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Brussels, Belgium
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.facman.ucl.ac.be → Lectures
When Visiting an Art Gallery or a Museum …
Would you prefer to see originals or copies?


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...

Your prescription, your choice.

£71
Thirty-day prescription of one brand name drug

£22
Thirty-day prescription of its generic equivalent

Much cheaper!
What shall we discuss?

1. A political choice (US and EU)
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.

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”.

TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

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

  Last accessed: 4 Oct 2019
What is required for the innovator...

The long drug development pathway of the innovator....

<table>
<thead>
<tr>
<th>Drug discovery</th>
<th>Drug development</th>
<th>Clinical trial</th>
<th>Manufacturing</th>
<th>Marketing application</th>
</tr>
</thead>
<tbody>
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<td>Target identification</td>
<td><strong>In vitro</strong> and <strong>in vivo</strong> test including toxicology/carcinogenicity/mutagenicity, pharmacokinetics, pharmacodynamics, animal tests, <strong>in vitro</strong> assays in silico methods drug delivery optimization</td>
<td>Phase I (safety data)</td>
<td>Good manufacturing practice safe, pure, effective, consistent quality</td>
<td>Investigational new drug Application/ New drug applications Marketing approval Regulatory compliance</td>
</tr>
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<td></td>
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<tr>
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<td></td>
<td>Phase III (drug safety &amp; efficacy)</td>
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<tr>
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<td>Phase IV (post marketing surveillance)</td>
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</table>
**What remains required from the generic producer**

What remains for the generic…

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<td></td>
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<td>Bioequivalence (in volunteers)</td>
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**point of discussion… Who is responsible?**
As a result...

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

* Once > 2 competitors are present

See: 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)
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
Last accessed: 5 Oct 2019

Generic Market Share (% of Total Rx) USA

Source: IQVIA Institute

Generic drugs account for about 90% of all prescription drug purchases in the U.S.
Posted: 16 Oct 2019
Last visited: 16 Oct 2019
As a result...

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

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)

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US Generics Market - Evolution of Indian Players - White Paper - Feb 08, 2019 – IQVIA Hiranandani Gardens, Powai, Mumbai - 400 076, India
Last accessed: 5 Oct 2019
The FDA says generics are OK… but others say NO

"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..."
In the European Union

**D**  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)

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• …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**…


Last accessed: 4 Oct 2019
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
Last accessed: 5 Oct 2019

Source: European Federation of Pharmaceutical Industries (EFPIA), Brussels Belgium
Last accessed: 5 Oct 2019

Graphing from Statista GmbH, Hamburg, Germany
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
France: data relate only to those active substances listed on the official list of medicines
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* DrugPatentWatch – Make Better Decisions

Business Intelligence on Biologic and Small Molecule Drugs


Figure 1: 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

U.K.: share of generics in pharmacy market sales
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Source: European Federation of Pharmaceutical Industries (EFPIA), Brussels Belgium
Last accessed: 5 Oct 2019

Graphing from Statista GmbH, Hamburg, Germany
Last accessed: 5 Oct 2019
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 \(\rightarrow\) < 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

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 marketed form differs from the form used in development…\(^2\))

• Primary metrics are\(^1,3\)
  
  - **AUC** (area under the plasma concentration–time profile of the active substance)
    \(\rightarrow\) extent of absorption
  
  - **C\(_{\text{max}}\)** (the maximum plasma concentration of the active substance)
    \(\rightarrow\) extent and rate of absorption
  
  - **T\(_{\text{max}}\)** (the time when C\(_{\text{max}}\) is reached)
    \(\rightarrow\) rate of absorption

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$C_{max} - T_{max}$

**Graph:**
- **$C_{max}$** is the maximum concentration of a drug, occurring at time **$T_{max}$**.
- The x-axis represents time (h) ranging from 0 to 6.
- The y-axis represents concentration (mg/L) ranging from 0 to 5.
- The graph shows the concentration over time, peaking at $C_{max}$ at $T_{max}$. 
$C_{\text{max}} - T_{\text{max}} - \text{AUC}$
What if the absorption is decreased?

![Graph showing concentration over time with C_max and AUC highlighted.](image-url)
What if absorption is delayed?

