Using a Foreign Reference Product as the Reference Listed Drug (RLD) Product for Bioequivalence Studies

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Draft regulations published by Government notice No 22235 in June 2001 in terms of the Medicines & Related Substances Control Act, 1965 (Act No 101 of 1965) as amended by Act No 90 of 1997 makes provision for generic substitution in section 22F, as follows:

Subject to subsections (2), (3), and (4), a pharmacist shall –

a) Inform all members of the public who visit his or her pharmacy with a prescription for dispensing, of the benefits of the substitution for a branded medicine of an interchangeable multi-source medicine; and
b) Dispense an interchangeable multi-source medicine prescribed by a medical practitioner, dentist, practitioner, nurse or other person registered under the Health Professions Act, 1974, unless expressly forbidden by the patient to do so.

Furthermore, subsection (4) states that “A pharmacist shall not sell an interchangeable multi-source medicine

• if the retail price of the interchangeable multi-source medicine is higher than that of the prescribed medicine; or

• where the product has been declared not substitutable by the council”
• Generic Substitution is mandated by Law and thus all generic products MUST be equivalent to the innovator product to be INTERCHANGEABLE!

How to ensure equivalence?

• use an “acceptable” reference product - usually the approved innovator or brand product and referred to as the reference listed drug (RLD) by the US FDA in the Orange Book.
• It is common knowledge that innovator/brand products available in a particular country may differ from the same innovator/brand product marketed in another country.

• e.g. Tegretol XR® tablets, a prolonged action carbamazepine product is marketed in the United States as a non-disintegrating dosage form using the OROS® mechanism.

• The same innovator is listed as the manufacturer of prolonged action carbamazepine dosage forms in various other countries where those dosage forms are also tablets but which disintegrate in aqueous fluid and are marketed as Tegretol CR® in South Africa.
The release mechanisms and formulation of the US RLD listed product and the product marketed by the same innovator in South Africa are clearly different. In some instances this is done intentionally due to patents.

In other cases, there may be unintended differences in release of the active ingredient(s), due to various factors such as the manufacturing process.
Bioavailability differences between products can be due to factors such as:

- sources of raw material and synthesis (nature) of the API including particle size and crystal forms (polymorphs, crystal shapes and degree of hydration or solvation, etc.)
- use of different methods of manufacture and manufacturing equipment, amongst others.

All of these factors can have significant effects on bioavailability with consequent implications for their bioequivalence.
In some countries, a “non-domestic” or “foreign” innovator/brand drug product has been permitted for use as the reference product in a bioequivalence study.

This raises serious concerns since, in the absence of specific confirmatory data, a non-domestic innovator/brand product used as the reference product where the generic medicine is intended for a particular domestic market cannot be assumed to be bioequivalent to the domestic innovator/brand product.

What does the drug product approved in a phase 3 study and submitted in the original NDA look like now??
Proof of safety and efficacy of generic drug products, have in the past been based on requirements described in earlier circulars from the MCC - subsequently withdrawn
2.2 Dissolution

2.2.1 Dissolution comparison between a T & R product as proof of efficacy may be used in the following instances:

• When a monograph for the active in the USP includes a dissolution requirement, and the active is not on the attached list A.
<table>
<thead>
<tr>
<th>Acyclovir</th>
<th>Etodolac</th>
<th>Megestrol</th>
<th>Ranitidine</th>
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</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>Etidronate</td>
<td>Misoprostol</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Felodipine</td>
<td>Moclobamide</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Flecainide</td>
<td>Nabumetone</td>
<td>Sotalol</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Fluconazole</td>
<td>Naproxen</td>
<td>Ticlopidine</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Fluoxetine</td>
<td>Omeprazole</td>
<td>Temazepam</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Flutamide</td>
<td>Oxybutynin</td>
<td>Terazosin</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Fluvoxamine</td>
<td>Oxaprozin</td>
<td>Terazosin</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Famotidine</td>
<td>Paroxetine</td>
<td>Trazadone</td>
</tr>
<tr>
<td>Danazol</td>
<td>Fenofibrate</td>
<td>Pravastatin</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Guanfacine</td>
<td>Prazocin</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Indapamide</td>
<td>Propafenone</td>
<td>Zopiclone</td>
</tr>
</tbody>
</table>
c) Comparative dissolution between a T & R must be done in 3 media, whereof:

i) the first medium must be that specified in the USP monograph,
ii) the other 2 media shall generally be from the following, spanning a wide pH range, and not the same as the medium specified in the USP:
   ii.i) an acidic medium eg. gastric fluid USP
   ii.ii) water
   ii.iii) an alkaline medium eg. intestinal fluid USP.

