# Product Safety and Quality: An act of social and ethical responsibility (a discussion about generic antibiotics)

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# Disclosures and slides availability

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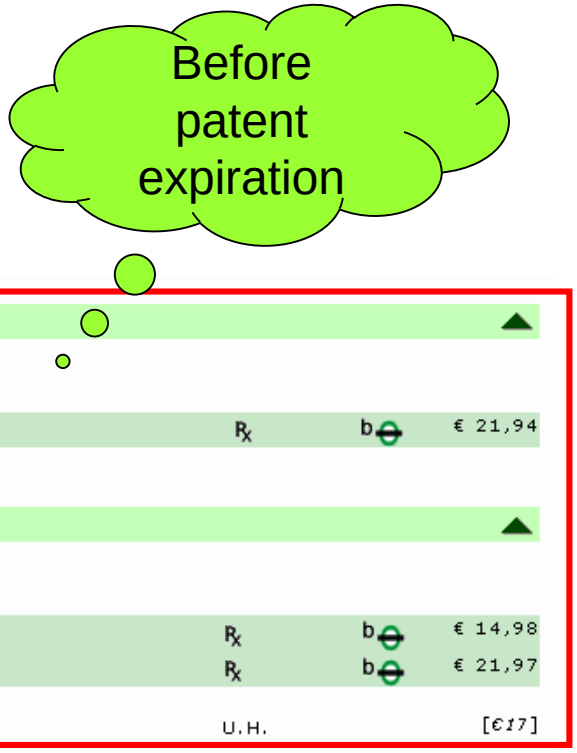
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions
- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

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

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




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

# A well known antibiotic in Belgium

After …

1 *Levofloxacine Actavis* (Actavis)

[lévofloxacine]
sac perf.
5 x 500mg / 100ml U.H. [€85]

2 *Levofloxacine EG* (Eurogenerics)

[lévofloxacine]
compr. (séc.)
10 x 500mg Rx b € 21,42
30 x 500mg Rx b € 57,66
sac perf.
1 x 500mg / 100ml U.H. [€17]

3 *Levofloxacine Fresenius Kabi* (Fresenius Kabi)

[lévofloxacine]
flacon perf.
1 x 500mg / 100ml U.H. [€17]

4 *Levofloxacin Hospira* (Hospira)

[lévofloxacine]
sac perf.
1 x 500mg / 100ml U.H. [€17]

5 *Levofloxacine Mylan* (Mylan)

[lévofloxacine]
compr. (séc.)
10 x 250mg Rx b € 14,98
14 x 250mg Rx b € 24,43
10 x 500mg Rx b € 21,98
14 x 500mg Rx b € 35,13
flacon perf.
10 x 500mg / 100ml U.H. [€170]

6 *Levofloxacine Sandoz* (Sandoz)

[lévofloxacine]
compr. (séc.)
10 x 250mg Rx b € 14,42
10 x 500mg Rx b € 21,09
30 x 500mg Rx b € 58,15

7 *Levofloxacine Teva* (Teva)

[lévofloxacine]
compr. (séc.)
10 x 250mg Rx b € 14,42
10 x 500mg Rx b € 21,09
30 x 500mg Rx b € 56,66
sac perf.
10 x 250mg / 50ml U.H. [€85]
10 x 500mg / 100ml U.H. [€170]

*Tavanic* (PI-Pharma)

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

*Tavanic* (Sanofi-Aventis)

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

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

# 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...

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

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

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

# The EU Directive (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**. …

# 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 main and only incentive in the promotion of the generics is, for governments, to acquire and 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 mareketed form differs from the form used in development…)[2]
- Primary metrics are [1,3]
  - **AUC** (area under the plasma concentration–time profile of the active substance)

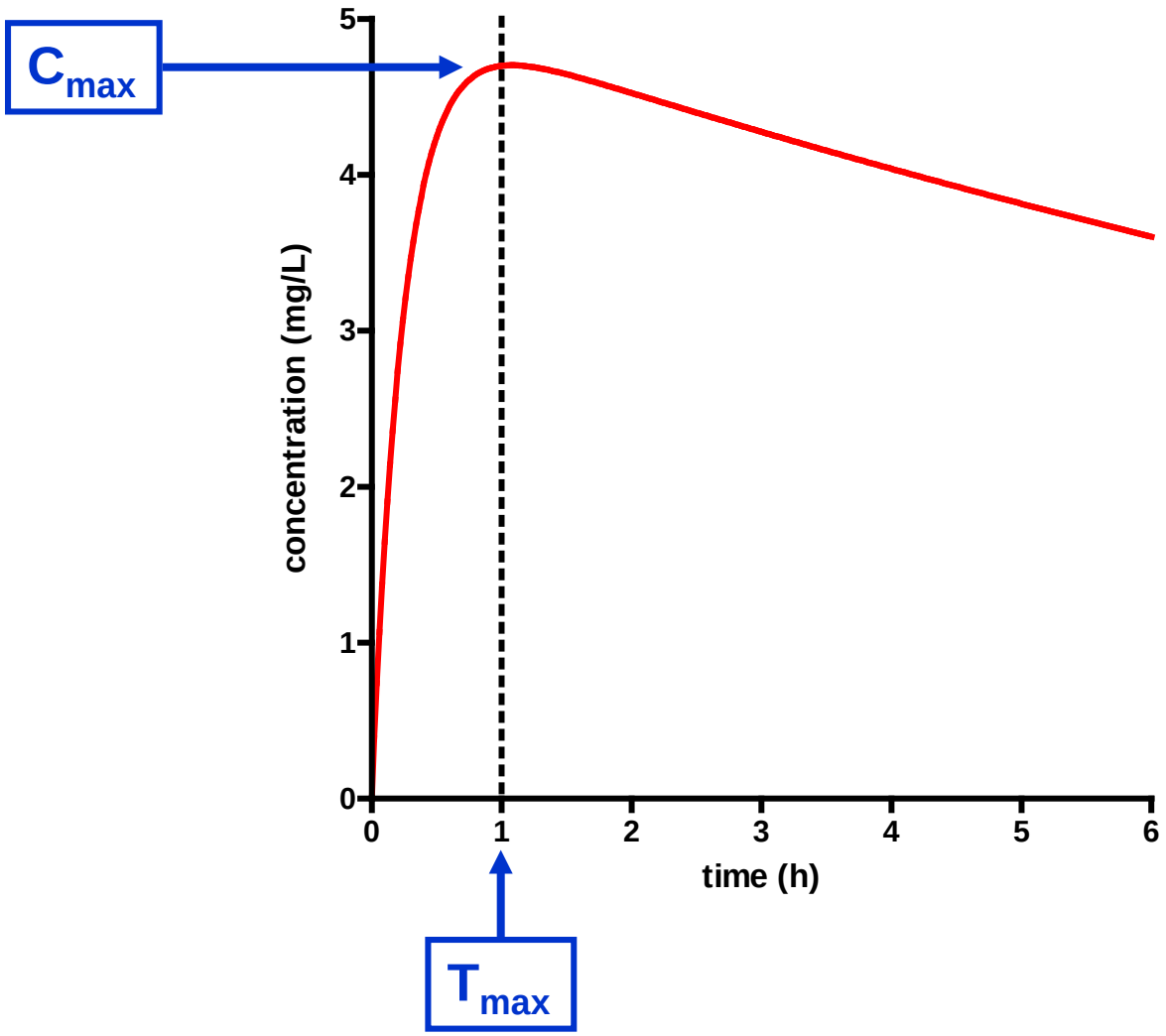
    → **extent of absorption**
  - **$C_{max}$** (the maximum plasma concentration of the active substance)

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

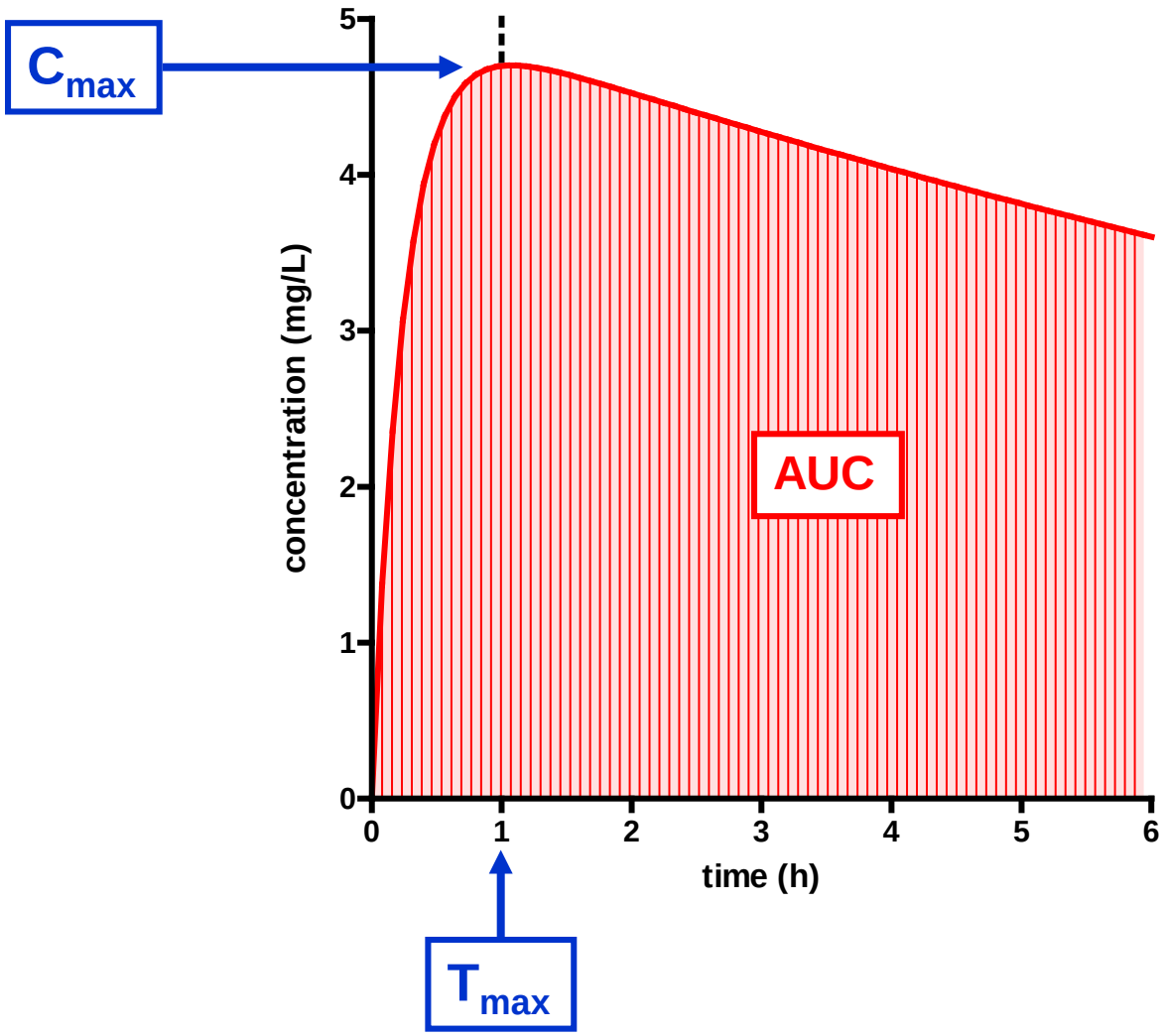
    → **rate of absorption**


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.

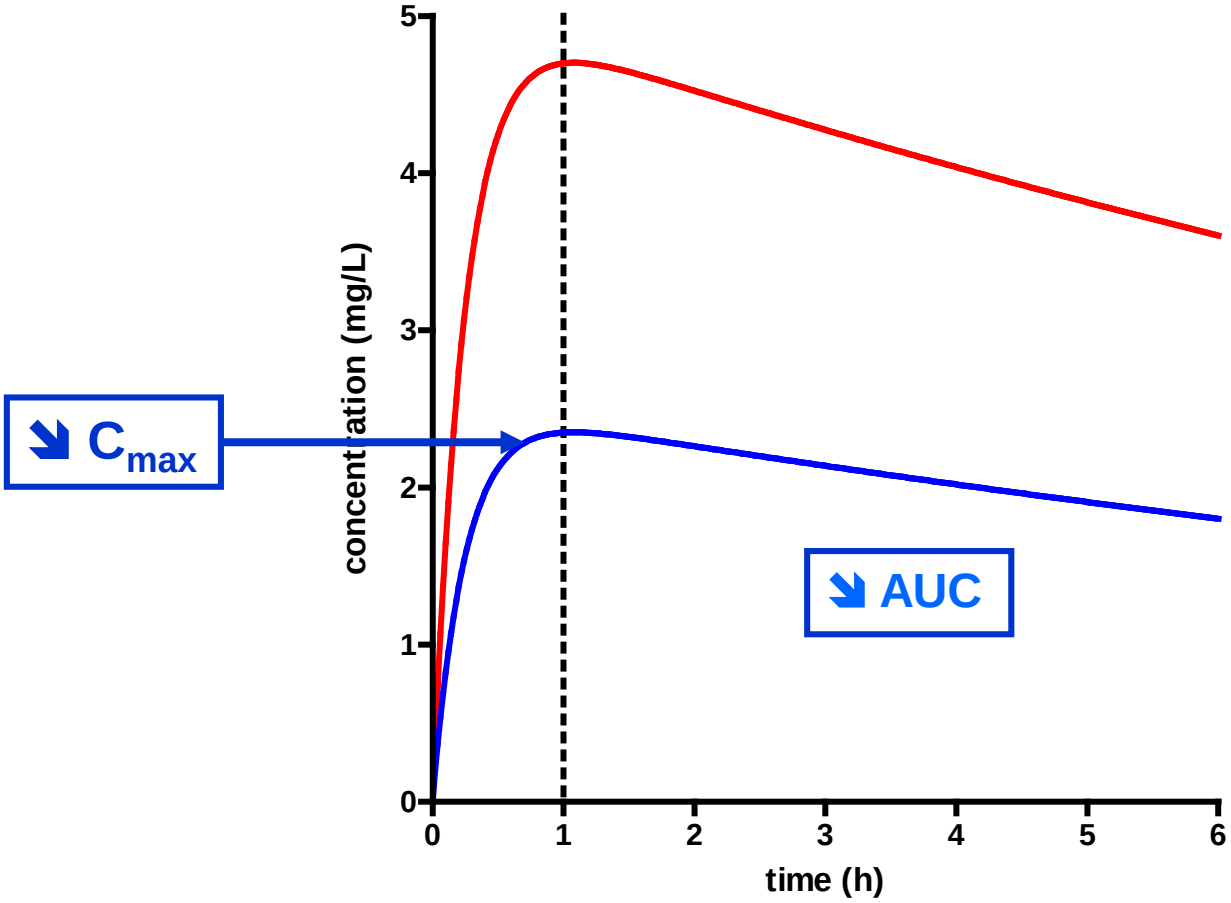
# AUC – $C_{max}$ – $T_{max}$



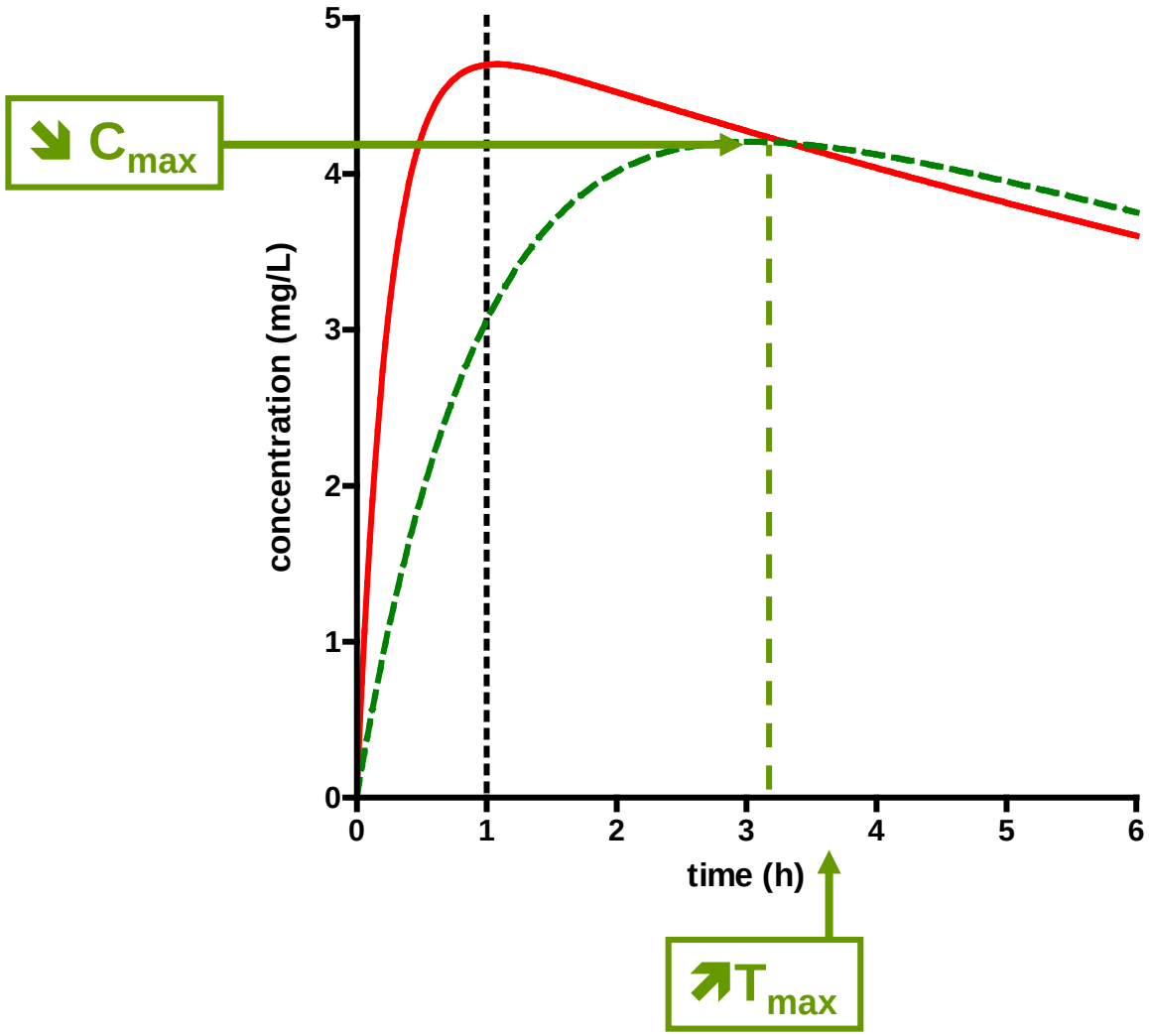
# AUC – $C_{max}$ – $T_{max}$



# What if the absorption is decreased ?

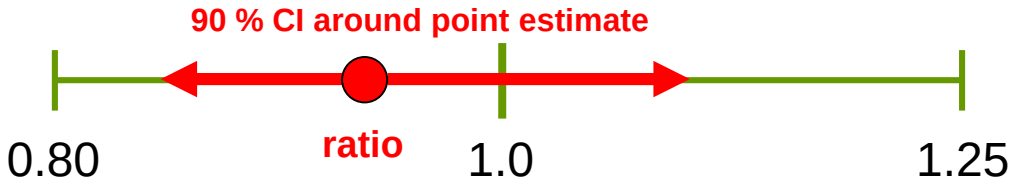


# What if absorption is delayed ?



# 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 inervals, Health Canada requires 0.9 – 1.12, but FDA accepts 0.8 – 1.25*