- $C_{\text{max}}$
- $T_{\text{max}}$
Criteria of bioequivalence (EMA* / FDA**) 

- Calculate the 90% confidence interval around the geometric mean ratios of both AUC and $C_{\text{max}}$ for Test (generic) and Reference (innovator) ($T_{\text{max}}$ [if relevant]: arithmetic mean).

- The 90% confidence intervals should, in most cases, be within the 0.80 – 1.25 (80-125%) acceptance limits.
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

** Guidance for Industry (BIOEQUIVALENCE GUIDANCE) - Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

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24 Oct 2019 Anti-Infective Master Class – Live Webcast
Bioequivalence evaluation of 320 mg gemifloxacin tablets in healthy volunteers

A.M. Al-Mohizea1, A.A. Kadi1, A.M. Al-Bekairi1, S.A. Al-Balla2, M.J. Al-Yamani1, K.I. Al-Khamis1, E.M. Niazy1 and Y.M. El-Sayed1

1Department of Pharmaceutics, College of Pharmacy, King Saud University,
2Department of Medicine, King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Saudi Arabia
One drug that showed bioequivalence...

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

Gemifloxacin
Factive

One drug that showed bioequivalence...

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test formulation</th>
<th>Reference formulation</th>
<th>Point estimate</th>
<th>Confidence limits</th>
<th>Level of confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-t} \ (\text{ng} \times \text{h/ml})$</td>
<td>Geometric mean 5,553</td>
<td>5,718</td>
<td>97.12</td>
<td>87.47 – 107.83</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Range 3,525 – 8,749</td>
<td>3,868 – 8,451</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty} \ (\text{ng} \times \text{h/ml})$</td>
<td>Geometric mean 5,873</td>
<td>5,995</td>
<td>97.97</td>
<td>88.72 – 108.19</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Range 3,822 – 9,025</td>
<td>4,097 – 8,770</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{C}_{\text{max}} \ \ (\text{ng/ml})$</td>
<td>Geometric mean 1,182</td>
<td>1,157</td>
<td>102.22</td>
<td>92.08 – 113.47</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Range 845 – 1654</td>
<td>807 – 1657</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{\text{max}} \ (\text{h})^*$</td>
<td>Arithmetic mean 1.441</td>
<td>1.483</td>
<td>0.00</td>
<td>-0.170 – 0.165</td>
<td>91.13</td>
</tr>
<tr>
<td></td>
<td>± SD 0.349</td>
<td>0.461</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>C$_{\text{max}}$ (µg/mL)</th>
<th>AUC$_{0-24\text{h}}$ (µg · h/mL) $^2$</th>
<th>T$_{\text{max}}$</th>
<th>t$_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE-A</td>
<td>10</td>
<td>Mean</td>
<td>S.D. $^3$</td>
<td>C.V. (%) $^4$</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.67</td>
<td>0.16</td>
<td>23.9</td>
<td>4.37</td>
</tr>
<tr>
<td>BE-B</td>
<td>10</td>
<td>1.117</td>
<td>0.056 (SE)</td>
<td>–</td>
<td>7.244</td>
</tr>
<tr>
<td>BE-C$^*$</td>
<td>24</td>
<td>1.124</td>
<td>0.230</td>
<td>20.5</td>
<td>7.881</td>
</tr>
<tr>
<td>BE-D$^*$</td>
<td>14</td>
<td>1.17</td>
<td>0.20</td>
<td>17.1</td>
<td>7.64</td>
</tr>
<tr>
<td>BE-E</td>
<td>20</td>
<td>1.1760</td>
<td>0.2526</td>
<td>21.5</td>
<td>7.5624</td>
</tr>
<tr>
<td>BE-F$^*$</td>
<td>14</td>
<td>1.61</td>
<td>0.30</td>
<td>18.6</td>
<td>8.99</td>
</tr>
<tr>
<td>BE-G</td>
<td>12</td>
<td>0.97</td>
<td>0.17</td>
<td>17.5</td>
<td>(AUC$_{0-12\text{h}}$) 0.67</td>
</tr>
<tr>
<td>Tarivit$^\text{®}$-PI$^*$</td>
<td>5</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
<td>6.02</td>
</tr>
</tbody>
</table>

