Génériques d'antibiotiques: Savez-vous ce que l'on vous sert ?

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et Professeur (émérite) à l'Université catholique de Louvain

23 février 2015

Transparence et disponibilité du matériel présenté

- Crédits de recherche
  - Theravance, Astellas, Cempra, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Debiopharm, Eumedica
  - Fonds de la Recherche Scientifique (*F.R.S.-FNRS*), Service public fédéral « Santé publique », Régions wallonne et de Bruxelles-capitale, Union Européenne (FP7 et JPIAMR)

- Honoraires de présentations
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, Vifor
  - *Opleidingsprogramma Antibioticabeleid Vlaanderen*

- Commissions (à pouvoir de décision et/ou de d'avis)
  - US National Institutes of Health (*grant reviewing*)
  - Assemblée générale et comité de pilotage de l' EUCAST
  - Expert extérieur pour l' European Medicines Agency (EMA)
  - Ancien membre de la Commission belge de remboursement des médicaments (CRM/CTG)
  - Membre du *Belgian Antibiotic Policy Coordination Committee* (BAPCOC)
  - Gouvernance du projet européen "DRIVE AB" (renouveau du cadre économique des antibiotiques)

Dias: http://www.facm.ucl.ac.be → Lectures → en français

Vous avez dit « génériques » ?
L'histoire d'un antibiotique bien connu…

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

Un antibiotique trop bien connu …

et peu après…

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]

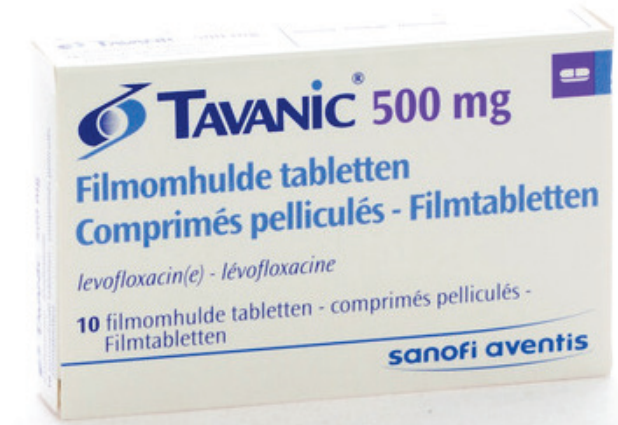
http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm

Mais pourquoi choisiriez-vous un générique ?

1. C’est comme les compagnies aériennes: le prix me guide …
2. Ils ont la même qualité que le produit original…
3. On peut les produire localement (dans mon pays)…
4. Parce que mes patients / mon hôpital / mon pays a des ressources limitées…
5. Parce que les anciens antibiotiques (dont le brevet est expiré) couvrent la plupart de mes besoins (de prescription…)
6. Tout ce qui est indiqué ci-dessus

Faites votre choix !

Je pense que la seule motivation raisonnable est…



Levofloxacine SANOFI (Tavanic®) 10 x 500 mg:
45.49 € en 2010 *

Beaucoup moins cher !

Levofloxacine EG (générique) 10 x 500 mg:
21,42 € en 2013 *

* Source: Répertoire commenté des médicaments (éditions 2010 et 2013)
Centre Belge d'information pharmacothérapeutique

De quoi allons nous discuter ?

1. Un choix **politique** (les lois américaine et européenne)
2. Introduction à la **bioéquivalence**
3. Données expérimentales sur
   - **l'équivalence microbiologique**
   - **équivalence pharmacodynamique**
   - **l'équivalence clinique**
4. Problèmes de **dissolution**, de **stabilité,** d'**impuretés,** d'**excipients** et de **non-conformités**
5. Les **risques cachés** des antibiotiques "bon marché"

1. Un choix politique fondé sur la loi … sur base de décisions démocratiques

http://blogs.ft.com/photo-diary/tag/european-parliament/
Last visited : 21 February 2016

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

http://www.augustinusparochie.nl/overwegingen/ambro281.html
Last visited: 20 Feruary 2015

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

- La FDA est autorisée à agir suivant les clauses du ***Drug Price Competition and Patent Term Restoration Act*** ("Hatch-Waxman Act" [Public Law 98-417]), qui **encourage** la fabrication et mise sur le marché de génériques
- Les producteurs de génériques peuvent déposer une ***Abbreviated New Drug Application*** (ANDAs) pour obtenir un enregistrement (*approval*)

Les exigences de la FDA en quelques mots *

- Publications scientifiques (pour les données pour lesquelles le déposant ne peut pas avoir accès directement aux résultats de base soumis lors de la demande d'enregsitrement du produit original)
- Les observations propres de la FDA (sécurité d'usage et efficacité du médicament original déjà enregistré et approuvé
- Comparaison avec la soumission du produit original (*New Chemical Entity/New Molecular Entity*) concernant
  - la forme galénique, la dose et la voie d'administration
  - la substitution d'un principe actif dans des médicaments combinant plusieurs produits ou en cas de changement de sel, d'ester etc…
- **Une étude de bioéquivalence pour les formes non-injectables**

"*The proposed product does not need to be shown to be clinically* ***better*** *than the previously approved product…*"

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

Dans l'Union européenne

28.11.2001 FR Journal officiel des Communautés européennes L 311/67

DIRECTIVE* 2001/83/CE DU PARLEMENT EUROPÉEN ET DU CONSEIL

du 6 novembre 2001

instituant un code communautaire relatif aux médicaments à usage humain

http://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:32001L0083&from=FR (texte original)
http://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:02001L0083-20121116&from=FR (version consolidée)

ACTES LIÉS

Directive 2003/94/CE de la Commission du 8 octobre 2003 établissant les principes et lignes directrices de bonnes pratiques de fabrication concernant les médicaments à usage humain et les médicaments expérimentaux à usage humain (JO L 262 du 14.10.2003, p. 22-26)

Lignes directrices du 5 novembre 2013 concernant les bonnes pratiques de distribution en gros des médicaments à usage humain (JO C 343 du 23.11.2013, p. 1-14)

Lignes directrices du 19 mars 2015 concernant les principes de bonnes pratiques de distribution des substances actives des médicaments à usage humain (JO C 95 du 21.3.2015, p. 1-9)

Lignes directrices du 19 mars 2015 relatives à l'évaluation formalisée du risque visant à déterminer les bonnes pratiques de fabrication appropriées pour les excipients utilisés dans les médicaments à usage humain (JO C 95 du 21.3.2015, p. 10-13)

http://eur-lex.europa.eu/legal-content/FR/TXT/HTML/?uri=URISERV:l21230&from=EN

* Acte législatif de l'Union européenne qui est ensuite traduit en lois spécifiques à chaque pays pour implémentation effective qui peut varier dans les détails entre pays (par opposition à un règlement de l'U.E. qui concerne des décisions qui s'implémentent d'elles mêmes et ne requièrent pas d'adaptation locale)

La directive européenne (extraits)

- le demandeur n'est pas tenu de fournir les résultats des essais précliniques et cliniques s'il peut démontrer que le médicament est un générique d'un médicament de référence qui est ou a été autorisé … depuis au moins huit ans dans un État membre ou dans la Communauté…

- on entend par «médicament générique», un médicament qui a la même composition qualitative et quantitative en substances actives et la même forme pharmaceutique que le médicament de référence et dont la bioéquivalence avec le médicament de référence a été démontrée par des études appropriées de biodisponibilité.

Voir "**Médicaments originaux et génériques"** pour un court résumé des règles telles qu'implémentées en Belgique et communiqués par l'Agence fédérale des médicaments et produits de santé (AFMPS):

http://www.fagg-afmps.be/fr/items-HOME/Generiques/

(dernière visite: 20 février 2016)

1eres conclusions et discussion

- Autoriser les génériques est une **décision politique**
- Elle trouve son origine dans
  - la **durée limitée de la protection apportée par le brevet** (le plus souvent 20 ans après dépôt), ce qui permet la mise sur le marché de génériques après environ 10 ans après autorisation de mise sur le marché (AMM) du produit original *
  - le fait que les **coûts de production d'un médicament sont le plus souvent très faibles** et ne représentent qu'une fraction souvent minime du prix demandé par le détenteur de l'AMM originale en début de commercialisation
- La **seule motivation** de la promotion des génériques par les autorités et les organisation sociales est de pouvoir acquérir et mettre à la disposition de la population des **médicaments moins chers** (en Europe, essentiellement via la **Sécurité Sociale**).

* en raison du temps de développement préclinique et clinique nécessaire pour obtenir l'AMM du produit original

De quoi allons nous discuter ?

1. Un choix **politique** (les lois américaine et européenne)
2. Introduction à la **bioéquivalence**

http://www.choosinggenerics.ca/Bioequivalence.aspx
Last visited: 15 March 2014

Bioéquivalence: principes

- La bioéquivalence est un **critère de substitution** accepté pour tenir lieu d'**équivalence thérapeutique** [1] (y compris pour un médicament original lorsque développé et/ou présenté sous des formes galéniques différentes…) [2]
- Les mesures (*metrics*) portent sur [1,3]
  - **AUC** (*area under the curve*): aire sous le profil "concentration plasmatique/temps" de la substance active

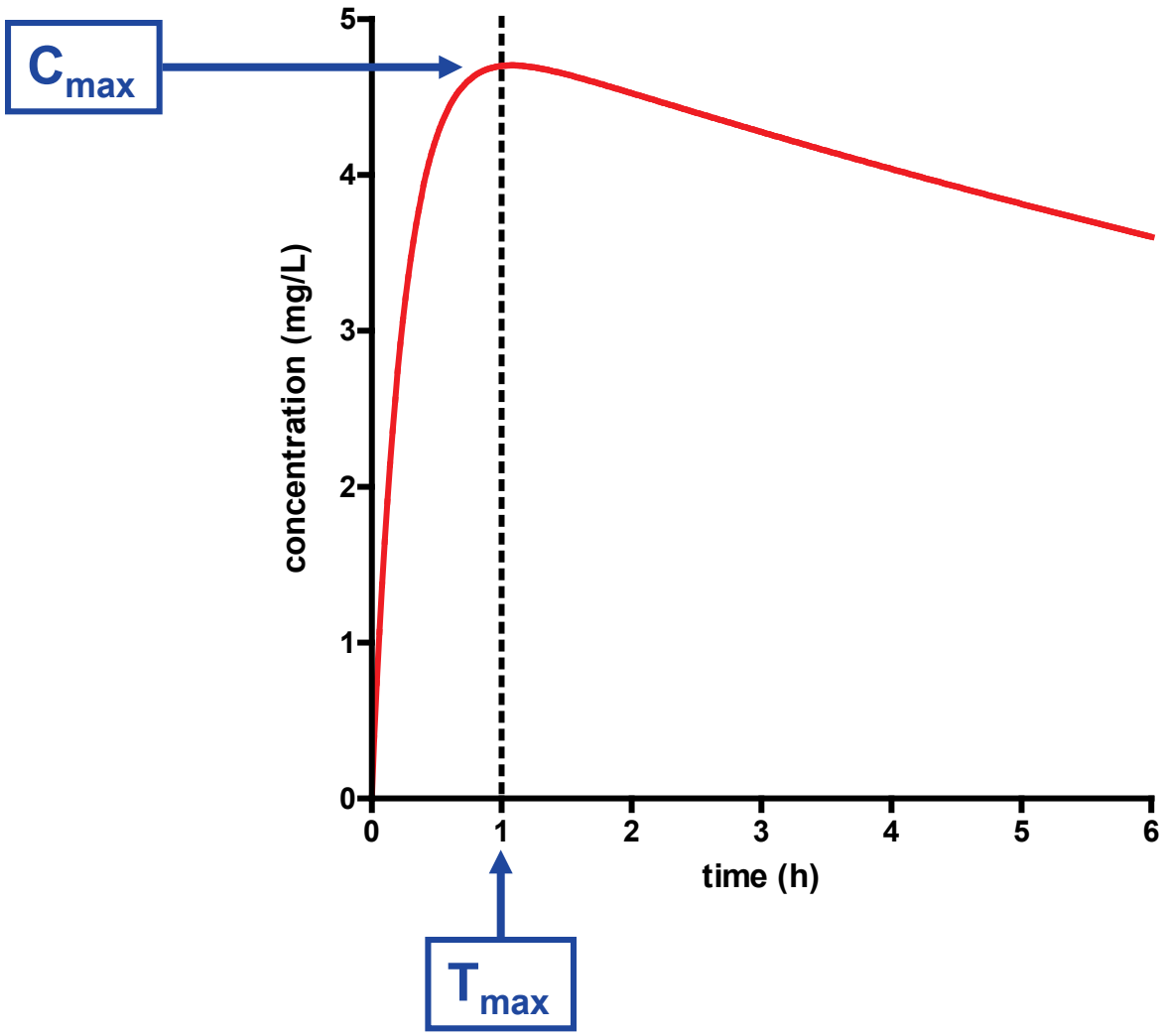
    → mesure le **niveau d'absorption**
  - **C_{max}** : concentration plasmatique maximale de la substance active

    → mesure le **niveau et la vitesse d'absorption**
  - **T_{max}** : temps auquel la C_{max} est obtenue

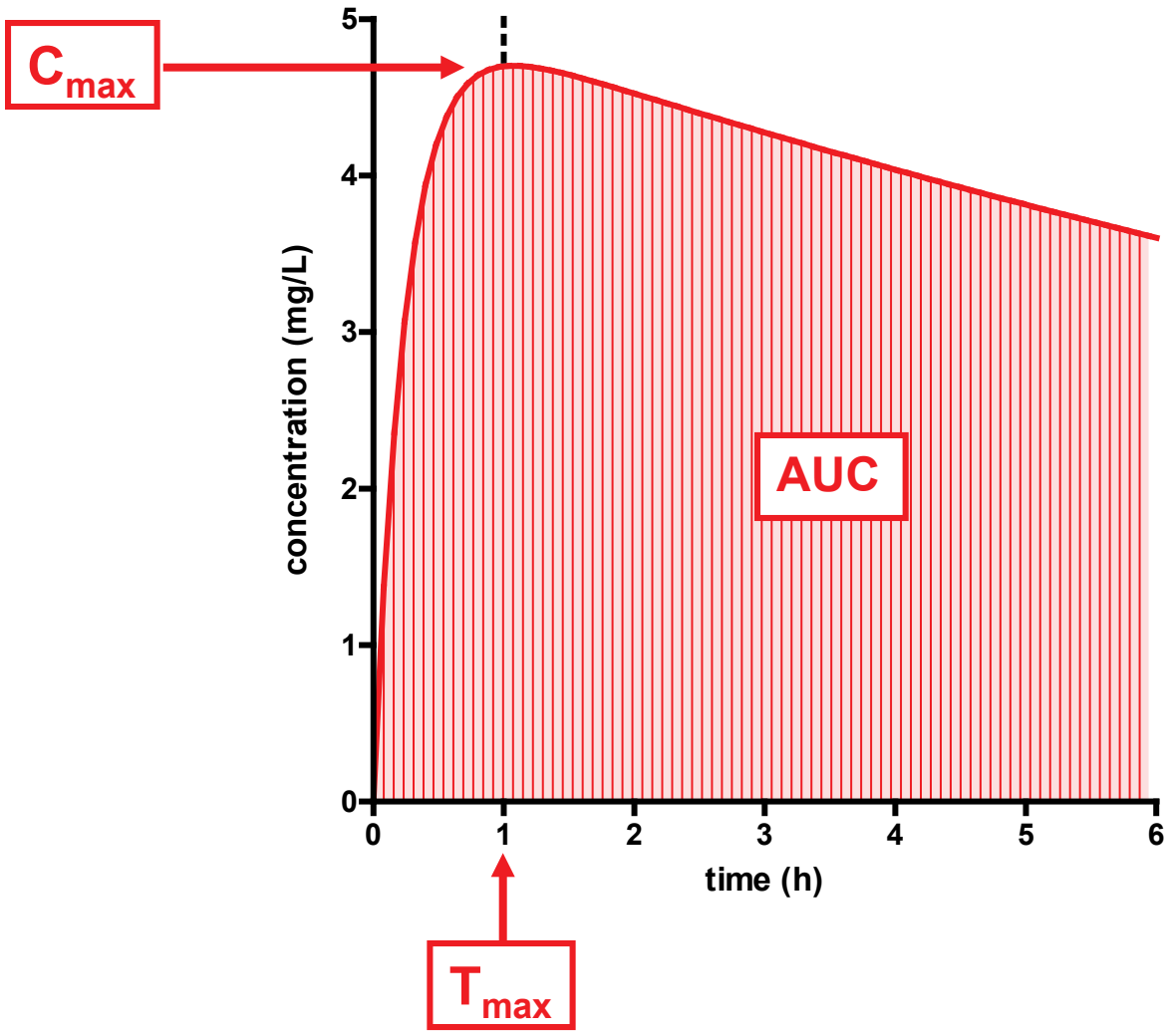
    → mesure la vitesse d'**absorption**

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.

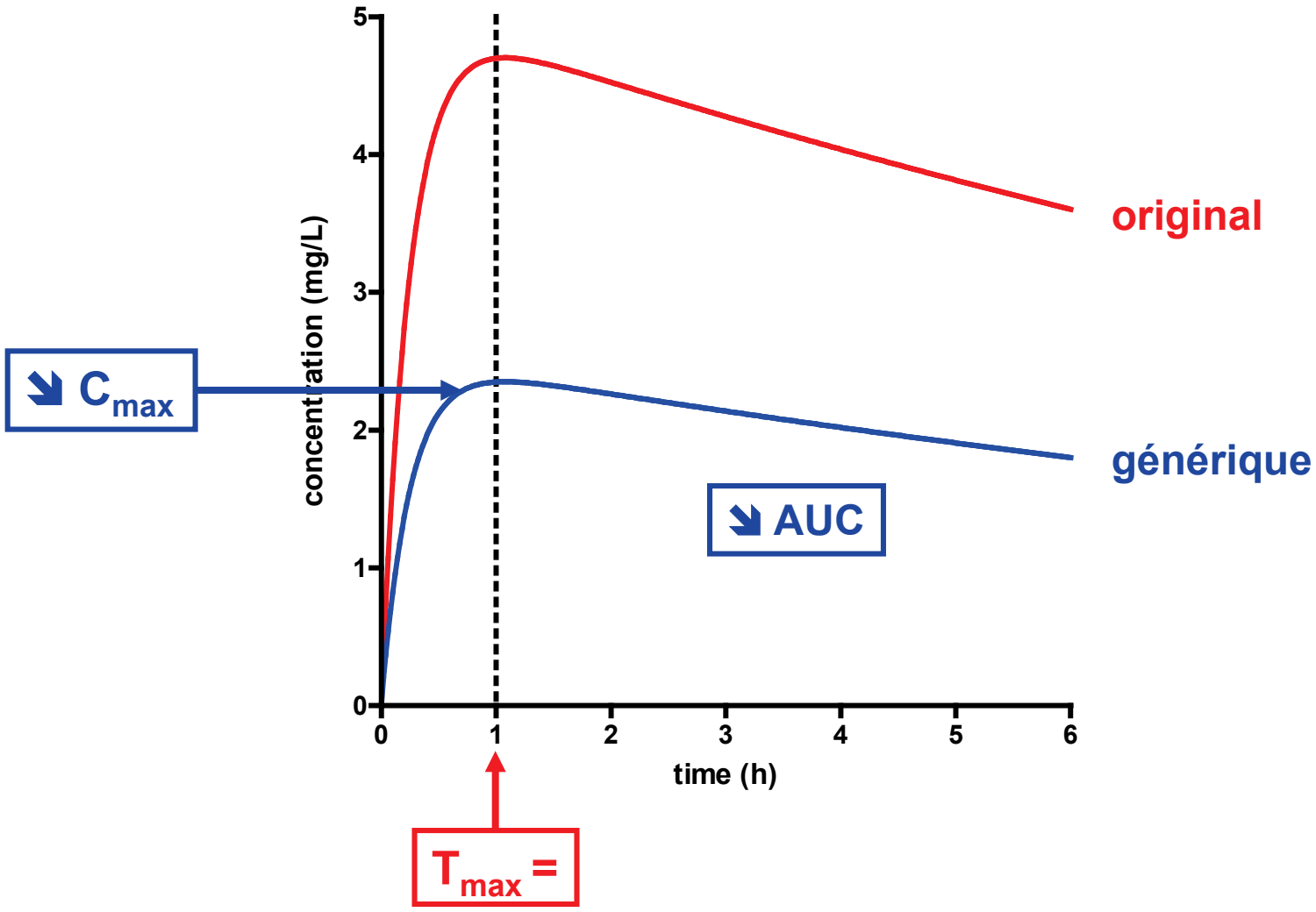
AUC – C_{max} – T_{max}



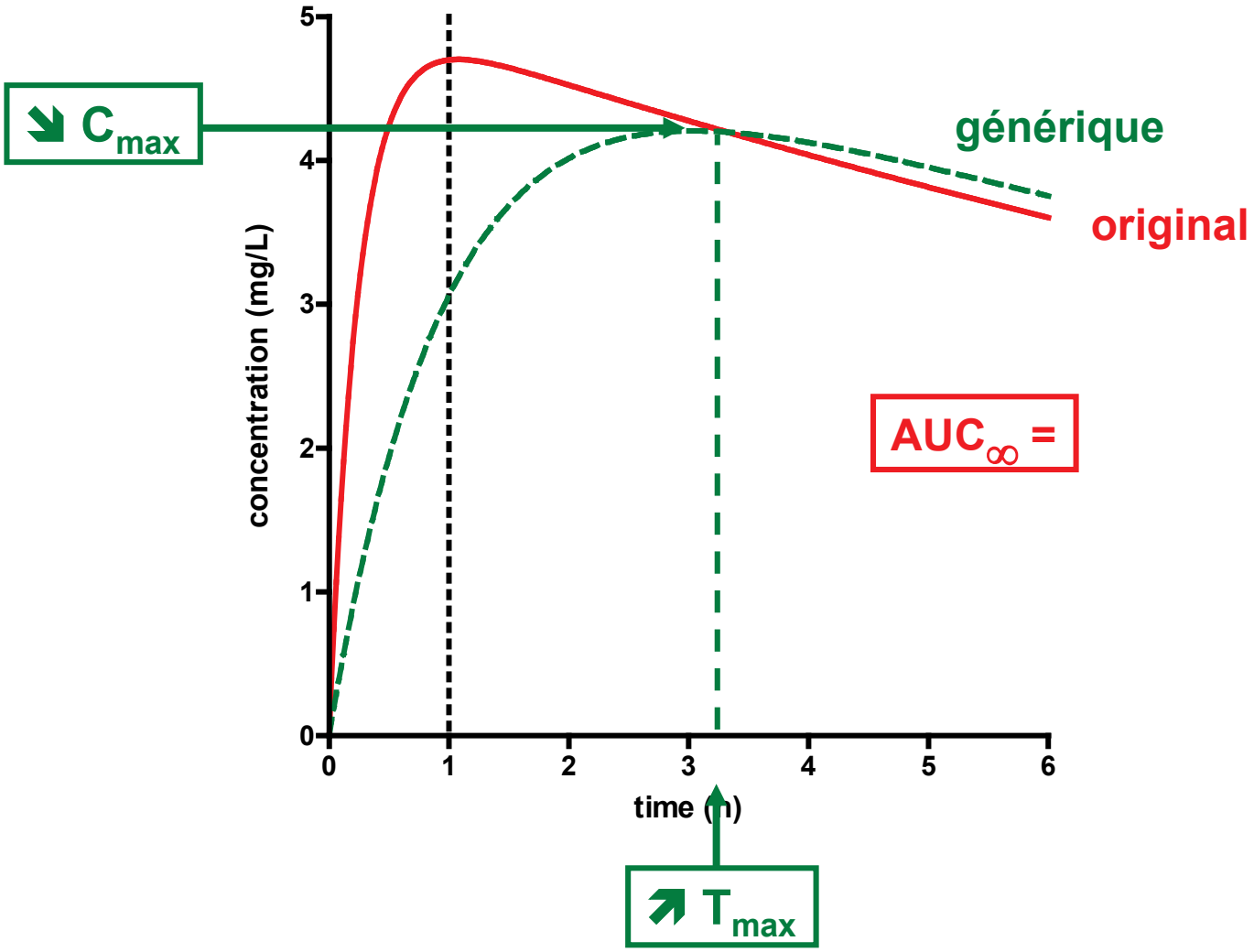
AUC – C_{max} – T_{max}



Que se passe-t-il si l'absorption est diminuée ?

