
The issue of therapeutic equivalence of generic drugs when purchasing drugs

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Conflict of interest

Conflict of interest: nothing to disclose

Introduction

- Similarities between generics
 - What are generics
 - Bioequivalence
 - Scientific research
- Unsimilarities between generics
 - Project
 - Checklist

Generic drugs

- Advantage of registration as a generic
- Refer to dossier from reference product
 - No clinical tests or clinical trials

FDA: 7.800 generics of total of 10.700 approved pharmaceuticals (73%)

In comparison to reference product

- Same qualitative and quantitative composition
- Same pharmaceutical form
- Bioequivalence has been demonstrated by bioavailability studies

Bioequivalence:

- Pharmaceutically equivalent or pharmaceutical alternatives
- Bioavailabilities (rate and extent) lie within acceptable predefined limits

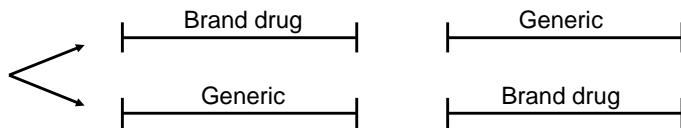
Parameters to be analysed:

- AUC
- Cmax (when relevant)

Acceptance interval: 90% CI in 80 – 125%

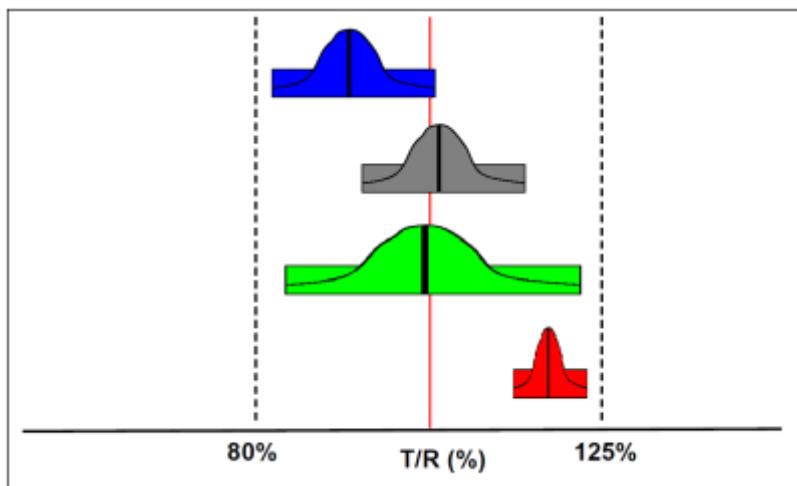
Recommended study design

- Randomised two-period, two-sequence single dose crossover
- Healthy volunteers



In vitro dissolution test

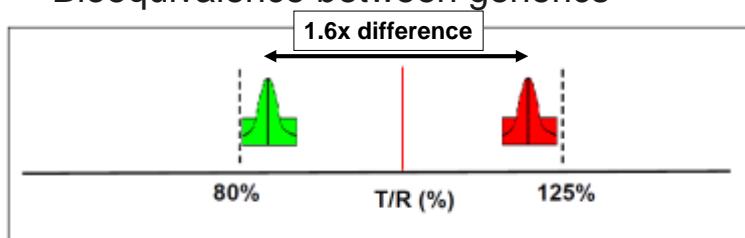
Bioequivalence



Bioequivalence

Limitations:

- Healthy volunteers
- Not right measure for some forms
 - Budesonide, mesalazine, inhalation
- Bioequivalence between generics



Narrow Therapeutic Index Drugs

- Acceptance interval (AUC and Cmax):
90% CI in 90 – 111%

Narrow Therapeutic Index Drugs

- EMEA: must be decided case by case
- Canada: Cyclosporine, Digoxin, Flecainide, Lithium, Phenytoin, ...
- FDA: no formal list: Major drug classes antiepileptics, antiarrhythmics, immunosuppressives, anticoagulants, others...

Biosimilars

SAHZ

Highlights of the equivalence of biosimilars

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ISO 9001

Scientific Research

Taber et al.

- Renal transplant patients
- Cyclosporine: Gengraf versus Neoral
- Neoral: jan 1999 – May 2001
- Gengraf: May 2001 – July 2002
- 88 versus 100 patient

Taber et al. Transplantation. 2005; 80:1633–5.

