Regulatory Year in Review

New Draft Guidelines

Vit Perlik
### Updated "Guidelines"

- **19 updated guidelines or guidance documents**
- **11 w/o veterinary and pharmacovigilance topics, mainly related to ICH guidelines and quality**

<table>
<thead>
<tr>
<th>Document title</th>
<th>Language</th>
<th>Status</th>
<th>First published</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH guideline Q4B Annex 1 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on residue on ignition/sulphated ash - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>01.11.2007</td>
<td>13.07.2017</td>
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<tr>
<td>ICH guideline Q4B Annex 10 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on polycrylamide gel electrophoresis - general chapter - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>11.02.2013</td>
<td>13.07.2017</td>
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<td>ICH guideline Q4B Annex 3 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for particulate contamination: sub-visible particles general chapter - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>01.12.2008</td>
<td>13.07.2017</td>
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<tr>
<td>ICH guideline Q4B Annex 4A on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on micro enumeration - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>01.06.2009</td>
<td>13.07.2017</td>
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<tr>
<td>ICH guideline Q4B Annex 4B on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on Tests for specified micro-organisms - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>01.06.2009</td>
<td>13.07.2017</td>
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<tr>
<td>ICH guideline Q4B Annex 4C on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>01.06.2009</td>
<td>13.07.2017</td>
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<td>ICH guideline Q4B Annex 5 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on disintegration test - general chapter - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>11.02.2013</td>
<td>13.07.2017</td>
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<tr>
<td>ICH guideline Q4B Annex 8 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions sterility test - general chapter - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>11.02.2013</td>
<td>13.07.2017</td>
</tr>
<tr>
<td>ICH guideline Q4B Annex 9 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on tablet friability - general chapter - Step 5</td>
<td>(English only)</td>
<td>adopted</td>
<td>11.02.2013</td>
<td>13.07.2017</td>
</tr>
<tr>
<td>Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances</td>
<td>(English only)</td>
<td>adopted</td>
<td>10.10.2014</td>
<td>06.07.2017</td>
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BioBridges 2017, September 21-22, 2017, Prague, CZ
44 new guidelines or guidance documents including product specific guidelines

- 29 w/o veterinary and pharmacovigilance topics

- 15 new product specific guidelines
New "Guidelines"

Cont.

- 44 new guidelines or guidance documents including product specific guidelines
- 29 w/o veterinary and pharmacovigilance topics
- 15 new product specific guidelines
Draft "Guidelines"

- 36 scientific guidelines or concept papers open for discussion
- 27 w/o veterinary and pharmacovigilance topics
- 8 new draft product specific guidelines
Draft "Guidelines"

Cont.

- 36 scientific guidelines or concept papers open for discussion
  - 27 w/o veterinary and pharmacovigilance topics
  - 8 new draft product specific guidelines
Selected Draft "Guidelines"

- Modeling, statistical methodology used for drug development
  - End of consultation March 31 2018

- Draft Reflection paper on the dissolution specification for generic oral immediate release products
  - End of consultation 13 August 2016

- Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action
  - Adopted by the CHMP June 2017
Selected Draft "Guidelines"

- Product specific guidelines - drafts for:
  - dimethyl fumarate gastro resistant cps;
  - dolutegravir;
  - dronedarone;
  - ibuprofen;
  - paracetamol;
  - prasugrel hydrochloride;
  - rilpivirine;
  - tadalafil - revision 1
**Product Specific Guidelines - Draft**

- **Ibuprofen 200 - 800 mg oral use, immediate release formulations**
  - product-specific bioequivalence guidance
    - end of consultation 31 October 2017

**What is suggested:**
- Single dose, cross over, fasting study in healthy volunteers using highest strength (linear PK 200 - 800 mg)
- Analyte: Parent compound using enantioselective analytical method
- Enantiomers have different PD and PK and the rate of absorption has been shown to affect the ratio of enantiomers
- Pharmacokinetic variables: Cmax, AUC(0-t) and Tmax for S enantiomer

- Different formulations available (suspensions to rapidly dissolving tbl, cps)
- Majority of generic products registered using non-enantioselective analytical method
- ? Shall be removed from the market? What will happen during the MA renewals?
Product Specific Guidelines - Draft

- Paracetamol oral use, immediate release formulations product-specific bioequivalence guidance
  - end of consultation 31 October 2017

What is suggested:
- BCS Class I biowaiver possible, Paracetamol is high solubility compound with >85% absorption or
- Single dose, cross over, fasting study in healthy volunteers (paracetamol is highly soluble and shows linear PK, in principle any strength may be used)
- Analyte: Parent compound
- Pharmacokinetic variables: Cmax, AUC(0-t) and Tmax
Product Specific Guidelines - Adopted

- Paliperidone palmitate depot suspension for injection 25, 50, 75, 100 and 150 mg product-specific bioequivalence guidance

  Regulatory requirements (EMA/CPMP/EWP/280/96 Corr1)

  - Abridged application general considerations
    - Healthy vs patients
    - Single dose and/or multiple dose studies
    - (...in patients, preferably after both single and multiple dose administration in line with recommendations below. If it is not feasible to conduct single dose studies in patients, these can be replaced by multiple dose studies.)

