Product Characteristics and Product Information – Links between Quality and Clinical

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A “Good” Medicinal Product

Pharmaceutical Quality

Efficacy and Safety (Bioequivalence)

Product information
Synopsis

- Divisibility (scoring)
- Crushing
- Measuring devices
- "Special" excipients
- Conclusions
Why is the product information relevant?

- Safe use of the product (for physicians and patients)
- Detection of counterfeit products by clear description of product specifics
  - Visual appearance of formulation
  - Detailed information on primary pack
Posology - Divisibility

PQTm guidance

(GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR A MULTISOURCE (GENERIC) FINISHED PHARMACEUTICAL PRODUCT FOR THE WHO PREQUALIFICATION OF MEDICINES PROGRAMME: QUALITY PART, TRS 970 Annex 4)

Scoring recommended / required, when

- indicated in WHO invitation for EOI
- specified for the comparator product (“innovator”)
- division into fractional doses is necessary according to posology
Content/mass uniformity tests: methodology in accordance with recommendations of PQTm Quality guideline

- Splitting of the tablets should be performed in a manner representative of that used by the consumer (e.g. manually split by hand).

- Presence of a score reflected in tablet description
  - in FPP specification and QIS
  - in product information (Summary of Product Characteristics, Labelling, Patient Information Leaflet)
Posology - Divisibility

Standard wording on score lines

- <The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.>

- <The score line is not intended for breaking the tablet.>

- <The tablet can be divided into equal doses.>
Posology - Practical issue

PQTm evaluation:
Some tablets are very difficult to split by hand

Options:
- Improve scoring (when detected at an early stage)
- Provide a tablet cutter with each pack
- Indicate in the product information that a tablet cutter or knife is needed for division of tablets.

Example (from prequalified product):
“For appropriate dosing in children from 2 to 11 months of age, the tablets have to be divided into equal halves. With this product this can only be achieved by using a knife or a tablet cutter (which is not included in the pack).“
Divisibility - Special cases

Atazanavir 300 mg / Ritonavir 100mg FDC

According to 2013 WHO HIV Guideline in adolescents from 35 kg BW
Divisibility - Special cases

AZT 300mg/ 3TC 150mg/NVP 200mg FDC

According to 2013 WHO HIV Guideline in children from 25 kg BW
Divisibility - Special cases

ABC 300mg/ AZT 300mg/3TC 150mg FDC

According to 2013 WHO HIV Guideline in children from 25 kg BW
Divisibility- Special case

Scoring not indicated in the EoI
No innovator available
Posology: One tablet once daily

However:
Clinicians in the team noted that patients may not be able to swallow the tablet whole.

Question:
Can the tablet be divided/crushed without changing the “performance” of the tablet?
Divisibility- Special case

- **Pharmaceutical formulation:**
  Halving not regarded as problematic from Q point

- **Divisibility:**
  Impossible to divide without a knife, with knife okay

- **Bioavailability:**
  Unknown, if dividing leads to changes
  - BE-study in most cases with whole tablets
  - Similar issue, if use of drug in paediatric patients is recommended by WHO
Divisibility - Crushing

Potential factors indicative of PK behaviour

- Q: Disintegration time
- Q/BE: critical excipients
- Q/BE: BCS-Class (I or III versus II or IV)
- Acidic stability of API(s)

Interdisciplinary approach: check treatment guidelines and section 4.2 (SmPC), consult with clinical- and BE-assessors
Decision tree for crushing in PQTm

Disintegration time ≤ 3 minutes

<table>
<thead>
<tr>
<th>BCS-class 1 or 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No critical excipients</td>
</tr>
<tr>
<td>Stable in acidic media</td>
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</tbody>
</table>

Disintegration time > 3 minutes

<table>
<thead>
<tr>
<th>BCS-class 2 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical excipients</td>
</tr>
<tr>
<td>Not stable in acidic media</td>
</tr>
</tbody>
</table>

Crushing discouraged

Supportive, if innovator(s) permit crushing and if dispersible tablets, powder, oral solution/suspension, or granules of API available with equivalent dosing (for all APIs)

