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

(with comments about overconsumption and economical aspects)

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Séminaire de Médecine Interne - 2 April 2014

Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions
- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

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

Information sources for Belgium

http://www.febelgen.be/index_fr.html
Last visited: 4 April 2014

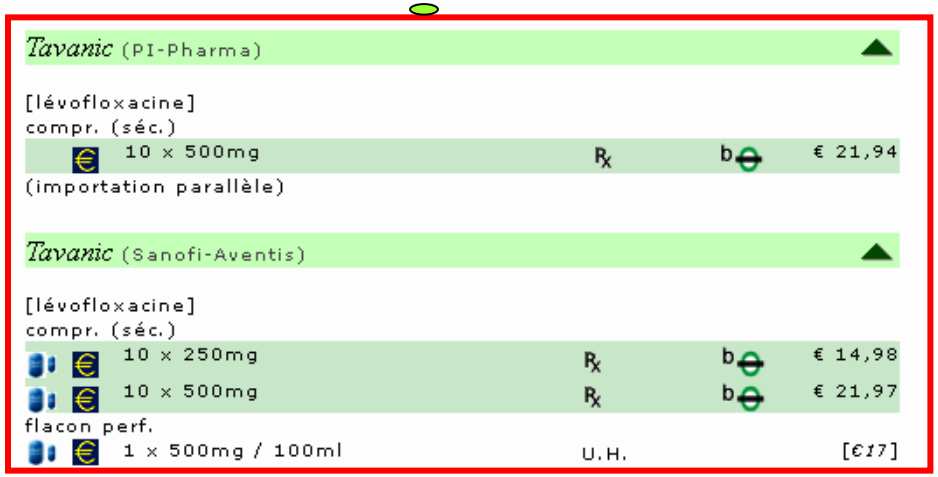
http://www.egagenerics.com/
Last visited: 4 April 2014

http://ec.europa.eu/health/human-use/index_en.htm
Last visited: 4 April 2014

http://www.fagg-afmps.be/fr/
Last visited: 4 April 2014

A well known antibiotic in Belgium…

Before patent expiration



Tavanic (PI-Pharma)

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

Tavanic (Sanofi-Aventis)

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

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm
Site as visited on 6 June 2013

A well known antibiotic in Belgium…

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]

After …

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.

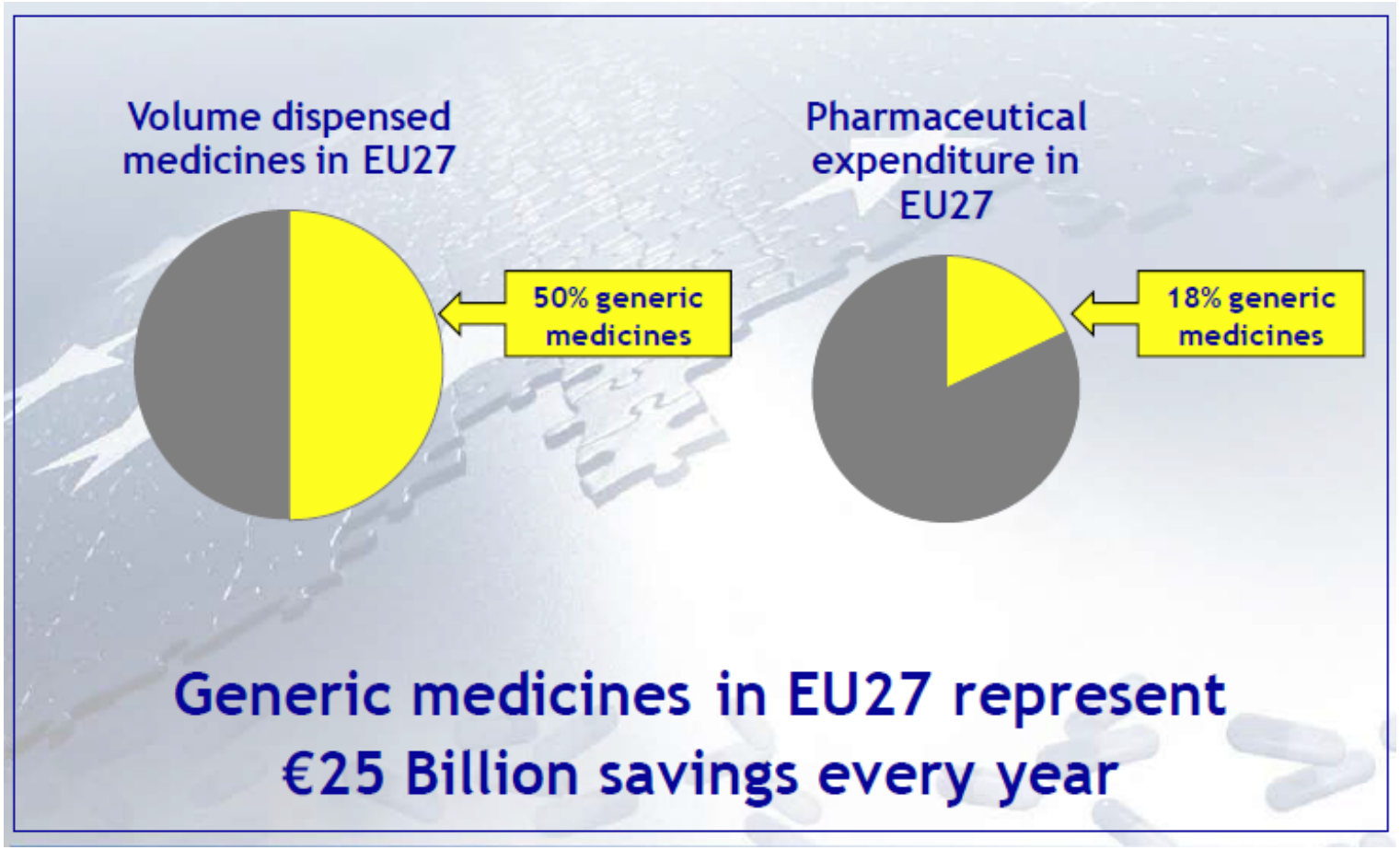
1 x 500mg / 100ml	U.H.	[€17]

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm
Site as visited on 6 June 2013

But why would you choose a "generic" drug ?

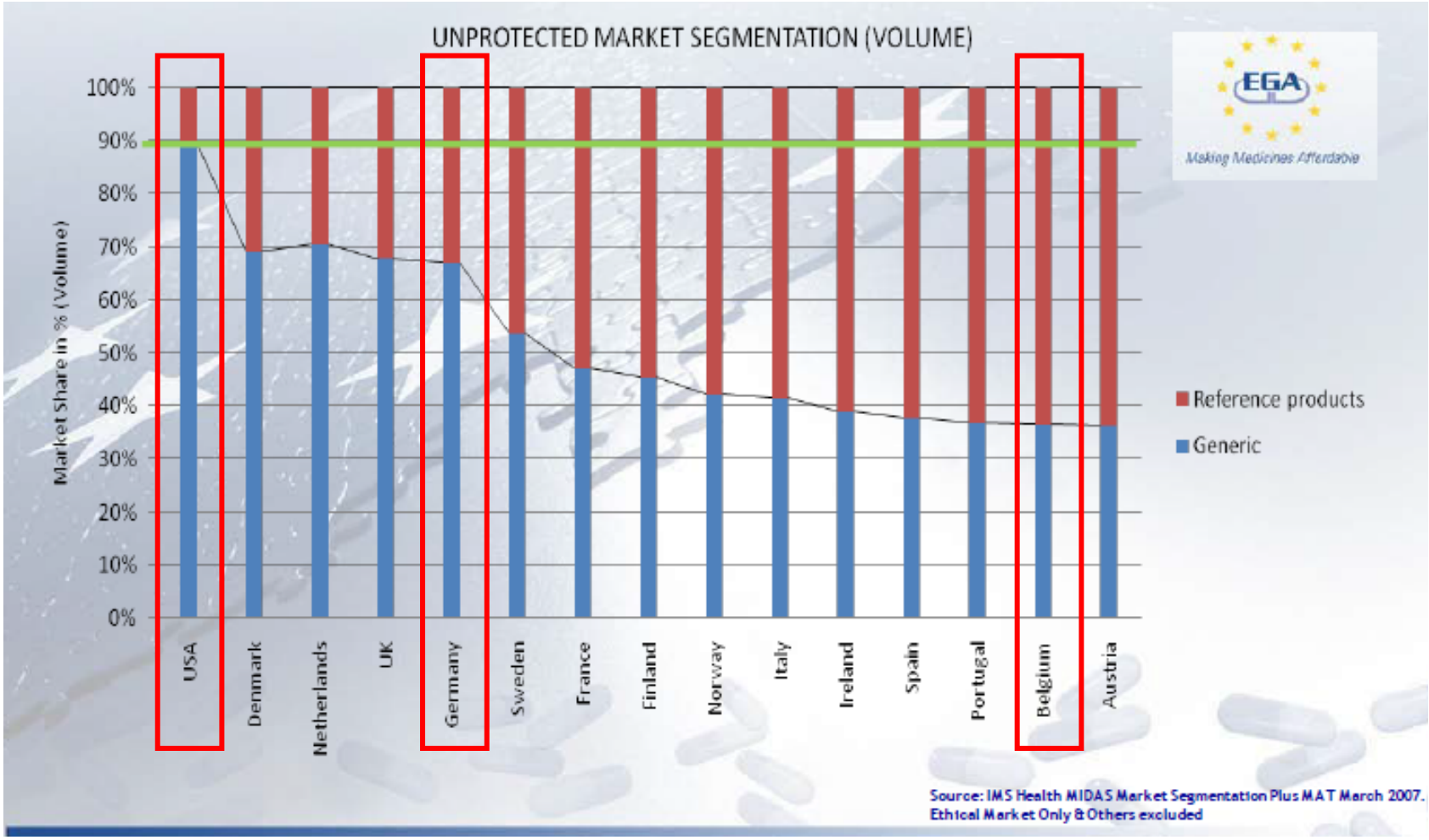
Because they are cheaper

But why would you choose a "generic" drug ?



Sustaining EU Healthcare Systems Through Sustainable Generic Competition
Greg Perry, EGA Director General - Brussels, 28 April 2009
http://www.febelgen.be/documents/FeBelGen-GME-Greg-Perry-090428.pdf
Last accessed: 16/03/2014

Are generics largely in all countries ?



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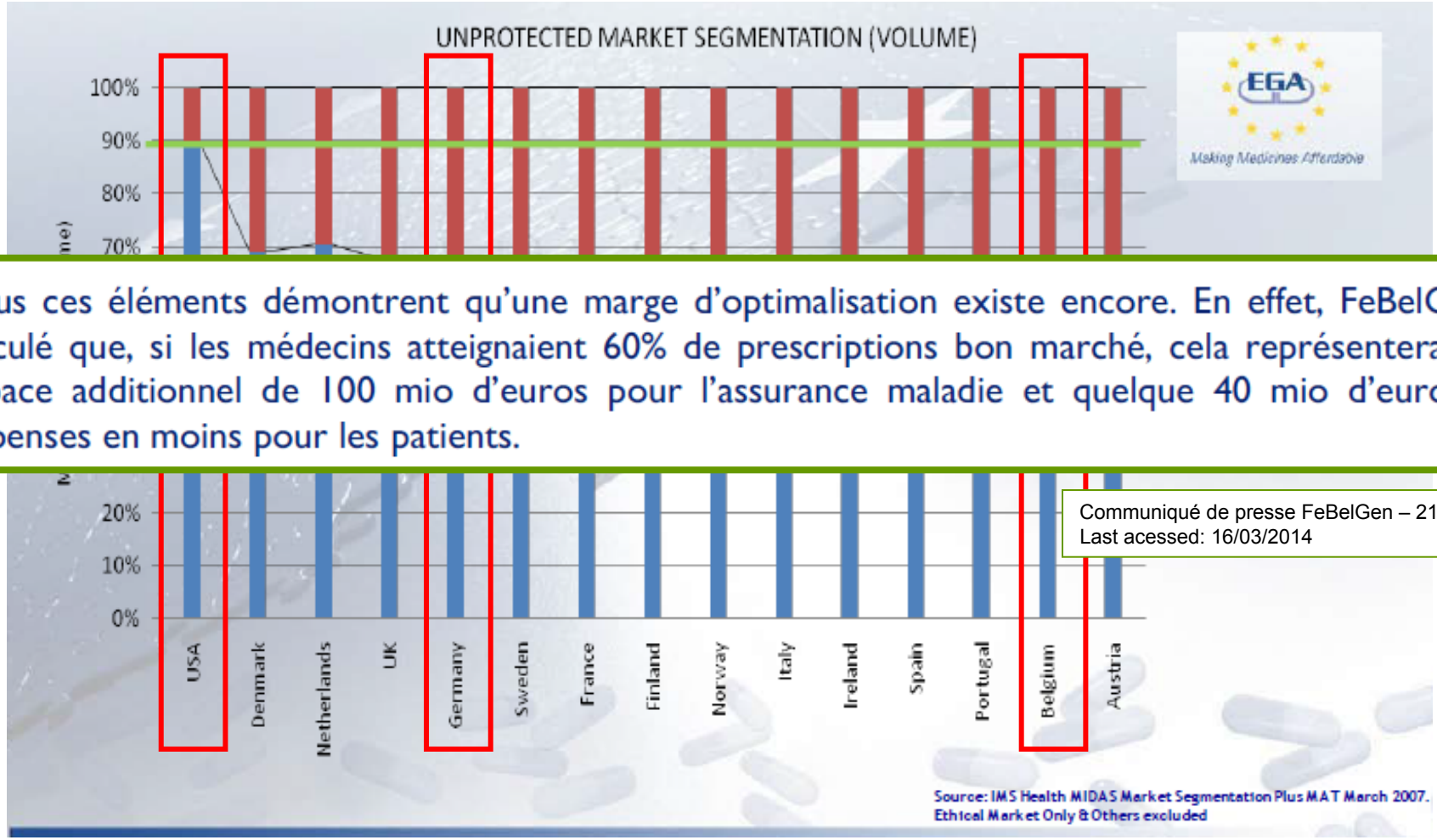


Tous ces éléments démontrent qu'une marge d'optimalisation existe encore. En effet, FeBelGen a calculé que, si les médecins atteignaient 60% de prescriptions bon marché, cela représenterait un espace additionnel de 100 mio d'euros pour l'assurance maladie et quelque 40 mio d'euros de dépenses en moins pour les patients.

Communiqué de presse FeBelGen – 21/09/2010
Last acessed: 16/03/2014

Sustaining EU Healthcare Systems Through Sustainable Generic Competition
Greg Perry, EGA Director General - Brussels, 28 April 2009
http://www.febelgen.be/documents/FeBelGen-GME-Greg-Perry-090428.pdf
Last accessed: 16/03/2014

What shall we discuss?

1. The US and the EU laws

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

The US Law

PUBLIC LAW 98-417—SEPT. 24, 1984 98 STAT. 1585

Public Law 98-417
98th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise the procedures for new drug applications, to amend title 35, United States Code, to authorize the extension of the patents for certain regulated products, and for other purposes.

Sept. 24, 1984
[S. 1538]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Drug Price Competition and Patent Term Restoration Act of 1984".

