

Generics of antibiotics: Are you sure of what you get ?

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The logo for Cliniques universitaires Saint-Luc UCL Bruxelles features a blue and green abstract graphic followed by the text "Cliniques universitaires SAINT-LUC UCL BRUXELLES" and the tagline "Un hôpital pour la Vie".A photograph of a woman in a white medical coat holding a baby, positioned next to a colorful, abstract graphic of overlapping circles.

8 January 2015

Disclosures and slides availability

- Research grants
 - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
 - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions
- Speaking fees
 - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
 - *Opleidingsprogramma Antibioticabeleid Vlaanderen*
- Decision-making and consultation bodies
 - US National Institutes of Health (grant reviewing)
 - General Assembly and steering committee of EUCAST
 - European Medicines Agency (external expert)
 - Former member of the Belgian Drug Reimbursement Committee (CRM/CTG)
 - Member of the Belgian Antibiotic Policy Coordination Committee (BAPCOC)

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

You said "generics": the recent story of a well known antibiotic

Before
patent
expiration

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

Levofloxacine 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]

But why would you choose a "generic" antibiotic ?

1. Because it is like airlines: low cost is better
2. Because they have the same quality as the original ones
3. Because they can be produced locally (in my country) (as opposed to countries of "Big Pharma")
4. Because my patients / my hospital / my country has/have limited resources
5. Because "old antibiotics" (no longer under patent) cover most of my needs
6. All of the above

Please, give your FIRST choice (1-5)
OR choose 6

I guess the real and only justifiable answer is...

Your prescription,
your choice.



\$71

Thirty-day
prescription of one
brand name drug



\$22

Thirty-day prescription
of its generic equivalent

Much
cheaper !

What shall we discuss?

1. A **political choice** (US and EU laws as an example)
2. Approach to PK **bioequivalence**
3. Approach to **microbiological equivalence**
4. Approach to **pharmacodynamic equivalence**
5. Problems related to **dissolution and stability**
6. **Impurities** and falsified medicines
7. The **hidden risks** of "low cost" antibiotics

What shall we discuss?

1. A political choice (US and EU laws as an example)



<http://vlpmaricopa.org/vlp/clc/Aboutus.htm>
Last visited: 25 March 2014

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

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>

In the European Union



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

The EU Directive (excerpts)

- ...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...
- ... ‘**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**. ...

See “**Médicaments originaux et génériques**” for a short summary of the rules as implemented in Belgium
(available from the web site of the *Agence fédérale des medicaments et produits de santé / Federale Agentschap voor geneesmiddelen en gezondheidsproducten*)
<http://www.fagg-afmps.be/fr/items-HOME/Generiques/>
(last visited: January 2015)

1st round of conclusions and discussions

- The decision to go for generics is a **political** decision
- It finds its origin and basis in
 - the **limited duration of the patent protection**
(usually about 20 years post patent application), which makes generics possible after about 10 years of effective commercialization)
 - the fact that **drug production costs are usually very low**
(often only a very minor fraction of the total requested by the innovator at the time of initial commercialization)
- The **only** incentive in the promotion of the generics by governments and social organizations to acquire and/or provide drugs **more cheaply** to the population

What shall we discuss?

1. The US and the EU laws
2. **Approach to PK bioequivalence**



<http://www.choosinggenerics.ca/Bioequivalence.aspx>

Last visited: 15 March 2014

Bioequivalence: principles

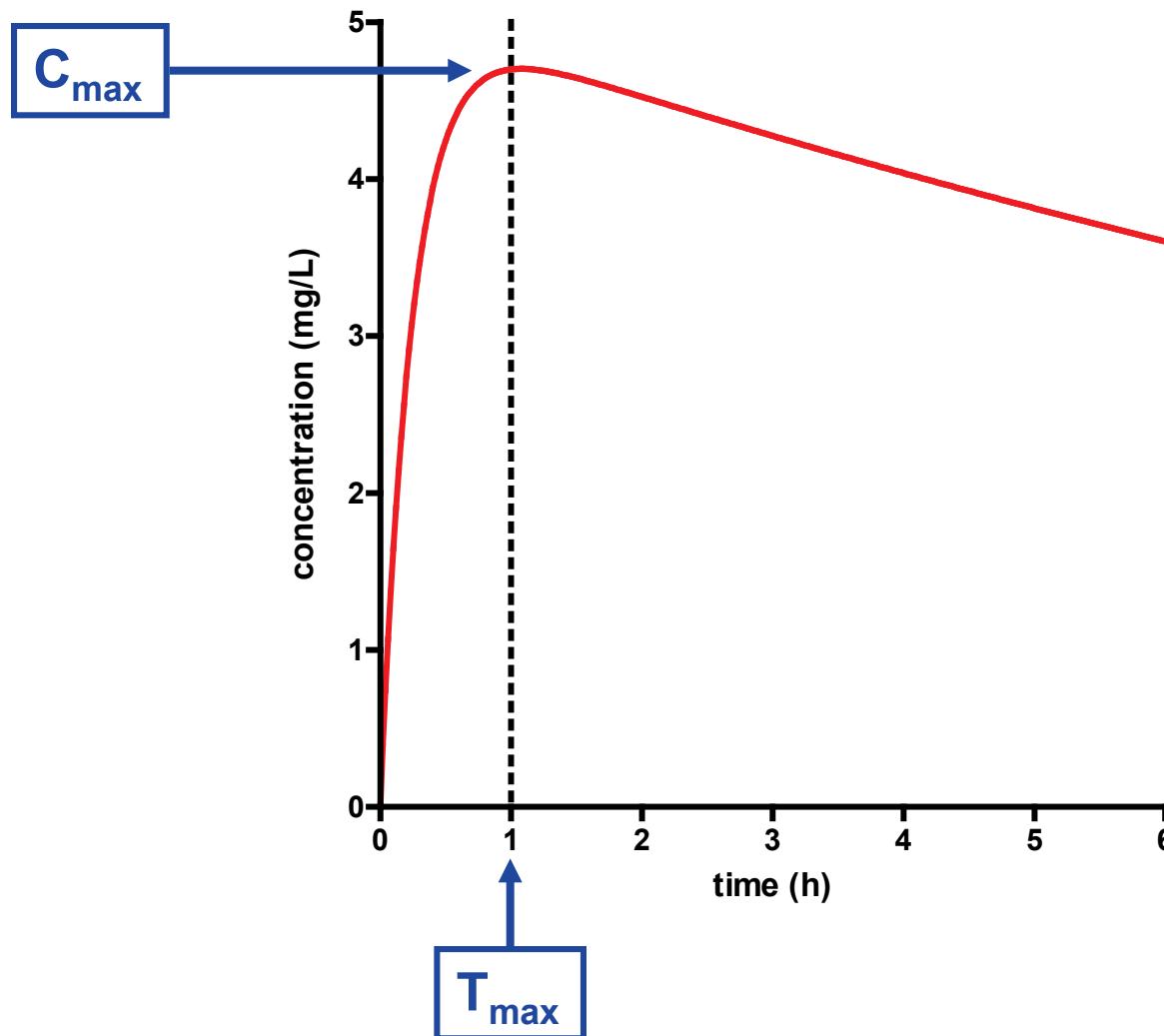
- Bioequivalence is an **accepted surrogate for therapeutic equivalence** ¹ (including for branded drugs when the marketed form differs from the form used in development...)²
- Primary metrics are ^{1,3}
 - **AUC** (area under the plasma concentration–time profile of the active substance)
→ **extent of absorption**
 - **C_{max}** (the maximum plasma concentration of the active substance)
→ **extent and rate of absorption**
 - **T_{max}** (the time when 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.

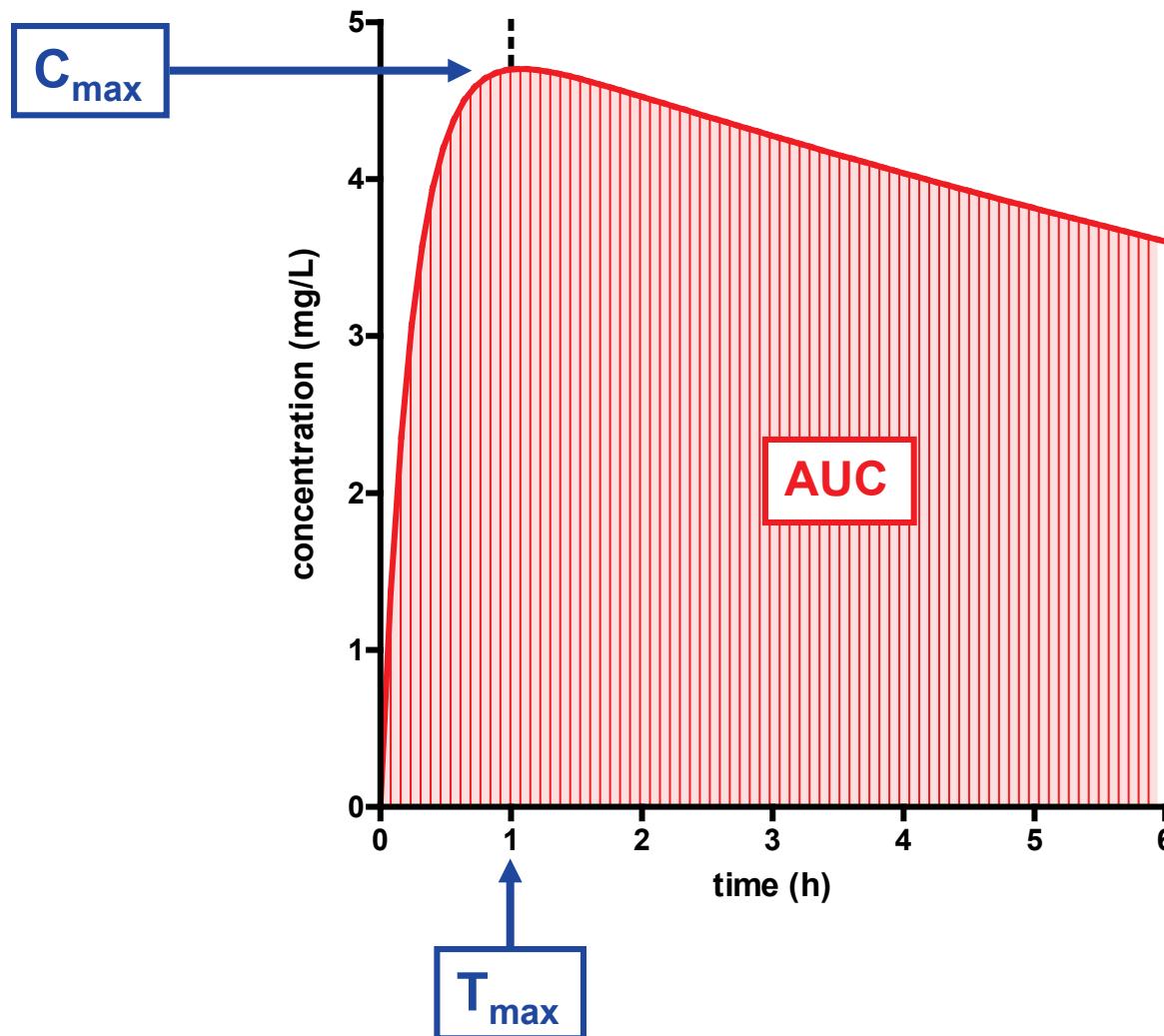
2. Benet LZ: Understanding bioequivalence testing. Transplant.Proc. 31 (Suppl 3A): 7S-9S, 1999.

3. Niazi SK: Handbook of Bioequivalence Testing, "Drugs and the Pharmaceutical Sciences", vol. 171, Informa Healthcare (New York), 2007.

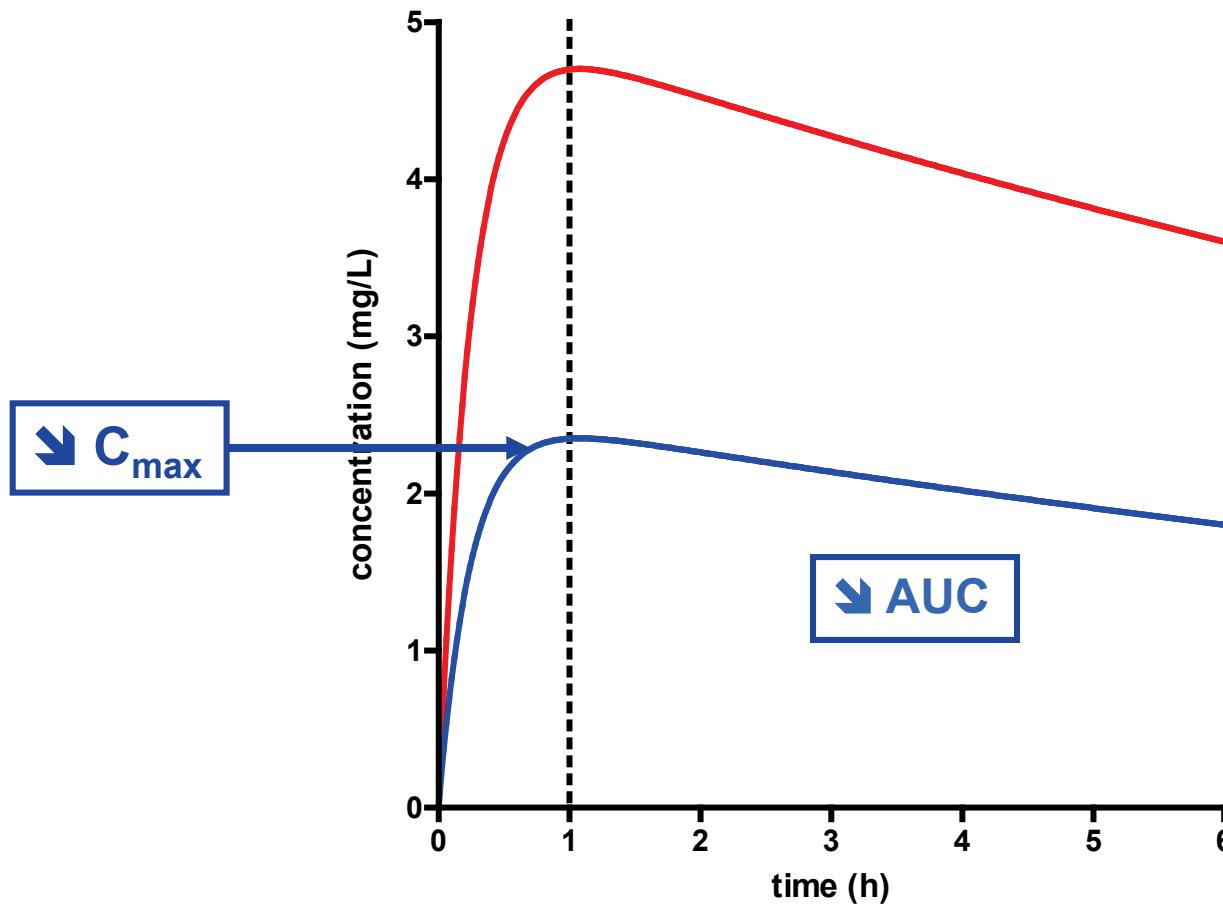
AUC – C_{max} – T_{max}



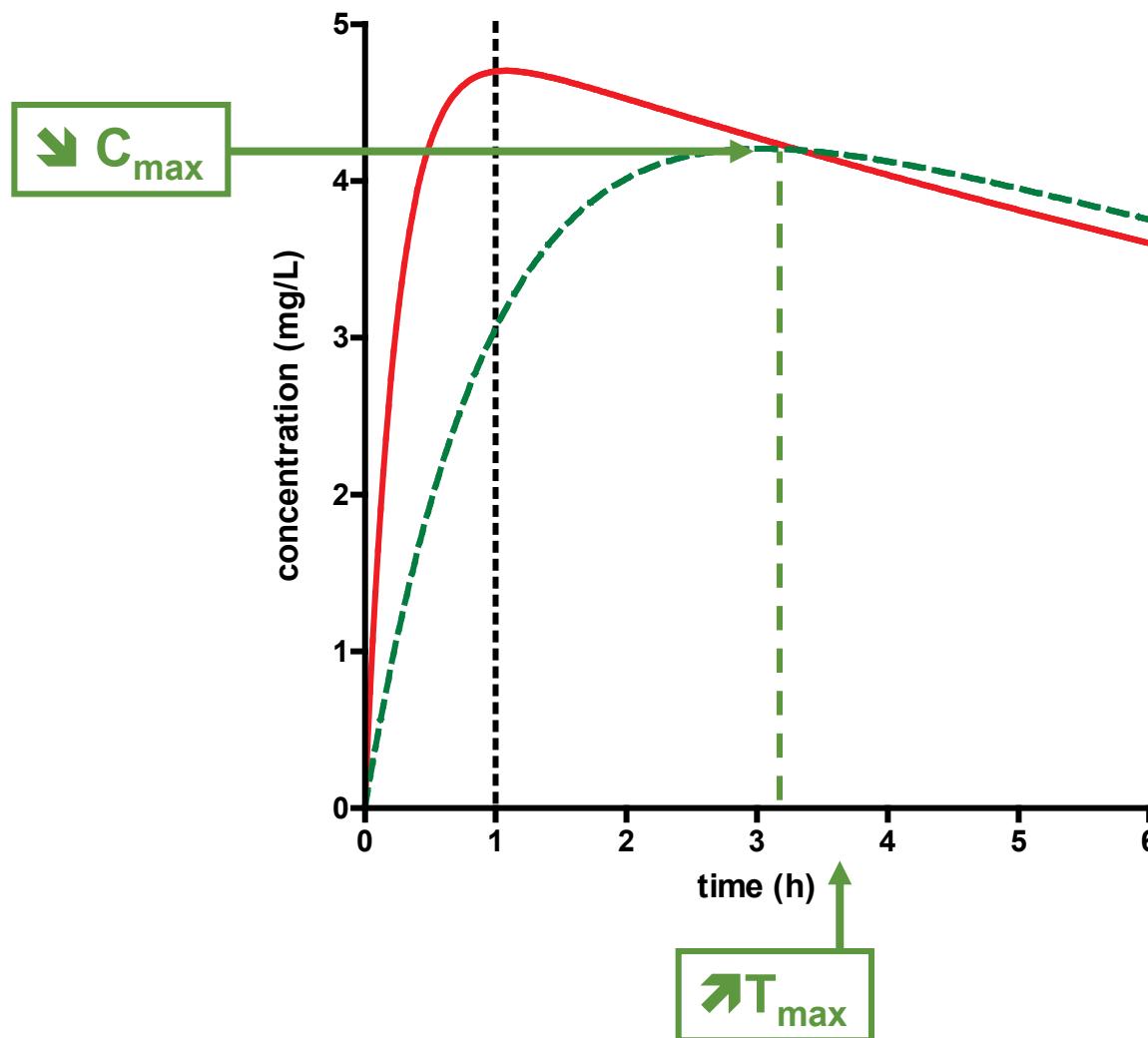
AUC – C_{max} – T_{max}



What if the absorption is decreased ?

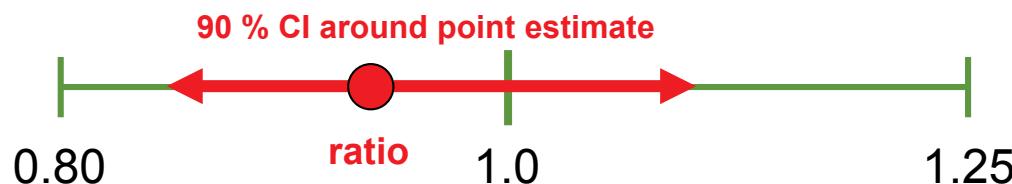


What if absorption is delayed ?



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 intervals, 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>

Caveats !

- Bioequivalence studies are NOT required for drugs administered by the intravenous route ! (since that route is the parameter against which the other routes are tested !)
 - Only demonstration that the drugs has the **same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product** is required.
- Complex drugs (such as biologicals, fractionated heparins, etc.) may require and will pass through more stringent requirements ^{1,2}

¹ Tothfalusi et al. Eur J Health Econ (2014) 15 (Suppl 1):S5–S11 / Ahn & Lee, Ungyong Tonggye Yongu (2011) 24(3): 495–503

² Lee et al. Nature Biotechnology (2013) 31:220-226

Is this enough ?

1. The US / EU laws (or the law of my country) are sufficient and convince me to say that generics are like the original products
2. While accepting the laws, I'm not convinced and would like to have additional information from the producers
3. What is required by law is insufficient and the laws need to be changed.

Only ONE answer (1, 2 or 3),
please !

What shall we discuss?

1. A political decision (US and EU laws as an example)
2. Approach and limits to PK bioequivalence studies
3. **Approach to microbiological and therapeutic equivalence**

- MIC (heteroresistance in back-up slides) ...
- Approach to pharmacodynamic equivalence
- PK/PD animal models and clinical data



<http://www.umu.se/english/research/research-excellence/strong-research/Infection+Biology>
Last visited: 25 March 2014



<http://www.gaebler.com/How-to-Start-a-Laboratory-Animals-Business.htm>
Last accessed: 29 March 2014



<http://www.buzzle.com/articles/staph-infections-staph-infection-treatment-and-symptoms.html>
Last visited: 25 March 2014

Potency (piperacillin)

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

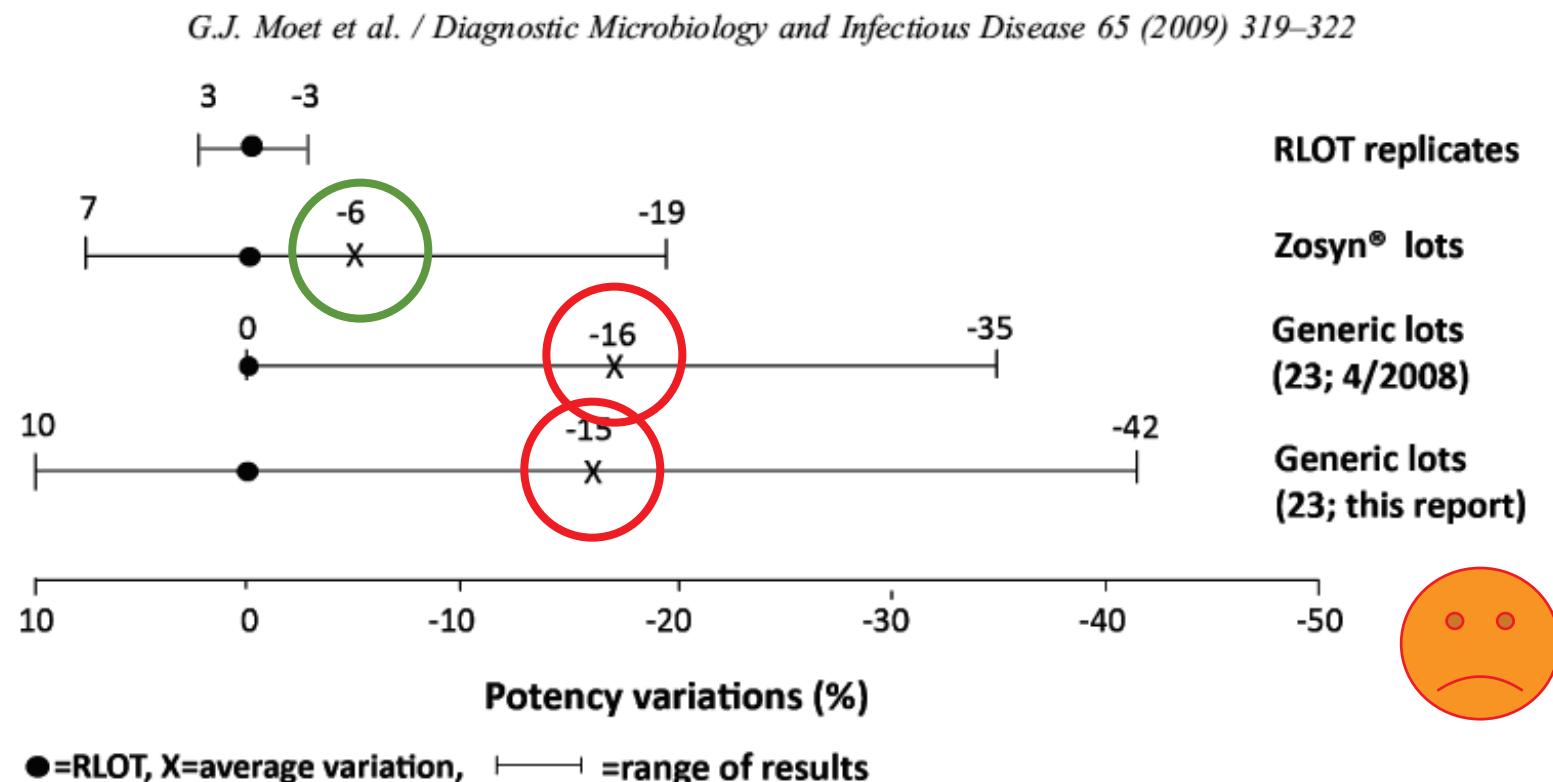


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

MIC 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 \pm 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 \pm 15.52	—	—	—	54.4	45.6	—	—
Teicoplanin	MRSA (147)	7	28.09 \pm 10.29	—	—	—	59.2	40.1	0.7	—
Cefotiam	<i>Staphylococcus aureus</i> (100)	7	8.71 \pm 3.04	—	—	—	87.0	13.0	—	—
	<i>Escherichia coli</i> (100)	7	12.00 \pm 5.89	—	—	—	77.0	22.0	1.0	—
Ceftriaxone	<i>Streptococcus pneumoniae</i> (126)	6	12.70 \pm 4.77	—	—	—	81.7	18.3	—	—
Ceftazidime	<i>Pseudomonas aeruginosa</i> (100)	2	3.00 \pm 2.83	—	—	—	95.0	5.0	—	—
Meropenem	<i>P. aeruginosa</i> (100)	7	18.57 \pm 3.46	—	—	—	78.0	19.0	2.0	1.0
Imipenem	<i>P. aeruginosa</i> (100)	4	9.00 \pm 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