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

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

# *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.

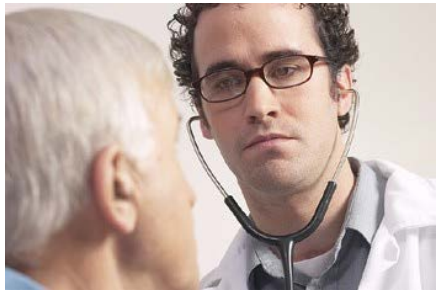
**Only ONE answer (1, 2 or 3), please !**

# 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).

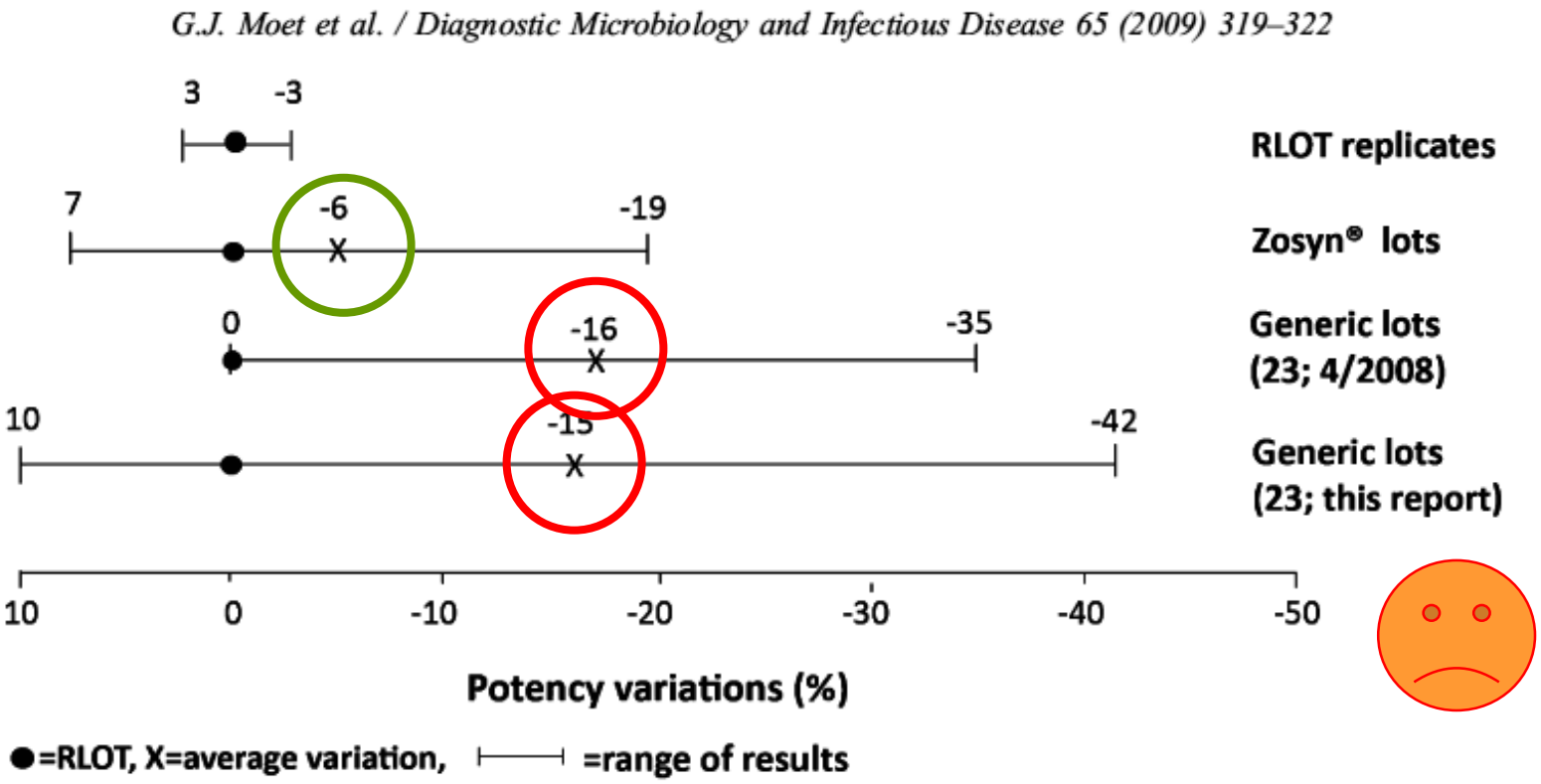



Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

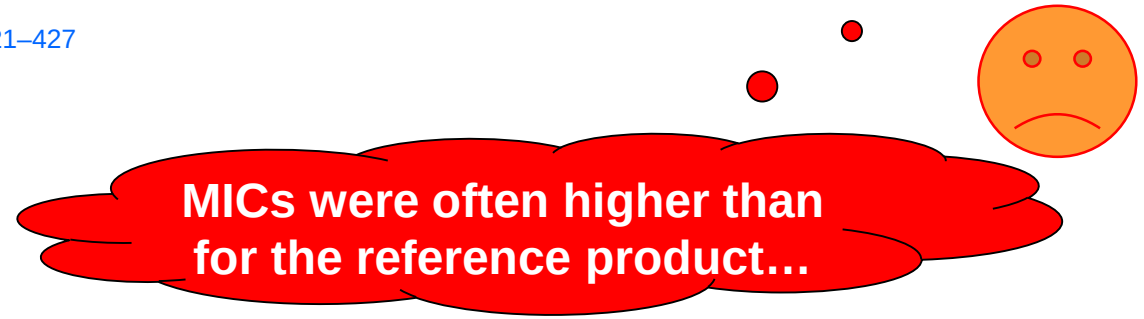
# MIC values (vancomycin)

**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 ± SD) | MIC distribution (%) of the most different generic versus brand name drug | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1/8 | 1/4 | 1/2 | 1[a] | 2 | 4 | 8 |
| Vancomycin | MRSA (90) | 5 | 25.00 ± 15.52 | – | – | – | 54.4 | 45.6 | – | – |
| Teicoplanin | MRSA (147) | 7 | 28.09 ± 10.29 | – | – | – | 59.2 | 40.1 | 0.7 | – |
| Cefotiam | *Staphylococcus aureus* (100) | 7 | 8.71 ± 3.04 | – | – | – | 87.0 | 13.0 | – | – |
| | *Escherichia coli* (100) | 7 | 12.00 ± 5.89 | – | – | – | 77.0 | 22.0 | 1.0 | – |
| Ceftriaxone | *Streptococcus pneumoniae* (126) | 6 | 12.70 ± 4.77 | – | – | – | 81.7 | 18.3 | – | – |
| Ceftazidime | *Pseudomonas aeruginosa* (100) | 2 | 3.00 ± 2.83 | – | – | – | 95.0 | 5.0 | – | – |
| Meropenem | *P. aeruginosa* (100) | 7 | 18.57 ± 3.46 | – | – | – | 78.0 | 19.0 | 2.0 | 1.0 |
| Imipenem | *P. aeruginosa* (100) | 4 | 9.00 ± 2.58 | – | – | – | 88.0 | 11.0 | 1.0 | – |

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

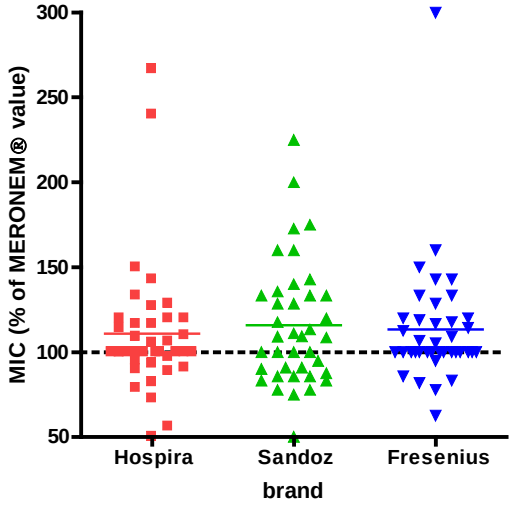
Fujimura & Watanabe J Infect Chemother (2012) 18:421–427



# MIC values (meropenem)

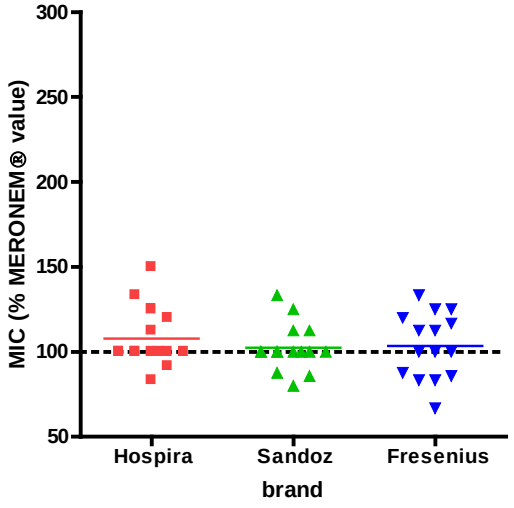
*MICs determined by arithmetic dilutions for strains displaying MICs ranging from 0.125 to 128 mg/L (geometric values)*

**Susceptible strains (MIC ≤ 2 mg/L)**



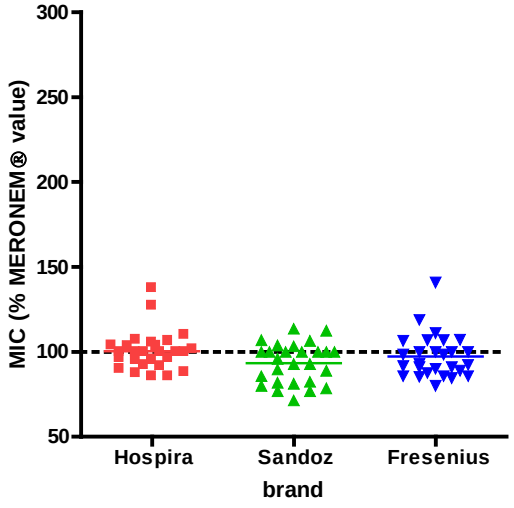

| | Hospira | Sandoz | Fresenius |
|---|---|---|---|
| mean = | 110.8 | 115.8 | 113.3 |
| SD= | 39.2 | 36.5 | 36.6 |

**Intermediate strains (≤ 2 MIC < 8 mg/L)**




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

**Resistant strains (MIC > 8 mg/L)**




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

Van Bambeke *et al*., in preparation

MERONEM® = meropenem commercialized by AstraZeneca

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

Neutropenic thigh mouse model

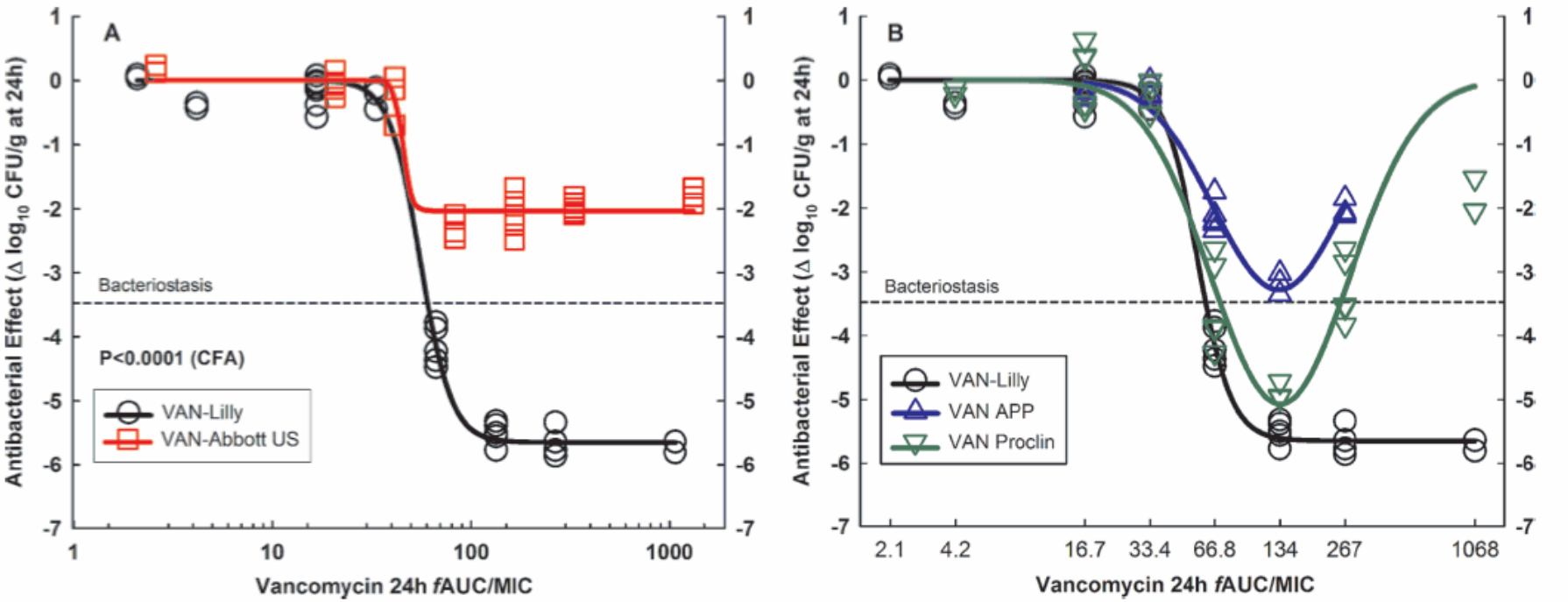



FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per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

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

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

Neutropenic thigh mouse model

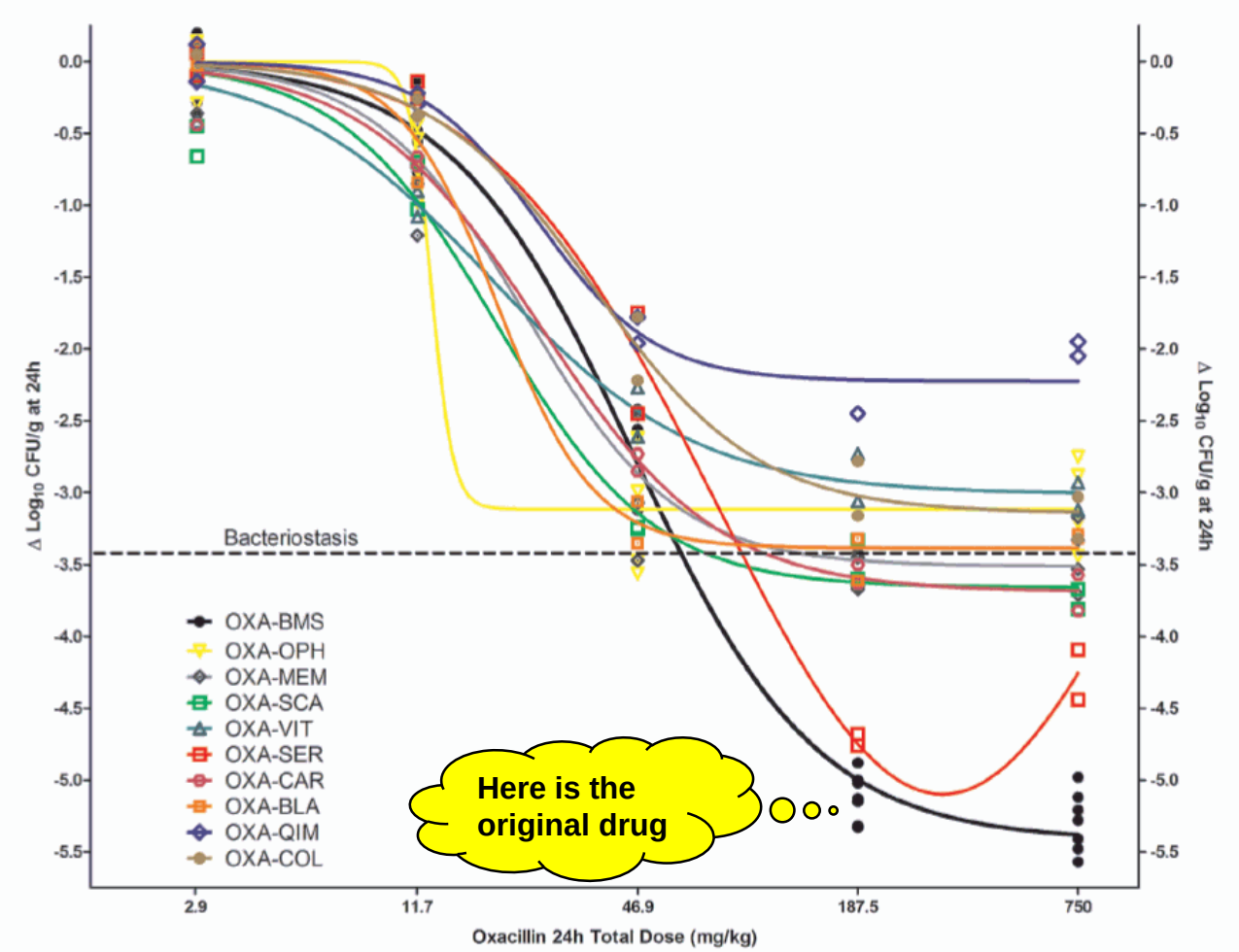



**Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model.** OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve).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

