1-6 Specifications

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WHO Prequalification Team – Medicines Assessment
Outline

- Definition
- Why are specifications important?
- Setting appropriate specifications
- PQT-medicines approach
- Selected test parameters
- Model dossier example
- Common deficiencies
Useful References

- PQ Generic Guideline – Quality Part
- WHO PQTm Model Dossier QOS
- ICH Q6A Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances
- ICH Q3A - Q3D: Impurities
- Ph Int, USP, BP, EP, JP (recognized pharmacopoeias in PQTm)
- Other regulatory guidelines
- PQ internal guidelines
What is a specification?

- A specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. (ICH Q6A)

- Section P.5.1 of PQ QOS-PD table Extract:

<table>
<thead>
<tr>
<th>Standard (e.g. Ph.Int., BP, USP, in-house)</th>
<th>Specification reference number and version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Acceptance criteria (release)</td>
</tr>
<tr>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>Identification</td>
<td></td>
</tr>
</tbody>
</table>
What is a specification?

- A specification establishes the set of criteria or quality standards to which an API or FPP should conform to be considered acceptable for its intended use.

- Implication: the API or FPP when tested according to the listed analytical procedures, will meet the acceptance criteria.

- Should be authorized by the responsible personnel, be version controlled and have an effective date.

- Proposed and justified by applicants and approved by NMRAs.
Why are specifications important?

- Part of the total control strategy for the API and FPP designed to ensure product quality and consistency: at release and during shelf life
  - In-process specifications at critical steps
- Confirm the quality of the API/FPP rather than to establish full characterization
  - Focus on quality attributes critical for safety & efficacy
Setting appropriate specifications

- Product specifications should be appropriate to the product (formulation, route of administration, API, manufacture method etc.)
- Reviewers need to be aware of the available literature on the API/FPP
- Important to check if the API or FPP has a monograph in a recognized pharmacopoeia (BP, USP, JP, Ph.Eur., Ph.Int.)
- Past experience with the API or FPP. Have there been any concerns/issues in the past? Is there an accepted DMF for an API?
- Applicant must declare the standard to which the product complies
Setting appropriate specifications…

- Considerations:
  - Method of manufacture: Manufacturing process specific impurities
    - Potential residual solvents
    - Inorganic impurities e.g. from catalysts, reagents etc.
  - Stability results of the API/FPP
  - Formulation: solid, liquid, dispersible, IR
    - Microbial limits
    - Dissolution test
    - Degradation products e.g. interaction of Isoniazid with lactose
    - Disintegration test
Setting appropriate specifications…

- **Route of administration: oral vs sterile injectable**
  - Sterility/microbial limits
  - Bacterial endotoxins
  - Particulate matter

- **API(s) involved**
  - Degradation products
  - Polymorphism e.g. low solubility API
  - Particle size distribution especially for low solubility API
  - Chirality – presence of chiral centres

- **Available pharmacopoeial monographs for the API/FPP**
### PQT approach

- **QOS PD Introduction**: Contains a table for the applicant/assessor to fill in details on the current status of API and FPP

  Identify available literature references for the API and FPP:

<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Monograph exists/does not exist/exists in other combination only</th>
<th>Most recent edition/volume consulted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>API status in pharmacopoeias and fora:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph.Int.</td>
<td>&lt;e.g. Monograph exists&gt;</td>
<td>&lt;e.g. Ph.Int. 4&lt;sup&gt;th&lt;/sup&gt; Edition Suppl. 4&gt;</td>
</tr>
<tr>
<td>Draft Ph.Int. monographs not yet published (through <a href="http://www.who.int">www.who.int</a>)</td>
<td>&lt;e.g. Draft monograph available&gt; &lt;e.g. No revised unpublished monograph&gt;</td>
<td>&lt;e.g. <a href="http://www.who.int">www.who.int</a> as of June 2014&gt;</td>
</tr>
<tr>
<td>USP</td>
<td>&lt;e.g. Monograph exists&gt;</td>
<td>&lt;e.g. USP 38&gt;</td>
</tr>
<tr>
<td>Pharmacopeial Forum</td>
<td>&lt;e.g. API monograph in 34 (3), change to reference now reflected in current USP monograph&gt;</td>
<td>&lt;e.g. 40 (4) July-August 2014&gt;</td>
</tr>
</tbody>
</table>
PQT approach…

