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

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Disclosures and slides availability

- **Research grants**
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  - Belgian Science Foundation (F.R.S.-FNRS), Ministry of Health (SPF), and Walloon and Brussels Regions

- **Speaking fees**
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

- **Decision-making and consultation bodies**
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

**Slides: [http://www.facm.ucl.ac.be ➔ Lectures]**
You said "generics":
the recent story of a well known antibiotic

http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/L.cfm
A well known antibiotic in Belgium

1. **Levofloxacin Actavis (Actavis)**
   - sac perf.
   - € 5 x 500mg / 100ml U.H. [€85]

2. **Levofloxacin BG (Eurogenerics)**
   - compr. (séc.)
   - € 10 x 500mg Rk b€ 21,42
   - € 30 x 500mg Rk b€ 57,66
   - sac perf.
   - € 1 x 500mg / 100ml U.H. [€17]

3. **Levofloxacin Fresenius Kabi (Fresenius Kabi)**
   - flacon perf.
   - € 1 x 500mg / 100ml U.H. [€17]

4. **Levofloxacin Hospira (Hospira)**
   - sac perf.
   - € 1 x 500mg / 100ml U.H. [€17]

5. **Levofloxacin Mylan (Mylan)**
   - compr. (séc.)
   - € 10 x 250mg Rk b€ 14,98
   - € 14 x 250mg Rk b€ 24,43
   - € 10 x 500mg Rk b€ 21,98
   - € 14 x 500mg Rk b€ 35,13
   - flacon perf.
   - € 10 x 500mg / 100ml U.H. [€170]

6. **Levofloxacin Sandoz (Sandoz)**
   - compr. (séc.)
   - € 10 x 250mg Rk b€ 14,42
   - € 10 x 500mg Rk b€ 21,09
   - € 30 x 500mg Rk b€ 58,15

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

8. **Tavanic (PI-Pharma)**
   - compr. (séc.)
   - € 10 x 500mg Rk b€ 21,94
   - (importation parallèle)

9. **Tavanic (Sanofi-Aventis)**
   - compr. (séc.)
   - € 10 x 250mg Rk b€ 14,98
   - € 10 x 500mg Rk b€ 21,97
   - flacon perf.
   - € 1 x 500mg / 100ml U.H. [€17]

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http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_L.cfm
But why would you choose a "generic" antibiotic?

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

Please, give your FIRST choice (1-5) OR choose 6
I guess the real and only justifiable answer is...

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 laws as an example)
2. Approach to PK bioequivalence
3. Approach to microbiological equivalence
4. Approach to pharmacodynamic equivalence
5. Problems related to dissolution and stability
6. Impurities and falsified medicines
7. The hidden risks of "low cost" antibiotics
What shall we discuss?

1. A political choice (US and EU laws as an example)

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

PUBLIC LAW 98–417—SEPT. 24, 1984
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


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

• Published literature (for data for which the applicant has no right of reference to the original raw data supporting the application)

• FDA's findings (safety and effectiveness of the already approved drug)

• Comparison with the original NCE/NME (New Chemical Entity/New Molecular Entity) application for
  – dosage form, strength, route of administration
  – substitution of an active ingredient in a combination product or change such as different salt, ester, complex, …

• Bioequivalence study

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

* 505 (B) (2) Application (Guidance to Industry)
In the European Union

**DIRECTIVE 2001/83/EC**

* OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

on the Community code relating to medicinal products for human use

(OJ L 311, 28.11.2001, p. 67)

Amended by:                                Official Journal

<table>
<thead>
<tr>
<th>Directive</th>
<th>Title</th>
<th>Original Date</th>
<th>Amended</th>
<th>No Page</th>
<th>Date</th>
</tr>
</thead>
</table>

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

The EU Directive (excerpts)

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

• …‘generic medicinal product’ shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. …
1st round of conclusions and discussions

- The decision to go for generics is a political decision

- It finds its origin and basis in
  - the limited duration of the patent protection
    (usually about 20 years post patent application), which makes generics possible after about 10 years of effective commercialization
  - the fact that drug production costs are usually very low
    (often only a very minor fraction of the total requested by the innovator at the time of initial commercialization)

- The main and only incentive in the promotion of the generics is, for governments, to acquire and provide drugs more cheaply to the population
What shall we discuss?

1. The US and the EU laws

2. Approach to PK bioequivalence

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

- Bioequivalence is an accepted surrogate for therapeutic equivalence\textsuperscript{1} (including for branded drugs when the marketed form differs from the form used in development…\textsuperscript{2})

- Primary metrics are\textsuperscript{1,3}
  - $\text{AUC}$ (area under the plasma concentration–time profile of the active substance)
    \rightarrow \text{extent of absorption}
  - $C_{\text{max}}$ (the maximum plasma concentration of the active substance)
    \rightarrow \text{extent and rate of absorption}
  - $T_{\text{max}}$ (the time when $C_{\text{max}}$ is reached)
    \rightarrow \text{rate of absorption}

\textsuperscript{1} Hauschke et al. Bioequivalence Studies in Drug Development – Methods and Applications, John Wiley & Sons Ltd. (UK), 2007.
AUC – $C_{\text{max}}$ – $T_{\text{max}}$
AUC – $C_{\text{max}}$ – $T_{\text{max}}$
What if the absorption is decreased?

![Graph showing concentration over time](image-url)

- $C_{\text{max}}$
- $\text{AUC}$
What if absorption is delayed?

![Graph showing concentration over time with peak concentration (C_max) and time to peak (T_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).

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

Notes:

1. if both AUC and $C_{\text{max}}$ are within range, the generic should have the same bioavailability than the reference
2. statistical evaluation of $T_{\text{max}}$ 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, Health Canada requires 0.9 – 1.12, but FDA accepts 0.8 – 1.25


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

• Bioequivalence studies are NOT required for drugs administered by the **intravenous route**! (since that route is the parameter against which the other routes are tested!)