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

TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf
Last accessed: 4 April 2014

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

US "Abbreviated New Drug Application"

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm
Site as visited on 6 June 2013

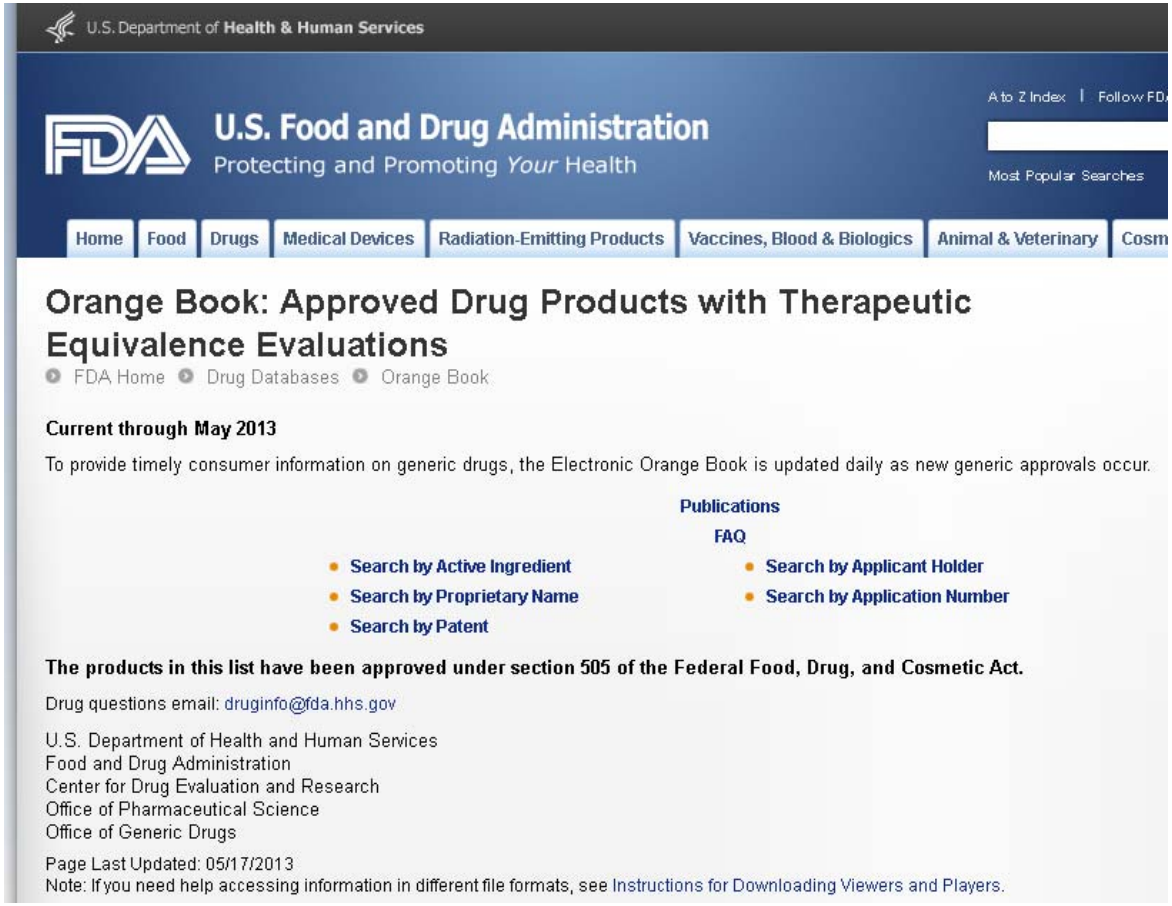
FDA requirements in a nutshell *

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

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

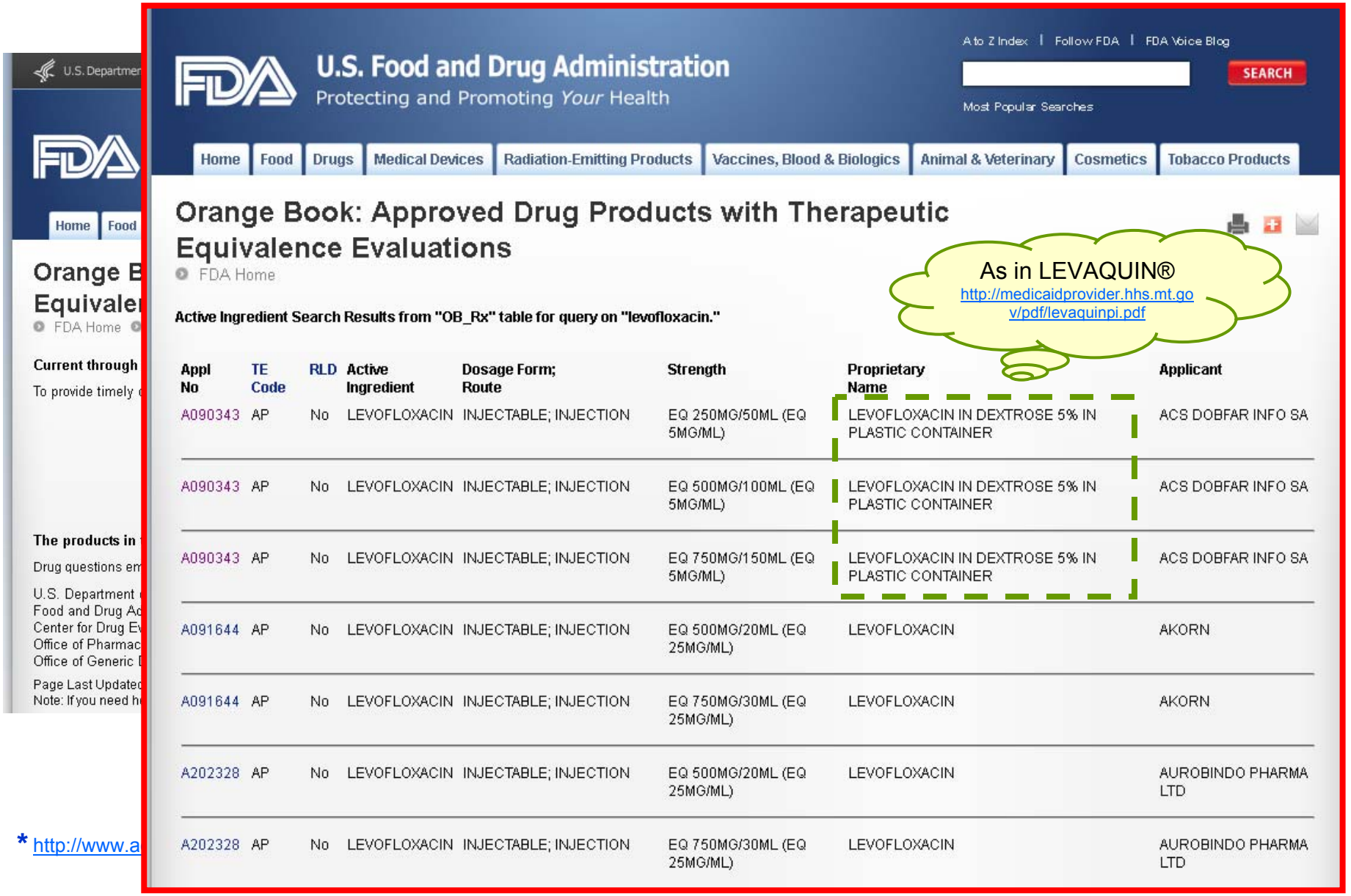
* 505 (B) (2) Application (Guidance to Industry)
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf
Last accessed: 4 April 2014

FDA approved generic drugs: "Orange book" *



* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
Site as visited on 6 June 2013

FDA approved generic drugs: "Orange book" *



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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home

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

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

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

* http://www.a

In the European Union

► B **DIRECTIVE 2001/83/EC * OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**

of 6 November 2001

on the Community code relating to medicinal products for human use

(OJ L 311, 28.11.2001, p. 67)

Amended by:

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

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

Site as visited on 6 June 2013 – This site has been modified since then but documents are still available through navigation

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

The EU Directive

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

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

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

What shall we discuss?

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

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

Bioequivalence: principles

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

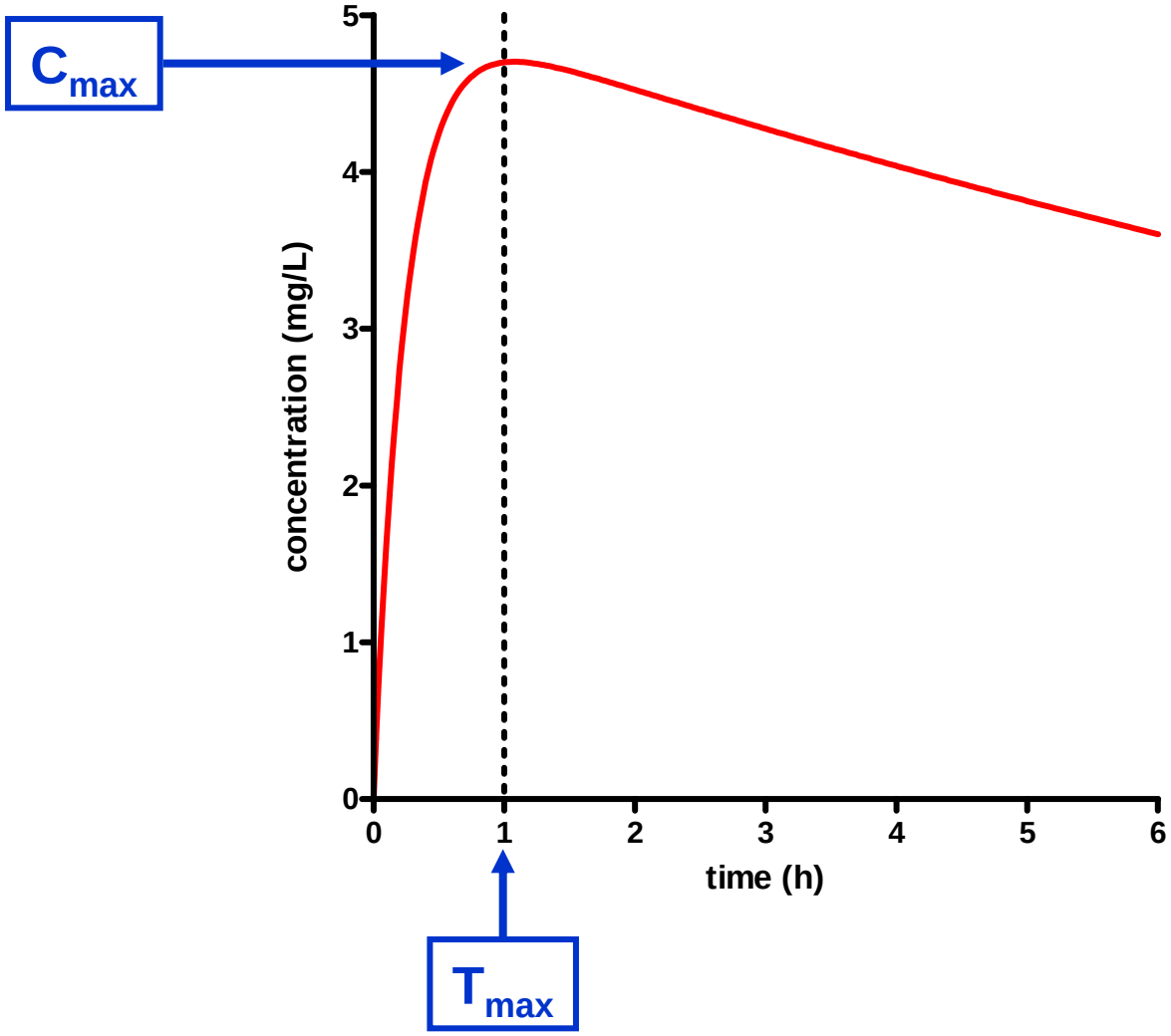
    → **extent of absorption**
  - **C_{max}** (the maximum plasma concentration of the active substance)

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

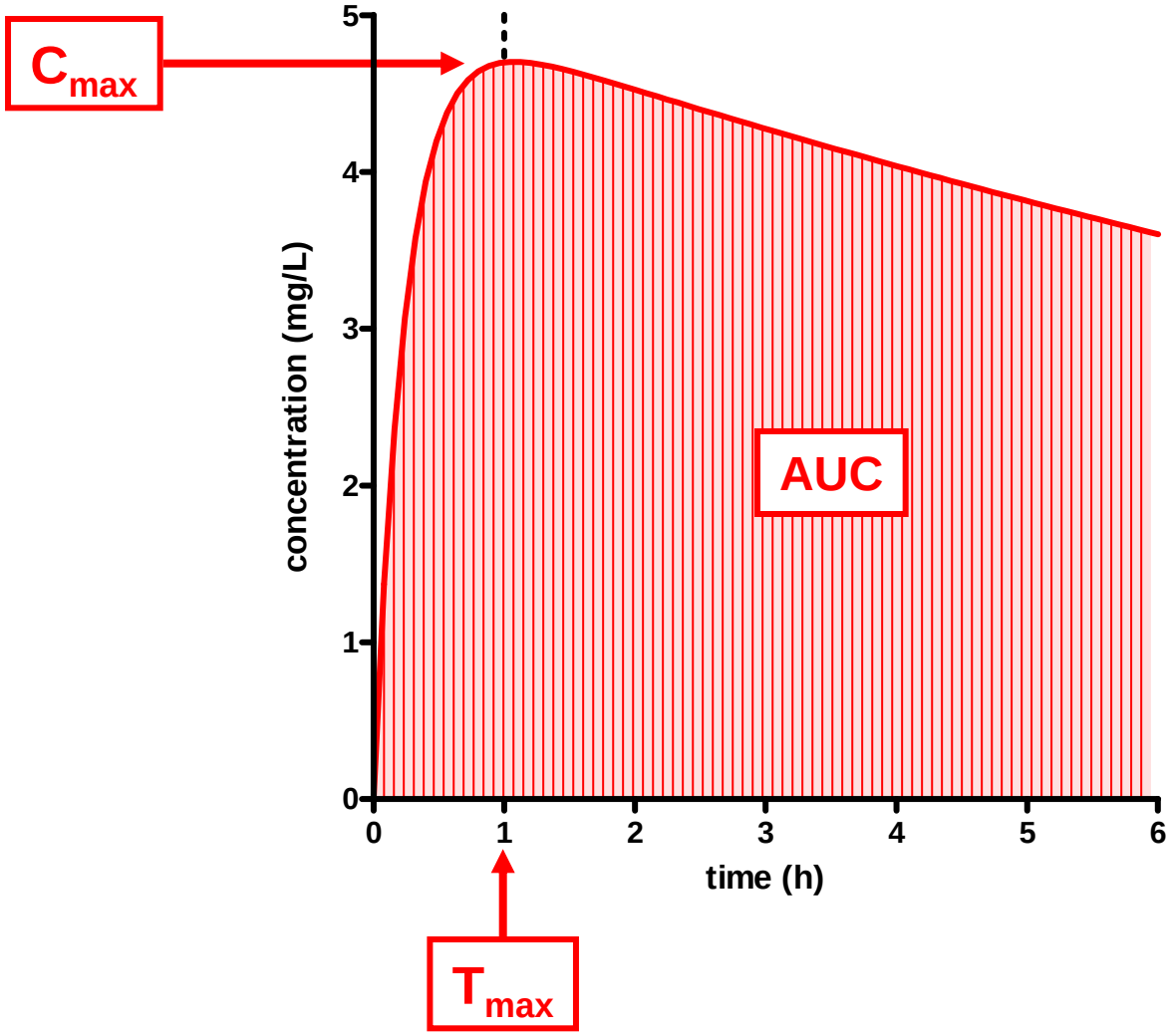
    → **rate of absorption**

1. Hauschke et al. Bioequivalence Studies in Drug Development – Methods and Applications, John Wiley & Sons Ltd. (UK), 2007.
2. Benet LZ: Understanding bioequivalence testing. Transplant.Proc. 31 (Suppl 3A): 7S-9S, 1999.
3. Niazi SK: Handbook of Bioequivalence Testing, "Drugs and the Pharmaceutical Sciences", vol. 171, Informa Healthcare (New York), 2007.