- The information collected will assist an applicant or assessor to be aware of current standards and literature on the API or FPP

- Specifications are required to meet the minimum pharmacopoeial standards where a monograph exists, and other requirements (ICH)

- Proposed tests and limits should be fully justified
  - Residual solvents: requirements of ICH Q3C
  - Impurities: Requirements of ICH Q3A/ICH Q3B
  - Dissolution: biolot profile

- Limits proposed should also take into account biobatch/primary batch results, manufacturing capability and stability results.
Tests

- ICH Q6A recommends tests (universal & specific) that may be considered when setting specifications for APIs and FPPs

- Some of the common tests for the API include:

  - Description
  - Identification
  - Assay
  - Impurities (Organic/Inorganic)
  - Particle size
  - Polymorph
  - Microbial limits/Sterility
  - Bacterial endotoxins
  - Water content
  - Chirality
Some of the common tests for the FPP include:

- Description
- Identification
- Assay
- Impurities
- Dissolution
- Disintegration
- Uniformity of dosage units
- Water content
- Bacterial endotoxins
- Microbial limits/Sterility
- Hardness
- Friability

Test methods should be validated, as appropriate (as per ICH Q2).
Model dossier - API specifications

- Levonorgestrel:
  - Structure
  - No polymorphs
  - Brief narrative description of manufacturing process:
    13-Ethyl-3-methoxy-Gona-2,5(10)-Dien-17-one (Methoxydienone) undergoes acetylation under basic condition to give crude Levonorgestrel. Crude Levonorgestrel is purified in methanol and ethyl acetate to give pure Levonorgestrel. The product is sampled and analyzed by Quality Control in accordance with specification of Levonorgestrel.
  - Monographs exist in the PhInt, USP, BP, PhEur
  - To be used to manufacture a tablet formulation
  - What likely tests would you propose for control of the API?
Considerations

- Levonorgestrel is poorly soluble in water i.e. DSV > 250 mL
- Has chiral centres but supplier claims to manufacture as single enantiomer
- Residual solvents used in the last step of synthesis: methanol and ethyl acetate
- No polymorphs
- To be used for manufacture of a tablet formulation
Tests for Levonorgestrel API (Model dossier)

- Description: Appearance
- Identification – IR
- Assay
- Specific optical rotation and enantiomeric purity
- Related substances: Process and degradation impurities, limit for unknowns
- Residual solvents incl. methanol and ethyl acetate (refer to ICH Q3C)
- Loss on drying
- Particle size
- Inorganic impurities: Heavy metals, sulphated ash
Other considerations

- Applicant claims BP/Ph.Eur. & In House standard
  - Check whether BP/Ph.Eur. tests and limits adopted
  - Confirm whether BP/Ph.Eur. test methods have been adopted and verified
  - If In House test methods used, these methods must be validated and equivalency to BP/Ph.Eur. methods demonstrated

- API fully dissolved in solvent during FPP manufacture: particle size no longer a critical parameter

- Refer to section 2.3.S.4.1 on page 16/96 of the QOS of Model dossier for summary of actual specifications
Identification test

- Identification test should be specific to the API i.e. should be able to discriminate between compounds of closely related structure e.g. IR spectroscopy for the API, whenever possible.

- A single HPLC retention time is not regarded as being specific. Two chromatographic procedures, where the separation is based on different principles (HPLC + TLC) or combination of tests into a single procedure is generally acceptable, such as HPLC/MS, or GC/MS.