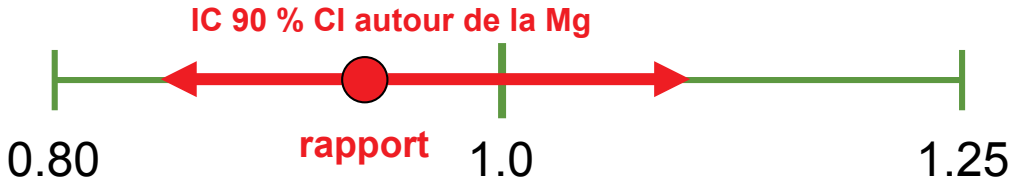


Et si l'absorption est retardée ?



Critères de bioéquivalence (EMA* / FDA**)

- Calculez l'**intervalle de confiance à 90%** autour de la **moyenne géometrique (Mg)** du **rapport** entre les **AUC** et les **C_{max}** du générique et du produit de référence (produit original).
- Cet **intervalle** doit se situer, dans la plupart des cas, **entre des limites d'acceptabilité** fixées à **0.80** (minimum) et **1.25** (maximum)



* 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

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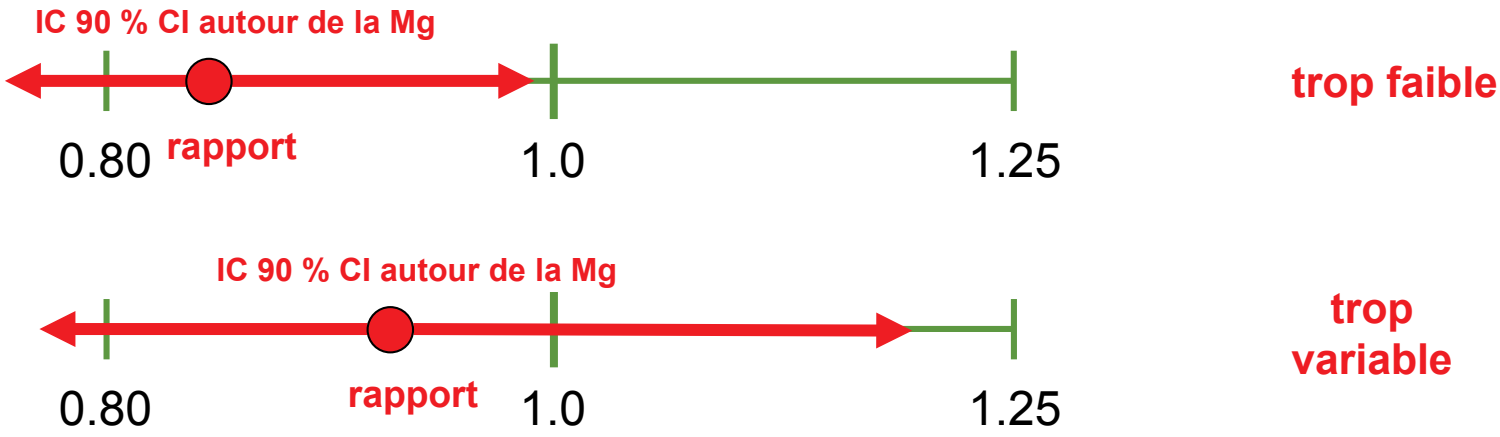

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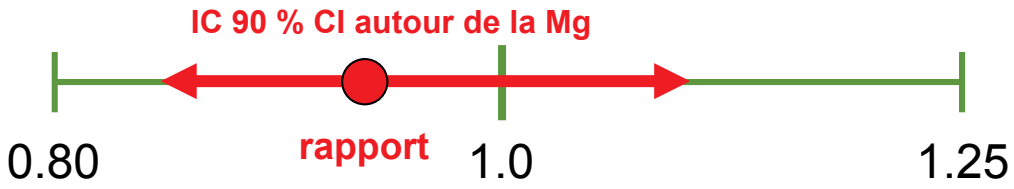

Note: Pour certains médicaments à indice thérapeutique étroit (mais aucun antibiotique), l'EMA recommande des limites d'acceptabilité plus étroites ("tightened acceptance inervals"), Health Canada demande 0.9 – 1.12, mais la FDA accepte 0.8 – 1.25

* 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

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http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052363.pdf

Caveats !

- Les études de **bioéquivalence** ne sont **pas demandées** pour les **médicaments administrés par voie intraveineuse**
  (cette voie est celle qui, par définition, procure une biodisponibilité de 100 % !)

  - Le demandeur soit uniquement montrer que son produit possède la **même composition qualitative et quantitative en substance(s) active(s) et la même forme pharmaceutique que le produit de référence**

- Pour les médicaments complexes (médicaments biologiques, héparines fractionnées, etc…[mais aucun antibiotique]), des exigences supplémentaires sont émises par les agences d'enregistrement [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

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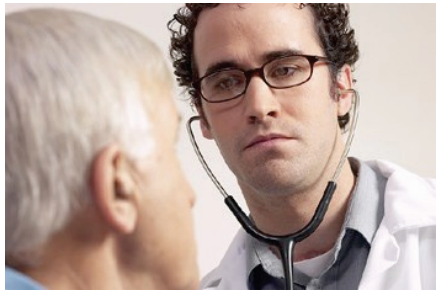
   - **équivalence pharmacodynamique**
   - **l'équivalence clinique**

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

Activité *in vitro* (*potency*) de la pipéracilline

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

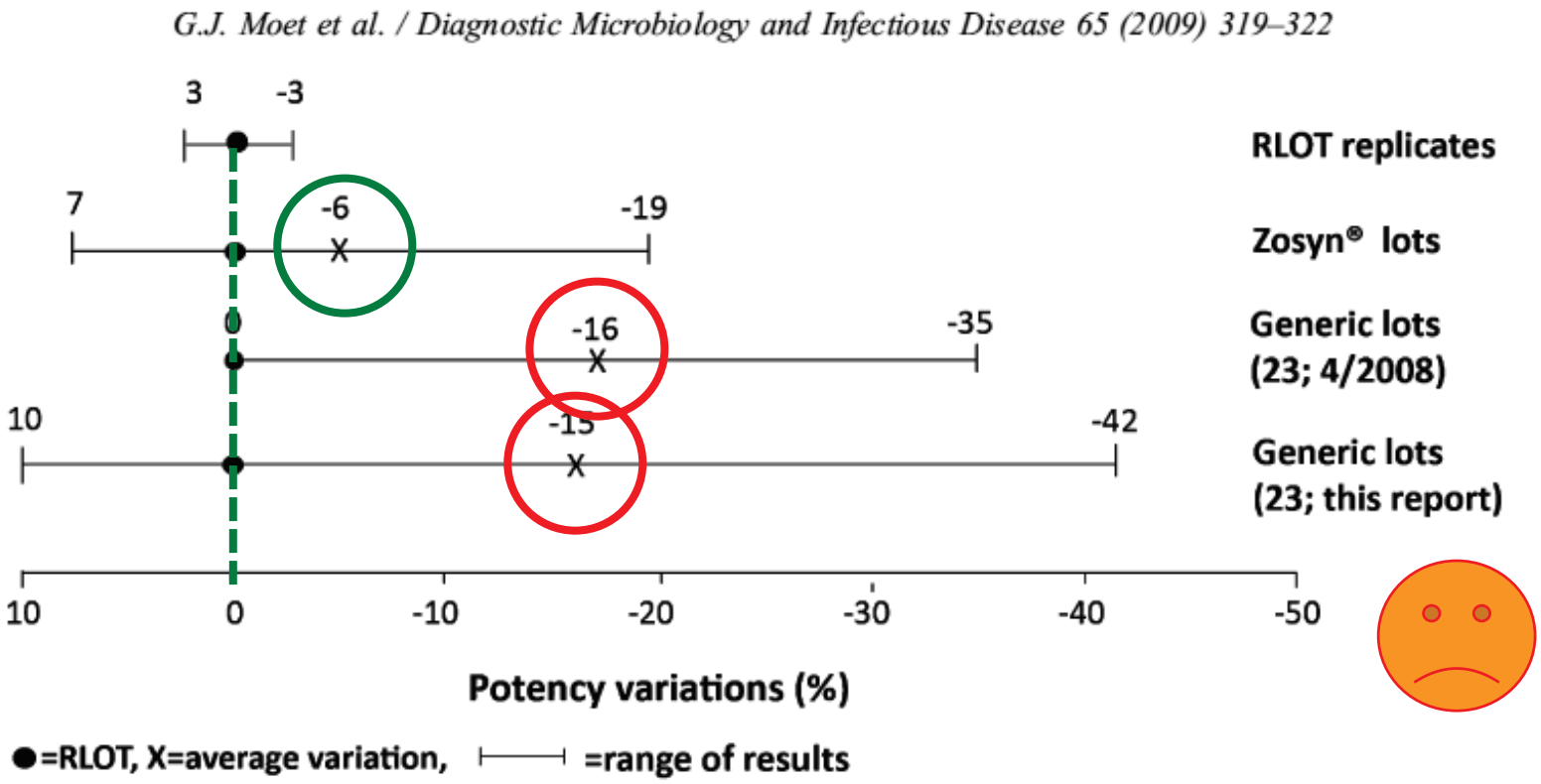


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

Mesures de CMI (vancomycine)

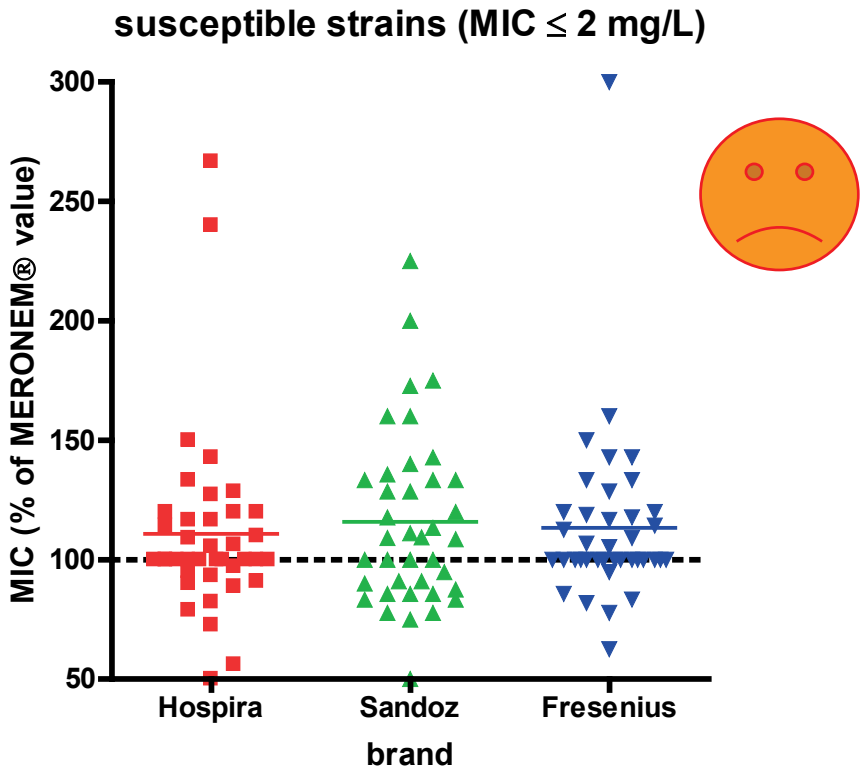
Table 1 Comparison of antimicrobial activity against various clinical isolates in a brand name and generic antibiotics

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

Mesures de CMI (méropénem)



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

CMI faites par dilution arithmétiques autour de la CMI mesurée par dilution géométrique

MERONEM® = meropenem commercialized by AstraZeneca

Van Bambeke *et al*., in preparation

Pharmacodynamie: évidence de non-équivalence dans un modèle PK/PD animal (vancomycine)

Neutropenic thigh mouse model

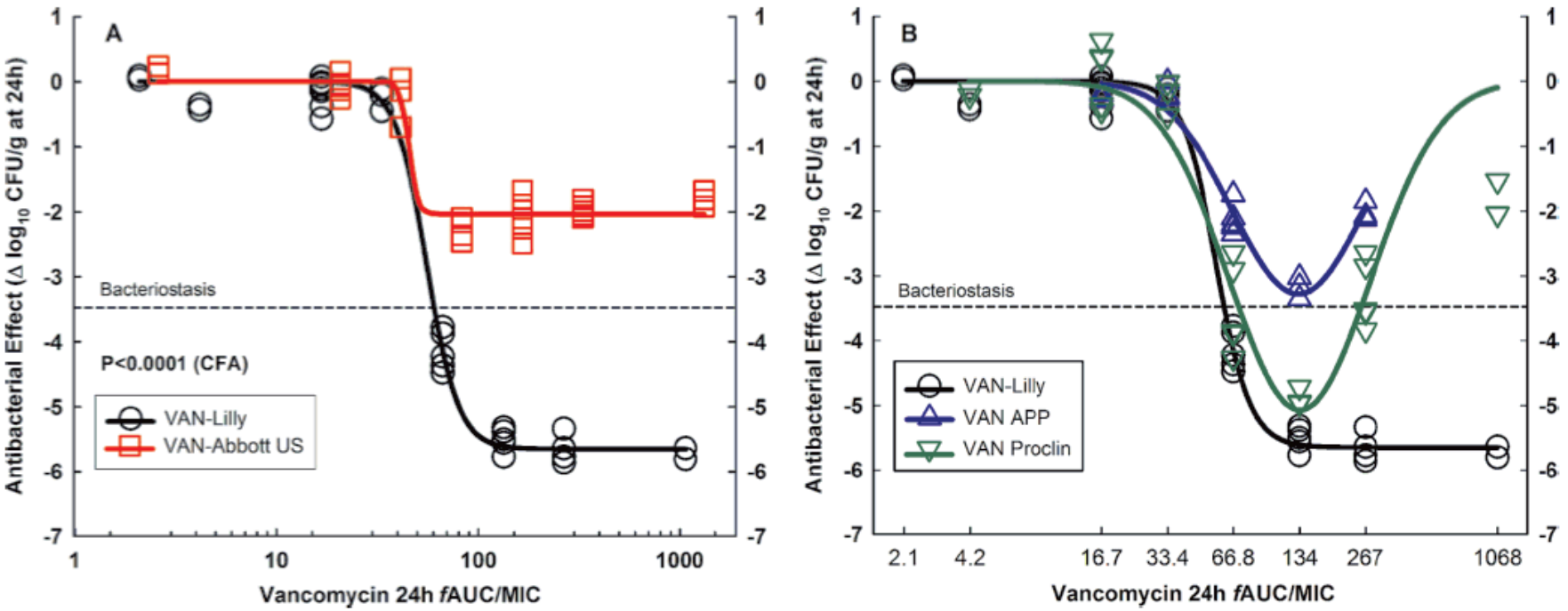


FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per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

Pharmacodynamie: évidence de non-équivalence dans un modèle animal (oxacilline)

Neutropenic thigh mouse model

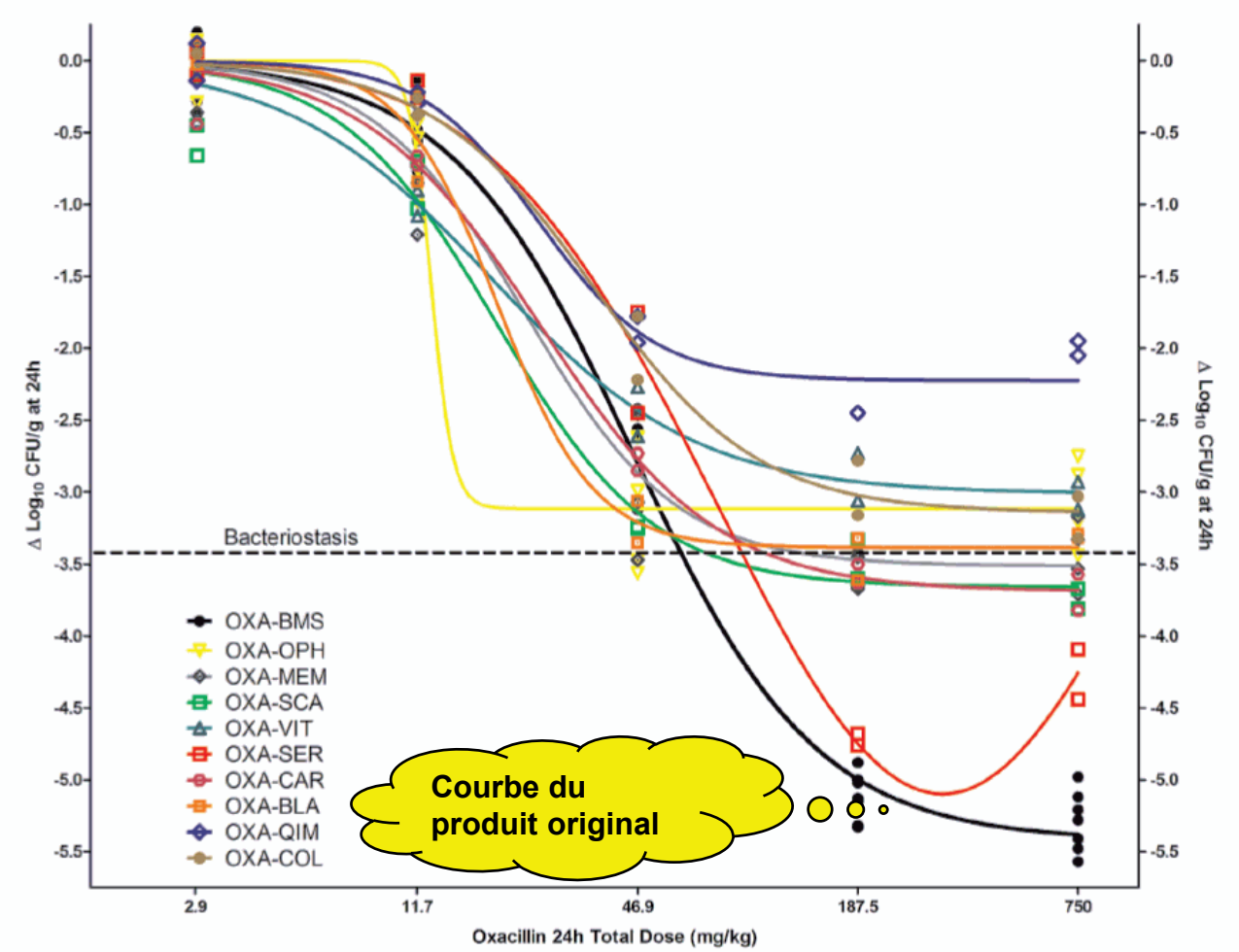


Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless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

Mais l'équivalence pharmacodynamique peut aussi être observée

AAC Journals.ASM.org

Antimicrob Agents Chemother 59:53–58.

