Generics of antibiotics: are you sure of what you get … and of what you pay?

Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Secteur des Sciences de la Santé
Université catholique de Louvain
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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, AstraZeneca

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

Slides: http://www.facm.ucl.ac.be ➔ Lectures
Whay are generics knocking at your doors?

Your prescription, your choice.

Generics are cheaper!

A well known antibiotic in Belgium…

Before patent expiration

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

## Levofloxacin Actavis (Actavis) [1]
- Sac perf.
  - 5 x 500 mg / 100 ml U.H. [€65]

## Levofloxacin BG (Eurogenerics) [2]
- Compr. (séc.)
  - 10 x 250 mg R b € 21,42
  - 30 x 500 mg R b € 57,56
- Sac perf.
  - 1 x 500 mg / 100 ml U.H. [€17]

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

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

## Levofloxacin Mylan (Mylan) [5]
- Compr. (séc.)
  - 10 x 250 mg R b € 14,98
  - 14 x 250 mg R b € 24,43
  - 10 x 500 mg R b € 21,98
  - 14 x 500 mg R b € 35,13
- Flacon perf.
  - 10 x 500 mg / 100 ml U.H. [€17]

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

1. The EU and US legal framework
2. What is bioequivalence (for a generic)?
3. Microbiological equivalence?
   - potency, heteroresistance, selection of resistance …
4. Pharmacodynamic equivalence?
   - PK/PD animal models, clinical alerts …
5. Dissolution, impurities/instability, true content, "substandard drugs"…
6. Over-consumption of "low cost" antibiotics?
7. Economic considerations in antibiotic discovery, development and use
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The EU Directive

**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)

<table>
<thead>
<tr>
<th>Amended by:</th>
<th>Official Journal</th>
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<td>L 348</td>
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<td>L 174</td>
</tr>
</tbody>
</table>

The EU Directive

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

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

Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.
EU rules: what needs to be supplied for non-biological product

• Data for Modules 1, 2 and 3 *
• **together** with data showing **bioavailability and bio-equivalence** with the original medicinal product

Special attention needs to be paid to:
• the grounds for claiming essential similarity;
• a summary of **impurities** (with an evaluation of these);
• an evaluation of the **bio-equivalence studies** or a justification why studies were not performed;
• an **update of published literature** relevant to the substance and the present application;
• every claim not known from or inferred from the properties of the medicinal product should be discussed and substantiated by published literature and/or additional studies.
• **equivalence of safety and efficacy properties of different salts, esters or derivatives** of an authorised active when he claiming essential similarity.

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* Module 1 = administrative information; Module 2 = Summaries; Module 3 = Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances; Module 4 = non-clinical reports; Module 5 = clinical reports
The US Law

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

US "Abbreviated New Drug Application"

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, the 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 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)
  
FDA approved generic drugs: "Orange book" *

FDA approved generic drugs: "Orange book" *

The list is 3 pages long...

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

• 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) → extent of absorption
  – **C<sub>max</sub>** (the maximum plasma concentration of the active substance) → extent and rate of absorption
  – **T<sub>max</sub>** (the time at which **C<sub>max</sub>** is reached) → rate of absorption

$C_{\text{max}}$

$T_{\text{max}}$

AUC

Concentration (mg/L)

Time (h)

AUC
What if the absorption is decreased?

\[
\text{C}_{\text{max}}
\]

\[
\text{AUC}
\]
What if absorption is delayed?

\[ \text{but AUC is } = \]
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


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

- Use the partial **AUC truncated** at the population median of **$T_{max}$** for the reference formulation for 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?)
  – …
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MIC determinations (piperacillin)


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

Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.
MIC determinations (meropenem)

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

susceptible strains (MIC \leq 2 \text{ mg/L})

intermediate strains (2 \leq \text{MIC} < 8 \text{ mg/L})

resistant strains (MIC > 8 \text{ mg/L})

Van Bambeke et al., in preparation
# MIC determinations (vancomycin)

