The Right Antibiotic: Potential Clinical Outcomes and the Hidden Risks of a Low Cost Therapy.

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Brussels, Belgium

Anti-infective Master Class
Live Webcast

An Educational Initiative By

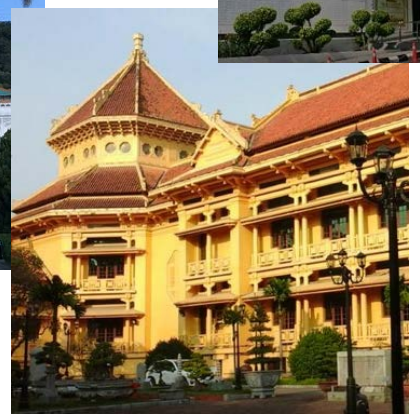
Disclosures and slides availability

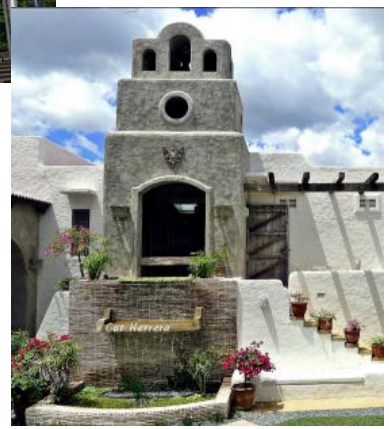
- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)
- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*] (governance)

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

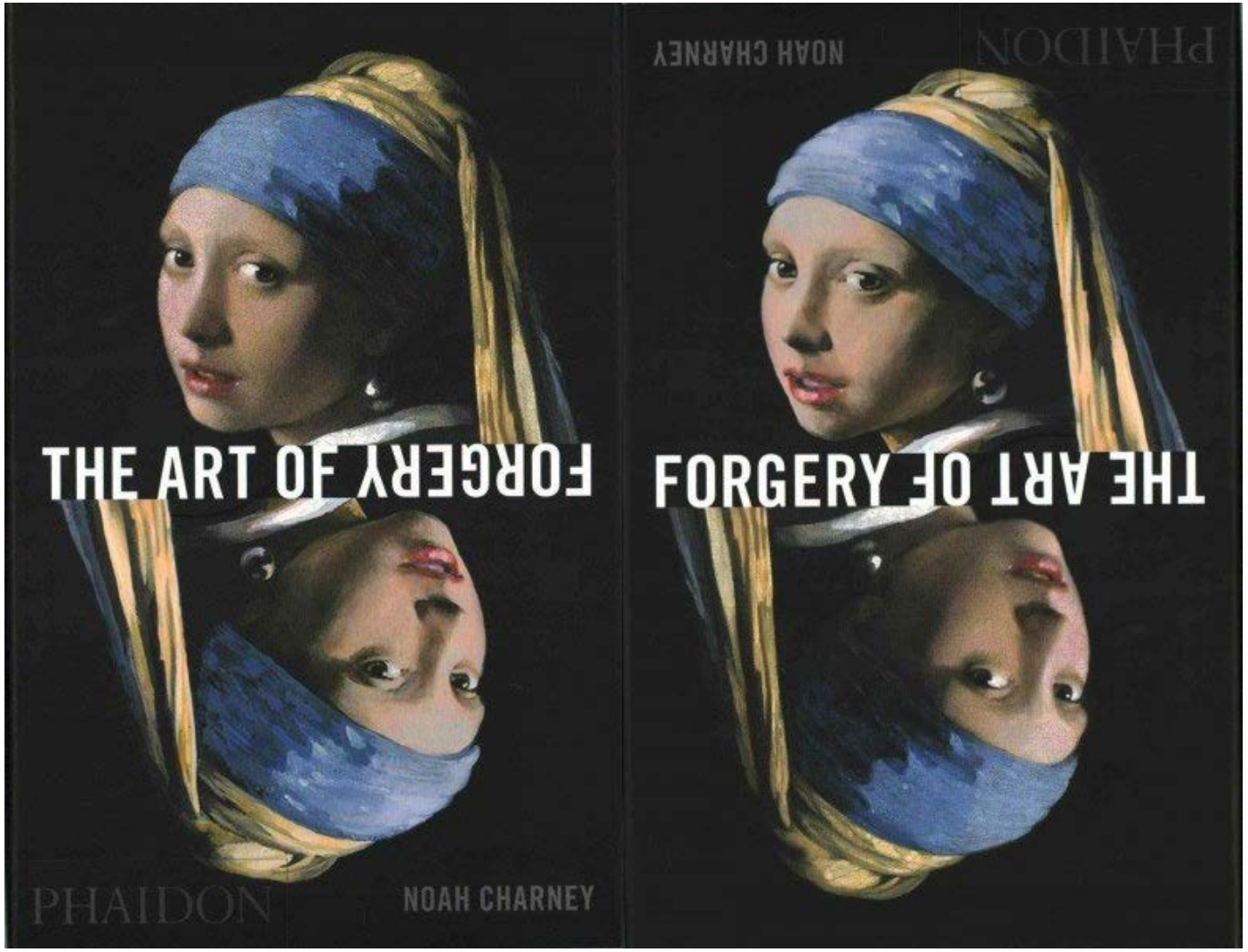
When Visiting an Art Gallery or a Museum …



Would you prefer to see originals or copies ?



https://www.npr.org/2015/06/23/412244490/could-the-masterpiece-be-a-fake-profit-revenge-and-the-art-of-forgery
Last visited: 8 Nov 2017

Why choosing a "generic" antibiotic ?

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

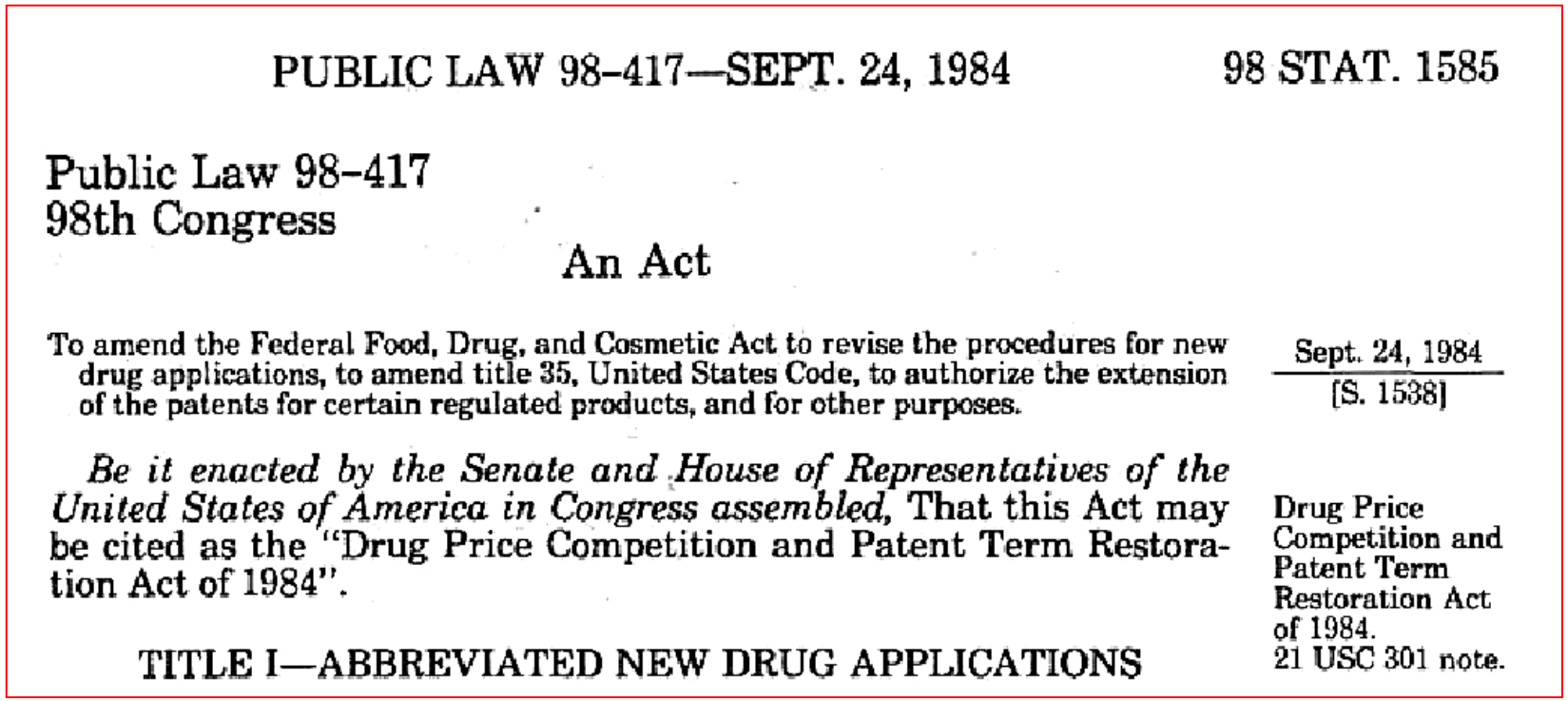
Please, think about what YOU would choose !

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

What shall we discuss?

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

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: 17 Oct 2017

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

FDA requirements in a nutshell

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

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

- **505 (b)(2) Application (Guidance to Industry)** https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2 (current as of 9 Apr 2019) Last accessed: 4 Oct 2019
- **Product-Specific Guidances for Generic Drug Development**:: https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development (current as of 22 Jul 2019) Last accessed: 4 Oct 2019

What is required for the innovator…

The long drug development pathway of the innovator….

Drug discovery	Drug development	Clinical trial	Manufacturing	Marketing application
Target identification Target validation Search for lead compounds Target receptor interaction study Optimization of properties Designing of drug Screening of drugs	*In vitro* and *in vivo* test including toxicology/carcinogenicity/ mutagenicity, pharmacokinetics, pharmacodynamics, animal tests, *in vitro* assays in sllico methods drug delivery optimization	Phase I (safety data) Phase II (drug safety & dose ranging) Phase III (drug safety & efficacy) Phase IV (post marketing surveillance)	Good manufacturing practice safe, pure, effective, consistent quality	Investigational new drug Application/ New drug applications Marketing approval Regulatory compliance

Table from: Venkatesh et al. J Pharm Bioallied Sci. 2011;3:101-8 - PMID 21430959

What remains required from the generic producer

What remains for the generic….

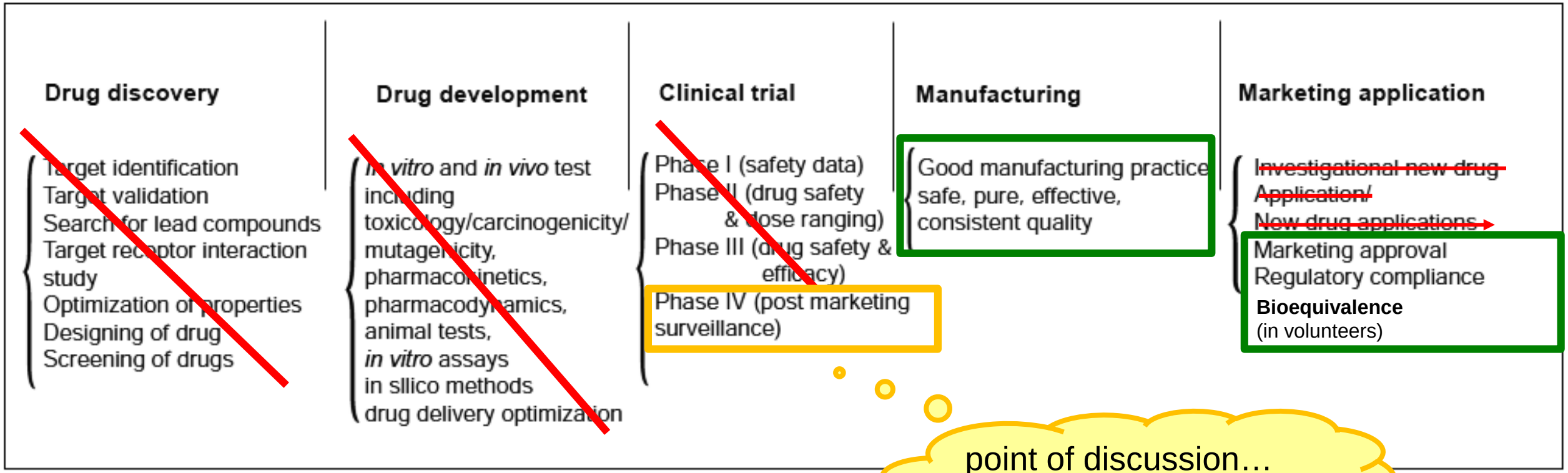
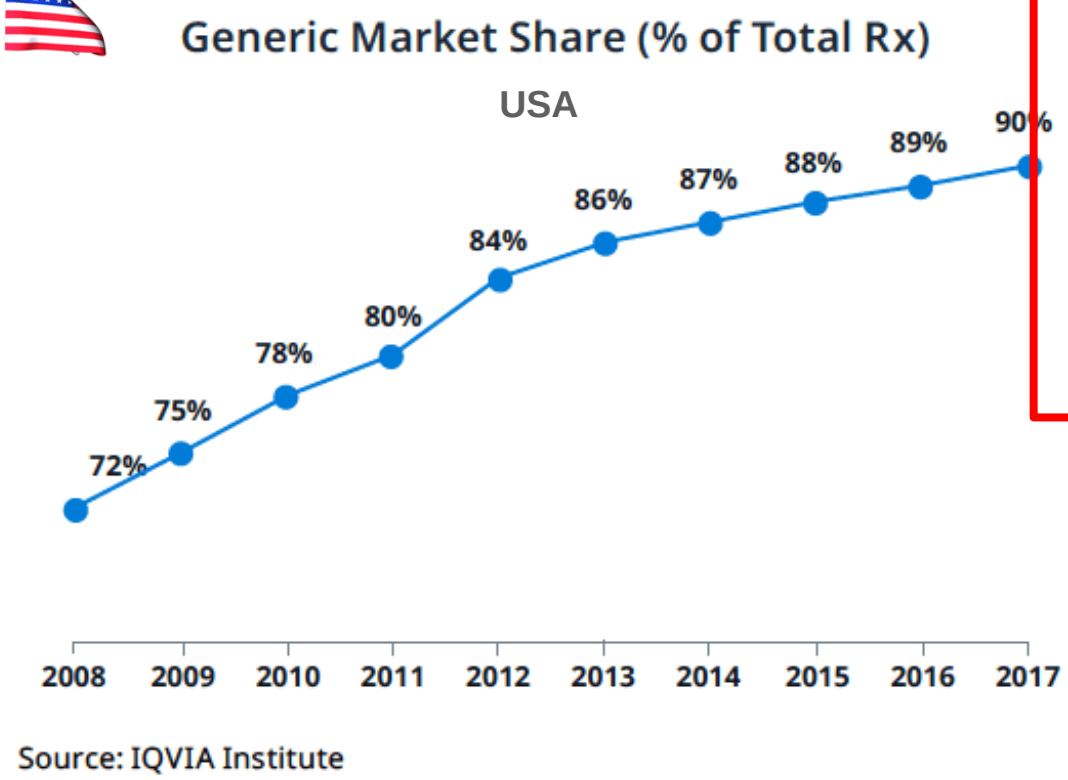


Table from: Venkatesh et al. J Pharm Bioallied Sci. 2011;3:101-8 - PMID 21430959

As a result…

Prices of generics are about 20-25% of the original price of the branded drug *



Source: IQVIA Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

Home / About FDA / Page Not Found

FDA STATEMENT

Statement on continued progress enhancing patient access to high-quality, low-cost generic drugs

FDA generic drug approvals reach record high in fiscal year 2019

Generic drugs account for about 90% of all prescription drug purchases in the U.S.

https://www.fda.gov/news-events/press-announcements/statement-continued-progress-enhancing-patient-access-high-quality-low-cost-generic-drugs?utm_campaign=101619_Statement_FDA%20statement%20on%20enhancing%20access%20to%20generic%20drugs
Posted: 16 Oct 2019
Last visited: 16 Oct 2019

* Once > 2 competitors are present
See: Generic Competition and Drug Prices
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices
Current as of 20 Nov 2017
Last accessed: 5 Oct 2019

See also:
Price Declines after Branded Medicines Lose Exclusivity in the U.S.
MS Institute for Healthcare Informatics (2016)
https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf
Last accessed: 5 Oct 2019

US Generics Market - Evolution of Indian Players - White Paper - Feb 08, 2019 – IQVIA Hiranandani Gardens, Powai, Mumbai - 400 076, India
Available from https://www.iqvia.com/-/media/iqvia/pdfs/ap-location-site/india/us-generics-market-evolution-of-indian-players.pdf
Last accessed: 5 Oct 2019

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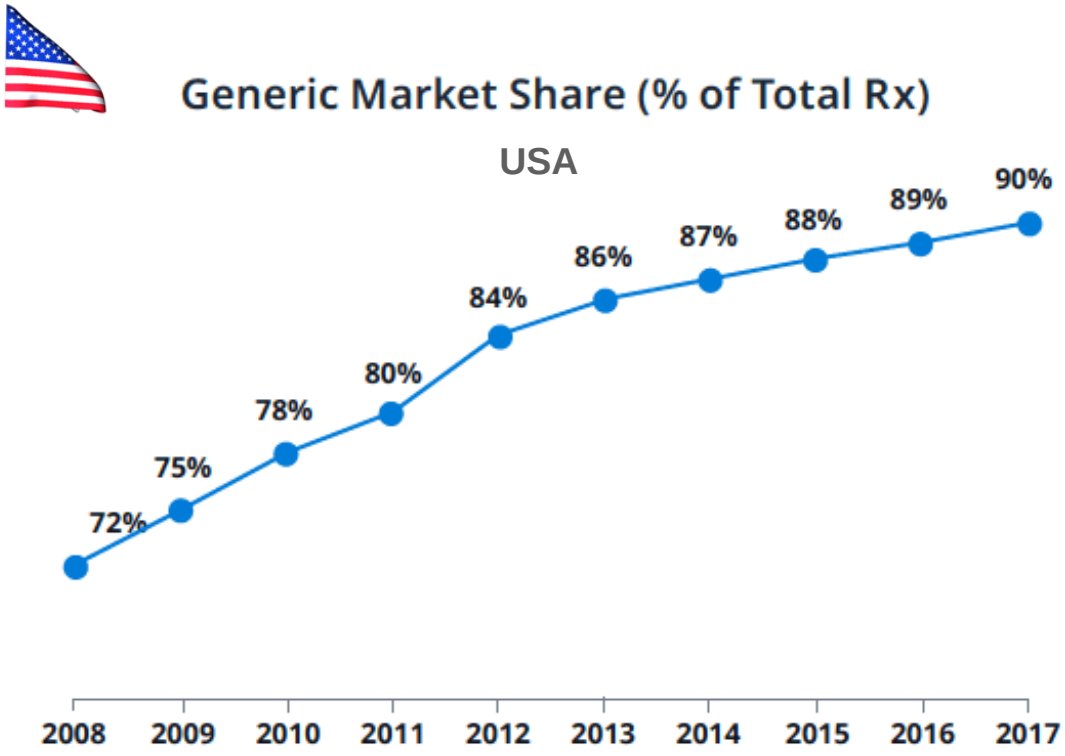

Source: IQVIA Institute

Reasons for increase:

- entry of generic players across therapies
- loss of exclusivity of patented products in the past decade.
- price difference (globally)
- since 2014 FDA requires only a single exhibit batch stability data (previously 3)

* Once > 2 competitors are present
See: Generic Competition and Drug Prices
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices
Current as of 20 Nov 2017
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See also:
Price Declines after Branded Medicines Lose Exclusivity in the U.S.
MS Institute for Healthcare Informatics (2016)
https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf
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Available from https://www.iqvia.com/-/media/iqvia/pdfs/ap-location-site/india/us-generics-market-evolution-of-indian-players.pdf
Last accessed: 5 Oct 2019

The FDA says generics are OK… but others say NO

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Drugs / Resources for You | Drugs / Drug Information for Consumers / Frequently Asked Questions on Popular Topics /

Generic Drugs: Questions & Answers

Share | Tweet | Linkedin | Email | Print

Spanish Language version - Medicamentos Genéricos: Preguntas y Respuestas (PDF - 213 KB)

- What are generic drugs?
- Do generic medicines work the same as brand-name medicines?
- Why do brand-name medicines look different from their generic versions?
- Why do generic medicines cost less than brand-name medicines?
- What standards must generic medicines meet to receive FDA approval?
- Is a generic version of my brand-name medicine available?
- Does FDA monitor side effects or safety issues with generic medicines?
- Where can I find more information about generic medicines?

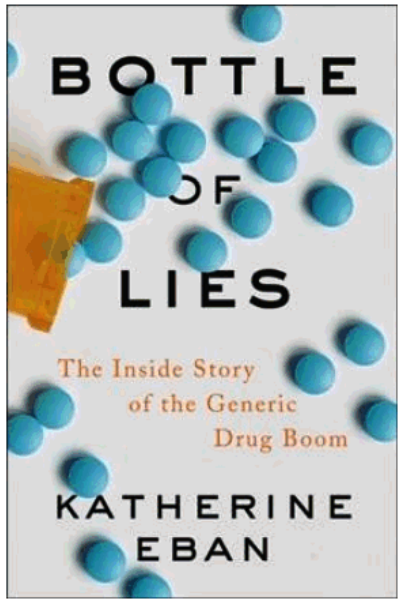
https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers
Current as of 1 Jun 2018 - Last accessed: 6 Oct 2019

HEALTH INC.

The Generic Drugs You're Taking May Not Be As Safe Or Effective As You Think

May 16, 2019 · 3:33 PM ET
Heard on Fresh Air

"As the cost of prescription medication soars, … health insurance plans require patients to switch to generics. But … some of these medications might not be as safe, or effective, as we think…"



Bottle of Lies
The Inside Story of the Generic Drug Boom
by Katherine Eban
Hardcover, 482 pages

https://www.npr.org/sections/health-shots/2019/05/16/723545864/the-generic-drugs-youre-taking-may-not-be-as-safe-or-effective-as-you-think - Posted: 16 May 2019 – Last accessed: 6 Oct 2019

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

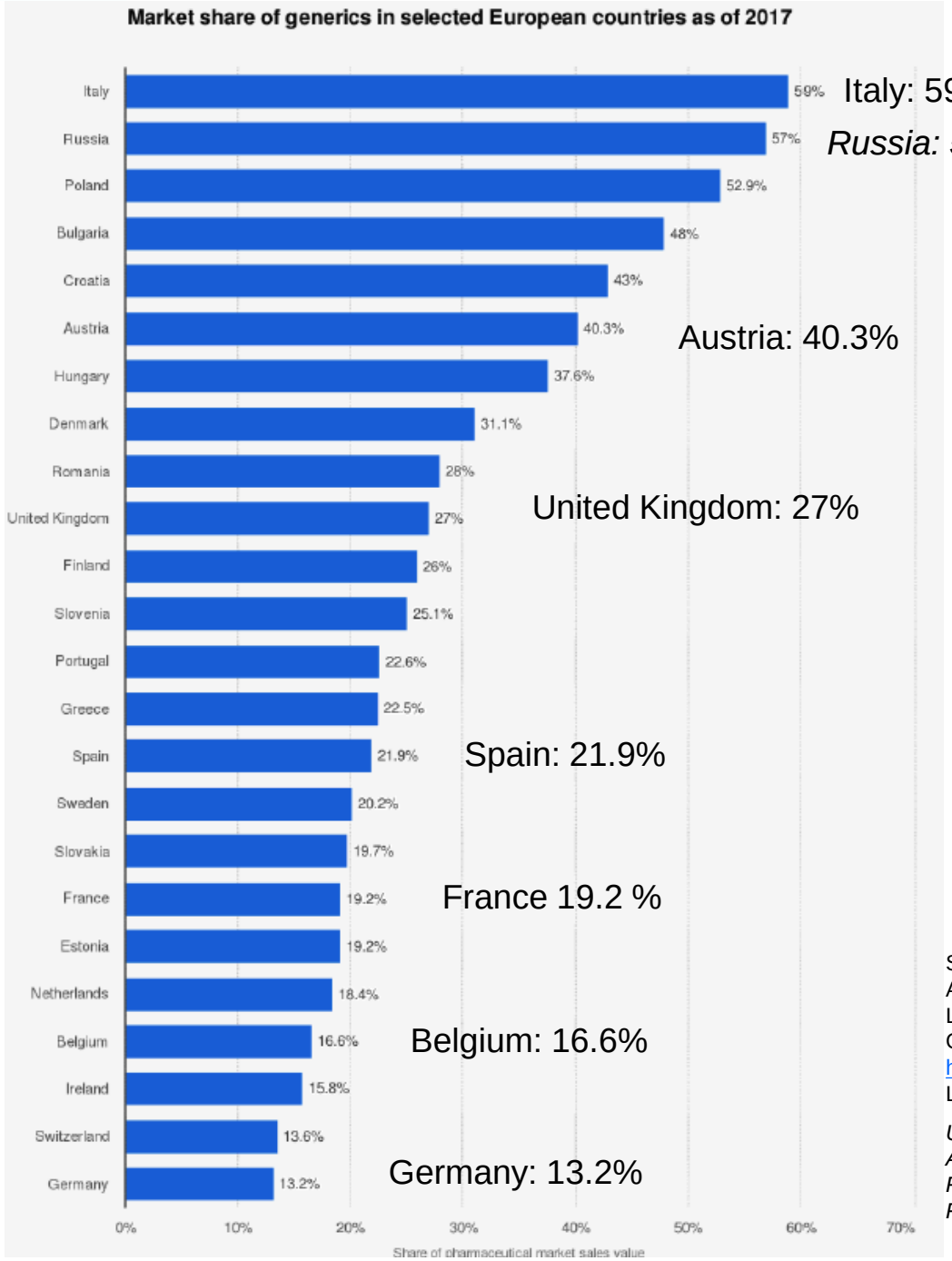
(OJ L 311, 28.11.2001, p. 67)

* 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 applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product**…