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]

GRIPE: Grupo Investigador de Problemas en Enfermedades Infecciosas,[a] Department of Pharmacology,[b] and Department of Internal Medicine,[c] School of Medicine, University of Antioquia, Medellin, Colombia; Infectious Diseases Unit, Hospital Universitario San Vicente Fundación, Medellin, Colombia[d]

Mais l'équivalence pharmacodynamique peut aussi être observée

AAC Journals.ASM.org

Antimicrob Agents Ch

Impact on Resistance of the Us Generics: the Case of Ciproflox

Carlos A. Rodriguez,[a,b] Maria Agudelo,[a,b,d] Andres F. Zu

GRIPE: Grupo Investigador de Problemas en Enfermedades Infecciosas,[a] D
University of Antioquia, Medellin, Colombia; Infectious Diseases Unit, Hosp

Mêmes auteurs que ceux ayant décrit la non-&quivalence de la vancomycine et de l'oxacilline

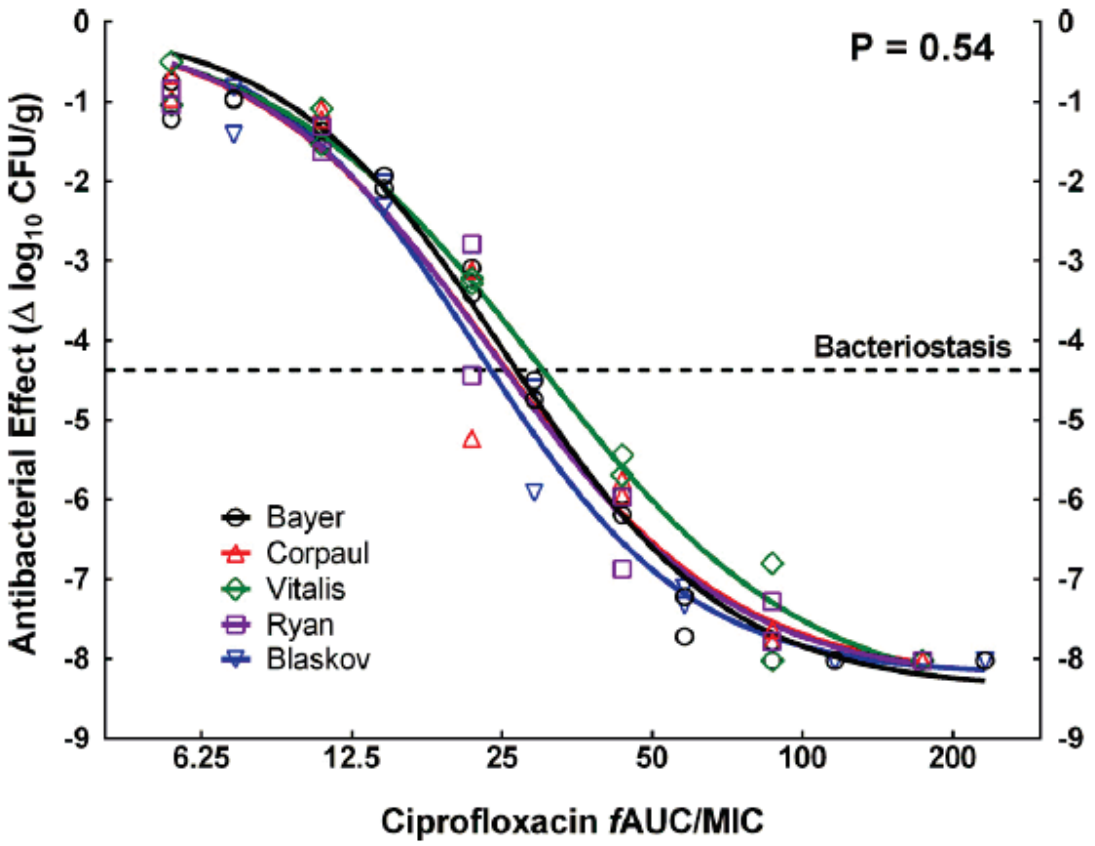


FIG 1 *In vivo* exposure-response relationship of ciprofloxacin against *P. aeruginosa* PAO1, comparing the innovator and four generic products. Global CFA indicated that all data belonged to the same population and could be described by a single curve, confirming the therapeutic equivalence of the generics. Stasis was achieved with a *f*AUC/MIC value of ~27 and 99.9% kill with a *f*AUC/MIC value of ~75.

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,*]

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[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

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 i 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.

2ème série de conclusions et discussion

- Les observations concernant les **équivalences microbiologiques, pharmacodynamiques et cliniques** des antibiotiques génériques par rapport aux produits originaux sont **variables** et parfois **contradictoires** (y compris dans le même groupe de recherches)

- Les raisons de non-équivalence (et de résultats différents) demeurent obscures mais pourraient être des **différences dans les propriétés biophysiques** influant la solubilité et la diffusion des molécules, ce qui **ne peut pas être détecté par une simple mesure des taux sériques qui se fait toujours par extraction du produit…**
  Ces propriétés peuvent varier de lot à lot et entre fabricants…

- Il y a aussi une ***possibilité d'interférence par les excipients*** (mais lesquels… voir plus loin)

- Tout cela demande des études soigneuses … **rs de portée du clinicien et du pharmacien d'hôpital** !

A qui pouvons nous faire confiance ?

Le rêve ou le cauchemar du pharmacien ?

Méropénem

Meronem (AstraZeneca)

[méropénem]
flacon i.v. - perf.

1 x 500mg poudre	Rx	a! b	€ 10,68
1 x 1g poudre	Rx	a! 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)

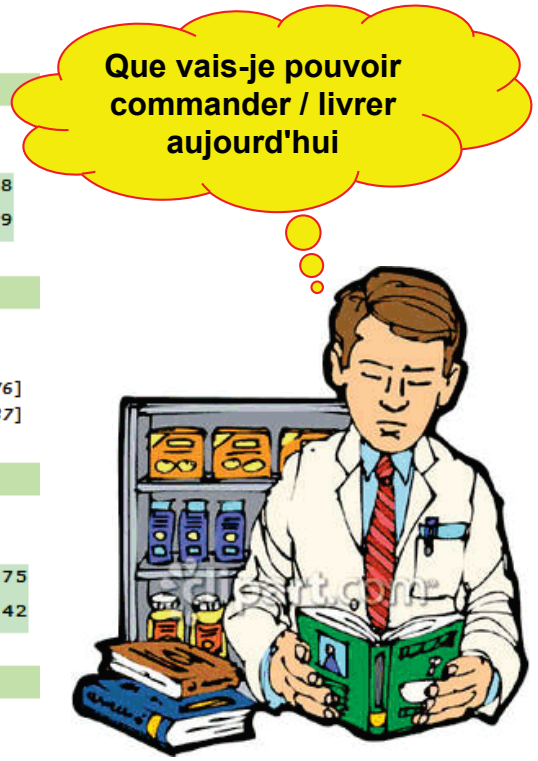
[méropénem]
flacon i.v. - perf.

10 x 500mg poudre	Rx	a! b	€ 87,75
10 x 1g poudre	Rx	a! 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 U.H. [€ 4]

[pipéracilline (sodium) 4g + tazobactam (sodium) 500mg]
flacon perf.
1 U.H. [€ 7]

Piperacilline / Tazobactam Fresenius Kabi (Fresenius Kabi)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon perf.
10 Rx a! b! € 66,02

[pipéracilline (sodium) 4g + tazobactam (sodium) 500mg]
flacon perf.
10 Rx a! b! € 112,66

Piperacilline / Tazobactam Hospira (Hospira)

[pipéracilline (sodium) 4g + tazobactam (sodium) 500mg]
flacon i.v. - perf.
12 Rx a! b! € 132,29

Piperacilline / Tazobactam Mylan (Mylan)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon i.v. - perf.
1 U.H. [€ 6]

[pipéracilline (sodium) 4g + tazobactam (sodium) 500mg]
flacon i.v. - perf.
1 U.H. [€ 11]

Piperacilline / Tazobactam Sandoz (Sandoz)

[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon perf.
10 U.H. [€ 62]

[pipéracilline (sodium) 4g + tazobactam (sodium) 500mg]
flacon perf.
10 U.H. [€ 112]

Tazocin (Pfizer)

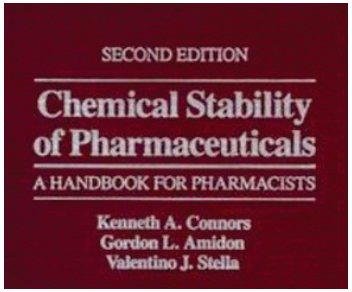
[pipéracilline (sodium) 2g + tazobactam (sodium) 250mg]
flacon perf.
1 Rx a! b! € 11,86

[pipéracilline (sodium) 4g + tazobactam (sodium) 500mg]
flacon perf.
1 Rx a! b! € 17,92

De quoi allons nous discuter ?

1. Un choix **politique** (les lois américaine et européenne)
2. Introduction à la **bioéquivalence**
3. Données expérimentales sur
   - **l'équivalence microbiologique**
   - **équivalence pharmacodynamique**
   - **l'équivalence clinique**
4. Problèmes de **dissolution**, de **stabilité,** d'**impuretés,** d'**excipients** et de **non-conformité…**

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



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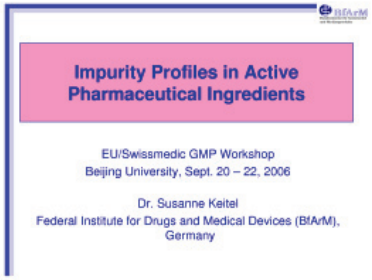

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Dissolution du méropénem au Japon

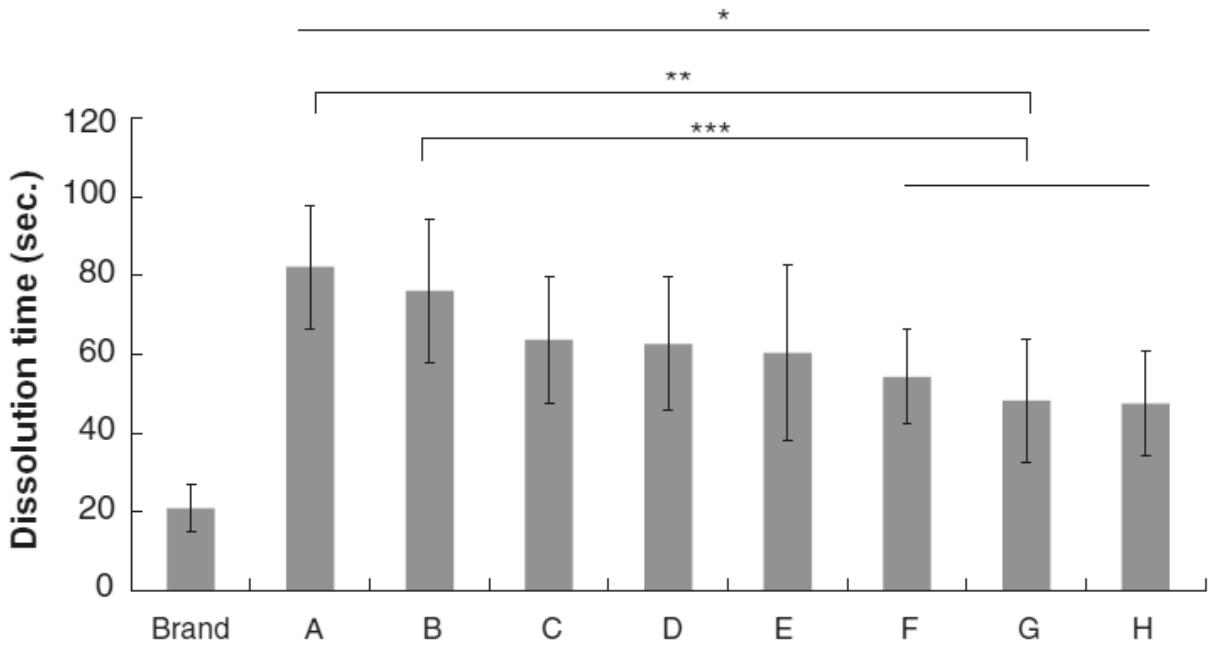


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

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

Dimension des cristaux au Japon

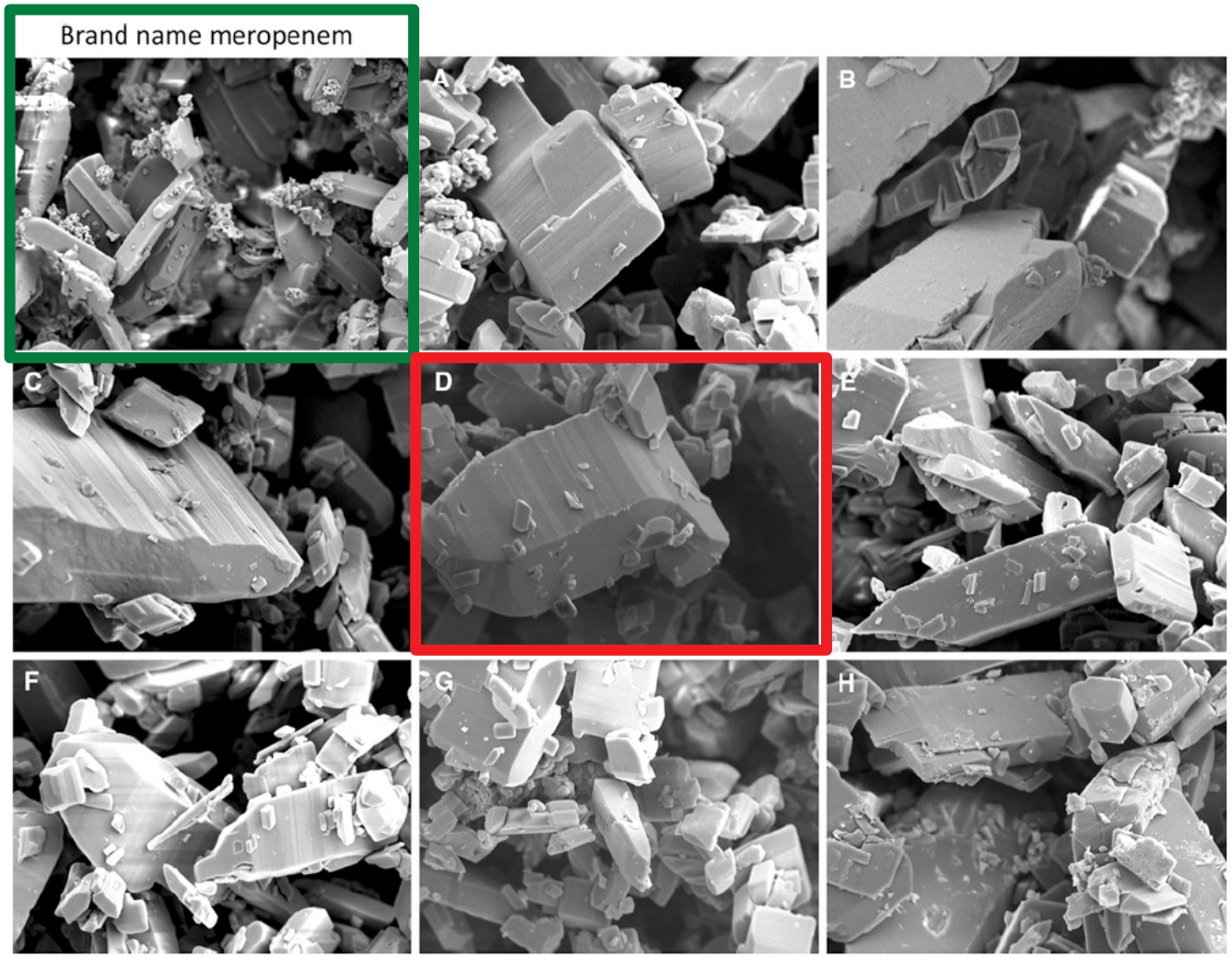
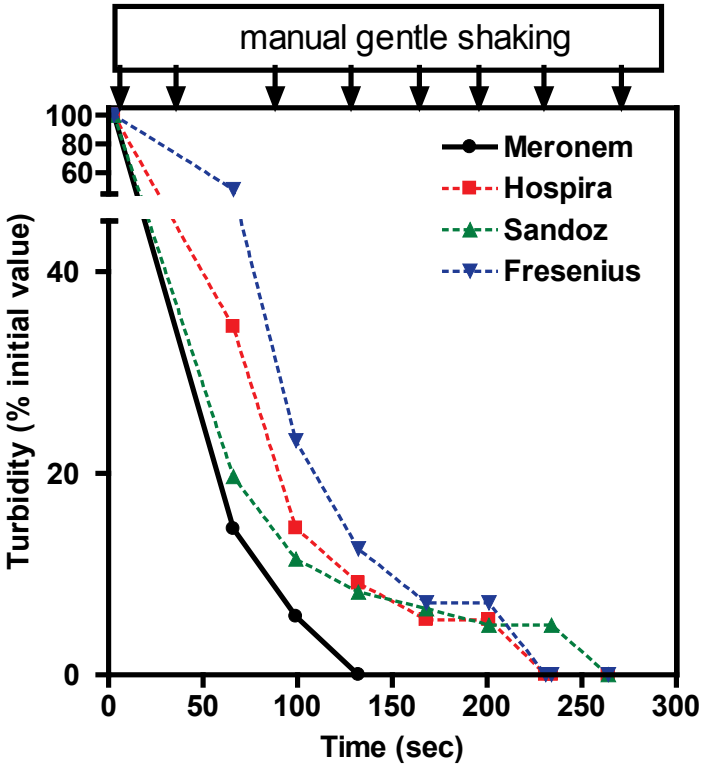


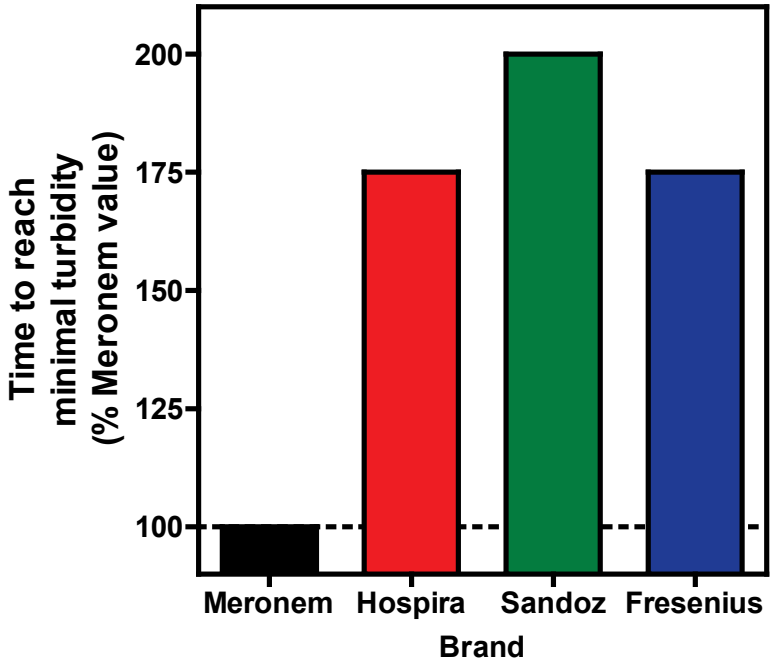
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

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

Dissolution du méropénem en Belgique

Concentration: 50 mg/mL (~ solution pour infusion)
Secouage modéré suivi de mesure de turbidité;
(température de chambre)