* Plasma concentrations were measured by HPLC. BE: bioequivalence study, Travit$^\text{®}$-PI: phase I study of original product (Travit$^\text{®}$).
1) Sampling point before oral dose is not included.
2) AUC$_{0-24\text{h}}$ 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.
But here is another one that created big problems …

Levothrox (levothyroxine) new formulation caused major controversy in France

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 Concordet1,2 • Peggy Gandia1,2 • Jean-Louis Montastruc1,2 • Alain Bousquet-Méhou1,2 • Peter Lees3 • Aude Ferran3 • Pierre-Louis Toutain1,3

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.
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**

• 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

Last accessed: 16 Oct 2019

Last visited: 25 March 2014 – No longer available
Potency (piperacillin)

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

Moet et al. *Diagnostic Microbiology and Infectious Disease* 65 (2009) 319–322

RLOT replicates
Zosyn® lots
Generic lots (23; 4/2008)
Generic lots (23; this report)

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

A series of other papers raising questions...

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

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

Moawi M. Al-Tabash 1,*, Khairi M. S. Fakhr Elbonb 2, Dana Emaad Eddin Obaid 1, and Sadik Sayed 1

1 Pharmaceutics Unit, College of Pharmacy and Health Sciences, Ajman University, PO. Box 64141, Ajman, UAE
2 Department of Pharmaceutical Sciences, College of Pharmacy, Al-Ain University of Science and Technology, PO. Box 64141, Al Ain, UAE
* Correspondence: sphmaa@hotmail.com; Tel.: +971-6-705-6288


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

Livia I.S. de Mattos 1, Raústo K. Ferraris 1, Tiago S.C. Machado 1, Thais M. de Brito 1, Amanda S. Chaves 1, Heliana M. Pereira 1, Douglas P. Pinto 1, Diego M.D. da Silva 1, Fabio C. Amendoeira 1, 2

1 Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz, (INNQF/CNPq); Av. Brasil, 435—Manguinhos, Rio de Janeiro, RJ, 21945-000, Brazil
2 Laboratório de Farmacologia, Faculdade Oswald Cruz (FOCPR), Manguinhos, Rio de Janeiro, RJ, Brazil

**Diagnostic Microbiology and Infectious Disease 2011, 37, 173-176; doi:10.3855/dm.37.2.173**

**Antimicrobial Susceptibility Studies**

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

Hsin-Yun Sun 1, Hsiao-Wei Liao 1, Meng-Huei Sheng 1, Hsi-Min Tai 1, Ching-Hua Kuo 1, 2, Wang-Huei Sheng 1, 2

1 Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
2 School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

**Journal of Infection and Public Health 2017, 10, 329-334; doi:10.1016/j.jiph.2017.03.004**

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

Carlos A. Rodriguez 1, Maria Agudelo 1, Andres F. Zuluaga 1, Omar Vegga 1, 2

1 GBMI (Grupo Investigadores de Problemas en Enfermedades Infecciosas); Facultad de Medicina, Universidad de Antioquia, Medellín, Antioquia, Colombia
2 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 ($4.30 \pm 0.05 \log_{10}$ CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per day) using the neutropenic mouse thigh infection model (each data point represents the mean CFU/g of both thighs from a single mouse). (A) Pharmacodynamic patterns of VAN-Abbott US and VAN-Lilly fitted to the Hill model. Despite containing a significantly greater concentration of API (125%), VAN-Abbott US was completely ineffective in vivo. VAN-Abbott US is shown in a separate graph because of its greater AUC/MIC ratio than that of VAN-Lilly (123%; their dosing regimens were identical). (B) VAN-APP and VAN-Proclin were both pharmaceutically equivalent to VAN-Lilly, but neither was therapeutically equivalent due to their marked Eagle effect. The curve for VAN-APP ends at 300 mg/kg (fAUC/MIC, 267 h) because this product was discontinued and the remaining amount was insufficient for the highest doses.

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.