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

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:l21230 (and navigate from there [last update 6 Aug 2015])
Last accessed: 4 Oct 2019



Italy: 59%

Russia: 57%

Austria: 40.3%

United Kingdom: 27%

Spain: 21.9%

France 19.2 %

Belgium: 16.6%

Germany: 13.2%

A much more variable acceptance in Europe …

Reasons (not limitative) *

- lower price difference than in the US
- branded drugs often sold at lower prices (reference price)
- no systematic tendering process
- distrust (variable)

* DrugPatentWatch – Make Better Decisions
Business Intelligence on Biologic and Small Molecule Drugs
https://www.drugpatentwatch.com/blog/generic-drug-market-entry-in-europe-why-a-tailored-approach-is-best/
Last accessed: 5 Oct 2019

Source: European Federation of Pharmaceutical Industries (EFPIA), Brussels Belgium
Available from https://www.efpia.eu/media/412931/the-pharmaceutical-industry-in-figures-2019.pdf
Last accessed: 5 Oct 2019
Graphing from Statista GmbH, Hamburg, Germany
https://www.statista.com/statistics/316079/european-pharmaceutical-market-generics-share-by-country/
Last accessed: 5 Oct 2019

U.K.: share of generics in pharmacy market sales
Austria, Belgium, France, Germany, Italy, Spain: share of generics in reimbursable pharmacy market sales
Russia: share of generics in total market sales
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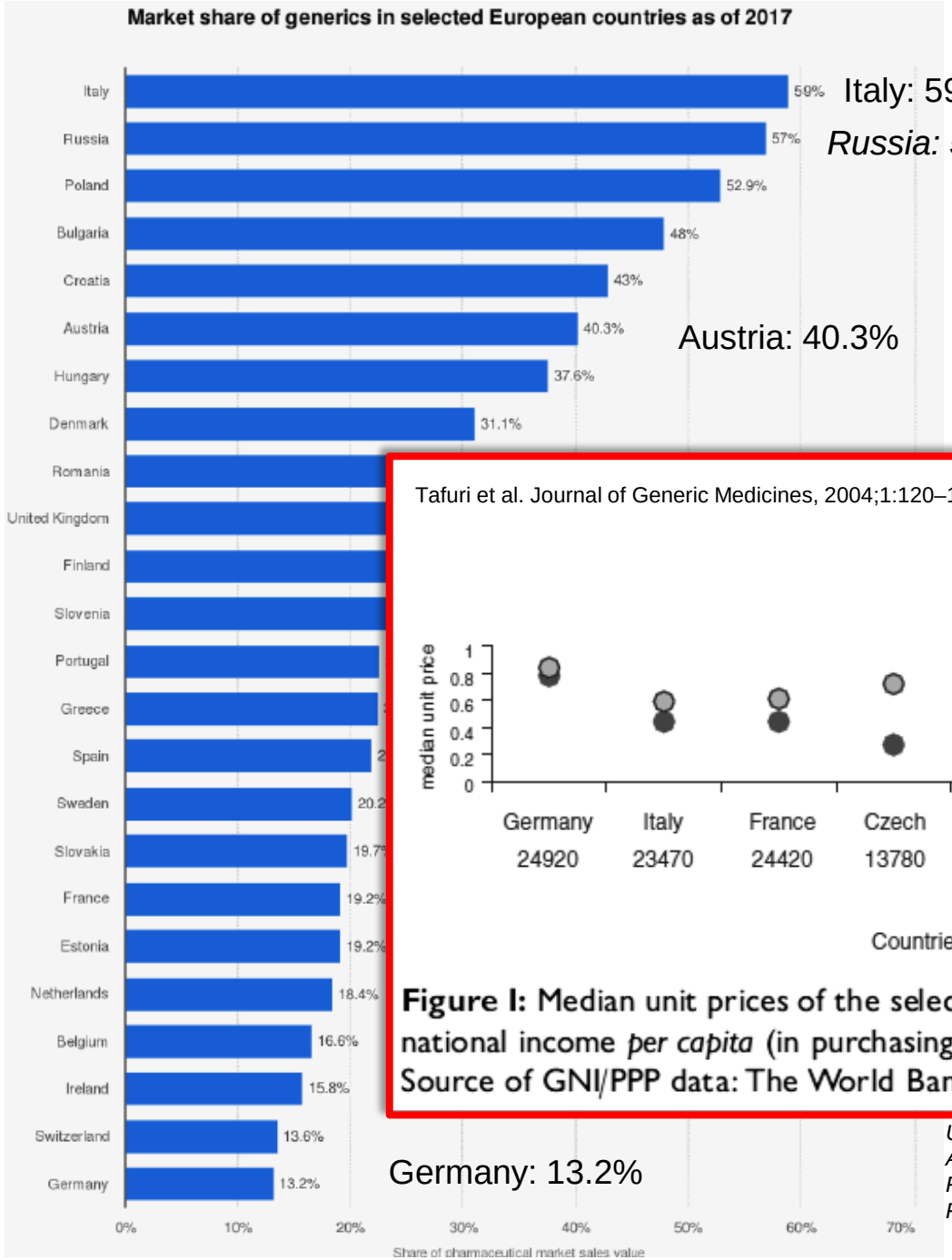

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…wer prices

…ss

Tafuri et al. Journal of Generic Medicines, 2004;1:120–127. https://doi.org/10.1057/palgrave.jgm.4940003

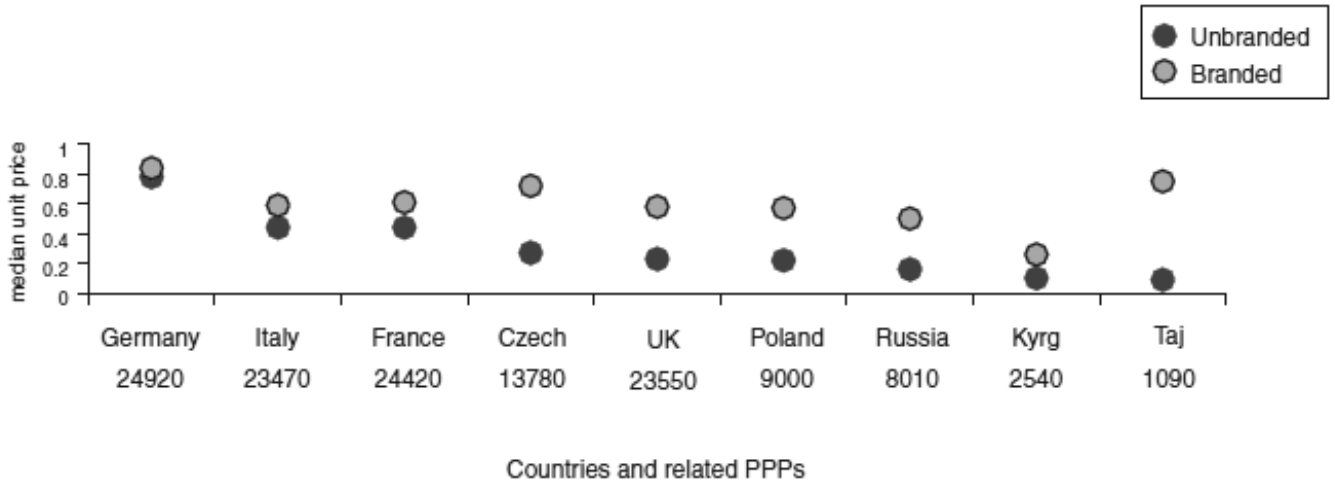

Figure I: Median unit prices of the selected medicines in the countries surveyed, with their gross national income *per capita* (in purchasing power parity)
Source of GNI/PPP data: The World Bank

…try-in-europe-why-a-tailored-approach-is-best/

…s-2019.pdf

…are-by-country/

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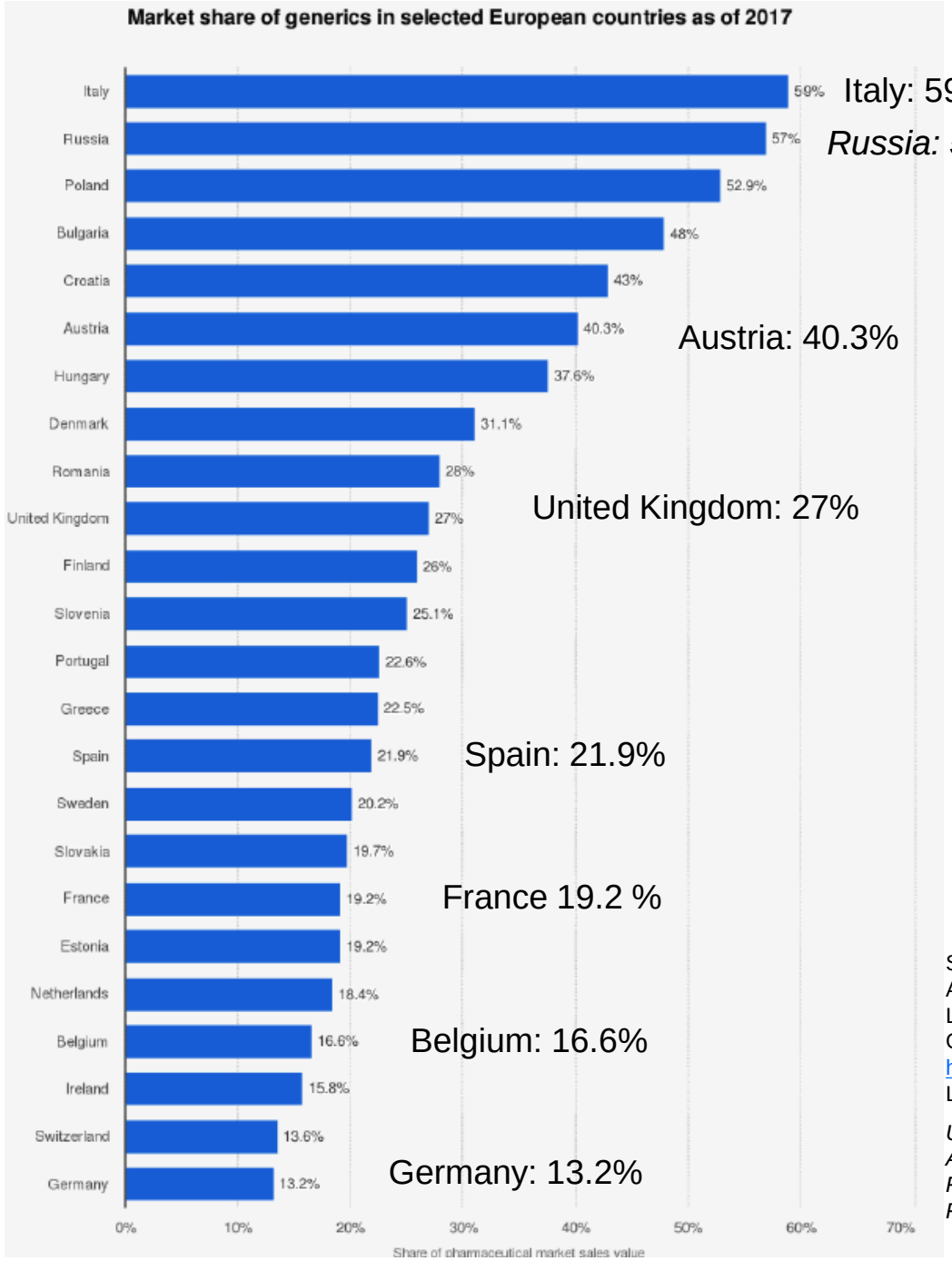

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Business Intelligence on Biologic and Small Molecule Drugs
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Source: European Federation of Pharmaceutical Industries (EFPIA), Brussels Belgium
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1st round of conclusions and discussions

- The decision to go for generics is **political**…
- It finds its origin and basis in
  - the **limited duration of the patent protection**
    (usually about 20 years post patent application → < 10 years after approval !!)
  - the fact that **drug production costs are usually very low**
    (often only a very minor fraction of the total requested by the innovator at the time of initial commercialization)
- The (much) **lower prices** compared to originator(s) is because of **savings (discovery and development costs)** and optimizing manufacturing processes (most often transferred to low wages countries) … *but can be variable*…
- The **only** incentive for going to generics **by governments** (and/or drug acquisition organizations) is to acquire and provide drugs **more cheaply** to the population (*cost minimization*)

What shall we discuss?

1. The US and the EU laws (as template)
2. **Approach to PK bioequivalence**

oral drugs !

http://www.choosinggenerics.ca/Bioequivalence.aspx
Last visited: 17 Oct 2017
No longer available on 4 Oct 2019

Bioequivalence: principles (for oral drugs)

- 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)

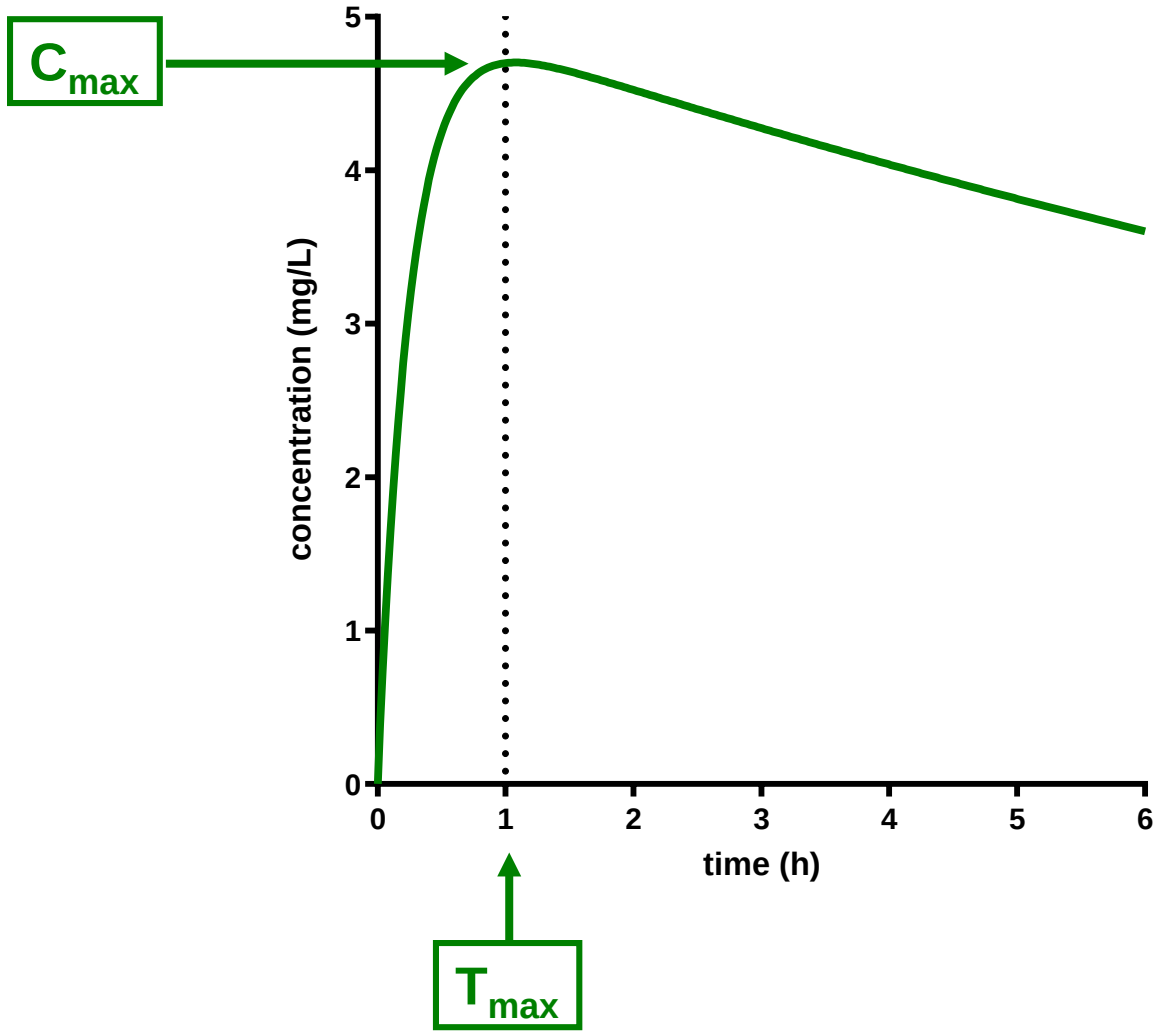
    → **extent of absorption**
  - **C_{max}** (the maximum plasma concentration of the active substance)

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

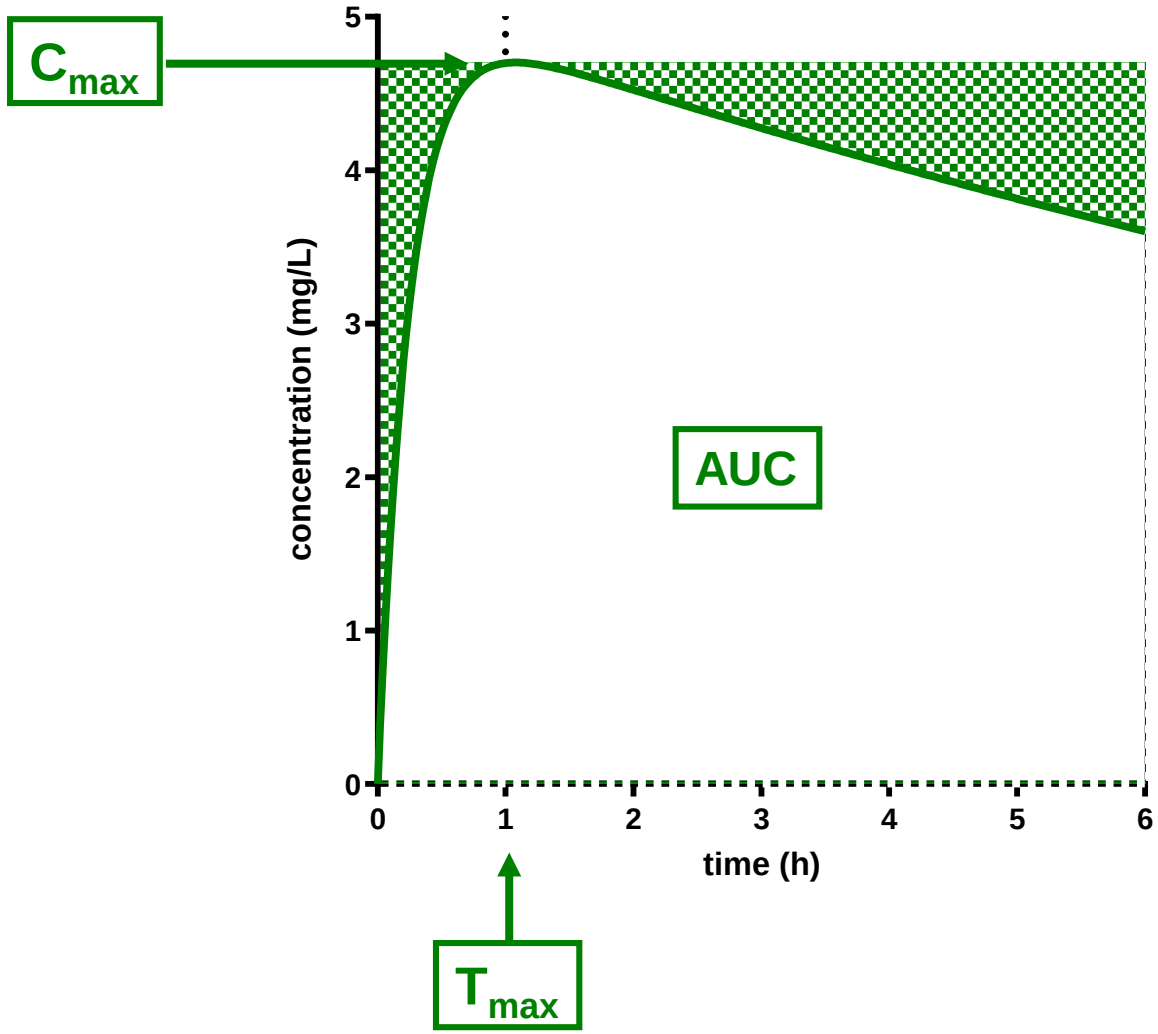
    → **rate of absorption**

1. Hauschke et al. Bioequivalence Studies in Drug Development – Methods and Applications, John Wiley & Sons Ltd. (UK), 2007. Available from the Publisher (last visited: 9 Oct 2019)
2. Benet LZ: Understanding bioequivalence testing. Transplant.Proc. 31 (Suppl 3A): 7S-9S, 1999 – PMID 10330950
3. Niazi SK: Handbook of Bioequivalence Testing, "Drugs and the Pharmaceutical Sciences", vol. 171, Informa Healthcare (New York), 2007. Free download (last visited: 9 Oct 2019)

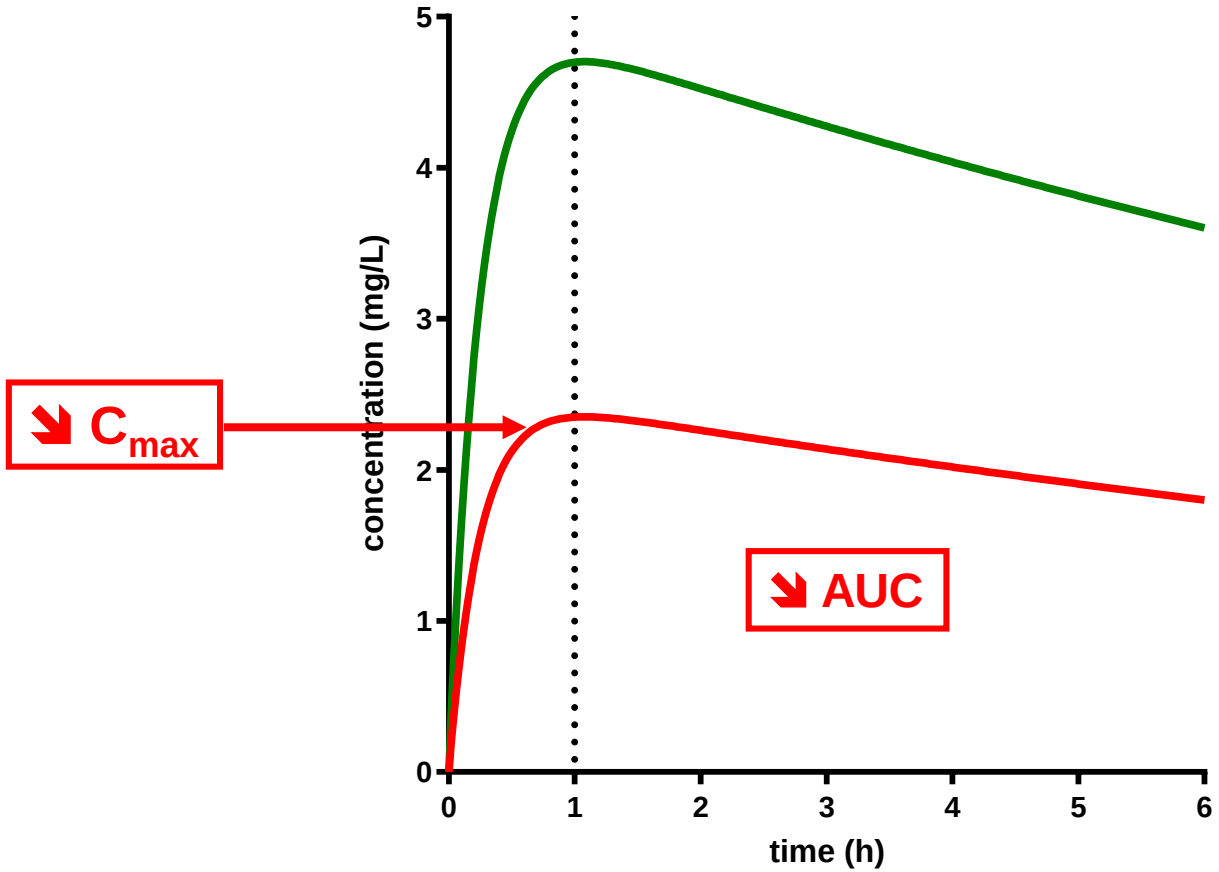
C_{max} – T_{max}



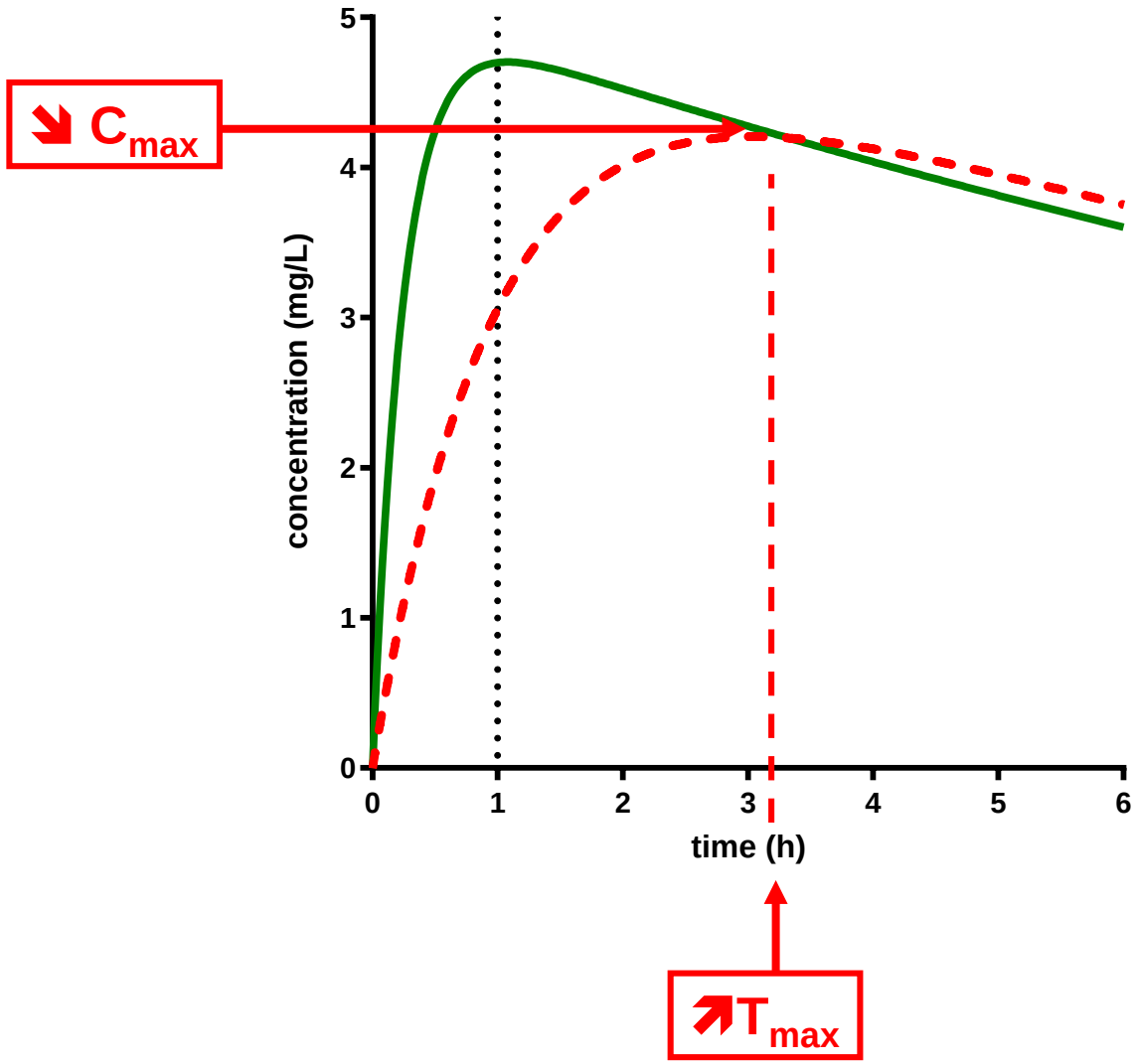
C_{max} – T_{max} – AUC



What if the absorption is decreased ?