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

# 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


**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#]

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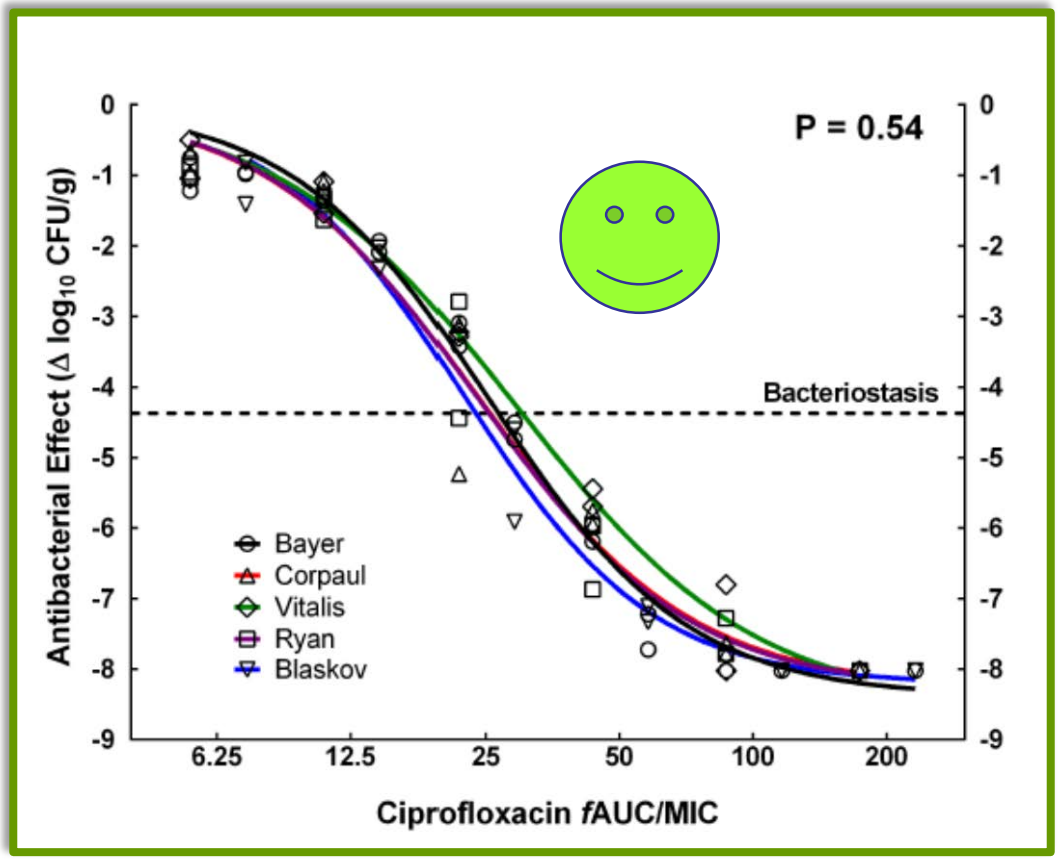


**Same authors as those describing the non-therapeutic equivalence of oxacillin !**

# 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

Corrado Blandizzi[a], Giuseppe Claudio Viscomi[b], Antonio Marzo[c], Carmelo Scarpignato[d,*]

[a] Division of Pharmacology, Department of Clinical & Experimental Medicine, University of Pisa, Via Roma 55, 56126 Pisa, Italy
[b] Research and Development Division, Alfa Wassermann Pharmaceuticals, Via Ragazzi del' 99 5, 40133 Bologna, Italy
[c] Institute for Pharmacokinetic and Analytical Studies SA, Via Mastri 36, 6853 Ligornetto, Switzerland
[d] Clinical Pharmacology and Digestive Pathophysiology Unit, Department of Clinical and Experimental Medicine, University of Parma, Cattani Pavillon, Maggiore University Hospital, Viale Gramsci 14, 43125 Parma, Italy

# Sometimes the generic has a problem of a "too good" bioavailability …

Pharmacological Research 85 (2014) 39–44

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journal homepage: www.elsevier.com/lo

Is generic rifaximin still a poorly absorbed antibiotic
branded and generic formulations in healthy volunt

Corrado Blandizzi [a], Giuseppe Claudio Viscomi [b], Antonio Marzo [c], C

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Maggiore University Hospital, Viale Gramsci 14, 43125 Parma, Italy



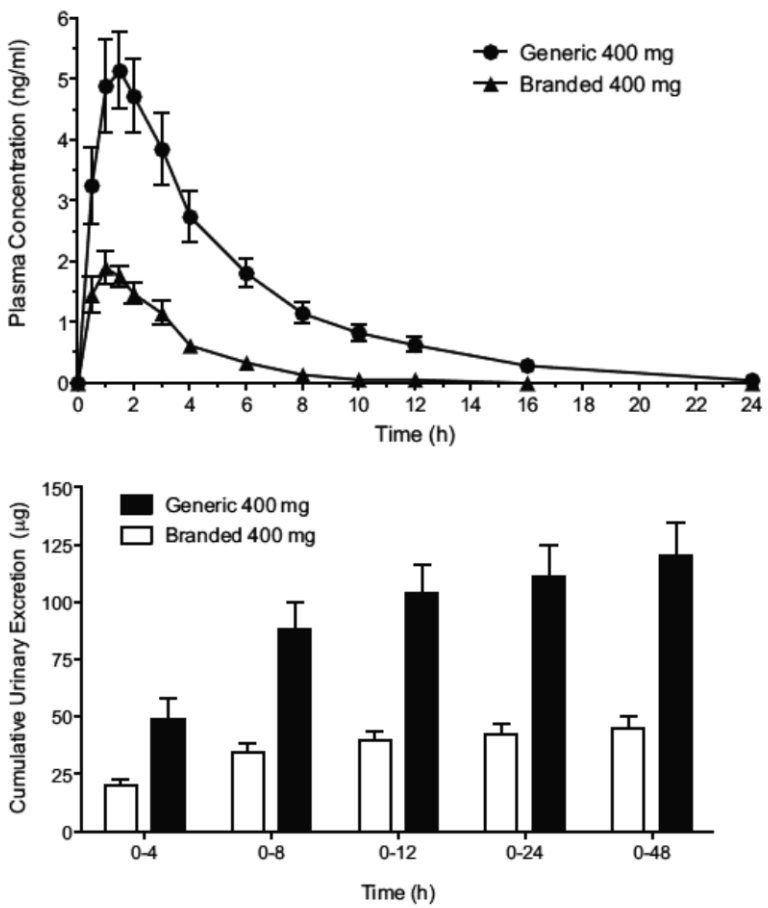


**Fig. 1.** Mean rifaximin concentration–time (top panel) and cumulative urinary excretion (bottom panel) profiles following administration of 400-mg single-dose generic or branded (polymorph-α) rifaximin to healthy volunteers. Each point or column represents the mean ± SEM (vertical lines) obtained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

# The reasons are subtle differences in composition…

ELSEVIER journal

Is generic rifaximin still a p
branded and generic formu

Corrado Blandizzi[a], Giuseppe Clauc

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Maggiore University Hospital, Viale Gramsci 14, 43125 Parm

**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 | Sodium starch glycolate |
| | Glycerol distearate | Glycerol monostearate |
| | Colloidal anhydrous silica | Colloidal anhydrous silica |
| | Talc | Talc |
| | Microcrystalline cellulose | Microcrystalline cellulose |
| Coating components | Hypromellose | Hypromellose |
| | Titanium dioxide | Titanium dioxide |
| | Disodium edetate | Disodium edetate |
| | Propylene glycol | Propylene glycol |
| | Red iron oxide E172 | Red iron oxide E172 |

The copy was almost perfect but …

# Clinical alerts (efficacy and safety) ?

## Safety and efficacy of generic drugs with respect to brand formulation

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

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

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

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

# Clinical alerts (efficacy and safety) ?

## Safety and efficacy of generi to brand formulation

**Luca Gallelli[1], Caterina Palleria[1], Antonio De Vuono[2], L Emilio Russo[1]**

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

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

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

**CONCLUSION**

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

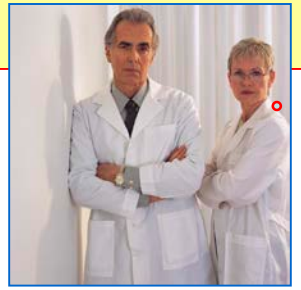
In agreement with Manning and Smith,[41] it is necessary to underline the importance that clinician's change their attitude toward pharmacovigilance and post-marketing surveillance systems, which can help to identify the lack of efficacy during the treatment with generic formulations.

**ACKNOWLEDGMENTS**

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

# 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**
- This needs to be further studied, but, at this point, is beyond the clinician's grip !



**Who can we <u>really</u> trust ?**

# And this brings me to pharmaceutical quality…

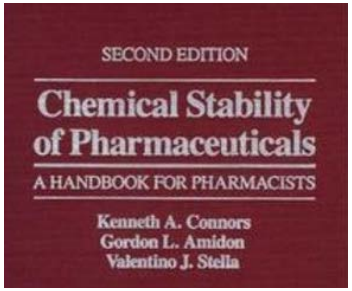
1. the generic must have the same solubility / dispersion properties than the original
2. the generic cannot contain more impurities (or give rise to more degradation products) than the original
3. I must be sure about the real content of what I prescribe
4. All of the above is important
5. None of the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


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

# Dissolution of meropenem in Japan

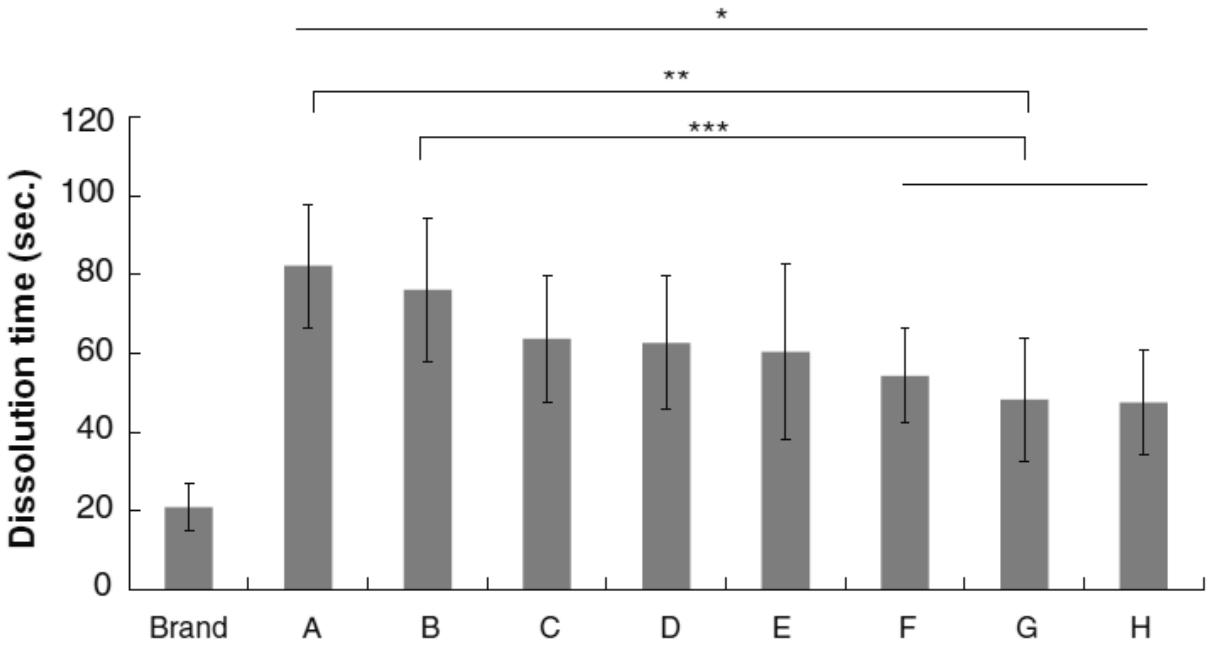



**Fig. 3** Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

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

# Crystals size in meropenem in Japan



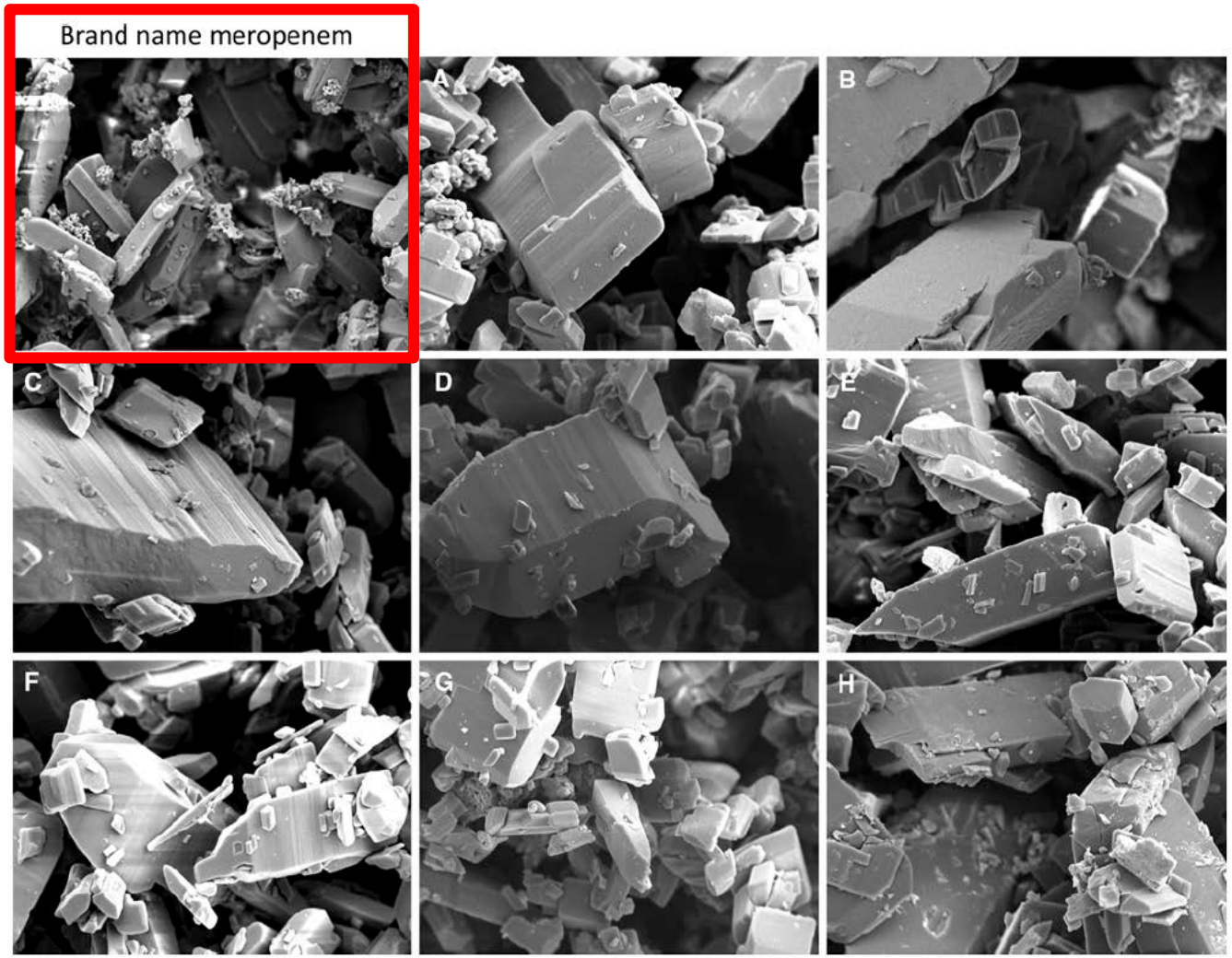
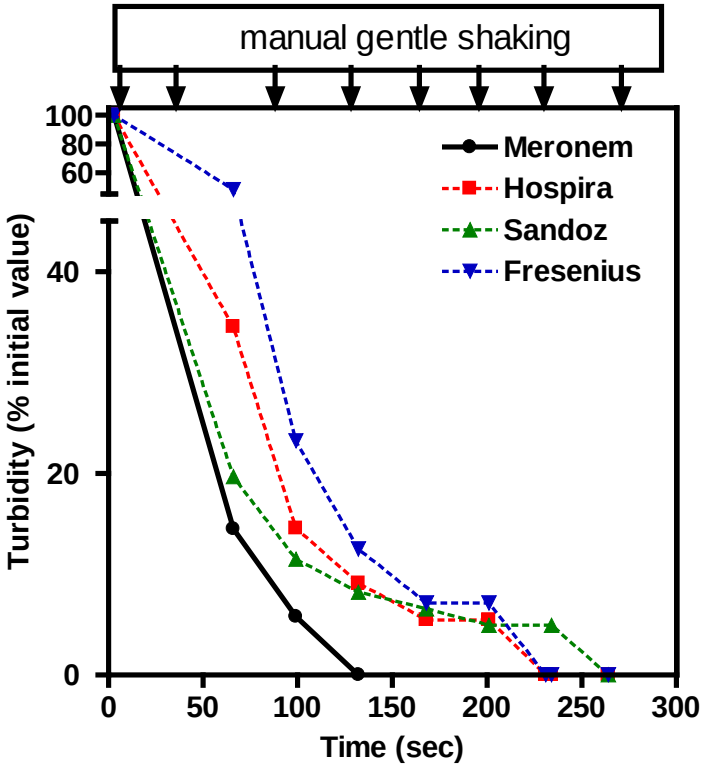