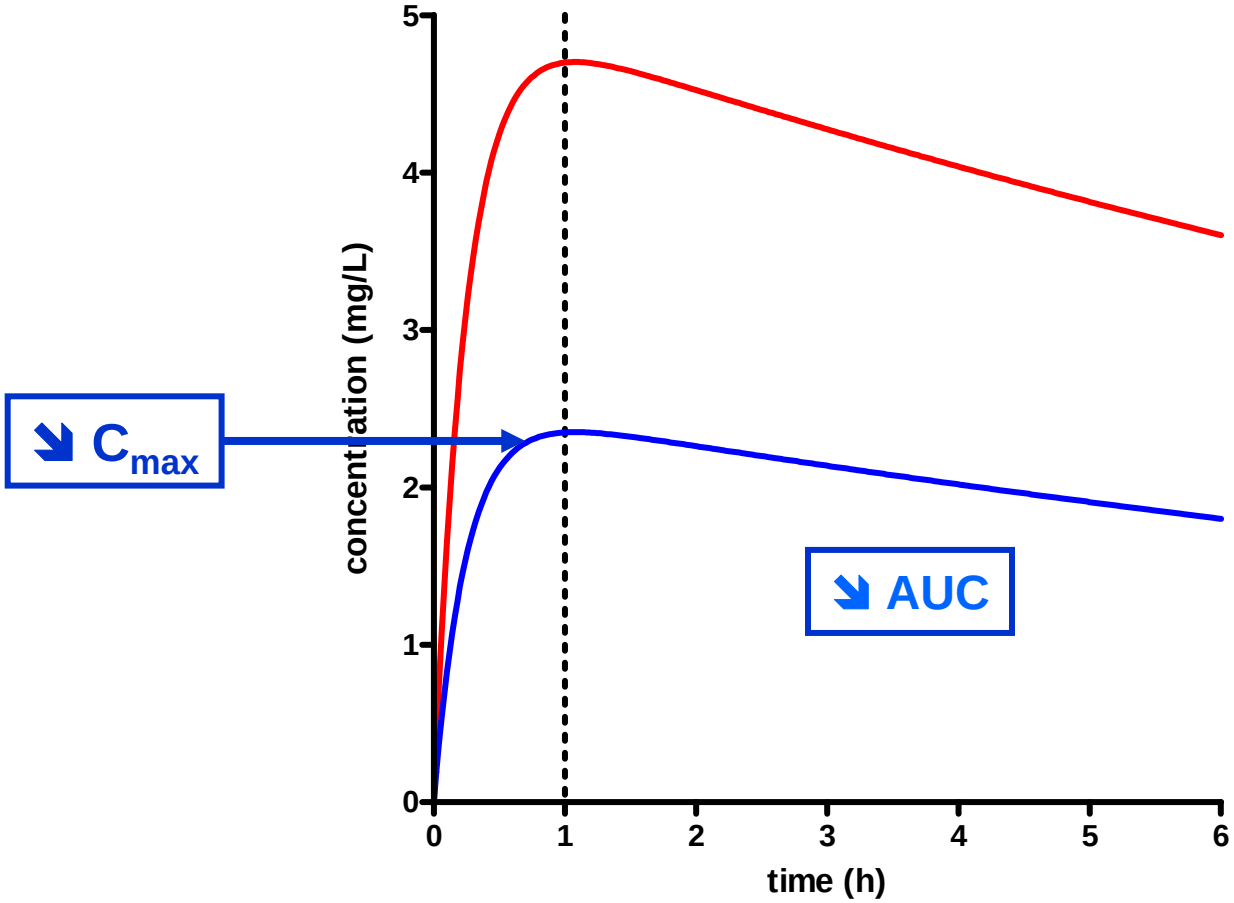
AUC – C_{max} – T_{max}



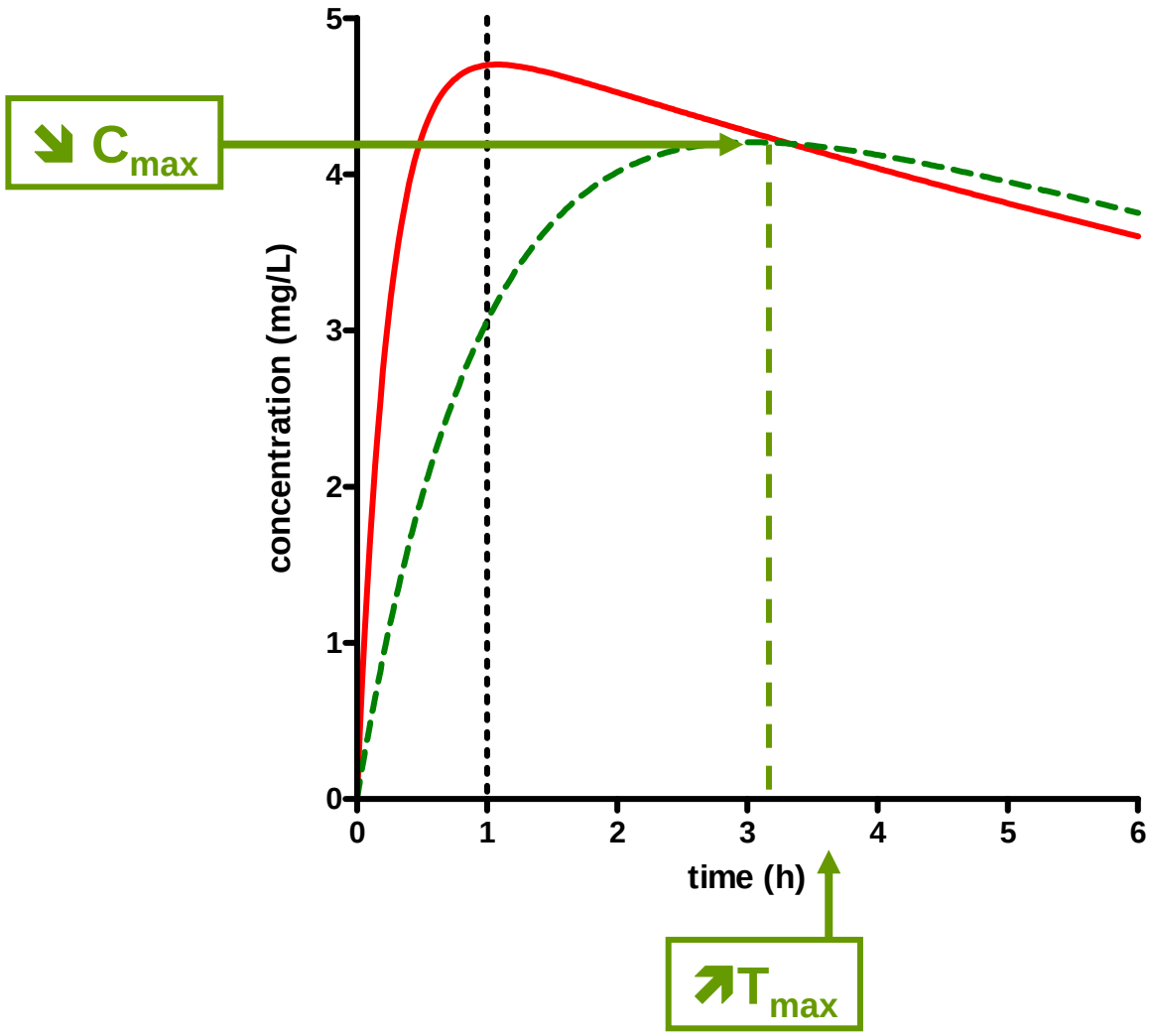
AUC – C_{max} – T_{max}



What if the absorption is decreased ?

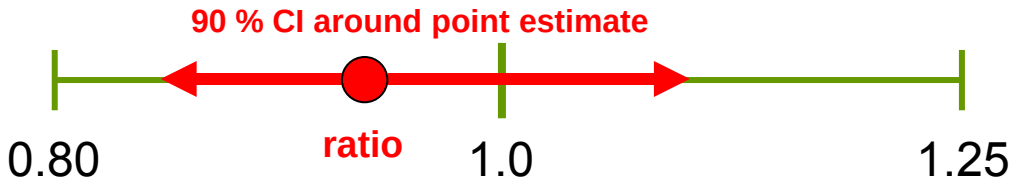


What if absorption is delayed ?



Criteria of bioequivalence (EMA* / FDA**)

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



Notes:

1. *if both **AUC** and C_{max} are within range, the generic should have the same bioavailability than the reference*
2. *statistical evaluation of T_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects (see next slide)*
3. *For drugs with narrow therapeutic index, EMA recommends "tightened acceptance inervals, Health Canada requires 0.9 – 1.12, but FDA accepts 0.8 – 1.25*

* Guideline to the Investigation of Bioequivalence, London, 20 January 2010 - Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf – Last accessed: 4 April 2014

** 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 – Last accessed: 4 April 2014
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052363.pdf – Last accessed: 4 April 2014

Is this enough ?

- Is PK-based bioequivalence (serum concentrations measured after extraction) a real surrogate of equitherapeutic effect(s) ?
- What about drugs with narrow therapeutic margins ?
- What about impurities, pharmaceutical aspects, and quality control (beyond the original dossier) ?

Even the Belgian authorities have some doubts...

"Prescription en Dénomination Commune Internationale (DCI)" : mise au point

- L'AFMPS déconseille le passage d'une spécialité à une autre du même groupe DCI (contenant la même molécule, le même dosage pour la même voie d'administration) en cours de traitement pour les molécules à marge thérapeutique étroite et/ou très toxiques et ceci par mesure de précaution, dans l'intérêt du patient et de la Santé publique (mention « no switch »). Il ne s'agit cependant pas d'une interdiction : si le « switch » doit malgré tout avoir lieu en cours de traitement, il est fortement conseillé que le patient soit suivi de manière rapprochée par le médecin.

- La notion de « no switch » pour les médicaments à marge thérapeutique étroite concerne de manière générale et au même niveau, le passage d'un innovateur à un innovateur, d'un innovateur à un générique, d'un générique à un innovateur ou d'un générique à un générique.

Mais aucun antibiotique n'est concerné *

http://www.fagg-afmps.be/fr/binaries/prescription-DCI-mise-au-point-FR-2010-06-11_tcm291-103015.pdf
Last accessed: 16/03/2014

* voir la liste des médicaments "no switch" dans les dias back-up

What shall we discuss?

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

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

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

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

Potency (piperacillin)

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

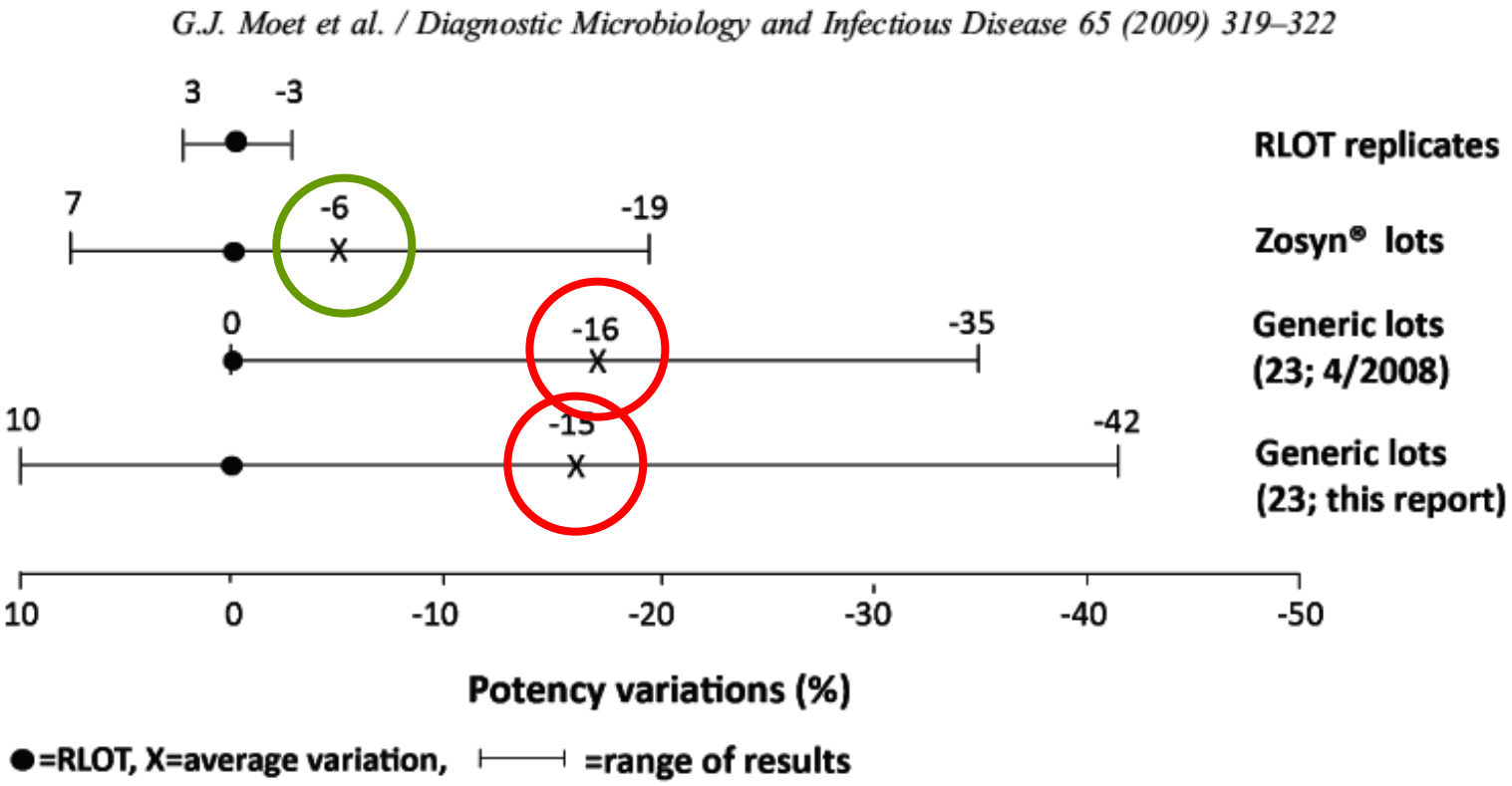


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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

MIC values (vancomycin)

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

Antibiotic	Pathogen (no.)	No. of generic markers	Nonidentical rate of the MIC value of all generics (mean ± SD)	MIC distribution (%) of the most different generic versus brand name drug						
				1/8	1/4	1/2	1[a]	2	4	8
Vancomycin	MRSA (90)	5	25.00 ± 15.52	–	–	–	54.4	45.6	–	–
Teicoplanin	MRSA (147)	7	28.09 ± 10.29	–	–	–	59.2	40.1	0.7	–
Cefotiam	*Staphylococcus aureus* (100)	7	8.71 ± 3.04	–	–	–	87.0	13.0	–	–
	Escherichia coli (100)	7	12.00 ± 5.89	–	–	–	77.0	22.0	1.0	–
Ceftriaxone	*Streptococcus pneumoniae* (126)	6	12.70 ± 4.77	–	–	–	81.7	18.3	–	–
Ceftazidime	*Pseudomonas aeruginosa* (100)	2	3.00 ± 2.83	–	–	–	95.0	5.0	–	–
Meropenem	*P. aeruginosa* (100)	7	18.57 ± 3.46	–	–	–	78.0	19.0	2.0	1.0
Imipenem	*P. aeruginosa* (100)	4	9.00 ± 2.58	–	–	–	88.0	11.0	1.0	–

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

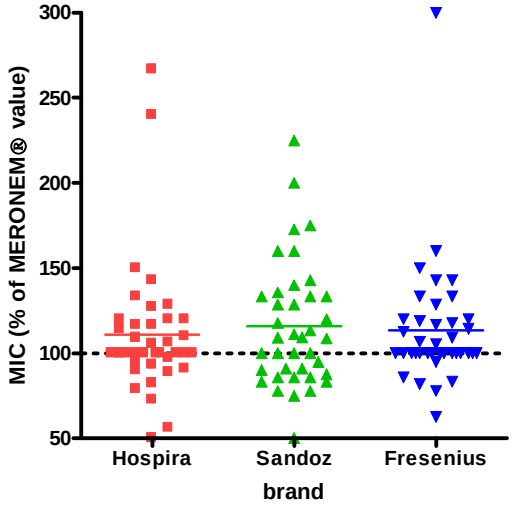
Fujimura & Watanabe J Infect Chemother (2012) 18:421–427

MICs were often higher than for the reference product…

MIC values (meropenem)

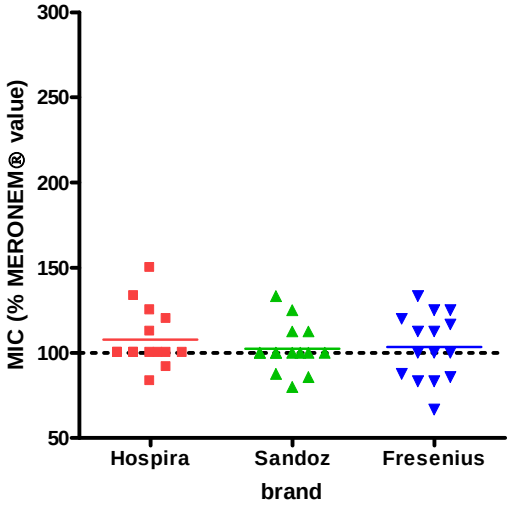
MICs determined by arithmetic dilutions for strains displaying MICs ranging from 0.125 to 128 mg/L (geometric values)

Susceptible strains (MIC ≤ 2 mg/L)



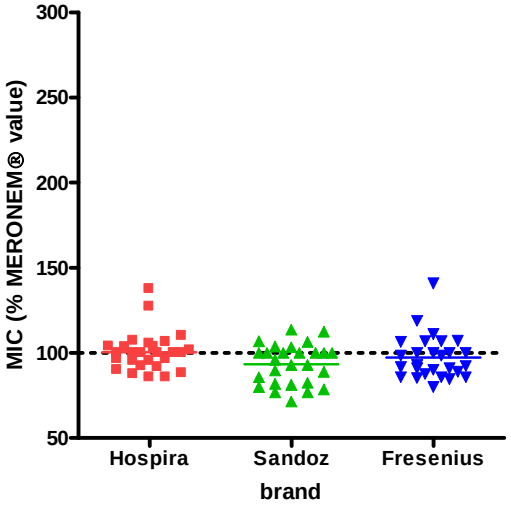
	Hospira	Sandoz	Fresenius
mean =	110.8	115.8	113.3
SD=	39.2	36.5	36.6

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



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

Resistant strains (MIC > 8 mg/L)



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

MERONEM® = meropenem commercialized by AstraZeneca

Van Bambeke *et al*., in preparation

Post-exposure hetero-resistance (vancomycin)

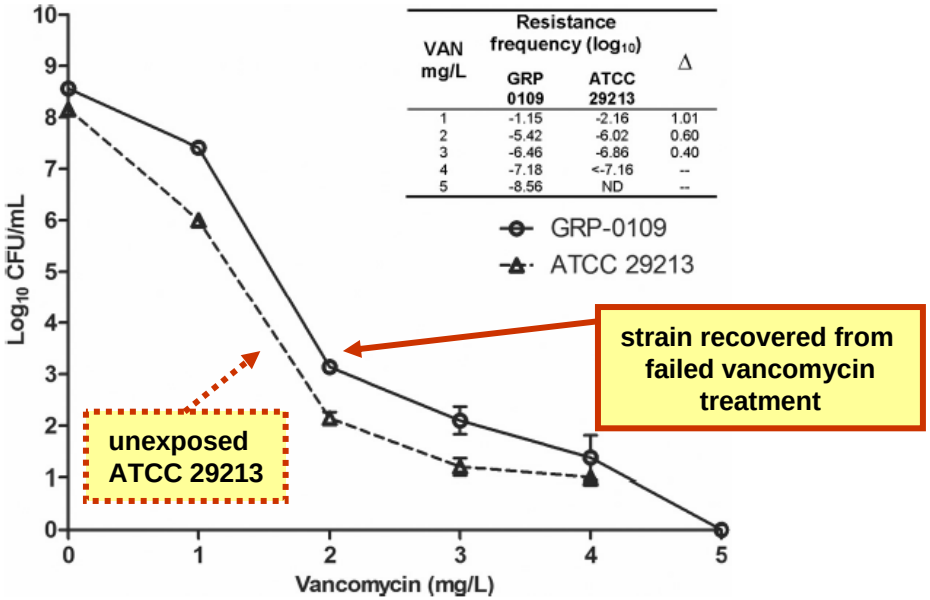
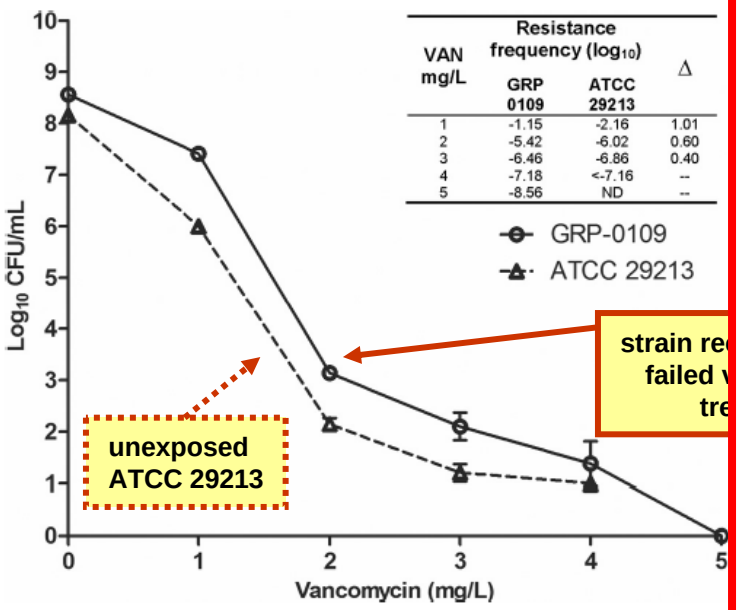