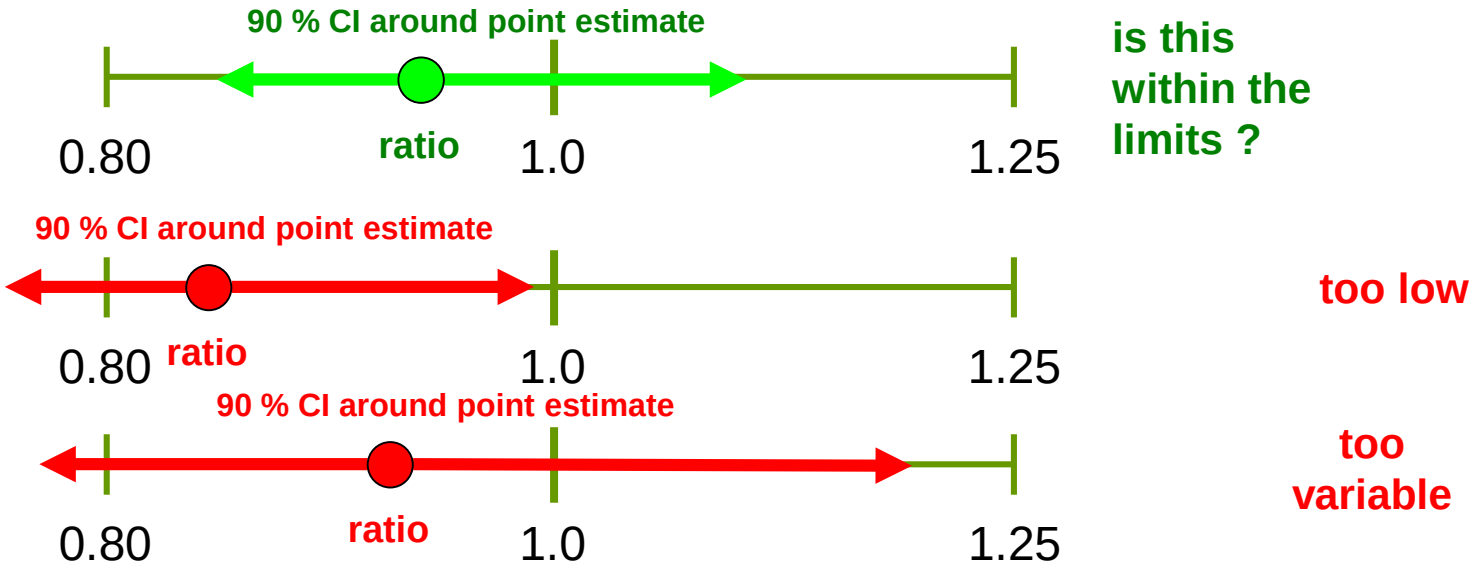


What if absorption is delayed ?



Criteria of bioequivalence (EMA* / FDA**)

- Calculate the **90% confidence interval** around the **geometric mean ratios** of **both AUC** and **C_{max}** for Test (generic) and Reference (innovator) (***T_{max}*** *[if relevant]: arithmetic mean).*
- The 90% confidence intervals should, in most cases, be **within the 0.80 – 1.25 (80-125%) acceptance limits**.



* 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: 9 Oct 2019)

** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf (Draft Guidance 2013 - Last accessed: 9 Oct 2019)
CVM GFI #35 Bioequivalence Guidance (Final Document)
https://www.fda.gov/media/70115/download (Current: 14 Aug 2018; Last accessed: 9 Oct 2019)

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**.

1. if both **AUC** and **C_{max}** are within range, the generic should have the same bioavailability as the reference
2. statistical evaluation of **T_{max}** only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects (see next slide)
3. for drugs with **narrow therapeutic index**, **EMA** recommends "tightened" acceptance intervals (**0.9 – 1.12**) but **FDA** still 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: 9 Oct 2019)

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One drug that showed bioequivalence …

International Journal of Clinical Pharmacology and Therapeutics, Vol. 45 – No. 11/2007 (617-622)

Bioequivalence evaluation of 320 mg gemifloxacin tablets in healthy volunteers

A.M. Al-Mohizea[1], A.A. Kadi[1], A.M. Al-Bekairi[1], S.A. Al-Balla[2], M.J. Al-Yamani[1], K.I. Al-Khamis[1], E.M. Niazy[1] and Y.M. El-Sayed[1]

[1]Department of Pharmaceutics, College of Pharmacy, King Saud University,
[2]Department of Medicine, King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Al-Mohizea et al. Int J Clin Pharmacol Ther. 2007;45:617-22 - PMID: 18077928.

One drug that showed bioequivalence …

International Journal of clinical pharmacology
Original
©2007 Dustri-Verlag Dr. K. Feistle
ISSN 0946-1965

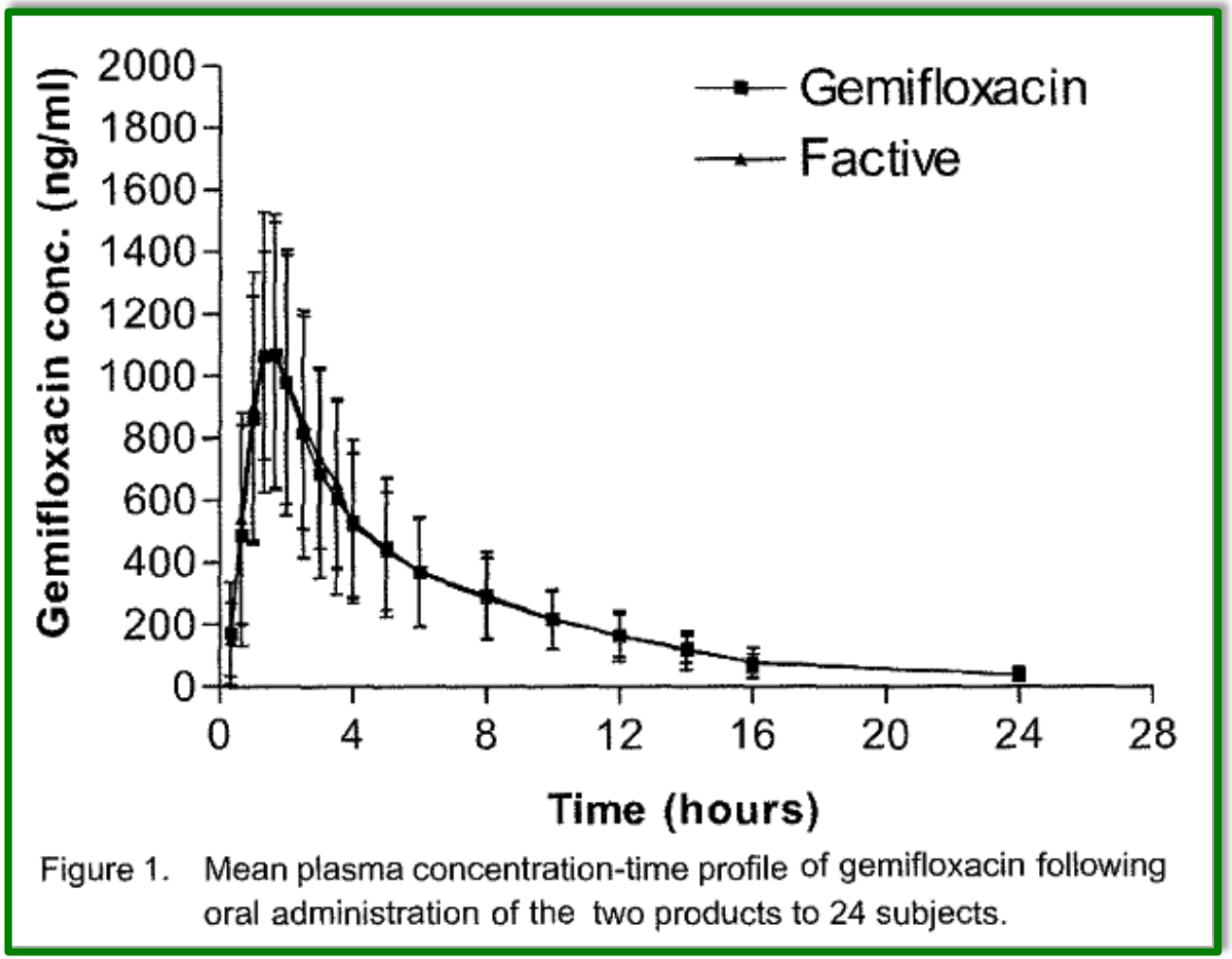

Figure 1. Mean plasma concentration-time profile of gemifloxacin following oral administration of the two products to 24 subjects.

Al-Mohizea et al. Int J Clin Pharmacol Ther. 2007;45:617-22 - PMID: 18077928.

One drug that showed bioequivalence …

International Journal of clinical pharmacology
Original
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ISSN 0946-1965

Table 1. Mean pharmacokinetic parameters for gemifloxacin formulations after administration to 24 subjects and the parametric 90% confidence intervals (using log-transformed data).

Parameter		Test formulation	Reference formulation	Point estimate	Confidence limits	Level of confidence
AUC_{0-t} (ng × h/ml)	Geometric mean	5,553	5718	97.12	87.47 – 107.83	90
	Range	3,525 – 8,749	3,868 – 8,451			
$AUC_{0-\infty}$ (ng × h/ml)	Geometric mean	5,873	5,995	97.97	88.72 – 108.19	90
	Range	3,822 – 9,025	4,097 – 8,770			
C_{max} (ng/ml)	Geometric mean	1,182	1,157	102.22	92.08 – 113.47	90
	Range	845 – 1654	807 – 1657			
t_{max} (h)*	Arithmetic mean	1.441	1.483	0.00	–0.170 – 0.165	91.13
	± SD	0.349	0.461			

Geometric mean = exp (mean(ln)), Range = exp (mean (ln) ± SD (ln)). * for t_{max}, non-parametric 90% confidence intervals using untransformed data.

Al-Mohizea et al. Int J Clin Pharmacol Ther. 2007;45:617-22 - PMID: 18077928.

But another one that did not…

Evaluation of the pharmacokinetic parameters of standard oral antibiotics in a bioequivalence study of generic products

T. Niwa, T. Hata, M. Hayashi, Y. Imagawa

Pharmazie 71: 363–377 (2016)

Niwa et al. Pharmazie. 2016;71:363-377 - PMID: 29441911

But another one that did not…

Evaluation of the p
in a bioequivalenc

T. Niwa, T. Hata, M. Hayashi, Y. Im

Pharmazie 71: 363–377 (2016)

C_{max} ↘
AUC ↘

C_{max} OK
T_{max} ↗

Table 4: Pharmacokinetic studies after a single oral administration of ofloxacin (standard product, 100 mg tablet) to healthy, fasting, male volunteers

Study No.	No. of subjects	C_{max} (µg/mL) Mean	S.D. [3]	C.V. (%) [4]	$AUC_{0\text{-}24\,h}$ (µg · h/mL) [2] Mean	S.D. [3]	C.V. (%) [4]	T_{max} (h)	$t_{1/2}$ (h)
BE-A	10	0.67	0.16	23.9	4.37	1.73	39.6	1.1	6.9
BE-B	10	1.117	0.056 (SE)	–	7.244	0.370 (SE)	–	1.3	5.2
BE-C*	24	1.124	0.230	20.5	7.881	0.941	11.9	1.042	6.592
BE-D*	14	1.17	0.20	17.1	7.64	1.30	17.0	1.6	7.0
BE-E	20	1.1760	0.2526	21.5	7.5624	1.3206	17.5	1.2	5.8
BE-F*	14	1.61	0.30	18.6	8.99	0.98	10.9	1.11	5.46
BE-G	12	0.97	0.17	17.5	($AUC_{0\text{-}12\,h}$)	0.67	13.7	2.00	2.71
Tarivit®-PI*	5	1.00	–	–	6.02	1.05	17.4	2	3.59

* Plasma concentrations were measured by HPLC. BE: bioequivalence study, Travit®-P1: phase I study of original product (Travit®).
1) Sampling point before oral dose is not included.
2) $AUC_{0\text{-}24\,h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation unless otherwise noted in parentheses as standard error (S.E.).
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.

Niwa et al. Pharmazie. 2016;71:363-377 - PMID: 29441911

But here is another one that created big problems ...

Levothrox (levothyroxine) new formulation caused major controversy in France

File photo: AFP

One of the most commonly prescribed drugs in France - Levothyrox - is at the centre of a controversy as thousands of people using the treatment complain of serious side effects in the wake of a formula change.

https://www.thelocal.fr/20170824/france-levothyrox-controversy-thryoid-treatment-thousands-of-patients-side-effects
Published: 24 August 2017 - 13:08 CEST+02:00
Last visited: 3-Oct-2019

What are the patients saying?

"We are facing a **major crisis**," Chantal L'Hoir, founder of the French thyroid disorder association told France Info.

"I had **cramps in my thighs** like **I've never had before**, to the point where I couldn't walk," she said. "I didn't dare to drive anymore because I was dizzy".

"I was **more tired than I've ever been.** Since stopping the treatment, I've had a new lease of life."

Others have complained of **suicidal thoughts**, memory loss, hair loss and **palpitations**, some of whom have been on the treatment for decades without complaint until the formula change, according to Ouest France.

"We're not scientists, but I find the lack of attention it's getting from the medical world deplorable," said L'Hoir.

A petition to stop the prescription of Levothyrox has received just over **97,000 signatures**, as of Thursday morning.

A problem of a (too) wide distribution…

CURRENT OPINION

Levothyrox® New and Old Formulations: Are they Switchable for Millions of Patients?

Didier Concordet[1] · Peggy Gandia[1] · Jean-Louis Montastruc[2] · Alain Bousquet-Mélou[1] · Peter Lees[3] · Aude Ferran[1] · Pierre-Louis Toutain[1,3]

Concordet et al. Clin Pharmacokinet. 2019;58:827-833 - PMID: 30949873

A problem of a (too) wide distribution…

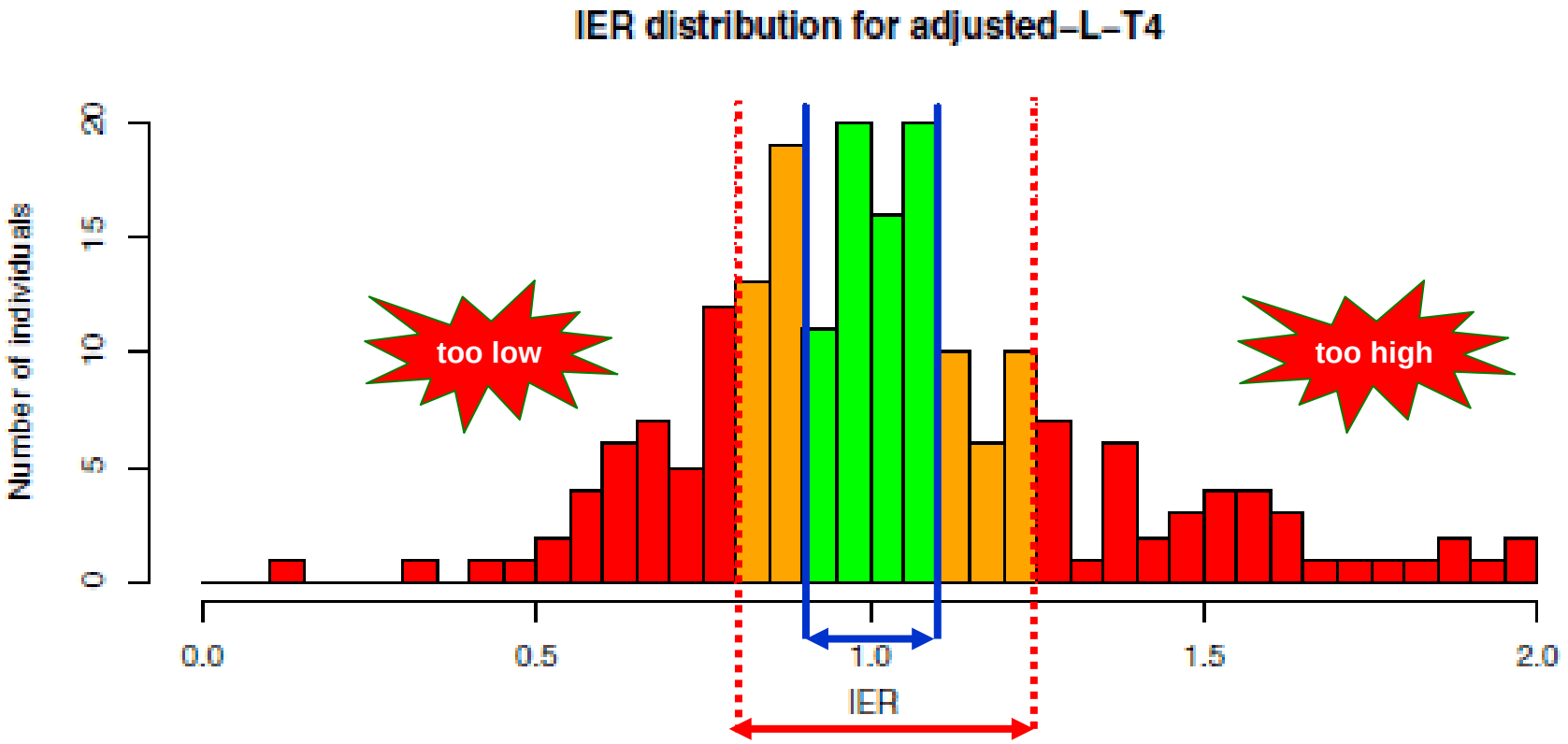


Fig. 1 Distribution of individual exposure ratio (IER) [area under the curve new/area under the curve old] obtained with baseline-adjusted T4 plasma concentrations.

drugs with a narrow therapeutic index:
0.9 ⟷ 1.1

accepted 90% confidence interval:
0.8 ⟷ 1.25

An average bioequivalence trial cannot guarantee the **switchability** of this formulation …

Concordet et al. Clin Pharmacokinet. 2019;58:827-833 - PMID: 30949873

Bioequivalence: Simple rules but with some questions…

- **Is the 90% CI acceptable ?**
  - ➔ This is the minimal difference a clinical trial can detect ! ....

- **What if we have wide patient-related distributions ?**
  - ➔ The drug may **prescribable** but **not switchable**

    Hauck & Anderson S. Measuring switchability and prescribability: when is average bioequivalence sufficient? J Pharmacokinet Biopharm. 1994;22:551–64 – PMID: 7473081

- **Does PK data tell you everything about clinical efficacy**
  - ➔ Many says "yes" but is this entirely proven ?

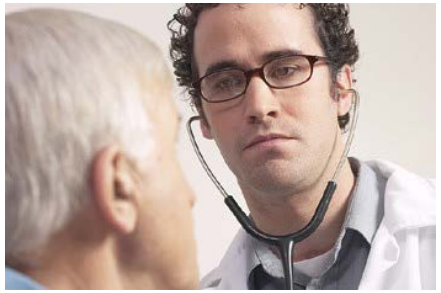
CAVEAT:
Bioequivalence studies are NOT required for drugs administered by the intravenous route ! (since that route provides, by definition a 100 % bioavailability and, therefore, full bioequivalence !)

What shall we discuss?

1. A political decision (US and EU laws as an example)
2. Approach and limits to PK bioequivalence studies
3. **Approach to microbiological and therapeutic equivalence**
   - **Potency**
   - **Efficacy (PK/PD and clinical)**
   - **Emergence of resistance**
   - **Clinical data**

http://www.umu.se/english/research/research-excellence/strong-research/Infection+Biology
Last visited: 25 March 2014 – No longer available

http://www.gaebler.com/How-to-Start-a-Laboratory-Animals-Business.htm
Last accessed: 16 Oct 2019



http://www.buzzle.com/articles/staph-infections-staph-infection-treatment-and-symptoms.html
Last visited: 25 March 2014 – No longer availaible

Potency (piperacillin)

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

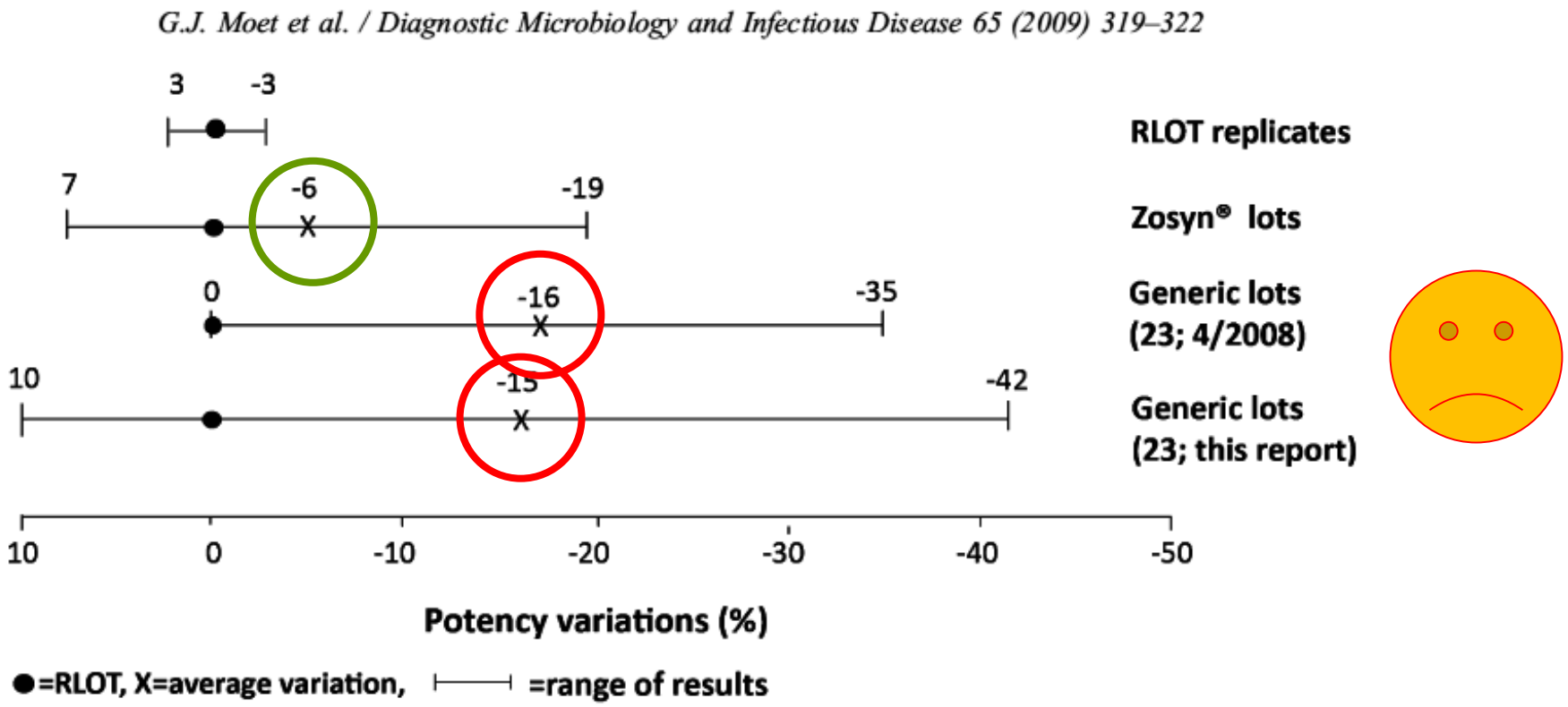
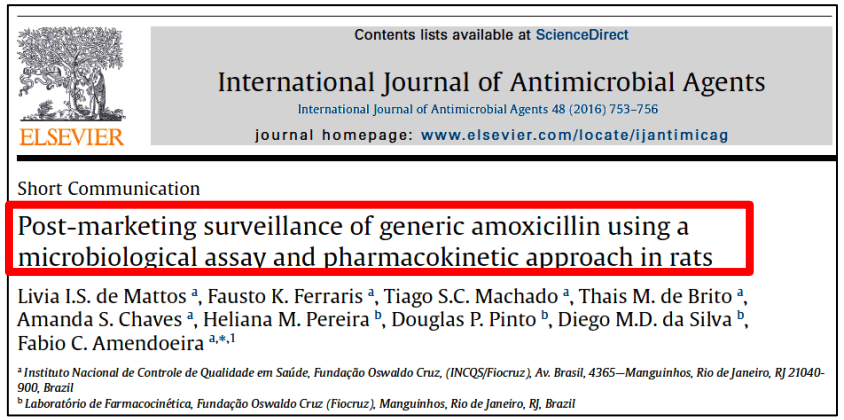