  ➢ Only demonstration that the drugs has the **same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product** is required.

• Complex drugs (such as biologicals, fractionated heparins, etc.) may require and will pass through more stringent requirements $^{1,2}$

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Is this enough?

1. The US / EU laws (or the law of my country) are sufficient and convince me to say that generics are like the original products

2. While accepting the laws, I'm not convinced and would like to have additional information from the producers

3. What is required by law is insufficient and the laws need to be changed.

Only ONE answer (1, 2 or 3), please!
What shall we discuss?

1. A political decision (US and EU laws as an example)
2. Approach and limits to PK bioequivalence studies
3. Approach to microbiological and therapeutic equivalence
   - MIC (heteroresistance in back-up slides) …
   - Approach to pharmacodynamic equivalence
   - PK/PD animal models and clinical data

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

Last accessed: 29 March 2014

Last visited: 25 March 2014
**Potency** (piperacillin)


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

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**Potency variations (%)**

- ● = RLOT, X = average variation, —— = range of results

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

*Moet et al.* Diagnostic Microbiology and Infectious Disease 2009;65: 319–322
# MIC values (vancomycin)

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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pathogen (no.)</th>
<th>No. of generic markers</th>
<th>Nonidentical rate of the MIC value of all generics (mean ± SD)</th>
<th>MIC distribution (%) of the most different generic versus brand name drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>MRSA (90)</td>
<td>5</td>
<td>25.00 ± 15.52</td>
<td>–</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>MRSA (147)</td>
<td>7</td>
<td>28.09 ± 10.29</td>
<td>–</td>
</tr>
<tr>
<td>Cefotiam</td>
<td><em>Staphylococcus aureus</em> (100)</td>
<td>7</td>
<td>8.71 ± 3.04</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em> (100)</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td><em>Streptococcus pneumoniae</em> (126)</td>
<td>6</td>
<td>12.70 ± 4.77</td>
<td>–</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td><em>Pseudomonas aeruginosa</em> (100)</td>
<td>2</td>
<td>3.00 ± 2.83</td>
<td>–</td>
</tr>
<tr>
<td>Meropenem</td>
<td><em>P. aeruginosa</em> (100)</td>
<td>7</td>
<td>18.57 ± 3.46</td>
<td>–</td>
</tr>
<tr>
<td>Imipenem</td>
<td><em>P. aeruginosa</em> (100)</td>
<td>4</td>
<td>9.00 ± 2.58</td>
<td>–</td>
</tr>
</tbody>
</table>

**MRSA** methicillin-resistant *Staphylococcus aureus*a

Note that the distribution of one minimal inhibitory concentration (1 MIC) shows the identical rate with the brand drug; MIC was determined by broth micro-dilution method using powder in each drug vial


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*MICCs were often higher than for the reference product...*
**MIC values (meropenem)**

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

**Susceptible strains**
- **MIC ≤ 2 mg/L**
  - Hospira: Mean = 110.8, SD = 39.2
  - Sandoz: Mean = 115.8, SD = 36.5
  - Fresenius: Mean = 113.3, SD = 36.6

**Intermediate strains**
- **≤ 2 MIC < 8 mg/L**
  - Hospira: Mean = 107.7, SD = 17.41
  - Sandoz: Mean = 102.7, SD = 13.9
  - Fresenius: Mean = 103.4, SD = 19.3

**Resistant strains**
- **MIC > 8 mg/L**
  - Hospira: Mean = 100.4, SD = 11.5
  - Sandoz: Mean = 93.4, SD = 11.7
  - Fresenius: Mean = 97.3, SD = 12.9

**MERONEM® = meropenem commercialized by AstraZeneca**

Van Bambke et al., in preparation
Vancomycin: evidence of non-equivalence in PK/PD animal model

Neutropenic thigh mouse model


FIG. 1. In vivo efficacy against *S. aureus* GRP-0057 (years 2002 and 2003) at a low inoculum (4.30 ± 0.05 log_{10} CFU per thigh when subcutaneous treatment q1h started). Vancomycin generic products are compared with the innovator (VAN-Lilly) in dose-effect experiments (2.34 to 1,200 mg/kg per day) using the neutropenic mouse thigh infection model (each data point represents the mean CFU/g of both thighs from a single mouse). (A) Pharmacodynamic patterns of VAN-Abbott US and VAN-Lilly fitted to the Hill model. Despite containing a significantly greater concentration of API (125%), VAN-Abbott US was completely ineffective in vivo. VAN-Abbott US is shown in a separate graph because of its greater AUC/MIC ratio than that of VAN-Lilly (123%; their dosing regimens were identical). (B) VAN-APP and VAN-Proclin were both pharmacologically 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 thigh mouse model

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

But pharmacodynamics equivalence can also be demonstrated

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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#}
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Same authors as those describing the non-therapeutic equivalence of oxacillin!
Sometimes the generic has a problem of a “too good” bioavailability ...
Sometimes the generic has a problem of a “too good” bioavailability ...
The reasons are subtle differences in composition...

<table>
<thead>
<tr>
<th>Active ingredient (crystalline status)</th>
<th>Branded rifaximin (Normix®) 200-mg film-coated tablet</th>
<th>Generic rifaximin 200-mg film-coated tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin (polymorph-α)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium starch glycinate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycerol distearate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colloidal anhydrous silica</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coating components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypromellose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disodium edetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylene glycol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red iron oxide E172</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The copy was almost perfect but …
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 Vasapollo², Brunella Piro³, 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.
Clinical alerts (efficacy and safety)?