FIG 1 Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin,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

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

Post-exposure hetero-resistance (vancomycin)



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

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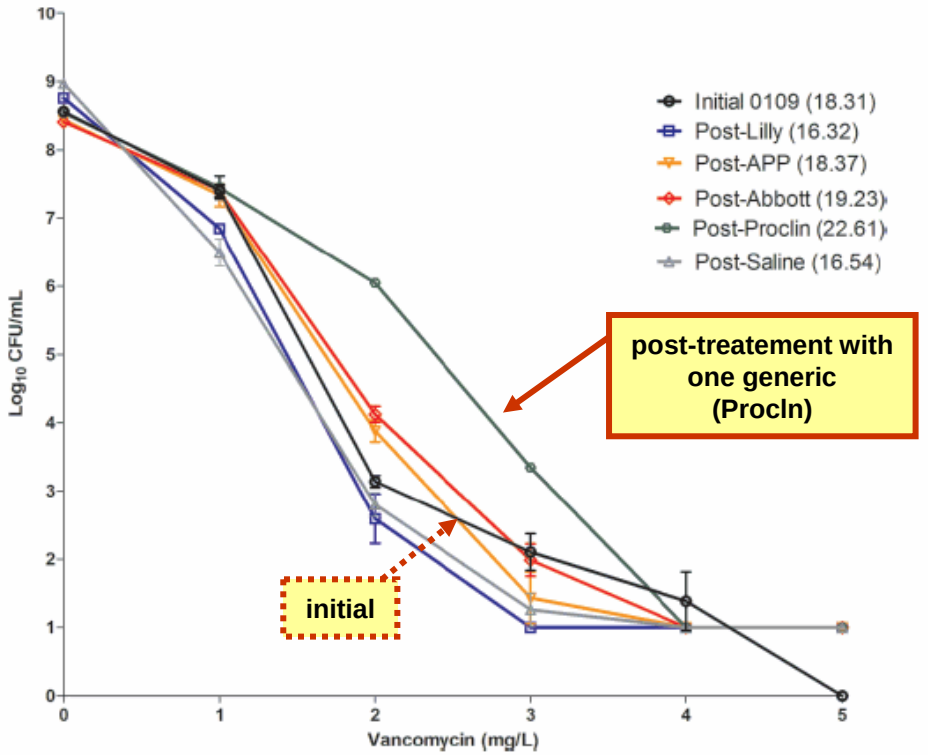

FIG 3 Pre- and postexposure PAP of *S. aureus* GRP-0109 (AUC in parentheses). Values for the initial isolate are plotted. Treatment with innovator vancomycin (Lilly) caused a down and left curve shift, indicating a reduction of the less susceptible subpopulations, which is sharply different from three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

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

Neutropenic thigh mouse model

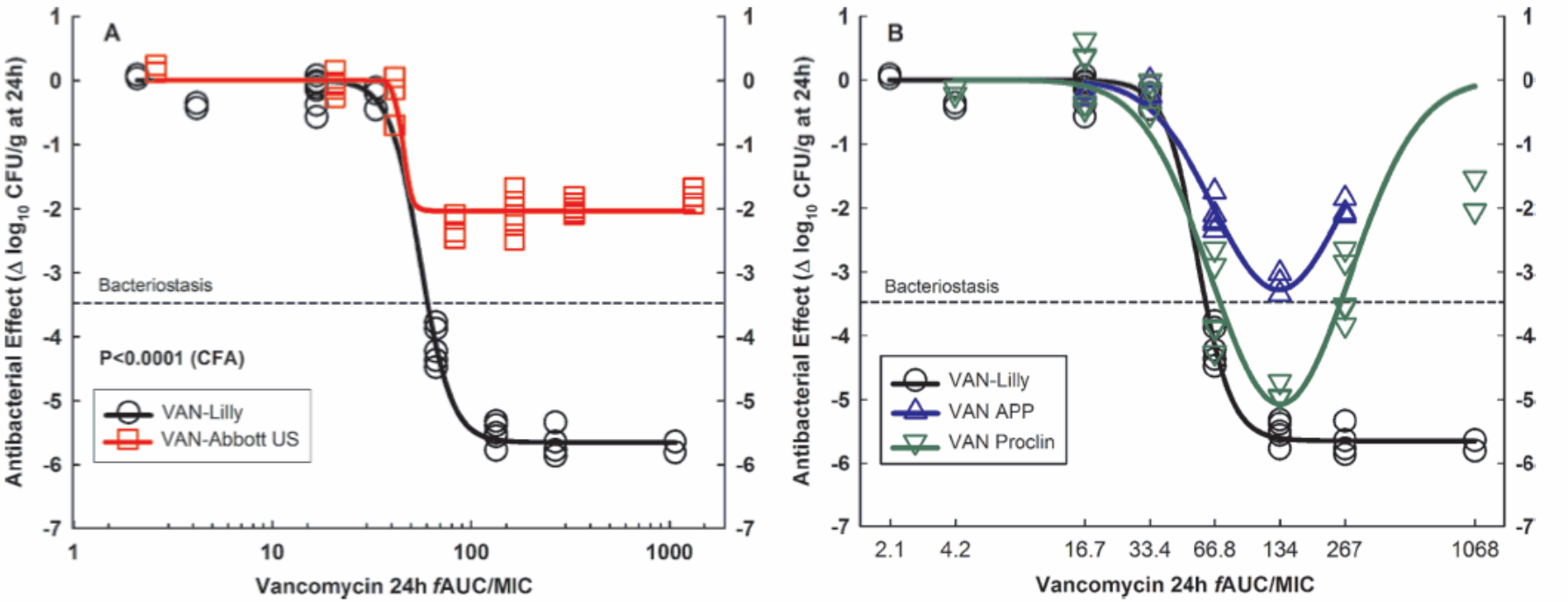

FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per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

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

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

Neutropenic thigh mouse model

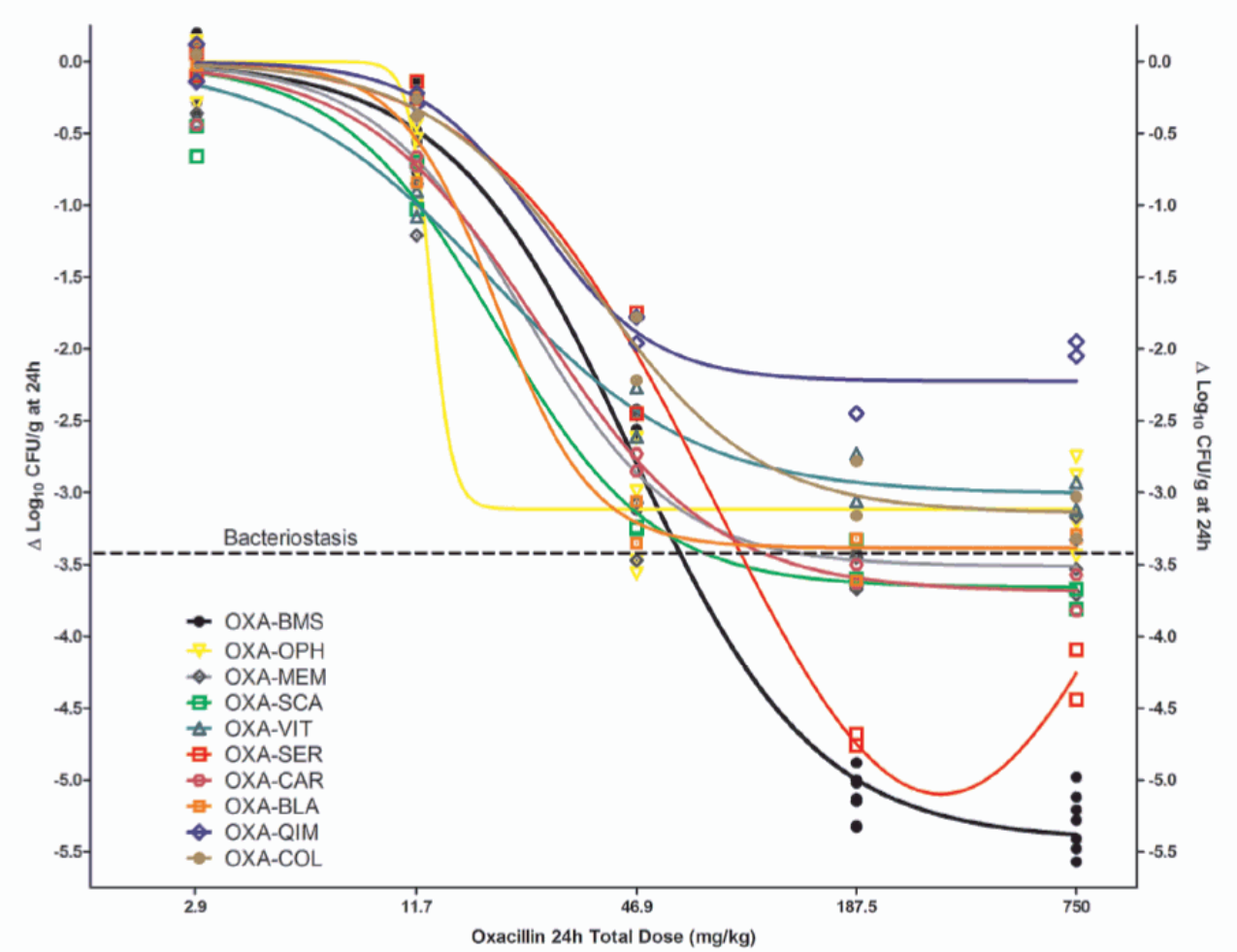

Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless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

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

Gentamicin: evidence of non-equivalence for survival in animals

Neutropenic thigh mouse model

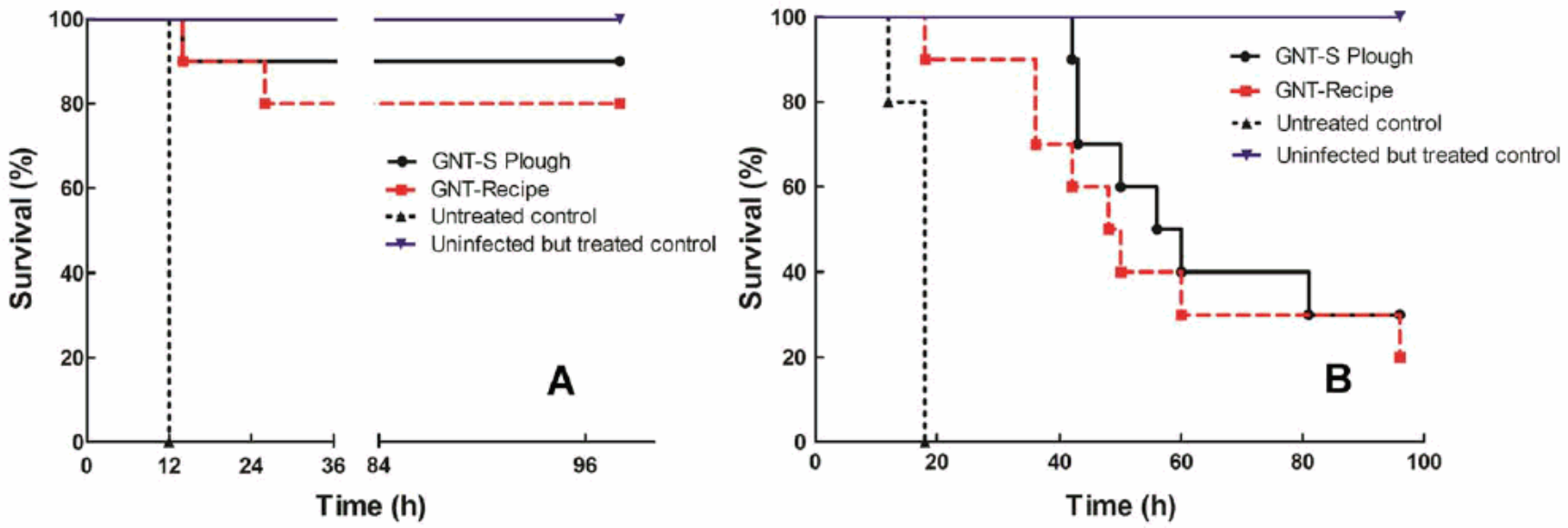

Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect (768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

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generic drugs with respect to brand formulation

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

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

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

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

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generi to brand formulation

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

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

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

CONCLUSION

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

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

ACKNOWLEDGMENTS

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

And what about pharmaceutical quality ?

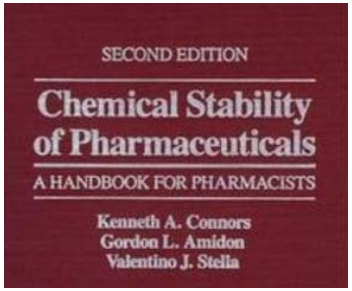
Three simple questions:

1. the generic must have the same solubility / dispersion properties than the original
2. the generic cannot contain more impurities (or give rise to more degradation products) than the original
3. The real content must be controlled

What shall we discuss ?

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

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



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

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

Dissolution of meropenem in Japan

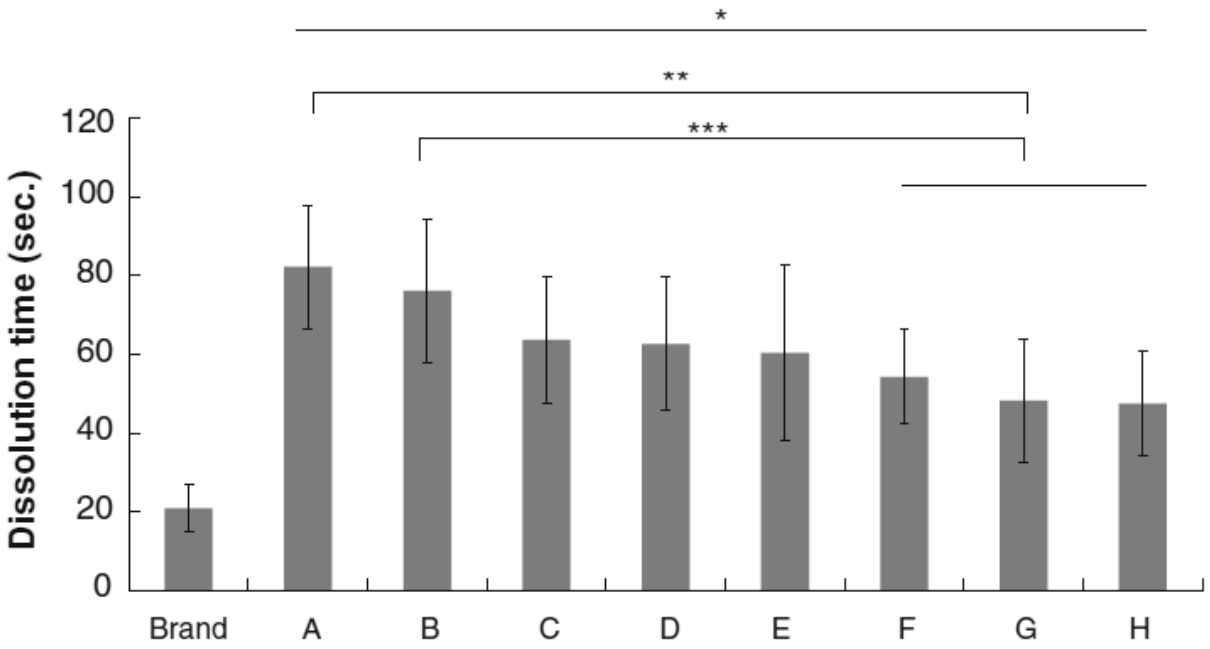


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

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

Crystals size of meropenem (Japan)