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

Moet *et al.* Diagnostic Microbiology and Infectious Disease 2009;65:319–322 – PMID 19822271

A series of other papers raising questions…



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

International Journal of Antimicrobial Agents 48 (2016) 753–756

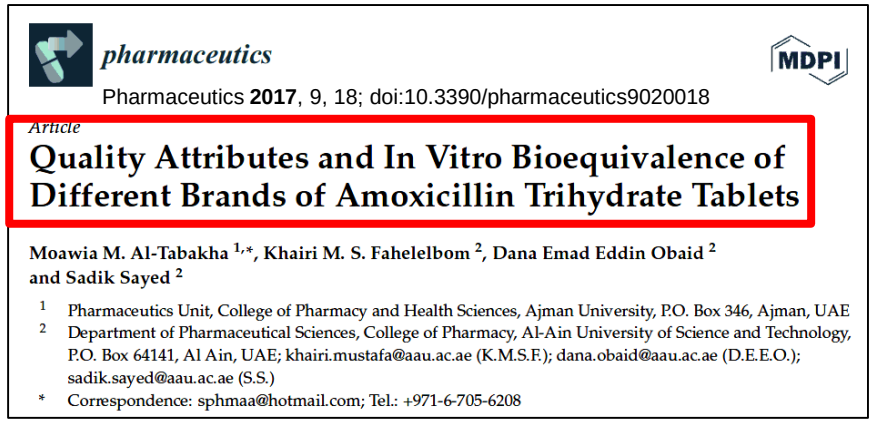
journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Post-marketing surveillance of generic amoxicillin using a microbiological assay and pharmacokinetic approach in rats

Livia I.S. de Mattos [a], Fausto K. Ferraris [a], Tiago S.C. Machado [a], Thais M. de Brito [a], Amanda S. Chaves [a], Heliana M. Pereira [b], Douglas P. Pinto [b], Diego M.D. da Silva [b], Fabio C. Amendoeira [a,*,1]

[a] Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz, (INCQS/Fiocruz), Av. Brasil, 4365—Manguinhos, Rio de Janeiro, RJ 21040-900, Brazil
[b] Laboratório de Farmacocinética, Fundação Oswaldo Cruz (Fiocruz), Manguinhos, Rio de Janeiro, RJ, Brazil



pharmaceutics

MDPI

Pharmaceutics **2017**, 9, 18; doi:10.3390/pharmaceutics9020018

Article

Quality Attributes and In Vitro Bioequivalence of Different Brands of Amoxicillin Trihydrate Tablets

Moawia M. Al-Tabakha [1,*], Khairi M. S. Fahelelbom [2], Dana Emad Eddin Obaid [2] and Sadik Sayed [2]

1 Pharmaceutics Unit, College of Pharmacy and Health Sciences, Ajman University, P.O. Box 346, Ajman, UAE
2 Department of Pharmaceutical Sciences, College of Pharmacy, Al-Ain University of Science and Technology, P.O. Box 64141, Al Ain, UAE; khairi.mustafa@aau.ac.ae (K.M.S.F.); dana.obaid@aau.ac.ae (D.E.E.O.); sadik.sayed@aau.ac.ae (S.S.)
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Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

Diagnostic Microbiology and Infectious Disease 85 (2016) 347–351

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

Antimicrobial Susceptibility Studies

Bioequivalence and in vitro antimicrobial activity between generic and brand-name levofloxacin

Hsin-Yun Sun [a], Hsiao-Wei Liao [b], Meng-Huei Sheng [c], Hui-Min Tai [a], Ching-Hua Kuo [b,d], Wang-Huei Sheng [a,*]

[a] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[b] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan
[c] Jia-Nan University of Pharmacy and Science, Tainan, Taiwan
[d] Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

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JIPH-687; No. of Pages 2

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Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Letter to the Edito

Relative potency of different generic brands of Piperacillin–Tazobactam: Implications for public health

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

International Journal of Antimicrobial Agents 49 (2017) 189–197

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

In vivo pharmacodynamics of piperacillin/tazobactam: implications for antimicrobial efficacy and resistance suppression with innovator and generic products

Carlos A. Rodriguez [a], Maria Agudelo [a,b], Andres F. Zuluaga [a], Omar Vesga [a,b,*]

[a] GRIPE (Grupo Investigador de Problemas en Enfermedades Infecciosas), Facultad de Medicina, Universidad de Antioquia, Medellín, Antioquia, Colombia
[b] Infectious Diseases Unit, Hospital Universitario San Vicente Fundación, Medellín, Colombia

Vancomycin: evidence of non-therapeutic equivalence revealed by a PK/PD animal model in Colombia

Neutropenic mouse thigh infection model

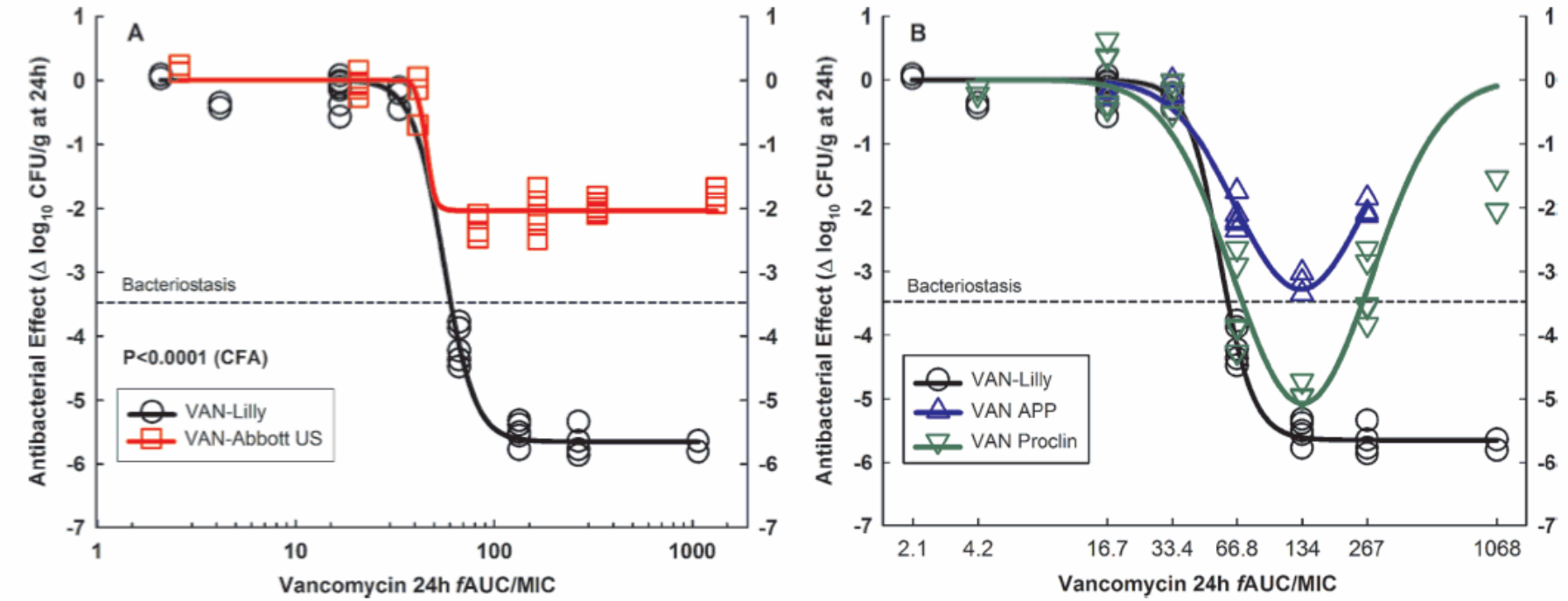

FIG. 1. *In vivo* efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 $\log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per 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 – PMID 20547818

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

Neutropenic mouse thigh infection model

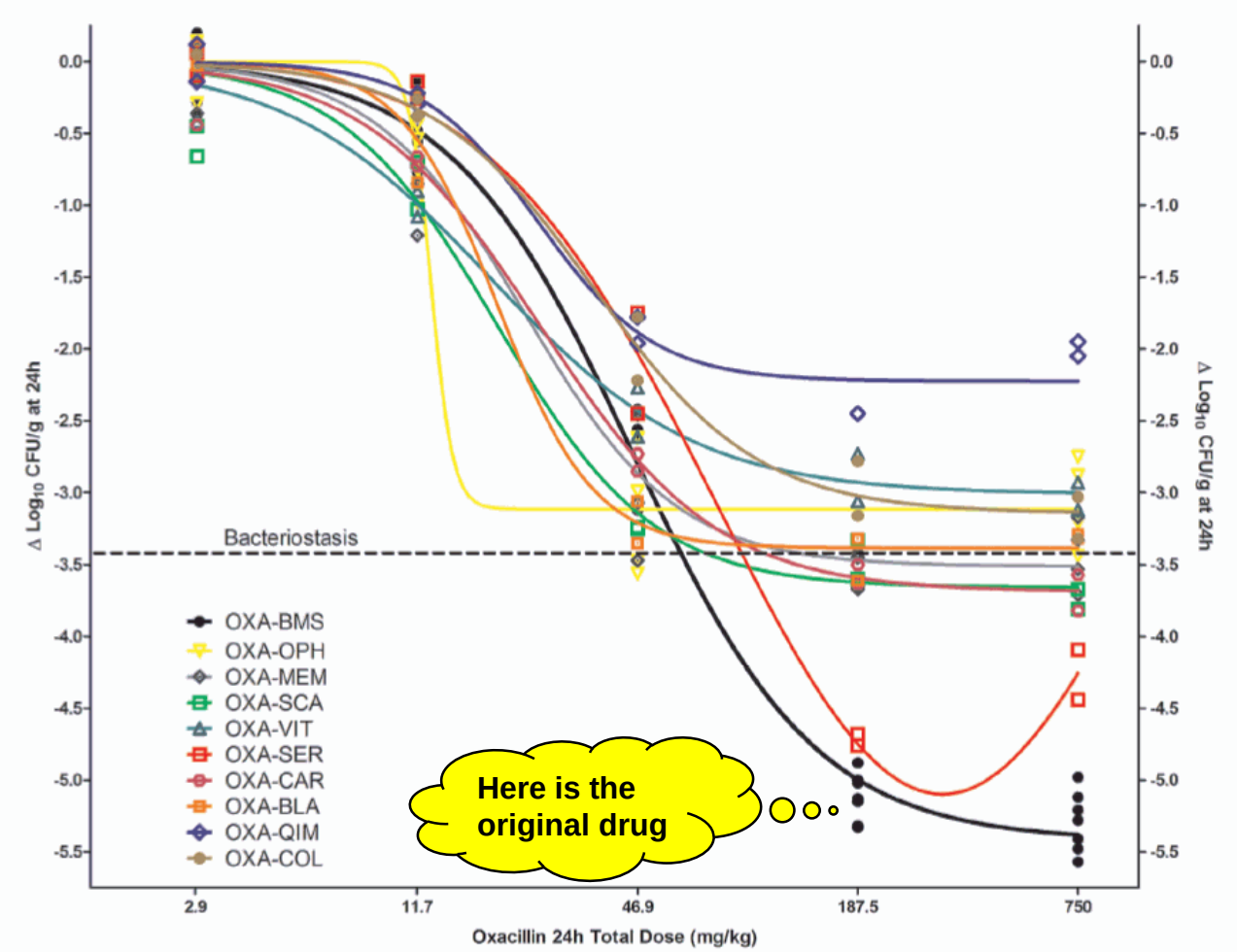

Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model. OXA-BMS (innovator, black curve) and 8 generics fitted to Hill's sigmoid model, while generic product OXA-SER fitted to the Gaussian U-shaped model (red curve). Regardless 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 Infect Dis. 2010 Jun 4;10:153 – PMID 20525378

But pharmacodynamics equivalence can also be demonstrated

AAC Journals.ASM.org

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]

Rodriguez *et al.* Antimicrob Agents Chemother 2015;59:53-58 - PMID 25313208

But pharmacodynamic equivalence can also be demonstrated

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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

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

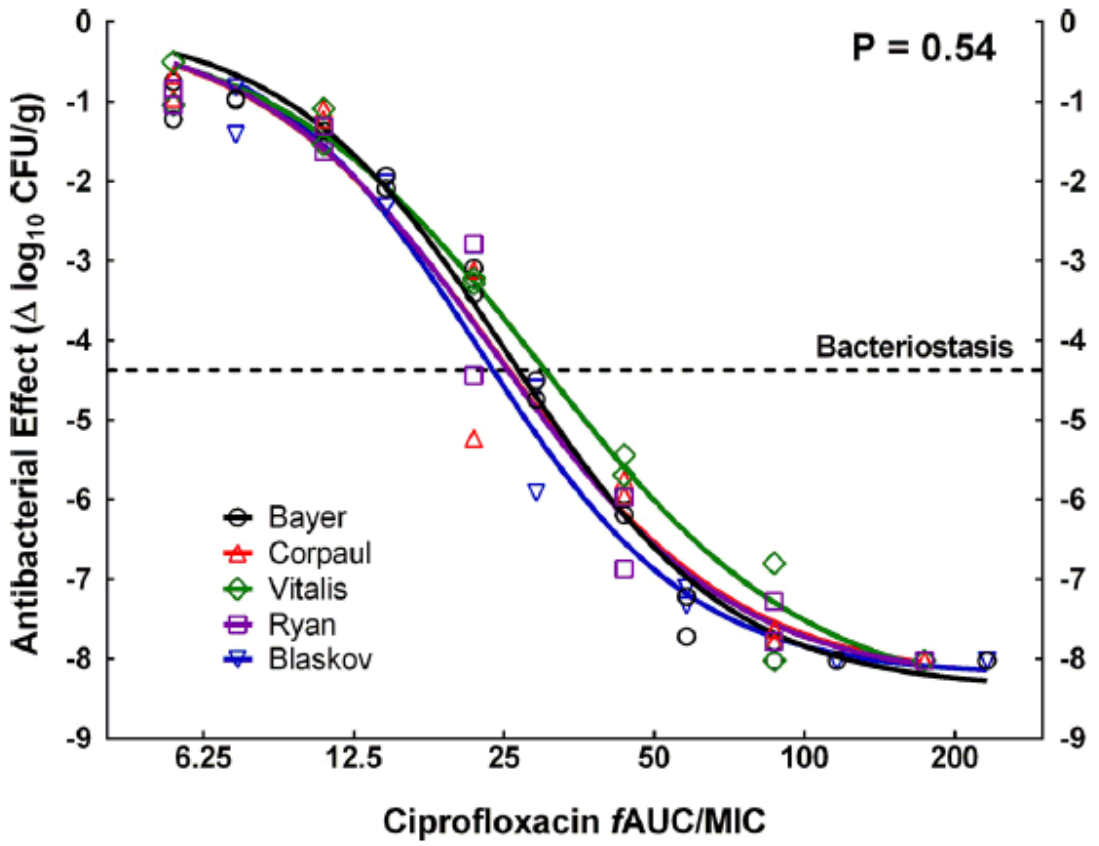


FIG 1 *In vivo* exposure-response relationship of ciprofloxacin against *P. aeruginosa* PAO1, comparing the innovator and four generic products. Global CFA indicated that all data belonged to the same population and could be described by a single curve, confirming the therapeutic equivalence of the generics.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

Rodriguez *et al.* Antimicrob Agents Chemother 2015;59:53-58 - PMID 25313208

Piperacillin/tazobactam generics and resistance

PLOS ONE

RESEARCH ARTICLE

Impact on Bacterial Resistance of Therapeutically Nonequivalent Generics: The Case of Piperacillin-Tazobactam

Carlos A. Rodriguez[1], Maria Agudelo[1,2], Yudy A. Aguilar[1], Andres F. Zuluaga[1], Omar Vesga[1,2]*

1 GRIPE (*Grupo Investigador de Problemas en Enfermedades Infecciosas*), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia, 2 Infectious Diseases Unit, Hospital Universitario San Vicente Fundación, Medellín, Colombia

Rodriguez *et al.* PLoS One. 2016;11:e0155806 - PMID 27191163

After only 24 hours of treatment in the neutropenic murine thigh infection model, the generic amplified the resistant subpopulation up to 20-times compared with the innovator.

Piperacillin/tazobactam generics and resistance

PLOS ONE

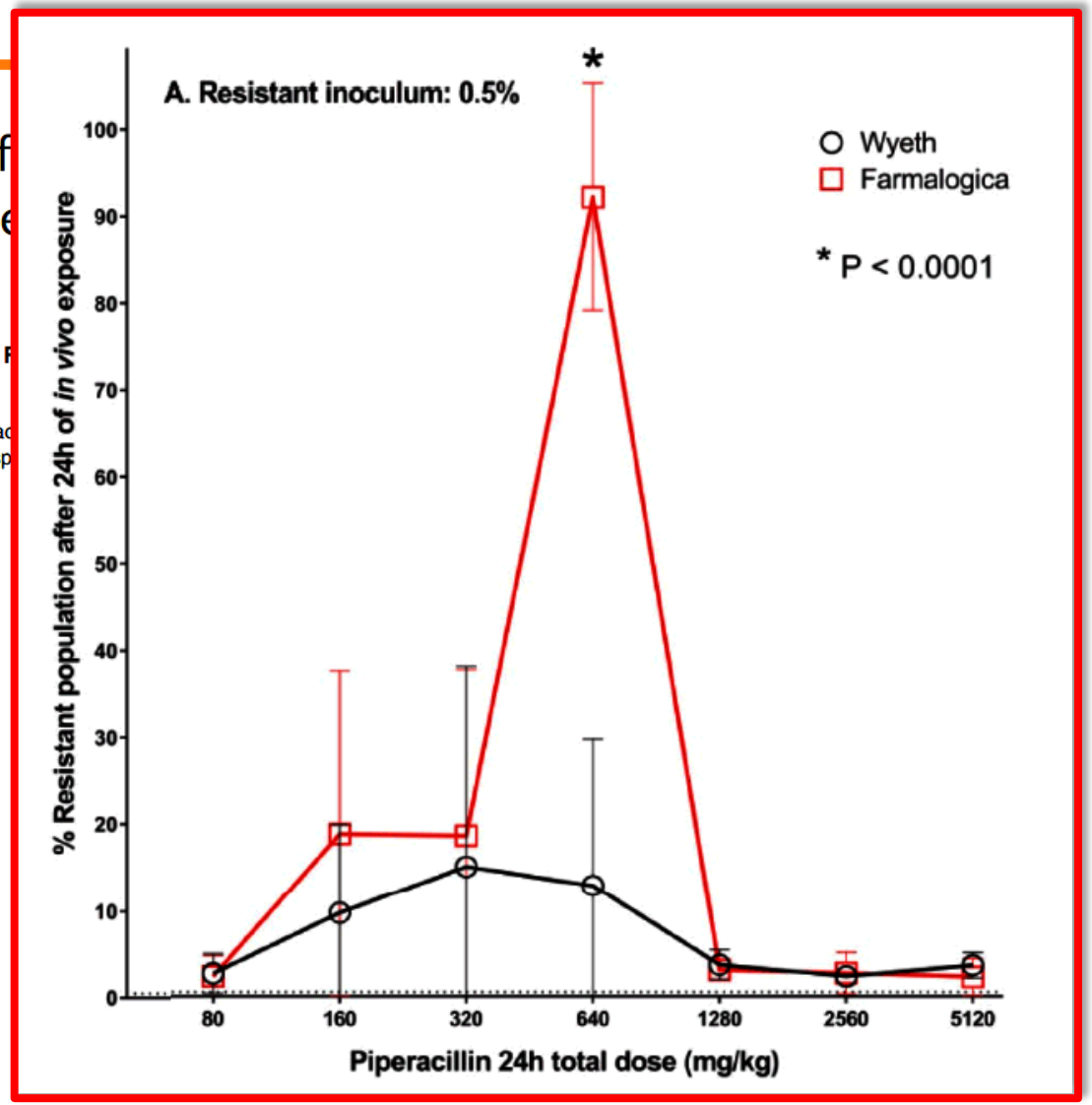
RESEARCH ARTICLE

Impact on Bacterial Resistance of Therapeutically Nonequivalent Ge Case of Piperacillin-Tazobactam

Carlos A. Rodriguez[1], Maria Agudelo[1,2], Yudy A. Aguilar[1], Andres F Omar Vesga[1,2]*

1 GRIPE (*Grupo Investigador de Problemas en Enfermedades Infecciosas*), Fac Universidad de Antioquia, Medellín, Colombia, 2 Infectious Diseases Unit, Hosp Vicente Fundación, Medellín, Colombia

Rodriguez *et al.* PLoS One. 2016;11:e0155806 - PMID 27191163



Resistance proportion after *in vivo* exposure of a mixed *E. coli* population to innovator (Wyeth) and generic (Farmalogica). The generic significantly enriched the resistant subpopulation at 640 mg/kg per day (P<0.0001), without differences at the other doses.

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

Gallelli *et al.* J Pharmacol Pharmacother. 2013;4(Suppl 1):S110-114 - PMID 24347975

> "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."

Interesting case reports…

Case 1

- 70-old patient with recurrent urinary infections with previous history of skin reaction after amoxicillin treatment.
- diagnosis of acute cystitis
  → 7 days treatment with ciprofloxacin (750 mg once daily)
  MIC 4.9 mg/L; range: 0.06-8)
- patient takes generic ciprofloxacin (Mylan Generics 750)…
- at day 7, persistence of cystitis !
- switch to Ciproxin® Bayer
  → improvement of clinical symptoms and laboratory values (no side effect)

this is fairly high… requiring full drug efficacy

Interesting case reports…

Case 2

- 72-old patient with acute bacterial bronchitis…
- prescribed levofloxacin 500 mg/day
- patient is given Ranbaxy ® by the pharmacist (cheaper…)
- after 4 days, no relief…

- switch to Tavanic® (Sanofi)
  → complete improvement of symptoms in 2 days without side-effects

dose is OK but on the low side…*

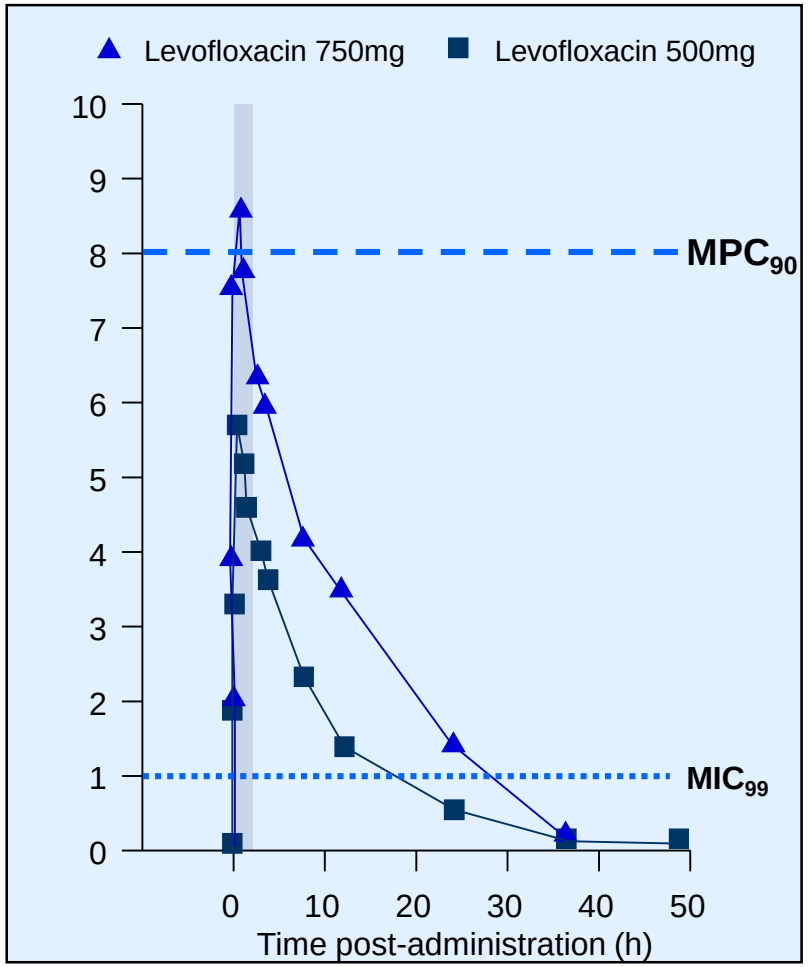
S. pneumoniae:
Most strains have an MIC of 1-2 mg/L, requiring high doses (2 x 500 mg/day)

European Committee on Antimicrobial Susceptibility Testing
Breakpoint tables for interpretation
http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf
Last updated: 1 Jan 2019
Last visited: 9 Oct 2019

Why could a low dose of levofloxacin also trigger emergence of resistance ?

Its all a question of **MPC** (mutant prevention concentration) and blood levels !