Safety and efficacy of generic to brand formulation

Luca Gallelli¹, Caterina Palleria¹, Antonio De Vuono¹, Lelia Malagutti², Emilio Russo¹

¹Department of Health Science, Regional Center on drug information, Matera School of Medicine, University of Catanzaro, ²Department of General Medicine, Cosenza, Italy


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

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

ACKNOWLEDGMENTS

The Italian Drug Agency (Agenzia Italiana del Farmaco) is kindly acknowledged for its financial and technical support.
2d round of conclusions and discussions

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

- The reasons for a non-equivalence remain often obscure but may be related to **differences in biophysical properties** that will impact on the inter- and intra-organ bioavailability, which **cannot be detected by simple measurements of serum levels**

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

Who can we really trust?
And this brings me to pharmaceutical quality…

1. the generic must have the same solubility / dispersion properties than the original

2. the generic cannot contain more impurities (or give rise to more degradation products) than the original

3. I must be sure about the real content of what I prescribe

4. All of the above is important

5. None of the above is important

Please, give your FIRST choice (1, 2 OR 3) OR choose 4 OR 5
What shall we discuss?

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

Brand name meropenem
Dissolution of meropenem in Belgium

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

Van Bambeke et al., in preparation
Dissolution of meropenem in Belgium

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

Van Bambeke et al., in preparation
Are Primary Health Care Professionals (nurses) happy? (meropenem)

**dissolution time**

Repeated Measures ANOVA
- P value: 0.1136
- P value summary: ns

**questionnaire - solubilisation**

Van Bambke et al., in preparation
Impurities in meropenem: coloured compounds

are you happy with the colour?

Van Bambeke et al., in preparation
Impurities in meropenem: coloured compounds

OD<sub>490 nm</sub> - 24°C

- Black: Meronem
- Red: Hospira
- Green: Sandoz
- Blue: Fresenius

OD<sub>490 nm</sub> - 37°C

- Black: Meronem
- Red: Hospira
- Green: Sandoz
- Blue: Fresenius

Van Bambeke et al., in preparation
The problem may be in the physical forms and in the impurities

Antimicrobial Original Research Paper

Pharmaceutical quality of eight generics of ceftriaxone preparation for injection in Eastern Asia

Isabelle Arnet¹, Matthias Altermatt², Yves Roggo², Gabriel Schnetzler²

¹Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, ²F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objectives: To compare the pharmaceutical quality of original and generic ceftriaxone sodium preparations for injection produced in Eastern Asia.
Methods: Standard physical and chemical laboratory tests were performed.
Participants/material: Ceftriaxone (Rocephin®, Roche, Switzerland) was the reference material. Generics produced in China, India, and Indonesia were sampled in China and Myanmar within their expiration dates.
Results: Eight generics obtained from Eastern Asia markets in January 2013 were analysed. All eight generics failed the specifications in three or more tests. Residues of solvents and metals were detected in all generics, four were not particle free, and two were not sterile.
Conclusions: All tested generic ceftriaxone products failed to meet the pharmaceutical quality standards of the branded original. The high levels of impurities and the identified contamination of particles and residues are of clinical concern, as they could impact tolerability and safety in patients in need of an effective parenteral antibiotic.
The problem may be in the impurities

Table 2 Specifications of Rocephin and physical characteristics of generic ceftriaxone products tested

<table>
<thead>
<tr>
<th>Product (manufacturer)</th>
<th>Container integrity</th>
<th>Crystallinity</th>
<th>Colour</th>
<th>Average fill mass (mg)</th>
<th>Content of ceftriaxone per vial (mg)</th>
<th>Particles per 1/10 containers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocephin (Roche)</td>
<td>Tight closed</td>
<td>Crystalline</td>
<td>White to off-white</td>
<td>1140–1284</td>
<td>900–1100</td>
<td>&lt;6/&lt;20</td>
</tr>
<tr>
<td>Becef (Nectar Lifesciences)</td>
<td>Tight closed</td>
<td><em>Mostly amorphous</em></td>
<td>Off-white</td>
<td>1189</td>
<td>974</td>
<td>4/23</td>
</tr>
<tr>
<td>Cefaxone (Lupin)</td>
<td>Tight closed</td>
<td><em>Mostly amorphous</em></td>
<td>Off-white</td>
<td>1205</td>
<td>969</td>
<td>2/10</td>
</tr>
<tr>
<td>Cefin (Panbiotic)</td>
<td>Tight closed</td>
<td><em>Mostly amorphous</em></td>
<td>White</td>
<td>1195</td>
<td>996</td>
<td>6/18</td>
</tr>
<tr>
<td>Ceftriaxon (CCPC)</td>
<td>Tight closed</td>
<td><em>Amorphous crystalline</em></td>
<td>White</td>
<td>1194</td>
<td>992</td>
<td>2/6</td>
</tr>
<tr>
<td>Ceftriaxon (NCP)</td>
<td>Tight closed</td>
<td><em>Amorphous crystalline</em></td>
<td>White</td>
<td>1168</td>
<td>974</td>
<td>2/3</td>
</tr>
<tr>
<td>Incept (Ind_Swift)</td>
<td>Tight closed</td>
<td><em>Mostly amorphous</em></td>
<td>Off-white</td>
<td>1209</td>
<td>981</td>
<td>8/31</td>
</tr>
<tr>
<td>Oframax (Ranbaxy)</td>
<td>Tight closed</td>
<td><em>Mostly amorphous</em></td>
<td>White</td>
<td>1170</td>
<td>963</td>
<td>3/6</td>
</tr>
<tr>
<td>Triacef (Dexa Medica)</td>
<td>Tight closed</td>
<td><em>Amorphous crystalline</em></td>
<td>White</td>
<td>1163</td>
<td>941</td>
<td>12/13</td>
</tr>
</tbody>
</table>

huge variations of the physical form
The problem may be in the impurities

Table 2  Specifications of Rocephin and physical characteristics of generic ceftriaxone products tested