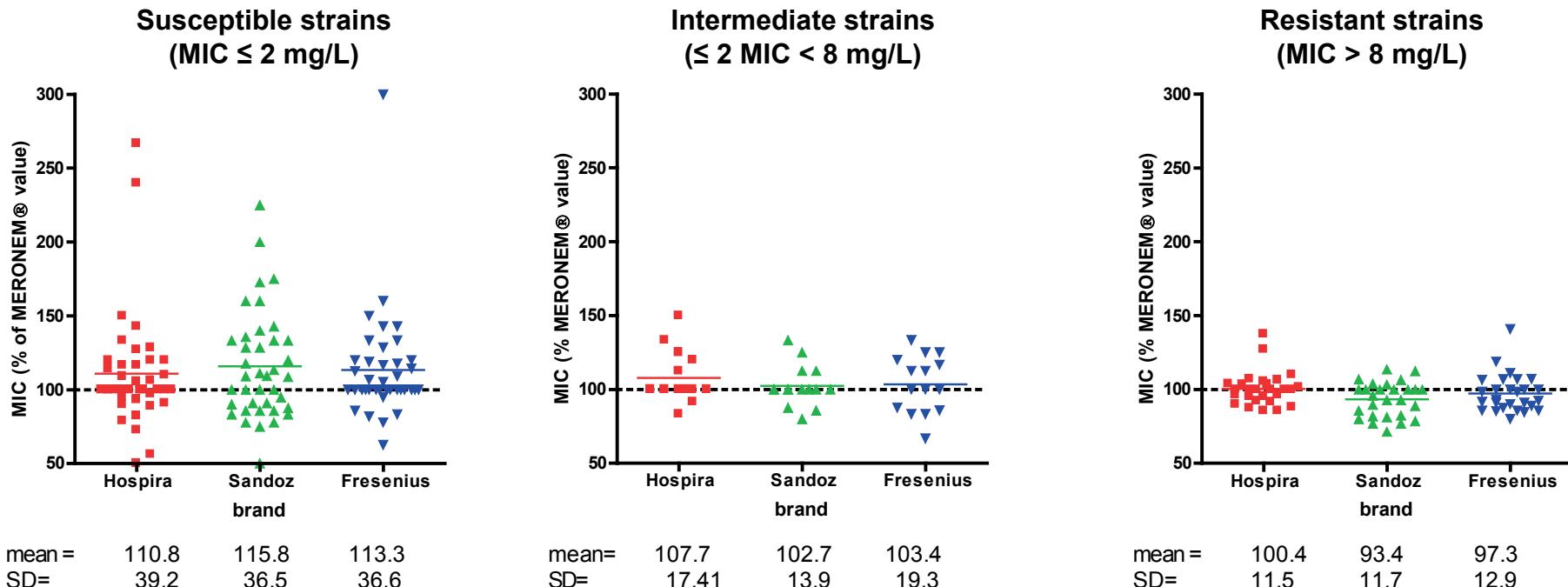
Fujimura & Watanabe J Infect Chemother (2012) 18:421–427

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)



MEROPENEM® = meropenem commercialized by AstraZeneca

Van Bambeke et al., in preparation

Vancomycin: evidence of non-equivalence in PK/PD animal model

Neutropenic thigh mouse model

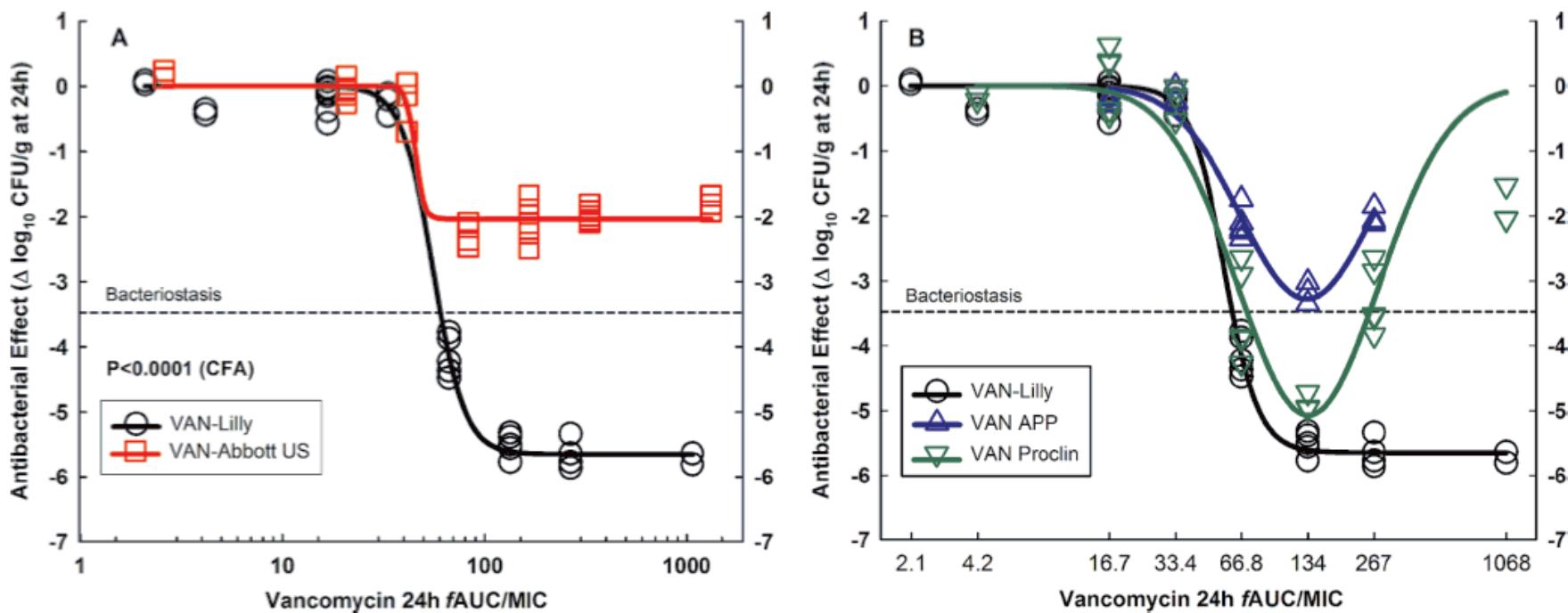
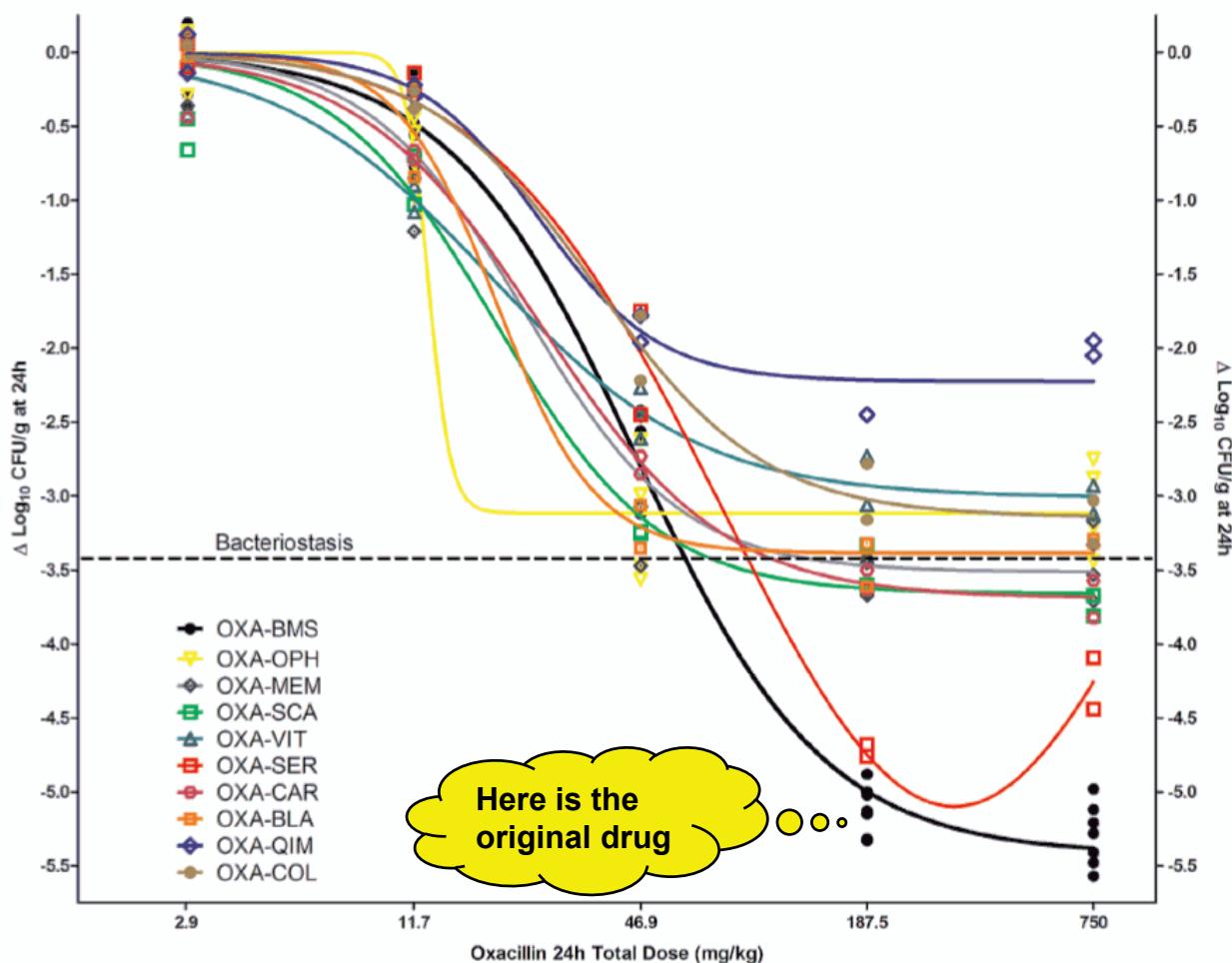


FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum ($4.30 \pm 0.05 \log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per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

Neutropenic thigh mouse model



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

But pharmacodynamics equivalence can also be demonstrated

AAC Accepts, published online ahead of print on 13 October 2014

Antimicrob. Agents Chemother. doi:10.1128/AAC.03633-14

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Impact on resistance of the use of therapeutically equivalent generics: the case of ciprofloxacin.

Carlos A. Rodriguez^{a,b}, Maria Agudelo^{a,b,d}, Andres F. Zuluaga^{a,b}, Omar Vesga^{a,b,c,d#}

But pharmacodynamics equivalence can also be demonstrated

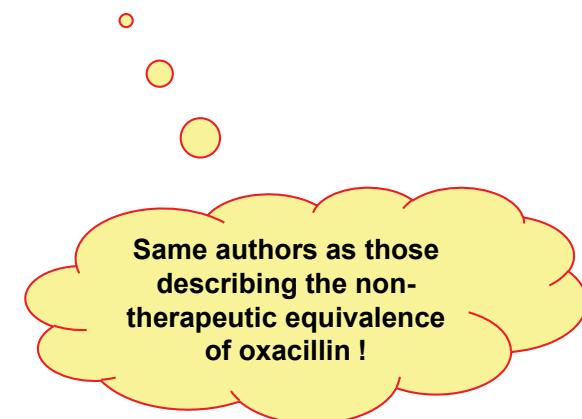
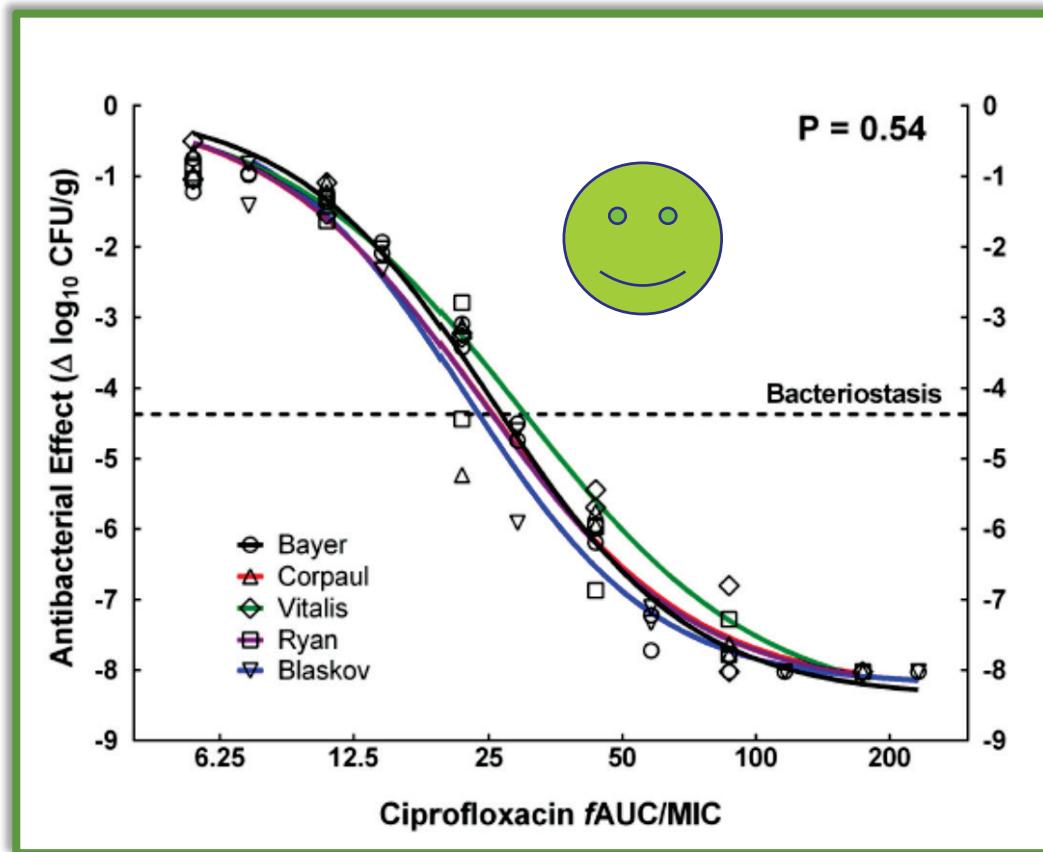
AAC Accepts, published online ahead of print on 13 October 2014

Antimicrob. Agents Chemother. doi:10.1128/AAC.03633-14

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Sometimes the generic has a problem of a “too good” bioavailability ...

Pharmacological Research 85 (2014) 39–44



Contents lists available at ScienceDirect

Pharmacological Research

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



Is generic rifaximin still a poorly absorbed antibiotic? A comparison of branded and generic formulations in healthy volunteers



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Sometimes the generic has a problem of a “too good” bioavailability ...



Pharmacological Research 85 (2014) 39–44

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Is generic rifaximin still a poorly absorbed antibiotic? Comparison of branded and generic formulations in healthy volunteers

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C. Blandizzi et al. / Pharmacological Research 85 (2014) 39–44

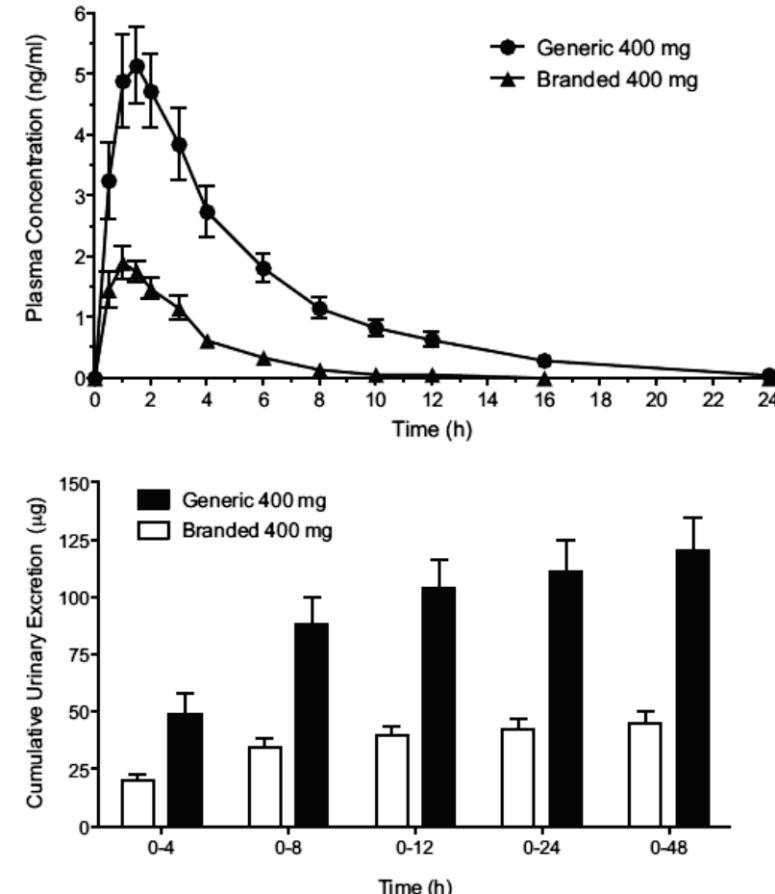


Fig. 1. Mean rifaximin concentration-time (top panel) and cumulative urinary excretion (bottom panel) profiles following administration of 400-mg single-dose generic or branded (polymorph- α) rifaximin to healthy volunteers. Each point or column represents the mean \pm SEM (vertical lines) obtained from 24 subjects.

The reasons are subtle differences in composition...



Is generic rifaximin still a perfect copy of the branded and generic formulations?

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^c Institute for Pharmacokinetic and Analytical Studies SA, Via

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The copy was almost perfect but ...

Table 1

Chemical composition of the rifaximin formulations employed in the present pharmacokinetic study. The only difference between the branded and generic formulations concerns one excipient (highlighted in gray).

	Branded rifaximin (Normix®) 200-mg film-coated tablet	Generic rifaximin 200-mg film-coated tablet
Active ingredient (crystalline status)	Rifaximin (polymorph- α)	Rifaximin (Amorphous form and polymorph- α)
Excipients	Sodium starch glycolate Glycerol distearate Colloidal anhydrous silica Talc Microcrystalline cellulose	Sodium starch glycolate Glycerol monostearate Colloidal anhydrous silica Talc Microcrystalline cellulose
Coating components	Hypromellose Titanium dioxide Disodium edetate Propylene glycol Red iron oxide E172	Hypromellose Titanium dioxide Disodium edetate Propylene glycol Red iron oxide E172

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generic drugs with respect to brand formulation

Luca Gallelli¹, Caterina Palleria¹, Antonio De Vuono², Laura Mumoli¹, Piero Vasapollo², Brunella Piro³, Emilio Russo¹

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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 generic drugs compared to brand formulation

Luca Gallelli¹, Caterina Palleria¹, Antonio De Vuono², Ilenia Sartori¹, Emilio Russo¹

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

In this case-review we will compare the treatment with generic drugs to that with brand formulation, discuss the relative merits and disadvantages of each and finally, we will analyze 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.

But what about the excipients ?

<http://www.fagg-afmps.be/fr/items-HOME/Generiques/>
(Last visited: 8 January 2015)

The screenshot shows a web browser window with the following details:

- Address bar:** www.fagg-afmps.be/fr/items-HOME/Generiques/
- Language:** Belgian flag icon indicates the site is in French.
- Search bar:** Search button and search input field.
- Toolbar:** Standard browser icons for print, refresh, back, forward, etc.
- Page Content:**
 - Section:** Excipients à effet notoire
 - Text:** Certaines spécialités contiennent un ou plusieurs excipients dits à effet notoire.
On entend par « excipient à effet notoire » un excipient dont la présence peut nécessiter des précautions d'emploi pour certaines catégories particulières de patients.
 - Text:** Ces effets sont parfois liés à la voie d'administration ou à l'exposition à une dose atteignant un certain seuil.
 - Text:** Afin de garantir le meilleur niveau de sécurité, il peut donc être utile de prendre également en compte les excipients à effet notoire, notamment lorsque le médecin souhaite passer de la prescription d'une spécialité à celle d'une autre contenant le ou les même(s) principe(s) actif(s).
 - Text:** Ont été considérés comme excipients à effet notoire les substances reprises dans la ligne directrice publiée par la Commission européenne [« Excipients in the label and package leaflet of medicinal products for human use »](#) révisée en juillet 2003.
 - Text:** Il convient donc de vérifier les excipients présents dans les médicaments.
 - Text:** Pour faciliter la vérification, une liste de ces excipients à effet notoire (.PDF) est disponible. Elle précise pour chacun d'eux les éventuelles doses seuil et la nature des effets potentiels.
- Bottom Note:** See http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf for the European Document
(Last visited: 8 January 2015)

Avez-vous des EEN (excipients à effet notoire)?

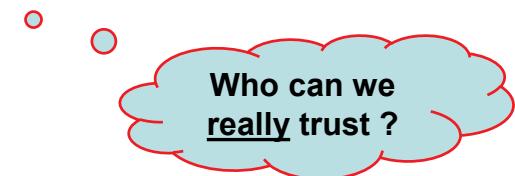
Liste des médicaments antibiotiques et antimycosiques commercialisés dans les officines ouvertes au public avec mention, s'il y a lieu, de leur(s) excipient(s) à effet notoire

Mise à jour: 10/12/2013

amoclane 125/31,25 100ml sir	J01CR02	sodium; aspartame
amoclane 250/62,5 100ml sir	J01CR02	sodium; aspartame
amoclane 500/125 16 comp	J01CR02	
amoclane 500/125 32 comp	J01CR02	
amoclane 875/125 10 comp	J01CR02	
amoclane 875/125 20 gran sachets	J01CR02	saccharose
amoclane 875/125 20 comp	J01CR02	
amoxicilline apotex comp eff 20x 1 g	J01CA04	aspartame; sodium
amoxicilline apotex comp eff 8x 1 g	J01CA04	aspartame; sodium
amoxicilline apotex sir 80ml 250mg/5ml	J01CA04	saccharose
amoxicilline eg comp eff 24x 1 g	J01CA04	aspartame; sodium
amoxicilline eg comp eff 8x 1 g	J01CA04	aspartame; sodium
amoxicilline eg caps 16x 500mg	J01CA04	
amoxicilline eg caps 30x 500mg	J01CA04	
amoxicilline eg sir 100ml 250mg/5ml	J01CA04	saccharose
amoxicilline eg comp 24x 1 g	J01CA04	
amoxicilline eg comp 8x 1 g	J01CA04	
amoxicilline mylan caps 16x 500mg	J01CA04	
amoxicilline mylan caps 24x 500mg	J01CA04	
amoxicilline sandoz comp disp 16x 500mg	J01CA04	aspartame
amoxicilline sandoz comp disp 20x 1 g	J01CA04	aspartame
amoxicilline sandoz comp disp 24x 1 g	J01CA04	aspartame
amoxicilline sandoz comp disp 30x 500mg	J01CA04	aspartame
amoxicilline sandoz comp disp 8x 1 g	J01CA04	aspartame
amoxicilline sandoz sir 100ml 250mg/5ml	J01CA04	aspartame
amoxicilline sandoz sir 100ml 500mg/5ml	J01CA04	aspartame
amoxicilline teva comp disp disp 16x 500mg	J01CA04	
amoxicilline teva comp disp disp 16x 750mg	J01CA04	
amoxicilline teva sir 80ml 250mg/5ml	J01CA04	saccharose
amoxiclavapotex 500/125 16 comp	J01CR02	
amoxiclavapotex 500/125 30 comp	J01CR02	
amoxiclavapotex 875/125 10 comp	J01CR02	

2d round of conclusions and discussions

- There are contradictory observations about the **pharmacodynamic and therapeutic equivalence** of generic antibiotics, (even from the same investigators when comparing different products !)
- The reasons for a non-equivalence remain often obscure but may be related to **differences in biophysical properties** that will impact on the inter- and intra-organ bioavailability, which **cannot be detected by simple measurements of serum levels**
- There is also a **possibility of interferences with excipients** (but which ones ?)
- This needs to be further studied, but, at this point, is **beyond the clinician's grip** !