Risk of alteration of PK by crushing considered low

Crushing can be recommended
Divisibility - Crushing

- Immediate release tablet (not dispersible tablet)
- Target patient population: adults and children
- Instructions for use include
  - swallow tablets whole
    - if not possible (e.g. in children less than 6 years of age):
      - crushing and mixing with (certain types of) food

"Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately."
Divisibility - Crushing

Other factors

- Q: Palatability (fineness of dispersion) / taste acceptability?
- If instructions differ from innovator: compatibility with (recommended types of) food?
Posology - Measuring devices

PQTm requirements

➢ As specified in the PhInt monograph “Liquid Preparations for Oral Use”: ‘Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. Usually
- a spoon or a cup for volumes of 5 ml or multiples thereof,
- or an oral syringe for other volumes
- or, for oral drops, a suitable dropper.’

➢ [WHOPAR dosing aspects indicated here]
Posology - Measuring devices

PQTm requirements (cont.)

- Inclusion of the device in the container closure system
- Submission of data on this packaging component, including
  1) specifications and
  2) uniformity of mass of doses delivered by the device
- The “Instructions on Use and Handling” should provide clear instructions.
- A sample of the device should be provided.
“WHOPAR dosing aspects“

Uniformity of the mass at the lowest intended dose should be demonstrated.

HOW TO DETERMINE THE LOWEST INTENDED DOSE?

- Consultation of
  - Company’s proposed Summary of Product Characteristics (SmPC)
  - SmPC of comparator product
  - Relevant guidelines (e.g. for PQTm: WHO treatment guidelines)

- Appropriateness of device may also depend on the pack size
Measuring devices - Practical case

Example 1: Zidovudine oral solution 50 mg / 5 ml

- **Therapeutic indications**
  1. Treatment of HIV-infection in infants and children weighing ≥ 3 kg
  2. Prevention of mother-to-child transmission (PMTCT)
Example 1: Zidovudine oral solution 50 mg / 5 ml

- **Paediatric posology**
  (according to WHO treatment guidelines)

  Treatment: 3 - 5.9 kg: 6 ml twice daily
  6 - 9.9 kg: 9 ml twice daily
  10 - 13.9 kg: 12 ml twice daily

  PMTCT: 4 mg/kg twice daily

According to WHO Weight-for-Age Charts more than 97% of the newborns *weigh at least 2 kg* (3rd percentile)

→ lowest single dose 10 mg → **1 ml** oral solution
Measuring devices - Practical case
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Measuring devices - Practical case

Zidovudine oral solution 50 mg / 5 ml

- HOW CAN THE PACK SIZE DETERMINE THE SUITABILITY OF THE DOSING DEVICE?

- Prequalified sizes:
  - HIV-Treatment: 12 ml to 24 ml/day
  - PMTCT: 2 ml to 3 ml/day

- Consider also in-use stability!
Example 2: Abacavir oral solution 20 mg / ml

- First evaluation of product sample

“A dosing device is not included in the pack. (…) You are requested to include a device in your container closure system which allows suitable dosing for children. It is of utmost importance that the device allows for accurate dosing also at the low end of the dose range. The paediatric dosing recommendations of WHO should be considered.”
Measuring devices - Practical case

Abacavir oral solution 20 mg / ml

Paediatric posology (according to WHO treatment guidelines)

3 - 5.9 kg: 3 ml twice daily
6 - 9.9 kg: 4 ml twice daily
10 - 13.9 kg: 6 ml twice daily

In Adults (according to innovator)

30 ml/day (= 600 mg)

PQTm pack sizes: 100 ml
240 ml
Measuring devices - Practical case

Abacavir oral solution 20 mg / ml

- Company‘s reply (a dosing cup with various markings at 2.5, 3, 5, 6, 7.5, 9, 10, 11, 13, 15 and 20 ml)