  - New chemical entity as Intramuscular/subcutaneous depot formulations SD, MD studies, dose proportionality, site of administration etc. (EMA/CPMP/EWP/280/96 Corr1)
Product Specific Guideline for Paliperidone

Healthy Volunteers vs Patients

- **Study population**
  - Release duration of paliperidone from 1st day until at least 4M (SPC Ch.5.2)
  - Aripiprazol: Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy volunteers
  - Healthy not feasible for any approached CRO

- **Product specific guideline**
  - Paliperidone palmitate, Extended-release suspension; intramuscular (FDA Recommended Aug 2011; Revised Dec 2013; Dec 2015)
  - **Additional comments**: FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment.

Patient population
Product Specific Guideline for Paliperidone

Study Design - Single Dose vs Multiple Dose

- Stable patients needed (1-3 month of stable patients conditions)
- Documented tolerability of investigated compound preferable
- Wash-out not feasible
- Co-administration under single dose conditions used for the explorative purposes only
- Significant consequences of co-administration for study participants documented
- Single dose study design not feasible for pivotal BE study design
- Regulatory requirements acknowledging abovementioned facts

Patient population under multiple dose conditions suggested
Paliperidone palmitate depot suspension for injection 25, 50, 75, 100 and 150 mg product-specific bioequivalence guidance

Draft

| Draft agreed by Pharmacokinetics Working Party | June 2016 |
| Adopted by CHMP for release for consultation | 21 July 2016 |
| Start of public consultation | 1 August 2016 |
| End of consultation (deadline for comments) | 31 October 2016 |

Comments should be provided using this template. The completed comments form should be sent to PKWP@secretariat@ema.europa.eu

Keywords: Bioequivalence, generics, paliperidone

Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party | June 2016
Adopted by CHMP for release for consultation | 21 July 2016
Start of public consultation | 1 August 2016
End of consultation (deadline for comments) | 31 October 2016
Agreed by Pharmacokinetics Working Party | December 2016
Adopted by CHMP | 23 February 2017
Date of coming into effect | 1 September 2017

Keywords: Bioequivalence, generics, paliperidone
# Product Specific Guideline for Paliperidone

## Draft guidance

<table>
<thead>
<tr>
<th>Bioequivalence study design**</th>
<th>Multiple dose: any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Background: single-dose studies in healthy volunteers are not considered feasible.</td>
</tr>
<tr>
<td></td>
<td>cross-over or parallel</td>
</tr>
</tbody>
</table>

## Adopted guidance

<table>
<thead>
<tr>
<th>Bioequivalence study design**</th>
<th>Single dose: any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), in healthy volunteers (if feasible) or in patients stabilized on other antipsychotic medication.</th>
</tr>
</thead>
<tbody>
<tr>
<td>in case a BCS biowaiver is not feasible or applied</td>
<td>Multiple dose: any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths) in patients.</td>
</tr>
<tr>
<td></td>
<td>cross-over or parallel</td>
</tr>
</tbody>
</table>
Selected Draft "Guidelines"

Draft guideline on locally applied and acting drugs in GIT
- End of consultation 30 September 2017

Drug interactions - concept paper
- End of consultation 30 June 2017 (potential impact on fixed dose combinations)

Medical devices - concept paper
- End of consultation 16 May 2017

Inhalation and nasal products quality - concept paper
- End of consultation 30 June 2017

Orally inhaled products therapeutic equivalence - concept paper
- End of consultation 31 May 2017
Draft "Guidelines" - Locally Applied, Locally Acting Products in GIT

- Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are locally applied, locally acting in the gastrointestinal tract as addendum to the guideline on the clinical requirements for locally applied, locally acting products containing known constituents

- End of consultation 30 September 2017
Key elements - executive summary

- Generic or hybrid applications
- Summary of requirements to waive the clinical trials or PD endpoint trials
- Strong emphasis on bioequivalence studies
- Defines use of in vitro equivalence tests

Why

- Alternative methods have higher sensitivity than traditional clinical or PD endpoint trials
- Direct or indirect comparison of concentrations at the site of action as a surrogate of similar clinical response

- Waiver of CT for immediate or modified release products
# Locally Applied, Locally Acting Products in GIT - Assay Sensitivity

<table>
<thead>
<tr>
<th>Dose of orlistat (mg)</th>
<th>FFE (% intake)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>5%</td>
</tr>
<tr>
<td>12 mg</td>
<td>8%</td>
</tr>
<tr>
<td>20 mg</td>
<td>17%</td>
</tr>
<tr>
<td>25 mg</td>
<td>14-18%</td>
</tr>
<tr>
<td>30 mg</td>
<td>21%</td>
</tr>
<tr>
<td>50 mg</td>
<td>20-24%</td>
</tr>
<tr>
<td>60 mg</td>
<td>30%</td>
</tr>
<tr>
<td>120 mg</td>
<td>36%</td>
</tr>
<tr>
<td>200 mg</td>
<td>32-35%</td>
</tr>
<tr>
<td>240 mg</td>
<td>31%</td>
</tr>
<tr>
<td>400 mg</td>
<td>27%</td>
</tr>
</tbody>
</table>