Van Bambeke *et al*., in preparation

Dissolution du méropénem en Belgique

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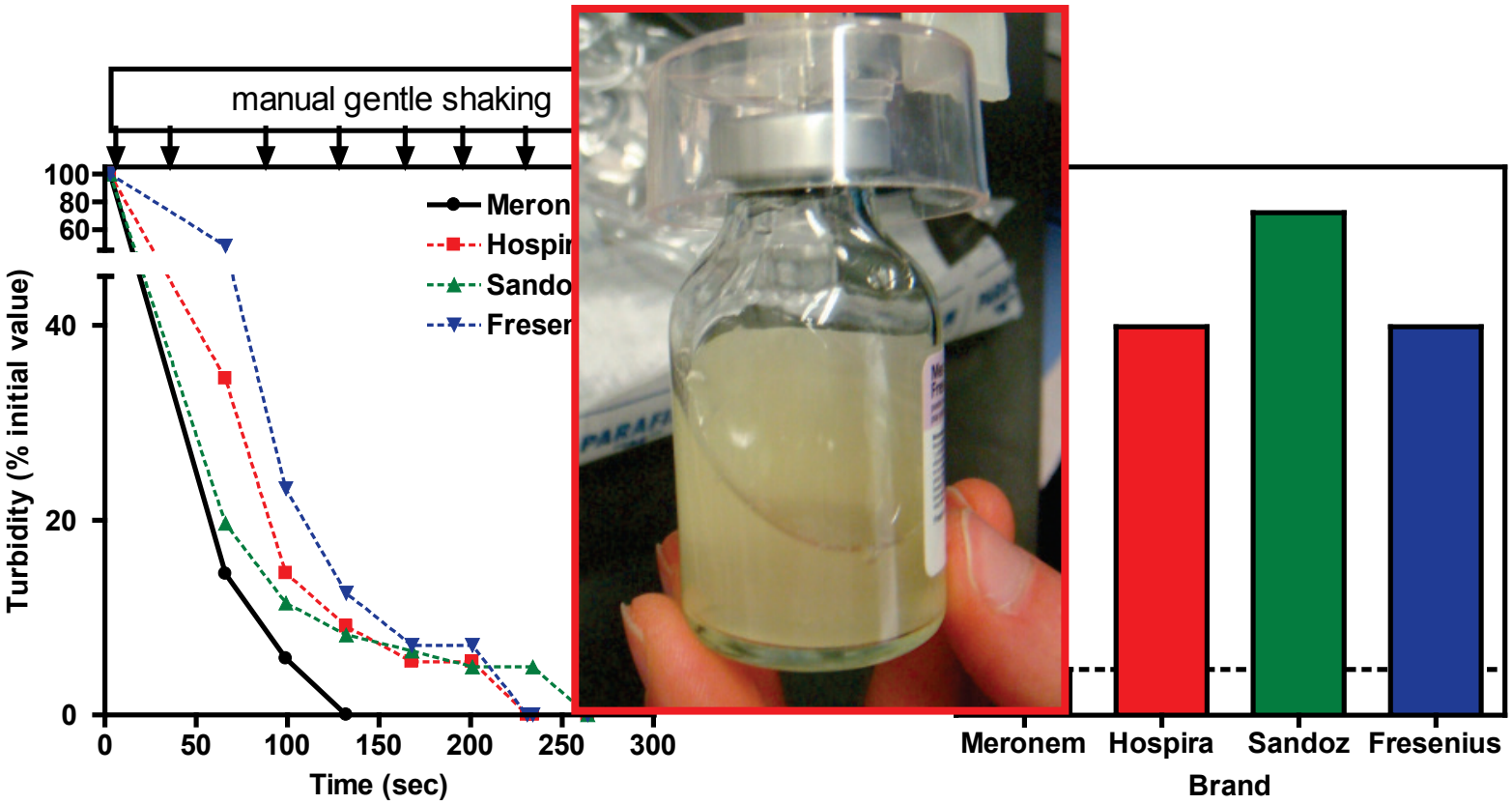
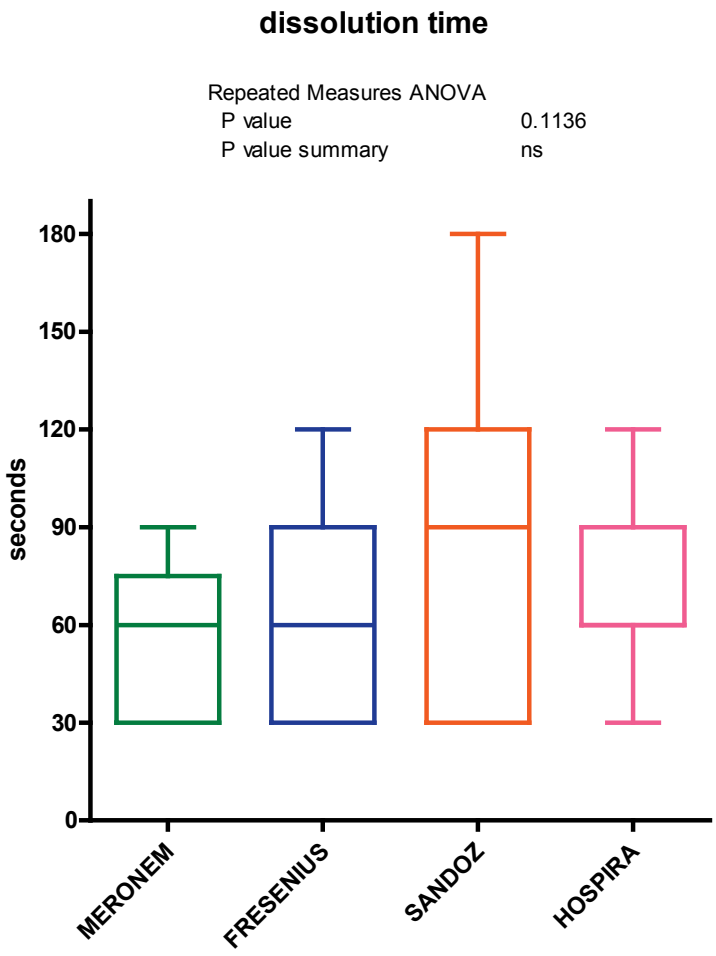
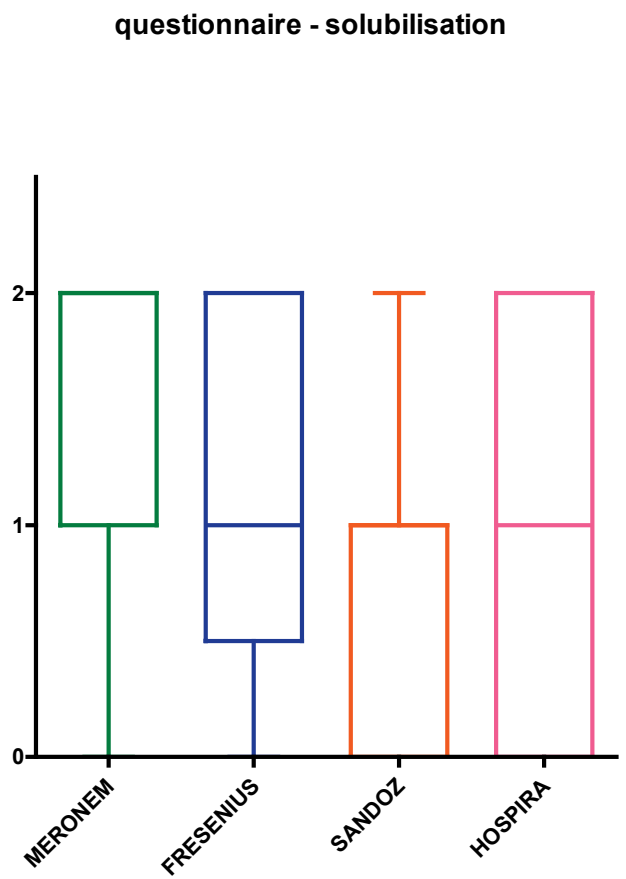


Van Bambeke *et al*., in preparation

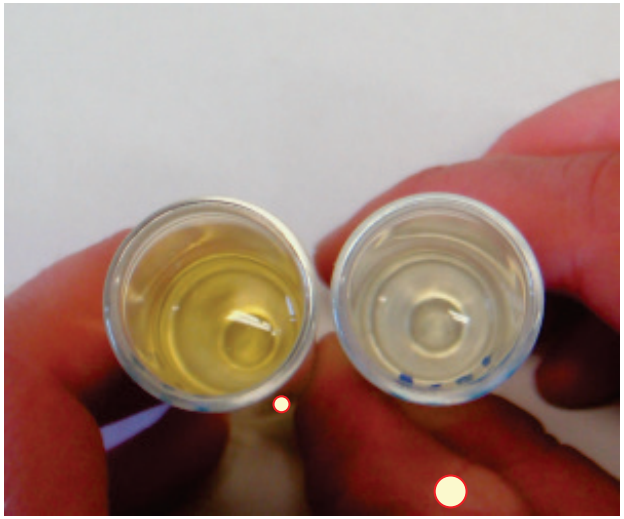
Les infirmières sont-elles contentes ? (méropénem)





Van Bambeke *et al*., in preparation

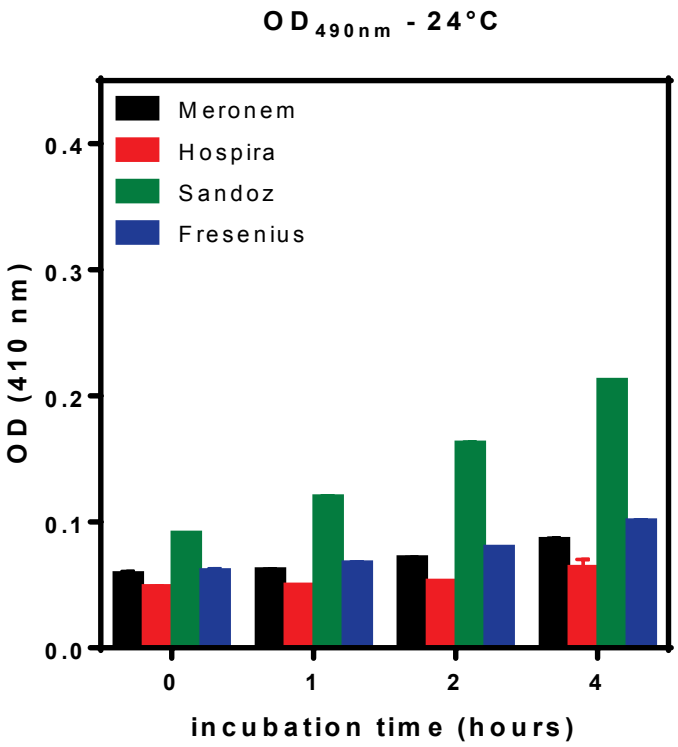
Dégradation du méropénem: libération de produits colorés

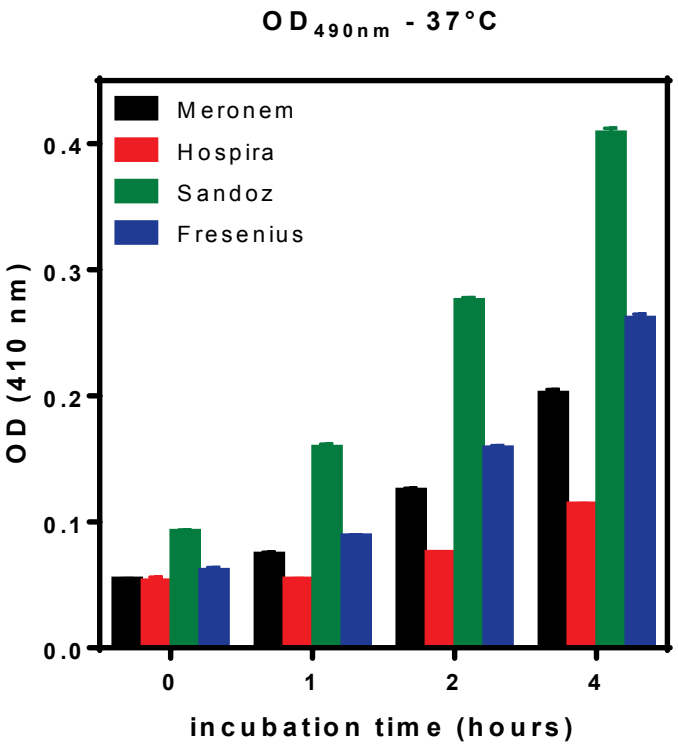


Etes vous heureux d'être jaune ?

Van Bambeke *et al*., in preparation

Dégradation du méropénem: libération de produits colorés





Van Bambeke *et al*., in preparation

Et si le problème était les impuretés ?

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.

Voici les impuretés dans la ceftriaxone … en Asie

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

Et des problèmes dans les formes physiques…

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

Impuretés dans la ciprofloxacine…

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

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

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

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

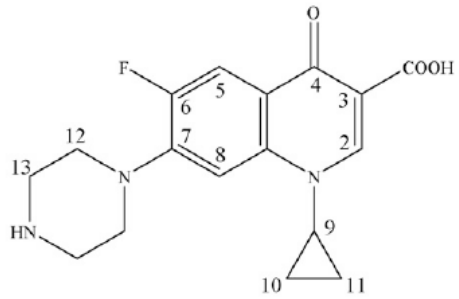
Abstract

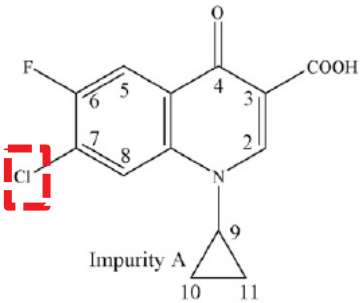
The objective of this study was to control the purity of 16 commercial formulations of ciprofloxacin tablets purchased in different countries or via the Internet using ^{19}F and ^{1}H nuclear magnetic resonance (NMR). Twelve out of the sixteen commercial formulations of ciprofloxacin measured by ^{19}F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

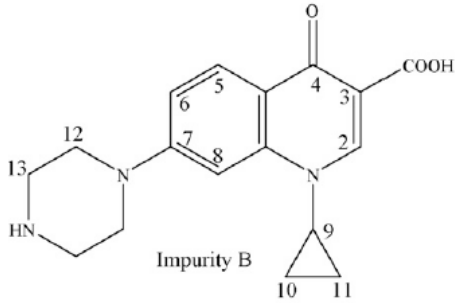
Keywords: ^{19}F NMR; ^{1}H NMR; DOSY ^{1}H NMR; Ciprofloxacin; Impurities

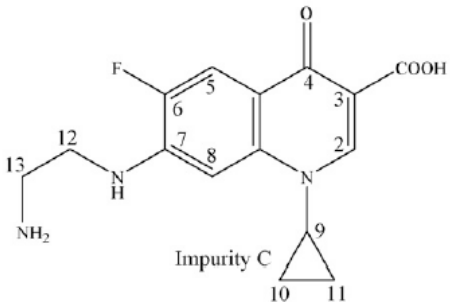
Impuretés dans la ciprofloxacine…

Tout bon chimiste verra la raison de ce contaminant









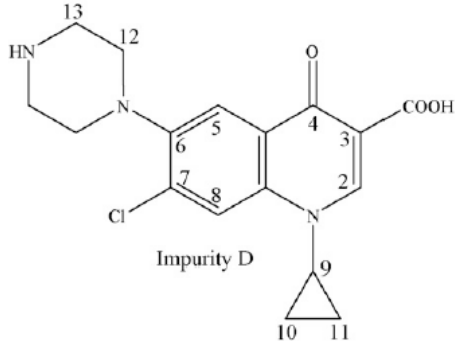
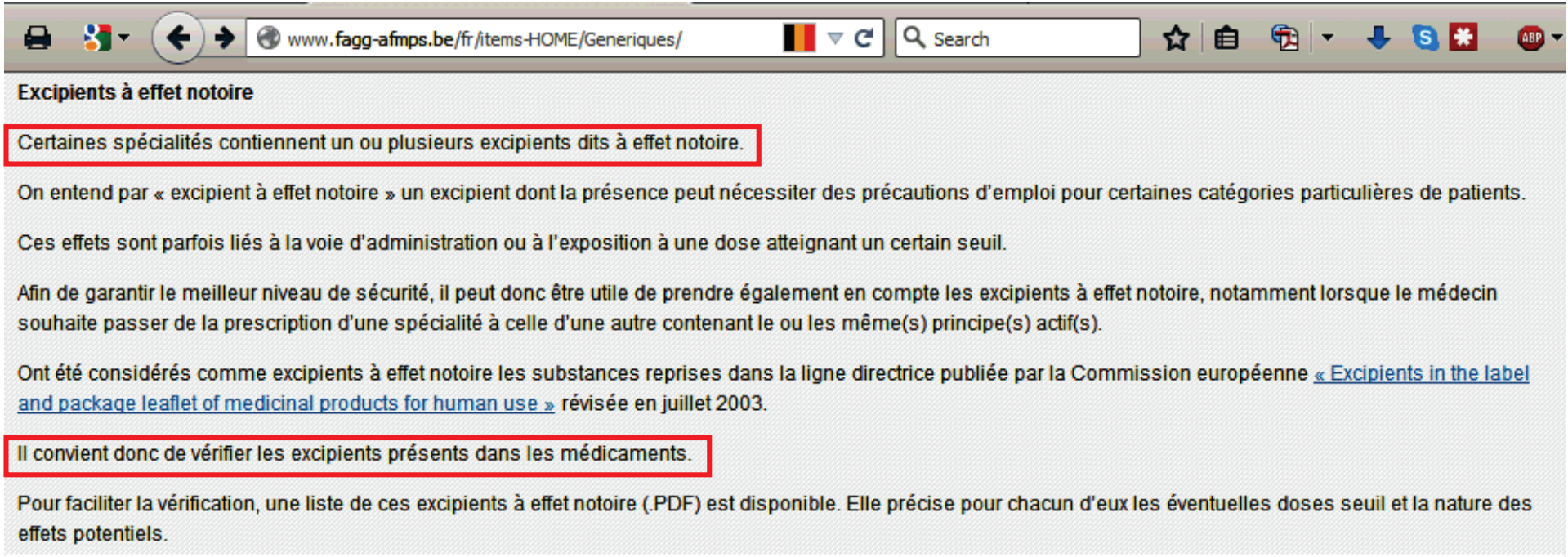


Fig. 1. Structure of ciprofloxacin and its main impurities.

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

Mais quoi à propos des excipients ?

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



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: 05/03/2015		
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 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; parahydroxybenzoate de méthyle (E218); parahydroxybenzoate de propyle (E216)
amoxicilline eg comp 20x 1 g	J01CA04	
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	

http://www.fagg-afmps.be/fr/binaries/antibiotiques-antimycosiques-EEN-FR-2015-03-05_tcm291-172642.pdf
Dernière visite: 20 fevrier 2016

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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 sir 80ml 250mg/5ml	J01CA04	saccharose
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amoxicilline eg comp 8x 1 g		
amoxicilline [illegible]		
amoxicilline mylan caps [illegible]		
amoxicilline [illegible]		
amoxicilline [illegible]		
amoxicilline sandoz comp disp 24x	J01CA04	aspartame
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amoxiclavapotex 500/125 16 comp	J01CR02	
amoxiclavapotex 500/125 30 comp	J01CR02	

la liste fait 13 pages

http://www.fagg-afmps.be/fr/binaries/antibiotiques-antimycosiques-EEN-FR-2015-03-05_tcm291-172642.pdf
Dernière visite: 20 fevrier 2016

Et les médicaments non-conformes ?

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

Correspondence
Professor Atholl Johnston, Clinical Pharmacology, Barts and The London, Charterhouse Square, London EC1M 6BQ, 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.

Est-ce un problème en Belgique ?

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

nl fr en

Autres informations et services officiels: www.belgium.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 préoccupati

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

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Mais voici ce que dit la France…

Mais voici ce que dit la France…

Et l'Europe ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2015
EMA/52196/2015
Procedure Management and Business Support

Products for which the marketing authorisations are recommended for suspension by the CHMP on 22 January 2015

Some of these medicinal products may be considered critical by the individual EU Member States. The suspension of the concerned marketing authorisation(s) may be deferred by the period for which the medicinal product is considered critical.

Article 31 of Directive 2001/83/EC Procedure number: EMEA/H/A-31/1408

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/01/WC500180894.pdf
Last accessed:08/02/2015

La liste fait 135 pages

3ème série de conclusions et discussion

- Les médicaments génériques **peuvent ou ne peuvent pas** être de même qualité que les produits originaux…

- Les raisons pour une qualité **variable** sont
  - les difficultés à **reproduire correctement les méthodes de production et de purification** du produit de référence
    (davantage une question de "savoir faire" que de connaissance brevetable)
  - une **course vers les prix les plus bas**, pouvant mener à des "simplifications" inappropriées des modes de production et/ou de purification
  - une **grande variété de procédures** pour obtenir l'autorisation de mise sur le marché (centralisée, décentralisée, nationale) à exigences variables… et dépendant de la **capacité d'analyse des autorités** [1]
  - une insuffisance de **contrôles après enregistrement** face au nombre et aux changements fréquents de producteurs des principes actifs (API) [2] …

[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: 21 February 2016

[2] Active Pharmaceutical Ingredient(s)
(see http://www.ich.org/products/guidelines/quality/quality-single/article/good-manufacturing-practice-guide-for-active-pharmaceutical-ingredients.html)
Last visited: 21 February 2016

3ème série de conclusions et discussion

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  - une insuffisance de **contrôles après enregistrement** face au **nombre** et aux changements fréquents de producteurs des principes actifs (API) [2] …

Vous rappelez-vous combien de levofloxacineS génériqueS sont autoriséeS en Belgique ?

[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
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Last visited: 21 February 2016

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  - une **course vers l** inappropriées
  - une **grande v** marché (centralis dépendant de
  - une insuffisance de **co** **s ap** **enregistrement** face au **nombre** et aux changements fréquents [illegible] producteurs des principes actifs (API) [2] …

Des contrôles continus par des laboratoires compétents sous la surveillance d'autorités attentives (Etat, autre…?) sont indispensables face au nombre de producteurs de toute origine…

ez-vous

ont
gique ?

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nise sur le
ces variabi… et
orités

[1] see "Best practice guidance on the common principle for collaboration between CMDh/RMS and EMA on generics and hybrids" EMA/234449/2012
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Last visited: 21 February 2016

De quoi allons nous discuter ?