<table>
<thead>
<tr>
<th>Opalescence</th>
<th>pH</th>
<th>Degradation products</th>
<th>Metals</th>
<th>Residual solvents</th>
<th>Sterility</th>
<th>Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear; &lt;3.0</td>
<td>6.0-8.0</td>
<td>&lt;2.29%</td>
<td>0</td>
<td>0</td>
<td>No growth</td>
<td>0</td>
</tr>
<tr>
<td>Strong opalescent; 22.6</td>
<td>6.9</td>
<td>0.52%</td>
<td>Mn$^<em>$ Fe$^</em>$ Zn$^<em>$ Br$^</em>$ S B TH +</td>
<td>No growth</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Opalescent; 14.2</td>
<td>6.3</td>
<td>0.84%</td>
<td>Fe$^<em>$ Zn$^</em>$ Br$^*$ S B TH +</td>
<td>No growth</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Clear; 2.1</td>
<td>6.8</td>
<td>0.23%</td>
<td>Zn$^*$</td>
<td>S B H +</td>
<td>No growth</td>
<td>4</td>
</tr>
<tr>
<td>Clear; 2.2</td>
<td>6.7</td>
<td>0.17%</td>
<td>Zn$^<em>$ Br$^</em>$</td>
<td>S B +</td>
<td>No growth</td>
<td>3</td>
</tr>
<tr>
<td>Faintly opalescent; 3.2 6.7</td>
<td>6.5</td>
<td>0.28%</td>
<td>Fe$^<em>$ Zn$^</em>$ Br$^*$</td>
<td>S B +</td>
<td>No growth</td>
<td>4</td>
</tr>
<tr>
<td>Opalescent; 13.2</td>
<td>6.5</td>
<td>0.64%</td>
<td>Zn$^*$</td>
<td>S B TH + Germs$^§$</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Opalescent; 7.7</td>
<td>6.5</td>
<td>0.54%</td>
<td>Fe$^<em>$ Zn$^</em>$</td>
<td>S B TH + Germs$^¶$</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Opalescent; 6.4</td>
<td>6.5</td>
<td>0.73%</td>
<td>Fe$^<em>$ Zn$^</em>$ Br$^*$</td>
<td>S B +</td>
<td>No growth</td>
<td>5</td>
</tr>
</tbody>
</table>

*Content 1–4 ppm;
†Content 5–9 ppm;
‡Content 16 ppm.
§Kocuria rhizophila, Brachybacterium muris, and gram-positive cocci.
¶Gram-positive sporulated rods.
S: siloxane; B: butylated hydroxytoluene; T: tetradecan; H: hexadecan; +: not identifiable.

Deviations are in italics.

A number of deviations
Impurities in ciprofloxacin...

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 ± 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.

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

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

Substandard (wrong) drugs in the world?

Substandard drugs: a potential crisis for public health

Atholl Johnston¹ & David W. Holt²

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

Poor-quality medicines present a serious public health problem, particularly in emerging economies and developing countries, and may have a significant impact on the national clinical and economic burden. Attention has largely focused on the increasing availability of deliberately falsified drugs, but substandard medicines are also reaching patients because of poor manufacturing and quality-control practices in the production of genuine drugs (either branded or generic). Substandard medicines are widespread and represent a threat to health because they can inadvertently lead to healthcare failures, such as antibiotic resistance and the spread of disease within a community, as well as death or additional illness in individuals. This article reviews the different aspects of substandard drug formulation that can occur (for example, pharmacological variability between drug batches or between generic and originator drugs, incorrect drug quantity and presence of impurities). The possible means of addressing substandard manufacturing practices are also discussed. A concerted effort is required on the part of governments, drug manufacturers, charities and healthcare providers to ensure that only drugs of acceptable quality reach the patient.
3d round of conclusions and discussion

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

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

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

---

Do you remember how many levofloxacinS we now have in Belgium
What shall we discuss?

1. The EU and US laws
2. Approach to PK bioequivalence
3. Approach to microbiological and therapeutic equivalence
   1. MIC, MPC, heteroresistance …
   2. Approach to pharmacodynamic equivalence
   3. PK/PD animal models and clinical data
4. Dissolution, stability, impurities
5. The hidden risks of "low cost" drugs
   1. overconsumption (and wrong publicity [in back-up])
   2. lack of innovative research ... unless you pay!
      (not addressed today, but see the back-up slides)
The efforts for a correct use of antibiotics...

Current problems related to the use of antibiotics in the United States are summarized. In 1979, pharmaceutical manufacturers shipped $1.55 billion worth of anti-infective drugs. It is estimated that in approximately one-half of all cases that involve administration of antibiotics in the hospital, either the medical condition does not require antibiotic treatment, the most effective and least expensive drug is not chosen, or the correct dosage or duration of therapy is not prescribed. Much of the high cost of antibiotic therapy can be attributed to the use of expensive antibiotics of the cephalosporin and aminoglycoside groups and to the excessive duration of antibiotic prophylaxis in surgery. This review presents methods that assess the magnitude of the problem by audit and analyzes the corrective approaches that have been suggested. The major issues of concern related to the use of antibiotics are the complex series of considerations that lead physicians to prescribe antibiotics and the problem of patient expectation and compliance. Excessive usage of antibiotics must be viewed as part of the problem of overusage of all drugs and laboratory procedures.
We are facing contradictory situations

Developing the first national antimicrobial prescribing and stewardship competences

D. Ashiru-Oredope1*, B. Cookson2 and C. Fry3 on behalf of the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection Professional Education Subgroup†


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

This is today!
We are facing contradictory situations

Developing the first national antimicrobial prescribing and stewardship competences

D. Ashiru-Oredope¹*, B. Cookson² and C. Fry³ 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

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

But this had already occurred in Germany…

Specifically, generic competition lowers prices, which can accelerate consumption and resistance.