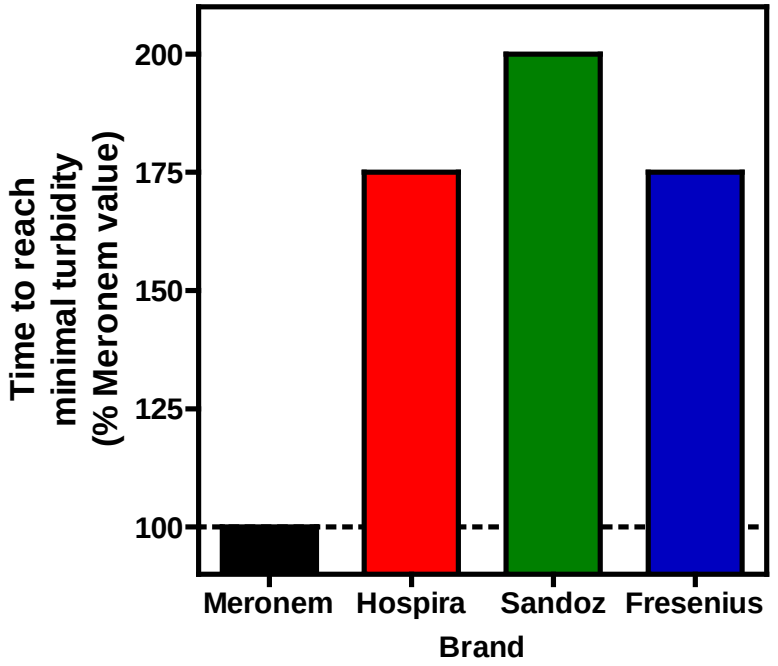

Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

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

# Dissolution of meropenem in Belgium

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




Van Bambeke *et al*., in preparation

# Dissolution of meropenem in Belgium

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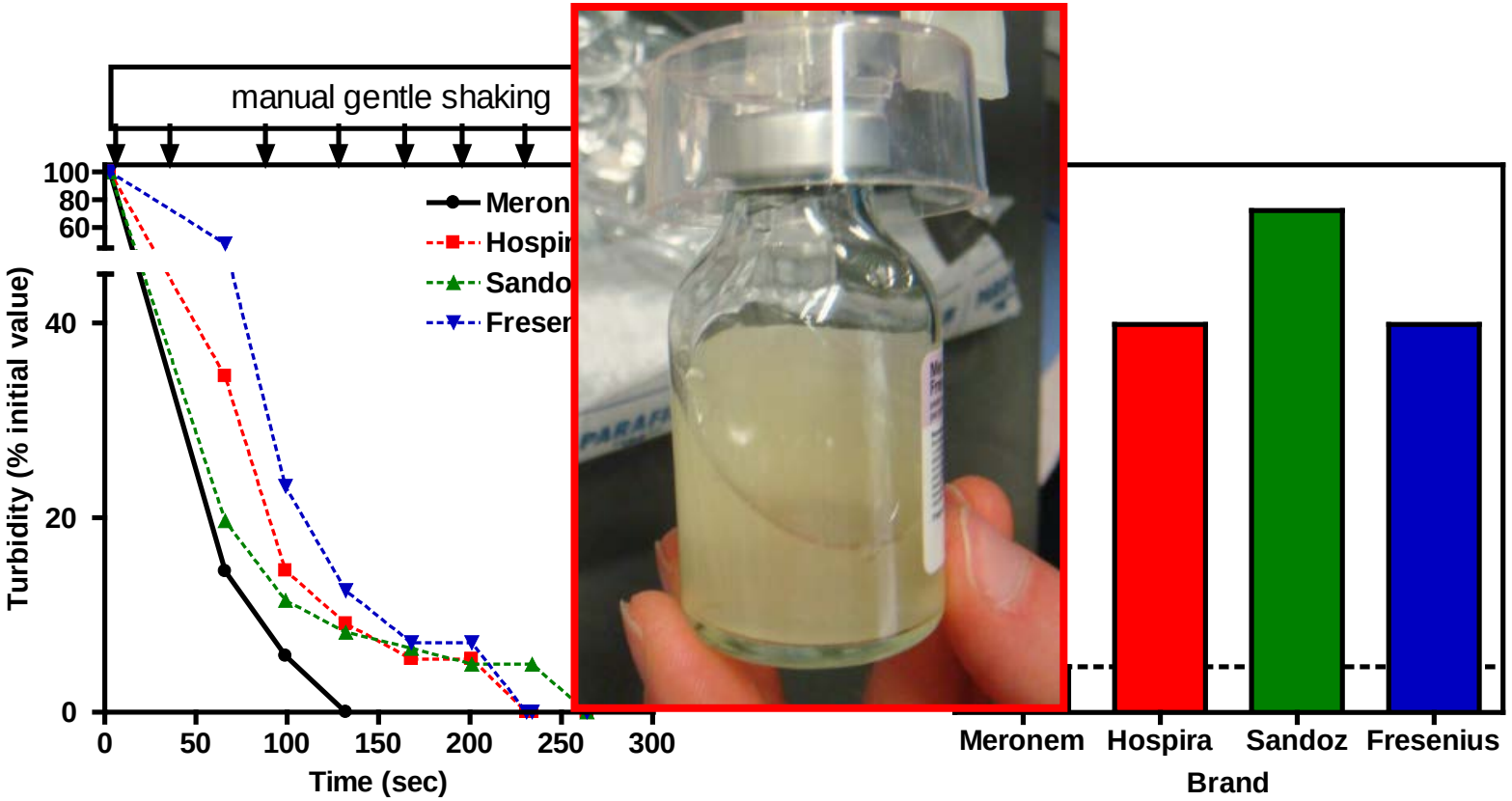
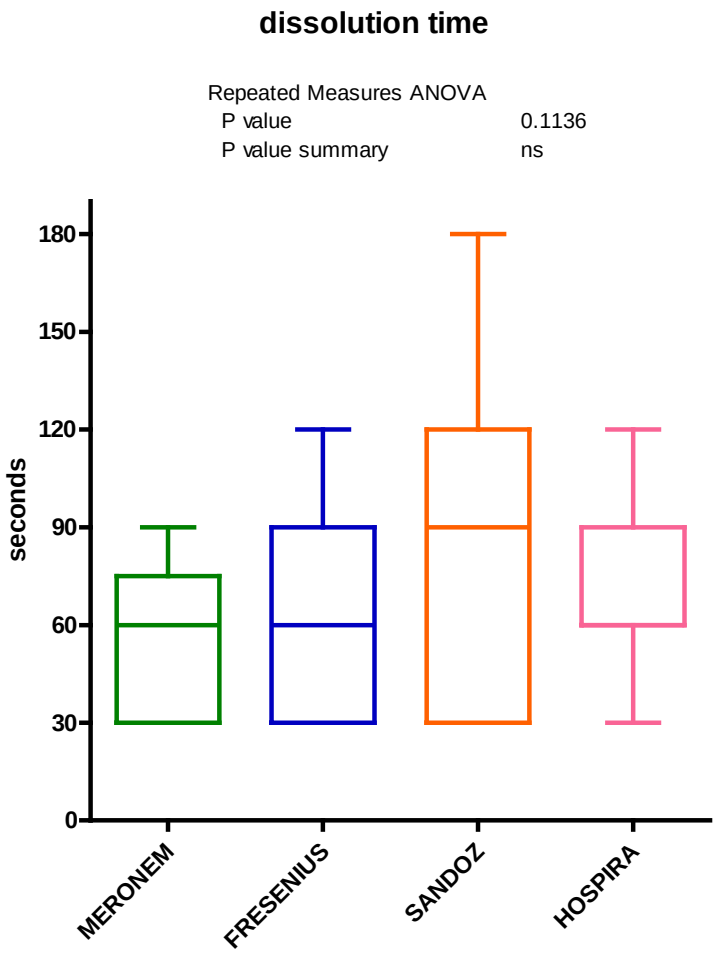
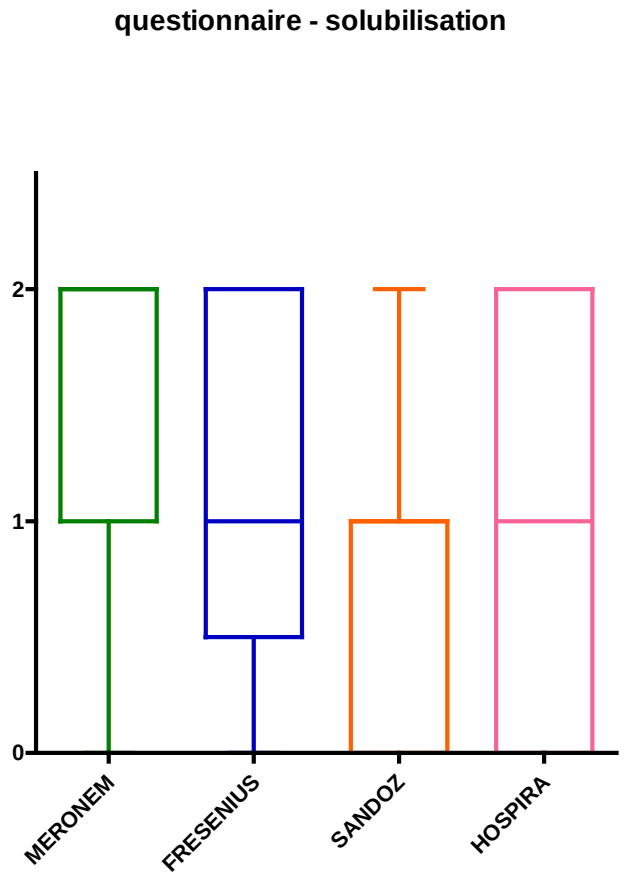



Van Bambeke *et al*., in preparation

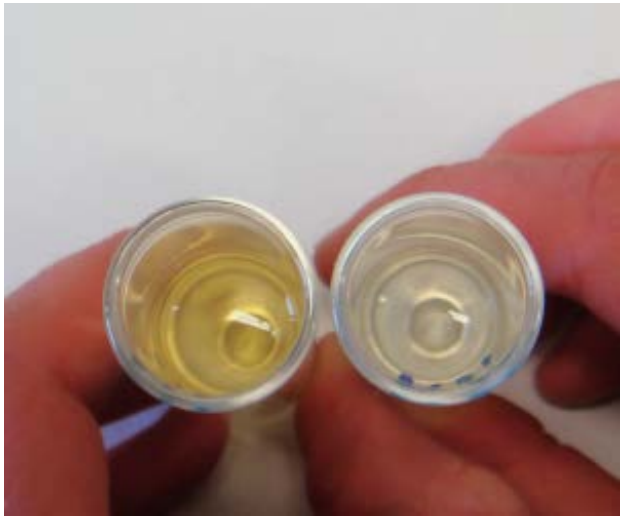
# Are Primary Health Care Professionals (nurses) happy? (meropenem)




Van Bambeke *et al.*, in preparation

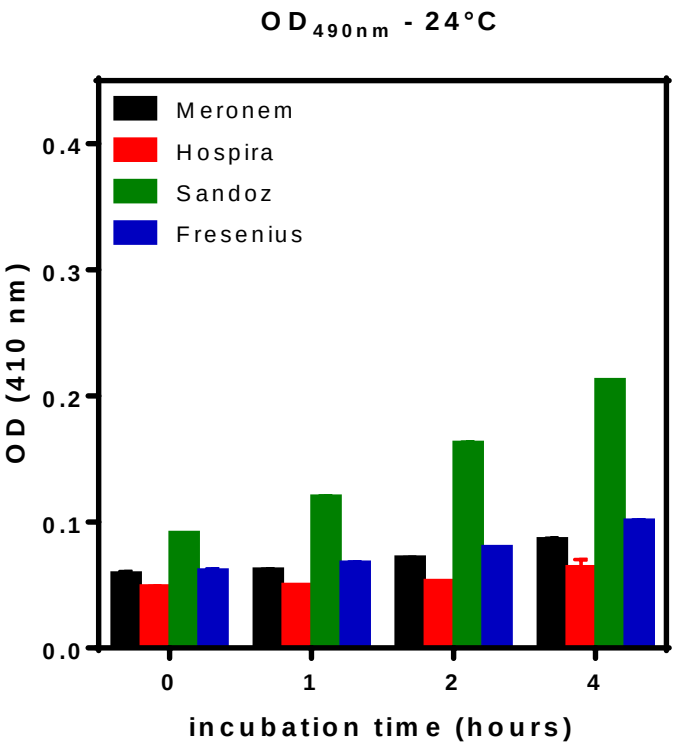
# Impurities in meropenem: coloured compounds

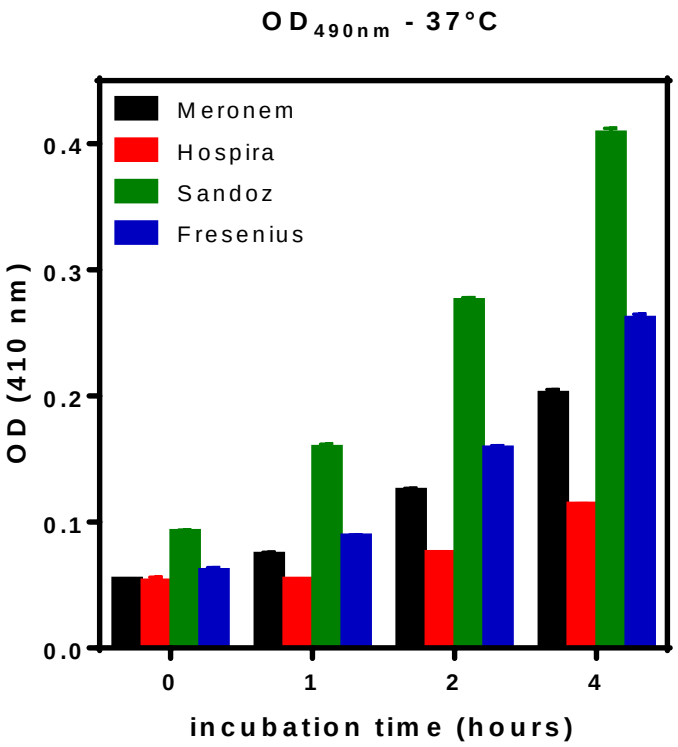


are you happy with the colour?

Van Bambeke *et al*., in preparation

# Impurities in meropenem: coloured compounds




Van Bambeke *et al.*, in preparation

# 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 Arnet[1], Matthias Altermatt[2], Yves Roggo[2], Gabriel Schnetzler[2]**

[1]Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, [2]F. 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**

| | Description vial/dry powder/vial | | | | | |
|---|---|---|---|---|---|---|
| **Product (manufacturer)** | **Container integrity** | **Crystallinity** | **Colour** | **Average fill mass (mg)** | **Content of ceftriaxone per vial (mg)** | **Particles per 1/10 containers** |
| 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**

| In solution | | | | | | |
|---|---|---|---|---|---|---|
| Opalescence | pH | Degradation products | Metals | Residual solvents | Sterility | Deviations |
| Clear; <3.0 | 6.0–8.0 | <2.29% | 0 | 0 | No growth | 0 |
| *Strong opalescent; 22.6* | 6.9 | 0.52% | *Mn* Fe* Zn* Br** | *S B TH +* | No growth | 5 |
| *Opalescent; 14.2* | 6.3 | 0.84% | *Fe* Zn* Br† Sr** | *S B TH +* | No growth | 4 |
| Clear; 2.1 | 6.8 | 0.23% | *Zn** | *S B H +* | No growth | 4 |
| Clear; 2.2 | 6.7 | 0.17% | *Zn* Br** | *S B +* | No growth | 3 |
| *Faintly opalescent; 3.2* | 6.7 | 0.28% | *Fe* Zn* Br** | *S B +* | No growth | 4 |
| *Opalescent; 13.2* | 6.5 | 0.64% | *Zn** | *S B TH +* | *Germs§* | 6 |
| *Opalescent; 7.7* | 6.5 | 0.54% | *Fe* Zn†* | *S B TH +* | *Germs‖* | 5 |
| *Opalescent; 6.4* | 6.5 | 0.73% | *Fe* Zn† Br‡* | *S B +* | 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
ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 743–754
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

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

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

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

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

**Abstract**

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


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

# Impurities in ciprofloxacin

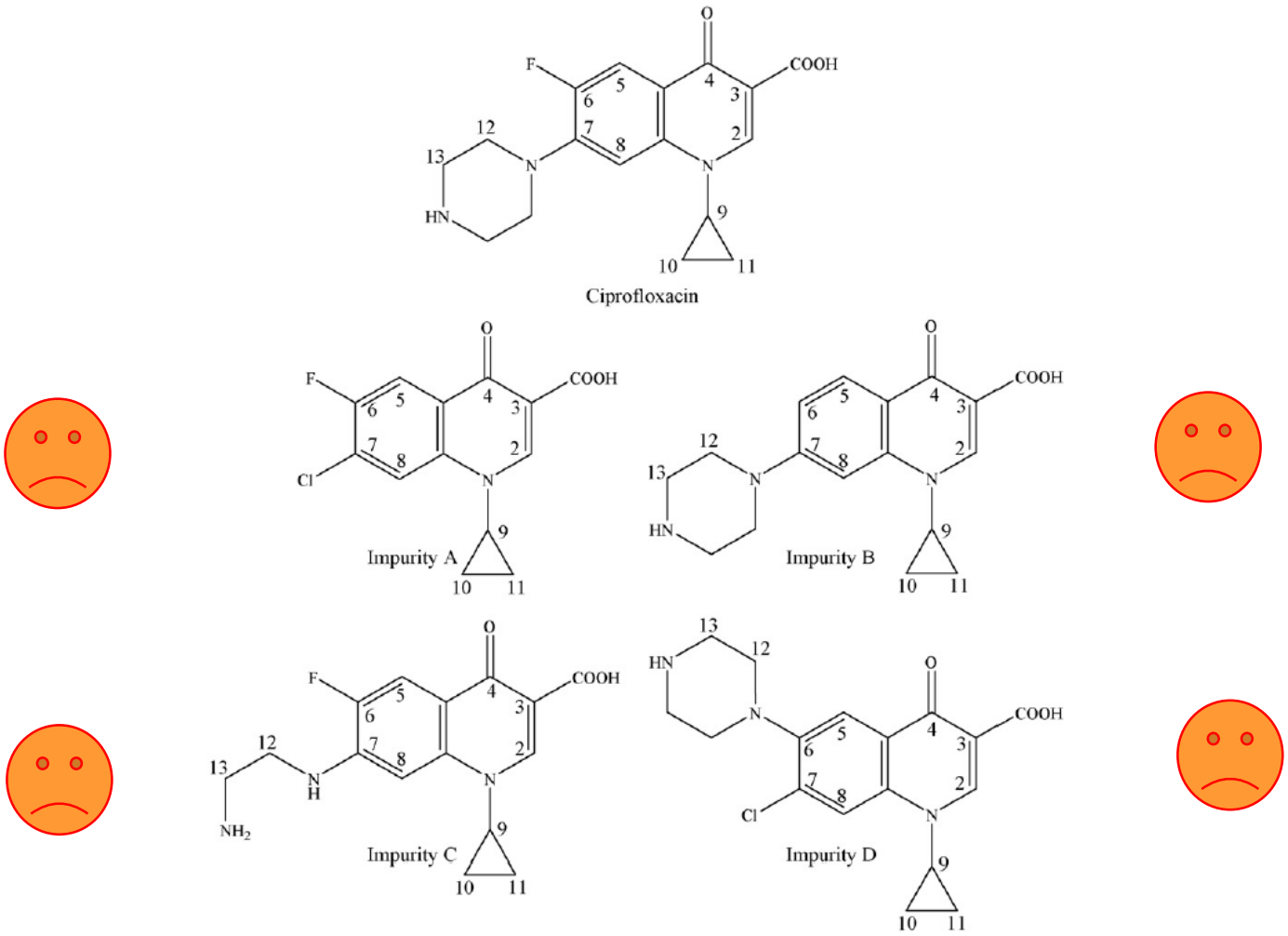



Fig. 1. Structure of ciprofloxacin and its main impurities.

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

# Substandard (wrong) drugs in the world ?

BJCP British Journal of Clinical Pharmacology

## Substandard drugs: a potential crisis for public health

Atholl Johnston[1] & David W. Holt[2]

[1]Clinical Pharmacology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK and [2]St George's – University of London, London, UK

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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.

# 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 lower 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**
  - 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)

**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 !**
       **(not addressed today, but see the back-up sllides)**

# The efforts for a correct use of antibiotics…

REVIEWS OF INFECTIOUS DISEASES • VOL. 3, NO. 4 • JULY-AUGUST 1981
 0162-0886/81/0304-0016$02.00

How many of you were practicing Medicine at that time ?

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.

**This has been known for years**

# We are facing contradictory situations

This is today !