And this brings me to pharmaceutical quality...

1. the generic must have the same solubility / dispersion properties than the original
2. the generic cannot contain more impurities (or give rise to more degradation products) than the original
3. I must be sure about the real content of what I prescribe
4. All of the above is important
5. None of the above is important

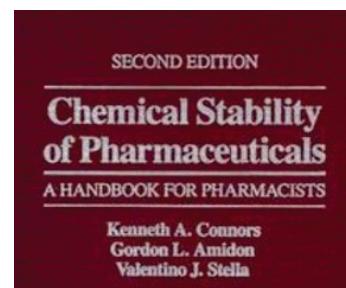
**Please, give your FIRST choice
(1, 2 OR 3)
OR choose 4 OR 5**

What shall we discuss ?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
 - MIC, MPC, heteroresistance ...
 - Approach to pharmacodynamic equivalence
 - PK/PD animal models and clinical data
4. **Dissolution, stability, impurities**



<http://www.astrosurf.com/luxorion/eau-intro-molecule2.htm>
Last visited: 25 March 2014



<http://www.wiley-vch.de ...>
Last visited: 25 March 2014

The poster is for the "EU/Swissmedic GMP Workshop" held at Beijing University from September 20 to 22, 2006. It features a pink header with the text "Impurity Profiles in Active Pharmaceutical Ingredients". The footer contains the logo for the Federal Institute for Drugs and Medical Devices (BfArM) and the text "Dr. Susanne Keitel, Federal Institute for Drugs and Medical Devices (BfArM), Germany".

<http://www.docstoc.com ...>
Last visited: 25 March 2014

Dissolution of meropenem in Japan

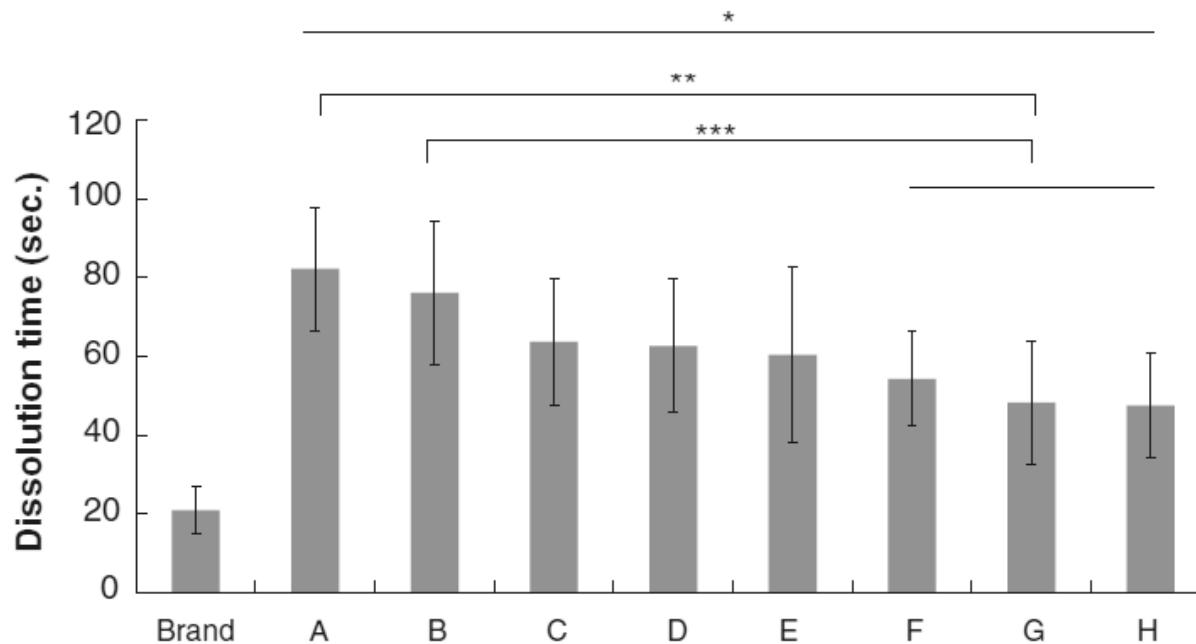


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. A–H Generic products of meropenem.
 $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

Crystals size in meropenem in Japan

J Infect Chemother (2012) 18:421–427

425

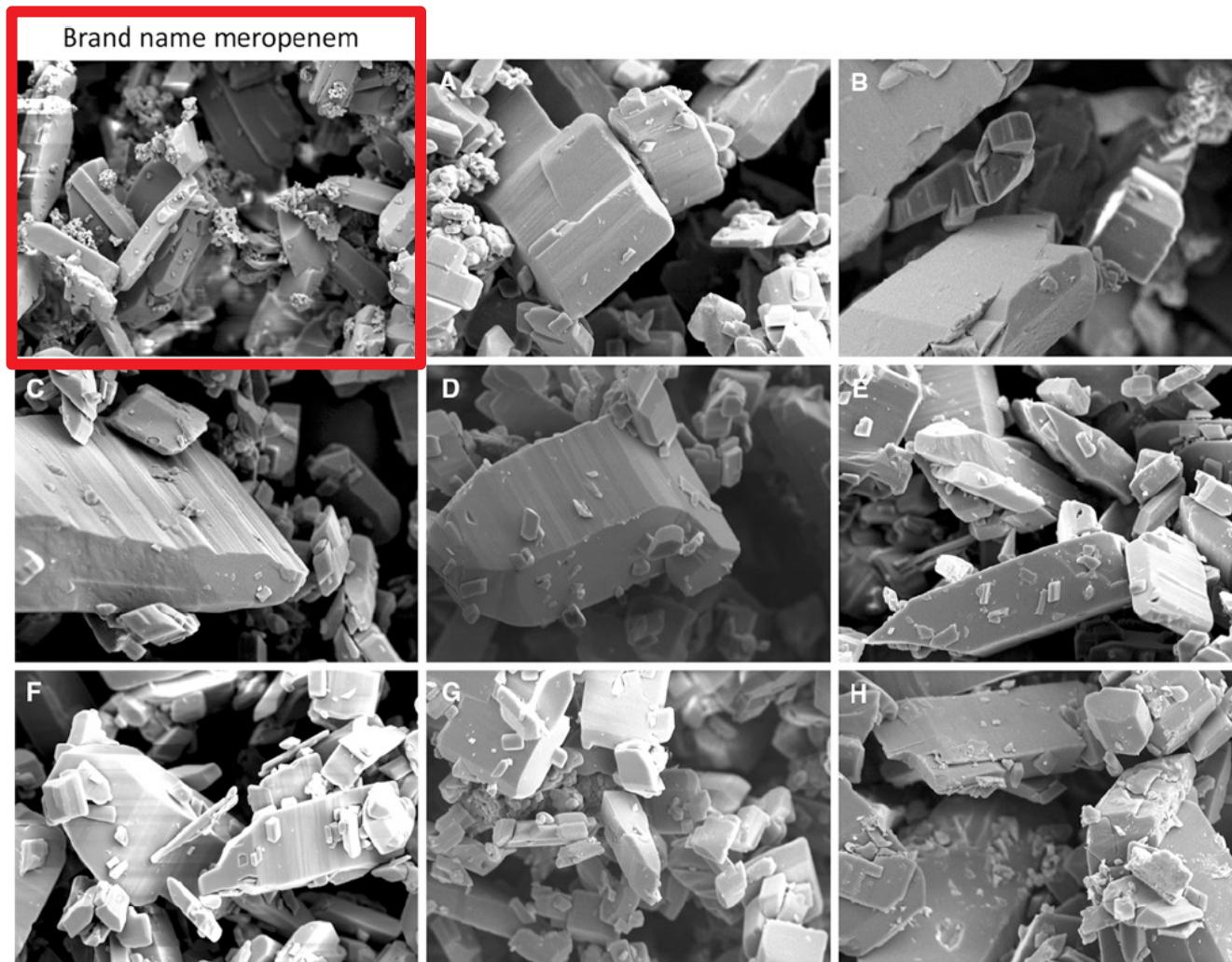
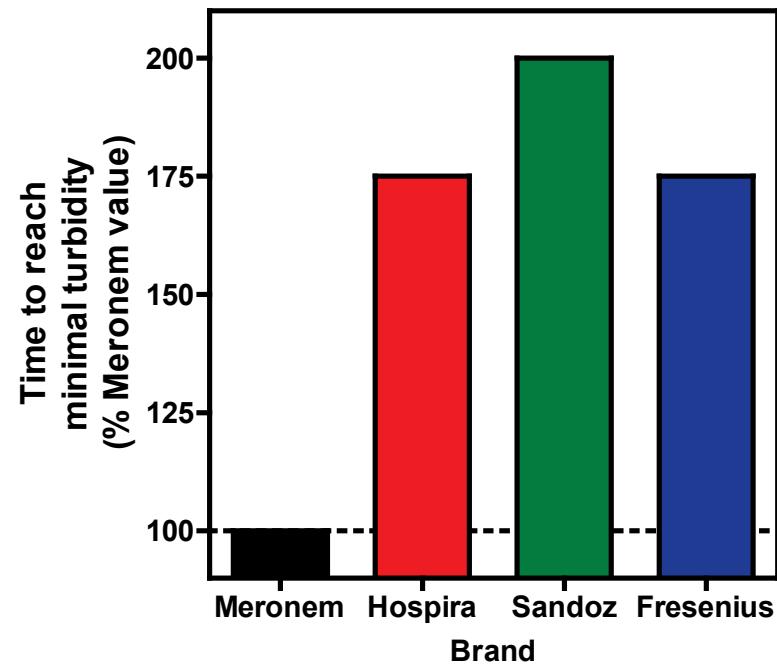
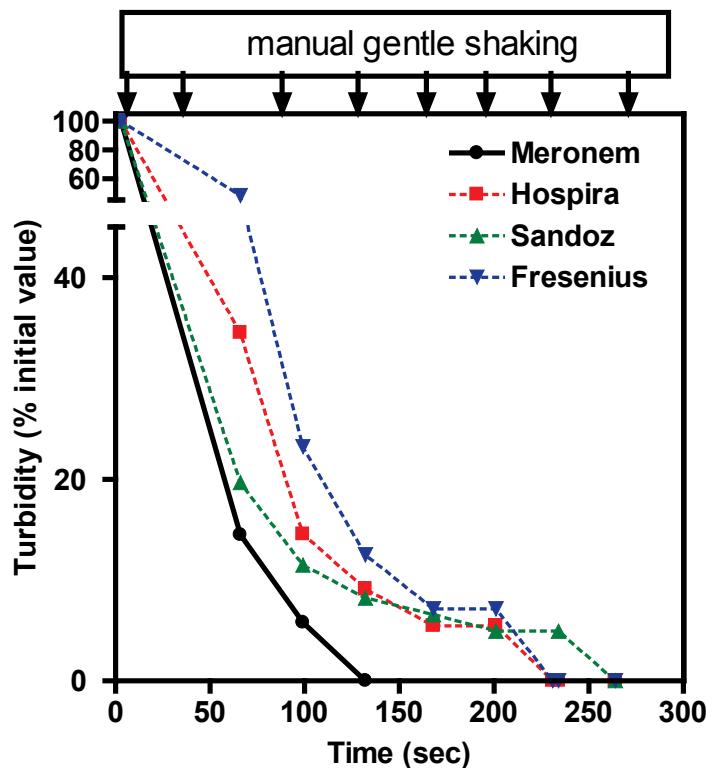


Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. a-h Generic products of meropenem. $\times 1,000$

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

Dissolution of meropenem in Belgium

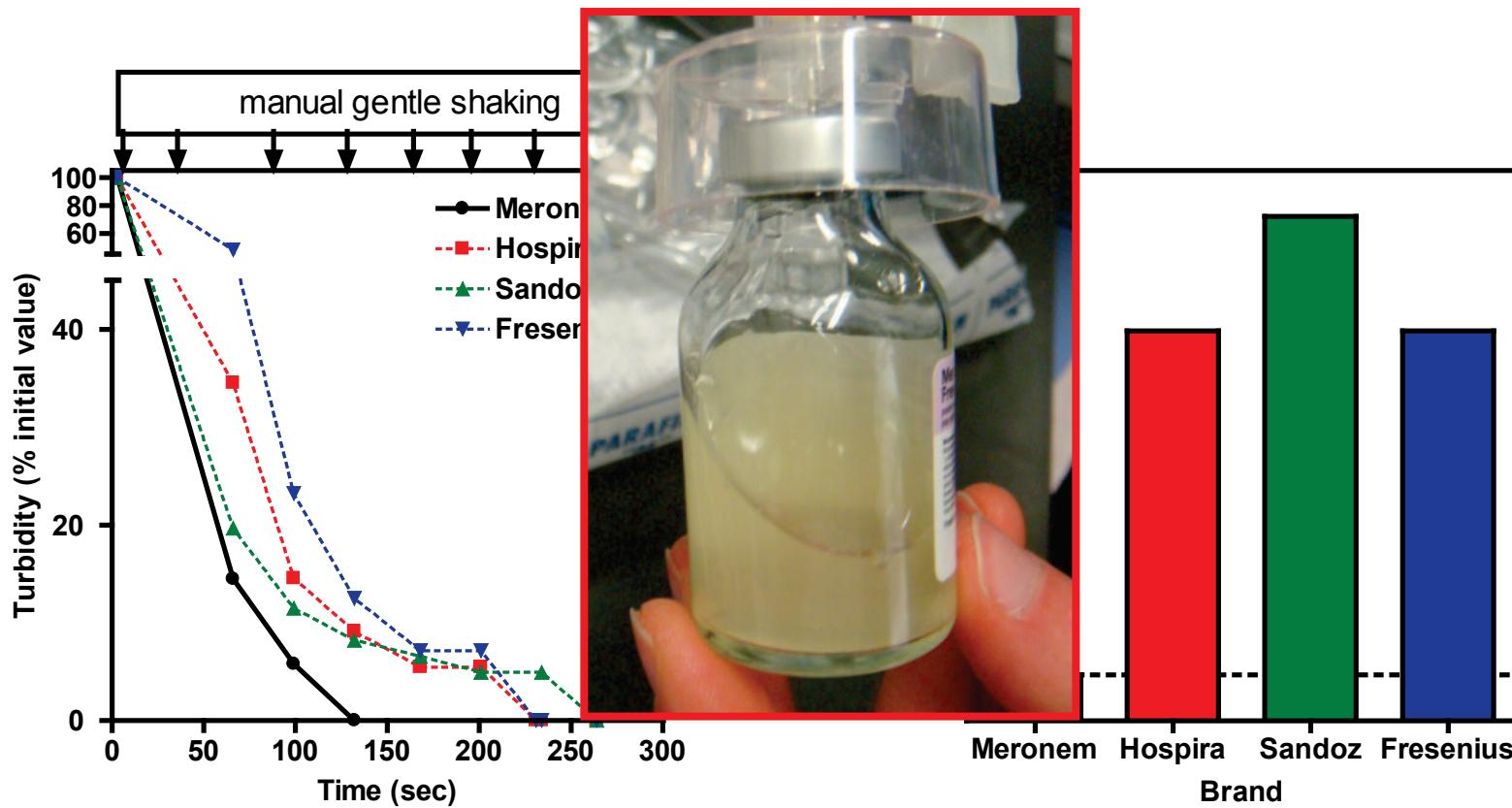
Drug concentration : 50 mg/mL (~ solution used for infusion)
gentle manual shaking followed by turbidity measures;
room temperature



Van Bambeke *et al.*, in preparation

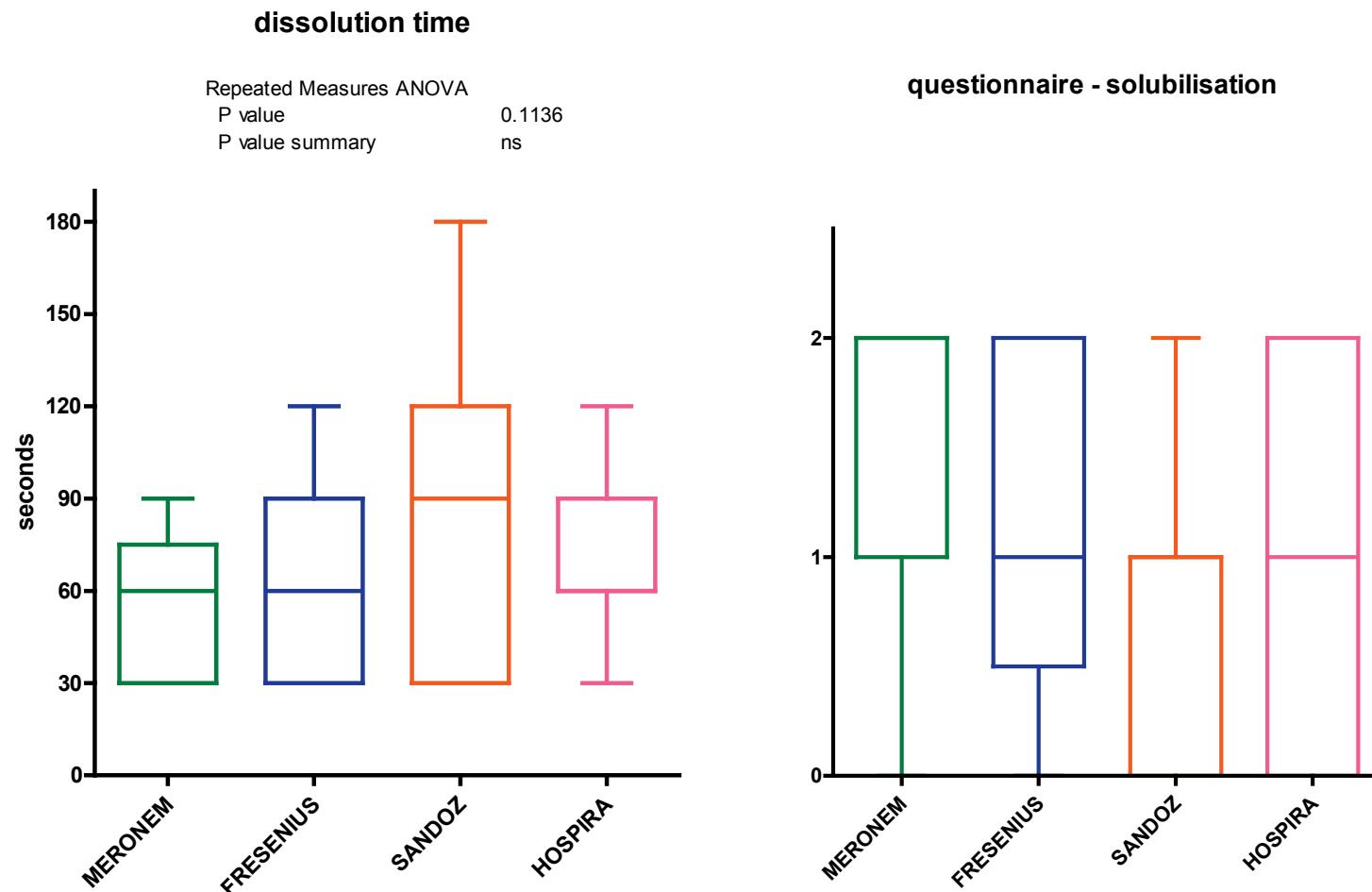
Dissolution of meropenem in Belgium

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



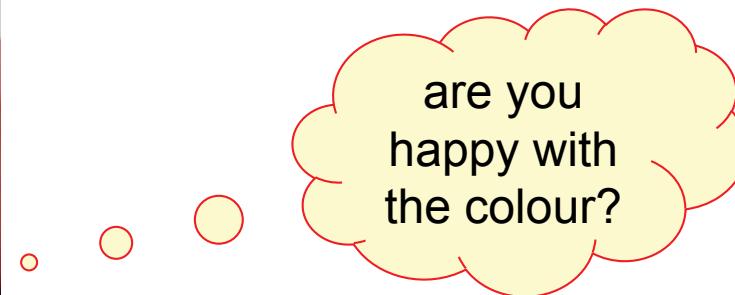
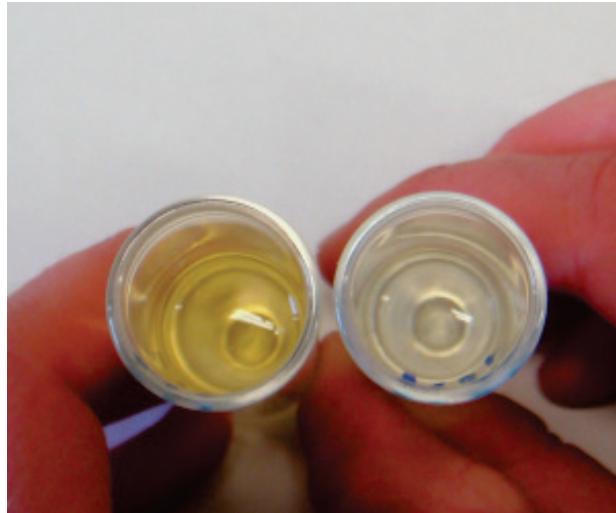
Van Bambeke et al., in preparation

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



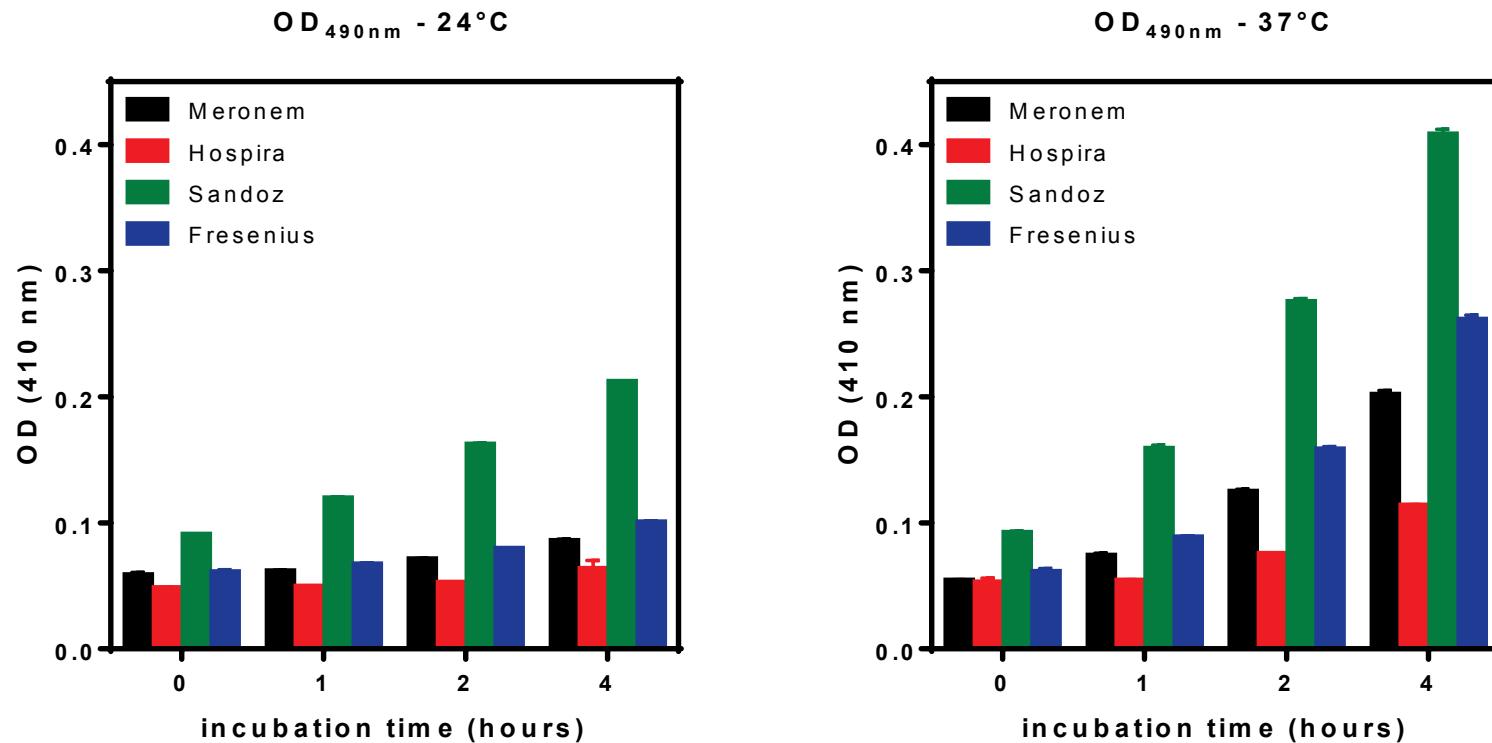
Van Bambeke *et al.*, in preparation

Impurities in meropenem: coloured compounds



Van Bambeke *et al.*, in preparation

Impurities in meropenem: coloured compounds



Van Bambeke *et al.*, in preparation

A pharmacist's dream or nightmare ?