D) The USP requirements for at least 6 units of the product, the apparatus, medium volume, and rotation speed specified in the monograph, for the media required by the USP, must be followed.
• The results shall be presented in a tabulated and graphical form. The tabulated form shall include the individual results of the dosage forms, the mean, and the standard deviation of the dosage forms. The graphical form will be the mean of the studies and the reference and test products set out on a graph for each medium.

• If the active is insoluble in the other 2 media a motivation may be submitted to Council for the omission of further testing in the other 2 media.

• **NB** NO ACCEPTANCE CRITERIA SPECIFIED!
In the early part of the previous decade (2001/2002) new guidelines for BIOEQUIVALENCE were developed in South Africa and the MCC Circular 14/95 was replaced.

• A “temporary” dispensation was made to allow generic products to be approved using a “foreign” reference product.

• A *proviso* was to require Sponsors to show “equivalence” between the foreign reference product used in the biostudy and the innovator product available on the local market.
MODUS OPERANDI

• Comparative dissolution profiles comparing $f_2$ values between the foreign and domestic reference product conducted in three different dissolution media at pH 1.5, 4.5, and 6.8 and meeting the requirement that $f_2 > 50$.

However, No consideration was given to the properties and use of the drug contained in the dosage form.
Proposal

• establish a process to determine equivalence using \textit{in vitro} dissolution testing between innovator/brand products approved and marketed in different countries

&

• thereby permit the use of a single universal and scientifically acceptable comparator product for use in a bioequivalence study
BENEFITS/ADVANTAGES

• obviate the efforts and expense of having to repeat bioequivalence studies for different world markets using that particular country’s domestic reference product (RLD in the USA).

Currently, if a generic product is intended for marketing in several countries around the world, say 5 different countries, regulatory authorities in many countries require that same generic product to be compared to their domestic reference product. i.e.

• this means that the same generic product would need to undergo 5 separate BE studies!

• Hence, once equivalence between reference products from different countries has been established using in vitro dissolution testing, no further BE study (country specific) will be necessary.
HOW DO WE DO THIS?

Waiver for all BCS class 1 APIs? Implications & consequences?

Establish requirements for BCS classes 2, 3 & 4 (?) APIs to declare equivalence

Dissolution testing conditions
- simple buffers
- addition of surfactants
- profiles and duration of tests
- evaluation using $f_2$ or other appropriate assessment
- single units &/or multiple units/flask
- USP Dissolution method 1, 2, 3 or 4 or other.
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EXAMPLES

• BCS Class 1

• The dosage form is *rapidly dissolving* and the dissolution profiles between the RLDs is similar at pH 1.2, pH 4.5 and pH 6.8 and meets the f2 criterion (or equivalent statistical criterion);

  OR

• if both RLDs are *very rapidly dissolving*, a profile comparison is not necessary
BCS Class II 2A

• BCS Class II weak acids, if the RLDs are rapidly dissolving (no less than 85% in pH 6.8 in 30 minutes) and their dissolution profiles are similar at 1.2, 4.5 and 6.8

BCS Class III

• BCS Class III drug products, if the multisource and comparator product are very rapidly dissolving (no less than 85% in 15 minutes at pH 1.2, 4.5 and 6.8)
• BCS Class
  • I
  • II-A
  • II-B
  • II-C
  • III
  • IV-A
  • IV-B
  • IV-C
RISK MANAGEMENT
OTHER CONSIDERATIONS TO BE LINKED TO DISSOLUTION TESTING ACCEPTANCE

• Drug properties:
  – potency
  – indications
  – stability
  – pharmacokinetic properties
  – pharmacologic classification
DOSAGE FORMS AND FORMULATION

• dose size and frequency
• toxicity and side effects
• excipients
TARGET PATIENT POPULATION

• paediatric use
• adult use
• geriatric use
Thank you for your attention