1. Un choix **politique** (les lois américaine et européenne)
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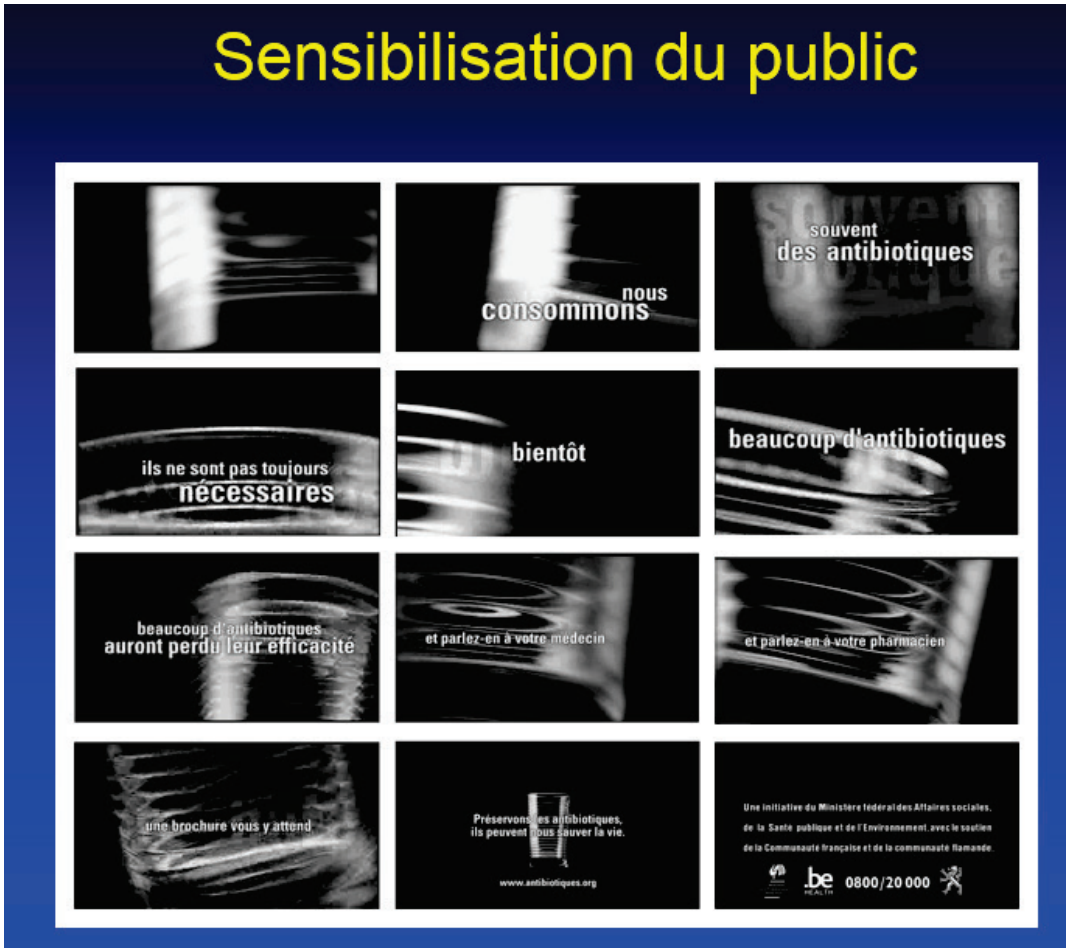
5. Les **risques cachés** des antibiotiques "bon marché"
   - **surconsommation …**
   - **nouveaux** antibiotiques **à charge de la communauté**

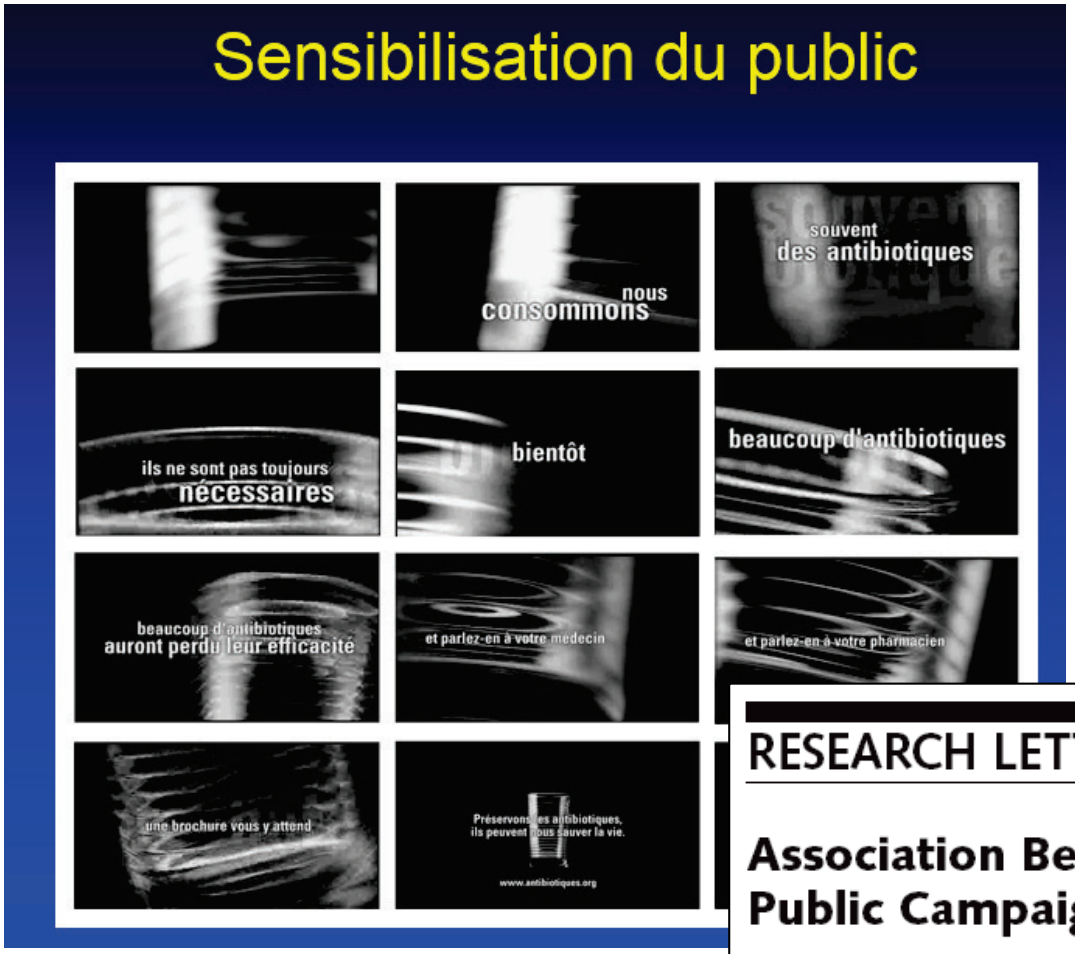
Les efforts pour un bon usage des antibiotiques



vous rappelez-vous la première campagne "antibiotiques"

Campagne "antibiotiques" 2000
http://www.antibiotiques.org/

Les efforts pour un bon usage des antibiotiques



Campagne "antibiotiques" 2010
http://www.antibiotiques.org/

Nous l'avons même publiée à un haut niveau …

RESEARCH LETTER

Association Between Antibiotic Sales and Public Campaigns for Their Appropriate Use

JAMA, November 24, 2004—Vol 292, No. 20 **2469**

Et ces idées sont reprises partout…

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.

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

Mais voici ce qui se passe au Danemark…

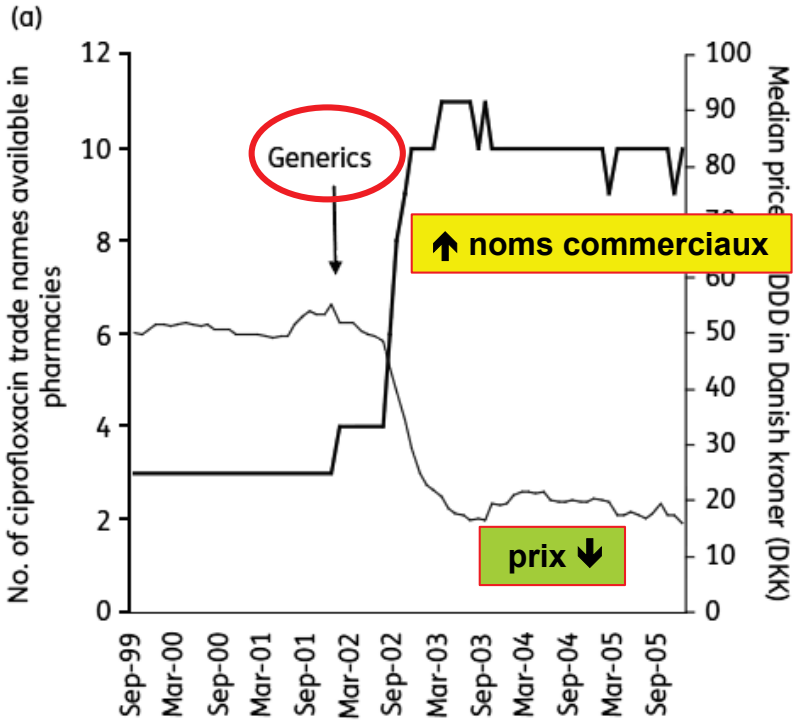
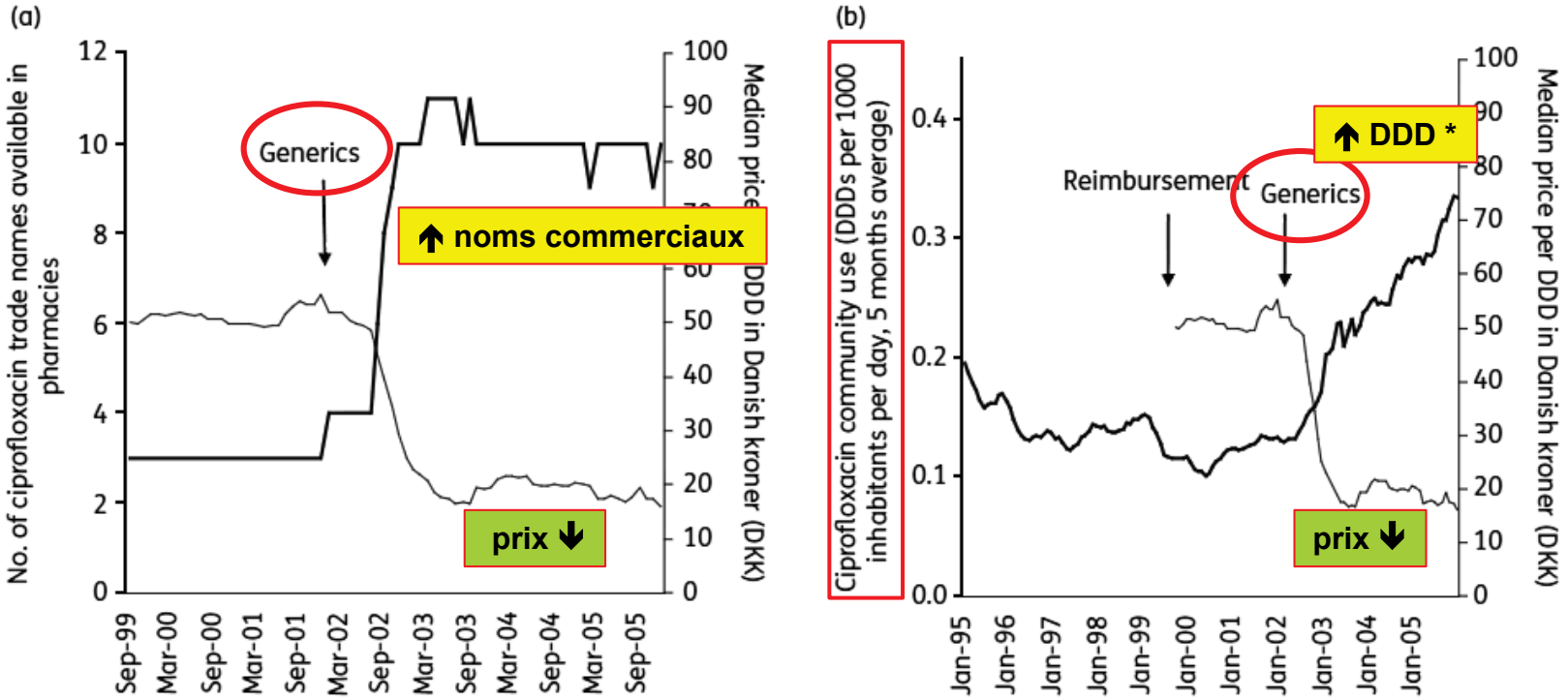


Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin.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

* DDD: *defined daily dose* (doses moyennes journalières)

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

Mais voici ce qui se passe au Danemark…



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

Et voici en Allemagne…

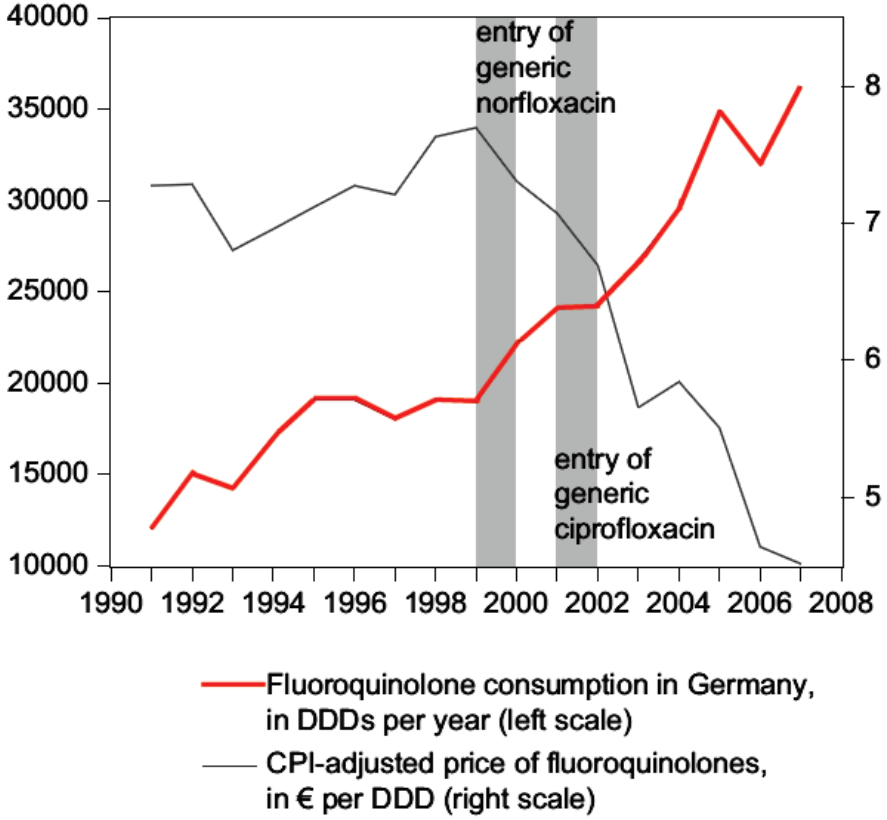

Figure 1. Fluoroquinolone consumption in Germany (SHI-related prescriptions, 1991–2007). SHI = statutory health insurance; DDD = defined daily doses; CPI = consumer price index

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

Et les producteurs de génériques utilisent tous les arguments (même stupides)

Trouvez les 4 erreurs (grossières)

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

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   - **surconsommation …**
   - **nouveaux** antibiotiques **à charge de la communauté**
     (2 dias … mais à discuter si vous le souhaitez…)

Investissements publics en Europe (un exemple)

- **2 milliards d'Euros de budget …**
- recherche "collaborative" et réseaux entre industries et universités…
- écosystème collaboratif pour la recherche et le développement pharmaceutique…
- augmenter la capacité compétitive globale de l'Europe
- ré-établir l'**Europe comme place la plus attractive pour le R&D pharmaceutique**

http://www.imi.europa.eu/
Last accessed: 26 May 2015

Mais du côté de l'Oncle Sam…

- **GAIN Act** (Generating Antibiotics Incentives Now) - 2012
  - priority FDA review
  - **additional five years of market exclusivity** fo… …arget serious or life-threatening pathogens
  - relaxed its criterion for non-inferiorit… comparability to drugs alread…

- **BARDA:** Biom… …lopment Authority [within the Off… …and Response in the U.S. Department of Health …

…proach to the **development and purchase of …, therapies, and diagnostic tools** for public health

Plus d'un milliard de $ d'argent public…

- 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: 26 May 2015

Résumé / Conclusions

- La **décision d'autoriser les génériques** est **politique** … mais pourrait (devrait ?) être revue pour éviter leur surconsommation
- Les **critères pharmacocinétiques** sont (essentiellement) les **seuls à être pris en considération** par les autorités d'enregistrement (EMA / FDA) … ce qui est probablement insuffisant.
- Le **contrôle de la qualité des génériques est essentiel** et doit être renforcé bien au-delà de ce qui est fait aujourd'hui… et par des organismes capables de réaliser les études nécessaires…
- **Les antibiotiques sont des médicaments précieux.** Un mauvais (exagéré) usage grâce à des prix faibles pourrait causer de graves problèmes et de (très) grandes dépenses dans le futur…
- Un **nouveau modèle économique** (moins d'utilisation sans perte de revenu pour le producteur et/ou une prise en charge par l'Etat) est probablement nécessaire…

Dias: http://www.facm.ucl.ac.be → Lectures → en français

Back-up

You said "generics"

Lead generic companies resort to multiple strategies for growth

These include

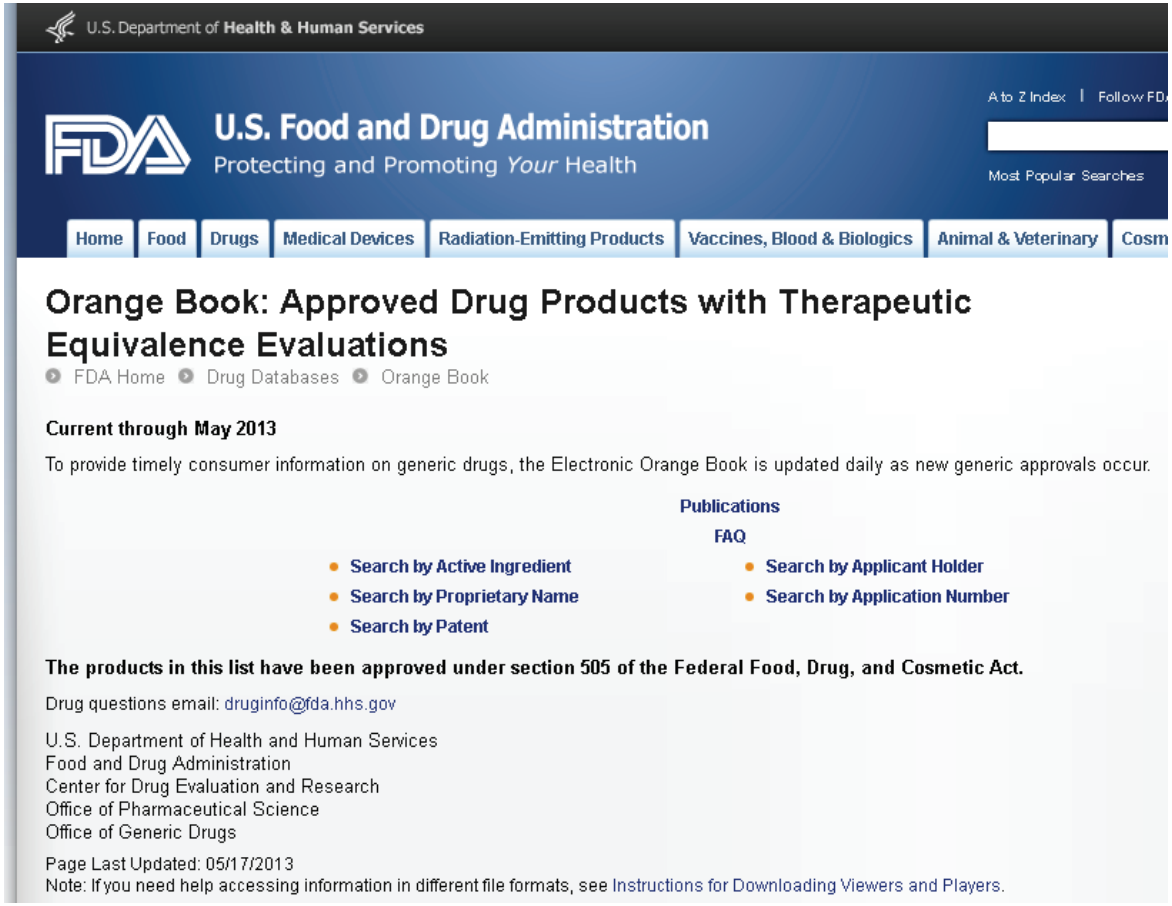
- applying for **generic approvals** with Food and Drug Administration (FDA) and European Medicines Agency (EMA);
- **merger and acquisitions**;
- developing a strong and innovative **generic drug pipeline**;
- **improving infrastructure** to enhance manufacturing and R&D capabilities;
- **new product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



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

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home › Drug Databases › Orange Book

Current through May 2013

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

Publications

FAQ

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

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

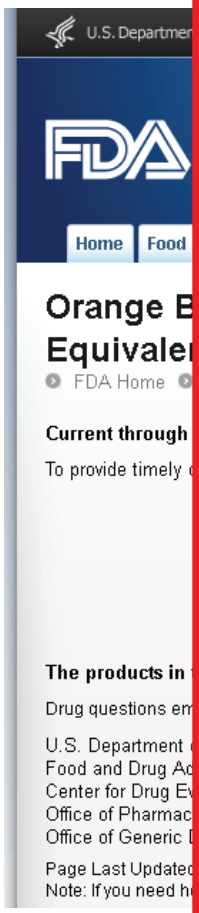
Drug questions email: druginfo@fda.hhs.gov