Méropénem

Meronem (AstraZeneca)

[méropénem]
flacon i.v. - perf.

€ 1 x 500mg poudre	Rx	af b	€ 10,68
€ 1 x 1g poudre	Rx	af b	€ 15,69

Meropenem Fresenius Kabi (Fresenius Kabi)

[méropénem]
flacon i.v. - perf.

€ 10 x 500mg poudre	U.H.		[€ 76]
€ 10 x 1g poudre	U.H.		[€ 137]

Meropenem Hospira (Hospira)

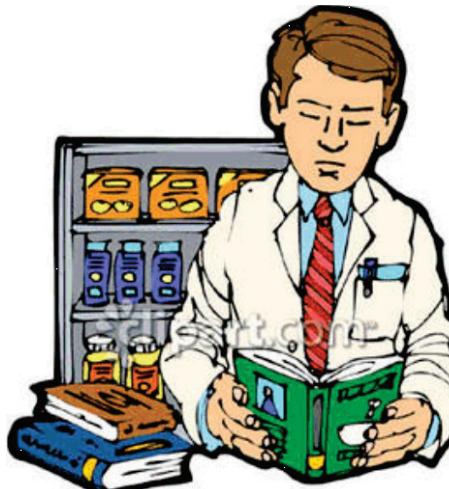
[méropénem]
flacon i.v. - perf.

€ 10 x 500mg poudre	Rx	af b	€ 87,75
€ 10 x 1g poudre	Rx	af b	€ 150,42

Meropenem Sandoz (Sandoz)

[méropénem]
flacon i.v. - perf.

€ 10 x 500mg poudre	U.H.		[€ 76]
€ 10 x 1g poudre	U.H.		[€ 137]



Piperacilline / Tazobactam EG (Eurogenerics)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon perf.

€ 1	Rx	af b	[€ 4]
€ 1	Rx	af b	[€ 7]

Piperacilline / Tazobactam Fresenius Kabi (Fresenius Kabi)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon perf.

€ 10	Rx	af b	€ 66,02
€ 10	Rx	af b	€ 112,66

Piperacilline / Tazobactam Hospira (Hospira)

[pipéracilline (sodium) 4g + tazobactam (sodium) 500mg]
flacon i.v. - perf.

€ 12	Rx	af b	€ 132,29
------	----	------	----------

Piperacilline / Tazobactam Mylan (Mylan)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon i.v. - perf.

€ 1	Rx	af b	[€ 6]
€ 1	Rx	af b	[€ 11]

Piperacilline / Tazobactam Sandoz (Sandoz)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon perf.

€ 10	Rx	af b	[€ 62]
€ 10	Rx	af b	[€ 112]

Tazocin (Pfizer)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon perf.

€ 1	Rx	af b	€ 11,86
€ 1	Rx	af b	€ 17,92

The problem may be in the physical forms and in the impurities

Antimicrobial Original Research Paper

Pharmaceutical quality of eight generics of ceftriaxone preparation for injection in Eastern Asia

Isabelle Arnet¹, Matthias Altermatt², Yves Roggo², Gabriel Schnetzler²

¹Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, ²F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: To compare the pharmaceutical quality of original and generic ceftriaxone sodium preparations for injection produced in Eastern Asia.

Methods: Standard physical and chemical laboratory tests were performed.

Participants/material: Ceftriaxone (Rocephin®; Roche, Switzerland) was the reference material. Generics produced in China, India, and Indonesia were sampled in China and Myanmar within their expiration dates.

Results: Eight generics obtained from Eastern Asia markets in January 2013 were analysed. All eight generics failed the specifications in three or more tests. Residues of solvents and metals were detected in all generics, four were not particle free, and two were not sterile.

Conclusions: All tested generic ceftriaxone products failed to meet the pharmaceutical quality standards of the branded original. The high levels of impurities and the identified contamination of particles and residues are of clinical concern, as they could impact tolerability and safety in patients in need of an effective parenteral antibiotic.

The problem may be in the impurities

Table 2 Specifications of Rocephin and physical characteristics of generic ceftriaxone products tested

Product (manufacturer)	Container integrity	Description vial/dry powder/vial		Average fill mass (mg)	Content of ceftriax one per vial (mg)	Particles per 1/10 containers
		Crystallinity	Colour			
Rocephin (Roche)	Tight closed	Crystalline	White to off-white	1140–1284	900–1100	<6/<20
Becef (Nectar Lifesciences)	Tight closed	Mostly amorphous	Off-white	1189	974	4/23
Cefaxone (Lupin)	Tight closed	Mostly amorphous	Off-white	1205	969	2/10
Cefin (Panbiotic)	Tight closed	Mostly amorphous	White	1195	996	6/18
Ceftriaxon (CCPC)	Tight closed	Amorphous crystalline	White	1194	992	2/6
Ceftriaxon (NCP)	Tight closed	Amorphous crystalline	White	1168	974	2/3
Incept (Ind_Swift)	Tight closed	Mostly amorphous	Off-white	1209	981	8/31
Oframax (Ranbaxy)	Tight closed	Mostly amorphous	White	1170	963	3/6
Triacef (Dexa Medica)	Tight closed	Amorphous crystalline	White	1163	941	12/13

huge variations of
the physical form

The problem may be in the impurities

Table 2 Specifications of Rocephin and physical characteristics of generic ceftriaxone products tested

Opalescence	pH	Degradation products	In solution			
			Metals	Residual solvents	Sterility	Deviations
Clear; <3.0	6.0–8.0	<2.29%	0	0	No growth	0
<i>Strong opalescent;</i> 22.6	6.9	0.52%	<i>Mn*</i> <i>Fe*</i> <i>Zn*</i> <i>Br*</i> <i>SB TH</i> +	No growth	5	
<i>Opalescent;</i> 14.2	6.3	0.84%	<i>Fe*</i> <i>Zn*</i> <i>Br†</i> <i>Sr*</i> <i>SB TH</i> +	No growth	4	
Clear; 2.1	6.8	0.23%	<i>Zn*</i>	<i>SB H</i> +	No growth	4
Clear; 2.2	6.7	0.17%	<i>Zn* Br*</i>	<i>SB</i> +	No growth	3
<i>Faintly opalescent;</i> 3.2	6.7	0.28%	<i>Fe*</i> <i>Zn*</i> <i>Br*</i>	<i>SB</i> +	No growth	4
<i>Opalescent;</i> 13.2	6.5	0.64%	<i>Zn*</i>	<i>SB TH</i> +	<i>Germs</i> [§]	6
<i>Opalescent;</i> 7.7	6.5	0.54%	<i>Fe*</i> <i>Zn†</i>	<i>SB TH</i> +	<i>Germs</i> [¶]	5
<i>Opalescent;</i> 6.4	6.5	0.73%	<i>Fe*</i> <i>Zn† Br‡</i>	<i>SB</i> +	No growth	5

*Content 1–4 ppm;

†Content 5–9 ppm;

‡Content 16 ppm.

[§]*Kocuria rhizophila*, *Brachybacterium muris*, and gram-positive cocci.

[¶]Gram-positive sporulated rods.

S: siloxane; B: butylated hydroxytoluene; T: tetradecan; H: hexadecan; +: not identifiable.

Deviations are in italics.

A number of deviations

Impurities in ciprofloxacin...



Available online at www.sciencedirect.com



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 , ^1H and DOSY NMR analysis

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

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Received 29 November 2006; received in revised form 19 February 2007; accepted 19 February 2007

Available online 1 March 2007

Abstract

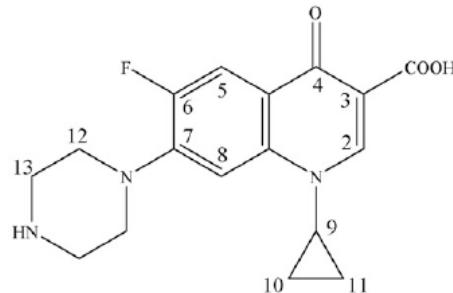
The objective of this study was to control the purity of 16 commercial formulations of ciprofloxacin tablets purchased in different countries or via the Internet using ^{19}F and ^1H nuclear magnetic resonance (NMR). Twelve out of the sixteen commercial formulations of ciprofloxacin measured by ^{19}F 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 ^1H 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 ^1H 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) ^1H NMR which allowed the characterisation of some excipients present in the formulations studied.

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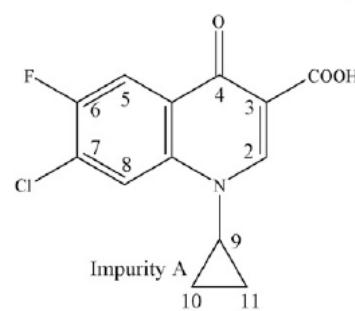
Keywords: ^{19}F NMR; ^1H NMR; DOSY ^1H NMR; Ciprofloxacin; Impurities

Impurities in ciprofloxacin

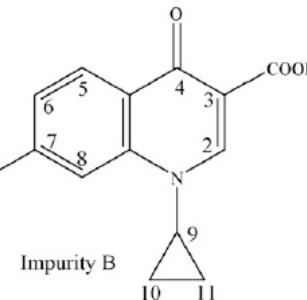
Every
pharmacochemist
will know why you
get this !



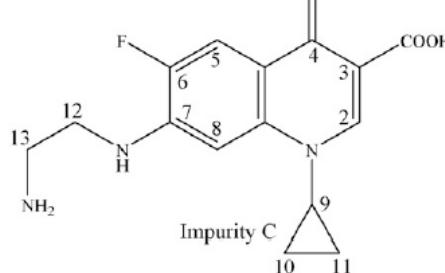
Ciprofloxacin



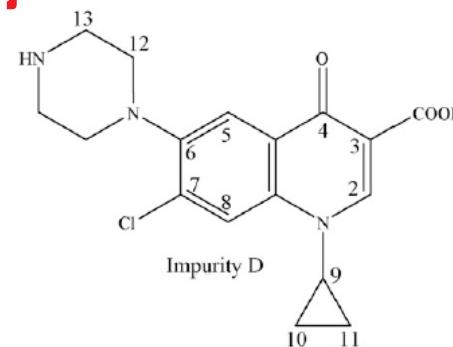
Impurity A



Impurity B



Impurity C



Impurity D

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

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

Substandard (wrong) drugs in the world ?

BJCP British Journal of Clinical Pharmacology

Substandard drugs: a potential crisis for public health

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Keywords

drug quality, falsification, inspection, regulation, substandard

Received

13 August 2013

Accepted

1 November 2013

Accepted Article

Published Online

29 November 2013

Poor-quality medicines present a serious public health problem, particularly in emerging economies and developing countries, and may have a significant impact on the national clinical and economic burden. Attention has largely focused on the increasing availability of deliberately falsified drugs, but substandard medicines are also reaching patients because of poor manufacturing and quality-control practices in the production of genuine drugs (either branded or generic). Substandard medicines are widespread and represent a threat to health because they can inadvertently lead to healthcare failures, such as antibiotic resistance and the spread of disease within a community, as well as death or additional illness in individuals. This article reviews the different aspects of substandard drug formulation that can occur (for example, pharmacological variability between drug batches or between generic and originator drugs, incorrect drug quantity and presence of impurities). The possible means of addressing substandard manufacturing practices are also discussed. A concerted effort is required on the part of governments, drug manufacturers, charities and healthcare providers to ensure that only drugs of acceptable quality reach the patient.

Is this a problem in Belgium ?

Infractions au niveau des "bonnes pratiques cliniques" chez GVK Biosciences, Inde -- AFMPS

nl fr en Autres informations et services officiels: www.belgium.be .be

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afmps agence fédérale des médicaments et des produits de santé

Vos médicaments et produits de santé, notre préoccupation

Usage humain Usage vétérinaire Information pour le public Notification d'effets/ réactions indésirables et/ou d'incidents

Home ▶ Actualité ▶ Infractions au niveau des "bonnes pratiques cliniques" chez GVK Biosciences, Inde

Infractions au niveau des "bonnes pratiques cliniques" chez GVK Biosciences, Inde

date: 05 décembre 2014

Une inspection menée chez GVK Biosciences Private Limited en Inde par l'agence Française en charge des médicaments (Agence Nationale de Sécurité du Médicament et des Produits de Santé - ANSM) a révélé des non-conformités majeures au niveau des directives en matière de bonnes pratiques cliniques (Good Clinical Practices, GCP). Des doutes sont apparus quant à la fiabilité de la partie clinique des études de bioéquivalence effectuées par le site inspecté, et, dès lors, quant à l'acceptabilité des données soumises lors des demandes d'obtention des autorisations de mise sur le marché des médicaments concernés.

Nouvelle campagne de sensibilisation

Les enfants sont souvent sujets à des affections bénignes qui ne doivent pas forcément être traitées par des médicaments, sauf si des symptômes inquiétants apparaissent. L'afmps vous propose quelques conseils pour vous aider à faire un bon usage des médicaments chez les enfants, en cas de fièvre, toux et rhume, régurgitations.

[En savoir plus](#)

Is this a problem in Belgium ?

Infractions au niveau des "bonnes pratiques cliniques" chez GVK Biosciences, Inde -- AFMPS

nl fr en Autres informations et services officiels: www.belgium.be .be

A propos de l'AFMPS Offres d'emploi Actualité Presse Contact Plaintes

afmps agence fédérale des médicaments et des produits de santé

Vos médicaments et produits de santé, notre préoccupation

Usage humain Usage vétérinaire Information pour le public Notification d'effets/ réactions indésirables et/ou d'incidents

Home ▶ Actualité ▶ Infractions au niveau des "bonnes pratiques cliniques" chez GVK Biosciences, Inde

Infractions au niveau des "bonnes pratiques cliniques" Nouvelle campagne de

Une inspection menée chez GVK Biosciences Private Limited en Inde par l'agence Française en charge des médicaments (Agence Nationale de Sécurité du Médicament et des Produits de Santé - ANSM) a révélé des non-conformités majeures au niveau des directives en matière de bonnes pratiques cliniques (Good Clinical Practices, GCP). Des doutes sont apparus quant à la fiabilité de la partie clinique des études de bioéquivalence effectuées par le site inspecté, et, dès lors, quant à l'acceptabilité des données soumises lors des demandes d'obtention des autorisations de mise sur le marché des médicaments concernés.

But what says France ?

Glossaire | Abonnement | Agenda | Newsletter 

ansm
Agence nationale de sécurité du médicament
et des produits de santé

Cliquez ici pour effectuer une recherche... 

L'ANSM S'informer Décisions Activités Dossiers Publications Services Produits de santé

Déclarer un effet indésirable

Accueil > S'informer > Actualité > L'ANSM lance une procédure de suspension, à compter du 18 décembre, de 25 médicaments commercialisés en France - Point d'Information 

S'informer

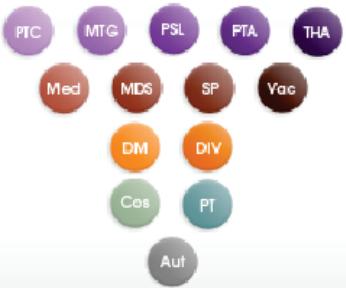
- > Actualité
- Points d'information**
- Informations de sécurité**
- Communiqués**
- Travaux de l'Agence Européenne des Médicaments (EMA)**

← précédent

L'ANSM lance une procédure de suspension, à compter du 18 décembre, de 25 médicaments commercialisés en France - Point d'Information

05/12/2014

 [Liste des spécialités commercialisées en France dont les AMM sont suspendues à compter du 18 décembre 2014 \(05/12/2014\) !\[\]\(8217f3e2a14b365f9c78bd68393a956d_img.jpg\) \(12 ko\)](#)


PTC MTG PSL PTA THA
Med MDS SP Vac
DM DIV PT
Cos Aut

Une inspection par l'ANSM d'un site de la société GVK Bio qui réalise des essais cliniques parmi lesquels des essais de bioéquivalence en Inde, a mis en évidence des irrégularités dans des documents associés à ces essais sur lesquels s'appuient les AMM (autorisation de mise sur le marché) de plusieurs médicaments. Même si ces documents ne sont pas indispensables à la démonstration de la bioéquivalence, l'ANSM a décidé, par mesure de précaution, de suspendre les AMM de 25 médicaments génériques commercialisés.

> Répertoire des médicaments
> Autorisation et déclaration

But what says France ?

The screenshot shows the homepage of the Agence nationale de sécurité du médicament et des produits de santé (ANSM) in France. The top navigation bar includes links for Glossaire, Abonnement, Agenda, Newsletter, and a Twitter icon. Below the header is the ANSM logo and a search bar. A menu bar offers links to L'ANSM, S'informer, Décisions, Activités, Dossiers, Publications, Services, and Produits de santé. A sidebar on the left provides a link to declare不良事件 (Déclarer un effet indésirable). The main content area features a large title about a suspension procedure for 25 medicines, dated December 5, 2014. A red box highlights a note from the ANSM regarding an inspection in India.

Glossaire | Abonnement | Agenda | Newsletter

an sm
Agence nationale de sécurité du médicament
et des produits de santé

Cliquez ici pour effectuer une recherche...

L'ANSM S'informer Décisions Activités Dossiers Publications Services Produits de santé

Déclarer un effet indésirable

Accueil > S'informer > Actualité > L'ANSM lance une procédure de suspension, à compter du 18 décembre, de 25 médicaments commercialisés en France - Point d'Information

PTC MTG PSL PTA THA

← précédent

L'ANSM lance une procédure de suspension, à compter du 18 décembre, de 25 médicaments commercialisés en France - Point d'Information

05/12/2014

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But what says France ?

The screenshot shows the homepage of the Agence nationale de sécurité du médicament et des produits de santé (ANSM) in France. The top navigation bar includes links for Glossaire, Abonnement, Agenda, Newsletter, and social media icons for Twitter and LinkedIn. Below the header is the ANSM logo and a search bar. A menu bar offers links to L'ANSM, S'informer, Décisions, Activités, Dossiers, Publications, Services, and Produits de santé. A green banner highlights the 'Déclarer un effet indésirable' (Report an不良 effect) service. The main content area features a large red-bordered box containing the following text:

L'ANSM lance une procédure de suspension, à compter du 18 décembre, de 25 médicaments commercialisés en France - Point d'Information

05/12/2014

Below the main title, a red box contains the following text:

Une inspection par l'ANSM d'un site de l'entreprise CIVI Bio, qui réalise des essais cliniques pour la preuve de la bioéquivalence en Inde, a mis en évidence des irrégularités dans des documents associés à ces essais sur lesquels s'appuient les AMM (autorisation de mise sur le marché) de plusieurs médicaments. Même si ces documents ne sont pas indispensables à la démonstration de la bioéquivalence, l'ANSM a décidé, par mesure de précaution, de suspendre les AMM de 25 médicaments génériques commercialisés.

3d round of conclusions and discussion

- Generic drugs **may or may not** be of the same pharmaceutical quality as the original products
- The reasons for **variable** quality are
 - difficulties in **correctly reproducing the manufacturing and purifications procedures** of the originator
(often more a “know how” than patentable matters)
 - the **race to low prices** that may lead to changes in production schemes
 - the **different routes followed for approval** (centralized, decentralized, national)¹
 - the fact that **controls may be insufficient** (after first registration)
- Only stringent and continuous controls can help avoiding the flood of low quality products
(but this may be difficult in face of the number of producers) 

¹ see “Best practice guidance on the common principle for collaboration between CMDh/RMS and EMA on generics and hybrids” EMA/234449/2012
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500135719.pdf
Last visited: 8 January 2014

Do you remember how many levofloxacinS we now have in Belgium

What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
 1. MIC, MPC, heteroresistance ...
 2. Approach to pharmacodynamic equivalence
 3. PK/PD animal models and clinical data
4. Dissolution, stability, impurities
5. **The hidden risks of "low cost" drugs**
 1. **overconsumption (and wrong publicity [in back-up])**
 2. **lack of innovative research ... unless you pay !**

The efforts for a correct use of antibiotics...

REVIEWS OF INFECTIOUS DISEASES • VOL. 3, NO. 4 • JULY-AUGUST 1981
© 1981 by The University of Chicago. All rights reserved. 0162-0886/81/0304-0016\$02.00

SESSION III

Evaluation of Antibiotic Usage: A Comprehensive Look at Alternative Approaches

Calvin M. Kunin *From the Department of Medicine, The Ohio State University School of Medicine, Columbus, Ohio*

Current problems related to the use of antibiotics in the United States are summarized. In 1979, pharmaceutical manufacturers shipped \$1.55 billion worth of anti-infective drugs. It is estimated that in approximately one-half of all cases that involve administration of antibiotics in the hospital, either the medical condition does not require antibiotic treatment, the most effective and least expensive drug is not chosen, or the correct dosage or duration of therapy is not prescribed. Much of the high cost of antibiotic therapy can be attributed to the use of expensive antibiotics of the cephalosporin and aminoglycoside groups and to the excessive duration of antibiotic prophylaxis in surgery. This review presents methods that assess the magnitude of the problem by audit and analyzes the corrective approaches that have been suggested. The major issues of concern related to the use of antibiotics are the complex series of considerations that lead physicians to prescribe antibiotics and the problem of patient expectation and compliance. Excessive usage of antibiotics must be viewed as part of the problem of overusage of all drugs and laboratory procedures.

How many of you were practicing Medicine at that time ?

This has been known for years

We are facing contradictory situations

J Antimicrob Chemother 2014; 69: 2886–2888

doi:10.1093/jac/dku350 Advance Access publication 11 September 2014

This is today !

Journal of
Antimicrobial
Chemotherapy

Developing the first national antimicrobial prescribing and stewardship competences

D. Ashiru-Oredope^{1*}, B. Cookson² and C. Fry³ on behalf of the Advisory Committee on Antimicrobial Resistance
and Healthcare Associated Infection Professional Education Subgroup

¹Antimicrobial Resistance, Stewardship and Healthcare Associated Infection (AMRS & HCAI) Programme, Public Health England,
London, UK; ²Division of Infection and Immunity, University College London, London, UK; ³Department of Health, London, UK

*Corresponding author. Tel: +44-(0)20-832-76689; E-mail: diane.ashiru-oredope@phe.gov.uk

†Members are listed in the Acknowledgements section.



Public Health
England

ARHAI

Department of Health
Expert Advisory Committee on Antimicrobial Resistance
and Healthcare Associated Infection

**Antimicrobial prescribing and
stewardship competencies**

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/253094/ARHAIprescregcompetencies_2_.pdf

We are facing contradictory situations

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^tMembers are listed in the Acknowledgements section.