Hauptman et al, 1992
## Locally Applied, Locally Acting Products in GIT
- **Assay Sensitivity**

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin (1,000 mg)</th>
<th>Azithromycin (500 mg)</th>
<th>Azithromycin (500 mg) plus loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>50</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td><strong>Average duration (h) of diarrhoea after beginning treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>34</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>All bacterial causes (n)</td>
<td>33.6 (21)</td>
<td>38.1 (31)</td>
<td>9.2 (36)</td>
</tr>
<tr>
<td><strong>Percent well at hours of study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>34</td>
<td>66</td>
</tr>
<tr>
<td>12</td>
<td>38</td>
<td>46</td>
<td>79</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>50</td>
<td>79</td>
</tr>
<tr>
<td>24</td>
<td>54</td>
<td>59</td>
<td>84</td>
</tr>
<tr>
<td>48</td>
<td>78</td>
<td>73</td>
<td>93</td>
</tr>
<tr>
<td>72</td>
<td>80</td>
<td>79</td>
<td>96</td>
</tr>
<tr>
<td><strong>Treatment failure: Total (%)</strong></td>
<td>10 (20)</td>
<td>12 (21)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Ericsson et al, 2007
Locally Applied, Locally Acting Products in GIT - Assay Sensitivity

![Graph showing the probability of TLUS for the intent-to-treat population](image)

**Figure 1.** Probability of TLUS for the intent-to-treat population.

- **Strength 1**
- **Strength 2 (2x Strength 1)**

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Types of locally applied and acting GIT products

- Site of action (mouth, stomach, intestine)
- Mechanism of action (antacids, osmotic agents...)
- Biopharmaceutical and PK properties (absorbable, non-absorbable)
- Pharmaceutical form (solutions, solid dosage forms, modified release...)
- The state of the drug in the dosage form (solute or solid in solution or solid)
Body of evidence

- pharmaceutical quality data alone,
- pharmaceutical quality data + \textit{in vitro} model,
- pharmaceutical quality data + \textit{in vivo} PK data
- pharmaceutical quality data + \textit{in vitro} model + \textit{in vivo} PK data

- In case PK data are used for safety demonstration, only the 90% confidence interval range for the ratio test/reference should not exceed the upper limit of the acceptance range
  - Otherwise within 80 - 125%
Locally Acting in the Mouth and/or Throat

- **Solution**
  - *In vitro* data (viscosity...)

- **Non-solution**
  - Saliva concentrations Cmax, AUC
  - Amounts remaining in dosage form at different time points
  - Charcoal study to evaluate absorption from mouth
Locally Acting in the Stomach

- **Solution**
  - *In vitro* data (pH stability...)

- **Non-solution**
  - Dynamic and static neutralizing test
  - Hypothetically also BES in case of some absorption
Locally Acting in the Intestine

Solution
- In vitro data (sorbitol, mannitol...)
- BES in case of any absorption

Non-solution
- In vitro study - binding assays
- BES in case of any absorption (fasting and fed)
- Modified release product - partial AUC
Locally Acting in the Rectum

- **Solution**
  - *In vitro* data (local residence, tolerance...)
  - BES in case of any absorption
- **Non-solution**
  - BES in case of any absorption
Draft "Guidelines" - Orally Inhaled Products

- Concept paper on revision of the guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the treatment of asthma in children and adolescents.

- End of consultation 30 June 2017
Draft "Guidelines" - Orally Inhaled Products - Original Concept

- **In vitro characterization**
  - Pharmaceutical equivalence/evaluation

- **In vivo characterization**
  - Pulmonary deposition - surrogate for efficacy
    - Describing extent (AUC) and rate (Cmax) of absorption delivered via lungs
    - Achieved by charcoal block
  - Systemic exposure - surrogate for safety
    - Describing extent (AUC) and rate (Cmax) of absorption delivered via lungs and gastrointestinal tract
  - Therapeutic equivalence/evaluation (PD endpoints acceptable)
Draft "Guidelines" - Orally Inhaled Products - Reflections

Reflections to locally applied, locally acting products in GIT

- Demonstration of equivalence based on the *in vitro* data only difficult
  - Batch to batch variability of reference product
  - Within batch variability or reference product
    - IVIVC, testing of the side batches etc.
- PK studies more discriminative
  - The only evidence?
- Issues: selection of batches, strength and study population

Reflection from regulatory experience for OIP

- PD/clinical study difficult because of assay sensitivity
  - Requirements should be specified
  - FDC LABA/LAMA
  - Handling studies
- Issues: selection of batches, strength and study population
  - Better drug delivery from devices
  - Children - challenging requirements
Thank You For Your Attention!

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