<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>Vancomycin</td>
<td>MRSA (90)</td>
<td>5</td>
<td>25.00 ± 15.52</td>
<td>54.4  45.6  –  –  –</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>MRSA (147)</td>
<td>7</td>
<td>28.09 ± 10.29</td>
<td>59.2  40.1  0.7  –</td>
</tr>
<tr>
<td>Cefotiam</td>
<td><em>Staphylococcus aureus</em> (100)</td>
<td>7</td>
<td>8.71 ± 3.04</td>
<td>87.0  13.0  –  –</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em> (100)</td>
<td>7</td>
<td>12.00 ± 5.89</td>
<td>77.0  22.0  1.0  –</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td><em>Streptococcus pneumoniae</em> (126)</td>
<td>6</td>
<td>12.70 ± 4.77</td>
<td>81.7  18.3  –  –</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td><em>Pseudomonas aeruginosa</em> (100)</td>
<td>2</td>
<td>3.00 ± 2.83</td>
<td>95.0  5.0   –  –</td>
</tr>
<tr>
<td>Meropenem</td>
<td><em>P. aeruginosa</em> (100)</td>
<td>7</td>
<td>18.57 ± 3.46</td>
<td>78.0  19.0  2.0  1.0</td>
</tr>
<tr>
<td>Imipenem</td>
<td><em>P. aeruginosa</em> (100)</td>
<td>4</td>
<td>9.00 ± 2.58</td>
<td>88.0  11.0  1.0  –</td>
</tr>
</tbody>
</table>

*MRSA* methicillin-resistant *Staphylococcus aureus* 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.


MICs were often higher than for the reference product...
Zone diameters (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
Post-exposure hetero-resistance (vancomycin)

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

### Post-exposure hetero-resistance (vancomycin)

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

Resistance frequencies after *in vivo* exposure (vancomycin)

**FIG 5** Changes in resistance frequencies (RFs) to 1, 2, and 3 mg/liter of vancomycin after *in vivo* exposure to innovator vancomycin (Lilly), generic versions (APP, Abbott, and Proclin), or sterile saline. At 1 mg/liter, compared to initial values (GRP-0109), Lilly reduced the RFs by almost 10-fold, while generics induced no significant change. At 2 mg/liter Lilly also reduced the RFs, but generic products significantly increased them 10- to 1,000-fold. At 3 mg/liter, again Lilly reduced the RFs, APP and Abbott did not change the baseline RF, and Proclin significantly increased it by 1 order of magnitude. In the saline group RFs were reduced about 1 log_{10} at all concentrations. The asterisk indicates that the postexposure value is significantly different from the preexposure value (Student’s *t* test): *P* values of 0.0002 and 0.0005 for Lilly and saline at 1 mg/liter, respectively; *P* values of 0.0258, 0.0012, 0.0002, <0.0001, and 0.0029 for Lilly, APP, Abbott, Proclin, and saline at 2 mg/liter, respectively; *P* values of 0.0140, 0.0152, and 0.0094 for Lilly, Proclin, and saline at 3 mg/liter, respectively. CFU counts at 4 mg/liter and higher were below the limit of detection.

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Vancomycin: evidence of non-equivalence in a dose-response mouse tight model (fAUC/MIC)

Neutropenic tight 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-Procin 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 a dose-response mouse thigh model (total dose)

Neutropenic tight 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.

Gentamicin: evidence of non-equivalence in a dose-response mouse thigh model (total dose)

Neutropenic thigh mouse model

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

doi:10.1371/journal.pone.0010744.g003

Gentamicin: evidence of non-equivalence in survival in the neutropenic mouse model

Neutropenic tight 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
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


Pontchaillou University Hospital, Rennes, France; INSERM U835, 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

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P. Tattevin, A. Saleh-Mghir, B. Davido, I. Ghout, L. Massias, C. Garcia de la Mar, A. C. Crémieux

Pontchaillou University Hospital, Rennes, France; INSERM U835, Université Rennes 1, Rennes, France; EA 3959, 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 aureus*, Charleroi, Belgium.