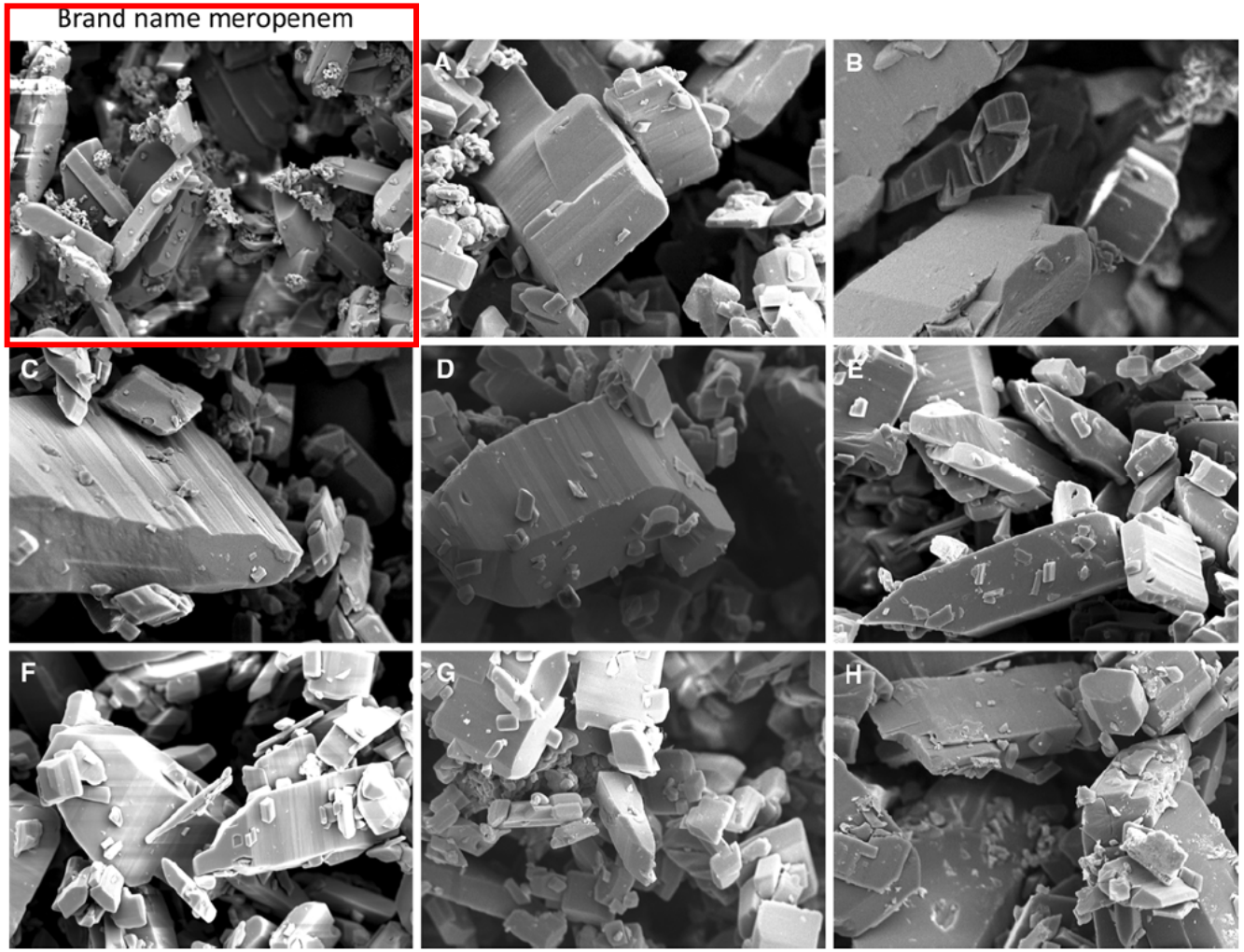
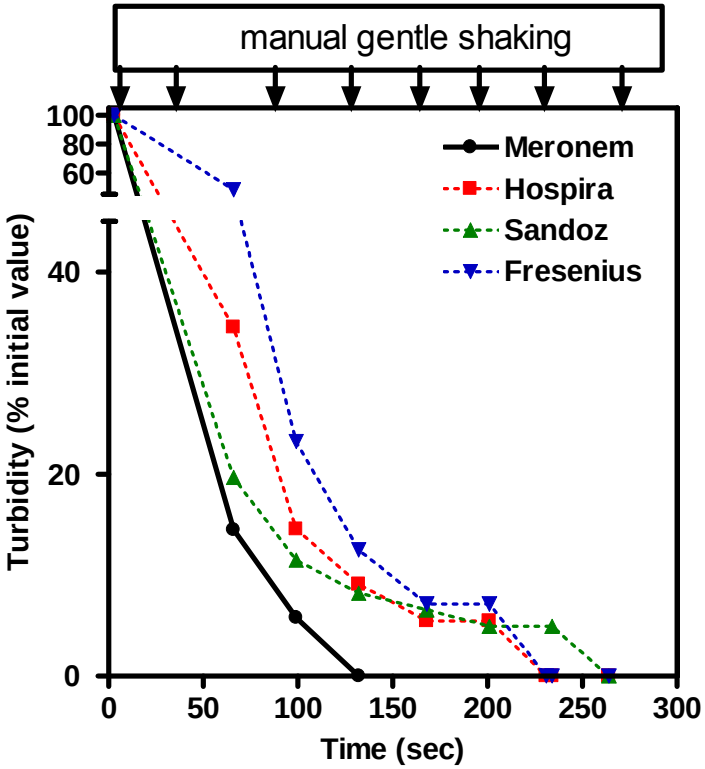


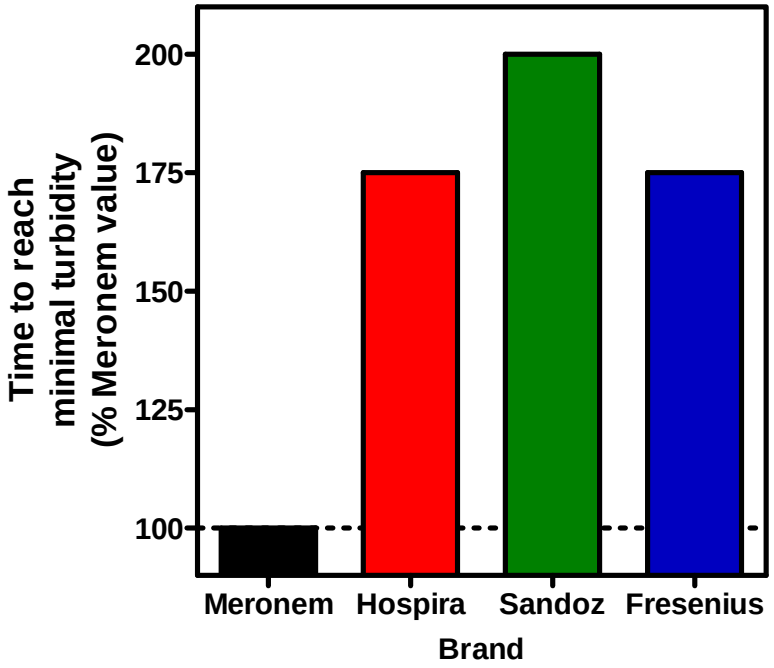
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

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

Dissolution of meropenem in Belgium

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





Van Bambeke *et al*., in preparation

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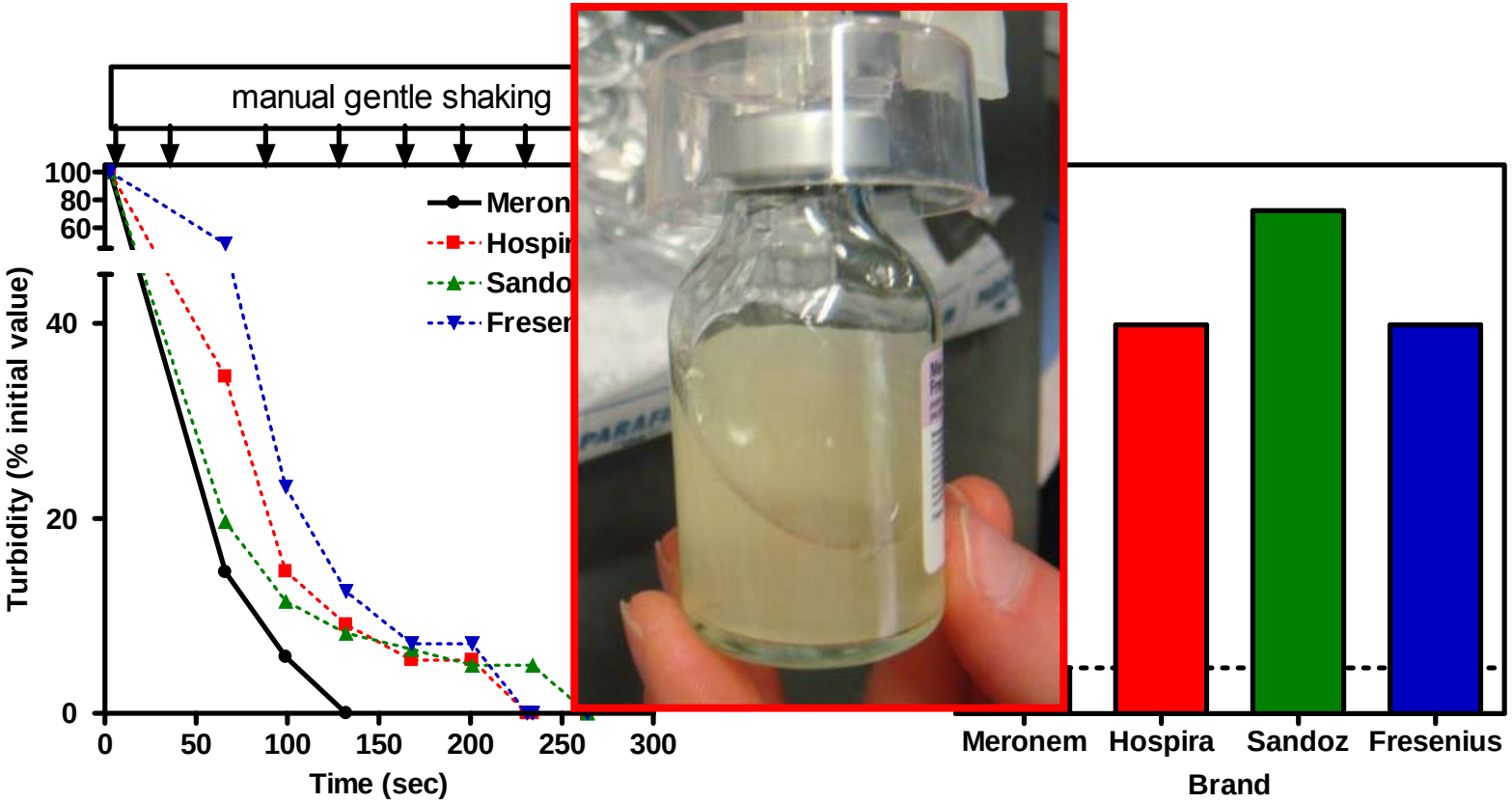
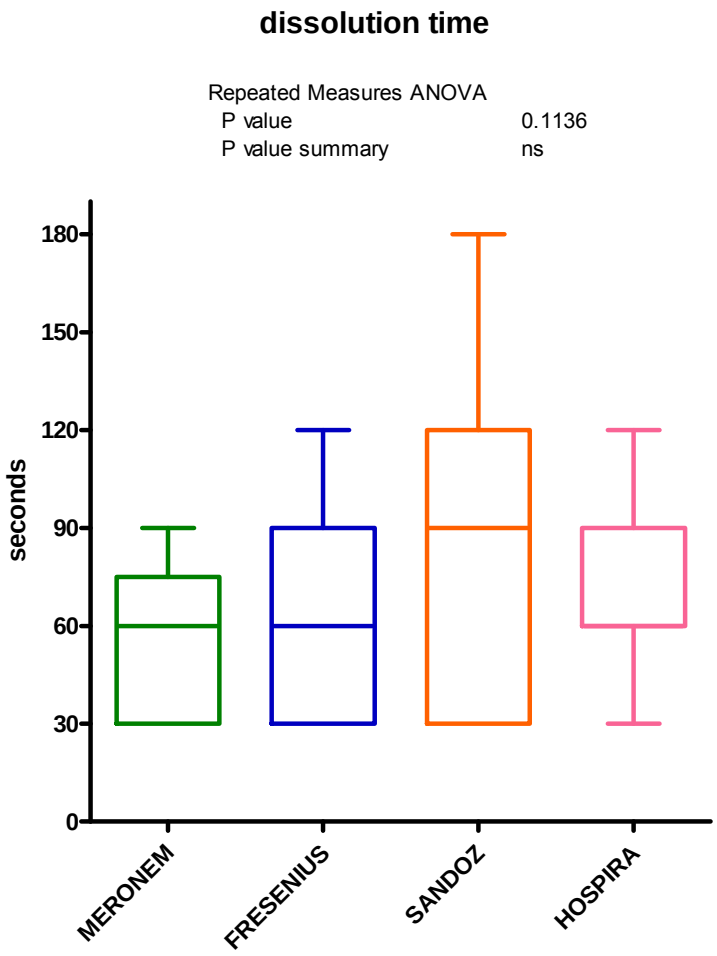
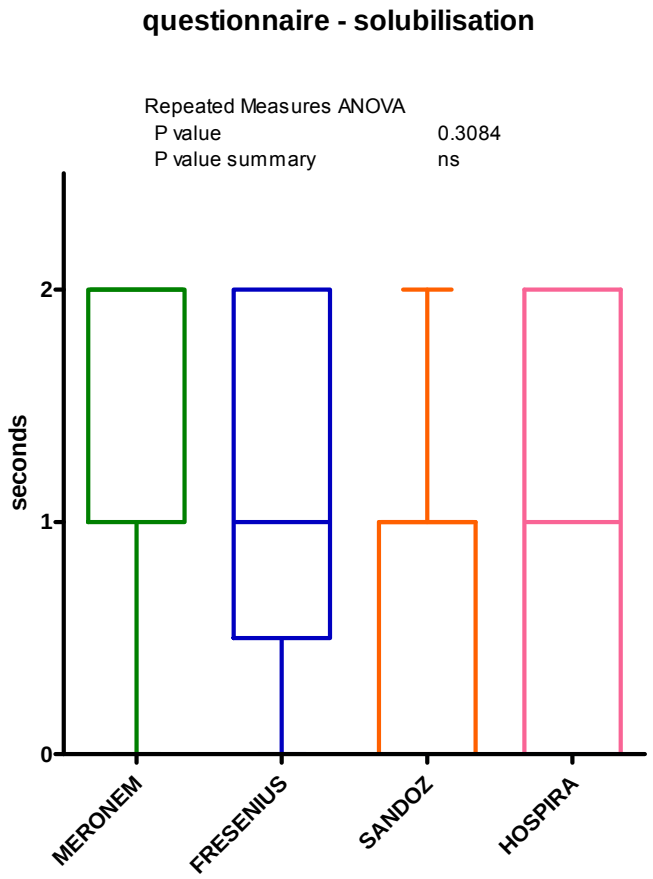


Van Bambeke *et al*., in preparation

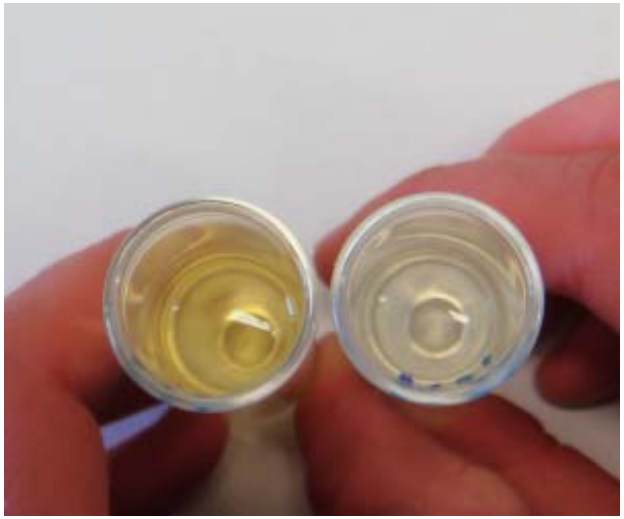
Are Primary Health Care Professionals (nurses) happy? (meropenem)





Van Bambeke *et al*., in preparation

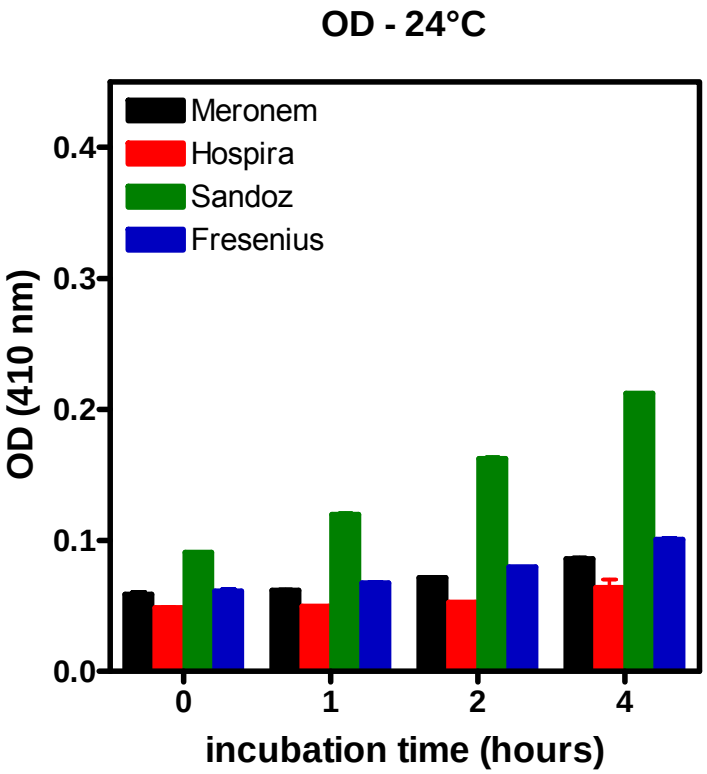
Impurities in meropenem: coloured compounds

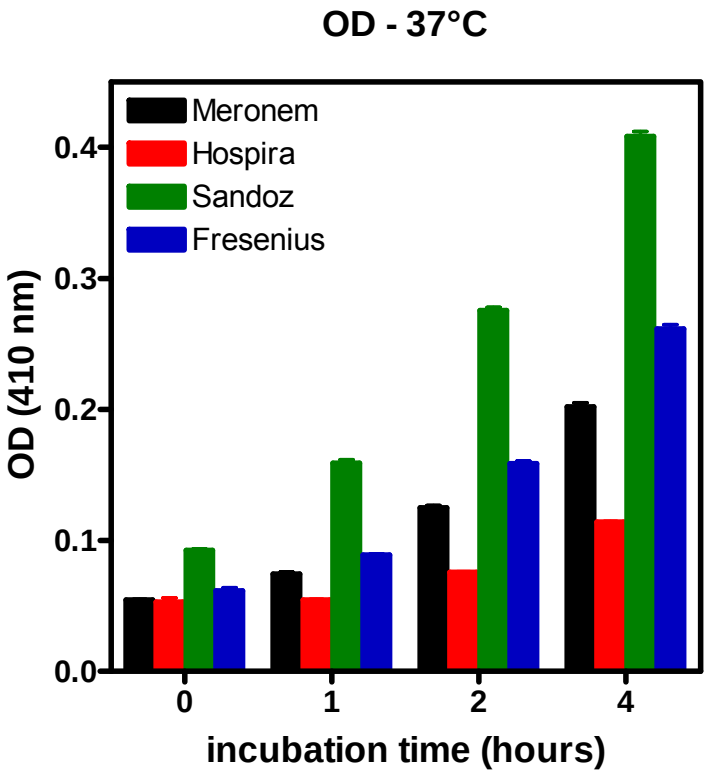


are you happy with the colour?