- No differences in 12h CyA concentrations
- More interpatient variability
- 2 fold higher risk of rejection (95% CI 1,26 – 4,9; p=0.008)

Limitations

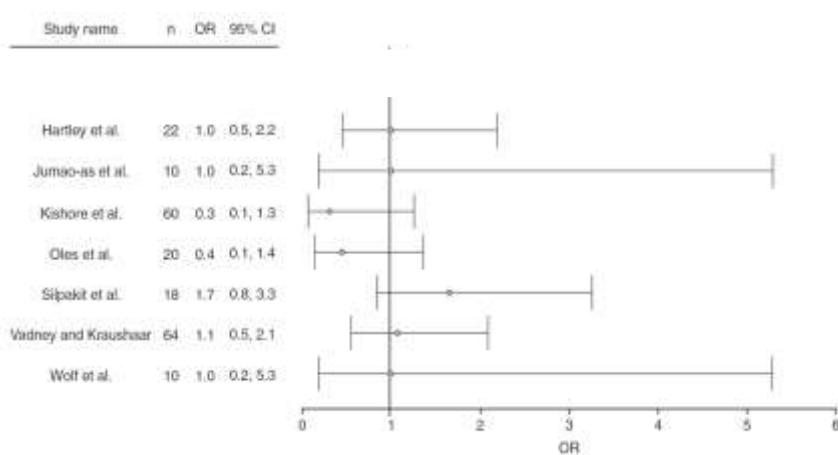
- Historical control group
- Publication bias

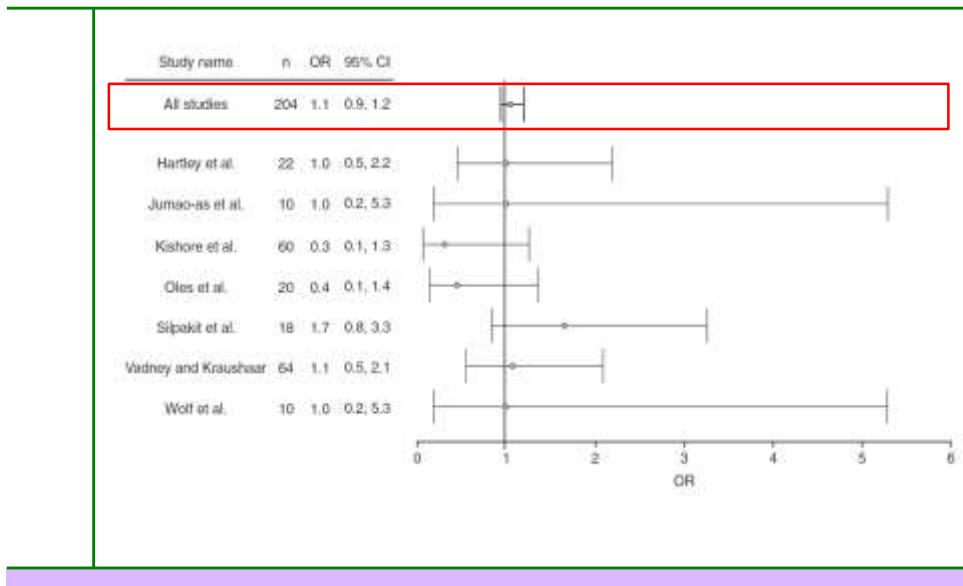
Kesselheim et al.

- Meta-analysis
- RCT's
- Seizure outcomes after switching antiepileptic drugs (Brand-Generic)

Kesselheim et al. Drugs 2010; 70: 605-621.

- Seven RCTs included
 - Carbamazepin (5), Phenytoin (1), Valproic acid (1)
 - Cross-over trial (6), new therapy (1)
- In total 204 patients





Project

Goal: to reduce the number of issues after changing between generic drugs

Method: Learn from issues in the past in three hospitals

Storage conditions

Epinephrine 1 mg/ml injection

- Generic A: store 15-25 °C
- Generic B: store 2-8 °C

Problem: Emergency set, Ambulance, etc.

Look alikes



Appearance



Apearance

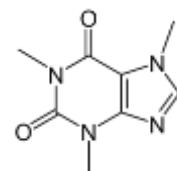
- USA: Trade Dress Law
- Not allowed to make similar appearance
- Differences in appearance:
 - Mistakes
 - Adherence



Coffeine for neonates

Coffeine base: Mw = 194 g/mol

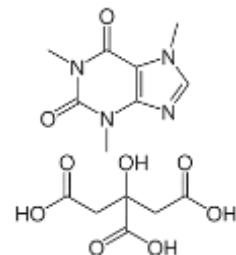
- Start dose 10 mg/kg/day sid,
- Maintenance dose 2,5 - 5 mg/kg/day sid



Coffeine citrate: Mw = 386 g/mol

- Start dose 20 mg/kg/day sid,
- Maintenance dose 5 - 10 mg/kg/day sid

Peyona
Coffeine citrate
50 mg/ml



Caffeine for neonates

Hospital A:

neonate treated with caffeine citrate (Peyona) 20 mg/kg daily

Transfer to our hospital:

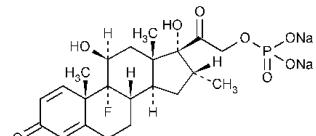
Physician prescribes caffeine 20 mg/kg daily

Is caffeine base

Seen during medication surveillance: once double overdose of caffeine

Salt forms

Similar product dexamethason:



Product A:

Dexamethason disodium phosphate 5 mg

Product B:

Dexamethason 3.8 mg (as dexamethason disodium phosphate)

Gemcitabine

Gemcitabine

Generic A: Powder for solution



Generic B: Concentrate for solution 38 mg/ml

Gemcitabine

Generic B: Concentrate for solution 38 mg/ml
421 mg/ml ethanol 96%

$$1.8 \text{ m}^2 \times 1250 \text{ mg/m}^2 = 2250 \text{ mg}$$

$$2250 \text{ mg} / 38 \text{ mg/ml} = 59 \text{ ml concentrate}$$

$$59 \text{ ml} \times 421 \text{ mg/ml} = 24 \text{ gram ethanol}$$

Is 2 to 2,5 glasses of beer!



Propranolol

Propranolol for children

Syprol oral solution 2 mg/ml
orange/tangerine flavour containing: ethanol
0.12 %v/v

Propranolol

4 year old child, 17 kg, 2 mg/kg/day

17 ml Syprol per day
 $0,12\% = 0,95 \text{ mg/ml}$
 $17 \text{ ml} \times 0,95 \text{ mg/ml} = 16 \text{ mg ethanol per day}$

1/1000th glass of beer

$\frac{1}{1000} \times$



How to prevent these issues?

Checklist!



Table 1 Checklist for the intercompatibility of generic				
Drug, route of administration, strength				
	Current product	Alternative product 1	Alternative product 2	Alternative product 3
Product:				
Registration number:				
Pack:				
Dosage:				
Name and declaration primary packaging				
Name and declaration secondary packaging				
Good readability label	Yes/No	Yes/No	Yes/No	Yes/No
Packaging	Unit packaging/Primary/Blank/.....	Unit packaging/Primary/Blank/.....	Unit packaging/Primary/Blank/.....	Unit packaging/Primary/Blank/.....
Packaging label in own language	Yes/no/other language.....	Yes/no/other language.....	Yes/no/other language.....	Yes/no/other language.....
Storage conditions	15-25°C/2-8°C/other... °C days/months/years	15-25°C/2-8°C/other... °C days/months/years	15-25°C/2-8°C/other... °C days/months/years	15-25°C/2-8°C/other... °C days/months/years
Shelf life	Yes/No	Yes/No	Yes/No	Yes/No
Flag label				
Barcode primary packaging	String/number/none	String/number/none	String/number/none	String/number/none
Barcode secondary packaging	String/number/none	String/number/none	String/number/none	String/number/none
Excipients:				
- Glycerol	Yes/No	Yes/No	Yes/No	Yes/No
- Glycerol alcohol	Yes/No	Yes/No	Yes/No	Yes/No
- Propylene glycol	Yes/No	Yes/No	Yes/No	Yes/No
- Ethanol	Yes/No	Yes/No	Yes/No	Yes/No
- Isopropanol (2-propanol)	Yes/No	Yes/No	Yes/No	Yes/No
- Solvent E223 (G223, methylcellosolve)	Yes/No	Yes/No	Yes/No	Yes/No
- Wheat starch	Yes/No	Yes/No	Yes/No	Yes/No
- Other deviating ingredients				
Compare both packages (size, readability text, risk of differentiation contact strength)				
Check the similarity with packages already used in the clinic (risk of making mistake)				
Compatibility with devices (real syringes, master doses, pressure infusion cuff, etc.)	Device:	Device:	Device:	Device:
Compatibility with containers	Plastic, metal	Plastic, metal	Plastic, metal	Plastic, metal
Solvent used in solvent	Yes/no	Yes/no	Yes/no	Yes/no
Water used in liquid	recomend	recomend	recomend	recomend
With parenterals:				
Route of administration allowed	W/infusion/W/inhalation/W/SC/IV/.....	W/infusion/W/inhalation/W/SC/IV/.....	W/infusion/W/inhalation/W/SC/IV/.....	W/infusion/W/inhalation/W/SC/IV/.....
Refrigeration	Ampoule/Blank	Ampoule/Blank	Ampoule/Blank	Ampoule/Blank
Reconstitution	Powder/concentrate/liquid/.....	Powder/concentrate/liquid/.....	Powder/concentrate/liquid/.....	Powder/concentrate/liquid/.....
(concern: the parenterals have to be prepared)				
Solvent used	W/W/0.9%/Glycerol/...../solvent included/.....	W/W/0.9%/Glycerol/...../solvent included/.....	W/W/0.9%/Glycerol/...../solvent included/.....	W/W/0.9%/Glycerol/...../solvent included/.....
Volume after addition of solventmlmlmlml
Volume, concentration after addition of solvent (max. testing)ml/.....mg=.....mlml/.....mg=.....mlml/.....mg=.....mlml/.....mg=.....ml
consistencymeasured/tpmeasured/tpmeasured/tpmeasured/tp
Results:				
judged by	Judging by: Swelling agreed, verified Agreed to:			
W/W: isotonic saline; tp: isotropic/0.9%; V: volume; SC: subcutaneous; IV: water for injection; no other details.				