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

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

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

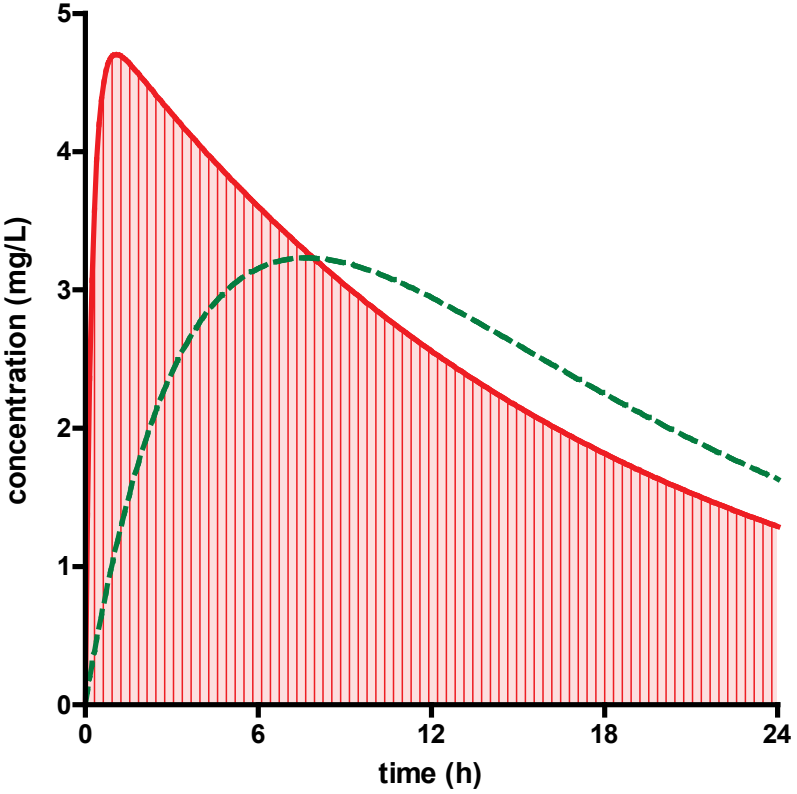
FDA approved generic drugs: "Orange book" *

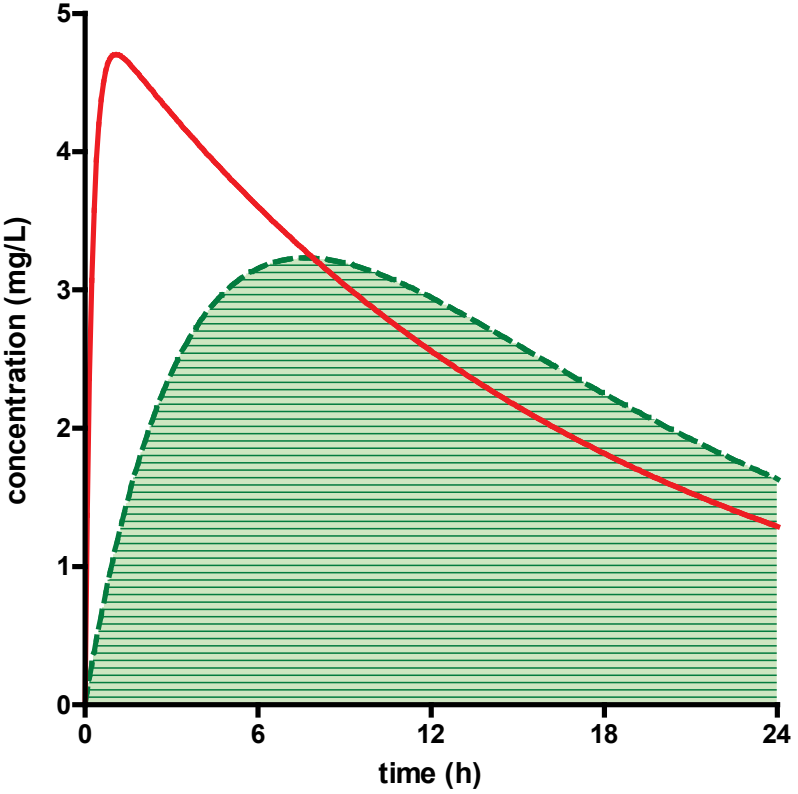


Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
A090343	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 250MG/50ML (EQ 5MG/ML)	LEVOFLOXACIN IN DEXTROSE 5% IN PLASTIC CONTAINER	ACS DOBFAR INFO SA
A090343	AP	No	LEVOFLOXACIN	INJECTABLE; INJECTION	EQ 500MG/100ML (EQ 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

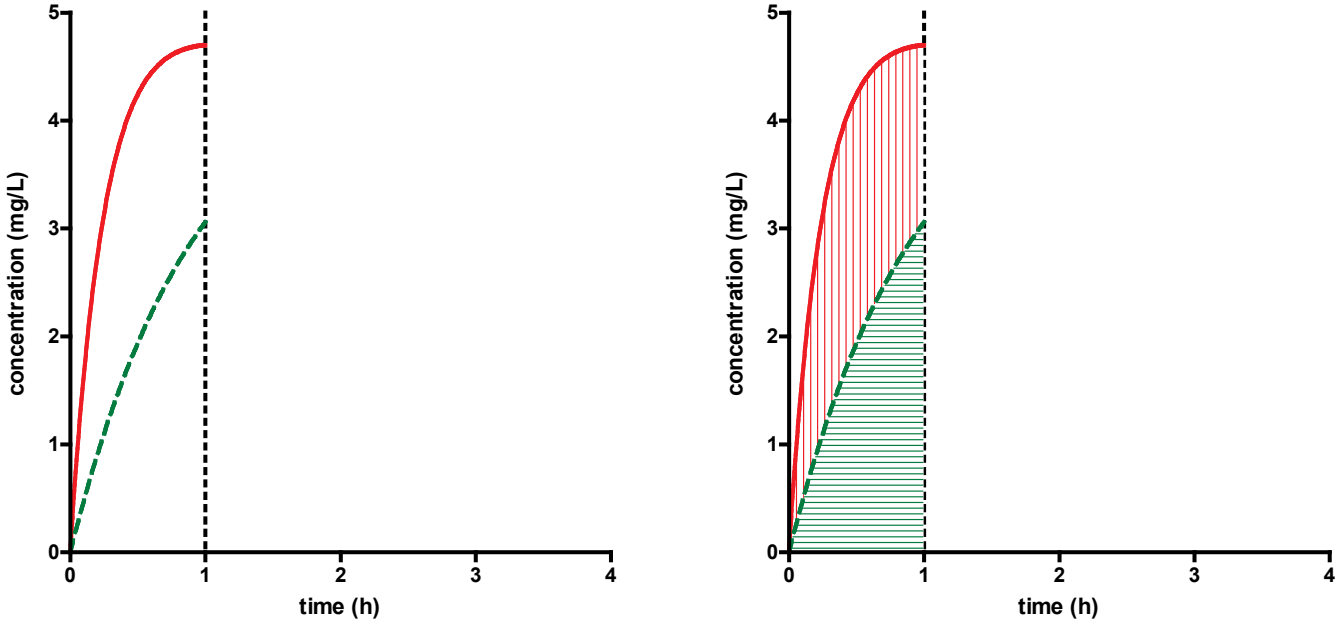
* http://www.a

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





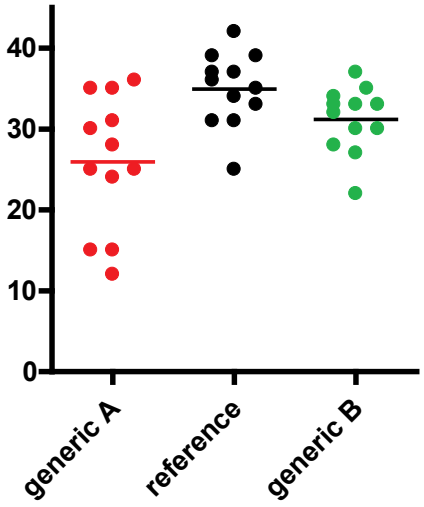
Additional criteria for early AUC (EMA) *



- 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

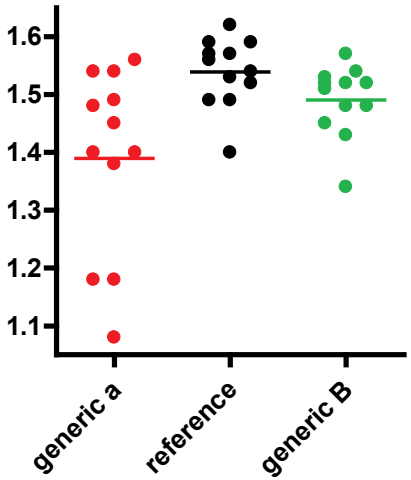
* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

Are generic really comparable ?



arithmetic comparison

geometric comparison

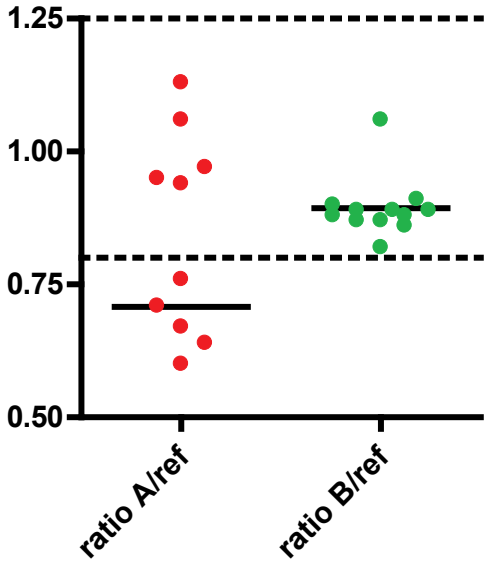


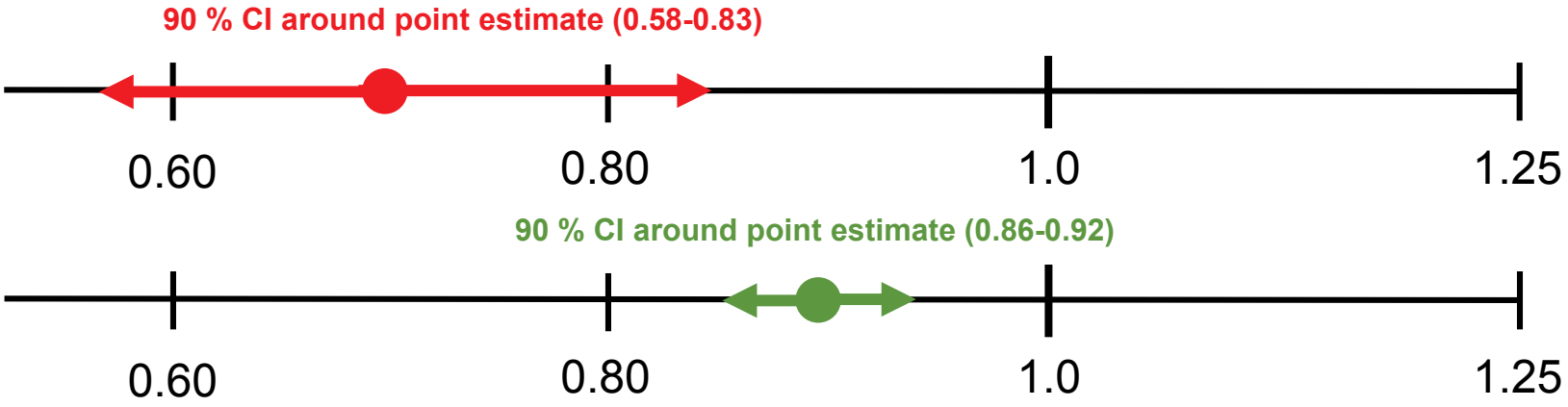
Are generic really comparable ?

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.

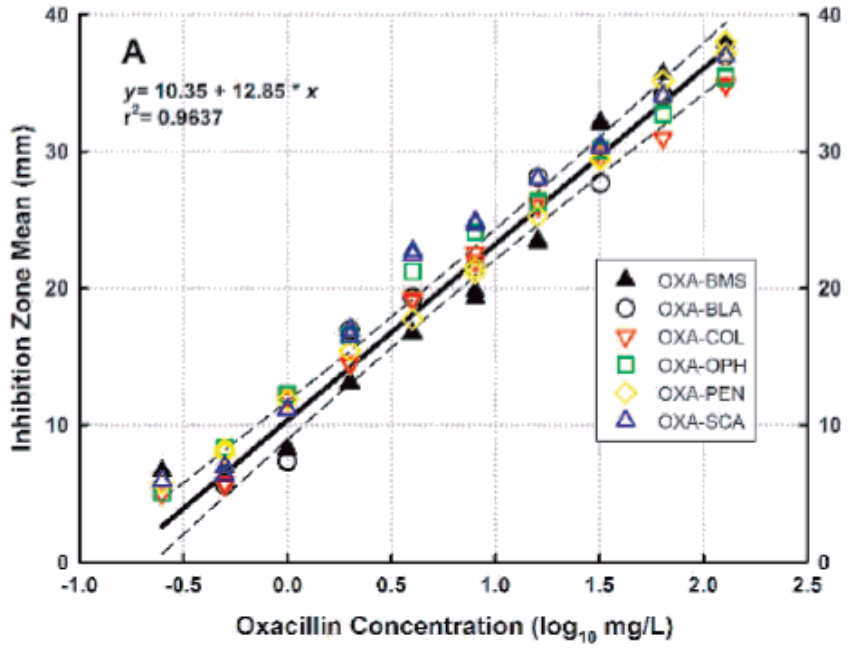
Highly variable drugs or drug products

- 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

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

Potency (oxacillin)



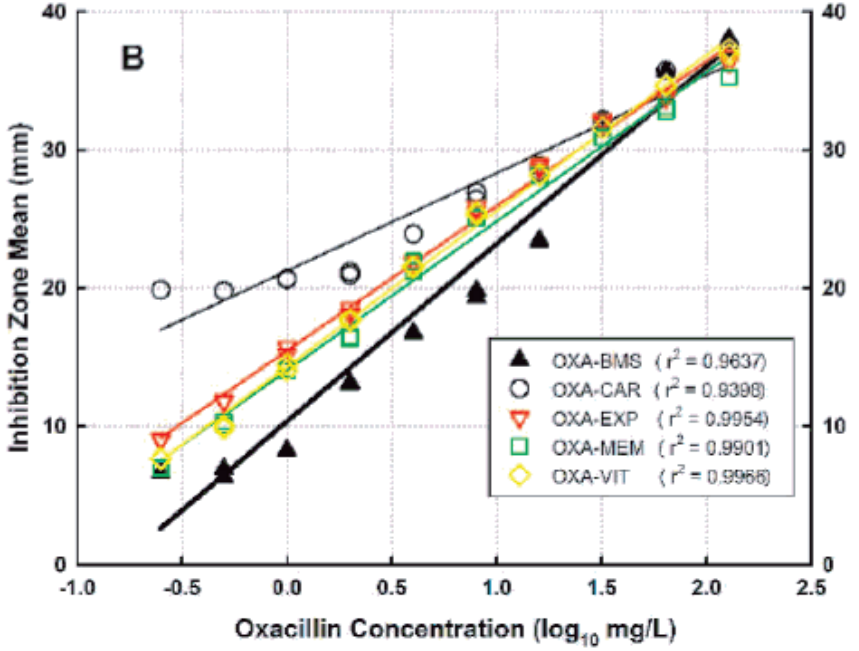
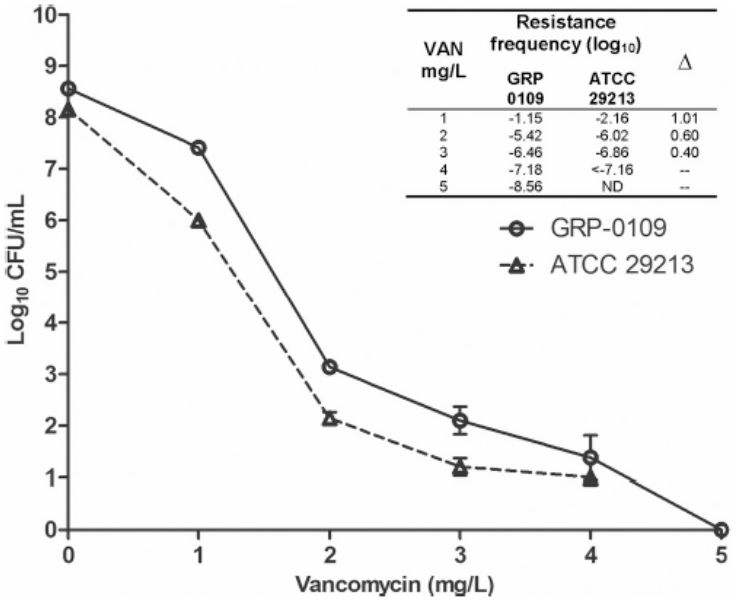


Figure 1 Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay. **A**. The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical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

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

Killing curves and hetero-resistance (vancomycin)

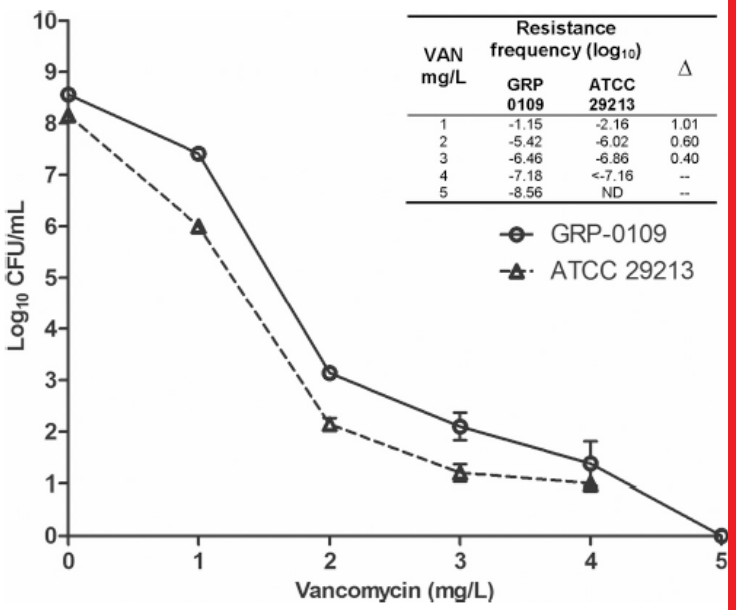


VAN mg/L	Resistance frequency (log_{10}) GRP 0109	ATCC 29213	Δ
1	-1.15	-2.16	1.01
2	-5.42	-6.02	0.60
3	-6.46	-6.86	0.40
4	-7.18	<-7.16	--
5	-8.56	ND	--

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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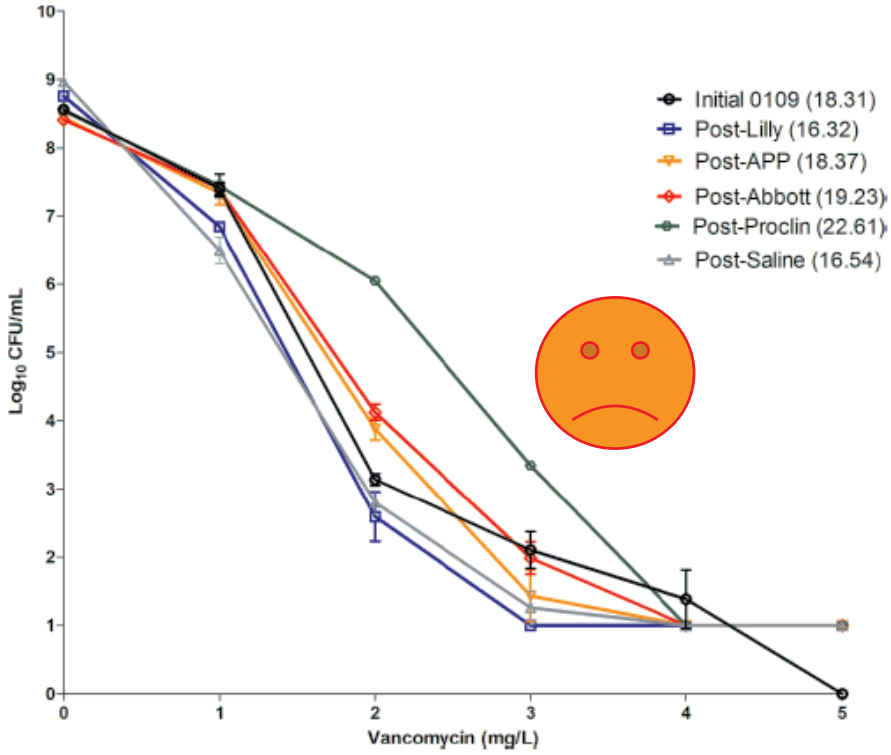

FIG 3 Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction of the less susceptible subpopulations, which is sharply different from three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