But pharmacodynamics equivalence can also be demonstrated

Impact on Resistance of the Use of Therapeutically Equivalent Generics: the Case of Ciprofloxacin

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

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

But pharmacodynamic equivalence can also be demonstrated.

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 fAUC/MIC value of ~27 and 99.9% kill with a fAUC/MIC value of ~75.

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

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

Carlos A. Rodriguez1, Maria Agudelo1,2, Yudy A. Aguilar1, Andres M. Lozano1, and Omar Vesga1,2

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


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 Gallelli1, Caterina Palleria1, Antonio De Vuono2, Laura Mumoli1, Piero Vasapollo1, Brunella Piro1, Emilio Russo1

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


“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.”
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)
  \[ \text{MIC } 4.9 \text{ mg/L; range: } 0.06-8 \]
• 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)
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

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!

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

Here is the MIC (= bacteria stop growing…)

Here are the blood levels
Why could a low dose of levofloxacin also trigger emergence of resistance?

It's all a question of **MPC** (mutant prevention concentration) and blood levels!

<table>
<thead>
<tr>
<th>Time post-administration (h)</th>
<th>Levofloxacin 750mg</th>
<th>Levofloxacin 500mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Here are the blood levels.

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...)

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 much longer above the MPC!

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.

**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

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


- 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

<table>
<thead>
<tr>
<th>Postoperative infections</th>
<th>oCFX (n = 313)</th>
<th>gCFX (n = 305)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Surgical site infections</td>
<td>6</td>
<td>31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>2</td>
<td>8</td>
<td>0.10</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0</td>
<td>6</td>
<td>0.04</td>
</tr>
<tr>
<td>Total postoperative infections</td>
<td>8</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

oCFX: original cefuroxime, gCFX: generic cefuroxime.

p < 0.05 statistically significant.

Clinical alert: a large comparative study

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</table>

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

Table 3: Pathogens isolated in the compared groups of patients

<table>
<thead>
<tr>
<th>Infecting pathogens</th>
<th>received oCFX</th>
<th>received gCFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staph. coag. negative</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Staph. hominis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Bacillus species</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>E. coli</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

oCFX: original cefuroxime, gCFX: generic cefuroxime.
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...)
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, generally 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…)

Who can we really trust?
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*  

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

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)
Dissolution of meropenem in Belgium

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

[Graph showing turbidity over time for different samples]

Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (2017)
Impurities in meropenem: coloured compounds

are you happy with the colour?

generic B
originator

Delattre et al. 30th International Congress of Chemotherapy, Taipei, Taiwan – poster #724 (2017)
Impurities in ciprofloxacin...

Available online at www.sciencedirect.com


Trefi et al.

Generic ciprofloxacin tablets contain the stated amount of drug and different impurity profiles: A $^{19}\text{F}$, $^1\text{H}$ 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 $^{19}\text{F}$ and $^1\text{H}$ nuclear magnetic resonance (NMR). Twelve out of the sixteen commercial formulations of ciprofloxacin measured by $^{19}\text{F}$ NMR contain the active ingredient within 100 ± 3% 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 $^{19}\text{F}$ and $^1\text{H}$ 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 $^{19}\text{F}$ NMR. Two other non-fluorinated impurities were observed in the seven formulations analysed with $^1\text{H}$ 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) $^1\text{H}$ NMR which allowed the characterisation of some excipients present in the formulations studied.

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

Impurities in ciprofloxacin

This is a synthesis precursor!

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

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)
  - H₂O 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

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. Vega,a,b,c,d

GIPE: Grupo Investigador de Problemas en Enfermedades Infecciosas; a Department of Pharmacology; b and Section of Infectious Diseases, Department of Internal Medicine; c School of Medicine, and Institute of Chemistry, School of Exact and Natural Sciences, Universidad de Antioquia, Medellín, Colombia; Infectious Diseases Unit, Hospital Universitario de San Vicente Fundación, Medellín, Colombia.4


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

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.

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

M. Agudelo, C. A. Rodriguez, C. A. Pelaez, O. Vegas

Grupo Investigador de Problemas en Enfermedades Infecciosas; Department of Pharmacology and Section of Infectious Diseases, School of Medicine, and Institute of Chemistry, School of Exact and Natural Sciences, Universidad de Antioquia, Hospital Universitario de San Vicente Fundación, Medellín, Colombia

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 ...
and issues warning letters...
and issues warning letters...