Markings not horizontal
Abacavir oral solution 20 mg / ml

- Second evaluation of product sample

“"The devices received were considered unacceptable. The 3 ml demarcation lines of two of the three devices are noted to be skewed. In addition, the device is considered impractically large for consistently providing the recommended doses ranging from 3 to 6 ml and could therefore lead to overdosing. We strongly encourage you to provide a more suitable device. Regardless of whether a new or the existing device is used, uniformity of the volume at the lowest intended dose should be demonstrated. In addition, if you retain the current device, you are requested to provide assurance that the device can be consistently manufactured with the appropriate, correctly oriented demarcations.”"
Measuring devices - Practical case

Abacavir oral solution 20 mg / ml

- Company’s reply

(According to WHO guidance patients with a BW ≥ 14 kg are recommended to use tablets. Therefore, the oral solution is considered primarily a paediatric formulation and the measuring device is acceptable.)
Example 3: Granules for Second line TB Therapy

- **Dosing recommendations:**
  345 mg/kg/day, divided into two equal daily doses.
  A 4.6 g measuring spoon with markings at 1, 2, 3, 4 and 4.6 g is provided with the product.

- **Issue 1:** Dosing accuracy for the weight of the child
  6 kg body weight (1035 mg/dose), 12 kg (2070 mg/dose),
  18 kg (3105 mg/dose), 24 kg (4140 mg/dose),
  27 kg (full spoon, 4657 mg/dose)… .

- **Issue 2:** Accuracy of the measured dose
Measuring devices - Practical case

- 2 g
- 4.6 g

Request company to submit new device with smaller diameter/surface and 0.5 ml markings
Measuring devices - Practical case
Measuring devices - Practical case
Another common deficiency...

Taste/Palatability of formulation:
e.g. liquid formulations, dispersible tablets

- Poor palatability and bad taste may lead to non-compliance, especially in children and when used in long-term therapy.

- Companies should be encouraged to improve these product characteristics.

► Difficulty: What is a generally acceptable taste?
   → potential intercultural differences

PQTm: Presently, palatability studies are only required for zinc tablets
Excipients

- In PQTm WHOPAR Guideline - reference to EC Guideline: Excipients in the label and package leaflet of medicinal products for human use (NOTICE TO APPLICANTS, VOLUME 3B, 2003)

- Whilst it is desirable that excipients should have little or no pharmacological action of their own, some do indeed have a recognised action or effect in certain circumstances.

- Warning statements relating to the presence of certain excipients in medicinal products.

- The Annex provides a list of the excipients which should be stated on the labelling and outlines the information which should appear in the patient information leaflet.
Excipients defined as the constituents of the pharmaceutical form that is taken by or administered to the patient, other than the active substance.

For example:

- colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring aromatic substances and liquid diluents

- Also the constituents of the outer covering of the medicinal products – capsules, gelatine capsules, rectal capsules, coating material or constituents of the printing ink.
Excipients

- Clinical condition to be treated has to be borne in mind for assessing the appropriateness of including warning statements (benefit/risk assessment; e.g. for treatment of MDR TB or for emergency contraception [one single dose] the warning on lactose content to be phrased more cautiously).

- For non-functional excipients (e.g. colouring agents), less harmful excipients should be used in the manufacture (e.g. inorganic colourants (e.g. iron oxide black/red/yellow or titanium dioxide) instead of azo organic colouring agents with a high sensitizing potential).

- Of note: Different thresholds may apply for medicines for paediatric use (‘Excipients guideline‘ currently under revision)

Excipients - „lactose warning“

- **SmPC**

  - **EU Guideline:**
    Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption **should not take this medicine.**

  - **WHOPAR - Moxifloxacin**
    Moxicip-400 Tablets contains a small amount of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption **may experience symptoms of intolerance.**
Excipients - „lactose warning“

- PIL
  - EU Guideline:
    If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product
  - WHOPAR - Moxifloxacin
    (moxifloxacin for second-line treatment of TB)
    As per guideline
Conclusions

The assessment of the pharmaceutical quality of a product includes the evaluation of the appropriateness of:

- the formulation

- the dosing device

- the product information (e.g. description of the visual appearance of the product, therapeutic indication, instructions for use, warnings on specific excipients and instructions for handling.

- and, if possible, also the palatability/taste.

→ when possible, discuss ‘tricky‘, non-standard-situations with medical staff/clinician
GRACIAS
THANK YOU
MEG!