J Antimicrob Chemother 2014; **69**: 2886–2888
doi:10.1093/jac/dku350 Advance Access publication 11 September 2014

Journal of Antimicrobial Chemotherapy

## Developing the first national antimicrobial prescribing and stewardship competences

**D. Ashiru-Oredope[1]*, B. Cookson[2] and C. Fry[3] on behalf of the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection Professional Education Subgroup†**

*[1]Antimicrobial Resistance, Stewardship and Healthcare Associated Infection (AMRS & HCAI) Programme, Public Health England, London, UK; [2]Division of Infection and Immunity, University College London, London, UK; [3]Department 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/ARHAIprescrcompetencies__2_.pdf

# We are facing contradictory situations

*J Antimicrob Chemother* 2014; **69**: 2886–2888
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Journal of Antimicrobial Chemotherapy

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*Corresponding author. Tel: +44-(0)20-832-76689; E-mail: diane.ashiru-oredope@phe.gov.uk
†Members 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/ARHAIprescrcompetencies__2_.pdf

# But see what happens with “Low cost antibiotics“…
## *The sour Danish Experience*

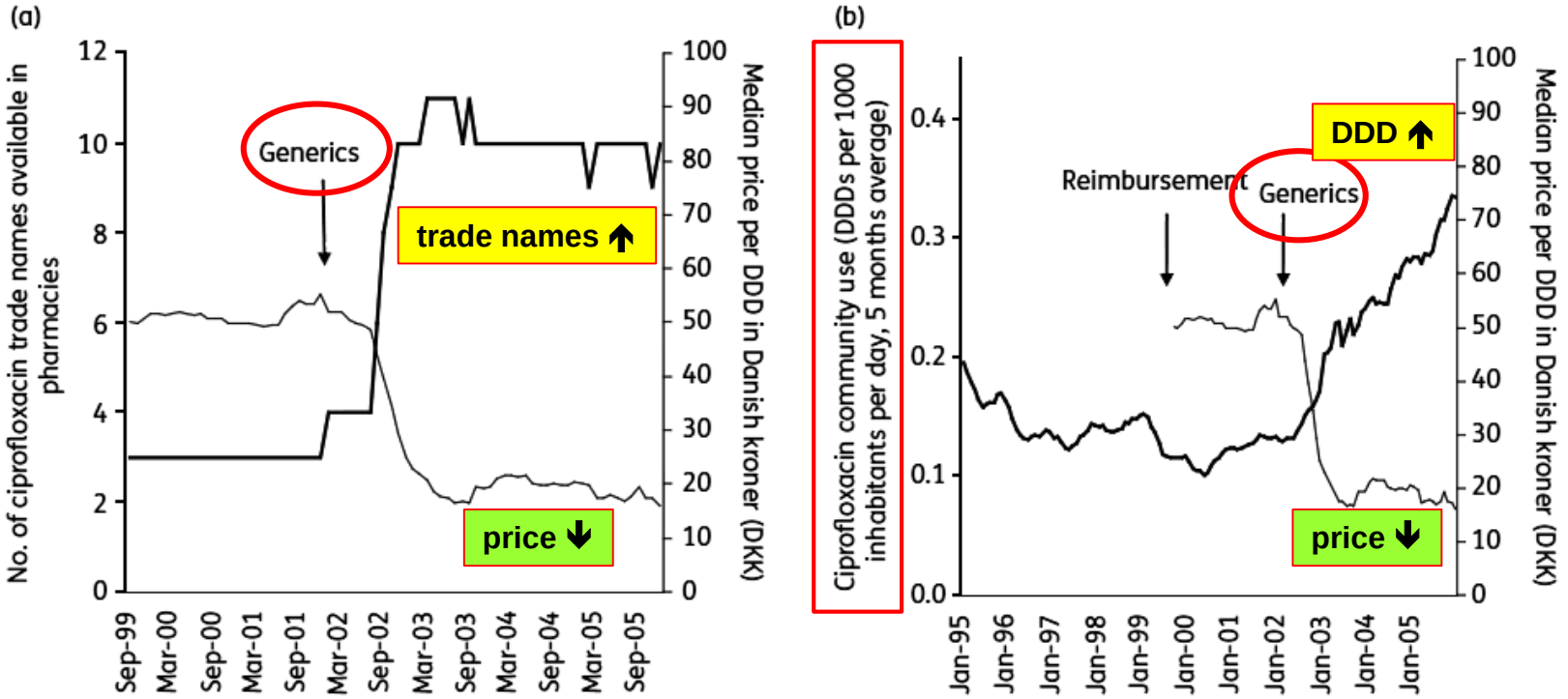



**Figure 1.** (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin.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

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

# But this had already occurred in Germany…

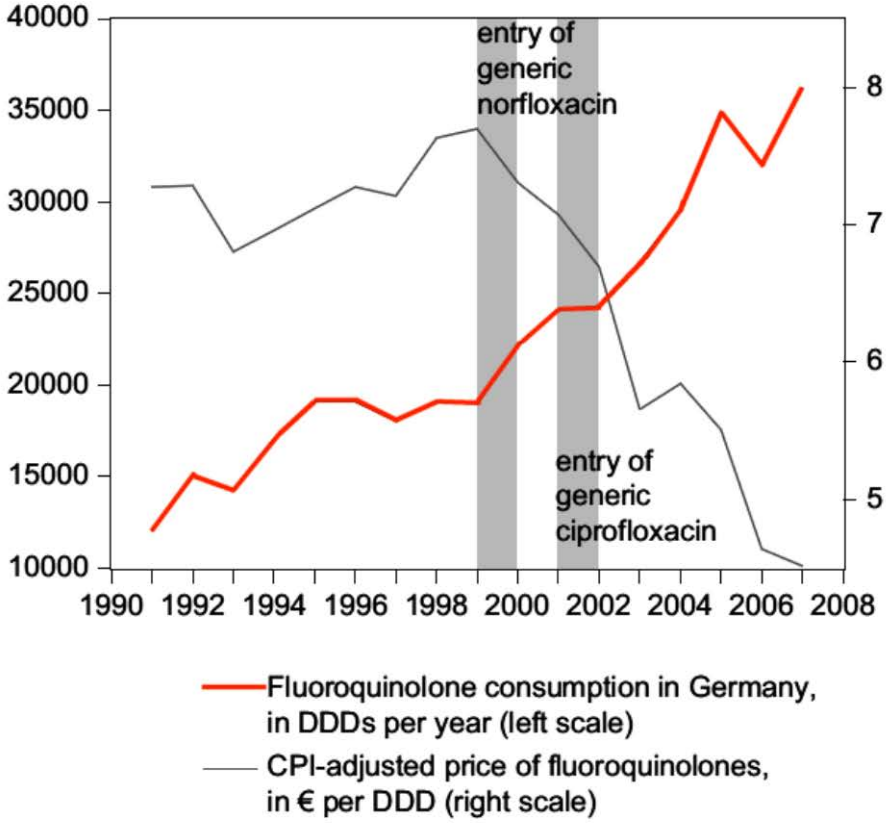



**Figure 1.** Fluoroquinolone consumption in Germany (SHI-related prescriptions, 1991–2007). SHI = statutory health insurance; DDD = defined daily doses; CPI = consumer price index

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

European Observatory on Health Systems and Policies

# 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**…

# Back-up

# You said "generics"


Lead generic companies resort to multiple strategies for growth

These include

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

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

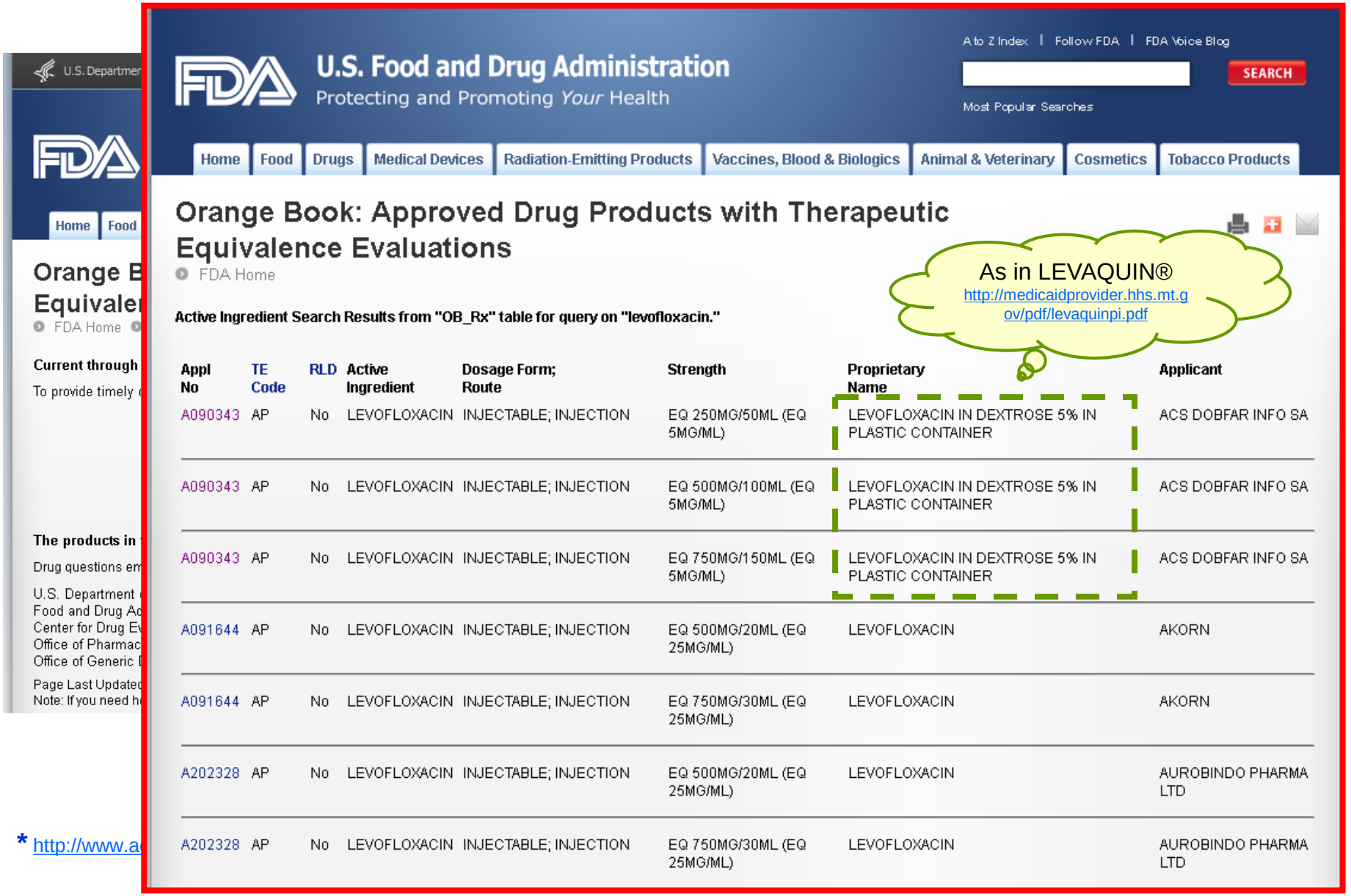
# US "Abbreviated New Drug Application"


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

# FDA approved generic drugs: "Orange book" *


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

# FDA approved generic drugs: "Orange book" *



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## Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home

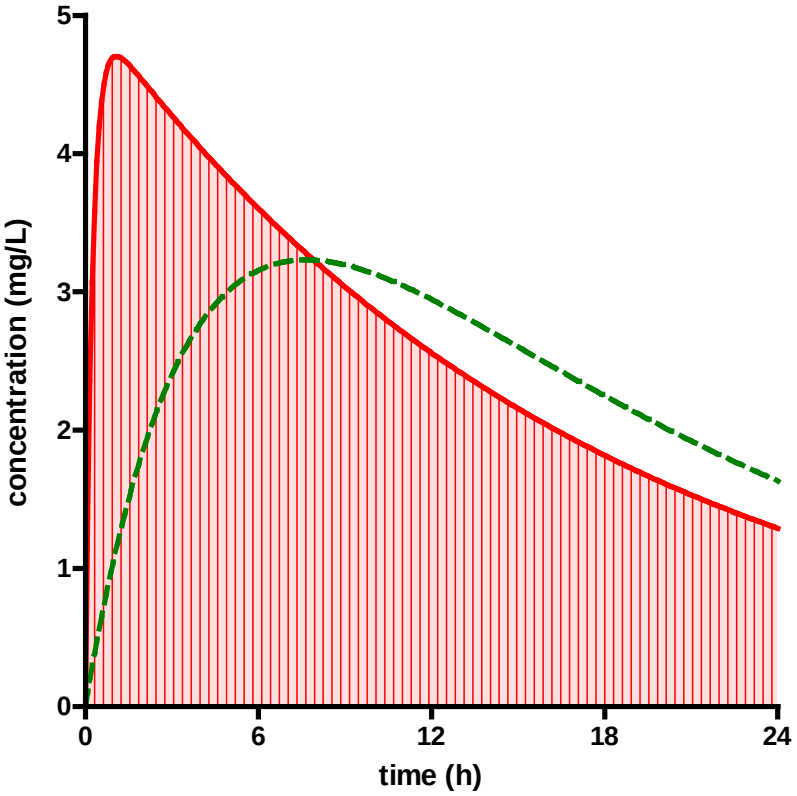
As in LEVAQUIN®
http://medicaidprovider.hhs.mt.gov/pdf/levaquinpi.pdf

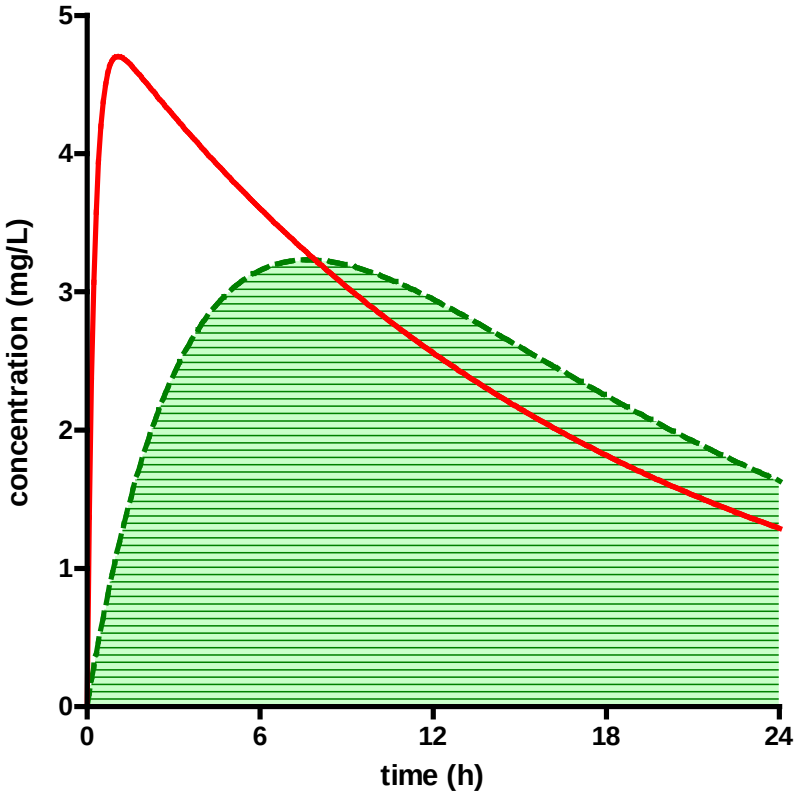
**Active Ingredient Search Results from "OB_Rx" table for query on "levofloxacin."**

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

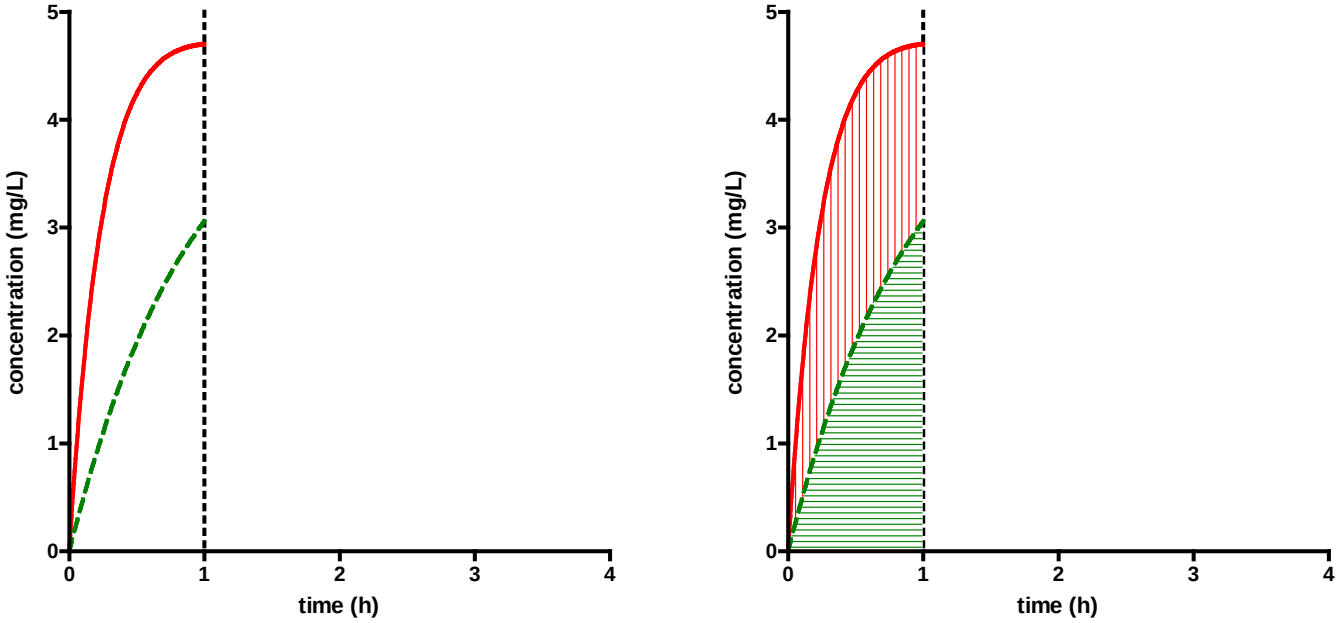
* http://www.a

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



# Additional criteria for early AUC (EMA) *



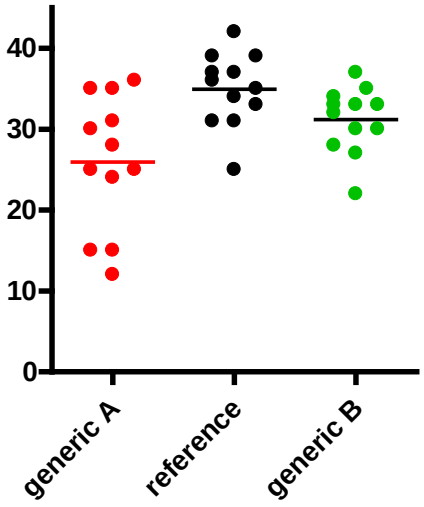

- Use the partial **AUC truncated** at the population median of $T_{max}$ for the reference formulation for for products where rapid absorption is of importance

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

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

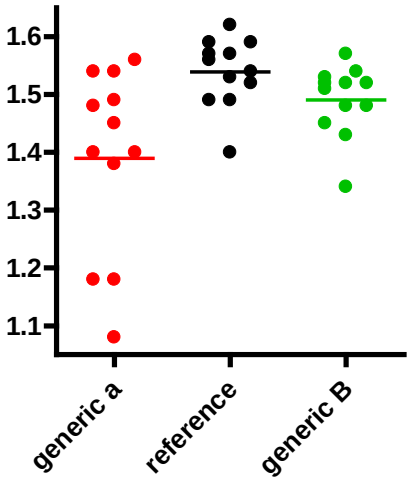
- Is **PK equivalence** leading to **pharmacological equivalence** ?
  - *in vitro* testing (MIC, MPC, impact on hetero-resistance) …
  - PK/PD models (animals)
  - Clinical studies (?)
- What about **intravenous forms** ?
  (that, by definition, are not amenable to conventional bioequivalence studies)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