In: Mossialos et al. *Policies and incentives for promoting innovation in antibiotic research*
LSE Health, London School of Economics & Political Science, Houghton Street, London, 199 pp
See also: http://www.euro.who.int/en/about-us/partners/observatory/studies/policies-and-incentives-for-promoting-innovation-in-antibiotic-research
Summary / Suggestions

• The decision to "go for generics" is a political one that may need revision (at political level) to avoid over-use of antibiotics

• **Pharmacokinetic criteria** are, so far, the (nearly) only ones adopted and accepted by the Regulatory Authorities (EMA / FDA)

• **Improved criteria** for anti-infective drugs (MIC, MPC, animal PK/PD, …) are probably necessary (but are not yet implemented)

• The **control of the quality of the generics** (and of all antibiotics in general) is critical and should go beyond simple declarations and initial lot analysis…

• **Antibiotics are a precious commodity** that should not be lost. Misuse through low prices may cause **HUGE expenses in the future**…
Back-up
Lead generic companies resort to multiple strategies for growth

These include

• applying for **generic approvals** with Food and Drug Administration (FDA) and European Medicines Agency (EMA);

• **merger and acquisitions**;

• developing a strong and innovative **generic drug pipeline**;

• **improving infrastructure** to enhance manufacturing and R&D capabilities;

• **new product launches**, and geographic expansion.

US "Abbreviated New Drug Application"

Abbreviated New Drug Application (ANDA): Generics

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

FDA approved generic drugs: "Orange book" *

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Current through May 2013

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

Publications
FAQ

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

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

Drug questions email: druginfo@hhs.gov

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

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

* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
FDA approved generic drugs: "Orange book" *

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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

<table>
<thead>
<tr>
<th>Appl No</th>
<th>TE Code</th>
<th>RLD</th>
<th>Active Ingredient</th>
<th>Dosage Form Route</th>
<th>Strength</th>
<th>Proprietary Name</th>
<th>Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>A090343</td>
<td>AP</td>
<td>No</td>
<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
<td>EQ 250MG/50ML (EQ 5MG/ML)</td>
<td>LEVOFLOXACIN IN DEXTROSE 5% IN PLASTIC CONTAINER</td>
<td>ACS DOEBAR INFO SA</td>
</tr>
<tr>
<td>A090343</td>
<td>AP</td>
<td>No</td>
<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
<td>EQ 600MG/100ML (EQ 5MG/ML)</td>
<td>LEVOFLOXACIN IN DEXTROSE 5% IN PLASTIC CONTAINER</td>
<td>ACS DOEBAR INFO SA</td>
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<tr>
<td>A090343</td>
<td>AP</td>
<td>No</td>
<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
<td>EQ 750MG/150ML (EQ 5MG/ML)</td>
<td>LEVOFLOXACIN IN DEXTROSE 5% IN PLASTIC CONTAINER</td>
<td>ACS DOEBAR INFO SA</td>
</tr>
<tr>
<td>A091644</td>
<td>AP</td>
<td>No</td>
<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
<td>EQ 500MG/20ML (EQ 25MG/ML)</td>
<td>LEVOFLOXACIN</td>
<td>AKORN</td>
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<tr>
<td>A091644</td>
<td>AP</td>
<td>No</td>
<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
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<td>AKORN</td>
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<td>A202328</td>
<td>AP</td>
<td>No</td>
<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
<td>EQ 500MG/20ML (EQ 25MG/ML)</td>
<td>LEVOFLOXACIN</td>
<td>AUROBINDO PHARMA LTD</td>
</tr>
<tr>
<td>A202328</td>
<td>AP</td>
<td>No</td>
<td>LEVOFLOXACIN</td>
<td>INJECTABLE; INJECTION</td>
<td>EQ 750MG/30ML (EQ 25MG/ML)</td>
<td>LEVOFLOXACIN</td>
<td>AUROBINDO PHARMA LTD</td>
</tr>
</tbody>
</table>

As in LEVAQUIN®
If absorption is markedly delayed, you also have a lower initial AUC
Additional criteria for early AUC (EMA) *

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

---

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

• Is PK equivalence leading to pharmacological equivalence?
  – *in vitro* testing (MIC, MPC, impact on hetero-resistance) …
  – PK/PD models (animals)
  – Clinical studies (?)

• What about intravenous forms?
  (that, by definition, are not amenable to conventional bioequivalence studies)

• What about
  – dissolution times (critical in a nursing environment)
  – stablility (penems, e.g.)
  – impurities (do you like them?)
  – …
Are generic really comparable?

**Arithmetic Comparison**

**Geometric Comparison**
Are generic really comparable?

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

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

90% CI around point estimate (0.58-0.83)

90% CI around point estimate (0.86-0.92)
Special situations (EU)

Narrow therapeutic index drugs

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

Highly variable drugs or drug products

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

<table>
<thead>
<tr>
<th>Within-subject CV (%)*</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>80.00</td>
<td>125.00</td>
</tr>
<tr>
<td>35</td>
<td>77.23</td>
<td>129.48</td>
</tr>
<tr>
<td>40</td>
<td>74.62</td>
<td>134.02</td>
</tr>
<tr>
<td>45</td>
<td>72.15</td>
<td>138.59</td>
</tr>
<tr>
<td>≥50</td>
<td>69.84</td>
<td>143.19</td>
</tr>
</tbody>
</table>

\[CV(\%) = 100\sqrt{e^{s^2_{WR}} - 1}\]
**Potency (oxacillin)**

**Figure 1** Concentration-response relationship of innovator and generic products of oxacillin in the microbiological assay. A. The slopes and intercepts of OXA-BLA, OXA-COL, OXA-OPH, OXA-PEN, and OXA-SCA were not statistically different from those of OXA-BMS (innovator), thus confirming their pharmaceutical equivalence ($P = 0.1165$). The standard curves of all products are better described by a single linear regression, shown here with the 95% confidence interval. B. The slopes and intercepts of OXA-CAR, OXA-EXP, OXA-MEM and OXA-VIT were significantly different to the innovator's ($P < 0.03458$), thus failing pharmaceutical equivalence. As generic products belong to populations different to that of the innovator, each is described by an independent linear regression with their respective coefficient of determination ($r^2$).