Van Bambeke *et al*., in preparation

Impurities in meropenem: coloured compounds





Van Bambeke *et al*., in preparation

Substandard (wrong) drugs in the world ?

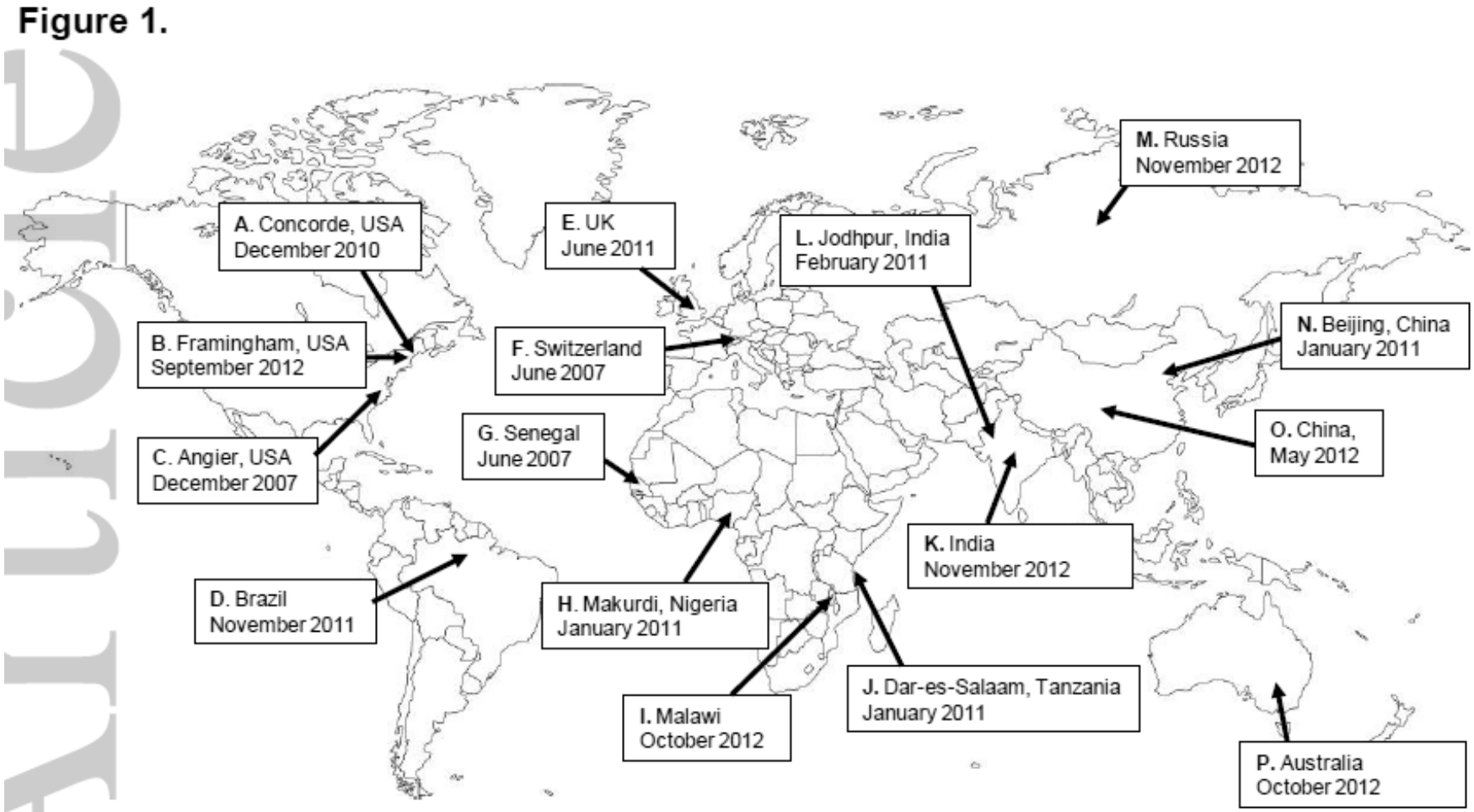


Figure 1. Examples of recent accounts of substandard drugs around the world

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

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)

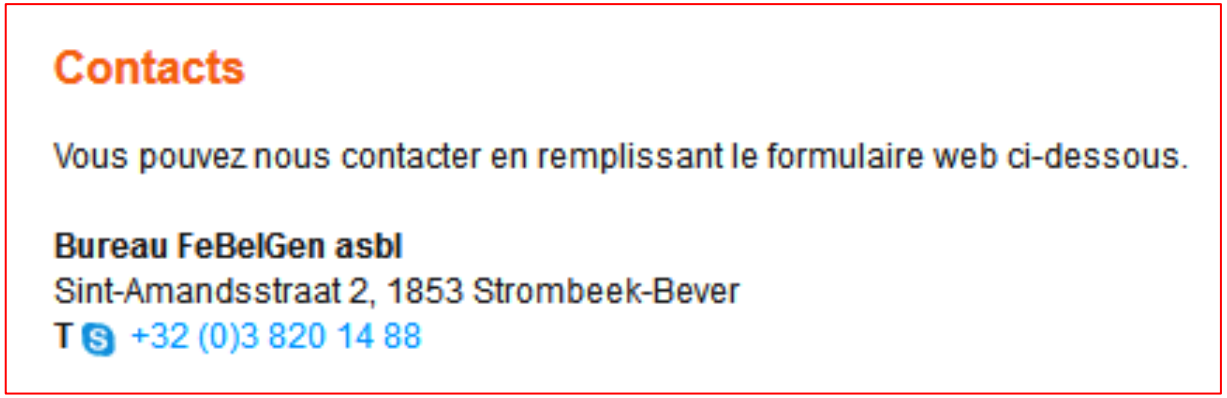
http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
Last visited: 4 April 2014

with an immediate follow-up from the Industry

http://www.egagenerics.com/index.php/publications
Last visited: 4 April 2014

An unanswered question in Belgium...

Le 16 mars 2014, j'ai interrogé FeBelGen (via leur site web) pour savoir quelle était la régularité des contrôle de qualité (entre lots et en cas de changement d'origine des produits)



Je n'ai pas eu de réponse jusqu'aujourd'hui (4 avril 2014)

What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
    1. MIC, MPC, heteroresistance …
    2. Approach to pharmacodynamic equivalence
    3. PK/PD animal models and clinical data
4. Dissolution, stability, impurities
5. **The hidden risks of "low cost" drugs**
    1. **overconsumption**
    2. **lack of innovative research ...**
       and research for those who pay ...

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

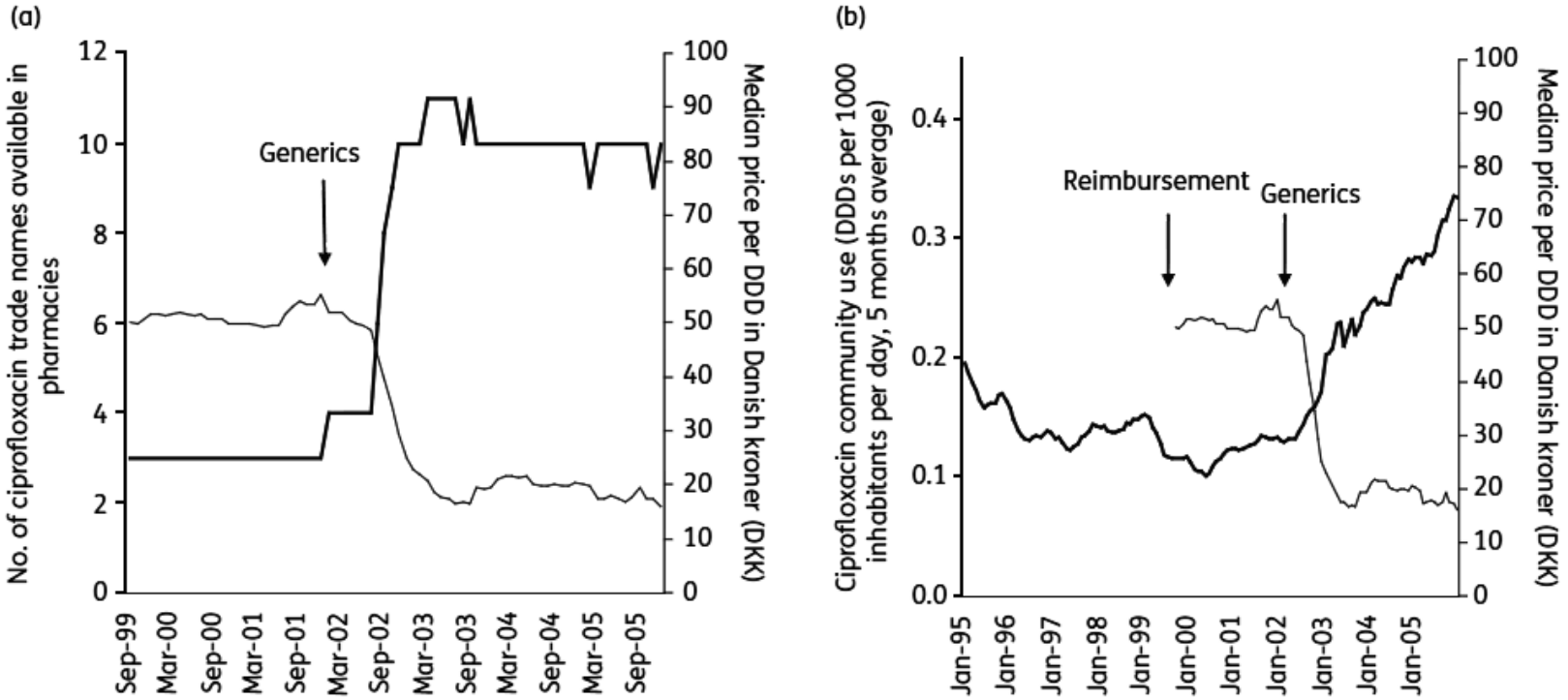
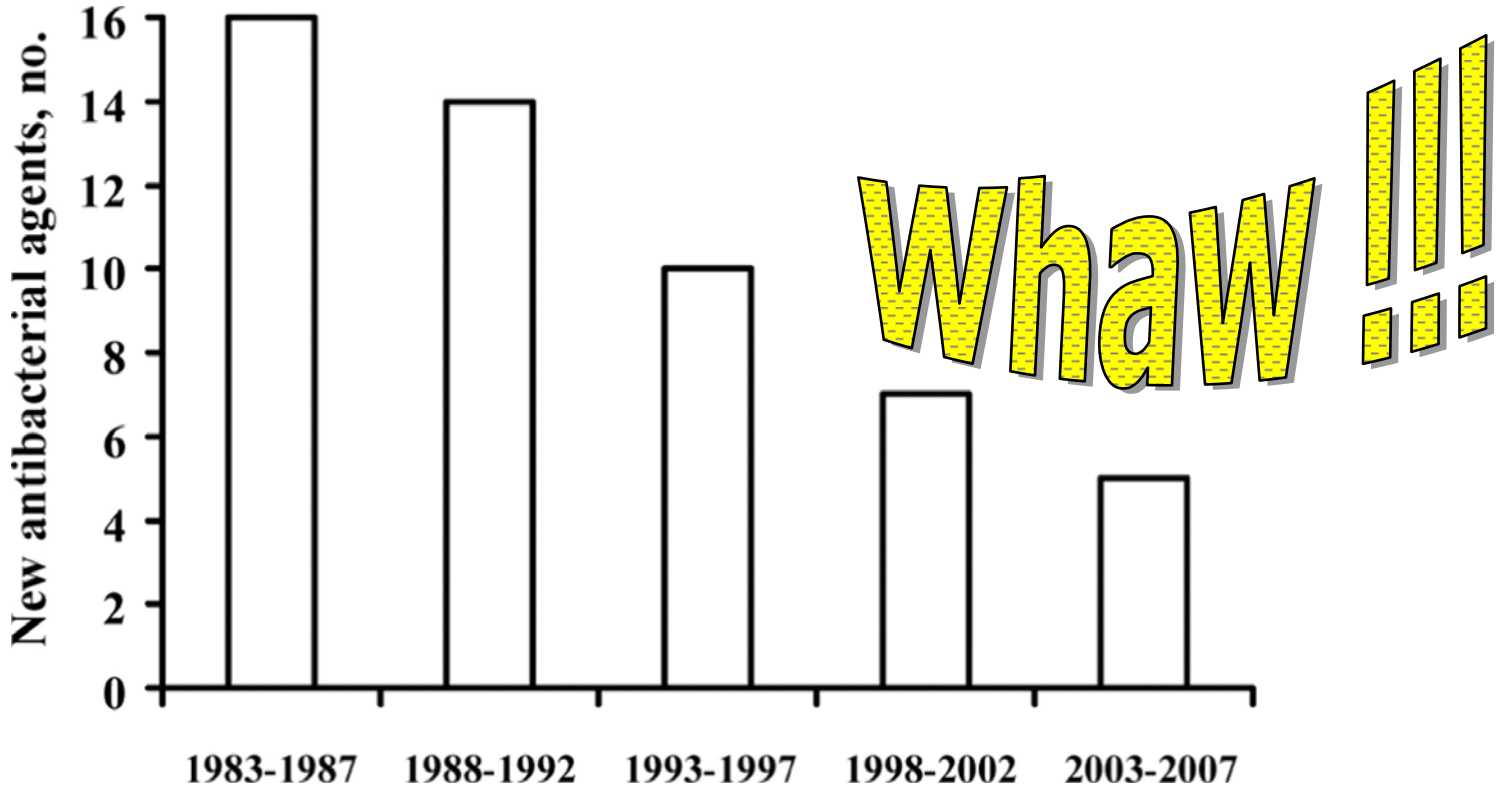


Figure 1. (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin. (b) The influence of removal of 50% reimbursement and of the introduction of generics on the total use of ciprofloxacin and median price per DDD registered monthly in PHC in Denmark (thin line). Consumption (thick line) is expressed in terms of DDDs per 1000 inhabitants per day. The arrows mark the times of removal of reimbursement of ciprofloxacin and the introduction of generic versions, respectively. 100 DDK≈13 EUR.