# Are generic really comparable ?




arithmetic comparison

geometric comparison

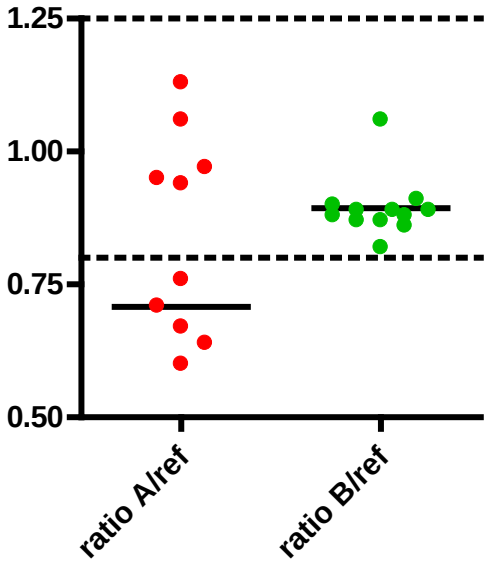


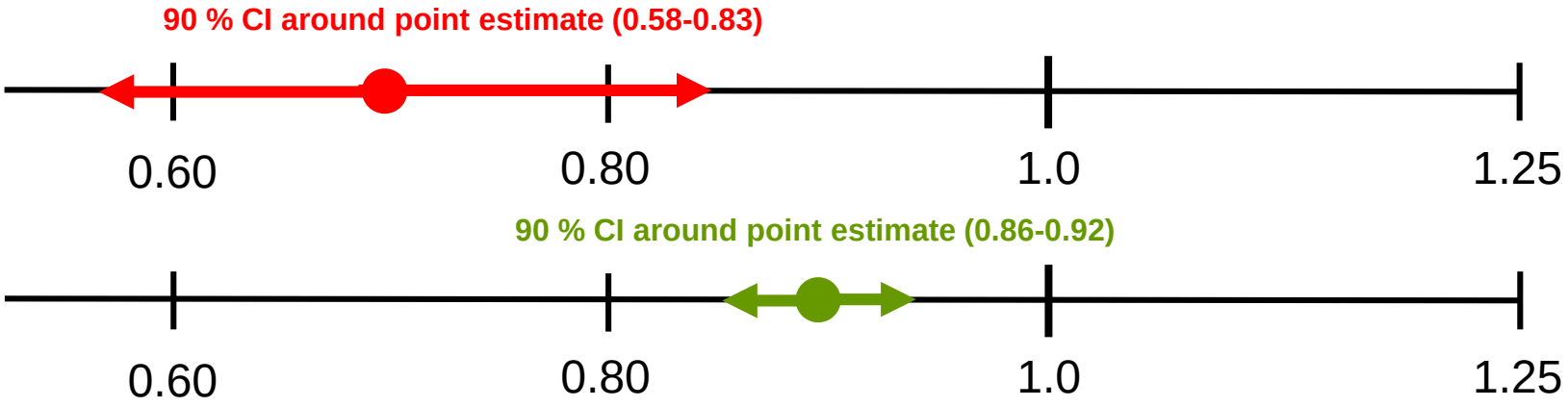
# Are generic really comparable ?

| 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.

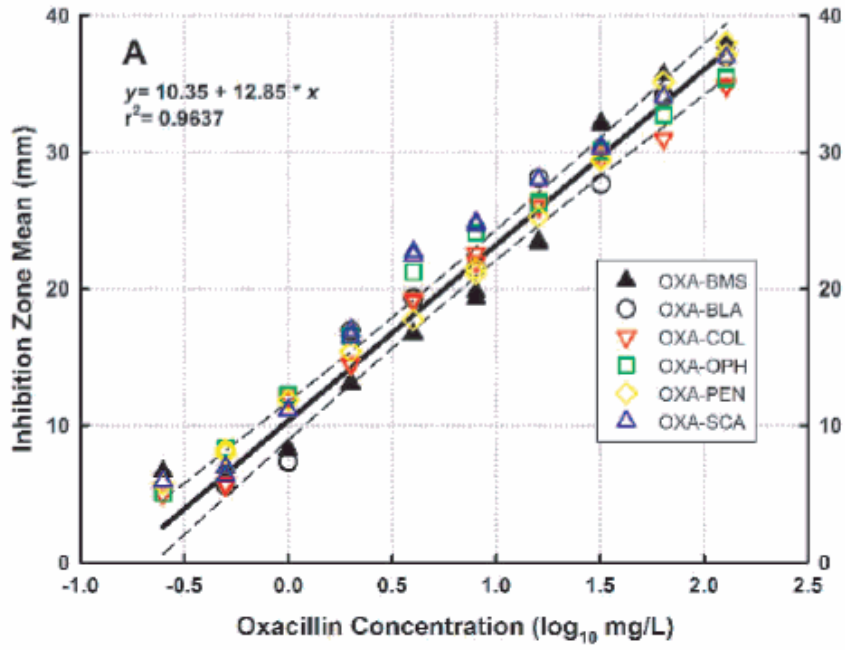
## Highly variable drugs or drug products

- 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 [±k·sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the within-subject standard deviation of the log-transformed values of Cmax of the reference product (Important: this applies to $C_{max}$ only, NOT to AUC)

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

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

# Potency (oxacillin)



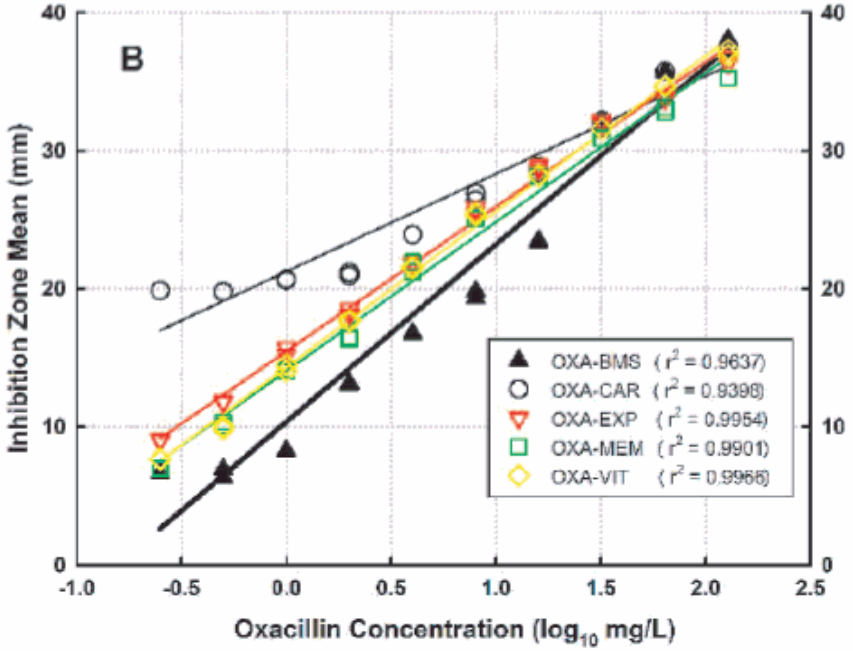
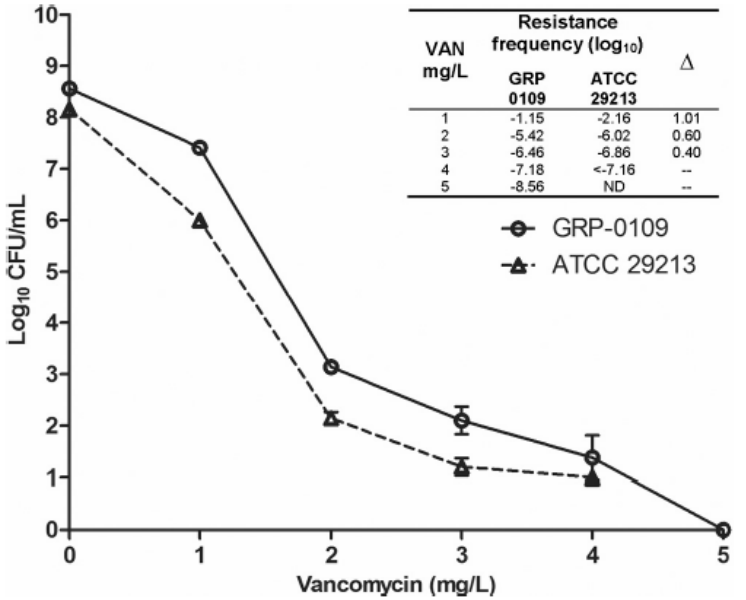




**Figure 1 Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay**. **A**. The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical 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 ($r^2$).

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

# Killing curves and hetero-resistance (vancomycin)

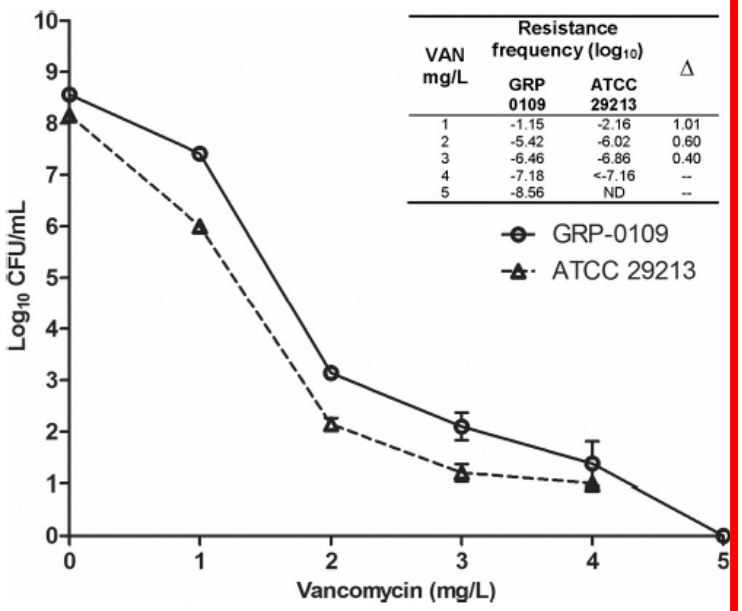



| VAN mg/L | Resistance frequency ($log_{10}$) GRP 0109 | ATCC 29213 | Δ |
|---|---|---|---|
| 1 | -1.15 | -2.16 | 1.01 |
| 2 | -5.42 | -6.02 | 0.60 |
| 3 | -6.46 | -6.86 | 0.40 |
| 4 | -7.18 | <-7.16 | -- |
| 5 | -8.56 | ND | -- |

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

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

# Killing curves and hetero-resistance (vancomycin)

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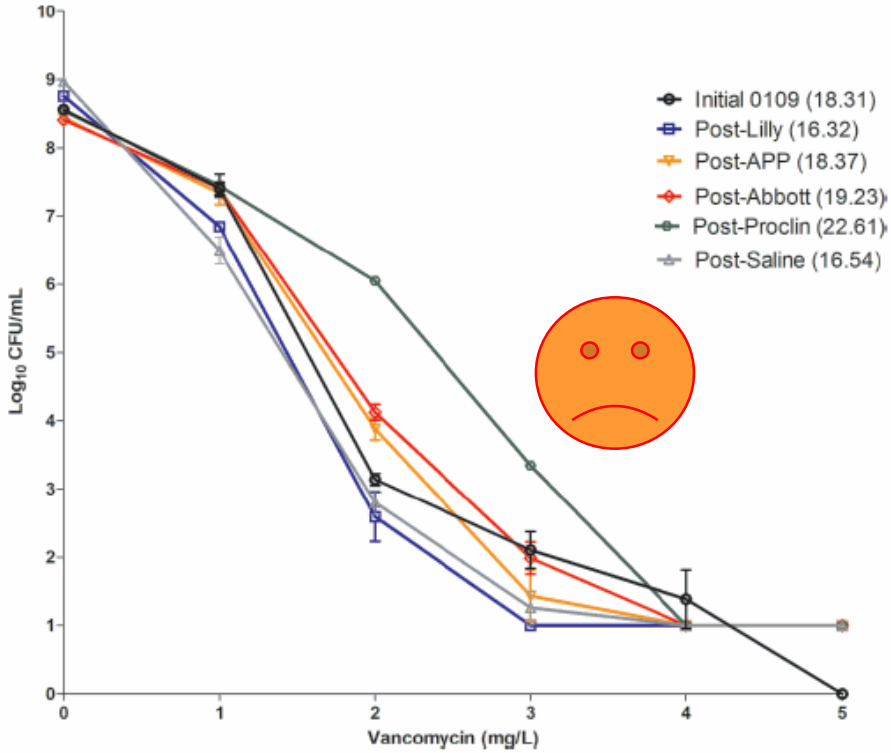


FIG 3 Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction of the less susceptible subpopulations, which is sharply different from three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

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

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

Neutropenic thigh mouse model

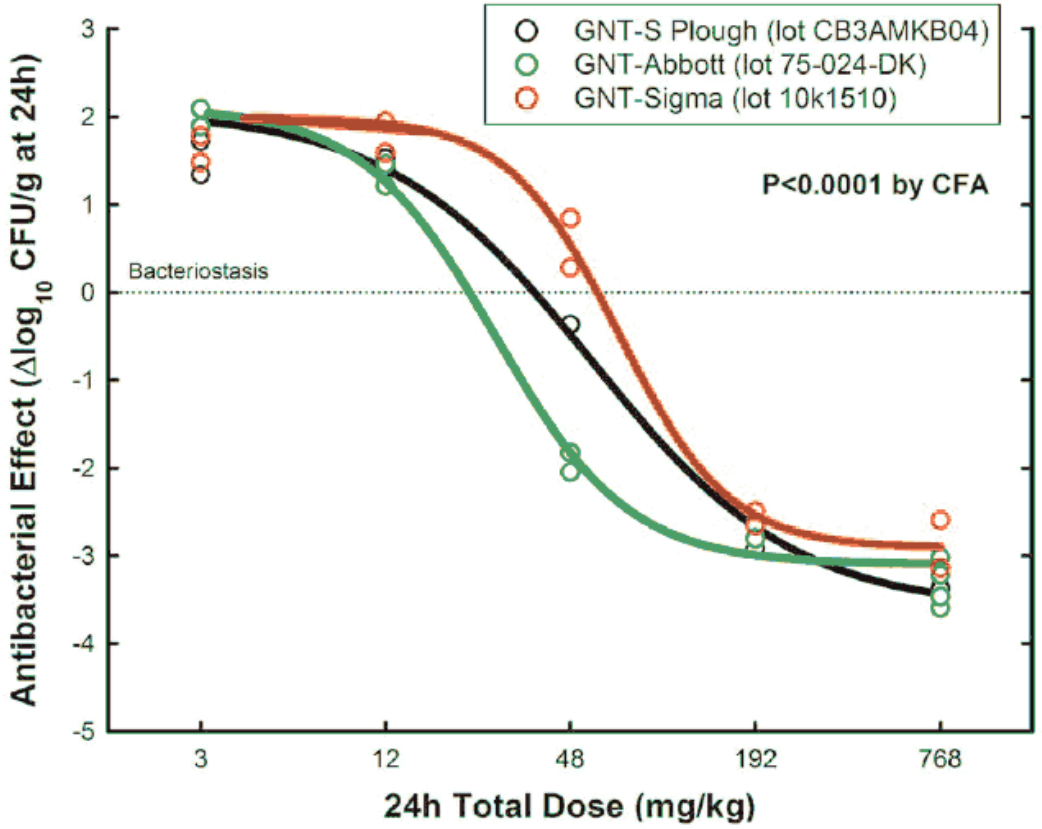


**Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence.** The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency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

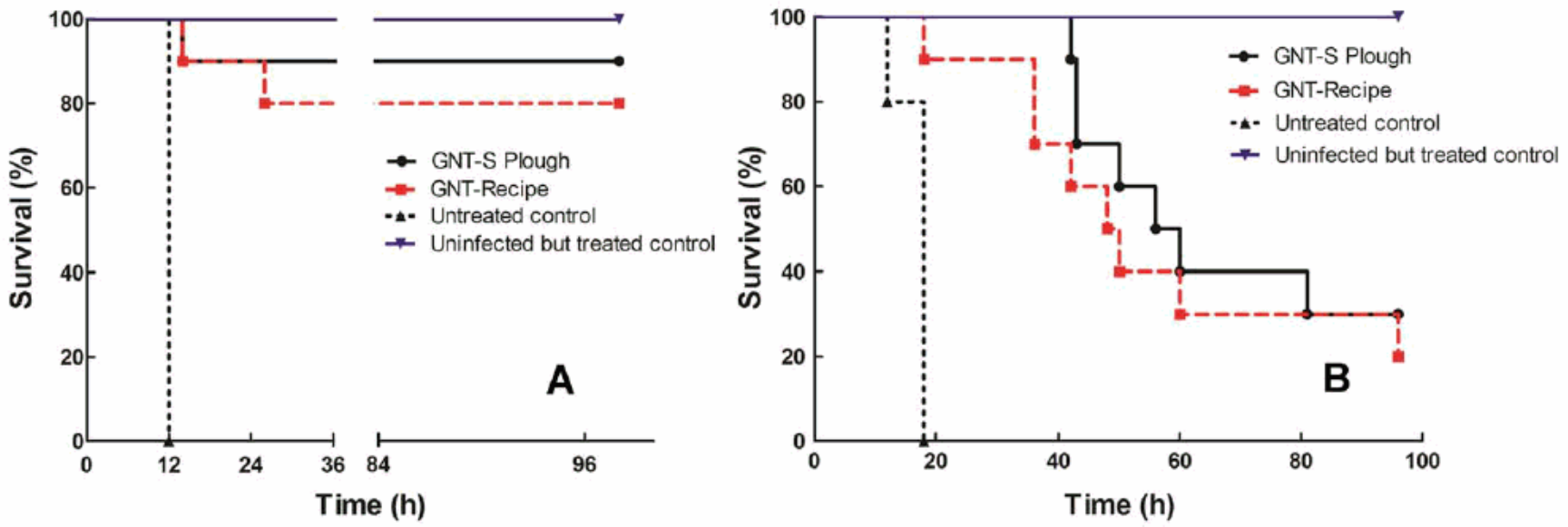


**Figure 4. Results from survival experiments.** Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect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