Here are the blood levels



But here is the concentration needed to **eliminate the first mutants** (**MPC**)

Here is the **MIC** (= bacteria stop growing…)

Drlica & Schmitz. *J Chemother* 2002; 14(Suppl 2): 5–12 – PMID: 12003139

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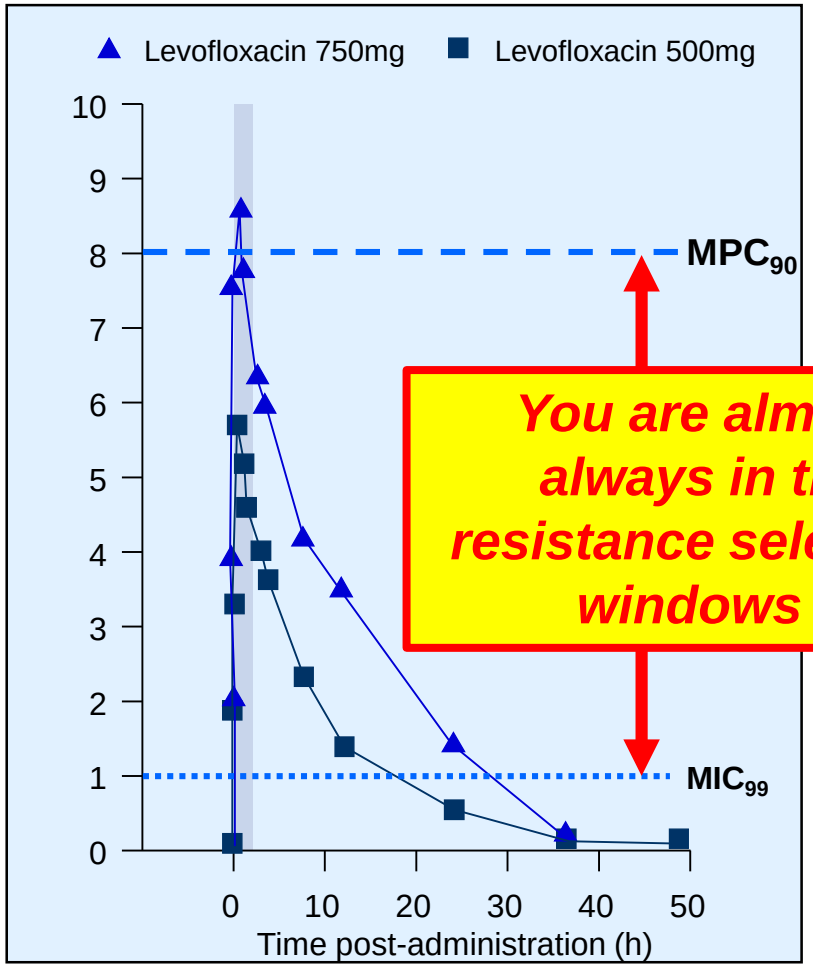


You are almost always in the resistance selection windows !

But here is the concentration needed to **eliminate the first mutants** (**MPC**)

Here is the **MIC** (= bacteria stop growing…)

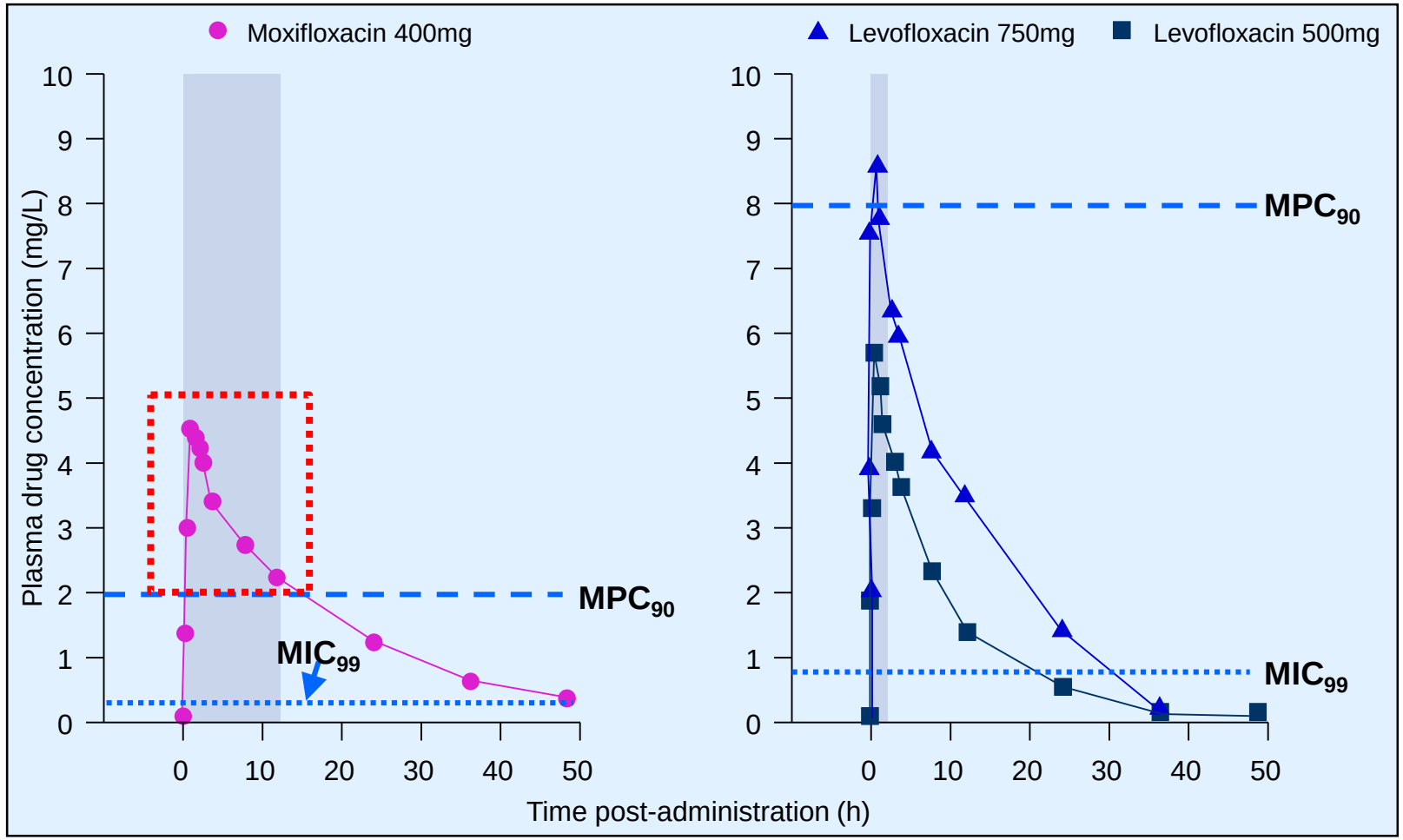
Drlica & Schmitz. *J Chemother* 2002; 14(Suppl 2): 5–12 – PMID: 12003139

Why is moxifloxacin at a lower risk of resistance ?

1. The blood levels are lower …

2. But the MPC and the MIC are much lower….

3. **You stay <u>much longer above</u> the MPC !**



Drlica & Schmitz. *J Chemother* 2002; 14(Suppl 2): 5–12 – PMID: 12003139

Clinical alerts (efficacy and safety) ?

Safety and efficacy of generic drugs wit to brand formulation

Luca Gallelli[1], Caterina Palleria[1], Antonio De Vuono[2], Laura Mumoli[1], Piero V Emilio Russo[1]

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

Gallelli *et al.* J Pharmacol Pharmacother. 2013;4(Suppl 1):S110-114 - PMID 24347975

"In this case-review, we report treatment with generic formula discuss the relative reasons als of 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.

Clinical alert: a large comparative study

ELSEVIER

BRITISH INFECTION SOCIETY

www.elsevierhealth.com/journals/jinf

Incidence of postoperative infections in patients undergoing coronary artery bypass grafting surgery receiving antimicrobial prophylaxis with original and generic cefuroxime☆

Ekaterini Mastoraki, Argyris Michalopoulos*, Ioannis Kriaras, Ero Mouchtouri, Matthew Falagas, Dimitra Karatza, Stefanos Geroulanos

Mastoraki et al. J Infect. 2008;56:35-9 - PMID: 17983660

- Study design: two parts study:
  - prospective
  - retrospective
- Treatment:
  - 4 weeks with original cefuroxime (oCFX) followed by 4 weeks with generic cefuroxime (gCFX) in each part
  - total study duration: 16 weeks
- Patient population:
  - 618 consecutive adult patients (pump coronary artery bypass grafting surgery).

Clinical alert: a large comparative study

Table 2 Postoperative infections in the compared groups of patients

Postoperative infections	oCFX ($n = 313$)		gCFX ($n = 305$)		p value
	n	%	n	%	
Surgical site infections	6	1.9	31	10.1	<0.0001
Bacteremia	2	0.6	8	2.6	0.10
Septic shock	0	0	6	2.0	0.04
Total postoperative infections	8	2.5	39	12.8	<0.001

oCFX: original cefuroxime, gCFX: generic cefuroxime.
$p < 0.05$ statistically significant.

Mastoraki et al. J Infect. 2008;56:35-9 - PMID: 17983660

Clinical alert: a large comparative study

Table 2 Postoperative infections in the compared groups of patients

Postoperative infections	oCFX ($n = 313$)		gCFX ($n = 305$)	p value
	n	%	*n*	
Surgical site infections	6	1.9	31	
Bacteremia	2	0.6	8	
Septic shock	0	0	6	
Total postoperative infections	8	2.5	39	

oCFX: original cefuroxime, gCFX: generic cefuroxime.
$p < 0.05$ statistically significant.

Table 3 Pathogens isolated in the compared groups of patients

Infecting pathogens	received oCFX	received gCFX
Staph. coag. negative	4	17
Staph. aureus	2	3
Staph. hominis	1	3
Enterococcus	–	2
Bacillus species	–	4
Klebsiella	–	3
E. coli	–	3
Others	1	4

oCFX: original cefuroxime, gCFX: generic cefuroxime.

Mastoraki et al. J Infect. 2008;56:35-9 - PMID: 17983660

2d round of conclusions and discussion

- There are contradictory observations about the **lack of pharmacodynamic and therapeutic equivalence** of generic antibiotics **showing acceptable bioequivalence** (even from the same investigators when comparing different products !)

  → These suggest **differences in biophysical properties** that will impact on the inter- and intra-organ bioavailability, which **cannot be detected by simple bioequivalence studies that rely on measurements of serum levels** after drug extraction…

- **Clinical data** are also **contradictory**, but, generally speaking, large databases are **difficult to assemble** (lack of funds) and studies with **well defined products for sufficient long periods** are made **almost impossible** (change of supplier, of batches…)

2d round of conclusions and discussion

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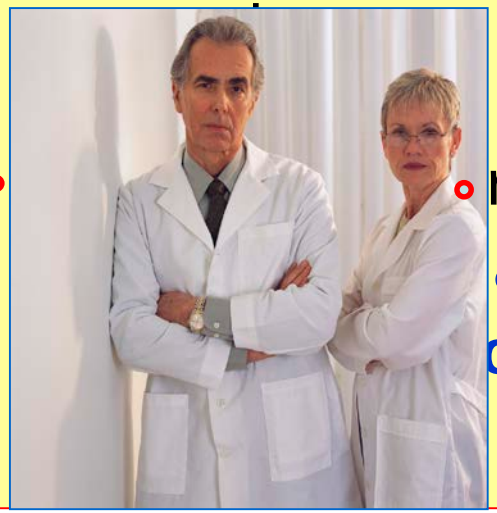


Who can we really trust ?

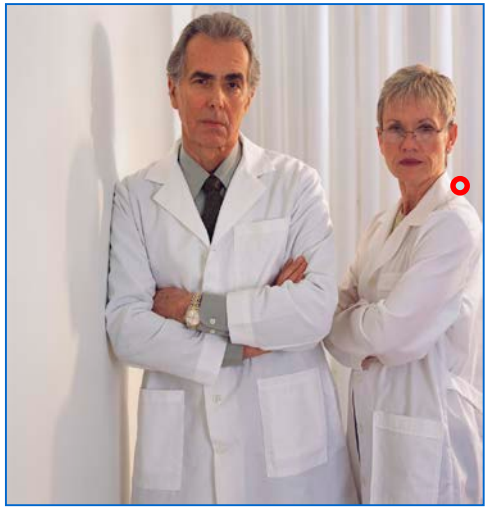
2d round of conclusions and discussion

Currently, purchasers have only limited information that can be used to assess the state of quality management of any specific facility and have little information linking the drug products they buy with the facilities where they were manufactured.

…

… [*As a result*], manufacturers are more likely to keep costs down by minimizing investments in manufacturing quality, which eventually leads to **quality problems**, triggering supply disruptions and shortages.

Guess who wrote that …



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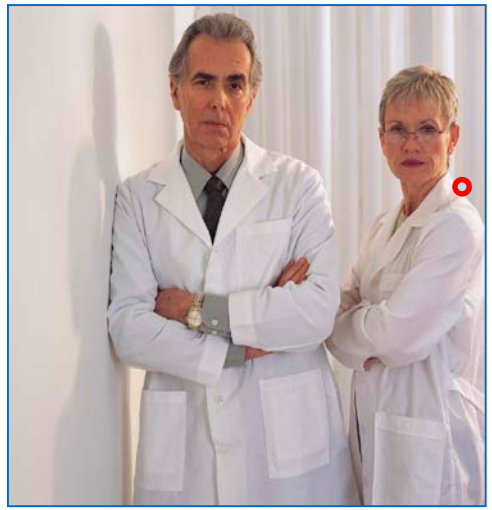


Who can we <u>really</u> trust ?

Guess who wrote that …

FDA U.S. FOOD & DRUG ADMINISTRATION

In Drug Shortages: root causes and potential solutions
Available from: https://www.fda.gov/media/131130/download - last visited: 29 Oct 2019

And this brings me to pharmaceutical quality…
What is your opinion ?

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

Please, think about what YOU would choose !

Dissolution of meropenem in Japan

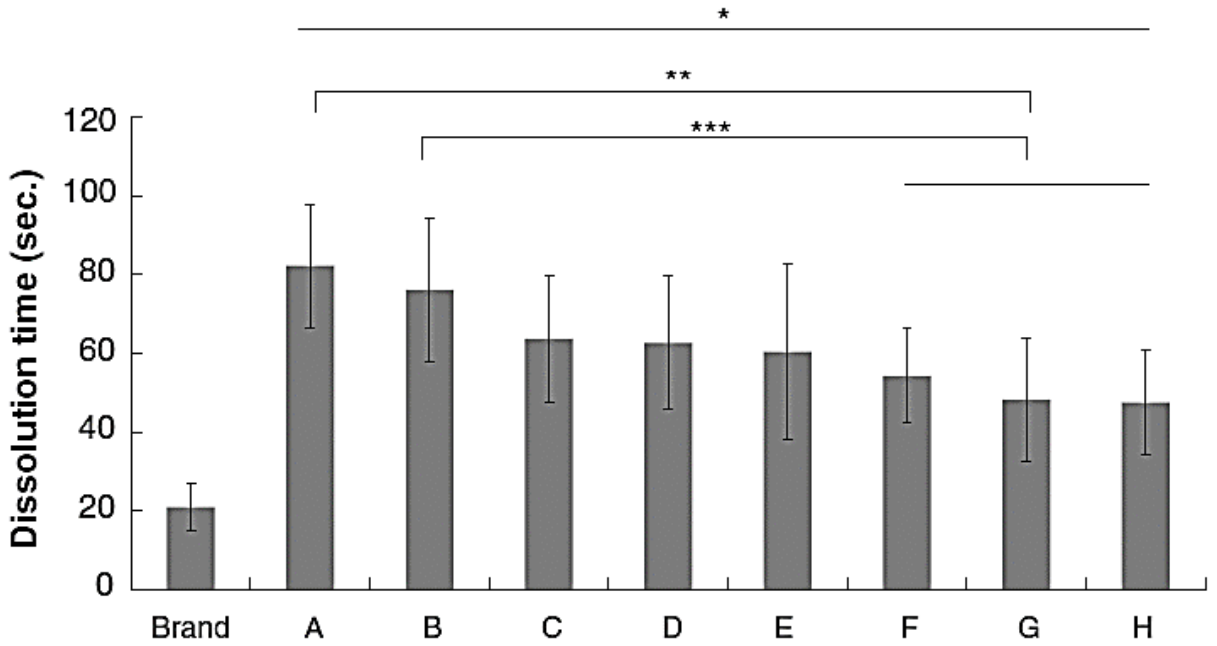


Fig. 3 Comparison of dissolution time between brand name meropenem and eight generics. *A–H* Generic products of meropenem. $*P < 0.001$ versus brand name drug; $**P < 0.001$ versus generic A drug; $***P < 0.001$ versus generic B drug

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427 – PMID 22684334

Crystals size in meropenem in Japan

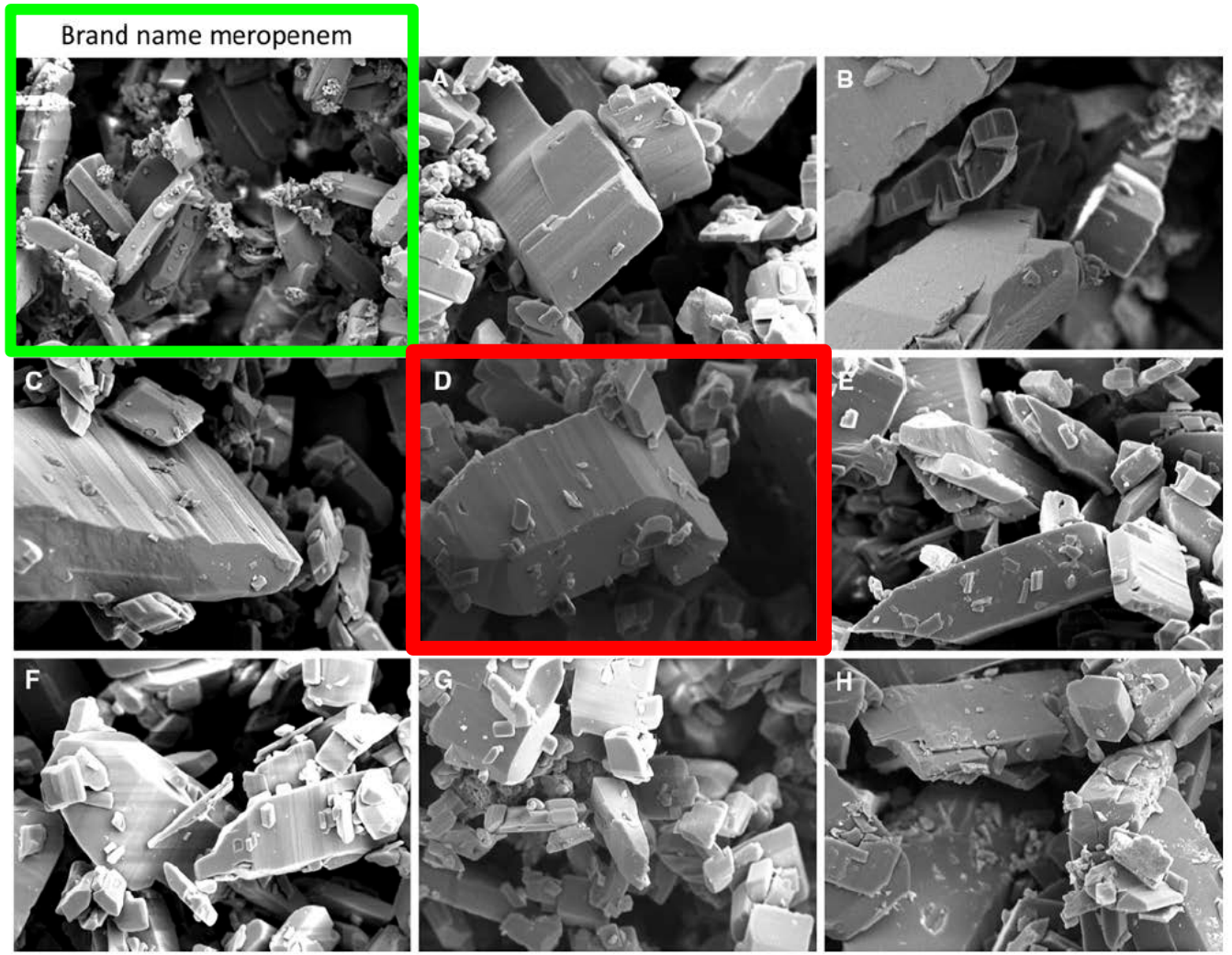
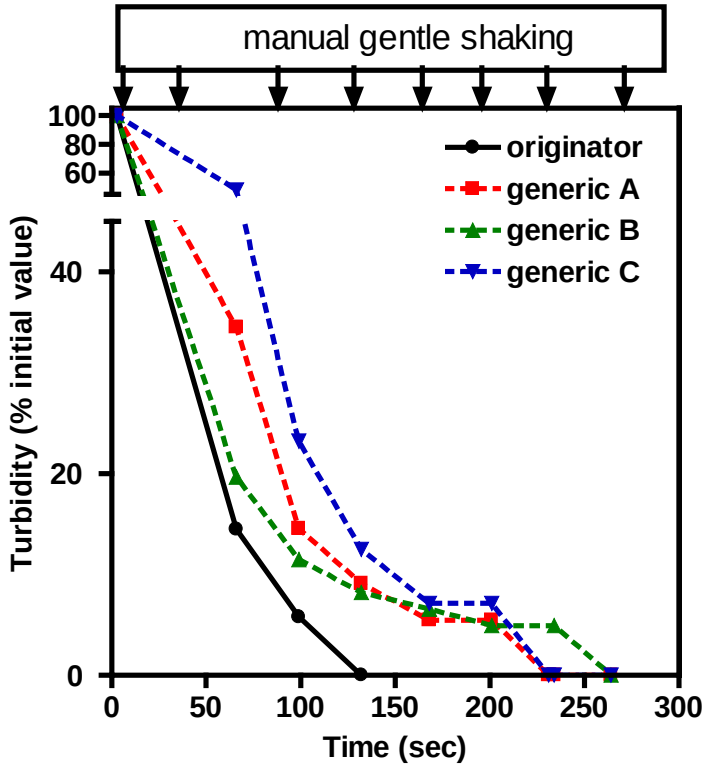


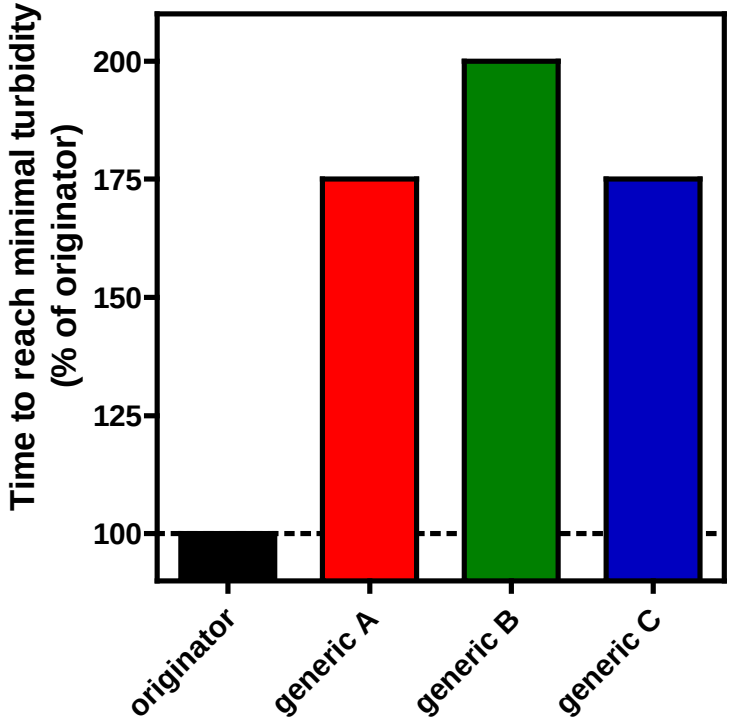
Fig. 4 Electron micrographs of drug particles of brand name meropenem and eight generics. **a–h** Generic products of meropenem. ×1,000

Fujimura & Watanabe J Infect Chemother (2012) 18:421–427 – PMID 22684334

Dissolution of meropenem in Belgium

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





Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (2017)
Delattre et al. Int J Antimicrob Agents 2019 – in press - https://doi.org/10.1016/j.ijantimicag.2019.10.006

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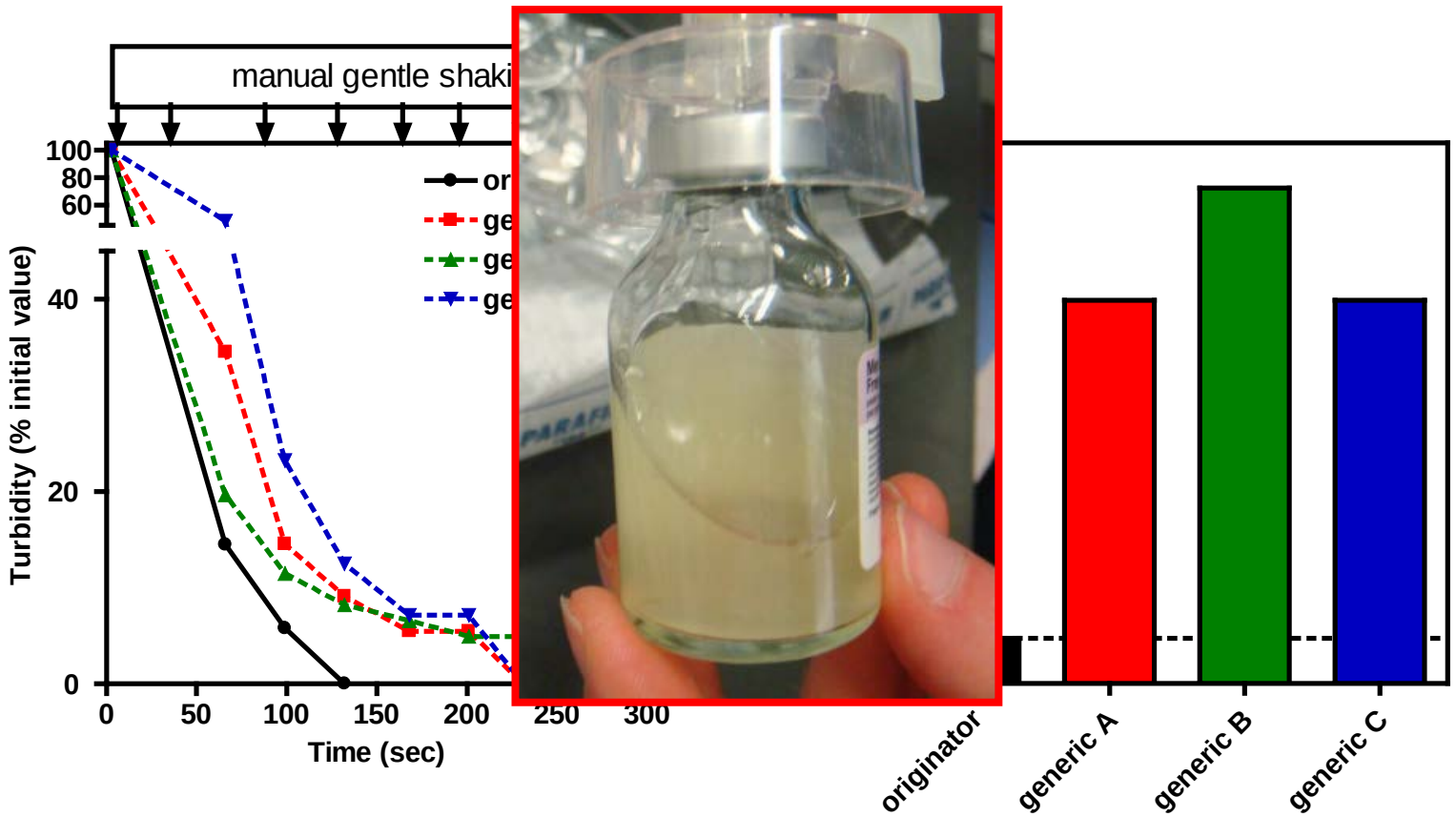

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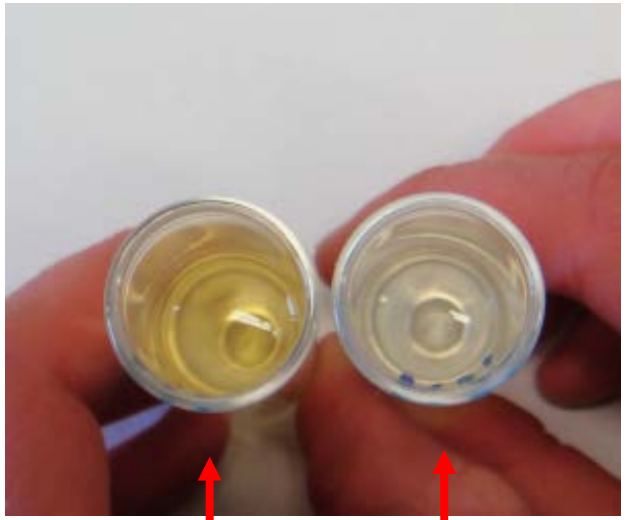
Impurities in meropenem: coloured compounds



generic B originator

are you happy with the colour?

Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (2017)
Delattre et al. Int J Antimicrob Agents 2019 – in press - https://doi.org/10.1016/j.ijantimicag.2019.10.006

Impurities in ciprofloxacin…

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

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

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

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

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

Abstract

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

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

Trefi *et al.* J Pharm Biomed Anal 2007;44:743-754 - PMID 17446031

Impurities in ciprofloxacin

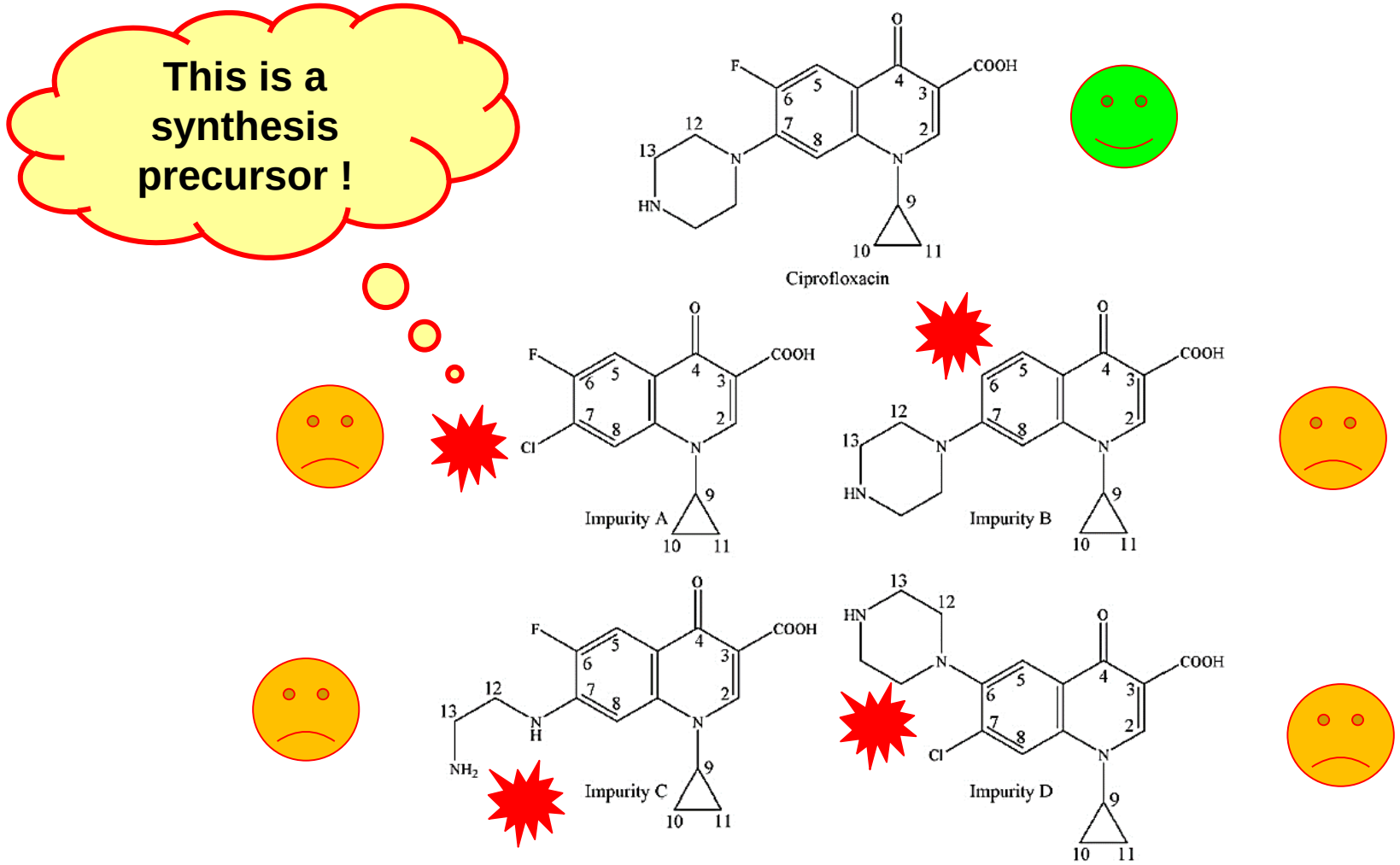
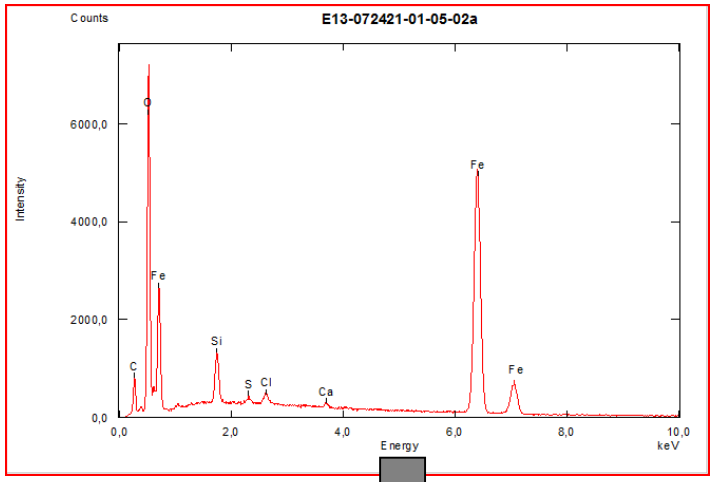


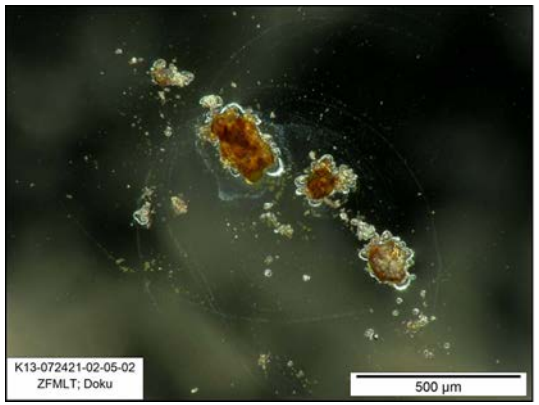
Fig. 1. Structure of ciprofloxacin and its main impurities.

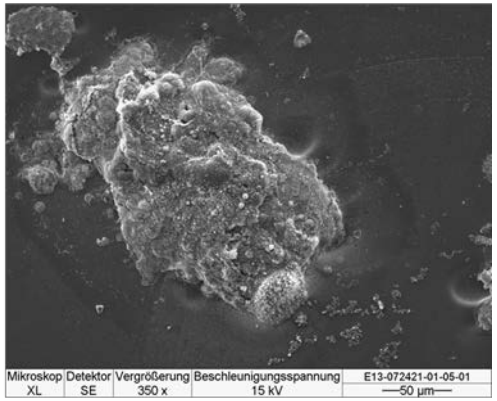
Trefi *et al.* J Pharm Biomed Anal 2007;44:743-754 - PMID 17446031

Difficulties to prepare particles-free IV moxifloxacin..

- Several development approaches were investigated
- Formulation work turned out to be more difficult than expected
- Initially, NaCl was preferred over glucose, to minimize the risks for patients with diabetes
- Character of the molecule led to problems of **subvisible particle formation over the storage time**
- Glucose and other sugars or sugar alcohols were patented for isotonization but never marketed, as formation of subvisible particles was assessed to be difficult to control
- NaCl formulation was considered to be the safest formulation for patients







From a presentation made by Linc Chen, PhD and Pharmacist, Head of GCPD China Bayer Healthcare Beikink, China, 26 Jun 2013.

Looking to some generics of IV-moxifloxacin

- **Turkish market product**
  – data are not available
- **Indian market product**
  (4 batches from 2 products)
  - 3 out of 4 batches have insufficient enantiomeric purity
  - 1 batch contains excessive unspecified impurity
- **Chinese product** (Primenor)
  - H_2O formulation, concentrated (0.4 g/20 mL)
  - higher pH (5.2; Avelox® 4.1–4.6)
  - requires dilution prior to use

Conclusion – Generic products

- may contain **insufficient quantity of active drug** and **excessive impurities**
- may not meet the regulatory requirements
  → causing **potential harm to patients**…
- may not be **not ready-to-use…**
  → risk when handling the medication
  (*variations in drug quality if using different diluents*)

From a presentation made by Linc Chen, PhD and Pharmacist, Head of GCPD China Bayer Healthcare Beikink, China, 26 Jun 2013.

Other subtle differences: the case of meropenem

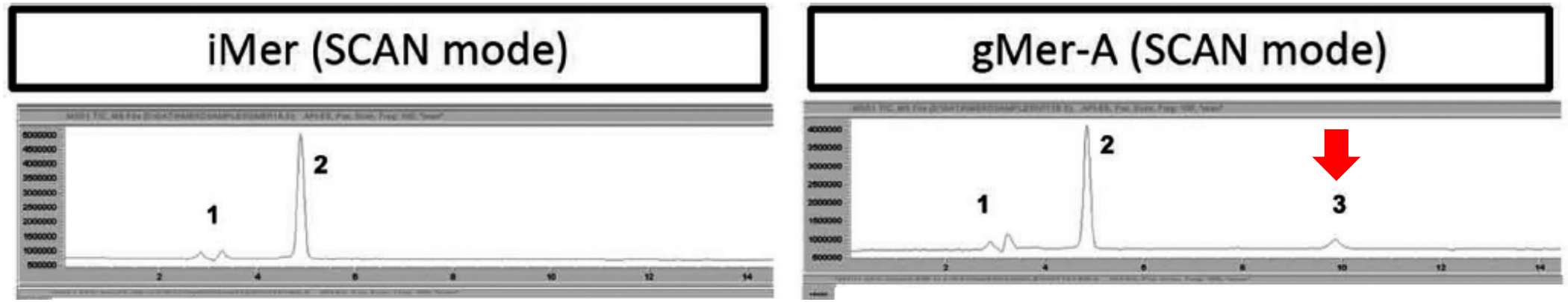
AAC Journals.ASM.org

Even Apparently Insignificant Chemical Deviations among Bioequivalent Generic Antibiotics Can Lead to Therapeutic Nonequivalence: the Case of Meropenem

M. Agudelo,[a,b] C. A. Rodriguez,[a,b] C. A. Pelaez,[c] O. Vesga[a,b,d,e]

GRIPE: Grupo Investigador de Problemas en Enfermedades Infecciosas,[a] Department of Pharmacology,[b] and Section of Infectious Diseases, Department of Internal Medicine,[d] School of Medicine, and Institute of Chemistry, School of Exact and Natural Sciences,[c] Universidad de Antioquia, Medellín, Colombia; Infectious Diseases Unit, Hospital Universitario de San Vicente Fundación, Medellín, Colombia[e]

Agudelo et al. Antimicrob Agents Chemother. 2014;58:1005-18. - PMID: 24277034



LC/MS scan mode (range, *m/z* 100 to 1,000) of the pharmaceutical forms of one generic and the innovator of meropenem (fresh samples). The generic product exhibited one additional peak, detected at 10 min (peak 3, right panel), with a main molecular mass of *m/z* 359 [M 1] that was absent in the mass spectra of the innovator.

Other subtle differences: the case of meropenem

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Even Apparently Insignificant Chemical Deviations Bioequivalent Generic Antibiotics Can Lead to The Nonequivalence: the Case of Meropenem

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Medicine,[d] School of Medicine, and Institute of Chemistry, School of Exact and Natural Sciences,[c] Universidad de Antioqui
Hospital Universitario de San Vicente Fundación, Medellín, Colombia[e]

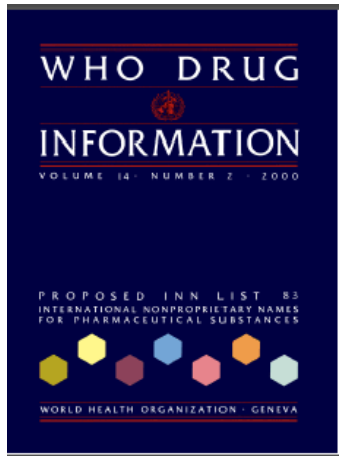
Agudelo et al. Antimicrob Agents Chemother. 2014;58:1005-18. - PMID: 24277034

Two generics differed significantly from the innovator in the guinea pig and mouse models, while the third generic was therapeutically equivalent under all conditions.

Trisodium adducts in a bioequivalent generic made it more susceptible to DHP-I hydrolysis and less stable at room temperature, explaining its **therapeutic nonequivalence.**

These failing generics are compliant with USP requirements and **would remain undetectable under current regulations**.

Problems known by the World Health organization since 2000…



WHO Drug Information Vol. 14, No. 2, 2000

General Policy Issues

Generic drugs: the hidden issues of quality and cost

Jean-Yves Videau, General Manager, Centrale humanitaire médicopharmaceutique (CHMP), France, (http://www.chmp.org) in collaboration with Bonnie Fundafunda, Echo International Health Services, United Kingdom (http://www.echohealth.org.uk)

Available for download at http://apps.who.int/medicinedocs/pdf/h1463e/h1463e.pdf
Last accessed: 6 Oct 2019

Although the manufacture of generic essential drugs offers a practical way of [providing an acceptable level of health care at a reasonable cost], the quality of these products tends to be jeopardized by overriding considerations of cost.

The FDA takes this seriously …

FDA U.S. FOOD & DRUG ADMINISTRATION

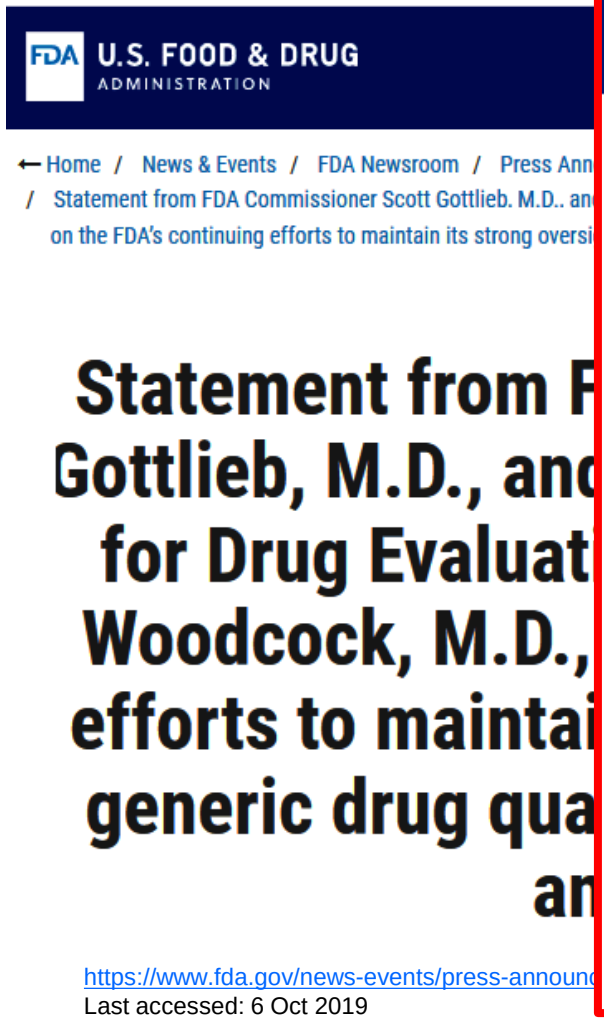
← Home / News & Events / FDA Newsroom / Press Announcements / Statement from FDA Commissioner Scott Gottlieb. M.D.. and Director of FDA's Center for Drug Evaluation and Research Janet Woodcock, M.D., on the FDA's continuing efforts to maintain its strong oversight of generic drug quality issues domestically and abroad

FDA STATEMENT

Statement from FDA Commissioner Scott Gottlieb, M.D., and Director of FDA's Center for Drug Evaluation and Research Janet Woodcock, M.D., on the FDA's continuing efforts to maintain its strong oversight of generic drug quality issues domestically and abroad

https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-director-fdas-center-drug-evaluation-and-research-0
Last accessed: 6 Oct 2019

and issues warning letters…



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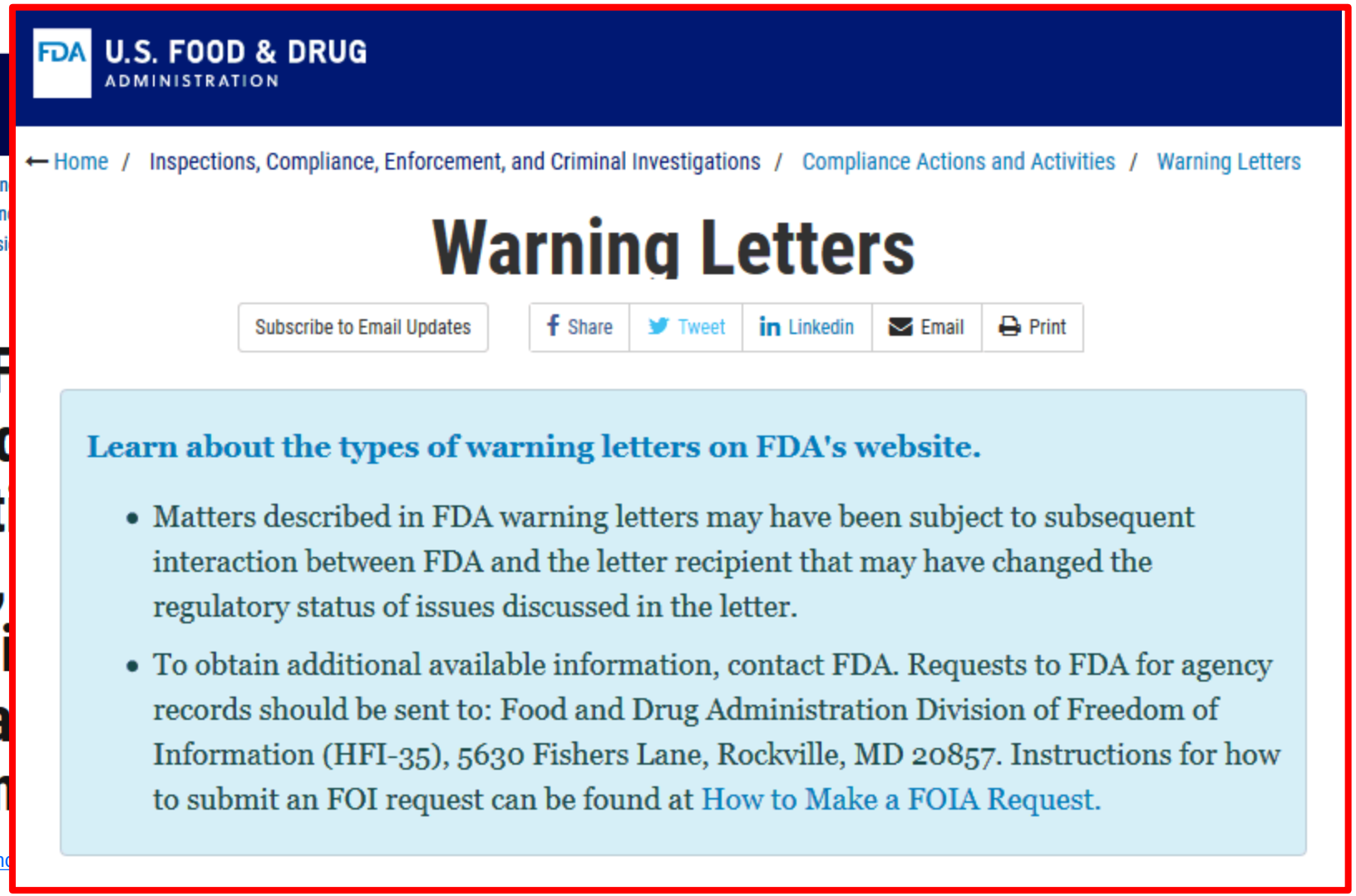
Last accessed: 6 Oct 2019



https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters
Current as of 10 Apr 2019
Last accessed: 6 Oct 2019

and issues warning letters…

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/ Statement from FDA Commissioner Scott Gottlieb. M.D.. an
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Last accessed: 6 Oct 2019

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Inspections, Compliance, Enforcement, and Criminal Investigations / Compliance Actions and Activities / Warning Letters

Warning Letters

Posted Date	Letter Issue Date	Company Name	Issuing Office	Subject	Response Letter	Closeout Letter
10/01/2019	08/29/2019	Shanghai Institute of Pharmaceutical Industry	Center for Drug Evaluation and Research	CGMP/Active Pharmaceutical Ingredient (API)/Adulterated /Refused Inspection		
10/01/2019	09/10/2019	Lupin Limited	Center for Drug Evaluation and Research	CGMP/Active Pharmaceutical Ingredient (API)/Adulterated		

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters
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Last accessed: 6 Oct 2019

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Current as of 10 Apr 2019
Last accessed: 6 Oct 2019

Which even led to criminal investigations…

THE UNITED STATES DEPARTMENT of JUSTICE

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JUSTICE NEWS

Department of Justice

Office of Public Affairs

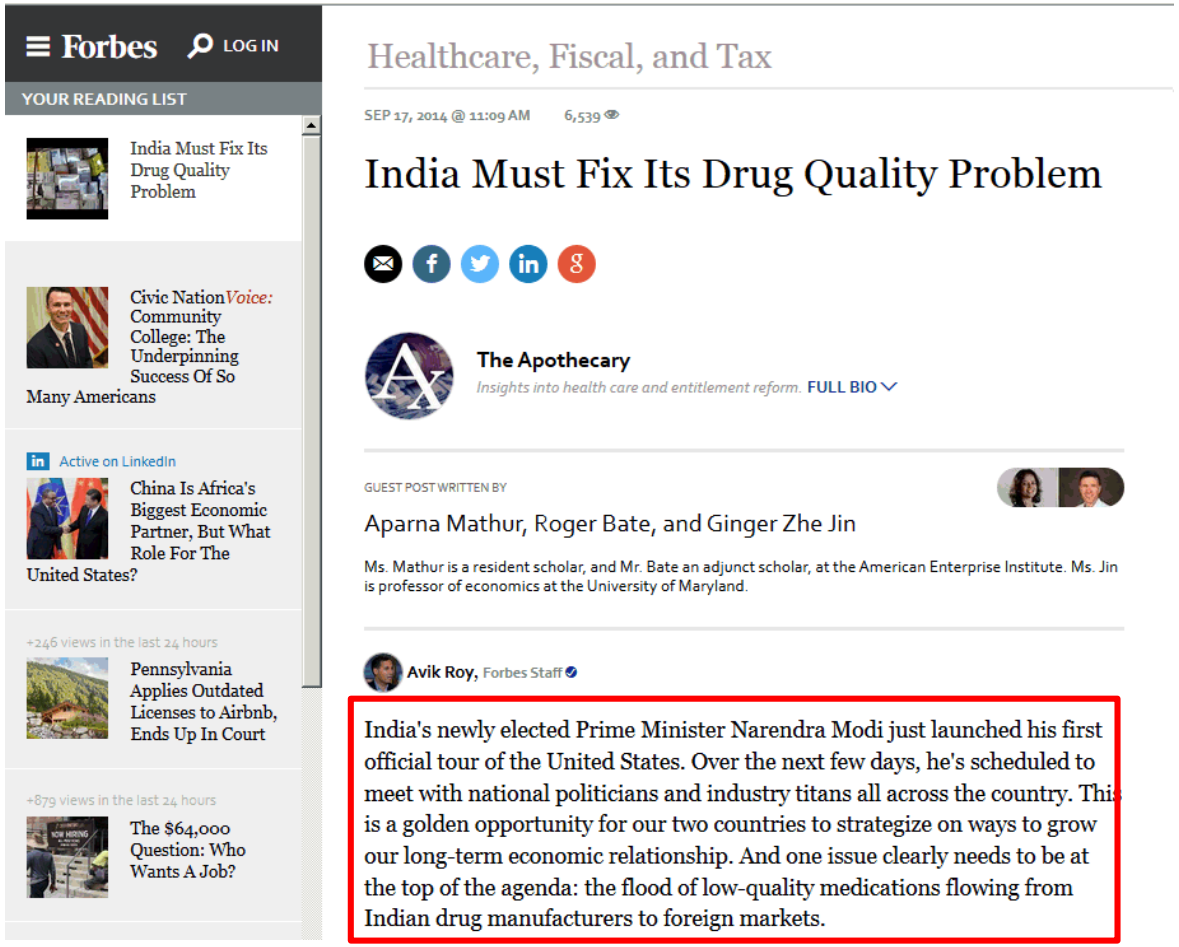
FOR IMMEDIATE RELEASE — Monday, May 13, 2013

Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to the FDA

In the largest drug safety settlement to date with a generic drug manufacturer, Ranbaxy USA Inc. , a subsidiary of Indian generic pharmaceutical manufacturer Ranbaxy Laboratories Limited, pleaded guilty today to felony charges relating to the manufacture and distribution of certain adulterated drugs made at two of Ranbaxy's manufacturing facilities in India, the Justice Department announced today. Ranbaxy also agreed to pay a criminal fine and forfeiture totaling $150 million and to settle civil claims under the False Claims Act and related State laws for $350 million.

https://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false
Last accessed: 6 Oct 2019

And we know the origins…



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The $64,000 Question: Who Wants A Job?