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

Innovative antibiotic development is abandoned



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

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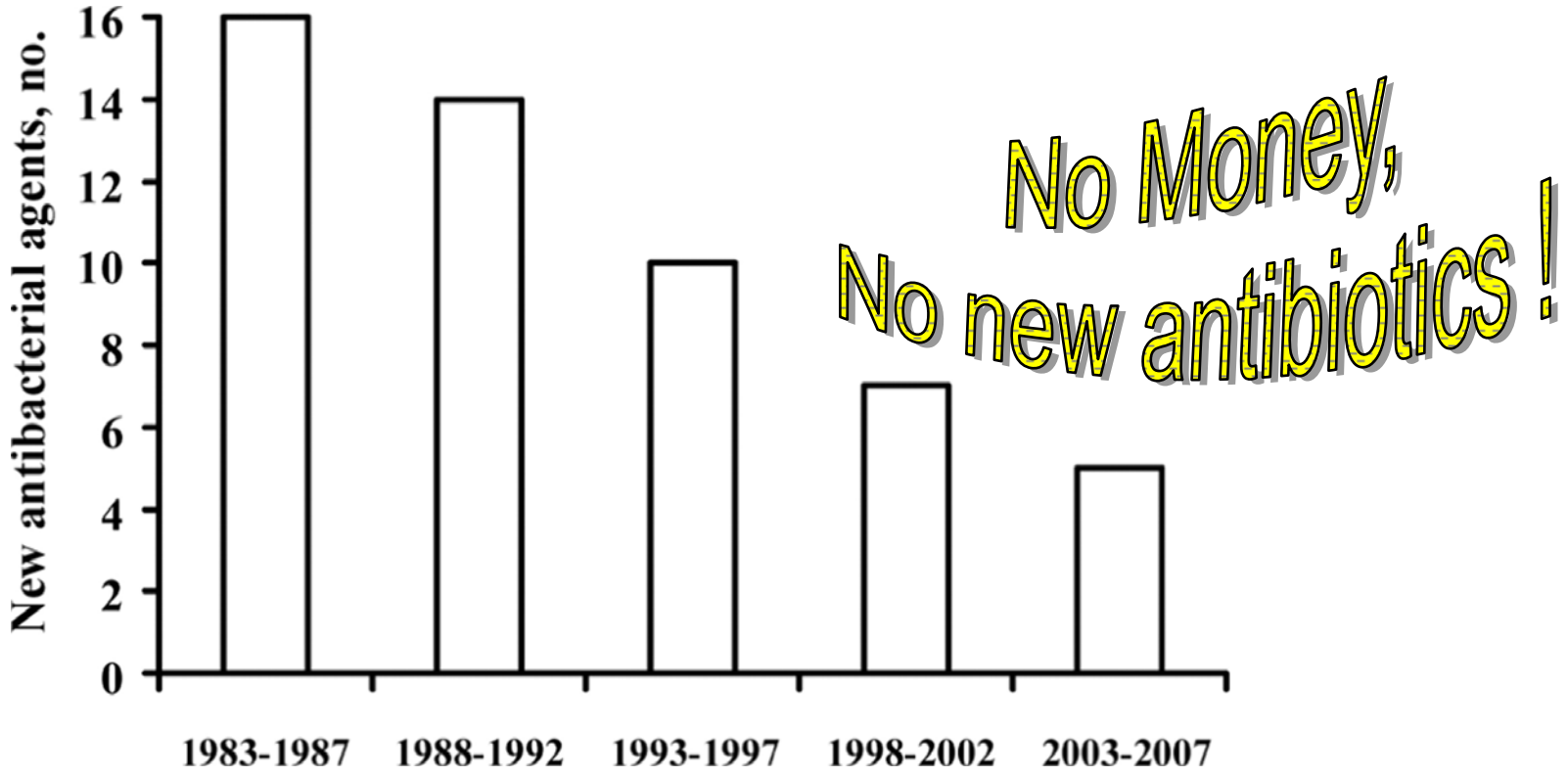

Boucher H W et al. Clin Infect Dis. 2009;48:1-12

A spiral to death (in Belgium) ?

- Pour les **antibiotiques** et les **antifongiques**, si un médecin/dentiste prescrit un antibiotique ou un antimycosique pour un **traitement aigu** :
  - sous le principe actif : les règles de la prescription sous DCI sont d'application
  - sous un le nom de la marque : **à partir du 1er mai 2012**, le pharmacien doit délivrer dans le groupe des « **médicaments les moins chers** ».

http://www.inami.fgov.be/drug/fr/drugs/general-information/antibiotic/index.htm
Last visited: 4 April 2014

- Le coût médicamenteux d'une **pneumonie communautaire** suivant les **recommandations BAPCOC** (amoxicilline [3 g par jour en 3 prises pendant 5-7j] n'atteint plus que **13-14 €** … (prix ex.usine: ~7 €)

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_A.cfm
Look for amoxicillin – Last visited: 4 April 2014

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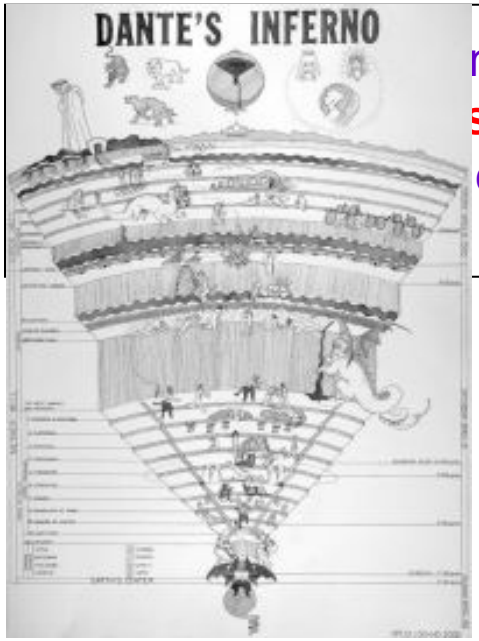

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http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_A.cfm

Cette spirale infernale entraine
le départ de tous les innovateurs…

The "Qualy" of antibiotics (*)

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

---

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

Unless Big Brother comes to your help…

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

Date: May 22, 2013

Company: GlaxoSmithKline of North Carolina

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

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

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

Press Release: HHS forms strategic alliance to develop new antibiotics

will this ever be available to YOUR patients

http://www.piersystem.com/go/doc/3803/1863406/
Last accessed: 4 April 2014

But EU is not too bad either

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

LATEST NEWS

04/04/2014 : RT @EFPIA: It's Friday... That means... NEW EFPIA NEWSLETTER!!! Take a read - and have a great Friday!

Back to overview

COMBACTE

Combatting Bacterial Resistance in Europe

ND4BB COMBACTE

Summary

Antimicrobial resistance (AMR) is a growing problem worldwide, and with few new drugs making it to the market, there is an urgent need for new medicines to treat resistant infections. Enter the IMI-funded COMBACTE project, which aims to give antibiotic drug development a much-needed boost by pioneering new ways of designing and implementing efficient clinical trials for novel antibiotics. COMBACTE forms part of the New Drugs for Bad Bugs (ND4BB) initiative, IMI's wider programme to tackle AMR.

more

Facts & Figures

Start Date	01/01/2013
Duration	84 months

Contributions	**€**
IMI funding	109 433 010
EFPIA in kind	133 922 382
Other	7 200 000
Total cost	250 484 591

http://www.imi.europa.eu/content/combacte
Last accessed: 4 April 2014

How can you COMBA(c)T(e) ?

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
Last visited: 4 April 2014

EU is funding selected hospitals and institutions for research on new antibiotics

COMBACTE
Combatting Bacterial Resistance in Europe

Participant Name	IMI Funding in €
AO Documentation and Publishing Foundation, Clinical	57 934
Centre Hospitalier Régional Universitaire de Besançon	4 380
Centre Hospitalier Universitaire de Limoges	10 887 942
CHU de Pointe-à-Pitre	360 120
Cliniques Universitaires Saint Luc	364 500
Consorci Institut D'Investigacions Biomediques August Pi i Sunyer	57 934
Eberhard Karls Universitaet Tuebingen	1 111 050
Erasmus Universitair Medisch Centrum Rotterdam	818 553
Ernst Moritz Arndt University Greifswald	711 788
Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico	57 934
Fundacio Centre De Recerca en Salut International de Barcelona	2 482 931
Helmholtz-Zentrum fuer Infektionsforschung GmbH	6 475 656
Hospices Cantonaux CHUV	100 500
Institut National de la Santé et de la Recherche Médicale	56 002 833
Instituto Nacional de Saude Dr. Ricardo Jorge	57 934
Julius Clinical Research BV	7 463 907
Linkopings Universitet	57 934
North Bristol National Health Service Trust	100 500
Servicio Andaluz de Salud	422 434
Servicio Madrileno de Salud	57 934
Stichting Katholieke Universiteit / Radboud University Nijmegen	145 500
Tel-Aviv Souraski Medical Center	57 934
Universitätsklinikum Freiburg	439 526
Universitätsklinikum Köln, AöR (University Hospital of Cologne)	422 434
Universite Claude Bernard Lyon 1	933 140
Université de Genève	4 949 263
Universite Joseph Fourier, Centre de Recherche Inserm/UJF	81 900
University Medical Center Utrecht	8 843 905
University of Antwerp	5 846 776
University of Athens Medical School	57 934
TOTAL	109 433 010

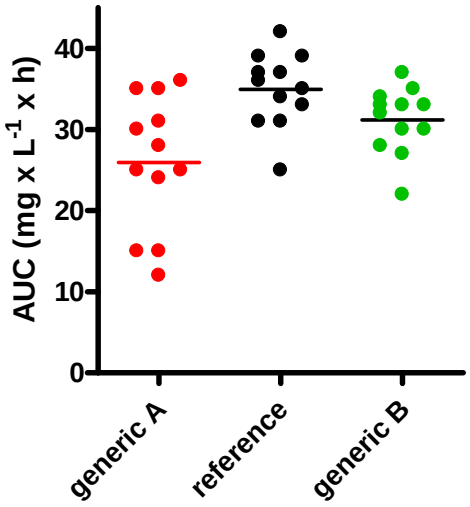
http://www.imi.europa.eu/sites/default/files/uploads/documents/6th_Call/COMBACTEv3_update%20with%20new%20participants_VP.pdf
Last accessed: 4 April 2014

Summary / Suggestions

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

Back-up

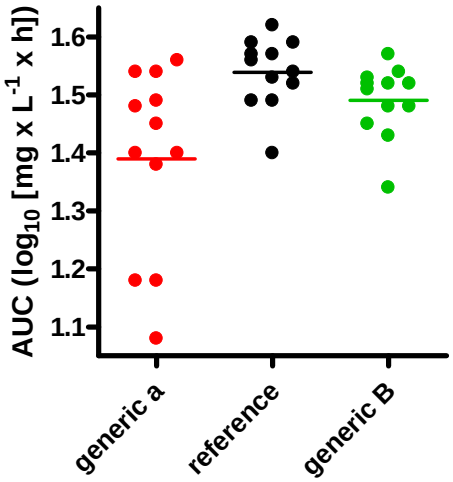
Are generic really comparable ?



	generic A	reference	generic B
Number of values	12	12	12
Minimum	12.00	25.00	22.00
25% Percentile	19.50	32.00	29.00
Median	26.50	35.50	32.50
75% Percentile	33.00	38.00	33.50
Maximum	36.00	42.00	37.00
Mean	25.92	34.92	31.17
Std. Deviation	8.262	4.542	4.064
Std. Error	2.385	1.311	1.173
Lower 90% CI	21.63	32.56	29.06
Upper 90% CI	30.20	37.27	33.27

arithmetic comparison

geometric comparison



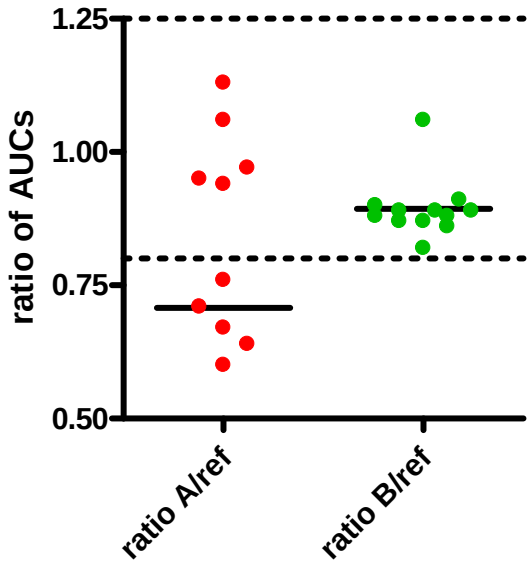
	generic a	reference	generic B
Number of values	12	12	12
Minimum	1.080	1.400	1.340
25% Percentile	1.280	1.505	1.465
Median	1.425	1.550	1.515
75% Percentile	1.515	1.580	1.525
Maximum	1.560	1.620	1.570
Mean	1.390	1.539	1.491
Std. Deviation	0.1596	0.05931	0.06142
Std. Error	0.04607	0.01712	0.01773
Lower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

Are generic really comparable ?

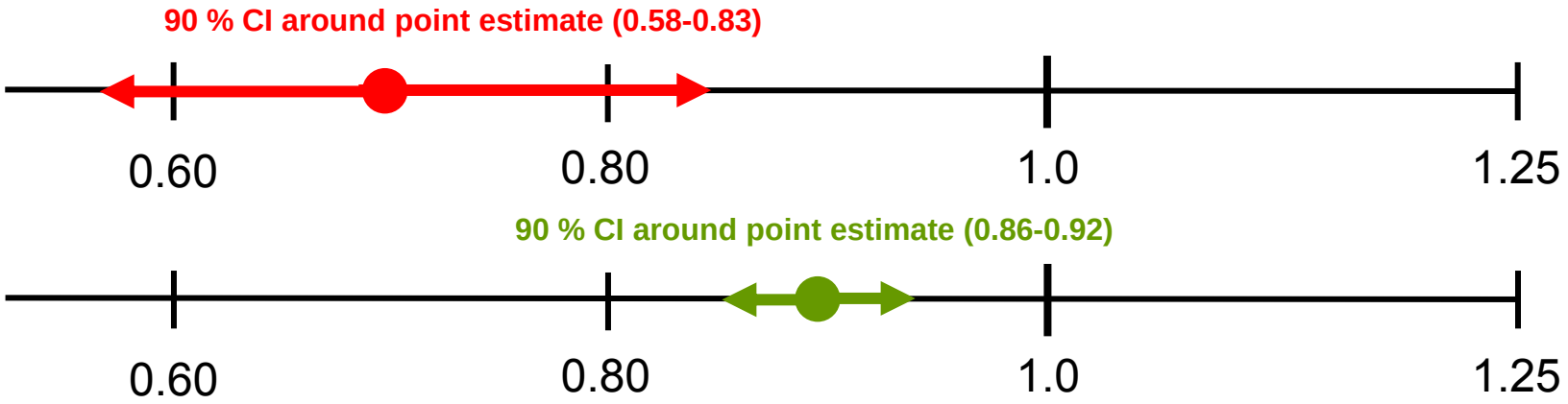
subject#	AUC generic A	AUC reference	AUC generic B	A/reference	B/reference
1	30.00	31.00	33.00	0.97	1.06
1	31.00	33.00	30.00	0.94	0.91
1	24.00	36.00	32.00	0.67	0.89
1	28.00	37.00	33.00	0.76	0.89
1	36.00	34.00	28.00	1.06	0.82
1	35.00	31.00	27.00	1.13	0.87
1	15.00	25.00	22.00	0.60	0.88
1	35.00	37.00	33.00	0.95	0.89
1	25.00	39.00	34.00	0.64	0.87
1	12.00	42.00	37.00	0.29	0.88
1	25.00	35.00	30.00	0.71	0.86
1	15.00	39.00	35.00	0.38	0.90
arithmetic mean	25.92	34.92	31.17	0.76	0.89
SD	8.26	4.54	4.06	0.26	0.06
geometric mean	24.49	34.63	30.90	**0.71**	**0.89**
CI 90				0.12	0.03
lower 90				**0.58**	**0.86**
higher 110				**0.83**	**0.92**

Are generic really comparable ?

Ratio of AUCs with calculation of the geometric means (point estimates)



	ratio A/ref	ratio B/ref
Number of values	12	12
Minimum	0.2900	0.8200
25% Percentile	0.6200	0.8700
Median	0.7350	0.8850
75% Percentile	0.9600	0.8950
Maximum	1.130	1.060
Mean	0.7583	0.8933
Std. Deviation	0.2620	0.05726
Std. Error	0.07565	0.01653
Geomean	**0.7072**	**0.8924**



Special situations (EU)

Narrow therapeutic index drugs

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

Highly variable drugs or drug products

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

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

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

No-switch drugs in Belgium

6.1.2. Liste des molécules à marge thérapeutique étroite et/ou très toxiques proposée[3-7],

Acénocoumarol	Disopyramide	Propafénone
Amiodarone*	Everolimus	Sirolimus
Antiépileptiques**	Phenprocoumone	Sotalol*
Azathioprine*	Flécaïnide*	Tacrolimus*
Cibenzoline	Levothyroxine*	Théophylline
Ciclosporine	Lidocaïne	Warfarine
Clozapine*	Lithium*	
Colchicine	Metildigoxine	
Digoxine	Mycophenolate*	

** molécules pour lesquelles il existe plusieurs médicaments commercialisés sur le marché belge dans un groupe DCI. La mention des molécules pour lesquels différents médicaments existent au sein d'un groupe DCI doit être mise à jour régulièrement.*

*** Tous les antiépileptiques ont été repris dans la liste, soit qu'ils ont été définis comme molécule à marge thérapeutique étroite, soit parce que que des problèmes possibles ont été rapportés dans la littérature lors du switch d'une spécialité à une autre en cours de traitement. Il existe plusieurs médicaments commercialisés sur le marché belge pour les antiépileptiques suivants : carbamazépine, gabapentine, lamotrigine, oxcarbazépine, phénytoine, phénobarbital, topiramate et valproate.*

http://www.fagg-afmps.be/fr/binaries/prescription-DCI-mise-au-point-FR-2010-06-11_tcm291-103015.pdf
Last accessed: 16/03/2014

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

Liste des médicaments antibiotiques et antimycosiques commercialisés dans les officines ouvertes au public avec mention, s'il y a lieu, de leur(s) excipient(s) à effet notoire
Mise à jour: 10/12/2013

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

Avez-vous des EEN ?

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

Mise à jour: 10/12/2013

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

AmoclaneEG (Eurogenerics)

[amoxicilline 125mg + acide clavulanique (sel potassique) 31,25mg / **5ml**]
sir.
100 ml Rx b€ € 6,64

[amoxicilline 250mg + acide clavulanique (sel potassique) 62,5mg / **5ml**]
sir.
100 ml Rx b€ € 8,45

Avez-vous des EEN ?

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

Mise à jour: 10/12/2013

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

Amoxicilline Sandoz (Sandoz)

[amoxicilline]

compr. (disp., séc.)