Rodriguez et al. BMC Infectious Diseases 2010, 10:153
http://www.biomedcentral.com/1471-2334/10/153
Killing curves and hetero-resistance (vancomycin)

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

Killing curves and hetero-resistance (vancomycin)

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


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

Figure 3. Unpredictability of therapeutic equivalence from pharmaceutical equivalence. The graph illustrates the dose-response curves of gentamicin made by three well-reputed makers: Abbott, Sigma and S. Plough. Abbott and Sigma were indistinguishable from S Plough in terms of concentration and potency of the active pharmaceutical ingredient, MIC, MBC, MBC/MIC ratios but significantly different in terms of therapeutic efficacy, although the same batch of each product was tested in vitro and in vivo. doi:10.1371/journal.pone.0010744.g003

Gentamicin: evidence of non-equivalence for survival in animals

Neutropenic thigh mouse model

Figure 4. Results from survival experiments. Log-rank test curves obtained from neutropenic mice infected in the thighs with *P. aeruginosa* GRP-0019 and treated during 4 days with placebo (n = 5), GNT-Recipe (n = 10), or the innovator of gentamicin (n = 10) at the dose required for maximal effect (768 mg/kg per day divided q6h), starting 2 h (panel A) or 6 h (panel B) post-infection. Uninfected neutropenic mice serving as toxicity controls received the same treatment and were identical to the other animals but, instead of *P. aeruginosa*, were mock-inoculated in the thighs with sterile saline (n = 5 mice per gentamicin product). No significant impact on survival was detected between both gentamicin products. doi:10.1371/journal.pone.0010744.g004
Vancomycin: complete equivalence in the rabbit endocarditis model

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

P. Tattevin, # A. Saleh-Mghir, # C. David, I. Ghout, L. Massias, C. Garcia de la Maria, J. M. Miro, C. Perronne, F. Laurent

Ponte Callo University Hospital Hospital, Rennes, France; INSERM U983, Université Rennes 1, Rennes, France; EA 3647, Versailles, Saint-Quentin University, Versailles, France; Raymond Poincaré University Hospital, Garches, France; Ambroise Paré University Hospital, Boulogne, France; Bichat-Claude Bernard University Hospital, Paris, France; Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain; National Reference Center for Staphylococci, Hôpital de la Croix Rousse, Lyon, France.

Vancomycin: complete equivalence in the rabbit endocarditis model

Comparison of Six Generic Vancomycin Products vs. Methicillin-Resistant Staphylococcus aureus Endocarditis in Rabbits

P. Tattevin, a,b A. Saleh-Mghir, c,d B. Davido, e I. Ghout, e L. Massias, f C. Garcia de la Mar, g A. C. Crémioux c,d
Pontchaillou University Hospital, Rennes, France; INSERM U105, Université Rennes 1, Rennes, France; EA 3684, Raymond Poincaré University Hospital, Garches, France; Ambroise Paré University Hospital, Boulogne, France; Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain; National Reference Center for Staphylococcus, Rennes, France


T0: no antibiotic
T1 – T6: generics of vancomycin

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

C<sub>max</sub>/MIC

Time>MIC

AUC/MIC

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

Falsified Medicines: An EU reaction

DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 8 June 2011

amending Directive 2001/83/EC on the Community code relating to medicinal products for human
use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products

(Text with EEA relevance)


with an immediate follow-up from the Industry

http://www.egagenerics.com/index.php/publications
But at the end of the day...

Research Briefs

Generic medications for you, but brand-name medications for me

Amy J. Keenum, D.O., Pharm.D.\textsuperscript{a,*}, Jennifer E. DeVoe, M.D., D.Phil.\textsuperscript{b}, Deena J. Chisolm, Ph.D.\textsuperscript{c}, Lorraine S. Wallace, Ph.D.\textsuperscript{d}

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\textsuperscript{d}Department of Family Medicine, The Ohio State University, Columbus, OH 43201, USA
Fig. 2. Participants’ perceptions of generic and brand-name medications for treating their hypothetical chronic or acute condition (n = 172). Note: % who agreed is the sum of participants who somewhat or strongly agreed with each item. *P < .05 using chi-square test.
Generic antibiotic drugs: Is effectiveness guaranteed?

R. Gauzit*, M. Lakdhari

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Received 3 October 2011; accepted 11 October 2011
Available online 4 April 2012

Abstract

There are recently published arguments suggesting all generic antibiotic drugs do not present the full reliability needed to claim therapeutic equivalence with branded drugs. The problem is especially crucial for generic intravenous drugs, which do not need any bioequivalence study before they can be marketed. The evaluation of generic antibiotic drug effectiveness yields an important dispersion of results according to antibiotic agents and for the same antibiotic agent all generic drugs are not equivalent. There are differences at all levels: drug components, levels of impurity, pharmacokinetics, pharmacokinetic/pharmacodynamic relationship, in vitro effectiveness, therapeutic effectiveness in experimental models, etc. So that finally, the specifications approved in the initial submission file of a brand name drugs are not always respected by a generic drug. There is also a specific problem of taste and treatment acceptability for pediatric oral antibiotic drugs. Available data on clinical effectiveness is excessively rare. The marketing of a great number of generic drugs of the same specialty is followed by a sometimes very important increase of their use, even in countries where consumption is low. The corollary of this increase in consumption is an increase of resistance, and this is especially true for oral fluoroquinolones. Even if most of this information needs to be verified, it seems necessary to review regulations for marketing authorization of generic antibiotic drugs.
A Journey to the statins ....

Do all those patients really need a statin?