Healthcare, Fiscal, and Tax

SEP 17, 2014 @ 11:09 AM 6,539

India Must Fix Its Drug Quality Problem

The Apothecary

Insights into health care and entitlement reform. FULL BIO

GUEST POST WRITTEN BY

Aparna Mathur, Roger Bate, and Ginger Zhe Jin

Ms. Mathur is a resident scholar, and Mr. Bate an adjunct scholar, at the American Enterprise Institute. Ms. Jin is professor of economics at the University of Maryland.

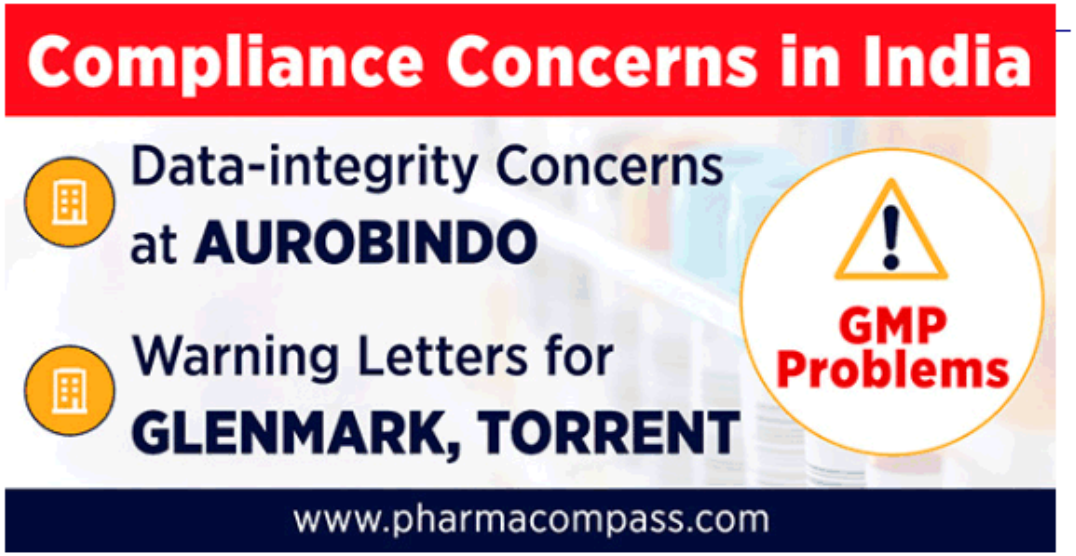
Avik Roy, Forbes Staff

India's newly elected Prime Minister Narendra Modi just launched his first official tour of the United States. Over the next few days, he's scheduled to meet with national politicians and industry titans all across the country. This is a golden opportunity for our two countries to strategize on ways to grow our long-term economic relationship. And one issue clearly needs to be at the top of the agenda: the flood of low-quality medications flowing from Indian drug manufacturers to foreign markets.

https://www.forbes.com/sites/theapothecary/2014/09/17/india-must-fix-its-drug-quality-problem/#5ebd4e0e70b3
Posted: 17 Sep 2014
Last accessed: 8 Oct 2019

And one issue clearly needs to be at the top of the agenda: **the flood of low-quality medications flowing from Indian drug manufacturers to foreign markets.**

And the problem persists…



India's leading generic drug manufacturers continue to be in the news for regulatory concerns regarding the state of their manufacturing compliance.

Data-integrity concerns at Aurobindo; FDA issues warning letters to Glenmark, Torrent

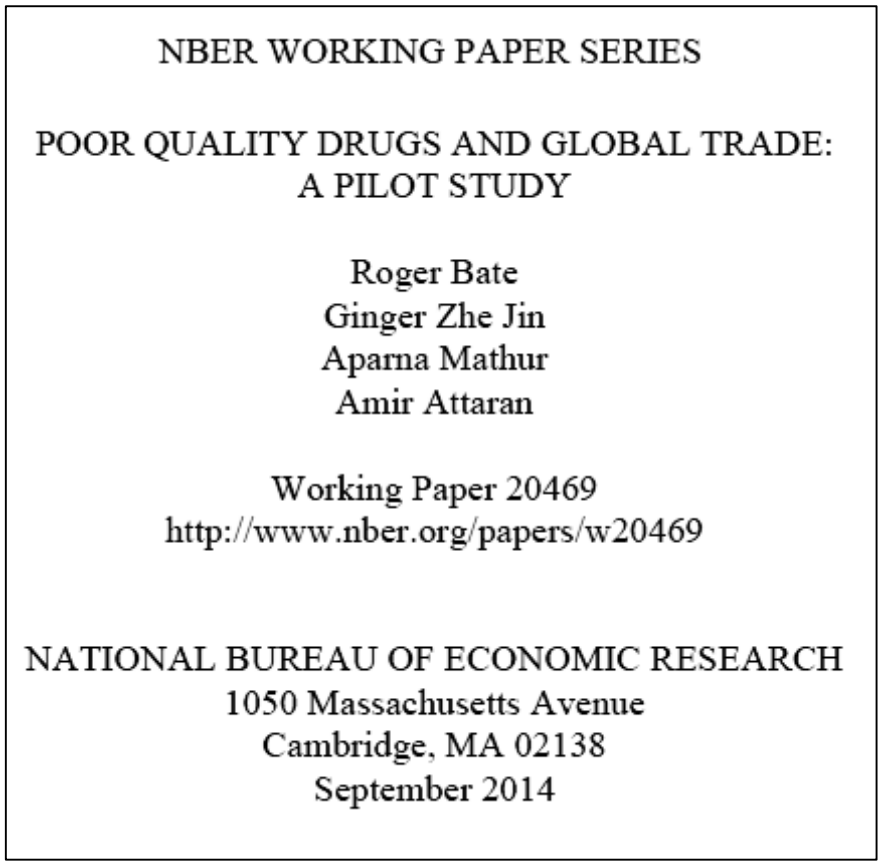
India's leading generic drug manufacturers continue to be in the news for regulatory concerns regarding the state of their manufacturing compliance.

Last week, after the US Food and Drug Administration (FDA) issued a warning letter to Lupin's Mandideep facility, there was news that Glenmark Pharmaceuticals has received a warning letter from the US agency for their facility in Baddi in Himachal Pradesh.

The regulatory concerns and actions being taken repeatedly by regulatory agencies only go on to reiterate that there are wide gaps in the manufacturing practices being adopted by some of the leading drug manufacturers of India.

https://www.pharmacompass.com/radio-compass-blog/data-integrity-concerns-at-aurobindo-fda-issues-warning-letters-to-glenmark-torrent
Posted: 10 Oct 2019
Last accessed: 10 Oct 2019

Caution: drug quality may vary according to where it is sold



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1050 Massachusetts Avenue
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September 2014

Available from https://www.nber.org/papers/w20469
Last accessed: 8 Oct 2019

"Pharmaceutical experts anecdotally have observed that some Indian manufacturers sell inferior medicines to markets where drug regulatory oversight is weak, and better medicines to markets where oversight is more effective."

Batches submitted to the FDA are (often) quite nice…

Quality Assessment of U.S. Marketplace Vancomycin for Injection Products Using High-Resolution Liquid Chromatography-Mass Spectrometry and Potency Assays

Michael E. Hadwiger,[a] Cynthia D. Sommers,[a] Daniel J. Mans,[a] Vikram Patel,[b] and Michael T. Boyne II[a]

Division of Pharmaceutical Analysis, CDER, Food and Drug Administration, St. Louis, Missouri, USA,[a] and Division of Drug Safety Research, CDER, Food and Drug Administration, Silver Spring, Maryland, USA[b]

In response to a published concern about the potency and quality of generic vancomycin products, the United States Food and Drug Administration investigated a small sampling of the vancomycin products available in North America with regard to purity, content, and potency. To facilitate identification of impurities, a new liquid chromatography method was developed using high-resolution mass spectrometry in addition to diode array detection to characterize impurities in several commercial products. Furthermore, a microbiological assay was utilized to link the analytical profiles with an *in vitro* potency. All products tested met the quality specifications outlined in the United States Pharmacopeia (USP) (vancomycin hydrochloride for injection monograph) for impurities and potency (USP, Vancomycin hydrochloride for injection. United States Pharmacopeia and National Formulary, vol USP 34-NF 29, 2011).

Hadwiger et al. Antimicrob Agents Chemother. 2012;56:2824-30 - PMID: 22371900

distributed in the US…

"All products tested met the quality specifications outlined in the United States Pharmacopeia (USP) (vancomycin hydrochloride for injection monograph) for impurities and potency (USP, Vancomycin hydrochloride for injection. United States Pharmacopeia and National Formulary, vol USP 34-NF 29, 2011)."

A recent review about the problems of sub-quality ciprofloxacin in some countries …

frontiers in Pharmacology

MINI REVIEW
published: 21 August 2017
doi: 10.3389/fphar.2017.00546

Interplay of the Quality of Ciprofloxacin and Antibiotic Resistance in Developing Countries

Deepali Sharma[1†], Rahul P. Patel[1†], Syed Tabish R. Zaidi[1], Md. Moklesur Rahman Sarker[2], Qi Ying Lean[3,4] and Long C. Ming[1,5*]*

[1] Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia, [2] Department of Pharmacy, State University of Bangladesh, Dhaka, Bangladesh, [3] Vector borne Diseases Research Group, Pharmaceutical and Life Sciences CoRe, Universiti Teknologi MARA, Shah Alam, Malaysia, [4] Faculty of Pharmacy, Universiti Teknologi MARA, Bertam, Malaysia, [5] School of Pharmacy, KPJ Healthcare University College, Negeri Sembilan, Malaysia

Sharma et al. Front Pharmacol. 2017;8:546 – PMID: 28871228

"The availability and use of substandard and spurious quality of oral ciprofloxacin formulations in the developing countries has been thought to have contributed toward increased risk of treatment failure and bacterial resistance.

Quality control and bioequivalence studies of the commercially available oral ciprofloxacin formulations should be monitored.

Appropriate actions should be taken against offending manufacturers in order to prevent the sale of substandard and spurious quality of ciprofloxacin formulations."

We should also address the CRIMINAL problem of counterfeited drugs

Packs bought at pharmacies in Lagos, Nigeria both sold as "CIPROTAB 500 ®"

The only noticeable difference is that the real package has a hologram on the back (left). **The fake was two-thirds talcum powder and contained no ciprofloxacin**. Even holograms can be faked.

- **25% of drugs sold worldwide are substandard and 50% in some Countries…**
- **It hurts low and middle income countries the most…**

Slide kindly communicated by S. Opal

Bate & Attaran A. Lancet. 2010;376(9751):1446-1448 - PMID 21036261

An unanticipated difficulty: the multicomponent drugs

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Discussion

Multicomponent antibiotic substances produced by fermentation: Implications for regulatory authorities, critically ill patients and generics

Adrian J. Brink[a,*], Guy A. Richards[b], Gaia Colombo[c], Fabrizio Bortolotti[c], Paolo Colombo[d], François Jehl[e]

Brink et al Int J Antimicrob Agents. 2014;43:1-6 - PMID: 23920094

Many antibiotics are multicomponent drugs:

- gentamicin (C_1, C_{1a}, C_2, C_{2b}
- teicoplanin (A_{2-1}, A_{2-2}, A_{2-3}, A_{2-4}, A_{2-5})
- colistin (E_1, E_2)
- …

An unancipated difficulty: the multicomponents drugs

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International Journal of Antimicrobial Agents

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Many antibiotics are multicomponent drugs:

- gentamicin (C$_1$, C$_{1a}$, C$_2$, C$_{2a}$, C$_{2b}$)

Polymyxin E_1 and E_2 variations from different colistin manufacturers assayed by HPLC with UV detection[a].

Manufacturer	No. of batches tested	Proportion (mean % ± S.D.)[b]		
		Polymyxin E_1	Polymyxin E_2	Polymyxin $E_1 + E_2$
1	7	15.6 ± 1.1	70.6 ± 0.5	86.2 ± 1.3
2	3	24.4 ± 1.4	64.5 ± 1.7	88.9 ± 0.3
3	1	47.8	43.9	91.7

HPLC, high-performance liquid chromatography; UV, ultraviolet; S.D., standard deviation.

[a] The table is original and reproduced with permission from Decolin et al. [22].

[b] Calculated by internal normalisation based on the area of the six main peaks.

Brink et alInt J Antimicrob Agents. 2014;43:1-6 - PMID: 23920094

3rd round of conclusions and discussion

- Generic drugs **may or may not** be of the same pharmaceutical quality as the original products

- The reasons for lower quality are
  - difficulties in **correctly reproducing the manufacturing and purifications procedures** of the originator
    (often more a “know how” than patentable matters)
  - the **race to low prices**
  - the fact that **controls may be insufficient** (after first registration)

- Only **stringent and continuous controls by public authorities** can help avoiding the flood of low quality products
  (but this may be difficult in face of the number of producers)

3rd round of conclusions and discussion

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We have 7 ciprofloxacinS **in Belgium … How many in your country and are they all fully tested ?**

What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
    1. MIC, MPC, heteroresistance …
    2. Approach to pharmacodynamic equivalence
    3. PK/PD animal models and clinical data
4. Dissolution, stability, impurities
5. **The hidden risks of "low cost" drugs**
    1. **overconsumption (and wrong publicity)**
    2. **lack of innovative research ...**
       unless the government (= you) pay !
    3. **Drug shortages …**
    4. **Price increases…**

We are facing contradictory situations …

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

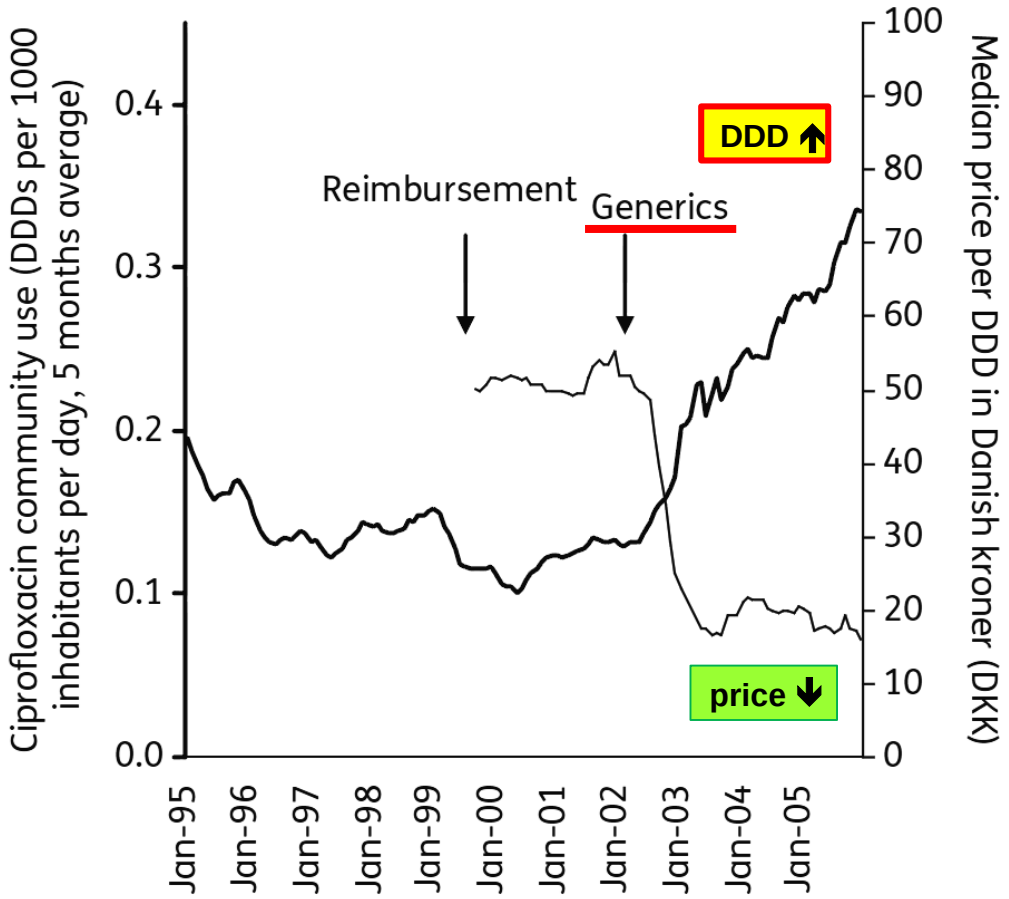
*Corresponding author. Tel: +44-(0)20-832-76689; E-mail: diane.ashiru-oredope@phe.gov.uk
†Members are listed in the Acknowledgements section.

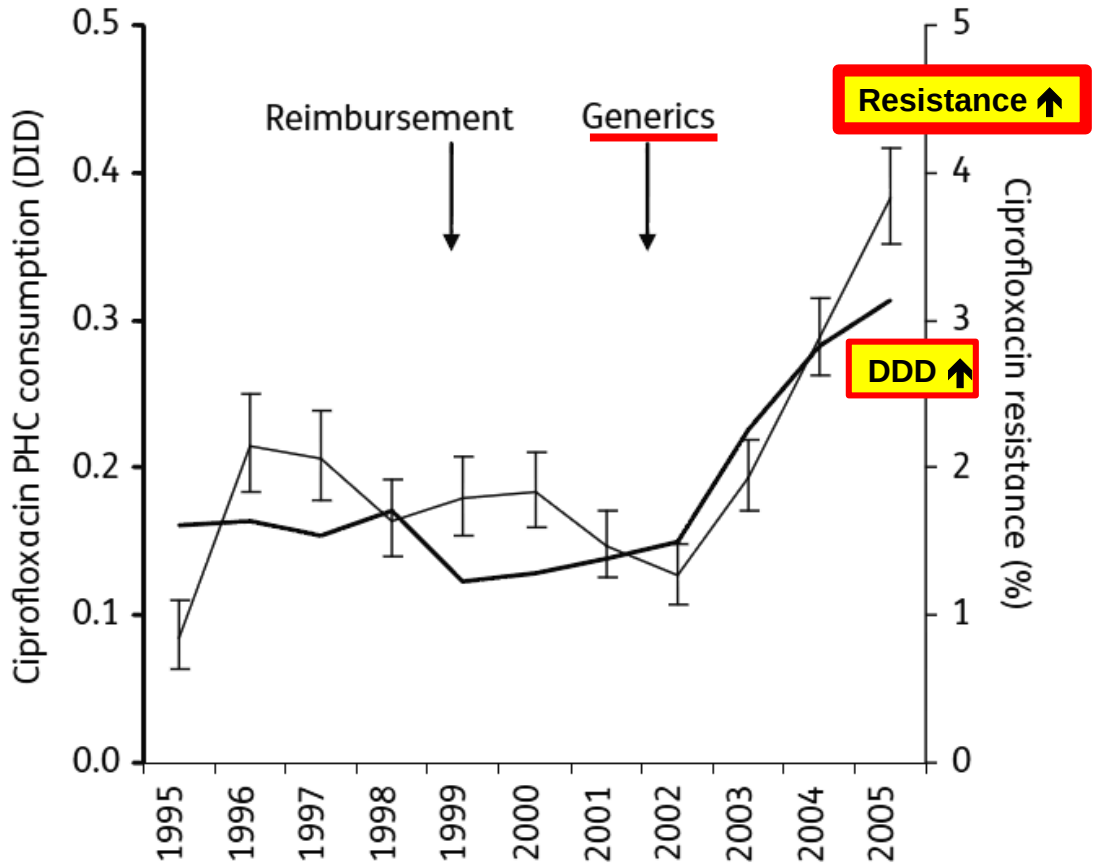
According to Doron and Davidson (2011) (6) three major goals for antimicrobial stewardship are to:

- 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
Published Sep 2013 - Last accessed: 17 Oct 2017

But see what happens with "Low cost antibiotics"…
The sour Danish Experience…





PMC: primary healthcare
DID: defined daily doses per 1,000 inhabitants

E. *coli* urine isolates

Jensen *et al.* J Antimicrob Chemother 2010; 65:1286–1291 – PMID 20363806

A British comment on human use of generics…

THE LANCET
Infectious Diseases
Volume 10, Issue 11, November 2010, Page 754

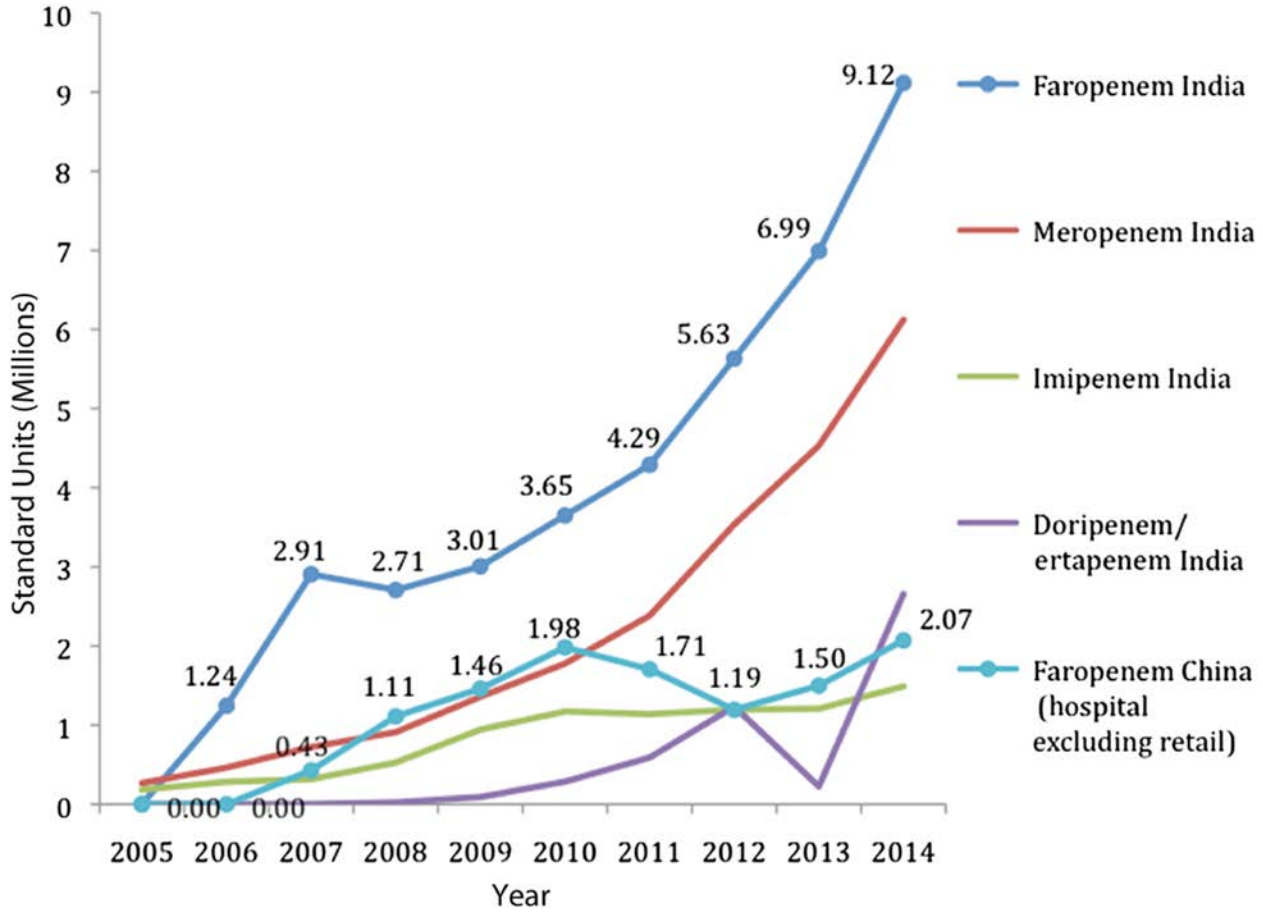
Correspondence

Generic antibiotics, antibiotic resistance, and drug licensing

Finch R. Lancet Infect Dis. 2010;10:754. - PMID: 21029992

Because of their widespread use, generic antibiotics have become increasingly resistant to many common pathogens. For example, about 70% and more than 20% of *Escherichia coli* isolates causing community or hospital-associated infections are resistant to amoxicillin and trimethoprim, respectively….