16 x 500mg	Rx	b	€ 6,81
30 x 500mg	Rx	b	€ 12,36
8 x 1g	Rx	b	€ 7,73
20 x 1g	Rx	b	€ 13,32
24 x 1g	Rx	b	€ 14,32

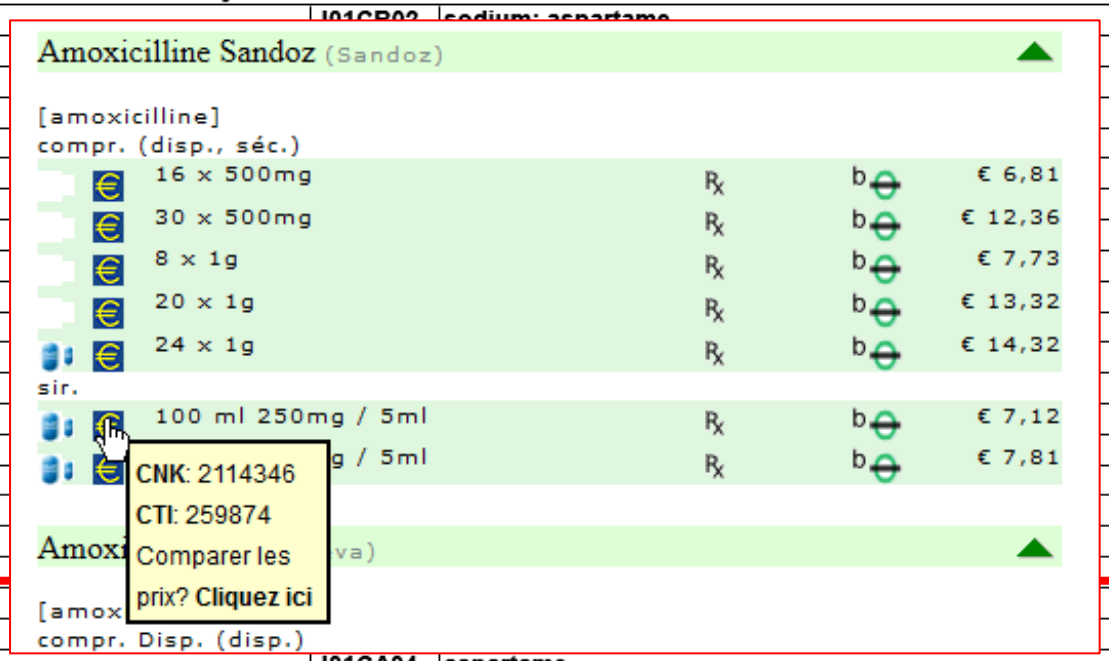
sir.

100 ml 250mg / 5ml	Rx	b	€ 7,12
100 ml 500mg / 5ml	Rx	b	€ 7,81

Avez-vous des EEN ?

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

Mise à jour: 10/12/2013



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

Avez-vous des EEN ?

Liste des médicaments antibiotiques et an mention, s'il y		
amoclane 125/31,25 100ml sir		
amoclane 250/62,5 100ml sir		
amoclane 500/125 16 comp		
amoclane 500/125 32 comp		
amoclane 875/125 10 comp		
amoclane 875/125 20 gran sachets		
amoclane 875/125 20 comp		
amoxicilline apotex comp eff 20x 1 g		
amoxicilline apotex comp eff 8x 1 g		
amoxicilline apotex sir 80ml 250mg/5ml		
amoxicilline eg comp eff 24x 1 g		
amoxicilline eg comp eff 8x 1 g		
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amoxicilline eg sir 100ml 250mg/5ml		
amoxicilline eg comp 24x 1 g		
amoxicilline eg comp 8x 1 g		
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amoxicilline mylan caps 24x 500mg		
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amoxicilline sandoz comp disp 20x 1 g		
amoxicilline sandoz comp disp 24x 1 g		
amoxicilline sandoz comp disp 30x 500mg		
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	
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amoxiclavapotex 875/125 10 comp	J01CR02	

PLAN | LE CBIP | RESPONSABLES | NOUS CONTACTER | LIENS | AIDE

CBIP BCFI Centre Belge d'Information Pharmacoth

Accueil | Bon à savoir | Répertoire | Folia | ATC | Télécharger

amoxicilline 250 mg / 5 ml (oral)

	EEN		
ATC		Amoxicilline Sandoz (Sandoz)	sir.
ATC		Flemoxin (Astellas)	sir.
ATC		Amoxicilline EG (Eurogenerics)	sir.
ATC		Amoxypen (Socobom)	sir.
ATC		Clamoxyl (GSK)	sir.
ATC		Amoxicilline Apotex (Apotex)	sir.
ATC		Amoxicilline Teva (Teva)	sir.

Avez-vous des EEN ?

Liste des médicaments antibiotiques et antimyco mention, s'il y a lieu Mi		
amoclane 125/31,25 100ml sir		
amoclane 250/62,5 100ml sir		
amoclane 500/125 16 comp		
amoclane 500/125 32 comp		
amoclane 875/125 10 comp		
amoclane 875/125 20 gran sachets		
amoclane 875/125 20 comp		
amoxicilline apotex comp eff 20x 1 g		
amoxicilline apotex comp eff 8x 1 g		
amoxicilline apotex sir 80ml 250mg/5ml		
amoxicilline eg comp eff 24x 1 g		
amoxicilline eg comp eff 8x 1 g		
amoxicilline eg caps 16x 500mg		
amoxicilline eg caps 30x 500mg		
amoxicilline eg sir 100ml 250mg/5ml		
amoxicilline eg comp 24x 1 g		
amoxicilline eg comp 8x 1 g		
amoxicilline mylan caps 16x 500mg		
amoxicilline mylan caps 24x 500mg		
amoxicilline sandoz comp disp 16x 500mg		
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amoxicilline sandoz comp disp 24x 1 g		
amoxicilline sandoz comp disp 30x 500mg	J01CA04	aspartame
amoxicilline sandoz comp disp 8x 1 g	J01CA04	aspartame
amoxicilline sandoz sir 100ml 250mg/5ml	J01CA04	aspartame
amoxicilline sandoz sir 100ml 500mg/5ml	J01CA04	aspartame
amoxicilline teva comp disp disp 16x 500mg	J01CA04	
amoxicilline teva comp disp disp 16x 750mg	J01CA04	
amoxicilline teva sir 80ml 250mg/5ml	J01CA04	saccharose
amoxiclavapotex 500/125 16 comp	J01CR02	
amoxiclavapotex 500/125 30 comp	J01CR02	
amoxiclavapotex 875/125 10 comp	J01CR02	

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 prescraiptins analayzed from 2004 trough 2008)

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

The situation may be worse in veterinary medicine

JOURNAL OF
Veterinary Pharmacology and Therapeutics

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

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

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

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

The situation may be worse in veterinary medicine

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

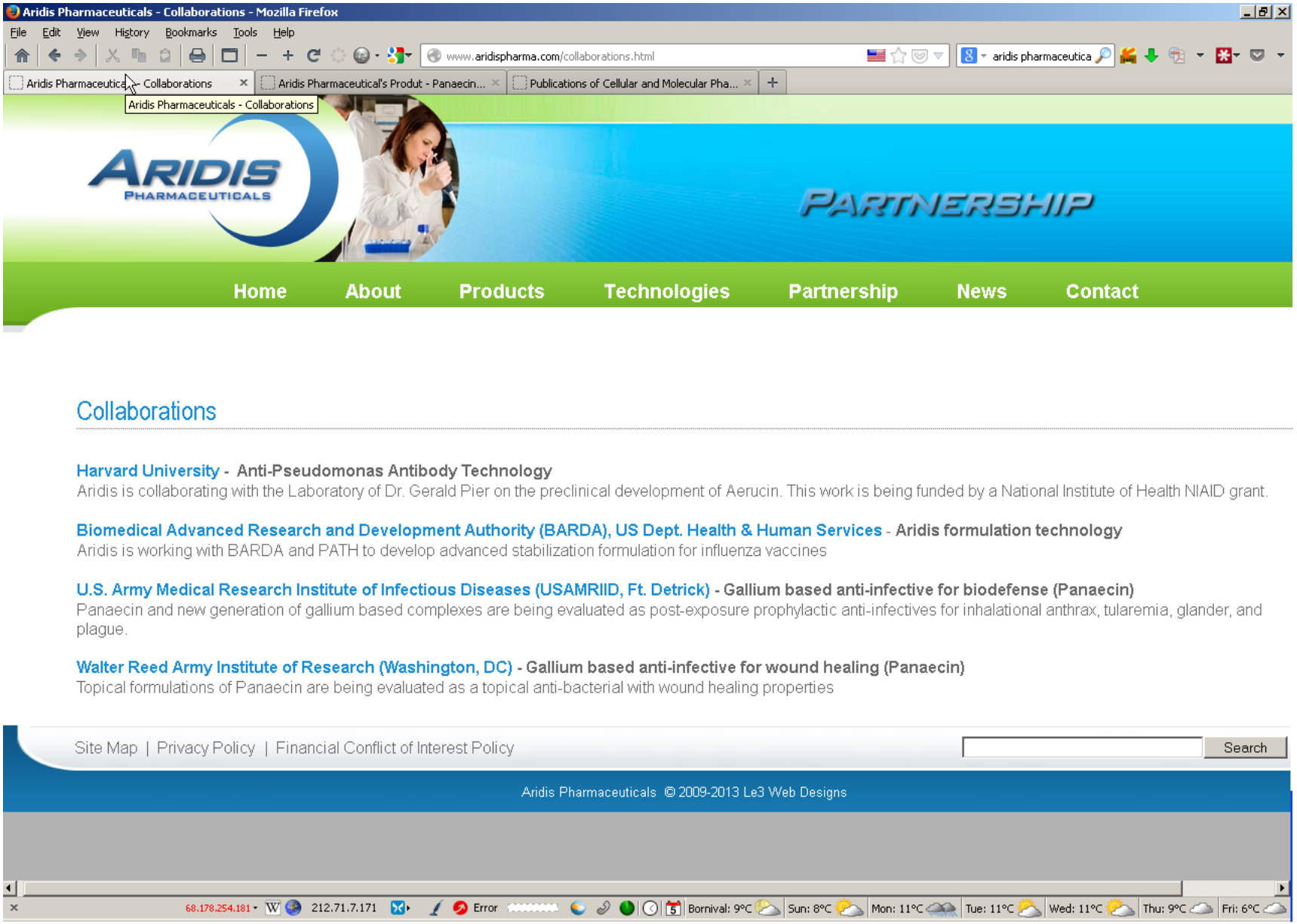
The consequences of generic marketing on antibiotic consumption and the spread

P.-L. TOUTAIN
A. BOUSQUET

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

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

Unless Big Brother comes to your help…



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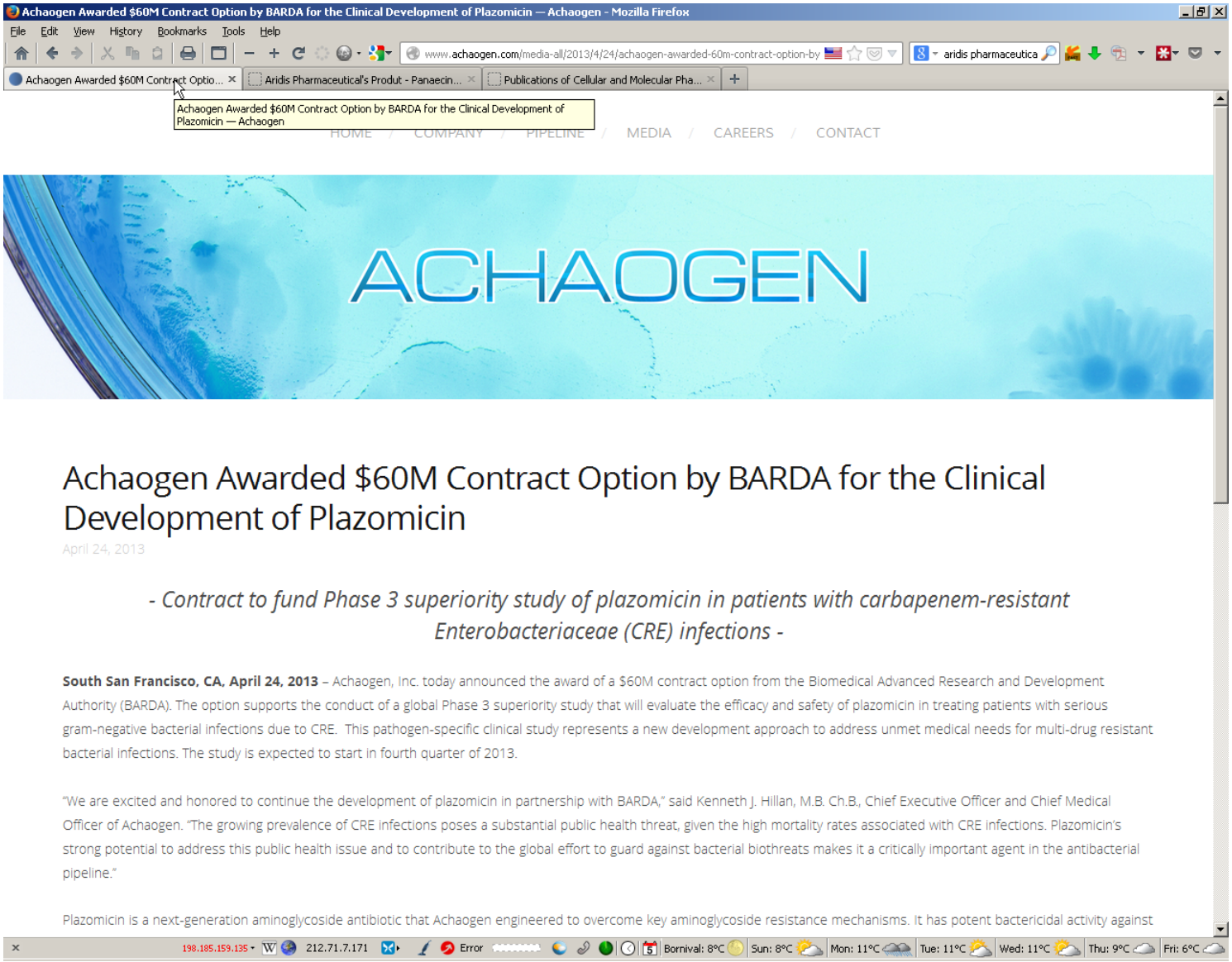

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MCM Procurements and Grants

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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…

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

Date: May 22, 2013

Company: GlaxoSmithKline of North Carolina

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

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

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

Press Release: HHS forms strategic alliance to develop new antibiotics

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

Unless Big Brother comes to your help…

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

Date: May 24, 2013

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

Contract amount: $17.7 million for two years

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

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

Press Release: HHS funds drug development for bioterror infections

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

Unless Big Brother comes to your help even in Switzerland…

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

Date: June 25, 2013

Company: Basilea Pharmaceutica International Ltd., Basel, Switzerland

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

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

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

Press Release: BARDA supports new broad-spectrum antibiotic

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

Unless Big Brother comes to your help… even in Switzerland

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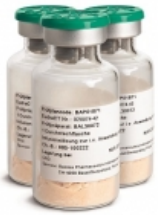
BAL30072



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

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

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

Ongoing phase 1 program

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

The need for new Gram-negative antibiotics

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

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

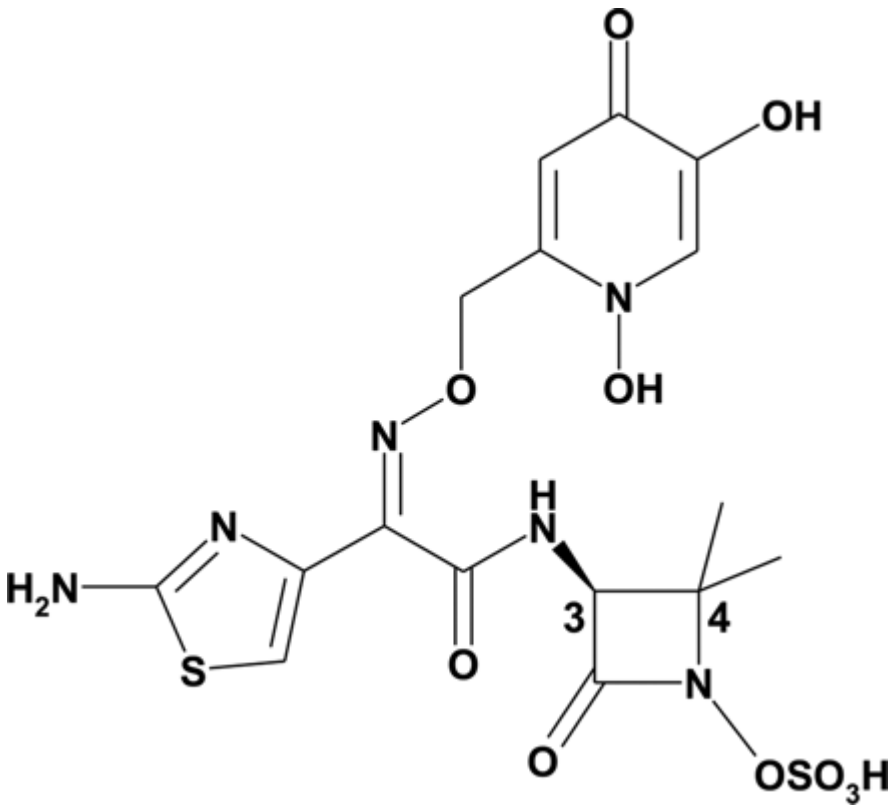
Info

Printable Version

IDSA
Infectious Diseases
Society of America
idsociety.org

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

Here is what Big Brother helps to develop…



Structure of BAL30072

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

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