**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 in a dose-response animal model (AUC/MIC)

**FIG 5** Influence of pharmacodynamic indices on the antimicrobial effect of metronidazole on *R. 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.
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 Russo⁴

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, Luca De Lucia2, Emilio Russo3
1Department of Health Science, Regional Center on drug information, Magna Graecia University School of Medicine, University of Catanzaro, 2Department of General Medicine, University of Catanzaro, Cosenza, Italy

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

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.
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Dissolution of amoxicillin

Evaluation and comparison of in-vitro dissolution profiles for different brands of amoxicillin capsules

*Kassaye L., Genete G

Food and Medicine quality Control Laboratory, Food, Medicine and Healthcare Administration and Control Authority, Ethiopia, Addis Ababa


Table 1: Samples of amoxicillin capsules

<table>
<thead>
<tr>
<th>Samples code</th>
<th>Country of origin</th>
<th>Mfg date</th>
<th>Exp date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxil™</td>
<td>United Kingdom</td>
<td>06/2009</td>
<td>06/2014</td>
</tr>
<tr>
<td>A</td>
<td>India</td>
<td>09/2009</td>
<td>08/2012</td>
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<tr>
<td>B</td>
<td>India</td>
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<td>H</td>
<td>India</td>
<td>12/2009</td>
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The label claim for all samples is amoxicillin 500 mg
Dissolution of amoxicillin

Evaluation and comparison of in-vitro dissolution profiles for different brands of amoxicillin capsules.

Food and Medicine quality Control Authority, Ethiopia, Addis Ababa.

Dissolution of meropenem (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 of meropenem (Japan)

![Brand name meropenem](image)

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

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 nurses happy with generic meropenem (in Belgium) ?

**dissolution time**

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

**questionnaire - solubilisation**

Repeated Measures ANOVA
- **P value**: 0.3084
- **P value summary**: ns
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 Pharmacopoeia. 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.

Instability and release of coloured compounds with meropenem

Van Bambeke et al., in preparation

are you happy with the colour?
Impurities in meropenem: coloured compounds

Van Bambeke et al., in preparation
Substandard drugs in the world?

Figure 1. Examples of recent accounts of substandard drugs around the world.
What shall we discuss?

1. The EU and US legal framework
2. What is bioequivalence (for a generic)?
3. Microbiological equivalence?
   - potency, heteroresistance, selection of resistance …
4. Pharmacodynamic equivalence?
   - PK/PD animal models, clinical alerts …
5. Dissolution, impurities/instability, true content, "substandard drugs"…
6. Over-consumption of "low cost" antibiotics?
7. Economic considerations in antibiotic discovery, development and use
A Journey to the statins in Belgium ....

Source: INAMI / RIZIV (Belgian National Institute for Sickness and Invalidity Insurance)
"Low cost antibiotics" and "prudent use" …
The sour Danish experience

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

Antibiotic reimbursements in Belgium

Source:
Belgian National Institute for Sickness and Invalidity Insurance
"Tableaux de bord pharmaceutiques: Délivrances pharmaceutiques dans le secteur ambulant – année 2012"

Last accessed: 20/01/2014
Antibiotic reimbursements in Belgium

Source:
Belgian National Institute for Sickness and Invalidity Insurance
"Tableaux de bord pharmaceutiques: Délivrances pharmaceutiques dans le secteur ambulant – année 2012"
Last accessed: 20/01/2014
A recent economic US study about "free of charge antibiotics"

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

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

SHANJUN LI\(^{a,*}\) and RAMANAN LAXMINARAYAN\(^{b,c}\)

\(^{a}\)Dyson School of Applied Economics and Management, Cornell University, Ithaca, NY, USA  
\(^{b}\)Center for Disease Dynamics, Economics & Policy, Washington DC, USA  
\(^{c}\)Princeton University, Princeton, NJ, USA