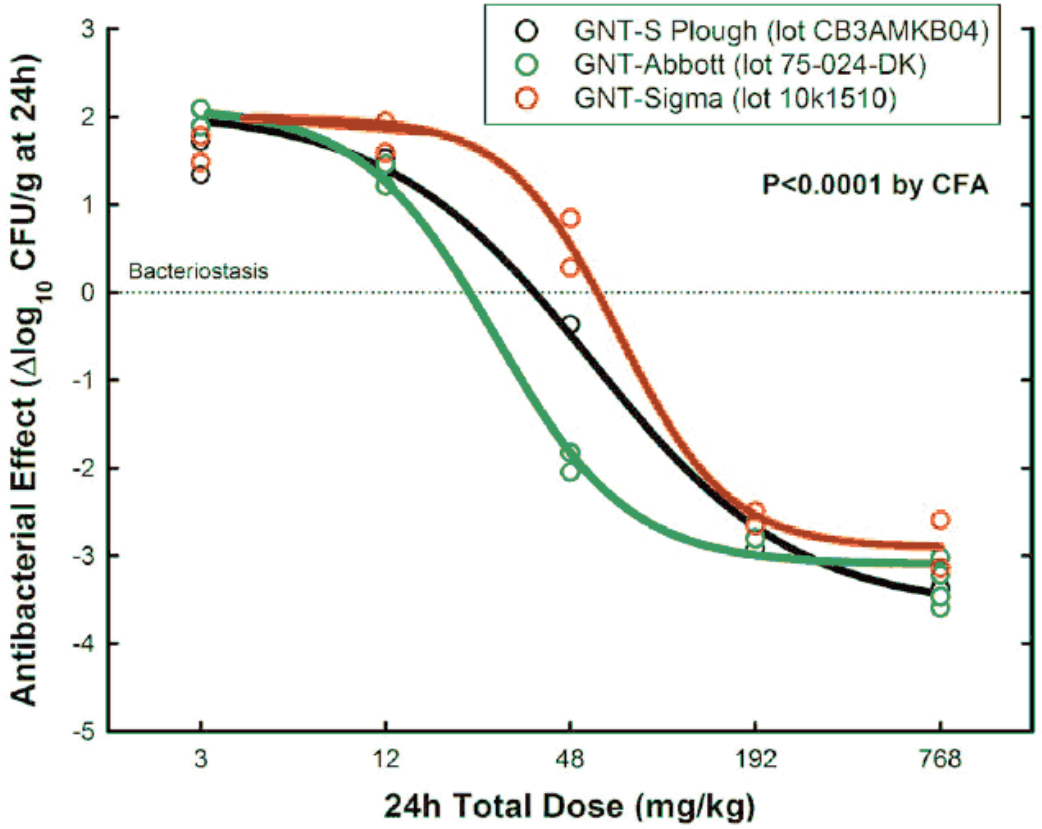

Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence. The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency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

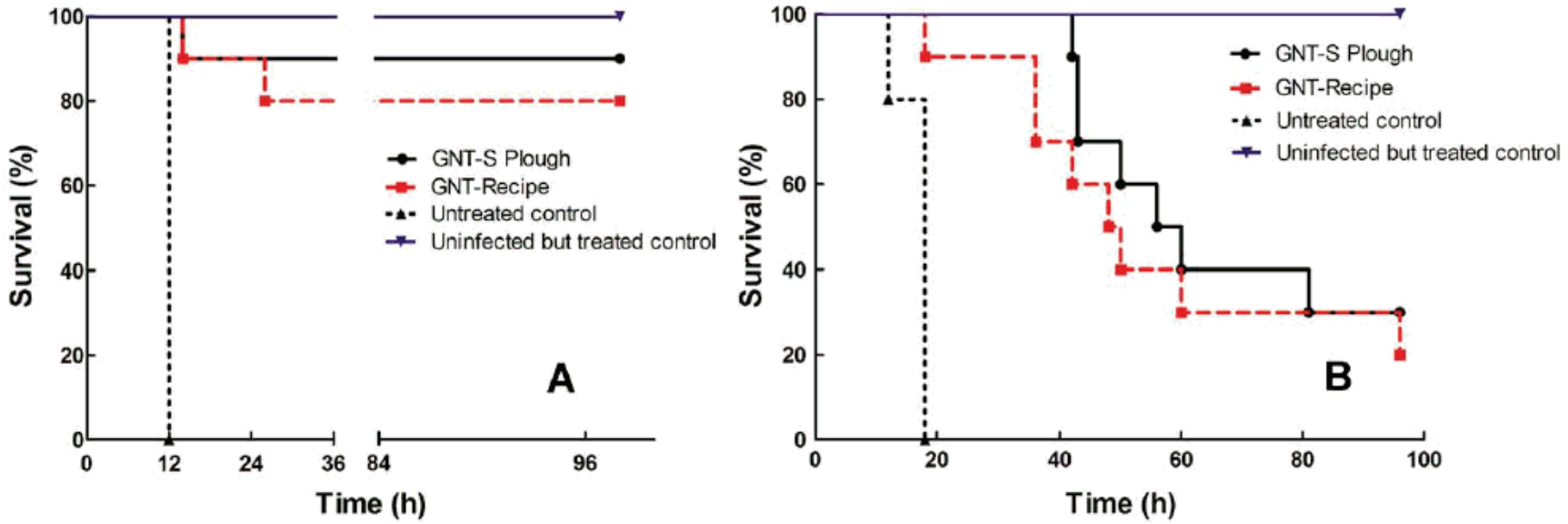

Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect (768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

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

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

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

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

Vancomycin: complete equivalence in the rabbit endocarditis model

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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

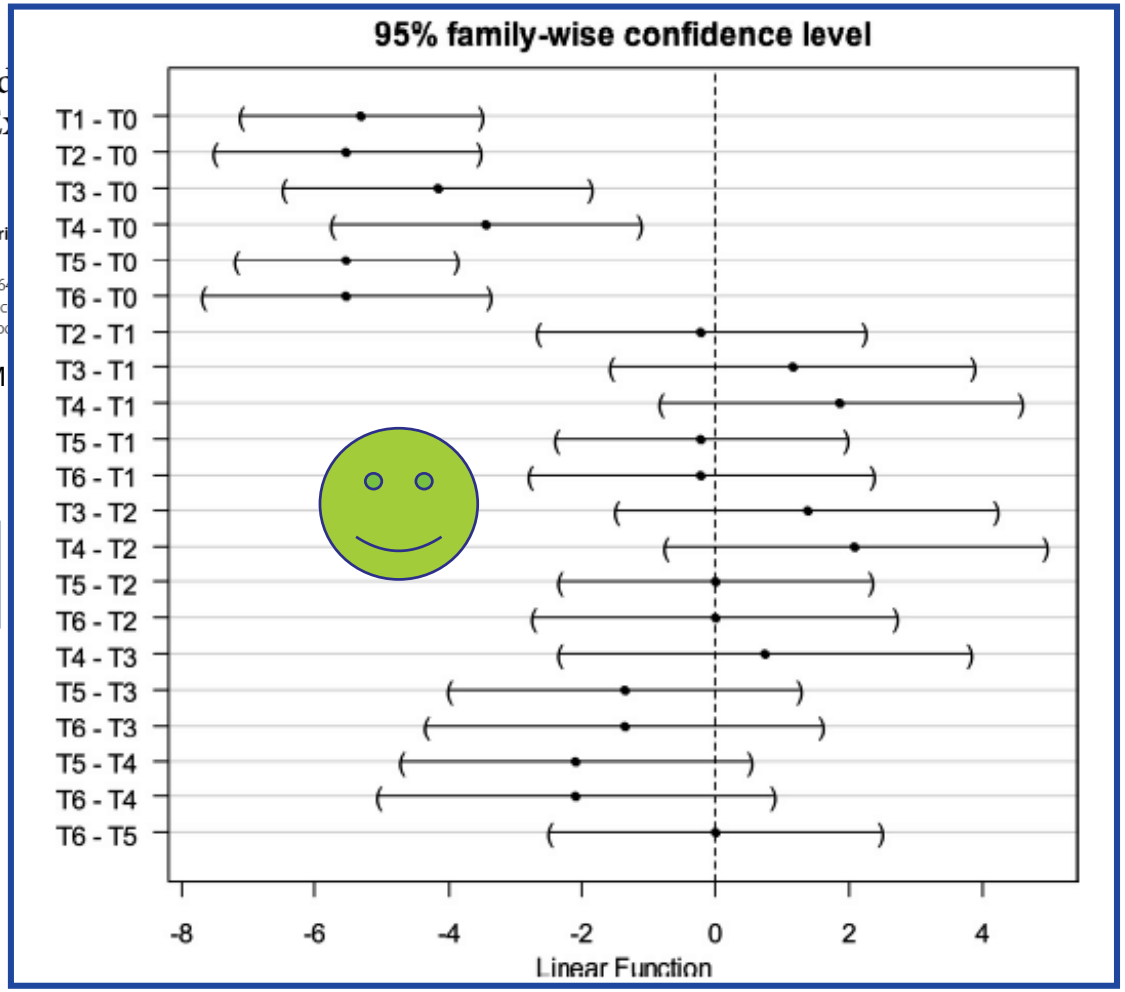

FIG 3 Differences between treatment groups in terms of organism titers in vegetations (log_{10} CFU/g). Dots are mean differences between treatment groups, and parentheses are the upper and lower bounds of their 95% confidence interval. Analysis was performed using the Tukey method, taking into account 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

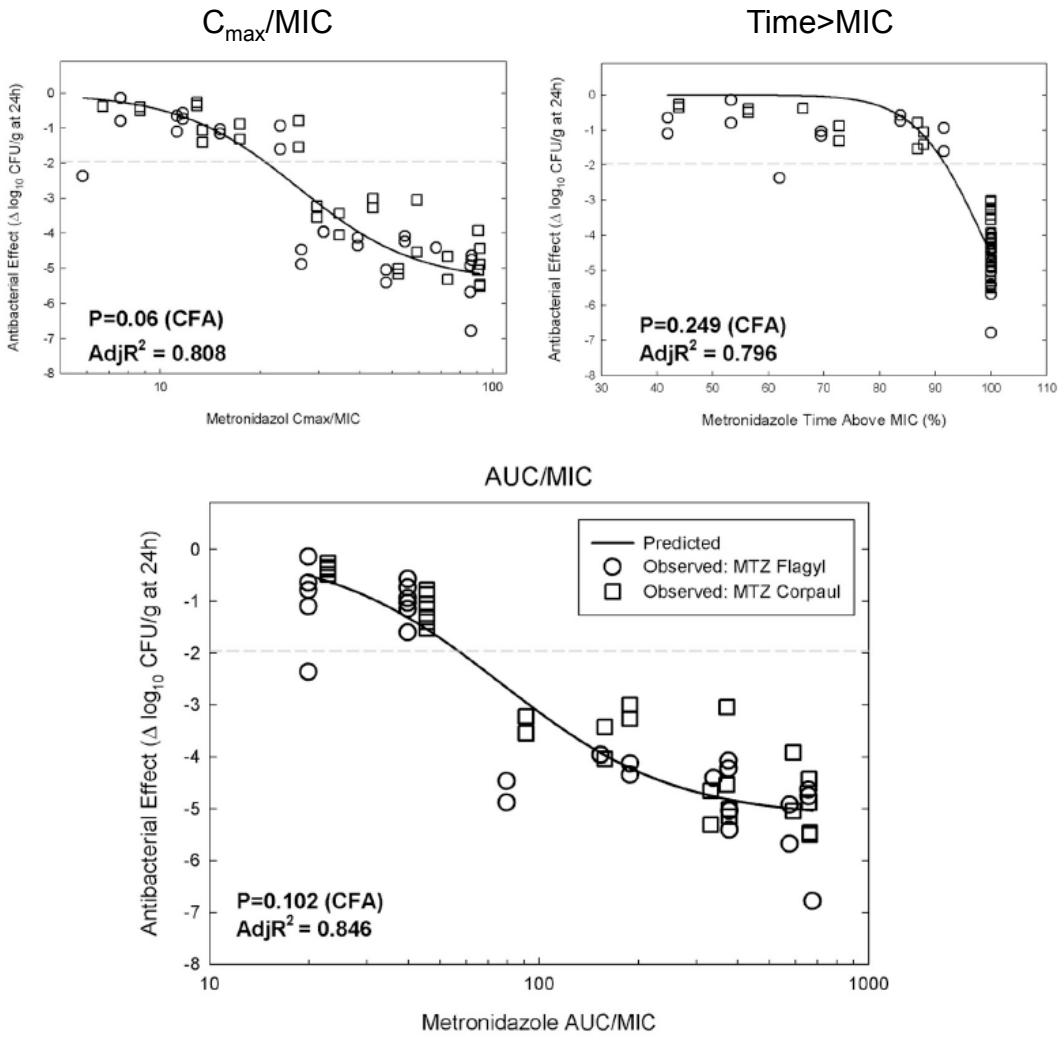

FIG 5 Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *B. fragilis* in a neutropenic mouse thigh anaerobic infection model. Only one curve is depicted because the data belong to a single population despite the fact that they were obtained after treatments of different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

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]

[a]*Department of Family Medicine, University of Tennessee Graduate School of Medicine, 1924 Alcoa Highway, U-67, Knoxville, TN 37920, USA*

[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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Generic medicatio
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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*

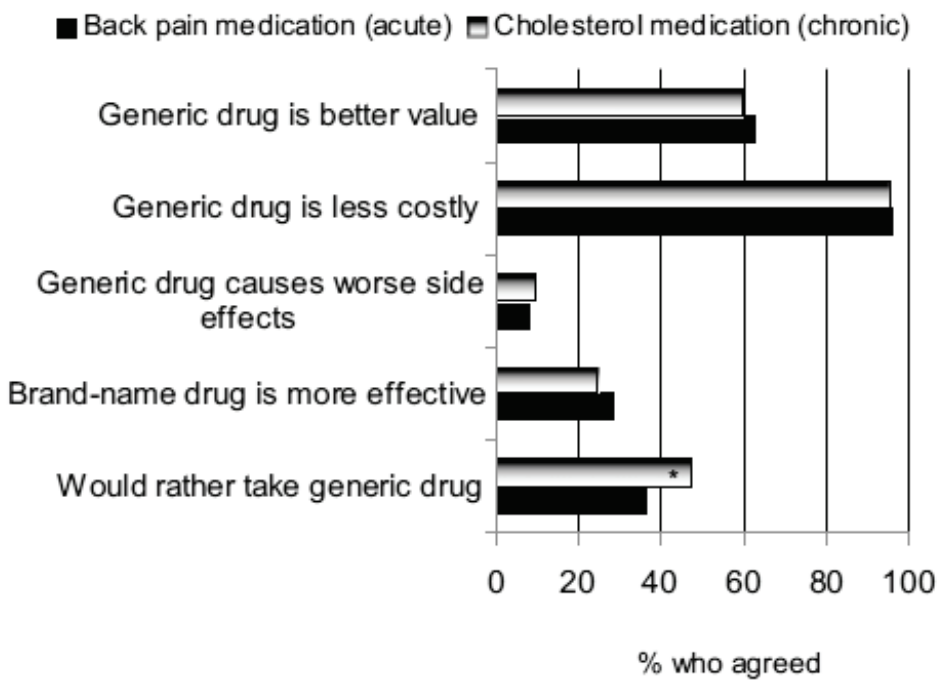

Fig. 2. Participants' perceptions of generic and brand-name medications for treating their hypothetical chronic or acute condition (n = 172). Note: % who agreed is the sum of participants who somewhat or strongly agreed with each item. *$P < .05$ using chi-square test.

The risk of overconsumption in France …

ELSEVIER MASSON

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www.em-consulte.com

Médecine et maladies infectieuses

Médecine et maladies infectieuses 42 (2012) 141–148

Generic antibiotic drugs: Is effectiveness guaranteed?

R. Gauzit *, M. Lakdhari

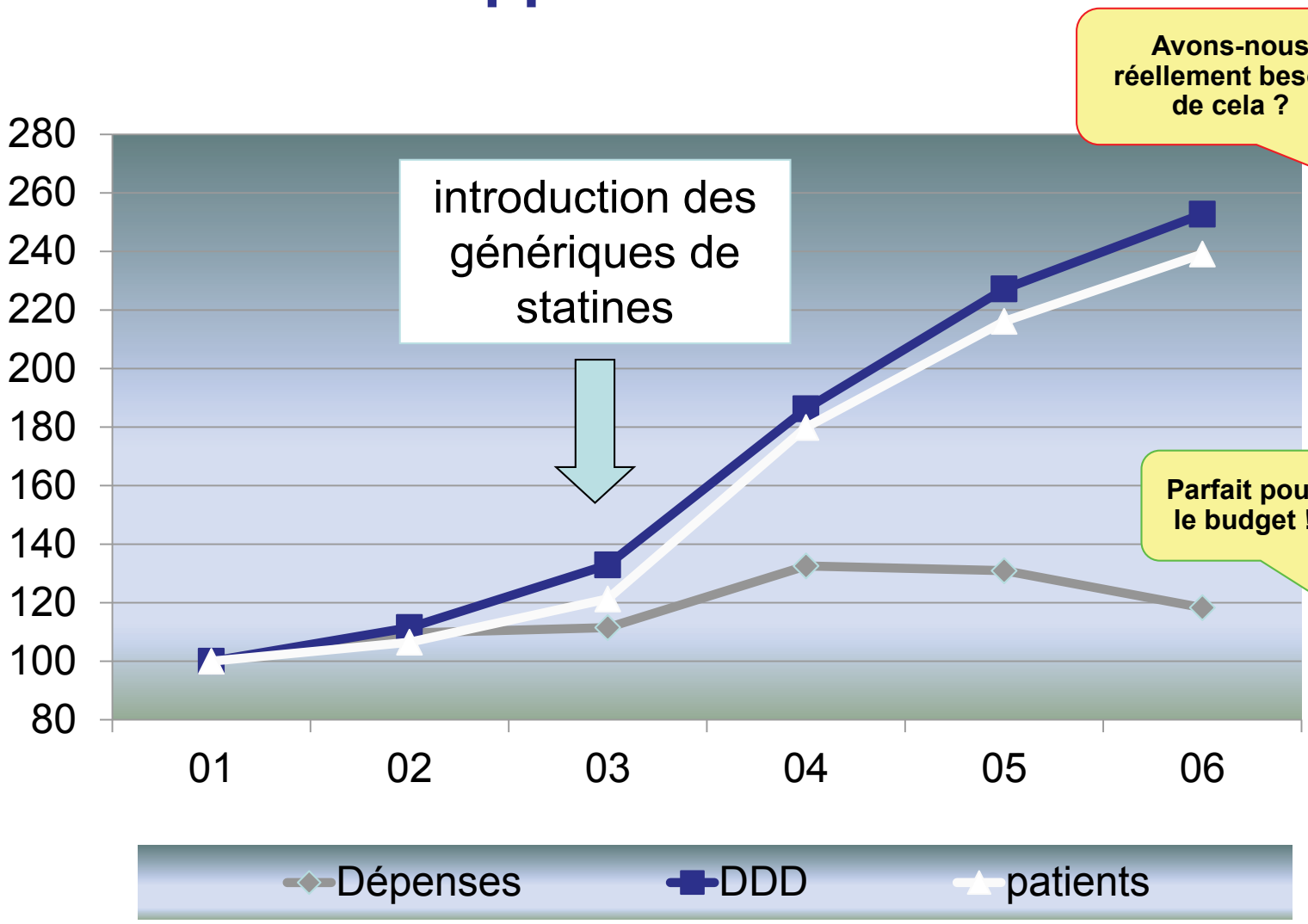
Unité de réanimation, Hôtel Dieu, place du Parvis-de-Notre-Dame, 75781 Paris cedex 04, France

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.

Vous rappelez-vous les statines ?