Very good for the budget

introduction of generics of statins

Source: INAMI / RIZIV
And generic companies will use any possible argument to foster sales…

This is an ad for a generic of moxifloxacin

Find the errors …

Choisissez les antibiotiques Sandoz, choisissez pour la sécurité et la qualité!
"Low cost antibiotics" and Internet

http://antidotum.org/index.php?showtopic=424075
A recent economic US study

HEALTH ECONOMICS
*Health Econ.* (2013)
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.3008

ARE PHYSICIANS’ PRESCRIBING DECISIONS SENSITIVE TO DRUG PRICES? EVIDENCE FROM A FREE-ANTIBIOTICS PROGRAM†

SHANJUN LI\textsuperscript{a,*} and RAMANAN LAXMINARAYAN\textsuperscript{b,c}

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\textsuperscript{b}Center for Disease Dynamics, Economics & Policy, Washington DC, USA
\textsuperscript{c}Princeton University, Princeton, NJ, USA

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

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

7/11/2014

Product safety and quality

88
The situation may be worse in veterinary medicine

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

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

UMR 1331 Toxalim INRA, INPT– Ecole Nationale Veterinaire de Toulouse, Toulouse Cedex, France
The situation may be worse in veterinary medicine

In France, introduction of generic fluoroquinolones increased their use by 30% in turkey (n=5500) production and 50% in chicken broiler (n=7000) production.

The level of resistance in Spain where cheap generics are available is associated with a higher use of fluoroquinolones in poultry and pigs vs Germany, UK or Denmark where prices are higher and practice better controlled.

Generic drug promotion in veterinary medicine is not consistent with the general objective of Public Health authorities to restrict the use of antibiotics in veterinary medicine…
A spiral to death (in Belgium)?

- For **antibiotics** and **antifungals**, if a medical doctor or a dentist prescribes for an **acute treatment**:
  - under the name of the active compound: the rules of prescription under INN (*) are of application (delivery of the cheapest preparation available)
  - under a trade name: as from 1\textsuperscript{st} May 2012, the pharmacist must deliver the product available in the group of « the cheapest drugs ».


- The drug acquisition cost for the treatment of a **community-acquired pneumonia** following the **recommendations of BAPCOC** (**) (amoxicillin [3 g / day in 3 administrations for 5 to7 days] is only **13-14 €** … (ex-factory price: ~7 €)


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* INN: International International Nonproprietary Name  
** BAPCOC: Belgian Antibiotic Policy Coordination Committee
But there is something worse…

Generic antibiotics, antibiotic resistance, and drug licensing

Although new drugs continue to be licensed, too few are based on novel chemical entities; drug resistance is more likely to occur when new agents are variants of existing classes.

There is a serious mismatch between clinical need and supply of new medicines for which there is no quick answer—it takes about 10 years and up to US$1 billion to develop a new antibiotic.

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

Will you do it for free?
Innovative antibiotic development is abandoned by Industry

Why do they abandon it?

A spiral to death (in Belgium)?

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

* INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee
The "Qualy" of antibiotics (*)

- The **quality-adjusted life year** or **quality-adjusted life-year** (QALY) is a measure of **disease burden**, including both the quality and the quantity of life lived. It is used in assessing the **value for money of a medical intervention**.

- If antibiotics **prolong your life of 2 to 10 years**, and the cost of one year of your life is **20,000 euros**, then the value of the "Qualy" of an antibiotic treatment is **40,000 to 200,000 euros**

- But the real cost and reimbursement of an antibiotic treatment is **MUCH less**

- For comparison, the cost of an anticancer treatment for 1 year survival is…. **up to 20,000 to 70,000 euros**… (and the accepted "Qualy" is close to that)

- Compare to the drug acquisition price to threat a pneumonia (as an example)

- Find where the problem lies…

2009 EU-US Summit Declaration called for the establishment of “...a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us.”
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In the US: resources for Researchers

Microbiology and Infectious Diseases Resources
The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV.

Funding Opportunities
Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.
- NIH-Wide Funding Opportunity Announcements
- NIAID Funding Opportunity Announcements and Requests for Proposals

Product Development Services and Research Tools and Biological Materials
Request development by DMID-funded contractors of critical information needed to move a product through the product development pathway. Note: Services are contingent upon availability of required preliminary data.

Click on labels below to view information on services.

Web Search Term: DMID Resources
Other key changes in the US …

• **GAIN Act** (Generating Antibiotics Incentives Now) - 2012
  – priority FDA review
  – additional five years of market exclusivity for breakthrough antibiotics that target serious or life-threatening pathogens
  – relaxed its criterion for non-inferiority to within 10%, making it easier to show comparability to drugs already on the market

• **BARDA**: Biomedical Advanced Research and Development Authority
  [within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services]
  – provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies.

• **FDA**:
  – new guidance documents (aBSSSI, cUTIs, cIAIs, …) that are considered being significantly better

• **Department of Health and Human Services** (HHS)
  – awarding funds to allow companies to shift funds around an antibiotic programs (portfolio approach; example: GSK antibiotic programme)

• Genetic Engineering and Biotechnology News 14 Aug 2013
  Last accessed: 8 May 2014

• Biomedical Advanced Research and Development Authority
  [http://www.phe.gov/about/barda/Pages/default.aspx](http://www.phe.gov/about/barda/Pages/default.aspx)
  Last accessed: 9 May 2014
Unless Big Brother comes to your help…