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

# Vancomycin: complete equivalence in the rabbit endocarditis model

AAC Journals.ASM.org

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

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

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

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

# Vancomycin: complete equivalence in the rabbit endocarditis model

AAC Journals.ASM.org

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

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

**T0: no antibiotic**
**T1 – T6: generics of vancomycin**

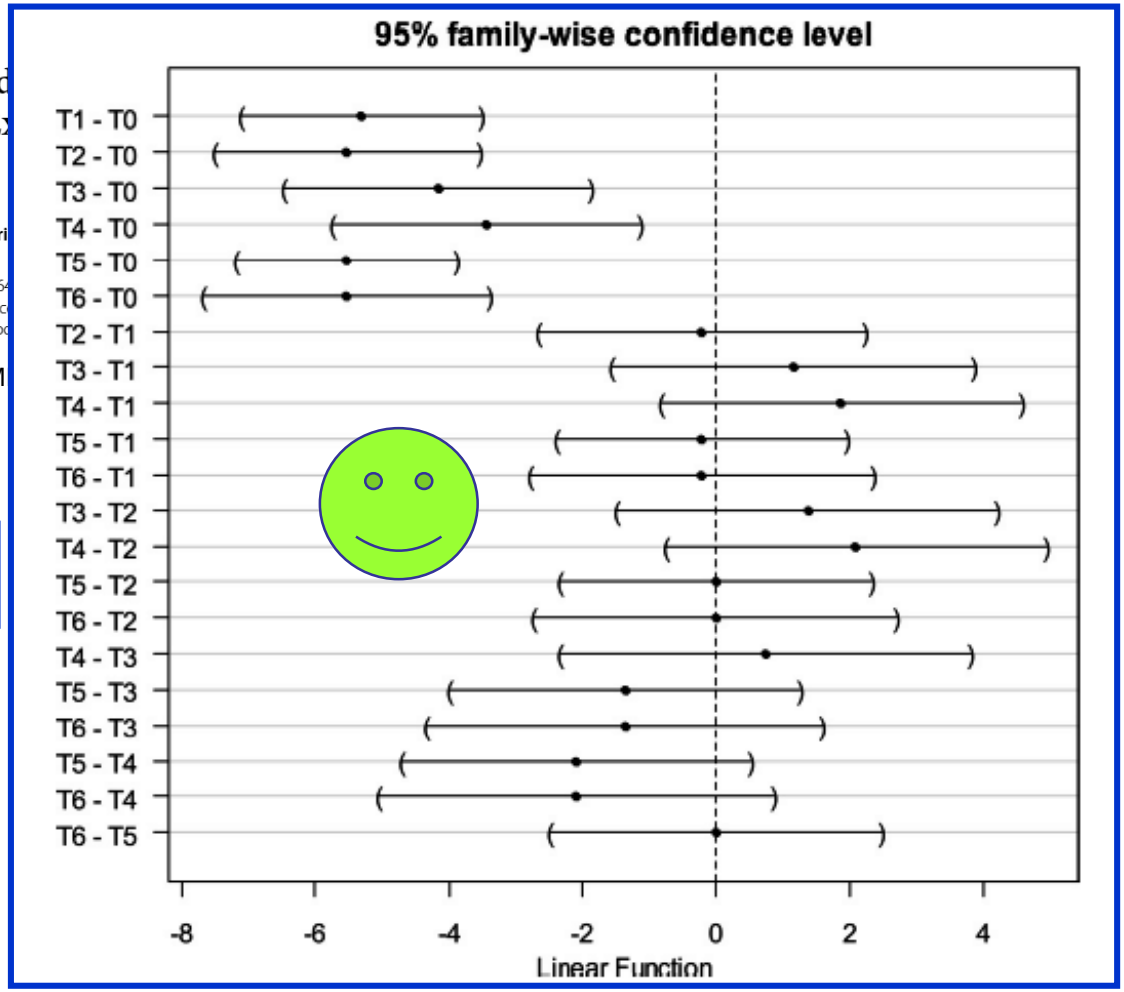
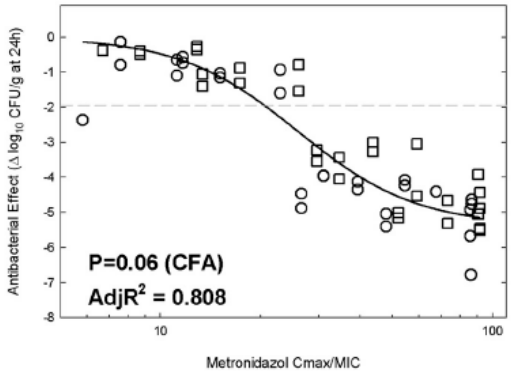



FIG 3 Differences between treatment groups in terms of organism titers in vegetations ($log_{10}$ CFU/g). Dots are mean differences between treatment groups, and parentheses are the upper and lower bounds of their 95% confidence interval. Analysis was performed using the Tukey method, taking into account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

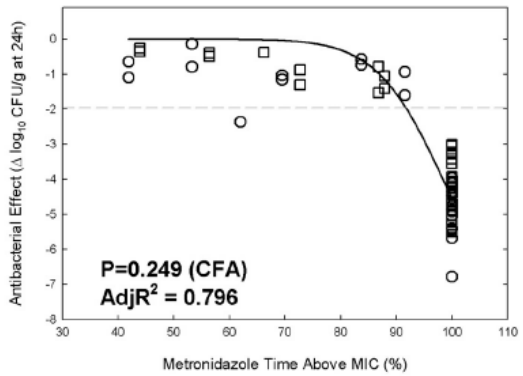
**Differences in terms of no. of organisms in vegetations**

# Metronidazole: complete equivalence

$C_{max}$/MIC




Time>MIC




AUC/MIC

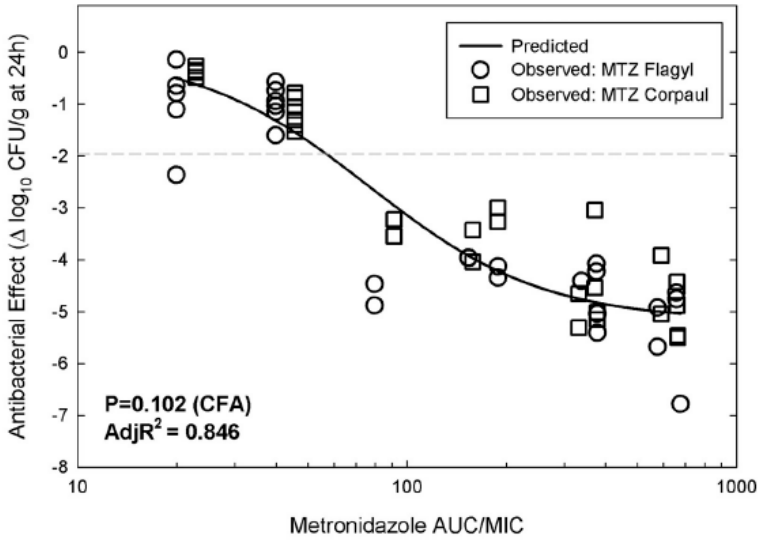



**FIG 5** Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *B. fragilis* in a neutropenic mouse thigh anaerobic infection model. Only one curve is depicted because the data belong to a single population despite the fact that they were obtained after treatments of different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

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

# 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.egagenerics.com/index.php/publications

# But at the end of the day…

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ScienceDirect

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

[c]*Department of Pediatrics, The Ohio State University, Columbus, OH 43201, USA*

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

# But at the end of the day…

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Amy J. Keenum, D.O., Pharm.
Deena J. Chisolm, Ph.

[a]*Department of Family Medicine, University of T*
*Kno*
[b]*Department of Family Medicine, Orego*
[c]*Department of Pediatrics, The*
[d]*Department of Family Medicine, T*

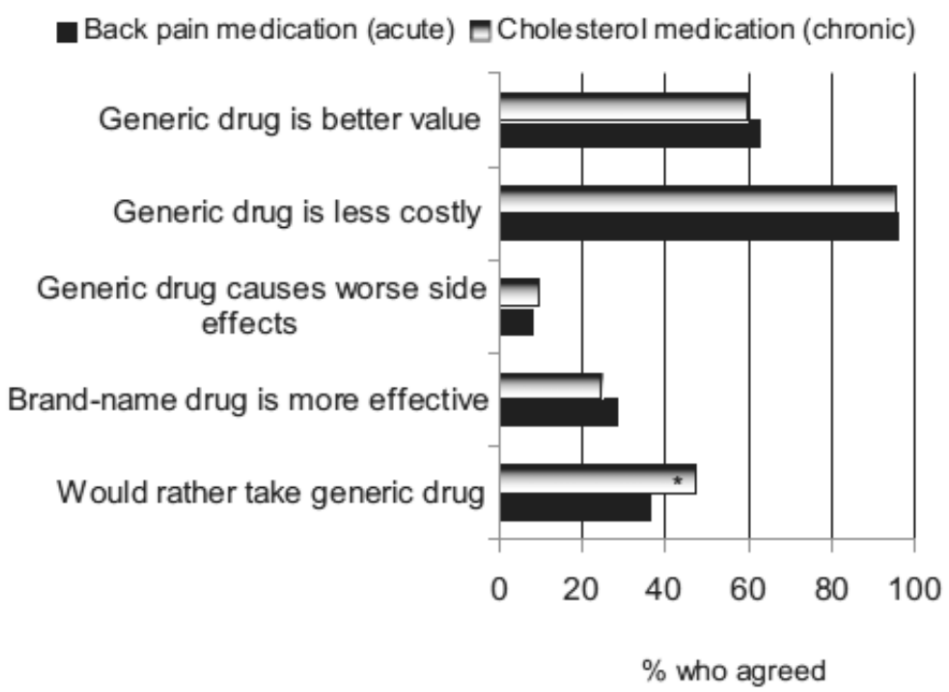


Fig. 2. Participants' perceptions of generic and brand-name medications for treating their hypothetical chronic or acute condition (n = 172). Note: % who agreed is the sum of participants who somewhat or strongly agreed with each item. *$P < .05$ using chi-square test.

# The risk of overconsumption in France …

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Médecine et maladies infectieuses

Médecine et maladies infectieuses 42 (2012) 141–148

## Generic antibiotic drugs: Is effectiveness guaranteed?

R. Gauzit*, M. Lakdhari

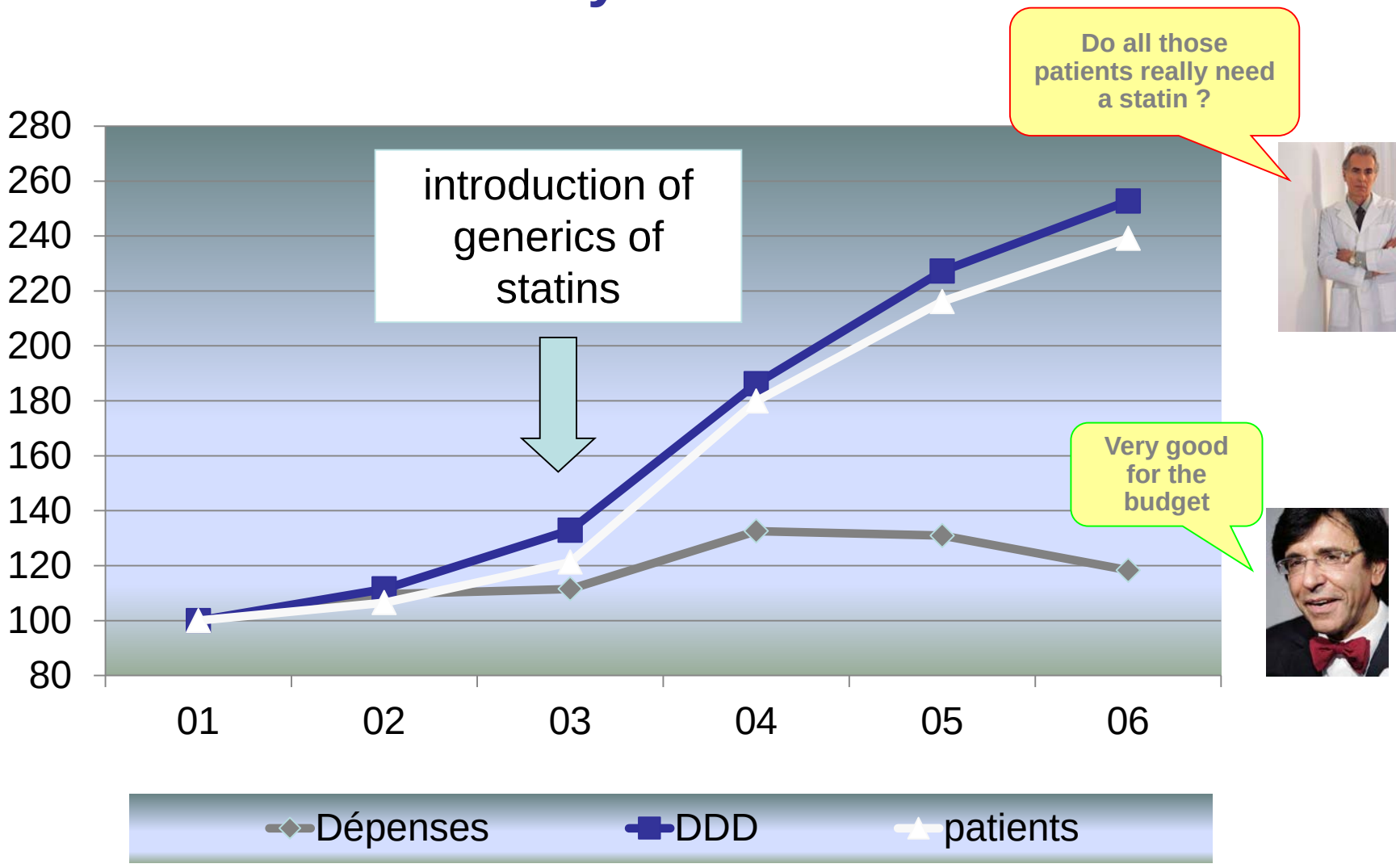
*Unité de réanimation, Hôtel Dieu, place du Parvis-de-Notre-Dame, 75781 Paris cedex 04, France*

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…

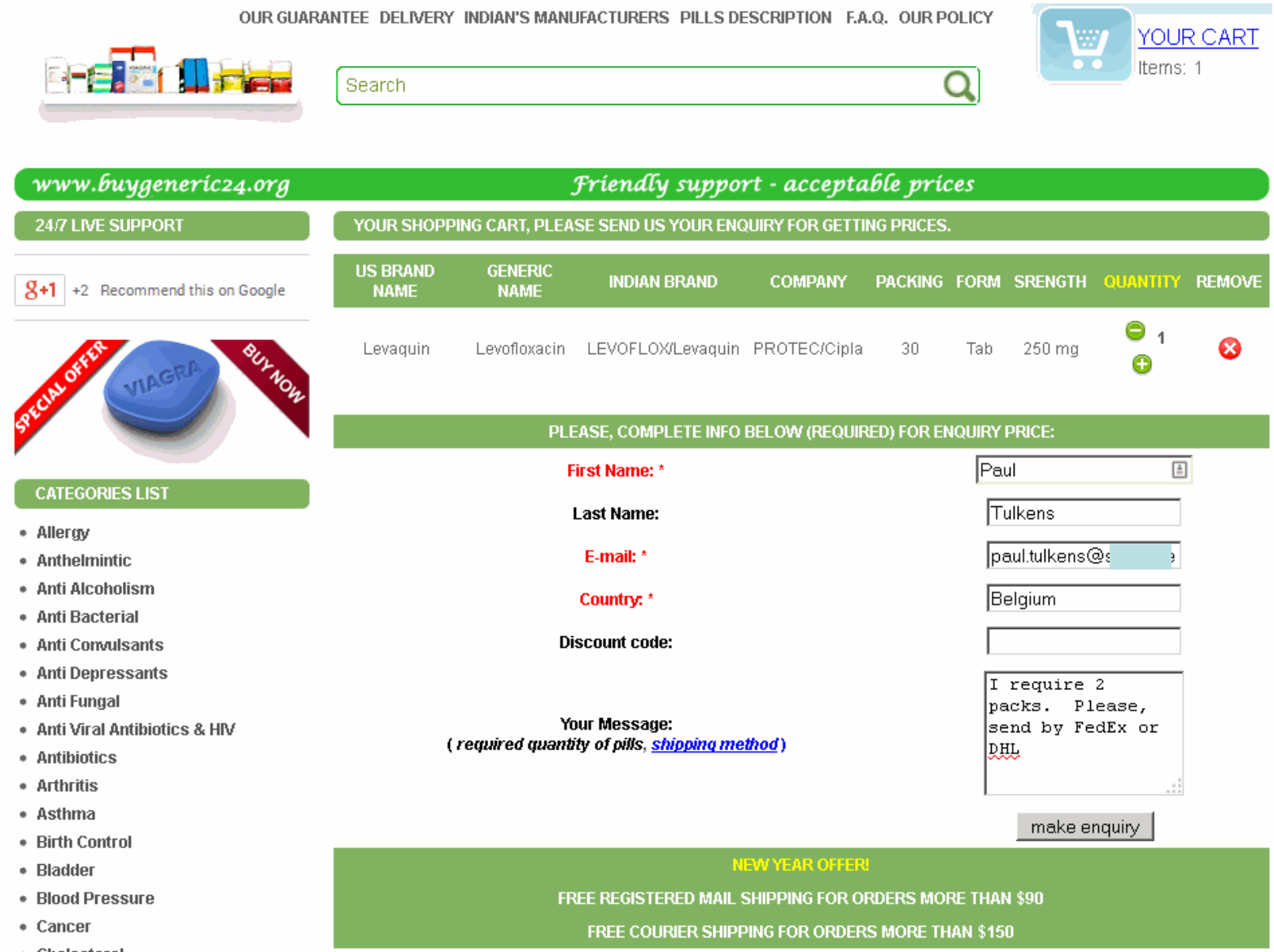

This is an ad for a generic of moxifloxacin

Find the errors …

# "Low cost antibiotics" and Internet


http://antidotum.org/index.php?showtopic=424075

# "Low cost antibiotics" and Internet




http://buygeneric24.org/cart_page.php

# 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†

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

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

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

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

# The situation may be worse in veterinary medicine

JOURNAL OF
Veterinary Pharmacology and Therapeutics

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

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

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

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

# The situation may be worse in veterinary medicine

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The consequences of generic marketing on antibiotic consumption and the spread

P.-L. TOUTAIN
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 to7 days] is only **13-14 €** … (ex-factory price: ~7 €)