Table 1 Checklist for the interchangeability of generics

Drug, route of administration, strength:	Current product	Alternative product 1	Alternative product 2	Alternative product 3
Producer:				
Registration number:				
PIN:				
Desired:				
Name and description primary packaging:				
Name and description secondary packaging:				
Good readability label:	Yes/No Unit packaging/flask/bottle... Yes/no/no/no/no/no/no/no	Yes/No Unit packaging/flask/bottle... Yes/no/no/no/no/no/no/no	Yes/No Unit packaging/flask/bottle... Yes/no/no/no/no/no/no/no	Yes/No Unit packaging/flask/bottle... Yes/no/no/no/no/no/no/no
Packaging:				
Packaging leaflet in own language:				
Storage conditions:				
Shelf life:				
Flag label:				
Other primary pack:				
Barcode secondary p:				
Excipients:				
- Glutens				
- Glycerol				
- Propylene glycol				
- Ethanol				
- Parabens (E216-E218)				
- Sulphites (E220-E223)				
- Wheat starch				
- Other deviating or common/brief packed differentiation names:				
Check this similarity:				
Similarity of active ingredients:				
Compatibility with other devices, pressure info:				
Communication with ph:				
Refill use for split?				
Take with cool liquid(s):				
With additives:				
Route of administration allowed:	IV/Inhalat/IV/Inhalat/IM/SC/ST/...	IV/Inhalat/IV/Inhalat/IM/SC/ST/...	IV/Inhalat/IV/Inhalat/IM/SC/ST/...	IV/Inhalat/IV/Inhalat/IM/SC/ST/...
Packaging:	Ampoule/flask	Ampoule/flask	Ampoule/flask	Ampoule/flask
Presentation:	Powder/concentrate/flask/...	Powder/concentrate/flask/...	Powder/concentrate/flask/...	Powder/concentrate/flask/...
Concise: the way the patients have to be prepared:				
Solvent used:	W/W/H2O 0.9%/Qa: 1%solvent included/...			
Volume after addition of solvent:mlmlmlml
Volume, concentration after addition of solvent (only if known):mg =mlmg =mlmg =mlmg =ml
Isomer:mg/ml/kgmg/ml/kgmg/ml/kgmg/ml/kg
consistency:mg/ml/kgmg/ml/kgmg/ml/kgmg/ml/kg
Periodic:				
Judged by:				
mg/ml/kgmg/ml/kgmg/ml/kgmg/ml/kg
	Judged by: Switching agreed yes/no			
	Agreed by:	Agreed by:	Agreed by:	Agreed by:

IM: intramuscular; IV: intravenous; SC: subcutaneous; ST: water for injection; no other details.

Becker et al. Switching to different generic medicines: a checklist for safety issues. *Eur J Hosp Pharm* 2013;20:74-77

Or

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Checklist (1/3)

Topics

- Packaging
 - Unit packaging, flask, etc.
 - Flag labels, leaflet
 - Similarity with other presentations
- Storage conditions & shelf life
- Barcoding

Checklist (2/3)

-
- Excipients
 - Gluten, benzyl alcohol, propylene glycol, ethanol, paraben, sulphite, wheat starch
 - Compatibility with devices
-

Checklist (3/3)

-
- Split tablets
 - Taste (oral liquids)
 - Administration (route)
 - Preparation
 - Ampoule, flask
 - Powder, concentrate
 - Solvent
-

Implementation

- Our hospital:
 - Contracting 800 products
 - Switching on average 70 products
- Use checklist
 - After selecting drug
 - Before contracting
 - Check by hospital pharmacist

Conclusion

- Although all legislation, still a lot of differences
- Use checklist to avoid unexpected issues
- Patient safety and costs
- Important role for the hospital pharmacist!
- For checklist: mbecker@sahz.nl



In cooperation with



- Hylke Jan Kingma (SAHZ)
- Nicole Hunfeld (Erasmus MC)
- Patricia van den Bemt (Erasmus MC)
- Arnold Vulto (Erasmus MC)
- Stijn Koolen (SAHZ)
- Ruud van der Hoeven (SAHZ)



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