A "natural experiment" in which Meijer, a popular Midwestern retail chain, offered 14-day supplies of certain generic oral antibiotics free of charge to customers with prescriptions from October 2006 (about 2 millions prescriptions analyzed 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, with an increase in overall antibiotic prescriptions.
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 Vétérinaire de Toulouse, Toulouse Cedex, France
The situation may be worse in veterinary medicine

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

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

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

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

  (last accessed: 7 November 2013)

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

  Source: Belgian "Répertoire commenté des médicaments" available at http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_A.cfm
  (last accessed: 7 November 2013)

*  INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee
A spiral to death (in Belgium)?

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


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

* INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee
The spiral to death in the US…

The spiral to death in the US...

The "Qualy" of antibiotics (*)

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

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

• But the real cost of an antibiotic treatment is usually <<< 40,000 euros for a treatment that gives you 2-10 years survival…

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

• Find where is the problem…

But 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 plasmodia 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 21, 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 development of a more effective skin graft to help burn patients after a radi/nuke event
June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis
May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tularemia
May 22, 2013: HHS forms strategic alliance to develop new antibiotics
April 3, 2013: HHS awards contract to create test to identify resistant influenza viruses

http://www.phe.gov/newsroom/Pages/mcm-procurements.aspx
When Big Brother helps Big Pharma…

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

**Date:** May 22, 2013

**Company:** GlaxoSmithKline of North Carolina

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

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

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

**Press Release:** HHS forms strategic alliance to develop new antibiotics

But EU is not too bad either

EU taxpayer funding: $83 x 10^6$ euros

http://www.imi.europa.eu/
How can you COMBACTE?

CLIN-Net Network Participants

As of April 2013, 281 clinical sites in 32 countries have expressed an interest in joining CLIN-Net. In the third quarter of 2013, these sites will be approached with an explorative questionnaire to establish their current experience with clinical trials, their facilities to conduct trials and their need for (additional) GCP training.

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

https://www.combacte.com/?q=node/32
Summary / Discussion

- 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, triggering of resistance, animal efficacy studies, dissolution, impurities…) are probably necessary (but are not yet really implemented)

- **Antibiotics are cheap** (compared to other chemotherapeutic agents), making discussion about still reducing costs somewhat surprising …

- Savings in this area may cause **HUGE expenses soon and later because of lack of proactive developments of new compounds or new approaches**

- Antibiotics might be a good starting point to **modify the current legislative framework** concerning generics at the level of the EU-Parliament and the US Congress…
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.

True content and release: the colistimethate/colistin problem

Pharmacokinetics of four different brands of colistimethate and formed colistin in rats

Hui He1††, Ji-Chang Li1††, Roger L. Nation1, Jovan Jacob1, Gong Chen1, Hee Ji Lee1, Brian T. Tsuji3, Philip E. Thompson4, Kade Roberts1†, Tony Velkov1 and Jian Li1*  

1Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; 2College of Veterinary Medicine, Northeast Agricultural University, Harbin 150030, P. R. China; 3School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA; 4Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia
True content and release
1. colistimethate diversity

1. HPLC

Atlantic

Forest
True content and release

2. colistin release

1. HPLC of colistimethate

2. Release of colistin

formed colistin in rats (n=4) following an intravenous dose of CMS (28.1 mg/kg).
May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tularemia

**Date:** May 24, 2013

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

**Contract amount:** $17.7 million for two years

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

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

**Press Release:** HHS funds drug development for bioterror infections

http://www.piersystem.com/go/doc/3803/1863410/
And even for an aminoglycoside …
Unless Big Brother comes to your help…
June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis

Date: June 25, 2013

Company: Basilea Pharmaceutica International Ltd., Basel, Switzerland

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

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

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

Press Release: BARDA supports new broad-spectrum antibiotic

http://www.piersystem.com/go/doc/3803/1863402/
Unless Big Brother comes to your help... even in Switzerland