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

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

# But there is something worse…

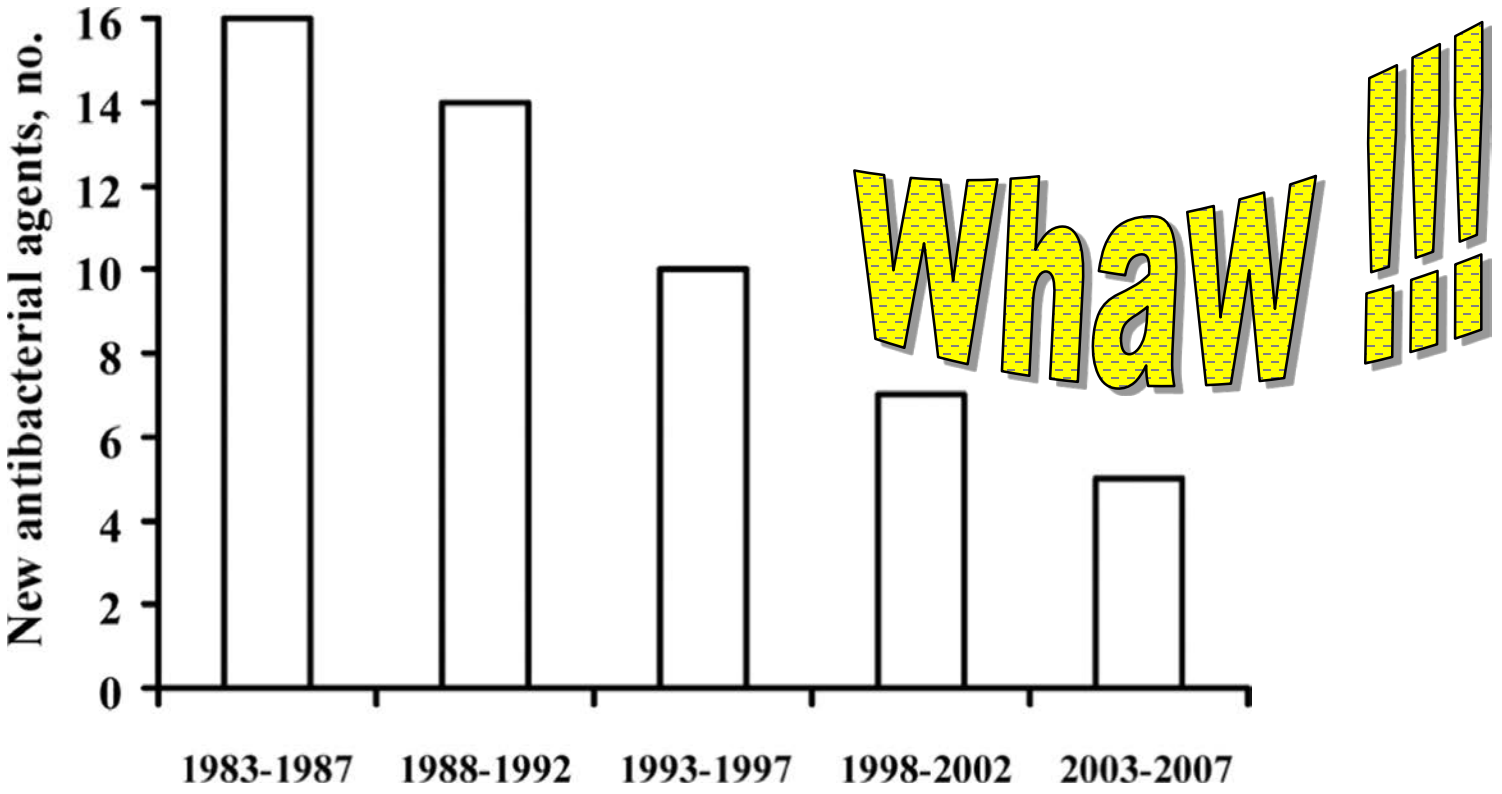
## Generic antibiotics, antibiotic resistance, and drug licensing

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**

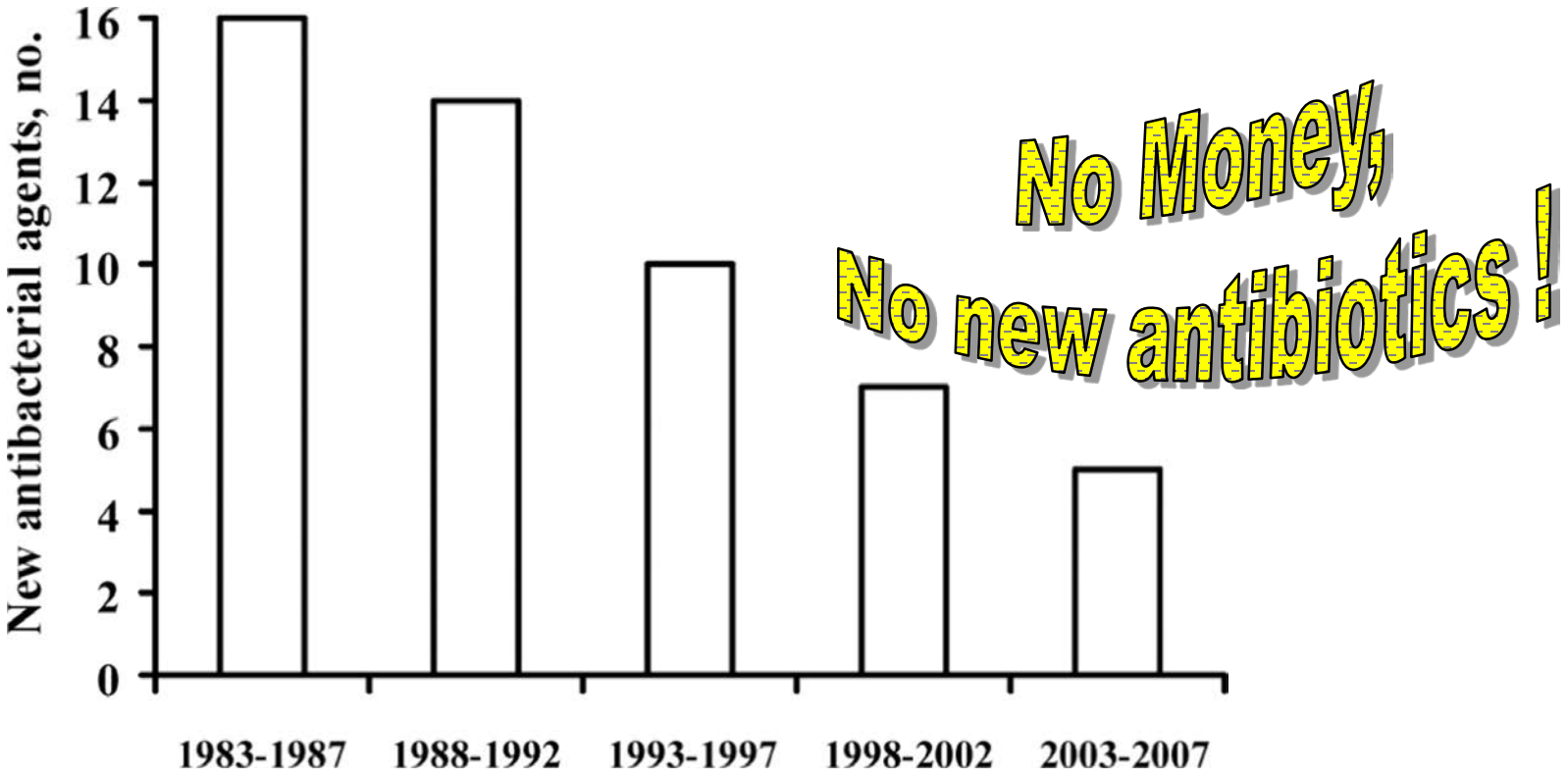
The Nottingham University Hospitals NHS Trust; and University of Nottingham, Nottingham, NG5 1PB, UK

# 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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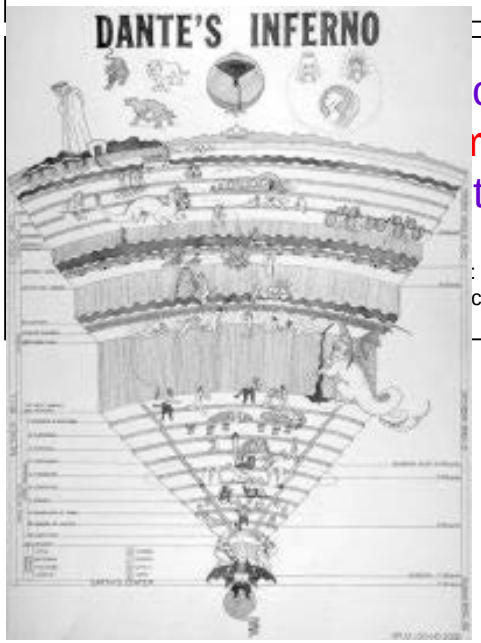


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cessed: 7 November 2013)

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

* INN: International 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 threat a pneumonia (as an example)
- Find where the problem lies…

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* 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

This slide from van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

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# In the US: resources for Researchers

## Resources for Researchers

Share this:

### 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

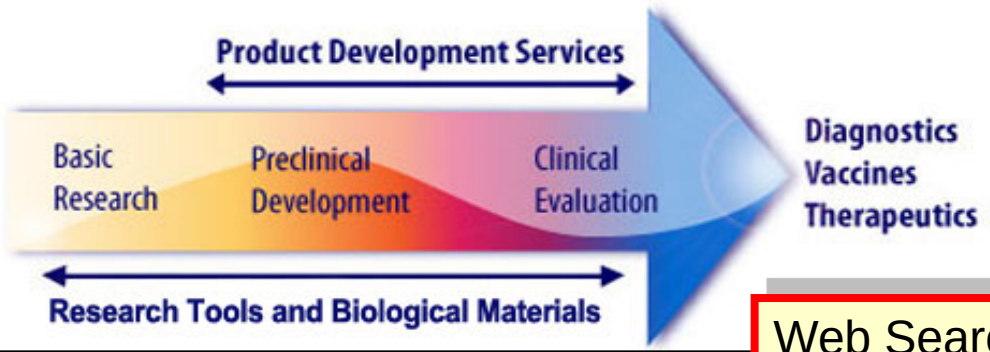
Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.

- 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.

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dmidresources@niaid.nih.gov

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**Additional Information From NIAID**

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Web Search Term: **DMID Resources**

This slide from van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

# 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 (portofolio 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

Preparedness | Emergency | About ASPR

Office of the Assistant Secretary for Preparedness and Response

Public Health Emergency

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

Search

PHE Home > PHE Newsroom > MCM Procurements and Grants

## MCM Procurements and Grants

**About BARDA**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

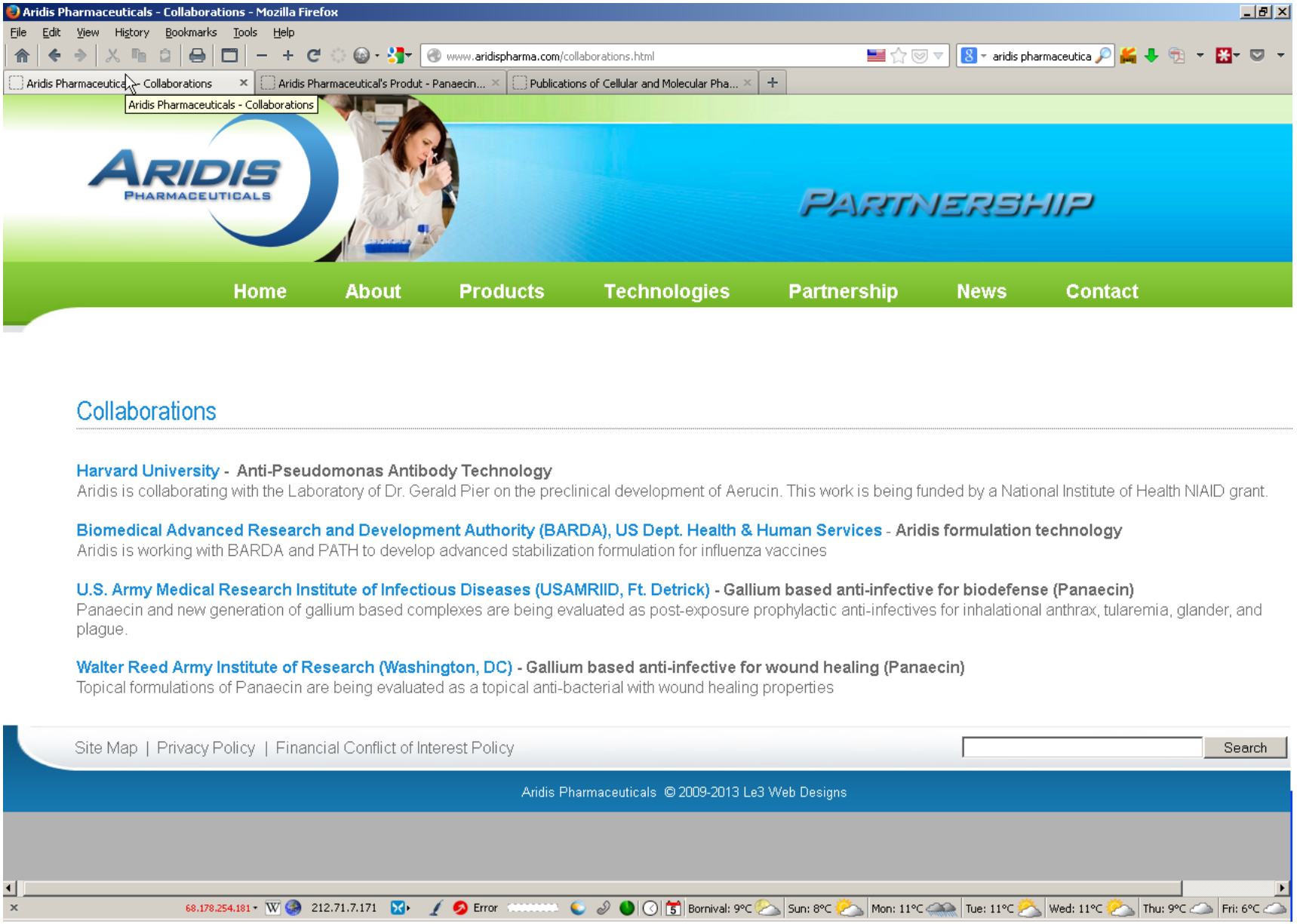
May 22, 2013: HHS forms strategic alliance to develop new antibiotics

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

This page last reviewed: January 03, 2014

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

# Unless Big Brother comes to your help…



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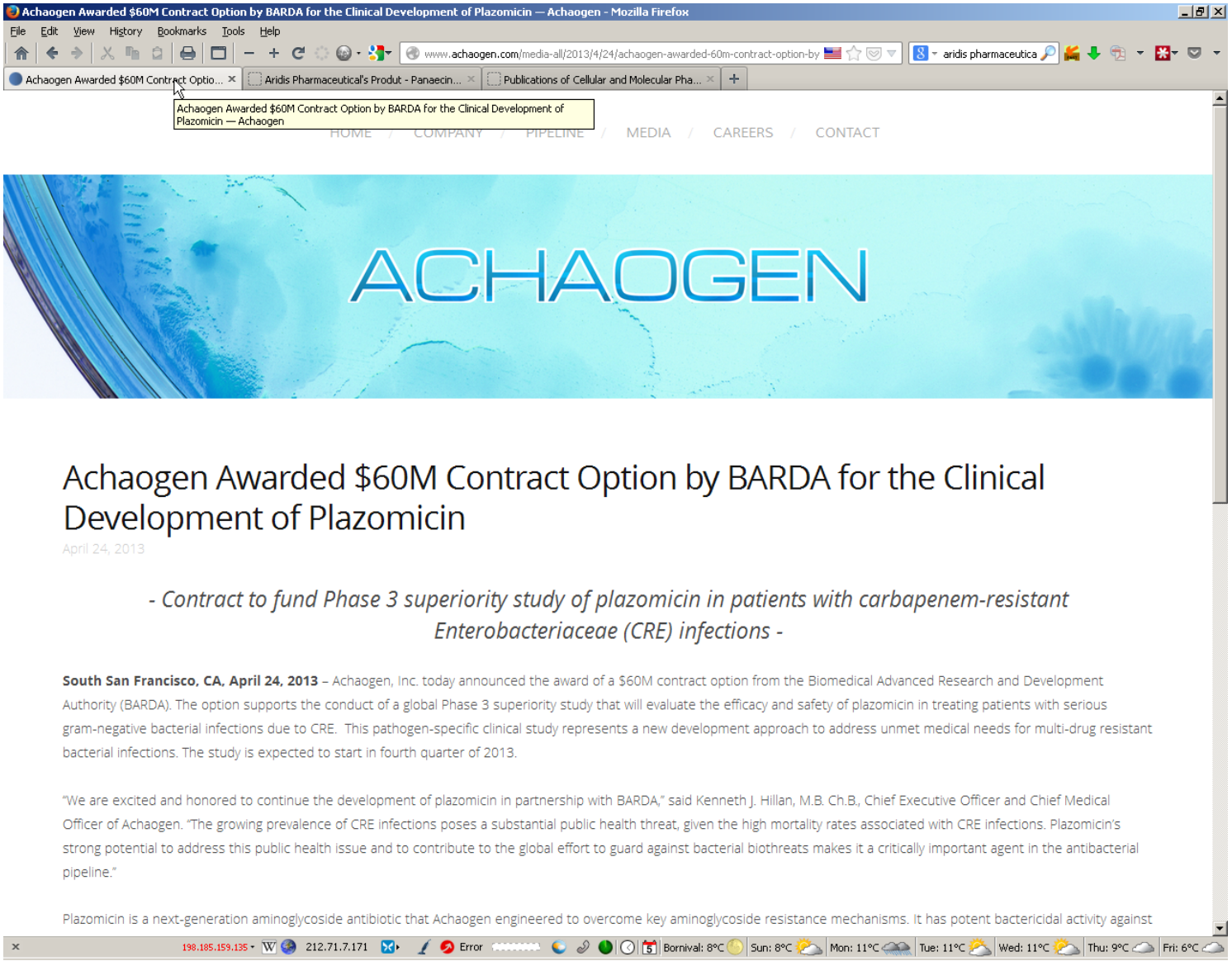


# What in Europe ?


**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

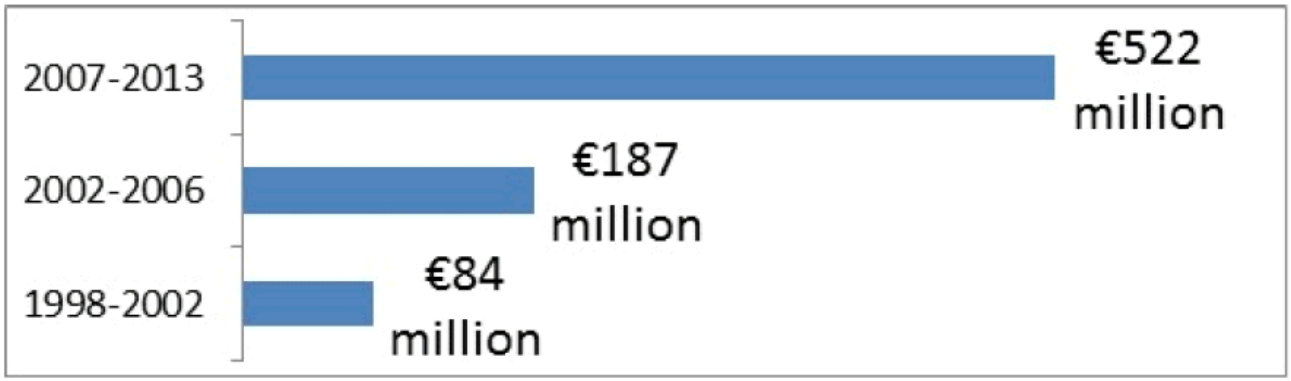
**EU launches new research projects to combat anti-microbial resistance**

http://europa.eu/rapid/press-release_MEMO-13-996_en.pdf
Last accessed: 8 May 2014

# Investments in Europe…

EU launches new
microbial resistan

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.

http://europa.eu/rapid/press-release_MEMO-13-996_en.pdf
Last accessed: 8 May 2014

# 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**

efpia
European Federation of Pharmaceutical Industries and Associations

# IMI in action …


- €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**

http://www.imi.europa.eu/
Last accessed: 8 May 2014

# 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.

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The European Observ
health policy-making
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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