According to Doron and Davidson (2011) (6) three major goals for antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse
- minimise development of resistance at patient and community levels

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/253094/ARHAlprescrevcompetencies_2_.pdf

But see what happens with “Low cost antibiotics”... *The sour Danish Experience*

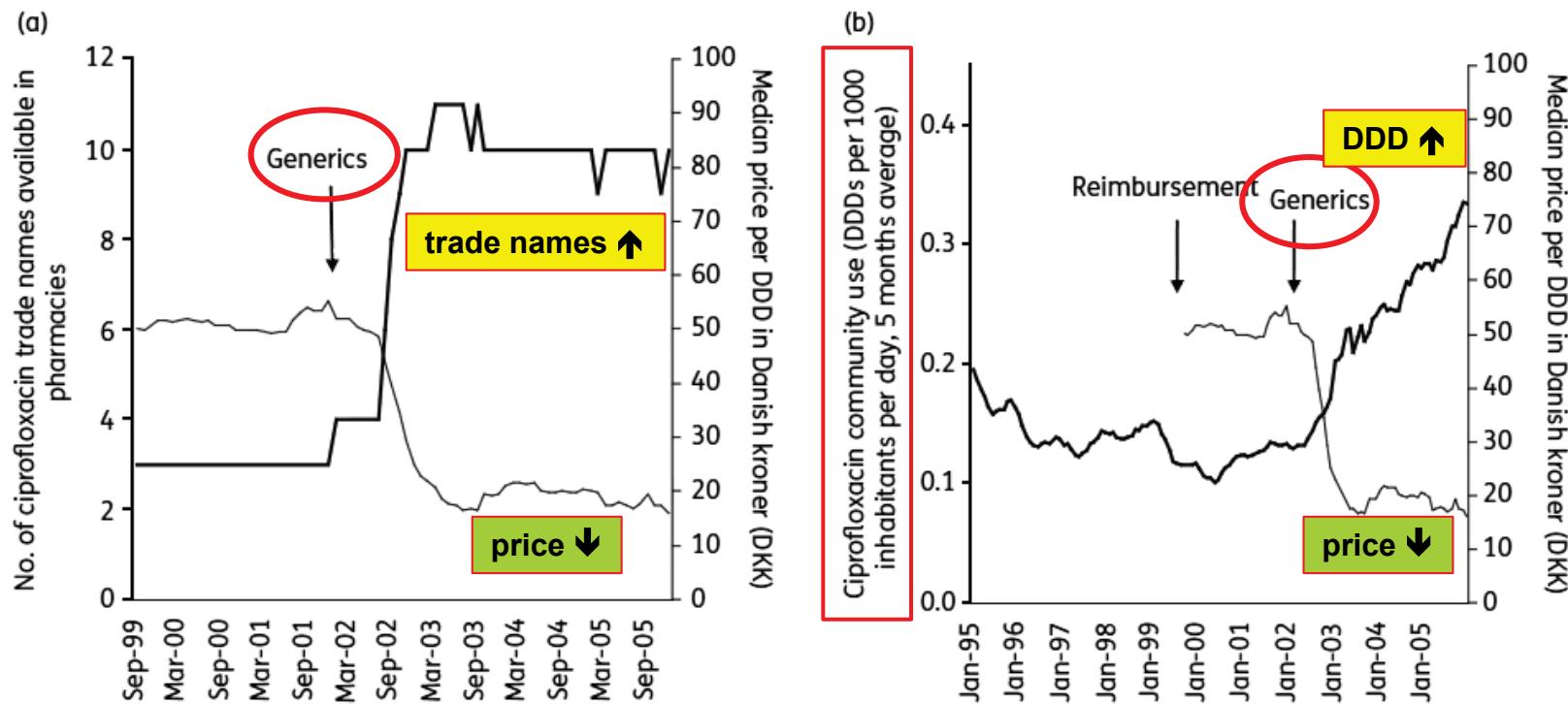


Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin. (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. $100 \text{ DDK} \approx 13 \text{ EUR}$.

But this had already occurred in Germany...

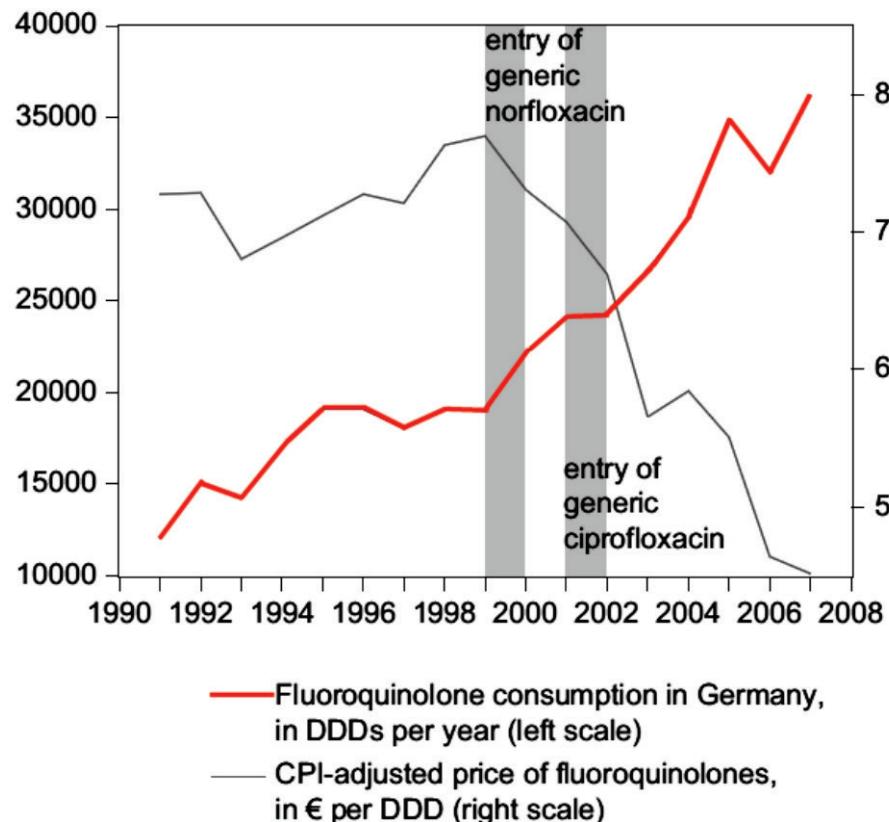


Figure 1. Fluoroquinolone consumption in Germany (SHI-related prescriptions, 1991–2007).
SHI = statutory health insurance; DDD = defined daily doses; CPI = consumer price index

Klaus Kaier: The impact of pricing and patent expiration on demand for pharmaceuticals: an examination of the use of broadspectrum antimicrobials
Health Economics, Policy and Law (2013) 8:7-20

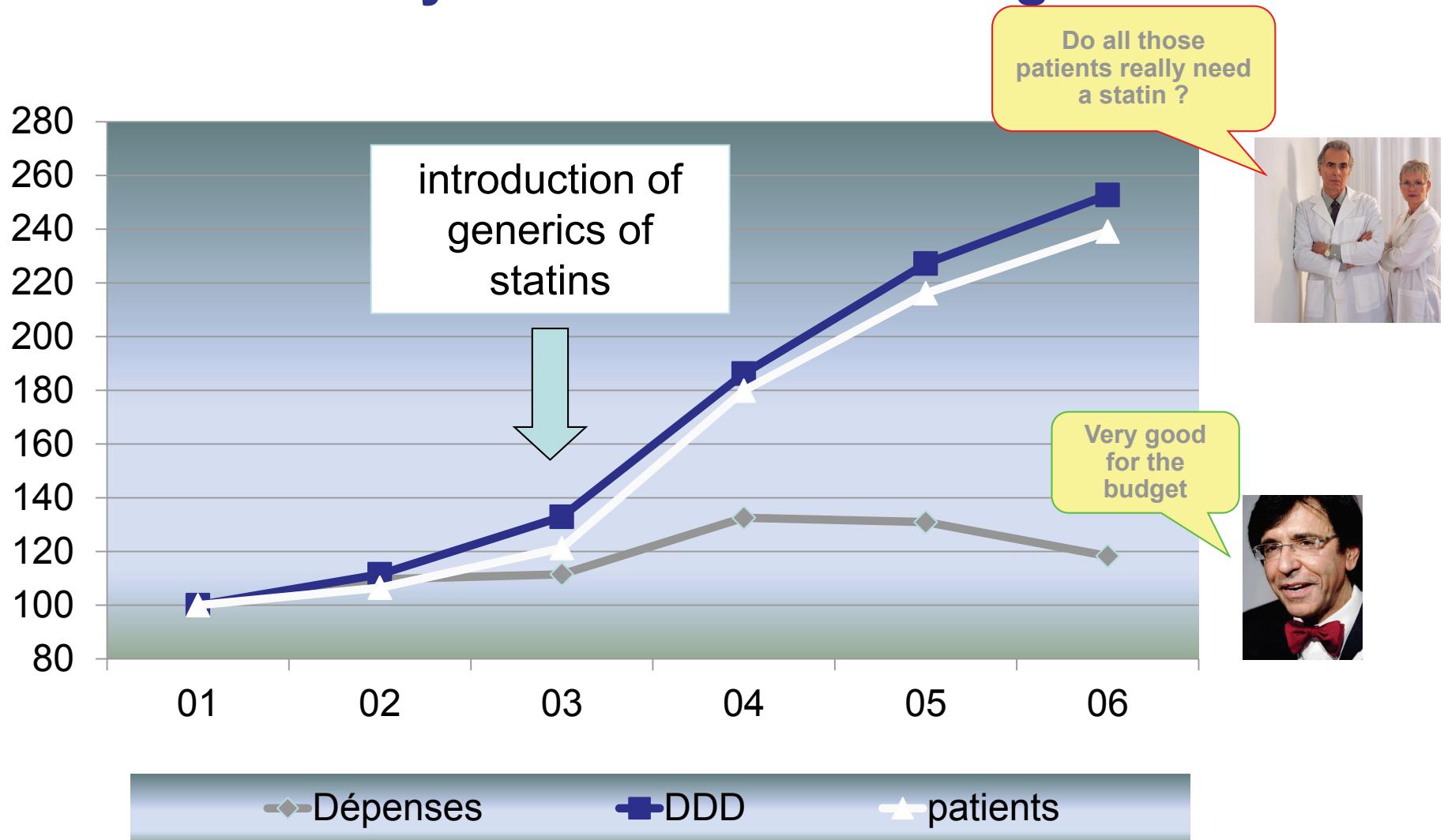
Specifically, generic competition lowers prices, which can accelerate consumption and resistance.

In: Mossialos et al. *Policies and incentives for promoting innovation in antibiotic research*
LSE Health, London School of Economics & Political Science, Houghton Street, London, 199 pp

Available from
http://www.euro.who.int/_data/assets/pdf_file/0011/120143/E94241.pdf

See also:
<http://www.euro.who.int/en/about-us/partners/observatory/studies/policies-and-incentives-for-promoting-innovation-in-antibiotic-research>

A Journey to the statins in Belgium



And generic companies will use any possible argument to foster sales...



Moxifloxacin Sandoz®	PP
400 mg x 5 compr.	€ 15,42
10 compr.	€ 26,14

This is an ad for a generic of a fluoroquinolone

Find the errors

...

Le générique d'Avelox®
Moxifloxacin Sandoz®

Choisissez les antibiotiques Sandoz,
choisissez pour la sécurité et la qualité !

What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
 1. MIC, MPC, heteroresistance ...
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4. Dissolution, stability, impurities
5. **The hidden risks of "low cost" drugs**
 1. overconsumption (and wrong publicity [in back-up])
 2. **lack of innovative research ... unless you pay !**

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 May 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 **recommendations of BAPCOC (**)** (amoxicillin [3 g / day in 3 administrations for 5 to 7 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 Nonproprietary Name

** BAPCOC: Belgian Antibiotic Policy Coordination Committee

But here is the consequence...

Generic antibiotics, antibiotic resistance, and drug licensing

Although new drugs continue to be licensed, too few are based on novel chemical entities; drug resistance is more likely to occur when new agents are variants of existing classes.

There is a serious mismatch between clinical need and supply of new medicines for which there is no quick answer—it takes about 10 years and up to US\$1 billion to develop a new antibiotic.

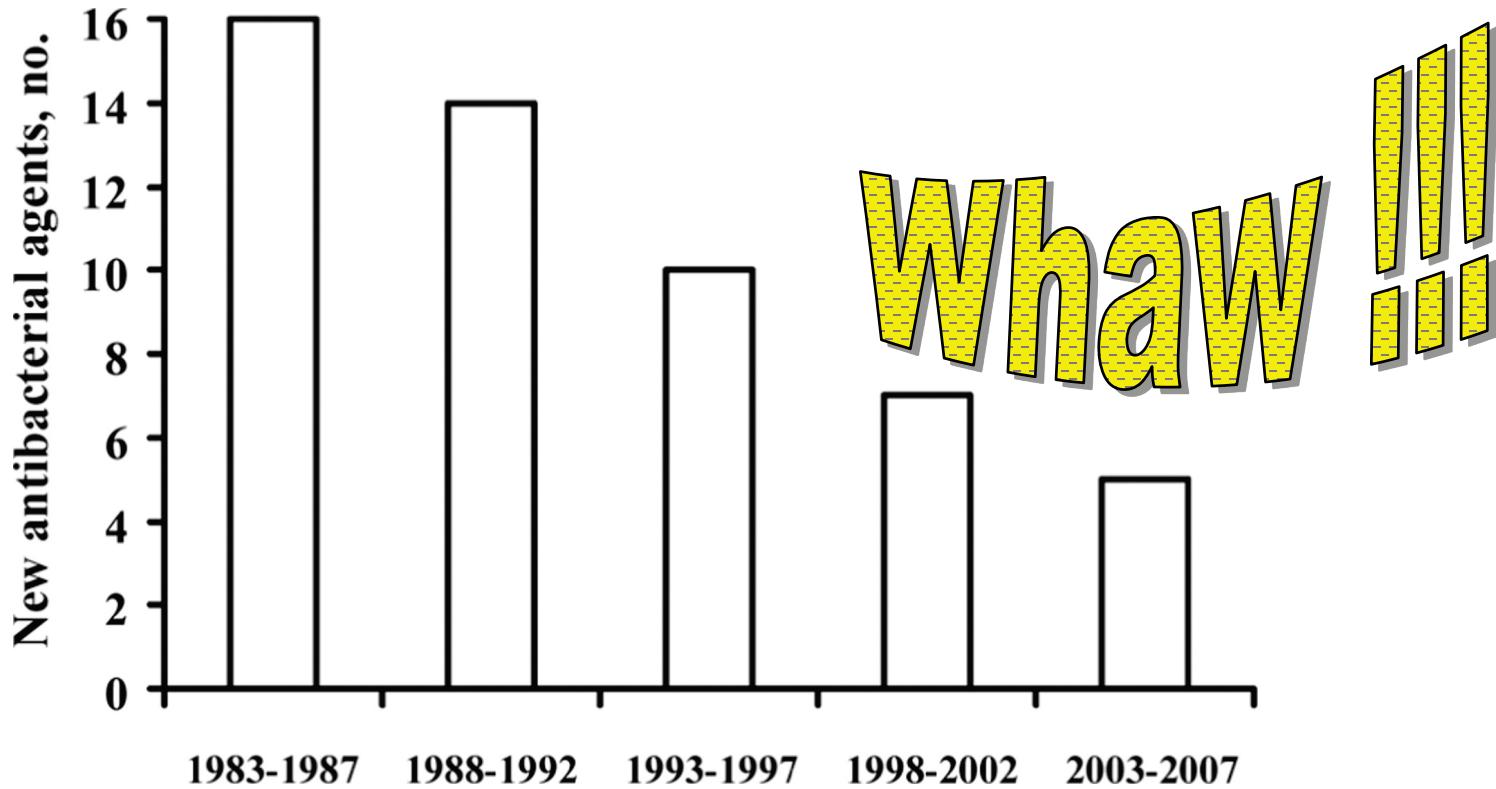
Roger Finch

r.finch@nottingham.ac.uk

The Nottingham University Hospitals NHS Trust;
and University of Nottingham, Nottingham,
NG5 1PB, UK

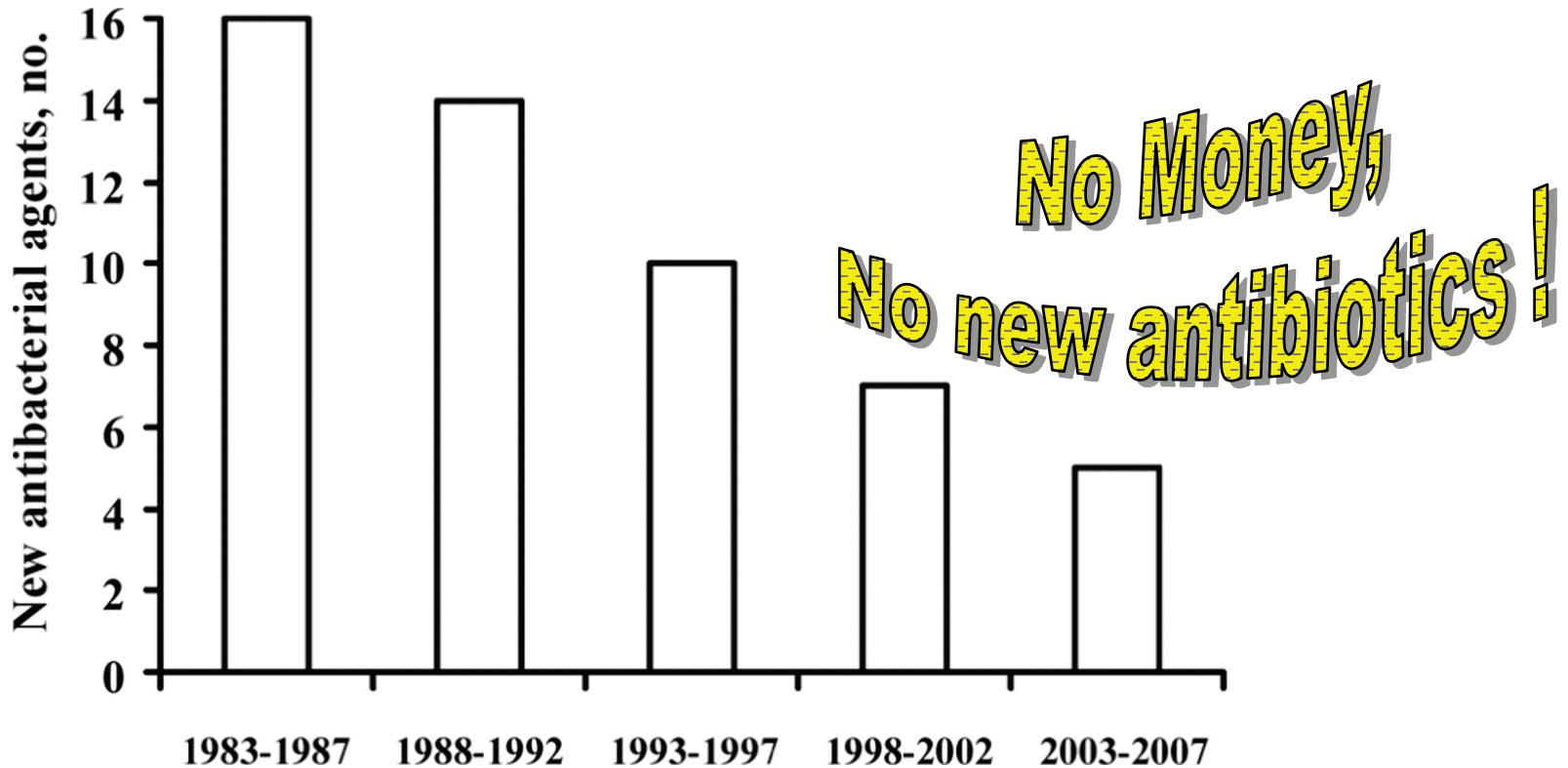


Innovative antibiotic development is abandoned by Industry



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

Why do they abandon it ?

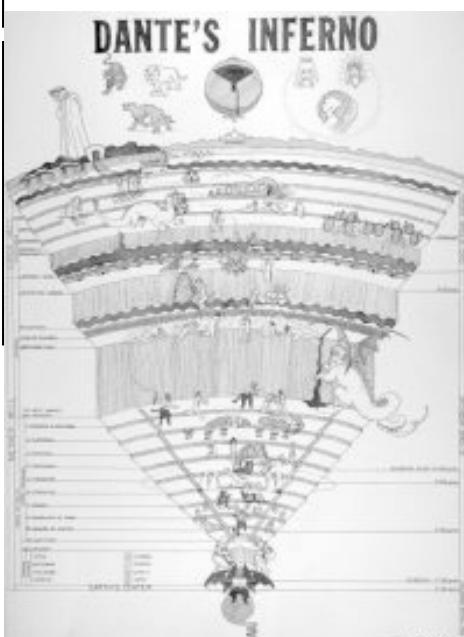


Boucher H W et al. Clin Infect Dis. 2009;48:1-12

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(last accessed: 7 November 2013)

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

* INN: International Nonproprietary Name

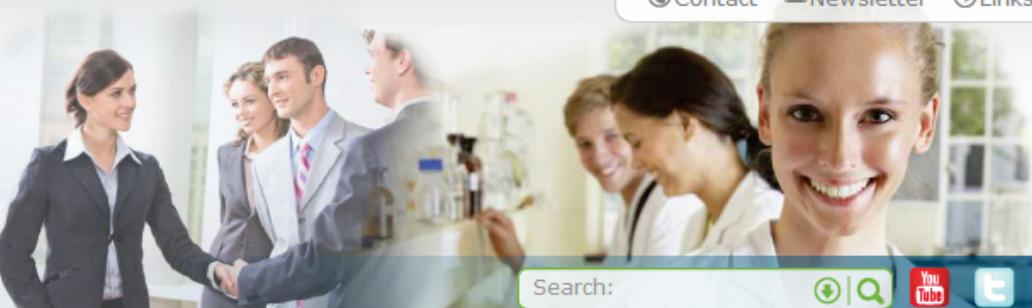
** BAPCOC: Belgian Antibiotic Policy Coordination Committee

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 and reimbursement of an antibiotic treatment is **MUCH less**
- For comparison, 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)
- Compare to the drug acquisition price to treat a pneumonia (as an example)
- Find where the problem lies...

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

Europe in Action ...



The Innovative Medicines Initiative (IMI) logo is located in the top left corner. The logo consists of the letters "imi" in a stylized green font, enclosed within a blue swoosh shape.

Header navigation links: Contact, Newsletter, Links.

Search bar and social media icons (Twitter, YouTube, LinkedIn) are located in the bottom right corner of the header banner.

Innovative Medicines Initiative

- ▶ Home
- ▶ About IMI
- ▶ Ongoing projects
- ▶ Calls for proposals
- ▶ News, Events & Media
- ▶ Reference documents
- ▶ FAQ

THE INNOVATIVE MEDICINES INITIATIVE

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA.



IMI NEWSFLASH



08/05/2014 : The citation impact of IMI research is twice the world average. Find out more <http://t.co/65dIAwLuLs> <http://t.co/H3uZgYVZ6r>

08/05/2014 : RT
@BenjaminRibba: Our review of mixed-effect models for population analysis in oncology published today in PSP
<http://t.co/eepmVsuaRI>
@DDM...

- €2 billions euro budget...
- collaborative research projects and networks of industrial and academic experts...
- collaborative ecosystem for pharmaceutical research and development (R&D)...
- increase Europe's competitiveness globally...
- establish Europe as **the most attractive place for pharmaceutical R&D**

And more generally speaking... with a caveat...

Policies and incentives for promoting innovation in antibiotic research



Elias Mossialos, Chantal M. Morel,
Suzanne Edwards, Julia Berenson,
Marin Gemmill-Toyama, David Brogan



The European Observatory on Health Systems and Policies supports and promotes evidence-based health policy-making through comprehensive and rigorous analysis of health systems in Europe. It brings together a wide range of policy-makers, academics and practitioners to analyse trends in health reform, drawing on experience from across Europe to illuminate policy issues.

And more generally speaking... with a caveat...

Policies and incentives for promoting innovation in antibiotic research



Elias Mossialos, Chantal M. Morel,
Suzanne Edwards, Julia Berenson,
Marin Gemmill-Toyama, David Brogan



- It is necessary for European public health authorities to emphasize rationing of existing antibiotics intended for severe infection (using generics as first-line therapies). However, this gives the impression that, if developed, new antibiotics will be kept as last resort treatments regardless of high levels of resistance to widely used antibiotics.

The European Observatory on Health Policy-Making
It brings together a wide range of actors involved in health reform, drawing on experience from across Europe to illuminate policy issues

So, you will keep on reserve

- ceferoline and ceftobiprole
- oritavancin and dalbavancin
- tedizolid ...
- ceftozolane/tazobactam
- solithromycin

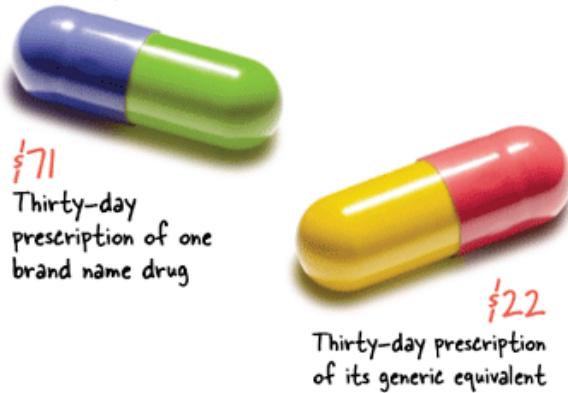
Summary / Suggestions

- 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)
- The **control of the quality of the generics** (and of all antibiotics in general) is critical and should go beyond simple declarations and initial lot analysis...
- **Antibiotics are a precious commodity** that should not be lost. Misuse through low prices may cause **HUGE expenses in the future**...
- May be we should move to **new economic frameworks**...

Back-up

You said "generics"

Your prescription,
your choice.



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.

