Hôpital, B36, B-4000 Liège, Belgium
[b] Service d'Analyse des Médicaments, Département de Galénique et d'Analyse des Médicaments, Université de Kinshasa, BP 212 Kinshasa XI, Democratic Republic of Congo
[c] Rwanda Biomedical Center (RBC)/Medical Production Division, P.O. Box 340 Butare, Rwanda

Innovative "Design Space optimization" strategy to simulatenously targeting 16 antibiotics and 3 beta-lactamase inhibitors

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[a] University of Liege (ULg), Department of Pharma
[b] Service d'Analyse des Médicaments, Départemen
Democratic Republic of Congo
[c] Rwanda Biomedical Center (RBC)/Medical Produc

Table 8
Assay results of three pharmaceutical medicines coded A, B and C, marketed in DRC. Results consist in the mean percentage of claimed nominal content and their 95% confidence interval computed on 3 independent samples. Specifications are set to 95–105% of the claimed nominal content (mg). Non-compliant results for the tested powder for injection are in bold.

Drug	CFT content	SUL content
A	1000 mg 96.7 ± 0.89%	500 mg 97.2 ± 1.32%
B	1000 mg **105.0 ± 2.73%**	500 mg 98.0 ± 2.06%
C	1000 mg **115.1 ± 1.76%**	500 mg 99.2 ± 1.81%

DRC: Democratic Republic of Congo
CFT: ceftriaxone
SUL: sulbactam