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

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

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

Ongoing phase 1 program

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

The need for new Gram-negative antibiotics

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

In hospitals, beta-lactam antibiotics form the mainstay antimicrobial therapy but their use is increasingly compromised by acquired beta-lactam resistance, especially in Gram-negative bacteria such as Enterobacteriaceae and Pseudomonas aeruginosa. In a recent survey involving thousands of patients from hospitals around the world, Gram-negative bacteria have been found in sixty percent of clinical isolates in intensive care units. The need for novel Gram-negative antibiotics with a broad coverage of clinically relevant pathogens is therefore undeniable.
A good (old) friend described about 4 years ago …

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

http://aac.asm.org/content/54/6/2291.full
AAC June 2010 vol. 54 no. 6 2291-2302
Are generic really comparable?

### Arithmetic Comparison

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Are generic really comparable?

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</tr>
<tr>
<td>higher 110</td>
<td></td>
<td></td>
<td></td>
<td>0.83</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Are generic really comparable?

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

<table>
<thead>
<tr>
<th>Number of values</th>
<th>ratio A/ref</th>
<th>ratio B/ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.2900</td>
<td>0.8200</td>
</tr>
<tr>
<td>25% Percentile</td>
<td>0.6200</td>
<td>0.8700</td>
</tr>
<tr>
<td>Median</td>
<td>0.7350</td>
<td>0.8850</td>
</tr>
<tr>
<td>75% Percentile</td>
<td>0.9600</td>
<td>0.8950</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.130</td>
<td>1.060</td>
</tr>
<tr>
<td>Mean</td>
<td>0.7583</td>
<td>0.8933</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>0.2620</td>
<td>0.05726</td>
</tr>
<tr>
<td>Std. Error</td>
<td>0.07565</td>
<td>0.01653</td>
</tr>
<tr>
<td>Geomean</td>
<td>0.7072</td>
<td>0.8924</td>
</tr>
</tbody>
</table>

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 \([U, L] = \exp[±k\cdot s_{WR}]\), 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 sWR is the within-subject standard deviation of the log-transformed values of Cmax of the reference product (Important: this applies to C_{max} only, NOT to AUC)

<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>

* \(CV(\%) = 100\sqrt{e^{\frac{s_{WR}}{2}} - 1}\)
True content: the Liège approach…

Application of an innovative design space optimization strategy to the development of LC methods for the simultaneous screening of antibiotics to combat poor quality medicines

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\textsuperscript{b} Service d'Analyse des Médicaments, Département de Galénique et d'Analyse des Médicaments, Université de Kinshasa, BP 212 Kinshasa XI, Democratic Republic of Congo
\textsuperscript{c} Rwanda Biomedical Center (RBC)/Medical Production Division, P.O. Box 340 Butare, Rwanda

Innovative "Design Space optimization" strategy to simultaneously targeting 16 antibiotics and 3 beta-lactamase inhibitors
True content: the Liège approach...

Table 8
Assay results of three pharmaceutical medicines coded A, B and C, marketed in DRC.

Results consist in the mean percentage of claimed nominal content and their 95% confidence interval computed on 3 independent samples. Specifications are set to 95–105% of the claimed nominal content (mg). Non-compliant results for the tested powder for injection are in bold.

<table>
<thead>
<tr>
<th>Drug</th>
<th>CFT content</th>
<th>SUL content</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1000 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>96.7 ± 0.89%</td>
<td>97.2 ± 1.32%</td>
</tr>
<tr>
<td>B</td>
<td>1000 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>105.0 ± 2.73%</td>
<td>98.0 ± 2.06%</td>
</tr>
<tr>
<td>C</td>
<td>1000 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>115.1 ± 1.76%</td>
<td>99.2 ± 1.81%</td>
</tr>
</tbody>
</table>

DRC: Democratic Republic of Congo
CFT: ceftriaxone
SUL: sulbactam