US "Abbreviated New Drug Application"

The screenshot shows the official website of the U.S. Food and Drug Administration (FDA). The header features the FDA logo and the text "U.S. Food and Drug Administration" and "Protecting and Promoting Your Health". Below the header is a navigation menu with links to Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, and a search bar. On the left, there is a sidebar titled "Development & Approval Process (Drugs)" which includes links for "How Drugs are Developed and Approved", "Types of Applications", "Abbreviated New Drug Application (ANDA): Generics", "Generic Drugs: Information for Industry", "Previous News and Announcements (Generic Drugs)", "ANDA Forms & Submission Requirements", "Paragraph IV Patent Certifications", and "Suitability Petitions". The main content area is titled "Abbreviated New Drug Application (ANDA): Generics" and contains text explaining what an ANDA is, how it compares to an innovator drug, and the process for generic drug approval. It also mentions the "Orange Book" and the bioequivalence requirement.

Abbreviated New Drug Application (ANDA): Generics

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

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

FDA approved generic drugs: "Orange book" *

The screenshot shows the official website of the U.S. Food and Drug Administration (FDA). The header features the FDA logo and the text "U.S. Food and Drug Administration" and "Protecting and Promoting Your Health". Below the header is a navigation bar with links for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, and Cosm. The main content area is titled "Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations". It includes a breadcrumb trail: FDA Home > Drug Databases > Orange Book. A note states "Current through May 2013" and explains that the information is updated daily. There are sections for "Publications" and "FAQ" with links to search by Active Ingredient, Proprietary Name, Patent, Applicant Holder, Application Number, and Patent. A footer contains contact information for drug questions and details about the FDA's structure, including the Center for Drug Evaluation and Research, Office of Pharmaceutical Science, and Office of Generic Drugs. It also notes the page was last updated on 05/17/2013.

U.S. Department of Health & Human Services

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

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosm

A to Z Index | Follow FDA

Most Popular Searches

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

• FDA Home • Drug Databases • Orange Book

Current through May 2013

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

Publications

FAQ

- [Search by Active Ingredient](#)
- [Search by Proprietary Name](#)
- [Search by Patent](#)
- [Search by Applicant Holder](#)
- [Search by Application Number](#)

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

Drug questions email: druginfo@fda.hhs.gov

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

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

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

FDA approved generic drugs: "Orange book" *

U.S. Department of Health and Human Services

FDA U.S. Food and Drug Administration
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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

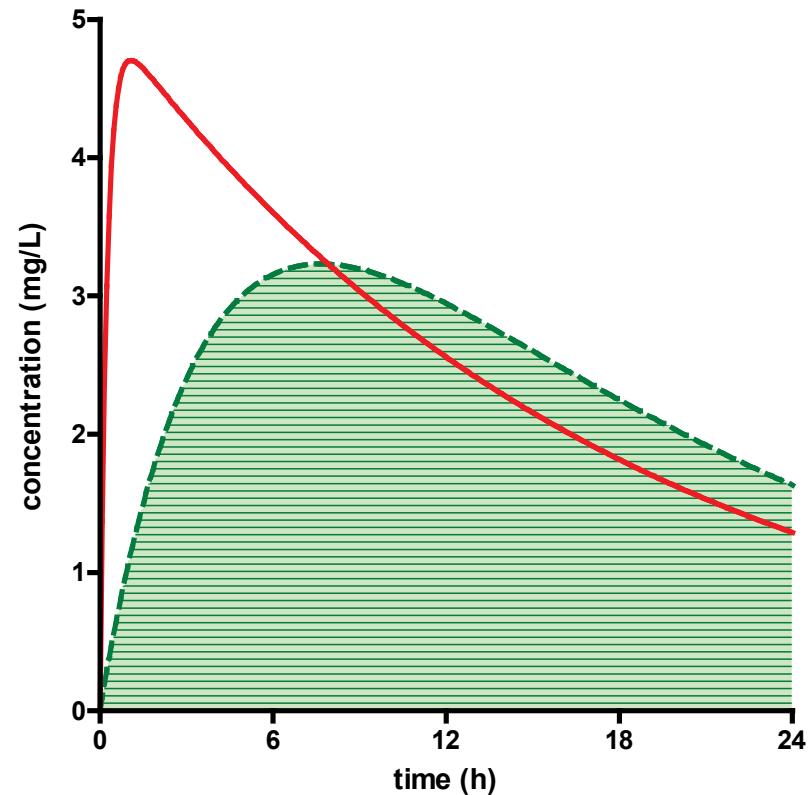
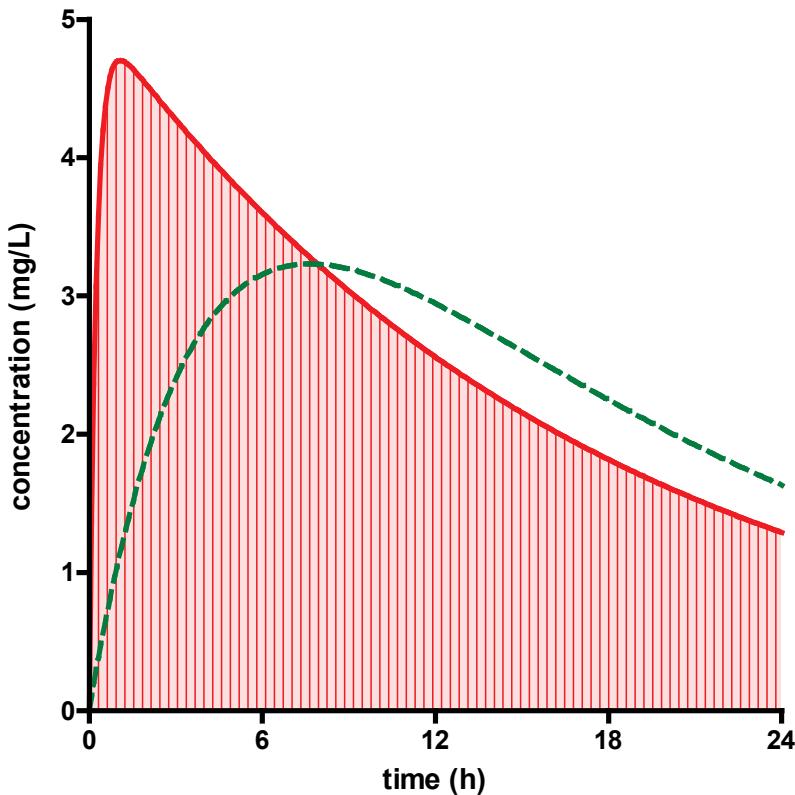
As in LEVAQUIN®
<http://medicaidprovider.hhs.gov/pdf/levaquinpi.pdf>

The products in this database are subject to periodic review by FDA. Drug questions email to CDER-Office-of-Pharmacovigilance-and-Adverse-Event-Monitoring@fda.hhs.gov. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Review, Office of Pharmacovigilance and Adverse Event Monitoring, Office of Generic Drugs.

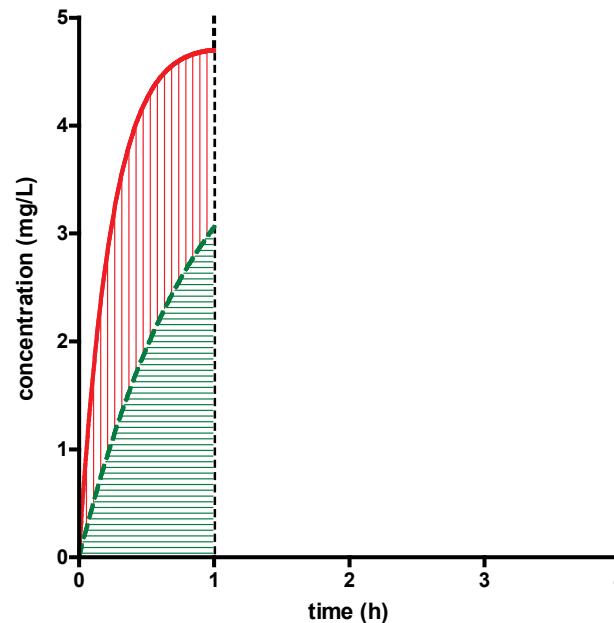
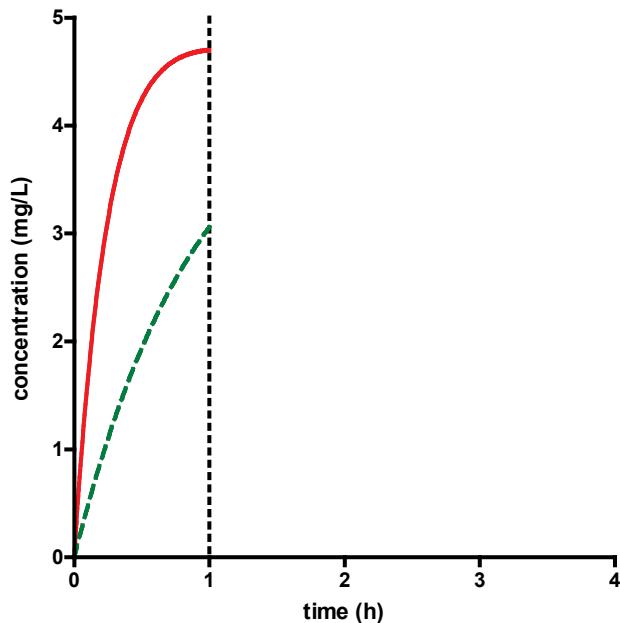
Page Last Updated: [REDACTED]
Note: If you need help with this site, contact CDER-Office-of-Pharmacovigilance-and-Adverse-Event-Monitoring@fda.hhs.gov.

* <http://www.accessdata.fda.gov>

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



Additional criteria for early AUC (EMA) *



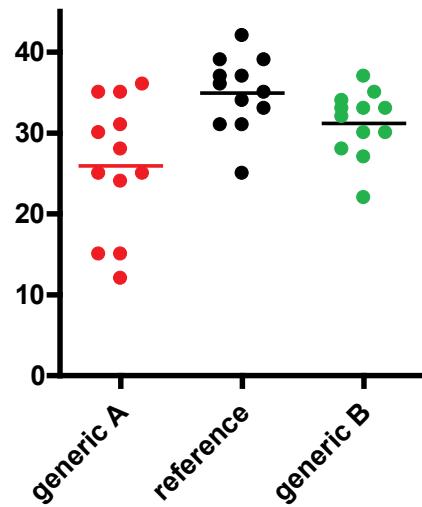
- Use the partial **AUC truncated** at the population median of T_{max} for the reference formulation for products where rapid absorption is of importance

* 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

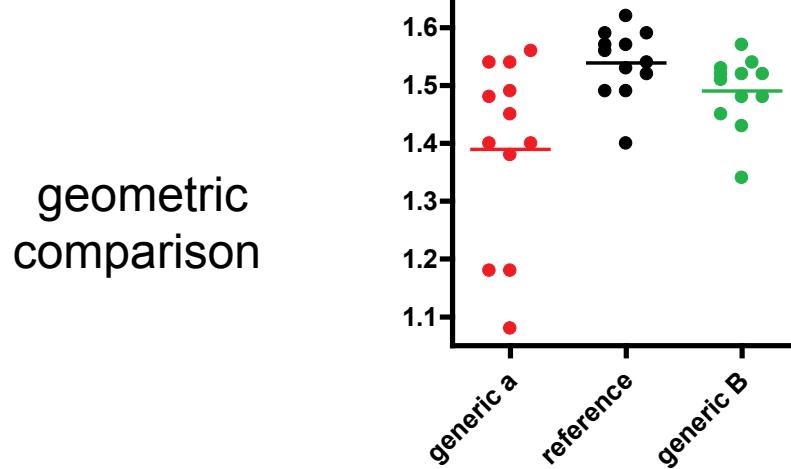
Unsolved problems with PK-based bioequivalence ... (application to antibiotics)

- 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)
 - stability (penems, e.g.)
 - impurities (do you like them ?)
 - ...

Are generic really comparable ?



arithmetic
comparison



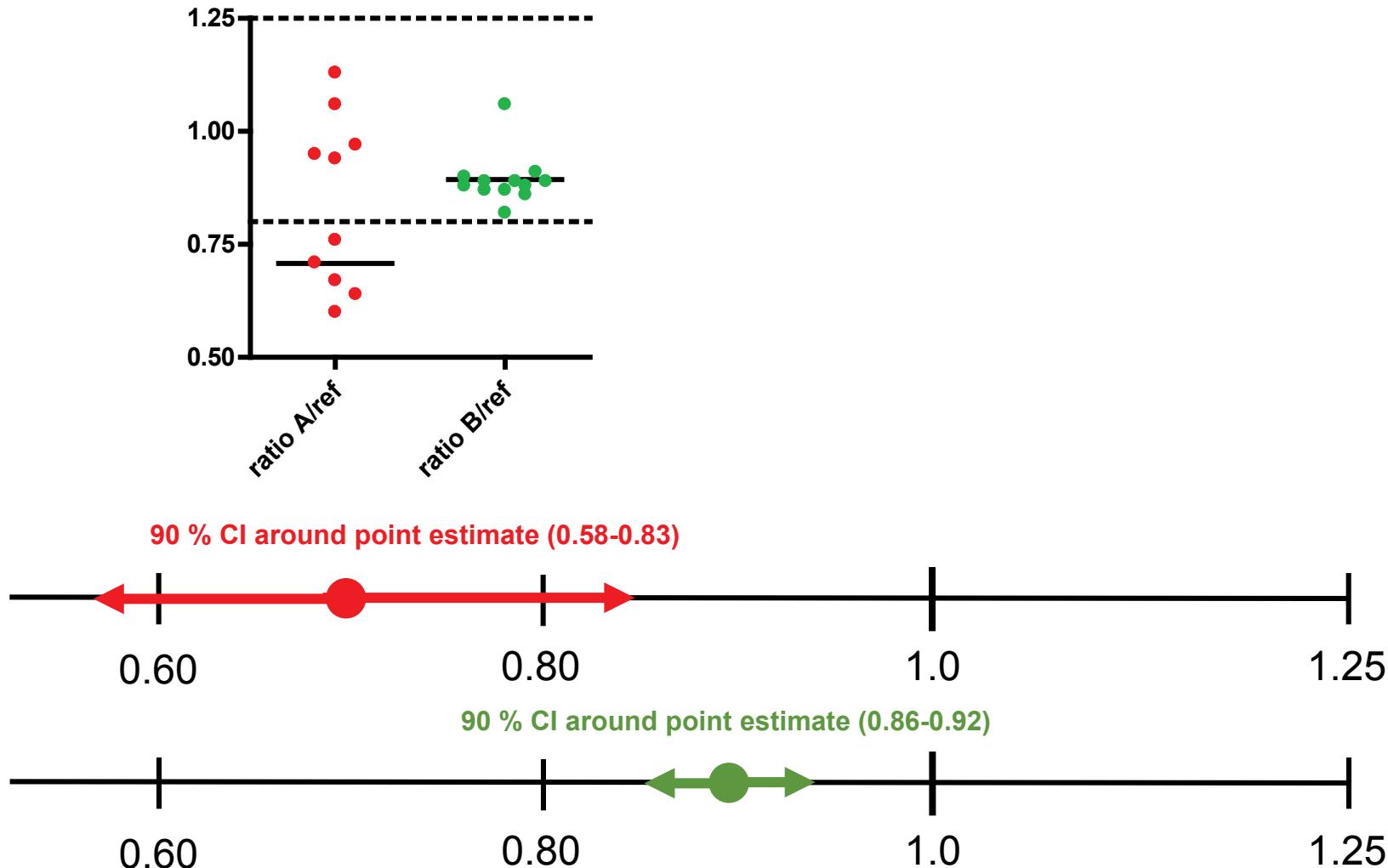
geometric
comparison

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)



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 $[U, L] = \exp [\pm k \cdot sWR]$, 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

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

Potency (oxacillin)

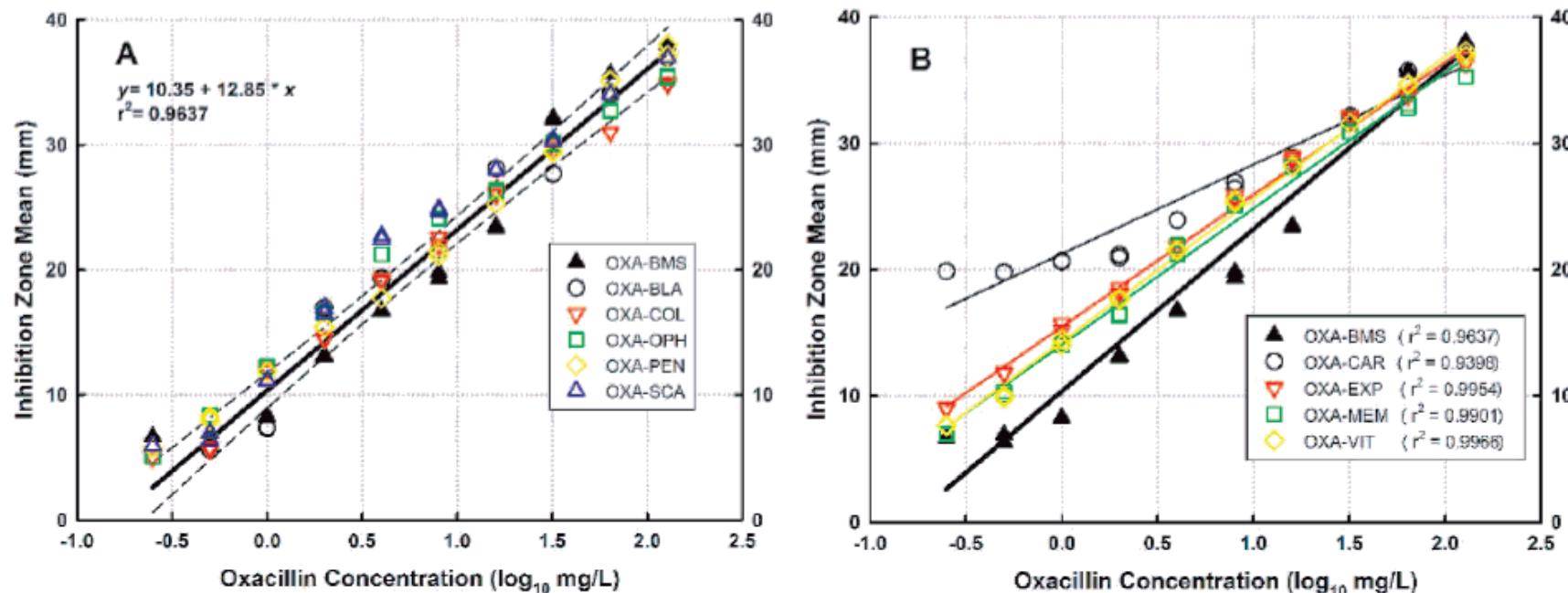


Figure 1 Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay. **A.** The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical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

Killing curves and hetero-resistance (vancomycin)

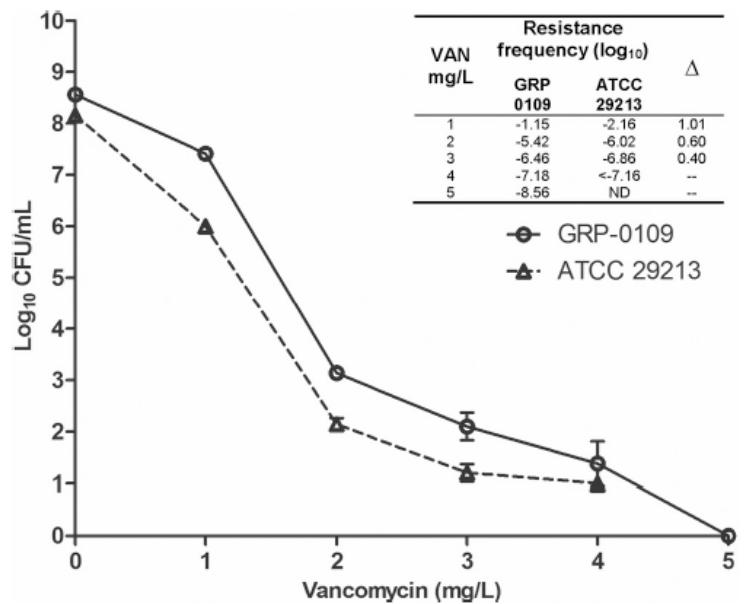


FIG 1 Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin,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

Killing curves and hetero-resistance (vancomycin)

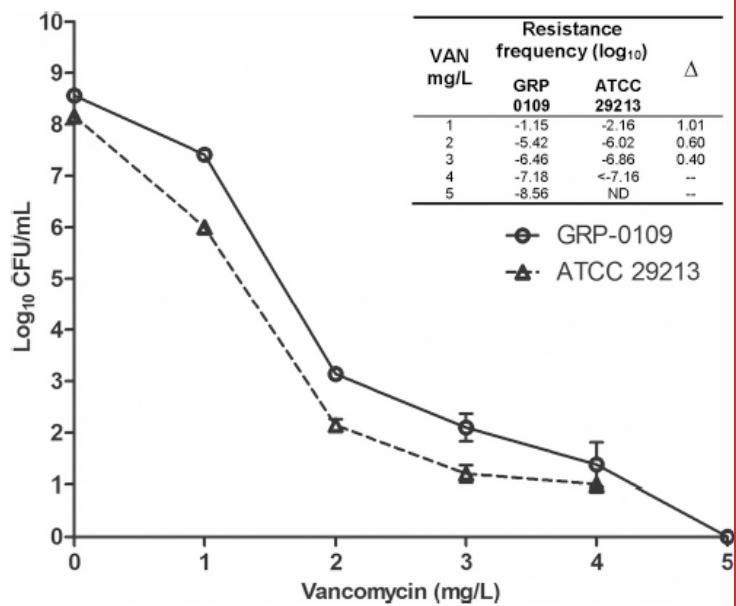


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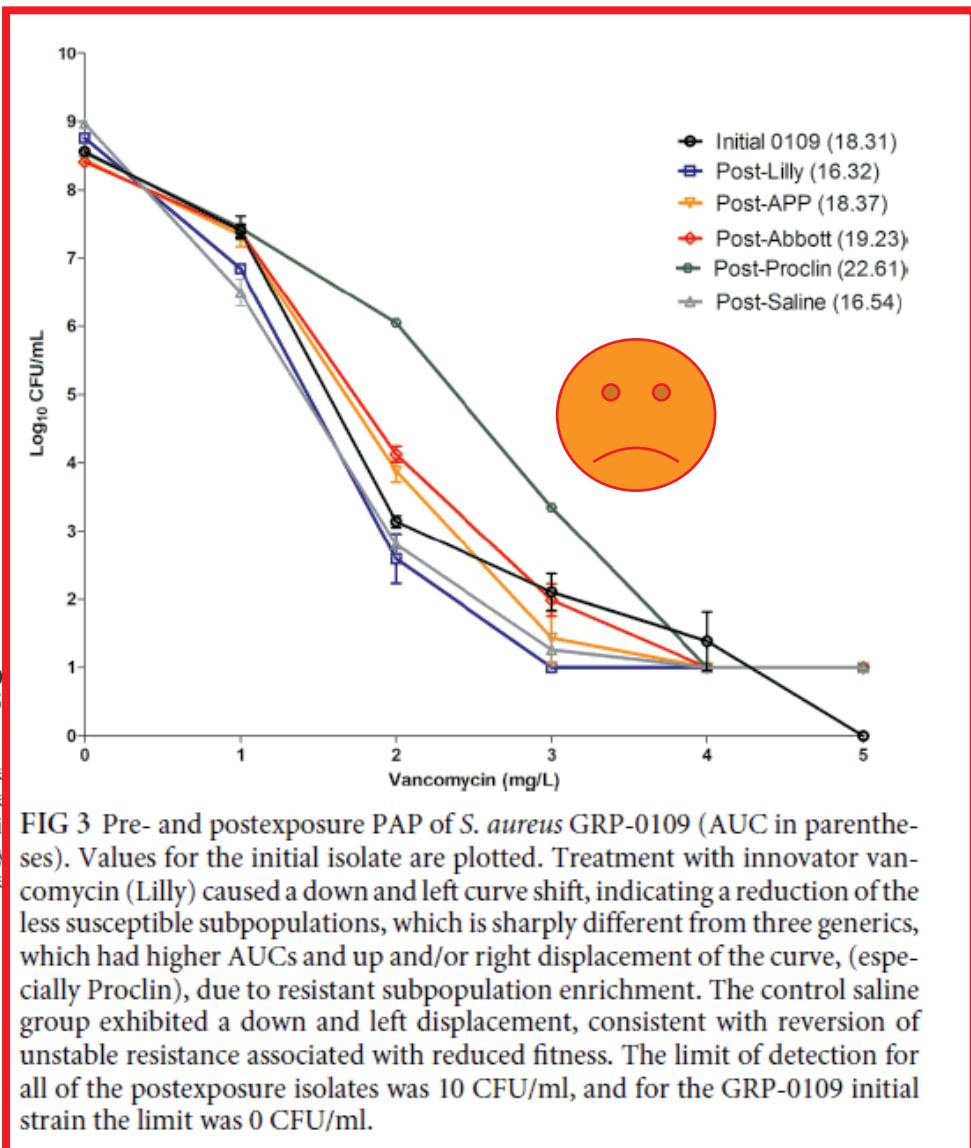