<table>
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<tr>
<th>Posted Date</th>
<th>Issue Date</th>
<th>Company Name</th>
<th>Issuing Office</th>
<th>Subject</th>
<th>Response Letter</th>
<th>Closeout Letter</th>
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<td>08/29/2019</td>
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<td>Center for Drug Evaluation and Research</td>
<td>CGMP/Active Pharmaceutical Ingredient (API)/Adulterated/Refused Inspection</td>
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<td>10/01/2019</td>
<td>09/10/2019</td>
<td>Lupin Limited</td>
<td>Center for Drug Evaluation and Research</td>
<td>CGMP/Active Pharmaceutical Ingredient (API)/Adulterated</td>
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<td></td>
</tr>
</tbody>
</table>

Last accessed: 6 Oct 2019


Current as of 10 Apr 2019

Last accessed: 6 Oct 2019
and issues warning letters...

Since 5 Oct 2017, the FDA has issued 219 Recalls, Market Withdrawals, & Safety Alerts…

The FDA is active!

But if there are so many, what does it mean?

Current as of 10 Apr 2019
Last accessed: 6 Oct 2019
Which even led to criminal investigations…

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.

Last accessed: 6 Oct 2019
And we know the origins...

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.

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.

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.

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

NBER WORKING PAPER SERIES

POOR QUALITY DRUGS AND GLOBAL TRADE: A PILOT STUDY

Roger Bate
Ginger Zhe Jin
Aparna Mathur
Amir Attaran

Working Paper 20469
http://www.nber.org/papers/w20469

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
September 2014

Available from https://www.nber.org/papers/w20469
Last accessed: 8 Oct 2019
Caution: drug quality may vary according to where it is sold

"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."

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Last accessed: 8 Oct 2019
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,² Cynthia D. Sommers,³ Daniel J. Mants,⁴ Vikram Patel,⁵ and Michael T. Boyne II⁶
Division of Pharmaceutical Analysis, CDER, Food and Drug Administration, St. Louis, Missouri, USA,³ and Division of Drug Safety Research, CDER, Food and Drug Administration, Silver Spring, Maryland, USA⁵

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).


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

"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

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 unanticipated difficulty: the multicomponents drugs

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 ($E_1, E_2$)

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Polymyxin E$_1$ and E$_2$ variations from different colistin manufacturers assayed by HPLC with UV detection.$^a$

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>No. of batches tested</th>
<th>Proportion (mean ± S.D.$^b$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Polymyxin E$_1$</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>15.6 ± 1.1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>24.4 ± 1.4</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>47.8</td>
</tr>
</tbody>
</table>

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.
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)
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- 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).

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 ...

Developing the first national antimicrobial prescribing and stewardship competences

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


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†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
But see what happens with “Low cost antibiotics“…

The sour Danish Experience…

Reimbursement
Generics
price ↓

Ciprofloxacin community use (DDDs per 1,000 inhabitants per day, 5 months average)

Reimbursement
Generics

DDD ↑

Median price per DDD in Danish kroner (DKK)

Price per DDD consumption (DKK)

Ciprofloxacin PHC consumption (DDD)


Resistence ↑

DDD ↑

PMC: primary healthcare
DID: defined daily doses per 1,000 inhabitants
E. coli urine isolates

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…
"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 ... a nightmare for pharmacists

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

... and the main affected products were known

Most products are injectables and generics

and the main reason is "market volatility"

Price increases!

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.

Posted: 15 Sep 2016; Last accessed: 19 Oct 2017
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United States Government Accountability Office
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

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?

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

Jonathan D. Alpern,1 Lei Zhang,1 William M. Staufler,1 and Aaron S. Kesselheim2

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

Why do prices increase?

It all depends from the competition!

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

Clinical Infectious Diseases
MAJOR ARTICLE

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3Division of Infectious Disease and International Medicine, Department of Internal Medicine and Clinical and Translational Science, University of Michigan, Ann Arbor, Michigan

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
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.


Thank you for your attention!

And ask questions