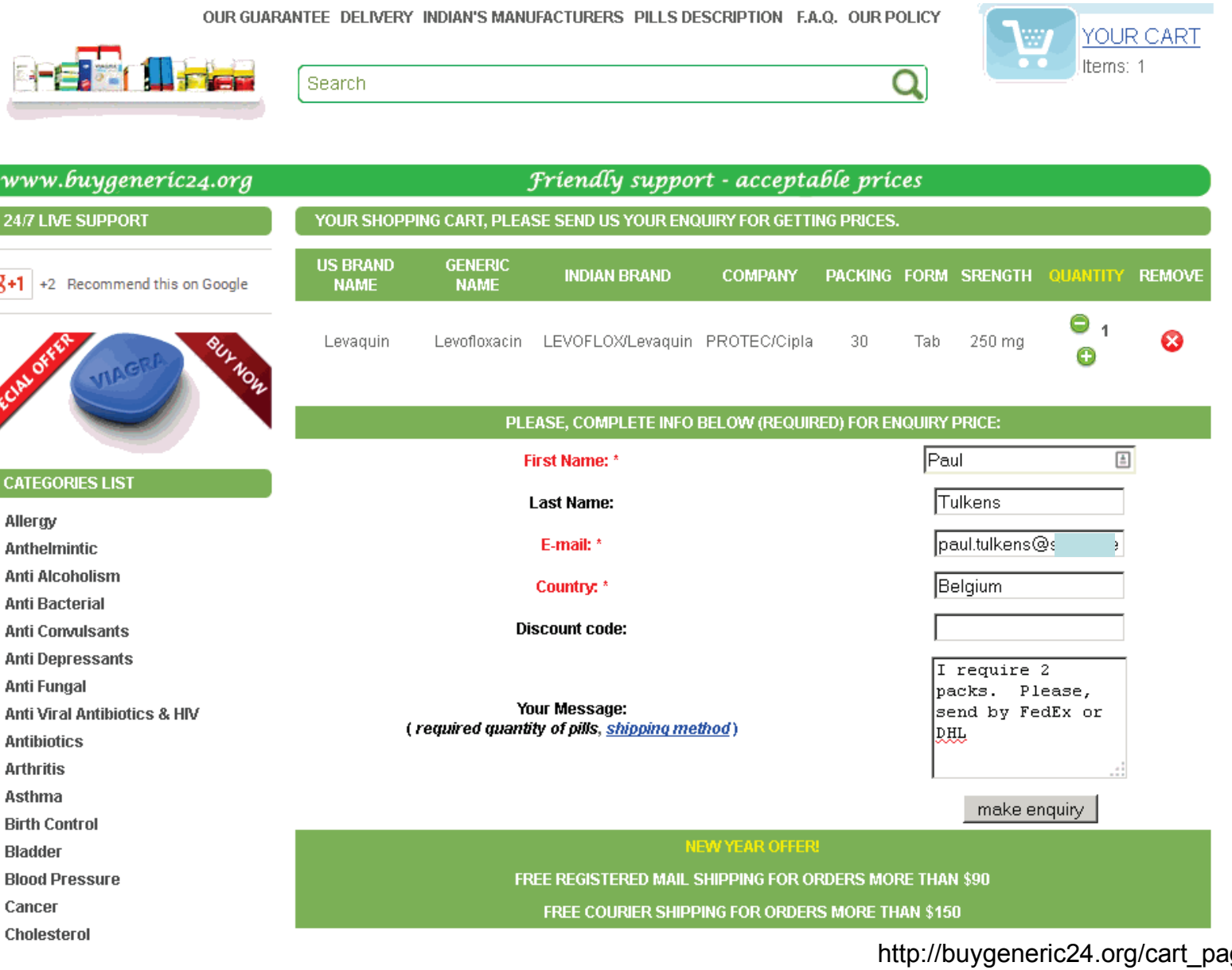


Source: INAMI / RIZIV

"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

JOURNAL OF
Veterinary Pharmacology and Therapeutics

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

The consequences of generic marketing on antibiotic consumption and the spread

P.-L. TOUTAIN
A. BOUSQUET

- In France, introduction of 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…

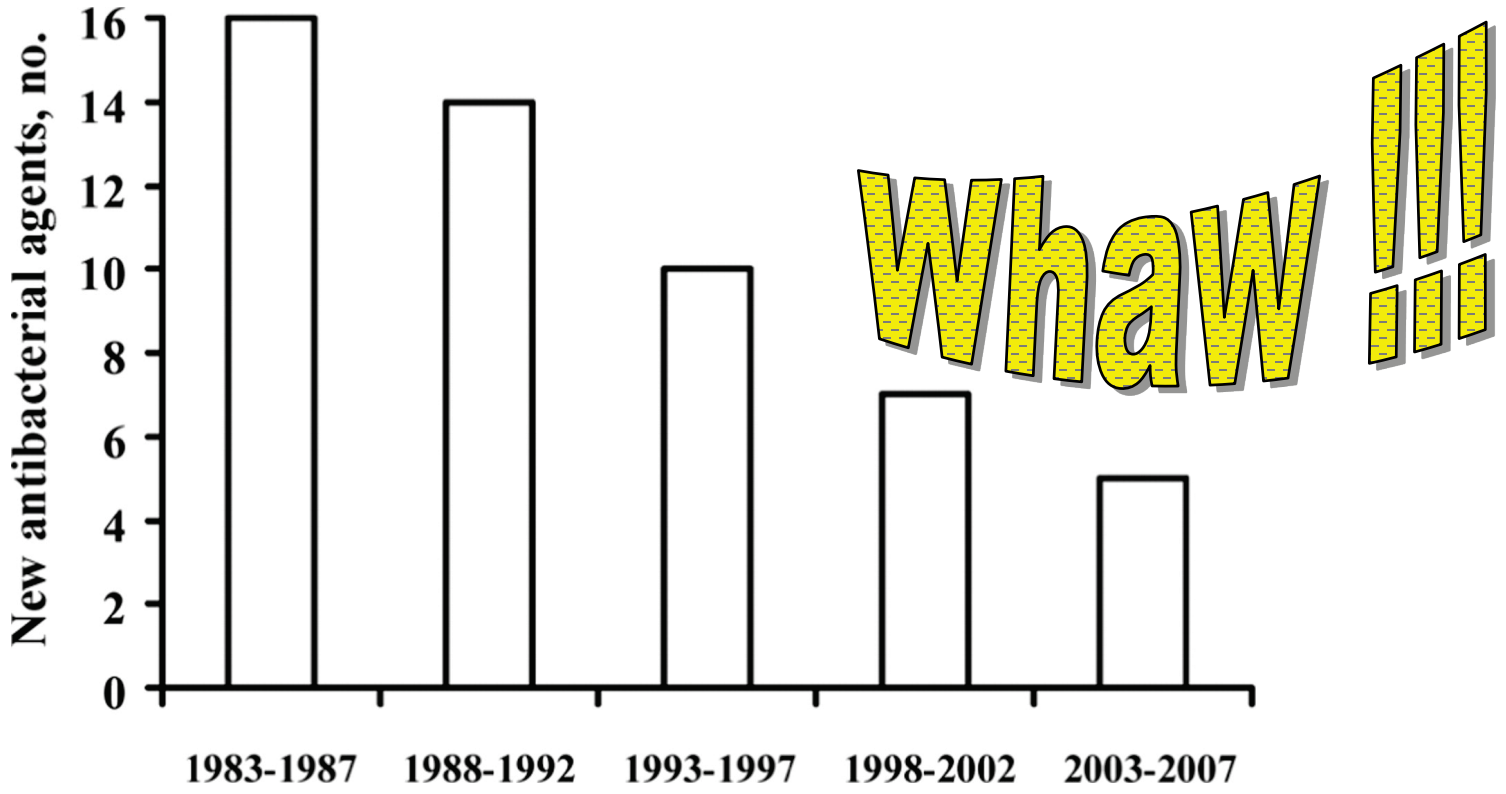
Generic antibiotics, antibiotic resistance, and drug licensing

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

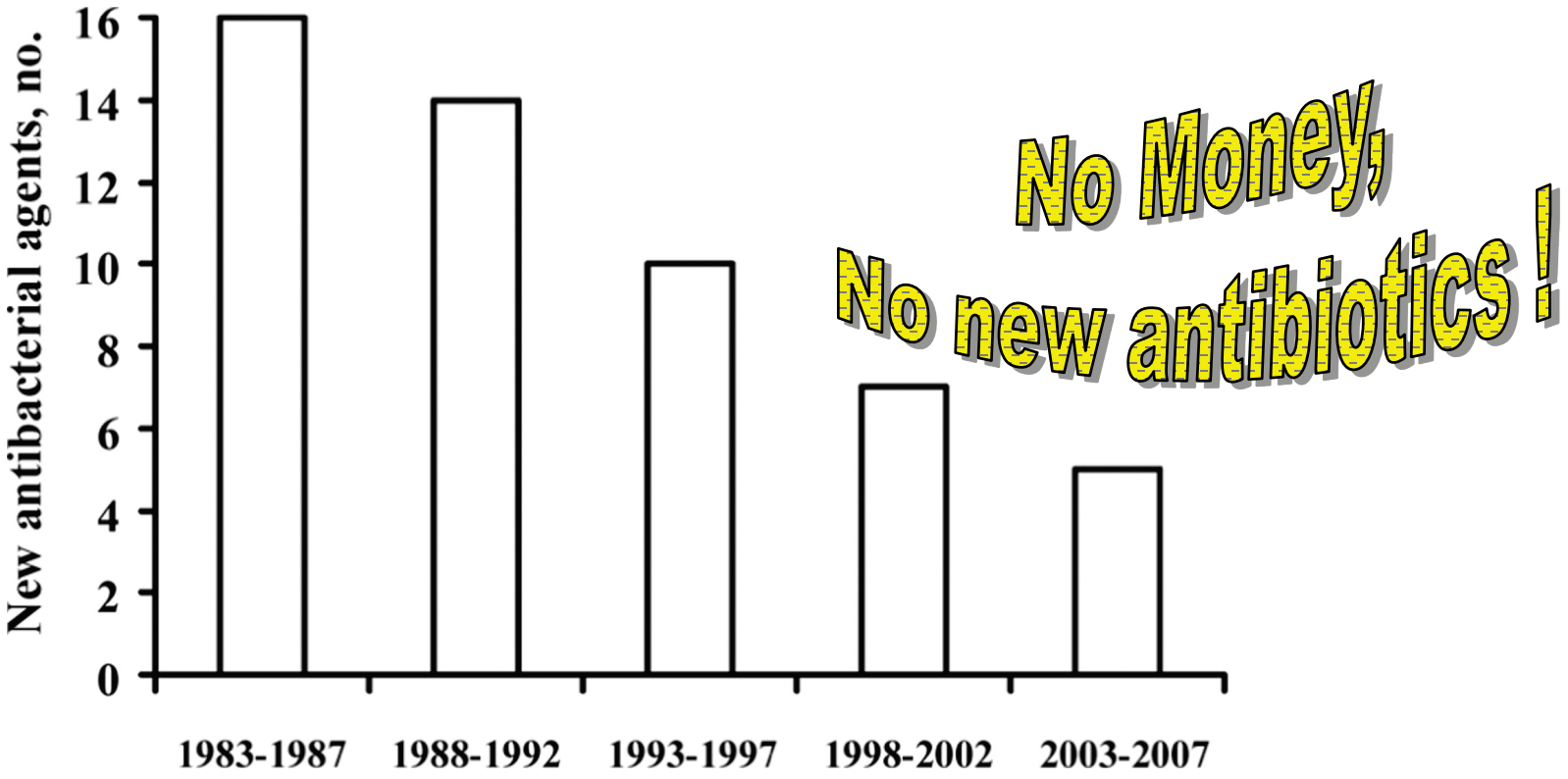
The Nottingham University Hospitals NHS Trust; and University of Nottingham, Nottingham, NG5 1PB, UK

Innovative antibiotic development is abandoned by Industry



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

Why do they abandon it ?



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

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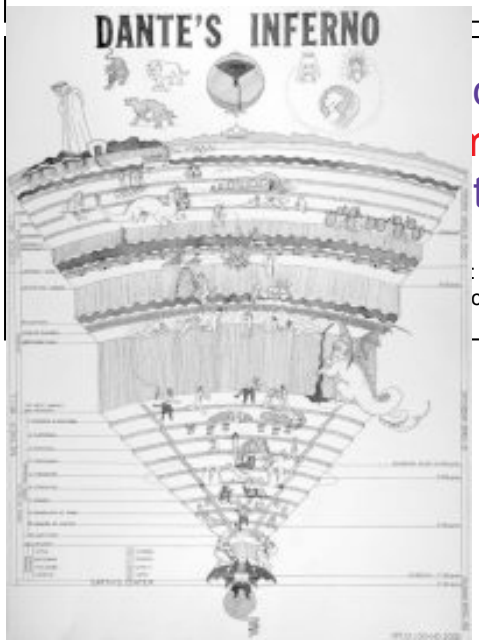

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cessed: 7 November 2013)

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

* INN: International International Nonproprietary Name
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The "Qualy" of antibiotics in Community acquired pneumonia (*)

- 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**, and without antibiotic you would lose 25% of your patients, then the value of the **"Qualy" of an antibiotic treatment of community-acquired pneumonia is between 16,000 to 50,000 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…**

* 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

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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

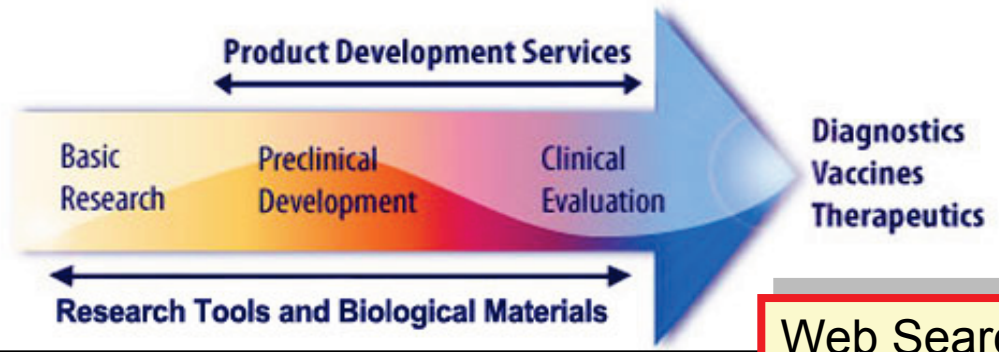
Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.

- 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.



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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

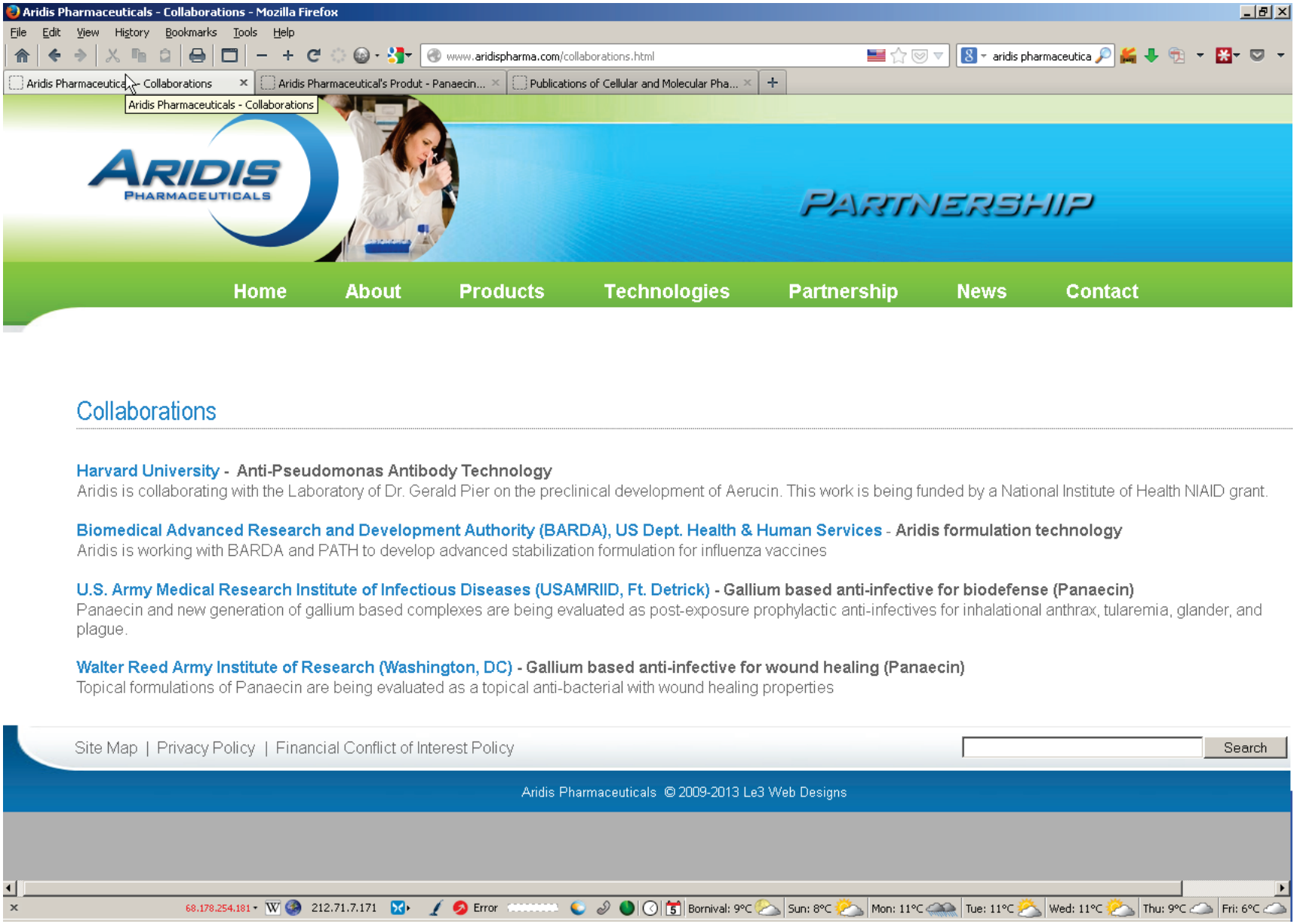
May 22, 2013: HHS forms strategic alliance to develop new antibiotics

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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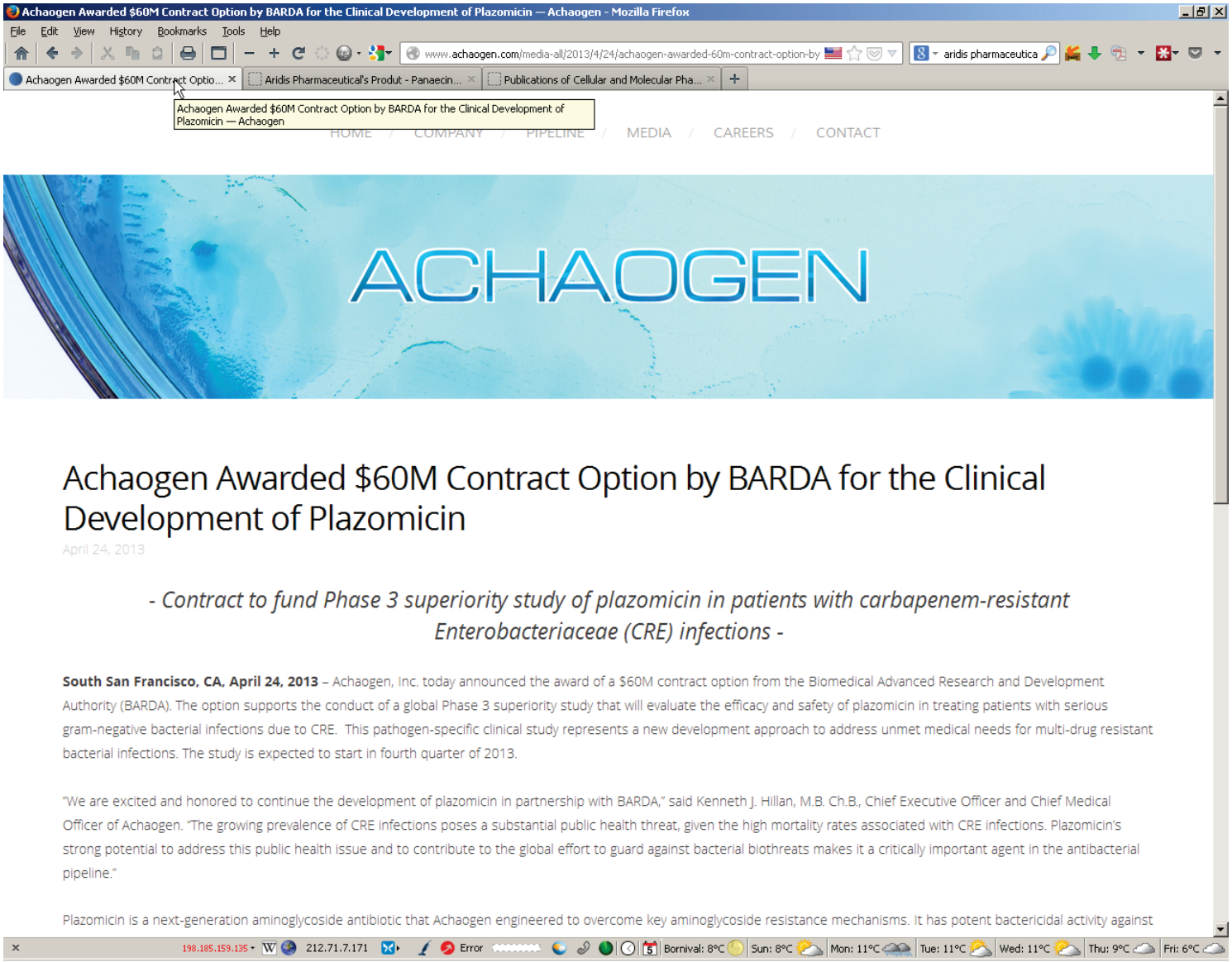


What in Europe ?

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

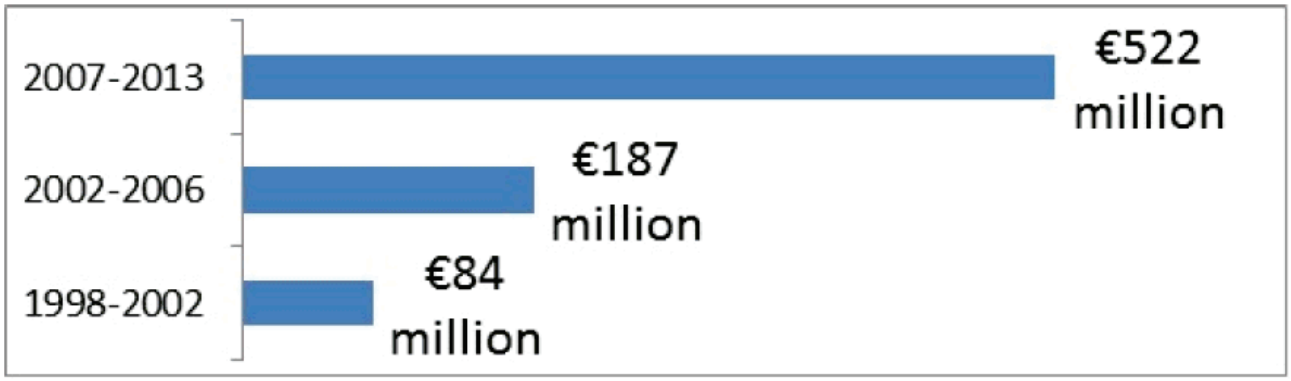
EU launches new research projects to combat anti-microbial resistance

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

Investments in Europe…

EU launches nev
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