FIG 3 Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction of the less susceptible subpopulations, which is sharply different from three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

Gentamicin: evidence of non-equivalence in animal PK/PD model

Neutropenic thigh mouse model

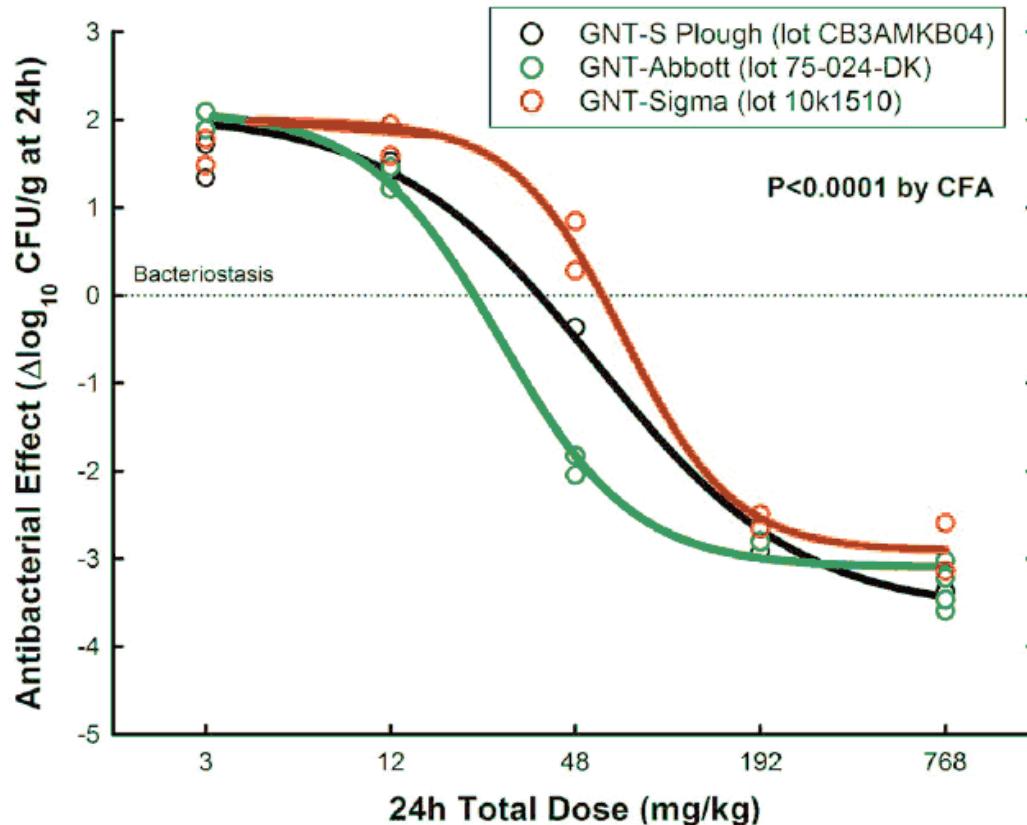


Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence. The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency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

Neutropenic thigh mouse model

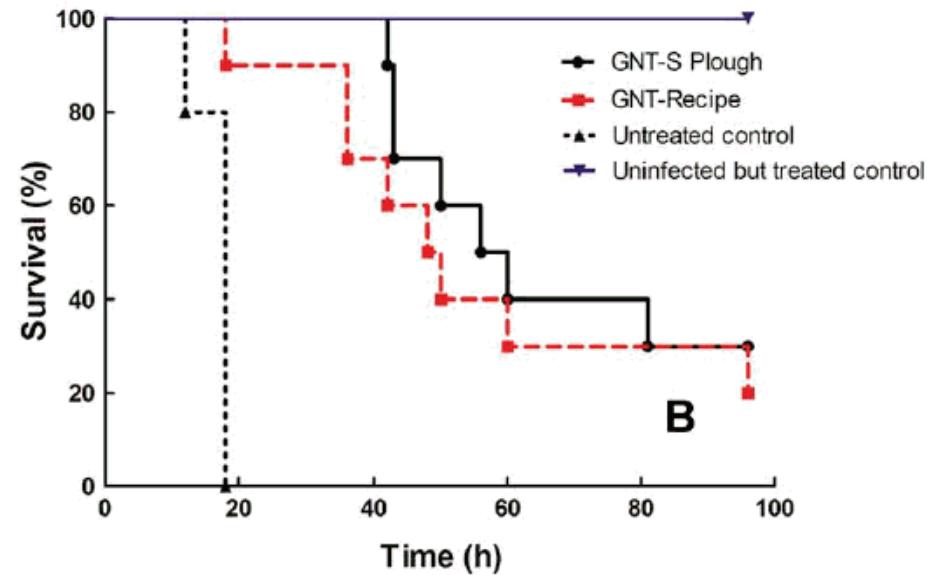
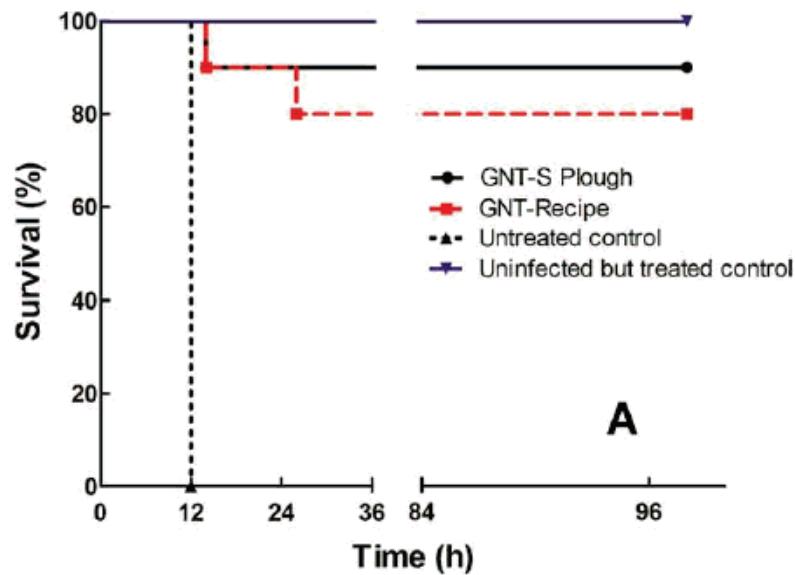


Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo ($n=5$), GNT-Recipe ($n=10$), or the innovator of gentamicin ($n=10$) at the dose required for maximal effect (768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

Vancomycin: complete equivalence in the rabbit endocarditis model



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



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

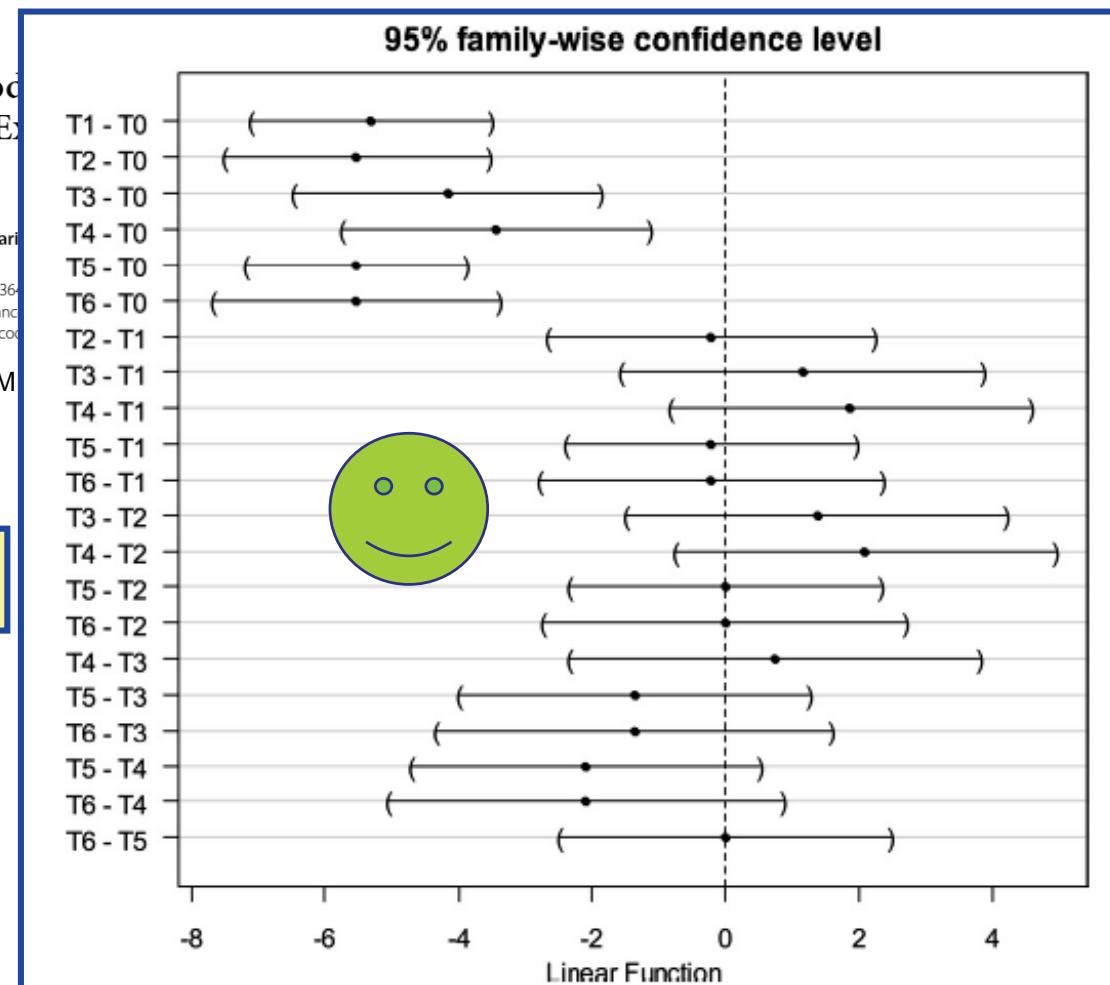
P. Tattevin,^{a,b} A. Saleh-Mghir,^{c,d} B. Davido,^c I. Ghout,^e L. Massias,^f C. Garcia de la Mar,^a A. C. Crémieux^{c,d}

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Antimicrob Agents Chemother. 2013 Mar;57(3):1157-62. PMID: 23375000

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

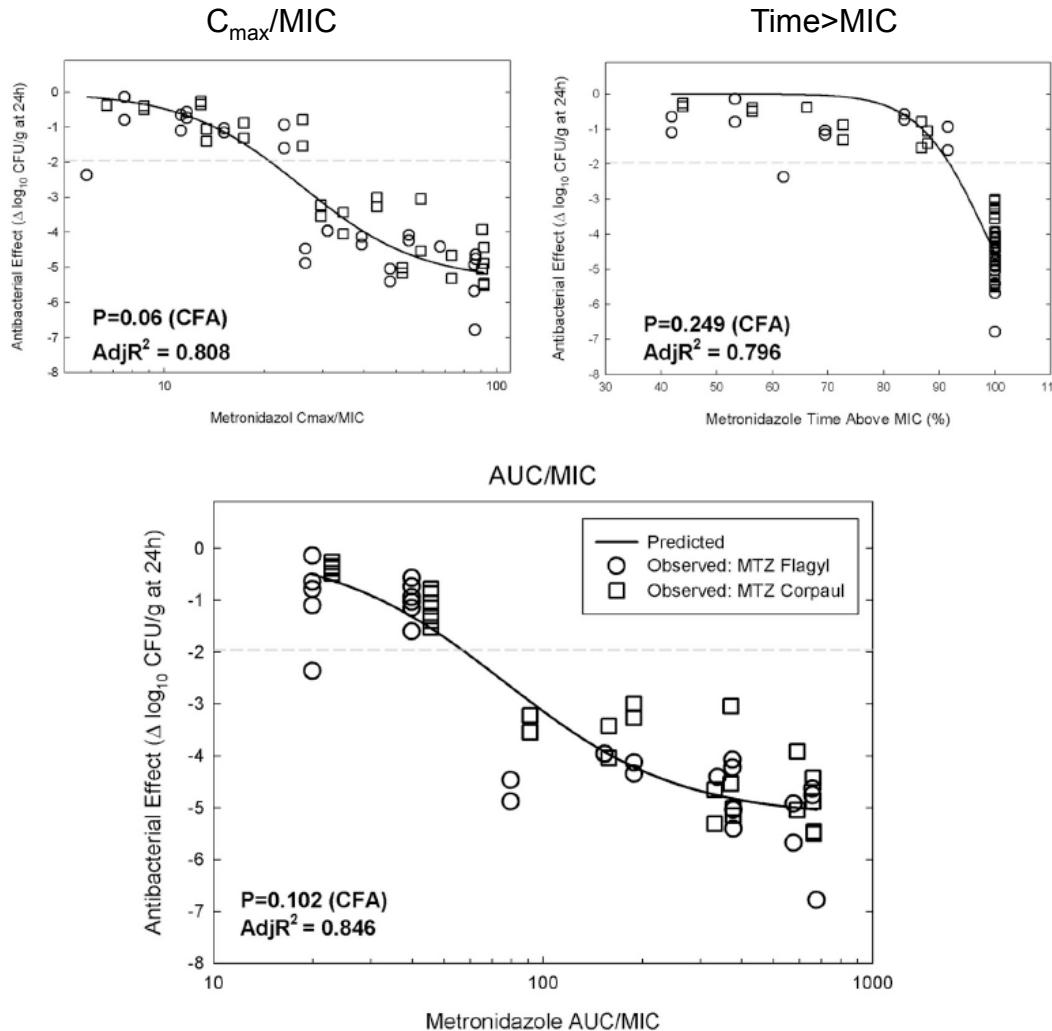


FIG 5 Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *B. fragilis* in a neutropenic mouse thigh anaerobic infection model. Only one curve is depicted because the data belong to a single population despite the fact that they were obtained after treatments of different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

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

Falsified Medicines: An EU reaction

L 174/74

EN

Official Journal of the European Union

1.7.2011

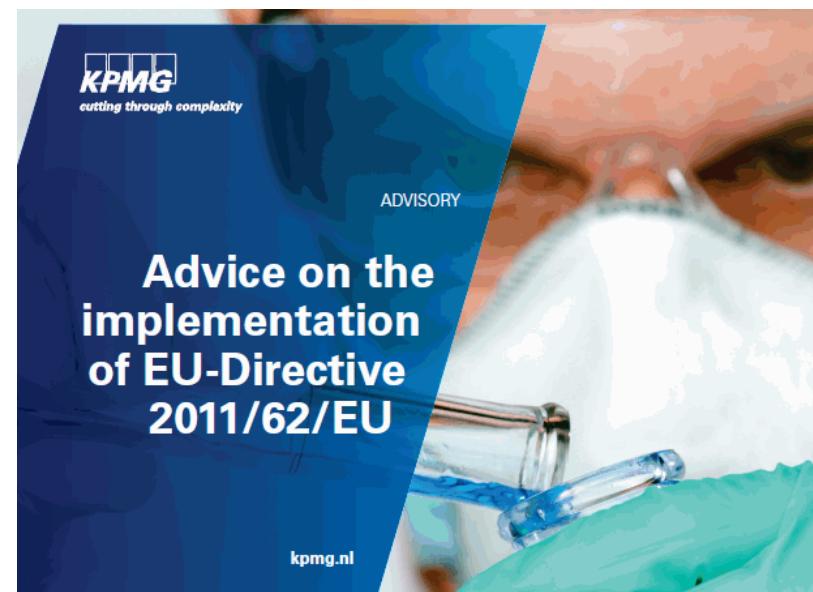
DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2011

amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products

(Text with EEA relevance)

http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf

with an
immediate
follow-up
from the
Industry



<http://www.eagenerics.com/index.php/publications>

But at the end of the day...



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Research in Social and
Administrative Pharmacy 8 (2012) 574–578

RESEARCH IN SOCIAL &
ADMINISTRATIVE PHARMACY

Research Briefs

Generic medications for you, but brand-name medications for me

Amy J. Keenum, D.O., Pharm.D.^{a,*}, Jennifer E. DeVoe, M.D., D.Phil.^b,
Deena J. Chisolm, Ph.D.^c, Lorraine S. Wallace, Ph.D.^d

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Knoxville, TN 37920, USA*

^b*Department of Family Medicine, Oregon Health & Science University, Portland, OR 97239, USA*

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^d*Department of Family Medicine, The Ohio State University, Columbus, OH 43201, USA*

But at the end of the day...



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Generic medication vs. brand-name medication

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Deena J. Chisolm, Pharm.D.

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Knoxville, TN

^bDepartment of Family Medicine, Oregon Health & Science University, Portland, OR

^cDepartment of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA

^dDepartment of Family Medicine, The University of Texas Health Science Center, San Antonio, TX

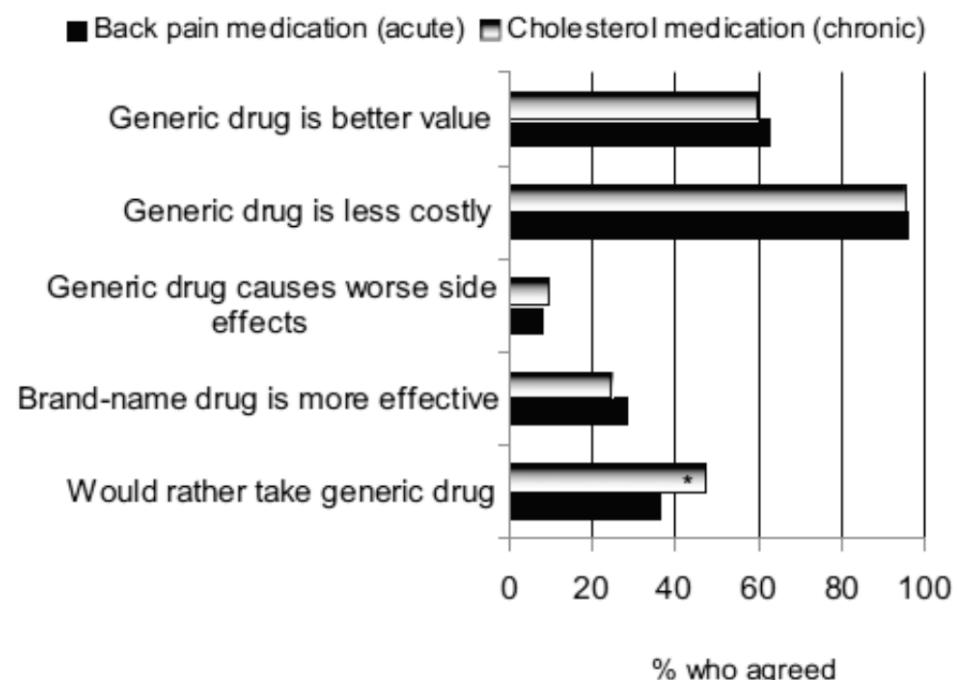


Fig. 2. Participants' perceptions of generic and brand-name medications for treating their hypothetical chronic or acute condition (n = 172). Note: % who agreed is the sum of participants who somewhat or strongly agreed with each item. *P < .05 using chi-square test.

The risk of overconsumption in France ...



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Médecine et maladies infectieuses 42 (2012) 141–148

**Médecine et
maladies infectieuses**

Generic antibiotic drugs: Is effectiveness guaranteed?

R. Gauzit*, M. Lakdhari

Unité de réanimation, Hôtel Dieu, place du Parvis-de-Notre-Dame, 75781 Paris cedex 04, France

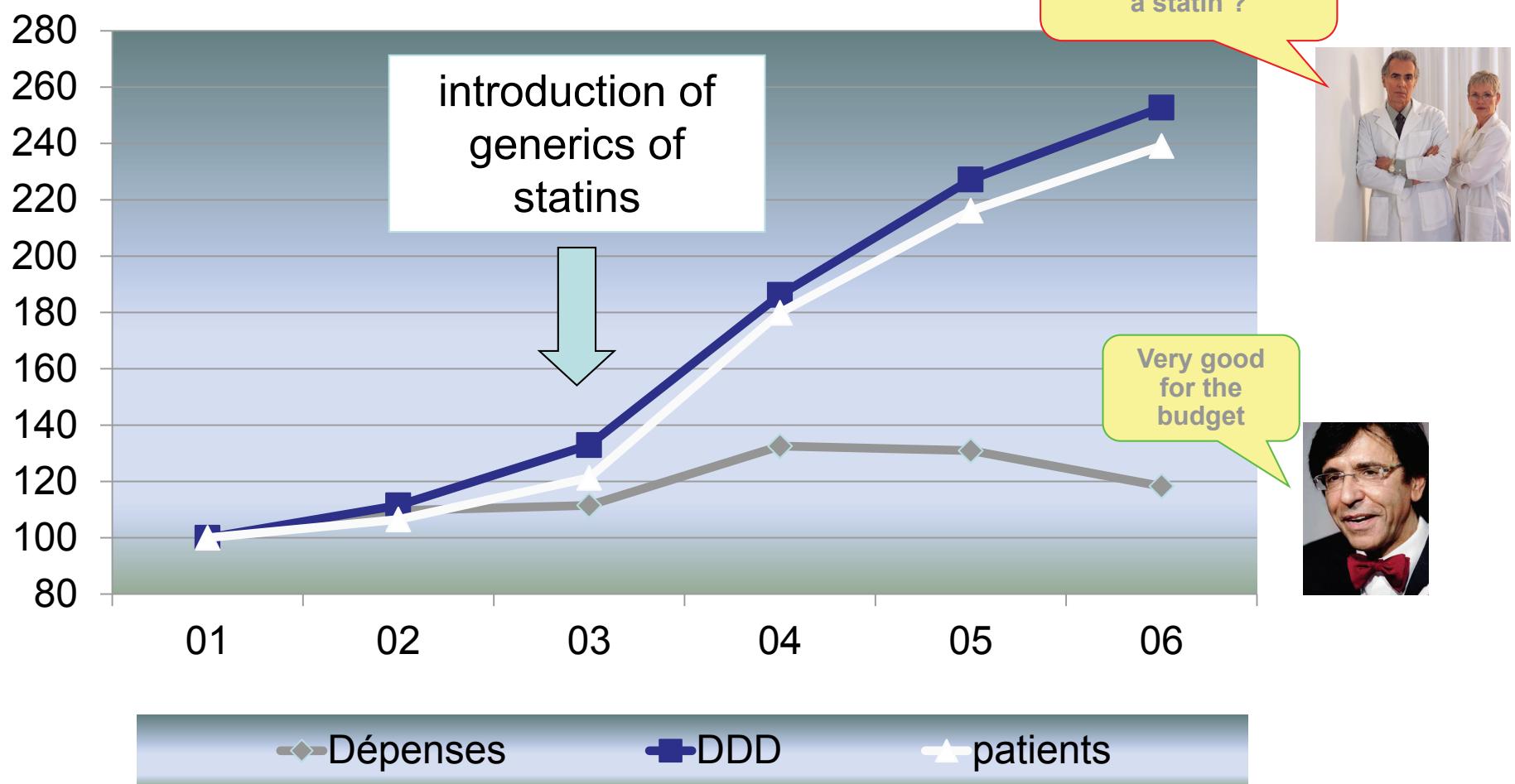
Received 3 October 2011; accepted 11 October 2011

Available online 4 April 2012

Abstract

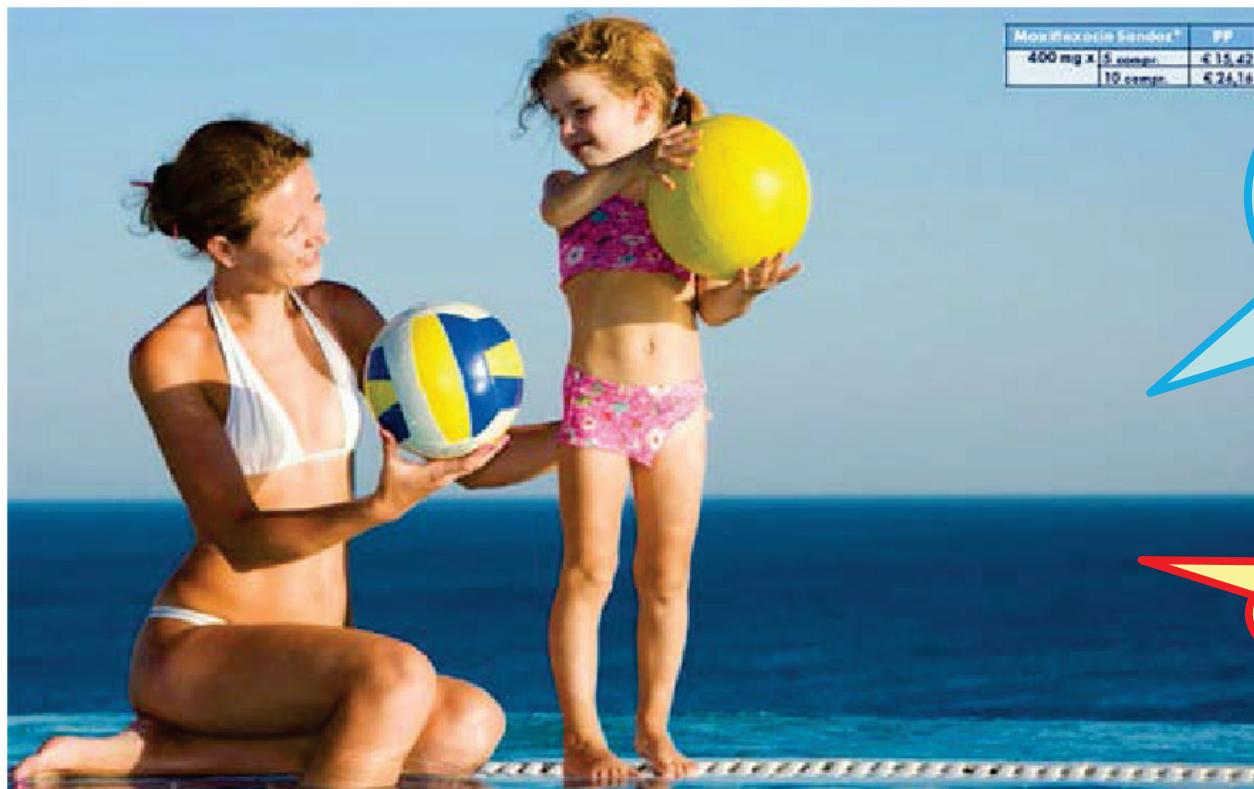
There are recently published arguments suggesting all generic antibiotic drugs do not present the full reliability needed to claim therapeutic equivalence with branded drugs. The problem is especially crucial for generic intravenous drugs, which do not need any bioequivalence study before they can be marketed. The evaluation of generic antibiotic drug effectiveness yields an important dispersion of results according to antibiotic agents and for the same antibiotic agent all generic drugs are not equivalent. There are differences at all levels: drug components, levels of impurity, pharmacokinetics, pharmacokinetic/pharmacodynamic relationship, in vitro effectiveness, therapeutic effectiveness in experimental models, etc. So that finally, the specifications approved in the initial submission file of a brand name drugs are not always respected by a generic drug. There is also a specific problem of taste and treatment acceptability for pediatric oral antibiotic drugs. Available data on clinical effectiveness is excessively rare. The marketing of a great number of generic drugs of the same specialty is followed by a sometimes very important increase of their use, even in countries where consumption is low. The corollary of this increase in consumption is an increase of resistance, and this is especially true for oral fluoroquinolones. Even if most of this information needs to be verified, it seems necessary to review regulations for marketing authorization of generic antibiotic drugs.