And a dramatic Indian experience…



Gandra *et al.* Clin Infect Dis. 2016;62:1050-1052 - PMID 26908807

And a French comment about uncontrolled use in animals

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*

Toutain et al. J Vet Pharmacol Ther. 2013;36:420-4. - PMID: 23713785

*"For veterinary medicine, the key issue surrounding antibiotics is **public health**.*

*Veterinary antibiotics and/or veterinary drug formulations should be innovative in terms of selectivity (no or minimal impact on the commensal gut flora), biodegradable (with minimal environmental disruption), and more expensive, with a strictly regulated market **rather than unselective, cheap, and freely available drugs.**"*

Drug shortages …

RESEARCH ARTICLE

Insights into European Drug Shortages: A Survey of Hospital Pharmacists

Kim Pauwels*, Steven Simoens, Minne Casteels, Isabelle Huys

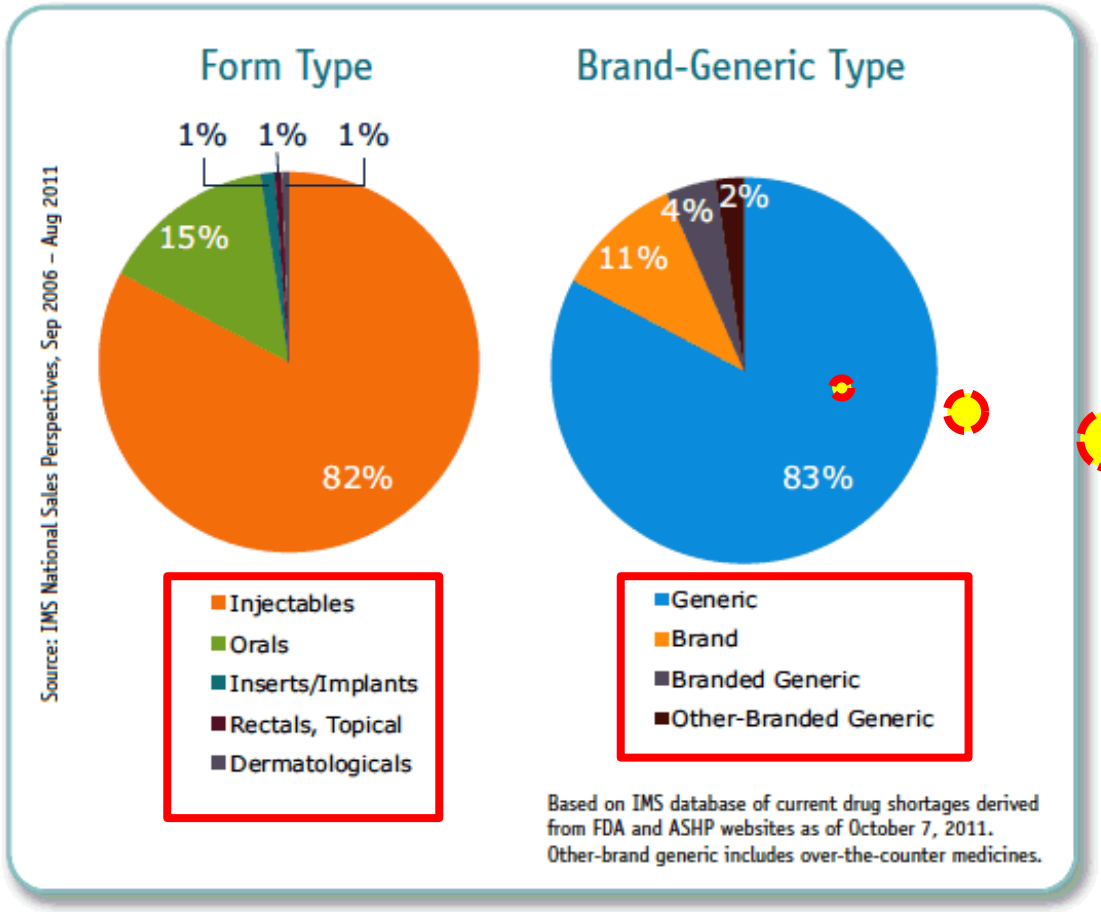
KU Leuven Department of Pharmaceutical and Pharmacological Sciences, 3000, Leuven, Belgium

Pauwels *et al*. PLoS One. 2015;10:e0119322 - PMID 25775406

a nightmare for pharmacists

… and the main affected products were known

Most products are injectables and generics



Drug Shortages: A closer look at products, suppliers and volume volatility.
Report by the IMS Institute for Healthcare Informatics

and the main reason is "market volatility"

https://www.imshealth.com/files/web/IMSH%20Institute/Reports/Drug%20Shortages%20A%20closer%20look/IHII_Drug_Shortage_Report.pdf
Last accessed: 18 Oct 2017 – no longer accessible on 9 Oct 2019

And the reasons are (now) well known…

Drug Shortages:
Root Causes and Potential Solutions
2019
U.S. FOOD & DRUG ADMINISTRATION

Despite public- and private-sector efforts to prevent and mitigate **drug shortages, they continue to occur and persist.** So, at the request of Congress last year, the FDA convened an inter-agency Drug Shortages Task Force to study the problem, **determine the root causes of drug shortages,** and make recommendations for enduring solutions.

Announced on https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions - **Current as of as of 29 Oct 2019**
Available from: https://www.fda.gov/media/131130/download - last visited: 29 Oct 2019

And the reasons are (now) well known…

Drug Shortages:

Despite public- and private-sector efforts to

After reviewing the FDA analysis, published research studies, and stakeholder input, the Task Force identified three major root causes:

- **Root Cause 1: Lack of Incentives to Produce Less Profitable Drugs**
  … Manufacturers of older generic drugs, in particular, face intense price competition, uncertain revenue streams, and high investment requirements, all of which limit potential returns. Current contracting practices contribute to a “race to the bottom” in pricing.
- **Root Cause 2: Market Does Not Recognize and Reward Manufacturers for Mature Quality Management Systems.**
  …. manufacturers are more likely to keep costs down by minimizing investments in manufacturing quality, which eventually leads to quality problems, triggering supply disruptions and shortages.
- **Root Cause 3: Logistical and Regulatory Challenges Make It Difficult for the Market to Recover After a Disruption.**

Announced on https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions - **Current as of as of 29 Oct 2019**
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- **Root Cause 1: Lack of Incentives …**
  … Manufacturers of older generic dr… …n revenue streams, and … …s. Current contracting practices contr…
- **Root Cause 2: Market Does … …ture Quality Management Sy…**
  …. manufacturers are fre… …oth manufacturing quality, which … …ng supply disruptions and shortages.
- **Root Cause 3: Logistical and Re… … Ch…nges Make It Difficult for the Market to Recover After a Disruption.**

For generic drugs, the task force notes that the market often does not provide incentives for manufacturers to invest in updated manufacturing technologies and improvements in quality management….

Ann… https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions - **Current as of as of 29 Oct 2019**
Available from: https://www.fda.gov/media/131130/download - last visited: 29 Oct 2019

Then… prices increase !

News

Some Generic Drugs See Huge Price Increases

Ken Terry

September 15, 2016

The prices of generic drugs covered under the Medicare Part D program dropped overall from 2010 to 2015, but a group of 315 drugs saw extraordinary price increases during that period, according to a new report from the US Government Accountability Office (GAO). The study was requested by members of Congress who were concerned about reports of spiking generic drug prices.

https://www.medscape.com/viewarticle/868812
Posted: 15 Sep 2016; Last accessed: 19 Oct 2017

Price increases: which ones ?

Medscape Infectious Diseases

NEWS & PERSPECTIVE DRUGS & DISEASES CME & EDU

News

Some Generic Drugs See

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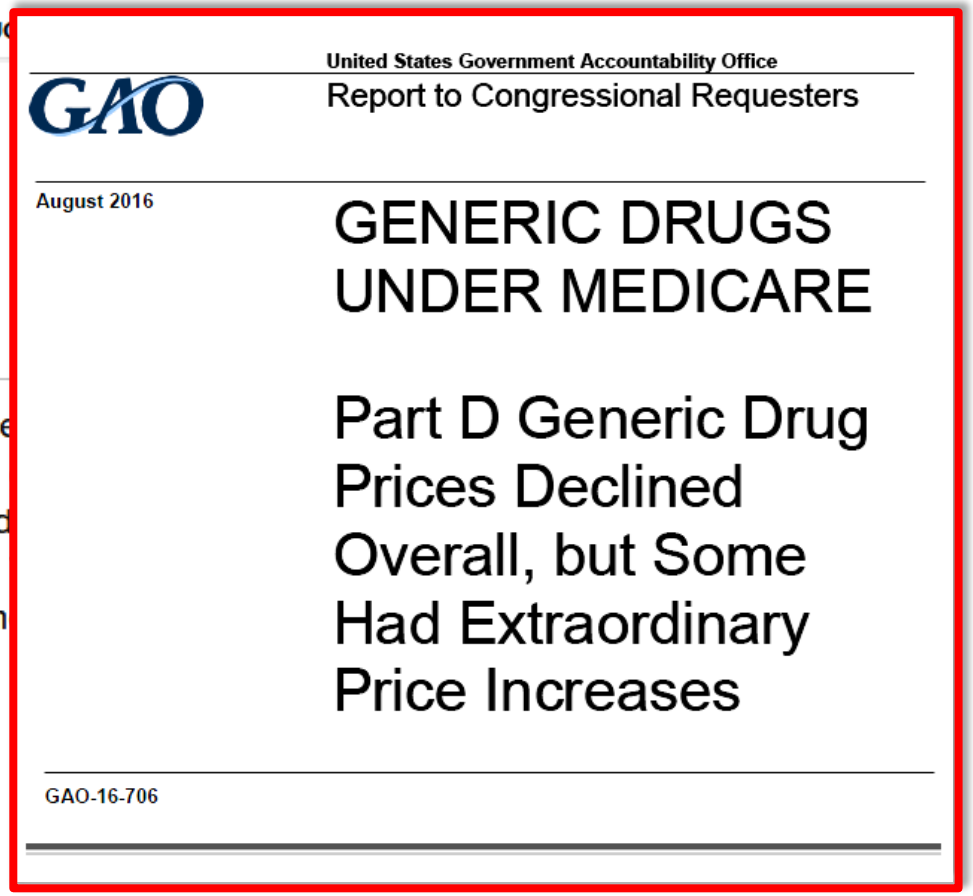

United States Government Accountability Office

GAO

Report to Congressional Requesters

August 2016

GENERIC DRUGS UNDER MEDICARE

Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases

GAO-16-706

http://www.gao.gov/assets/680/679022.pdf
Posted Aug 2016 - Last accessed: 9 Oct 2019

Observed for:

- cefuroxime axetil
- cephalexin
- ciprofloxacin
- clarithromycin
- clindamycin
- doxycycline
- erythromycin
- gentamicin
- metronidazole
- ofloxacin
- tobramycin

Why do prices increase ?

Clinical Infectious Diseases

MAJOR ARTICLE

Trends in Pricing and Generic Competition Within the Oral Antibiotic Drug Market in the United States

Jonathan D. Alpern,[1] Lei Zhang,[2] William M. Stauffer,[1] and Aaron S. Kesselheim[3]

[1]Division of Infectious Disease and International Medicine, Department of Internal Medicine and [2]Clinical and Translational Science Institute, University of Minnesota, Minneapolis; and [3]Program on Regulation, Therapeutics, and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Alpern et al. Clin Infect Dis 2017; 65:1848-1852 - PMID 29020146

Why do prices increase ?

Clinical Infectious Diseases

MAJOR ARTICLE

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on Regulation, Therapeutics, and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Departm
Massachusetts

Alpern et al. Clin Infect Dis 2017; 65:1848-1852 - PMID 29020146

It all depends from the competition !

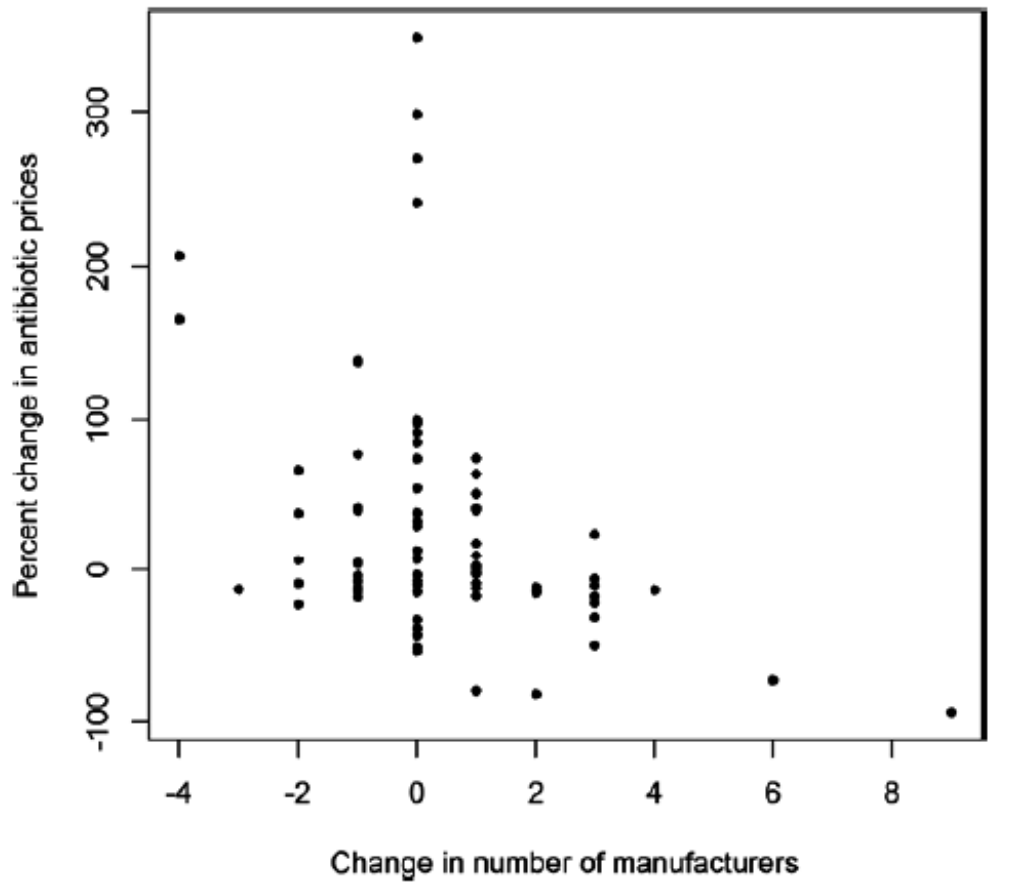
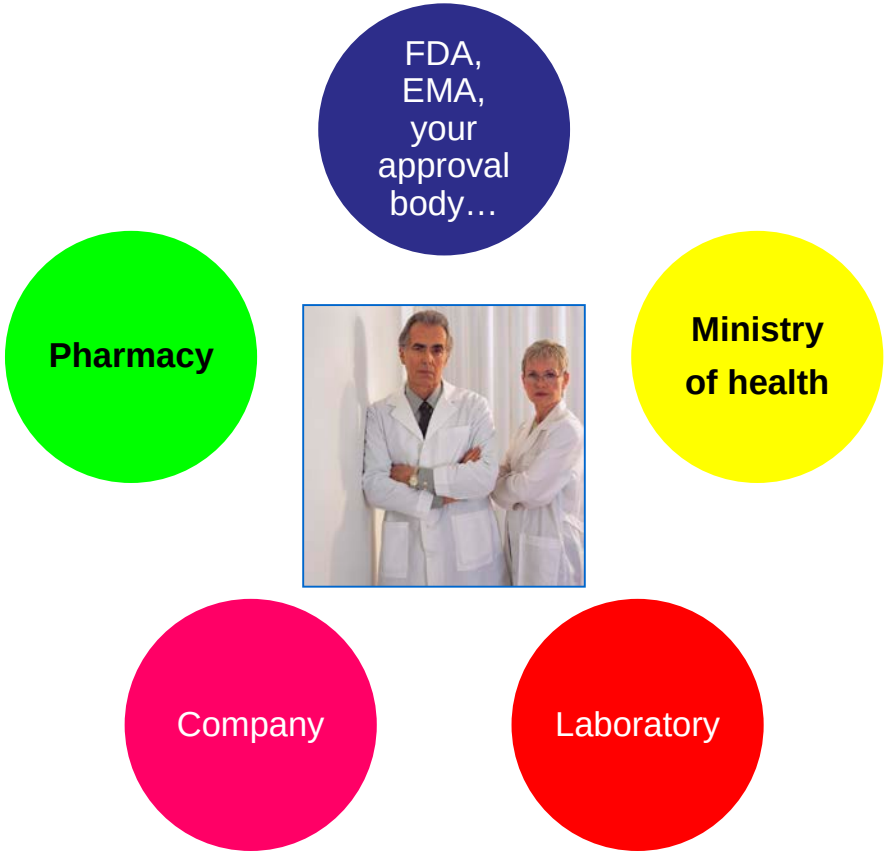


Figure 1. Association between the change in number of manufacturers and the change in antibiotic prices.

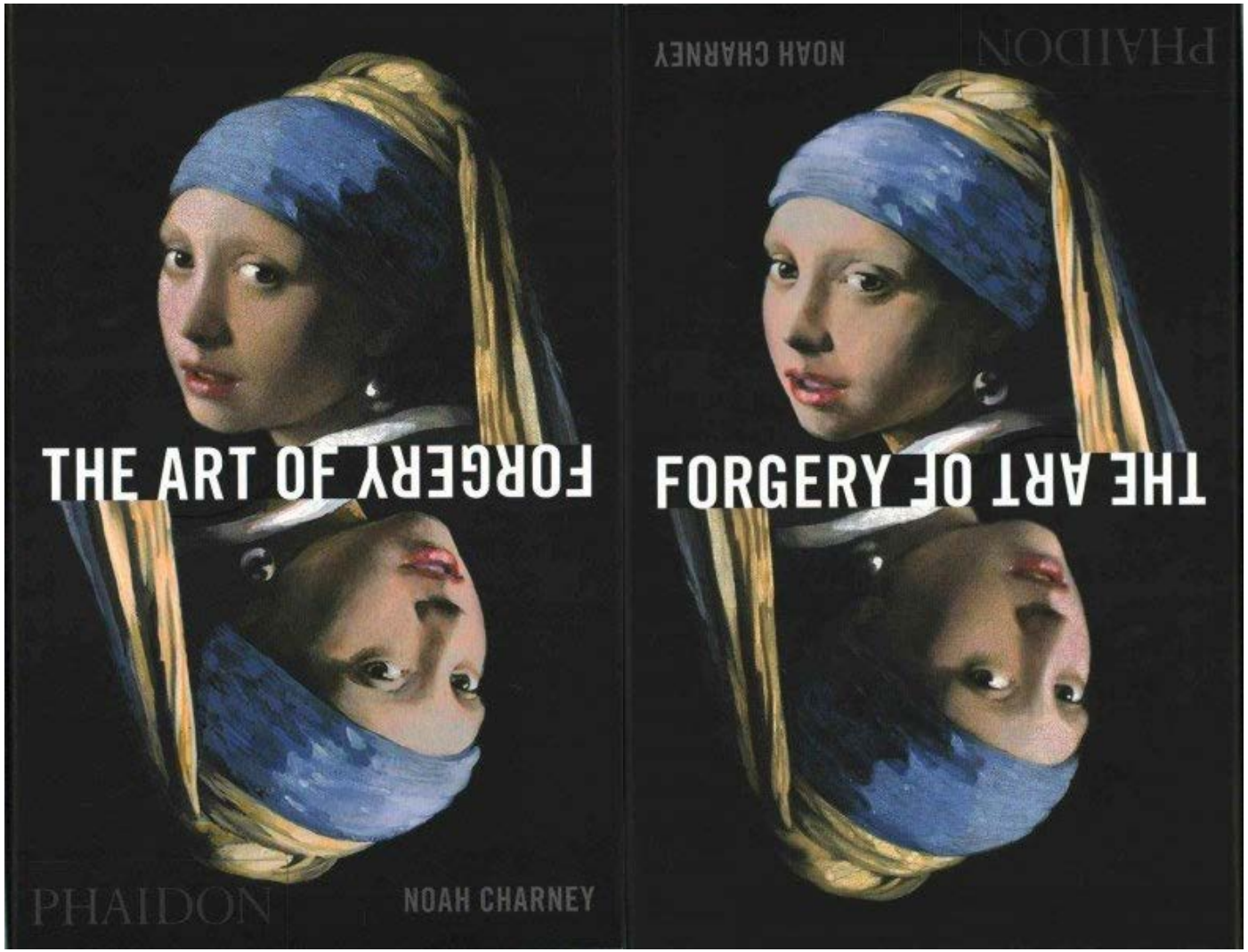
Now, what can I do as a clinician ?



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 / others…)
- **Improved criteria** for **anti-infective drugs** (MIC, MPC, animal PK/PD, …) are probably necessary (but are not yet implemented)
- The **control of the quality of the generics** (and of all antibiotics in general), of their **availability**, and of their **responsible use** are all critical and should go beyond declarations and initial lot analysis…
- **Antibiotics are a precious commodity** that should not be lost. Misuse may cause **HUGE expenses in the future…**

Remember: a true copy must be a piece of art

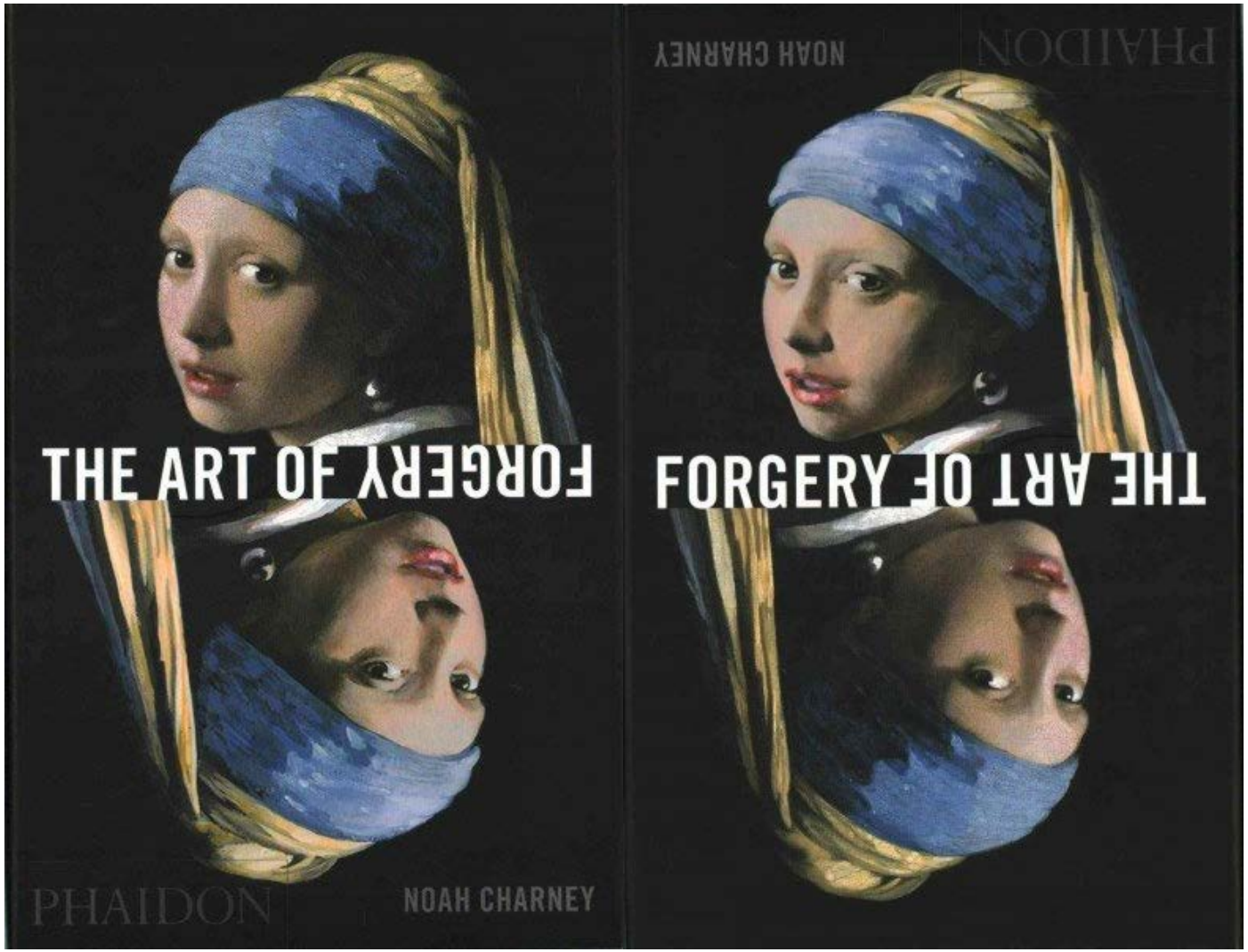


https://www.npr.org/2015/06/23/412244490/could-the-masterpiece-be-a-fake-profit-revenge-and-the-art-of-forgery
Last visited: 5 Oct 2019

And you have a choice…

Increasing the availability of generic drugs helps to create competition in the marketplace, which then helps to make treatment more affordable and increases access to healthcare for more patients.

https://www.fda.gov/drugs/buying-using-medicine-safely/generic-drugs Current as of 26 Aug 2019
Last accessed:6 Oct 2019



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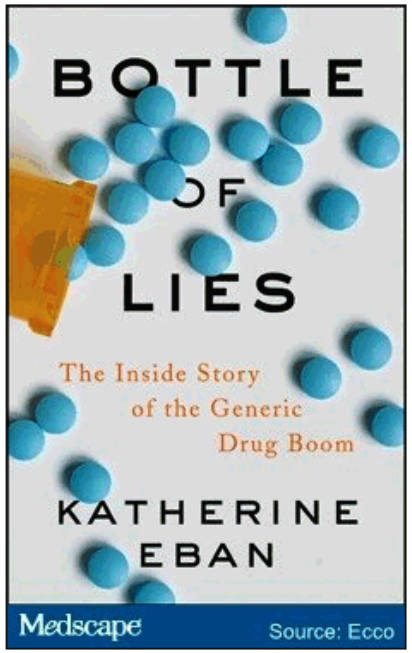

https://www.medscape.com/viewarticle/914067
Posted: 6 Jun 2019
Last accessed: 6 Oct 2019

Thank you for your attention!

And ask questions