MCM Procurements and Grants

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

October 21, 2013: New blood test would provide fast results for medical care after anthrax attack
September 26, 2013: BARDA boosts global ability to respond to pandemics
September 20, 2013: HHS funds development of freeze-dried platelets for disaster response
September 19, 2013: BARDA funds development of device to aid burn patients in disasters
September 19, 2013: HHS replenishes nation’s supply of anthrax antitoxin
September 18, 2013: HHS explores new emergency response use for approved steroid
September 17, 2013: BARDA funds study of therapy for thermal burns
September 16, 2013: BARDA evaluates burn dressing for radiation, sulfur mustard burns
August 23, 2013: BARDA Contract Supports Evaluation of Therapy for Severe Thermal Burns
August 22, 2013: BARDA Supports Proof-Of-Concept Studies for Small Molecule Development
July 30, 2013: BARDA contract supports the development of a more effective skin graft to help burn patients after a radiocyte event
June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis
May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tularemia
May 22, 2013: HHS forms strategic alliance to develop new antibiotics
April 3, 2013: HHS awards contract to create test to identify resistant influenza viruses

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

This page last reviewed: January 03, 2014
Unless Big Brother comes to your help…

Collaborations

**Harvard University** - Anti-Pseudomonas Antibody Technology
Aridis is collaborating with the Laboratory of Dr. Gerald Pier on the preclinical development of Aerucin. This work is being funded by a National Institute of Health NIAID grant.

**Biomedical Advanced Research and Development Authority (BARDA), US Dept. Health & Human Services** - Aridis formulation technology
Aridis is working with BARDA and PATH to develop advanced stabilization formulation for influenza vaccines.

**U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID, Ft. Detrick)** - Gallium based anti-infective for biodefense (Panaecin)
Panaecin and new generation of gallium based complexes are being evaluated as post-exposure prophylactic anti-infectives for inhalational anthrax, tularemia, glander, and plague.

**Walter Reed Army Institute of Research (Washington, DC)** - Gallium based anti-infective for wound healing (Panaecin)
Topical formulations of Panaecin are being evaluated as a topical anti-bacterial with wound healing properties.
Unless Big Brother comes to your help...

Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin

April 24, 2013

"Contract to fund Phase 3 superiority study of plazomicin in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections -

South San Francisco, CA. April 24, 2013 - Achaogen, Inc. today announced the award of a $60M contract option from the Biomedical Advanced Research and Development Authority (BARDA). The option supports the conduct of a global Phase 3 superiority study that will evaluate the efficacy and safety of plazomicin in treating patients with serious gram-negative bacterial infections due to CRE. This pathogen-specific clinical study represents a new development approach to address unmet medical needs for multi-drug resistant bacterial infections. The study is expected to start in fourth quarter of 2013.

"We are excited and honored to continue the development of plazomicin in partnership with BARDA," said Kenneth J. Hillan, M.B.Ch.B., Chief Executive Officer and Chief Medical Officer of Achaogen. "The growing prevalence of CRE infections poses a substantial public health threat, given the high mortality rates associated with CRE infections. Plazomicin's strong potential to address this public health issue and to contribute to the global effort to guard against bacterial biothreats makes it a critically important agent in the antibacterial pipeline."

Plazomicin is a next-generation aminoglycoside antibiotic that Achaogen engineered to overcome key aminoglycoside resistance mechanisms. It has potent bactericidal activity against
What in Europe?

ECDC/EMEA Joint Working Group
- assigned on 28 February 2008.
- circulated for information on 20 August 2009.

Last accessed: 9 May 2014
Investments in Europe ...

EU launches new research projects to combat antimicrobial resistance

Last accessed: 8 May 2014
Investments in Europe…

The rising awareness of the AMR threat is reflected in a six fold increase in the amount being invested, from some €84 million during the EU's 1998-2002 research programme to about €522 million for the 2007-13 period.

<table>
<thead>
<tr>
<th>Period</th>
<th>Investment (€ million)</th>
</tr>
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<tbody>
<tr>
<td>1998-2002</td>
<td>€84</td>
</tr>
<tr>
<td>2002-2006</td>
<td>€187</td>
</tr>
<tr>
<td>2007-2013</td>
<td>€522</td>
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Most of the EU investment is used to support collaborative projects i.e. international research and innovation teams involving the most capable players from across Europe and abroad.

Last accessed: 8 May 2014
Public/Private shares in Europe

Public-private partnerships

- Pooling expertise, knowledge and resources
- Developing incentives to address major unmet medical needs
- Providing a neutral trusted platform to align public and private interests

An opportunity to combine public and private resources for new antimicrobials
• €2 billion euro budget…
• collaborative research projects and networks of industrial and academic experts…
• collaborative ecosystem for pharmaceutical research and development (R&D)…
• increase Europe's competitiveness globally…
• establish Europe as the most attractive place for pharmaceutical R&D
And more generally speaking… with a caveat…

Policies and incentives for promoting innovation in antibiotic research

Elias Mossialos, Chantal M. Morel, Suzanne Edwards, Julia Berenson, Marin Gemmill-Toyama, David Brogan

The European Observatory on Health Systems and Policies supports and promotes evidence-based health policy-making through comprehensive and rigorous analysis of health systems in Europe. It brings together a wide range of policy-makers, academics and practitioners to analyse trends in health reform, drawing on experience from across Europe to illuminate policy issues.
And more generally speaking… with a caveat…

Policies and incentives for promoting innovation in antibiotic research

Elias Mossialos, Chantal M. Morel,
Suzanne Edwards, Julia Berenson,
Marin Gemmill-Toyama, David Brogan

- It is necessary for European public health authorities to emphasize rationing of existing antibiotics intended for severe infection (using generics as first-line therapies). However, this gives the impression that, if developed, new antibiotics will be kept as last resort treatments regardless of high levels of resistance to widely used antibiotics.

So, you will keep on reserve
- cefaroline and ceftobiprole
- oritavancin and dalbavancin
- tedizolid …
How can you COMBACTE?

CLIN-Net Network Participants

As of April 2013, 261 clinical sites in 32 countries have expressed an interest in joining CLIN-Net. In the third quarter of 2013, these sites will be approached with an explorative questionnaire to establish their current experience with clinical trials, their facilities to conduct trials and their need for (additional) GCP training.

Further auditing, site visits and certification will start in 2014.