A Journey to the statins



Source: INAMI / RIZIV

And generic companies will use any possible argument
to foster sales...



Moxifloxacin Sandoz®	PF
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10 compr.	€ 24,14

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for a generic
of
moxifloxacin

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E-mail: *

Country: *

Discount code:

Your Message:
(required quantity of pills, [shipping method](#))

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A recent economic US study

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[†]

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^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 prescriptions analysed from 2004 through 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 Vétérinaire de Toulouse, Toulouse
Cedex, France

The situation may be worse in veterinary medicine

The consequences of generic marketing on antibiotic consumption and the spread

P.-L. TOUTAII
A. BOUSQUET

- In France, introduction of generic 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 May 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 **recommendations of BAPCOC (**)** (amoxicillin [3 g / day in 3 administrations for 5 to 7 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 Nonproprietary Name

** BAPCOC: Belgian Antibiotic Policy Coordination Committee

But there is something worse...

Generic antibiotics, antibiotic resistance, and drug licensing

Although new drugs continue to be licensed, too few are based on novel chemical entities; drug resistance is more likely to occur when new agents are variants of existing classes.

There is a serious mismatch between clinical need and supply of new medicines for which there is no quick answer—it takes about 10 years and up to US\$1 billion to develop a new antibiotic.

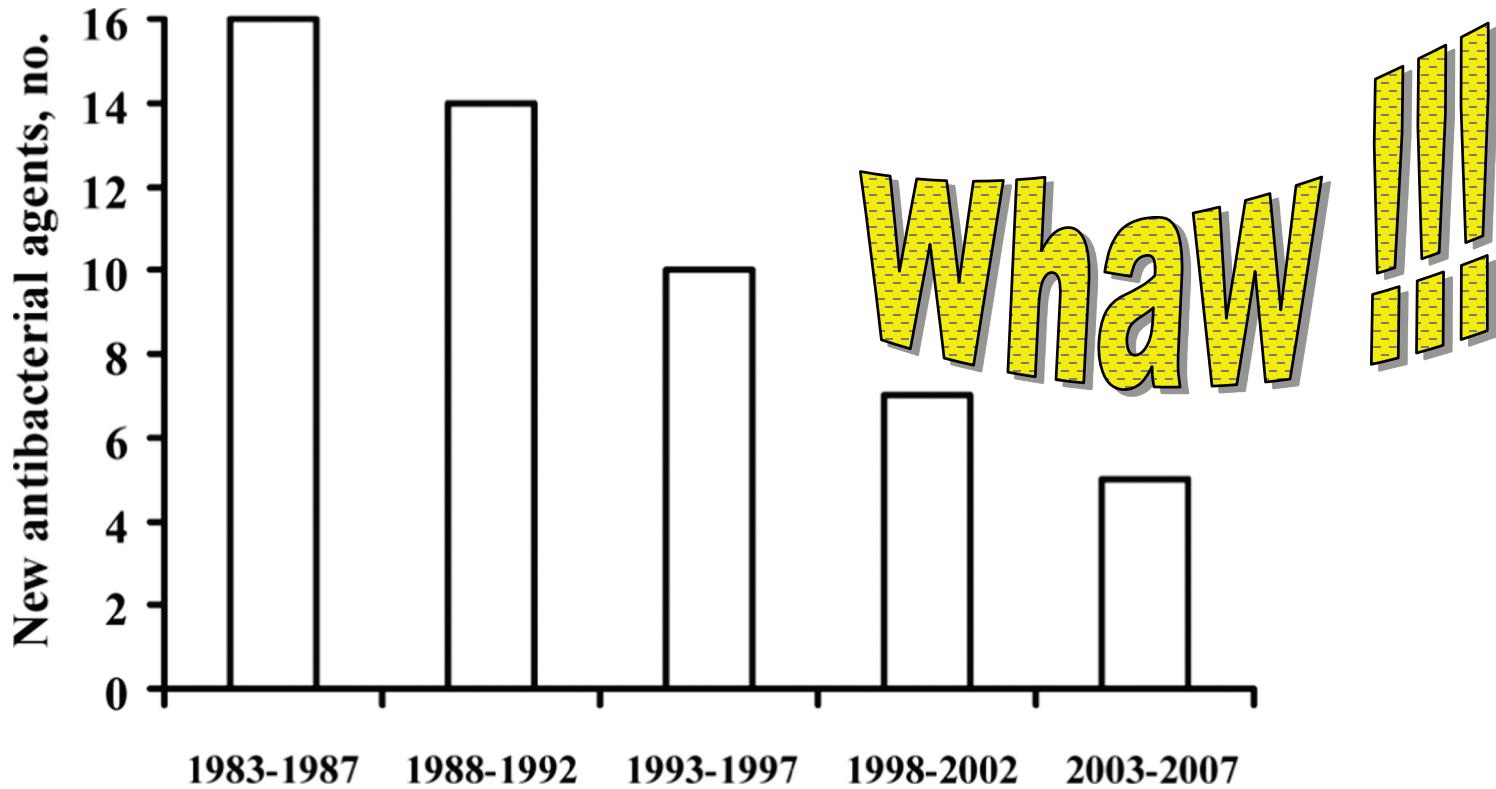
Roger Finch

r.finch@nottingham.ac.uk

The Nottingham University Hospitals NHS Trust;
and University of Nottingham, Nottingham,
NG5 1PB, UK

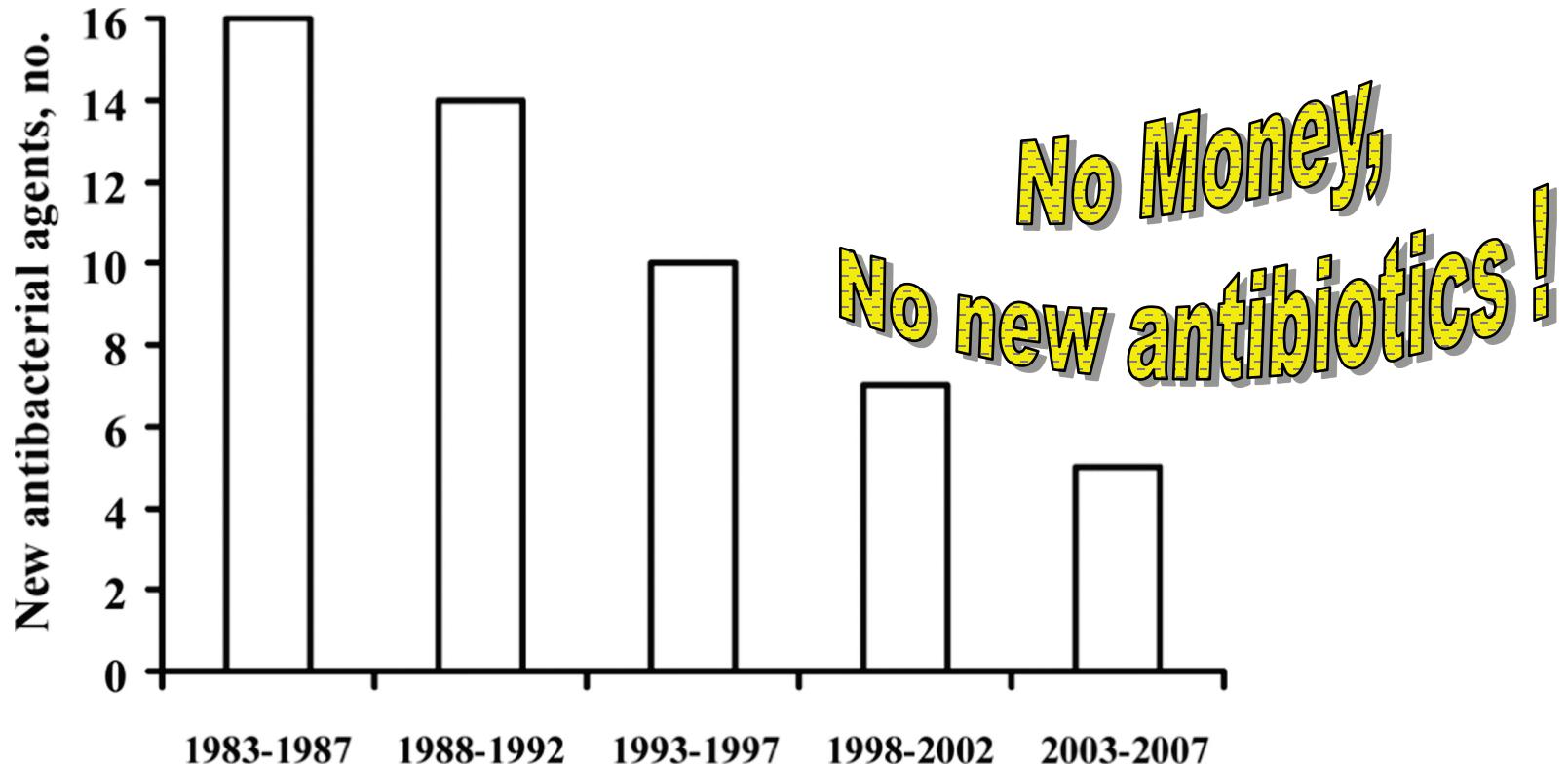


Innovative antibiotic development is abandoned by Industry



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

Why do they abandon it ?

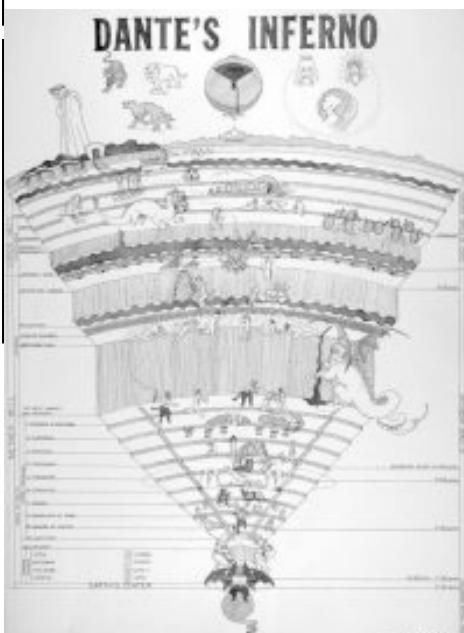


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(last accessed: 7 November 2013)

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

* INN: International Nonproprietary Name

** BAPCOC: Belgian Antibiotic Policy Coordination Committee

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 and reimbursement of an antibiotic treatment is **MUCH less**
- For comparison, 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)
- Compare to the drug acquisition price to treat a pneumonia (as an example)
- Find where the problem lies...

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

Trans Atlantic Task Force on Antimicrobial Resistance - TATFAR

2009 EU-US Summit Declaration called for the establishment of "...a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us."



EU-US Summit – Washington 3 November 2009

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EU-US Summit – Washington 3 November 2009

In the US: resources for Researchers

Resources for Researchers

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Microbiology and Infectious Diseases Resources

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV.

Funding Opportunities

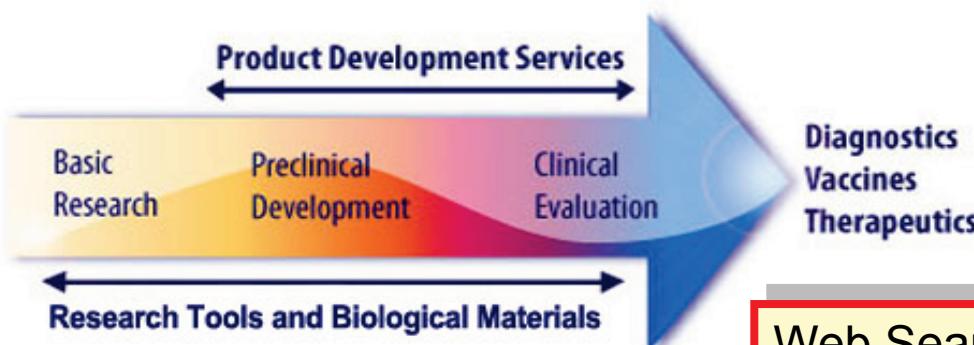
Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.

- NIH-Wide Funding Opportunity Announcements
- NIAID Funding Opportunity Announcements and Requests for Proposals

Product Development Services and Research Tools and Biological Materials

Request development by DMID-funded contractors of critical information needed to move a product through the product development pathway. Note: Services are contingent upon availability of required preliminary data.

Click on labels below to view information on services.

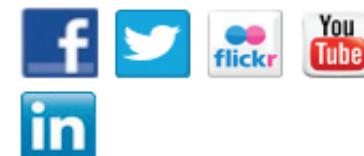


Web Search Term: **DMID Resources**

Website Tools

- [Email this page](#)
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Contact Info

dmidresources@niaid.nih.gov

Highlight

Sharing Scientific Success Stories: [DMID WOWS](#)

Additional Information From NIAID

[All NIAID resources](#)

Other key changes in the US ...

- **GAIN Act** (Generating Antibiotics Incentives Now) - 2012
 - priority FDA review
 - additional five years of market exclusivity for breakthrough antibiotics that target serious or life-threatening pathogens
 - relaxed its criterion for non-inferiority to within 10%, making it easier to show comparability to drugs already on the market
- **BARDA: Biomedical Advanced Research and Development Authority**
[within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services]
 - provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies.
- **FDA:**
 - new guidance documents (aBSSSI, cUTIs, cIAIs, ...) that are considered being significantly better
- **Department of Health and Human Services (HHS)**
 - awarding funds to allow companies to shift funds around an antibiotic programs (portfolio approach; example: GSK antibiotic programme)
 - Genetic Engineering and Biotechnology News 14 Aug 2013
<http://www.genengnews.com/insight-and-intelligenceand153/biopharmas-drive-antibiotic-development/77899874/>
Last accessed: 8 May 2014
 - Biomedical Advanced Research and Development Authority
<http://www.phe.gov/about/barda/Pages/default.aspx>
Last accessed: 9 May 2014

Unless Big Brother comes to your help...

U.S. Department of Health & Human Services

Office of the Assistant Secretary for Preparedness and Response

Preparedness Emergency About ASPR

 **Public Health Emergency**
Public Health and Medical Emergency Support for a Nation Prepared

PHE Home > PHE Newsroom > MCM Procurements and Grants **Search**

MCM Procurements and Grants

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, tulermia

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

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

This page last reviewed: January 03, 2014

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

Unless Big Brother comes to your help...

The screenshot shows a Mozilla Firefox browser window with the title bar "Aridis Pharmaceuticals - Collaborations - Mozilla Firefox". The address bar displays the URL "www.aridispharma.com/collaborations.html". The main content area features the Aridis Pharmaceuticals logo on the left and a circular image of a scientist working in a lab. To the right, the word "PARTNERSHIP" is prominently displayed. Below this, a green navigation bar contains links for Home, About, Products, Technologies, Partnership, News, and Contact. The "Partnership" link is highlighted.

Collaborations

[Harvard University - Anti-Pseudomonas Antibody Technology](#)

Aridis is collaborating with the Laboratory of Dr. Gerald Pier on the preclinical development of Aerucin. This work is being funded by a National Institute of Health NIAID grant.

[Biomedical Advanced Research and Development Authority \(BARDA\), US Dept. Health & Human Services - Aridis formulation technology](#)

Aridis is working with BARDA and PATH to develop advanced stabilization formulation for influenza vaccines

[U.S. Army Medical Research Institute of Infectious Diseases \(USAMRIID, Ft. Detrick\) - Gallium based anti-infective for biodefense \(Panaecin\)](#)

Panaecin and new generation of gallium based complexes are being evaluated as post-exposure prophylactic anti-infectives for inhalational anthrax, tularemia, glanders, and plague.

[Walter Reed Army Institute of Research \(Washington, DC\) - Gallium based anti-infective for wound healing \(Panaecin\)](#)

Topical formulations of Panaecin are being evaluated as a topical anti-bacterial with wound healing properties

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Aridis Pharmaceuticals © 2009-2013 Le3 Web Designs

Search



Unless Big Brother comes to your help...

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

File Edit View History Bookmarks Tools Help

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

Achaogen Awarded \$60M Contract Option by BARDA for the Clinical Development of Plazomicin — Achaogen Aridis Pharmaceutical's Produt - Panaecin Publications of Cellular and Molecular Ph... aridis pharmaceutica

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

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ACHAOGEN

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

What in Europe ?



The image shows the cover of a technical report titled "The bacterial challenge: time to react". The cover features a white and green design with a globe icon. The ECDC and EMEA logos are present. The text on the cover includes "Antibio", "TECHNICAL REPORT", "The bacterial challenge: time to react", and "A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents".

ECDC/EMEA Joint Working Group

- assigned on 28 February 2008.
- technical Report accepted by ECDC/EMEA on 23 July 2009
- circulated for information on 20 August 2009.
- published in September 2009

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf

Last accessed: 9 May 2014

Investments in Europe ...



EUROPEAN COMMISSION

MEMO

Brussels, 15 November 2013

EU launches new research projects to combat anti-microbial resistance

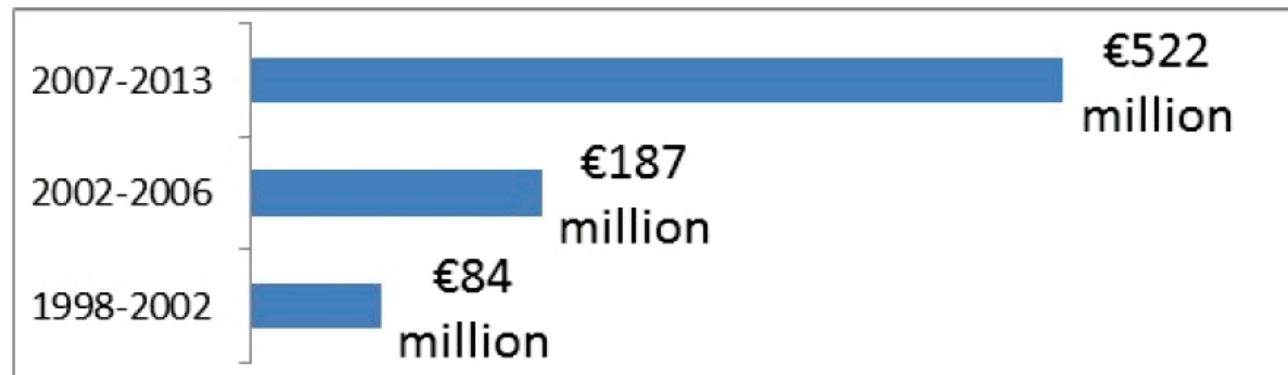
http://europa.eu/rapid/press-release_MEMO-13-996_en.pdf

Last accessed: 8 May 2014

Investments in Europe...

EU launches new microbial resistance

The rising awareness of the AMR threat is reflected in a six fold increase in the amount being invested, from some €84 million during the EU's 1998-2002 research programme to about €522 million for the 2007-13 period.



Most of the EU investment is used to support collaborative projects i.e. international research and innovation teams involving the most capable players from across Europe and abroad.

Public/Private shares in Europe



Public-private partnerships



Innovative Medicines Initiative

- ❖ Pooling expertise, knowledge and resources
- ❖ Developing incentives to address major unmet medical needs
- ❖ Providing a neutral trusted platform to align public and private interests

An opportunity to combine public and private resources for new antimicrobials



IMI in action ...



The Innovative Medicines Initiative (IMI) logo is located in the top left corner. The header navigation bar includes links for Contact, Newsletter, and Links.

Search:    

- ▶ Home
- ▶ About IMI
- ▶ Ongoing projects
- ▶ Calls for proposals
- ▶ News, Events & Media
- ▶ Reference documents
- ▶ FAQ

THE INNOVATIVE MEDICINES INITIATIVE

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA.



IMI NEWSFLASH



08/05/2014 : The citation impact of IMI research is twice the world average. Find out more <http://t.co/65dIAwLuLs> <http://t.co/H3uZgYVZ6r>

08/05/2014 : RT
@BenjaminRibba: Our review of mixed-effect models for population analysis in oncology published today in PSP <http://t.co/eepmVsuaRI> @DDM...

- €2 billion euro budget...
- collaborative research projects and networks of industrial and academic experts...
- collaborative ecosystem for pharmaceutical research and development (R&D)...
- increase Europe's competitiveness globally...
- establish Europe as **the most attractive place for pharmaceutical R&D**

And more generally speaking... with a caveat...

Policies and incentives for promoting innovation in antibiotic research



Elias Mossialos, Chantal M. Morel,
Suzanne Edwards, Julia Berenson,
Marin Gemmill-Toyama, David Brogan



The European Observatory on Health Systems and Policies supports and promotes evidence-based health policy-making through comprehensive and rigorous analysis of health systems in Europe. It brings together a wide range of policy-makers, academics and practitioners to analyse trends in health reform, drawing on experience from across Europe to illuminate policy issues.

And more generally speaking... with a caveat...

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The European Observatory on Health Policy-making
It brings together a wide range of actors involved in health reform, drawing on experience from across Europe to illuminate policy issues.

- It is necessary for European public health authorities to emphasize rationing of existing antibiotics intended for severe infection (using generics as first-line therapies). However, this gives the impression that, if developed, new antibiotics will be kept as last resort treatments regardless of high levels of resistance to widely used antibiotics.

So, you will keep on reserve

- cefaroline and ceftobiprole
- oritavancin and dalbavancin
- tedizolid ...

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>