- Identification test for the salt, where applicable e.g. test for sulfate

- A test for optical rotation for chiral APIs
Related substances

- Process related or degradation products

- Appropriate test and limits should be included for
  - Specified (identified / unidentified)
  - Unspecified (individual unknowns)
  - Total related substances

- Should be monitored during stability

- Take cognizance of ICH Q3A and ICH Q3B reporting, identification and qualification thresholds when setting limits

- Consult ICH Q6A, Decision trees #1 & #2 on setting limits
API impurity thresholds

- Based on maximum daily dose

<table>
<thead>
<tr>
<th>Maximum Daily Dose&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Reporting Threshold&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>Identification Threshold&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Qualification Threshold&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2g/day</td>
<td>0.05%</td>
<td>0.10% or 1.0 mg per day intake (whichever is lower)</td>
<td>0.15% or 1.0 mg per day intake (whichever is lower)</td>
</tr>
<tr>
<td>&gt; 2g/day</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

- Must be aware of the Total daily intake thresholds in addition to the % thresholds (the lower of the two)

- Identification threshold for Levonorgestrel is 0.10% (MDD < 2g/day)
# FPP impurity thresholds

- Also based on maximum daily dose

## Reporting Thresholds

<table>
<thead>
<tr>
<th>Maximum Daily Dose$^1$</th>
<th>Threshold$^{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq$ 1 g</td>
<td>0.1%</td>
</tr>
<tr>
<td>$&gt;$ 1 g</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

## Identification Thresholds

<table>
<thead>
<tr>
<th>Maximum Daily Dose$^1$</th>
<th>Threshold$^{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;$ 1 mg</td>
<td>1.0% or 5 $\mu$g TDI, whichever is lower</td>
</tr>
<tr>
<td>1 mg - 10 mg</td>
<td>0.5% or 20 $\mu$g TDI, whichever is lower</td>
</tr>
<tr>
<td>$&gt;$ 10 mg - 2 g</td>
<td>0.2% or 2 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>$&gt;$ 2 g</td>
<td>0.10%</td>
</tr>
</tbody>
</table>

## Qualification Thresholds

<table>
<thead>
<tr>
<th>Maximum Daily Dose$^1$</th>
<th>Threshold$^{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;$ 10 mg</td>
<td>1.0% or 50 $\mu$g TDI, whichever is lower</td>
</tr>
<tr>
<td>10 mg - 100 mg</td>
<td>0.5% or 200 $\mu$g TDI, whichever is lower</td>
</tr>
<tr>
<td>$&gt;$ 100 mg - 2 g</td>
<td>0.2% or 3 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>$&gt;$ 2 g</td>
<td>0.15%</td>
</tr>
</tbody>
</table>

- Note: Total daily intake thresholds in addition to the % thresholds
What this means

Any impurity:

- > reporting threshold should be reported and added to the total impurities
- > Identification Threshold (IT) should be specified
- > Qualification Threshold (QT) should be qualified
- Unspecified (individual unknowns) ≤ Identification threshold
- Critical to correctly establish thresholds
Assay Test

- Specific, stability-indicating assay test in the specifications
- Non-specific assay methods (when justified) should be used with suitable test for impurities to achieve overall specificity e.g. titration for assay, HPLC for related substances.
- Tighter limits set at release of the FPP e.g. 95.0-105.0%.
- Wider FPP limits may be accepted during shelf life e.g. 90.0-110.0%
- Monitored during stability
- Limit narrow for APIs, 98.0-102.0% for most APIs using HPLC
Uniformity of dosage units

- Critical especially for low dose FPP formulations.
- PQP requirements aligned with those of the Ph. Int.
  - Content uniformity (CU): a test and limit for CU is required for each API present in the FPP at < 5 mg or < 5% of the weight of the dosage unit.
  - Mass uniformity: a test and limit for weight variation for API(s) present at ≥ 5 mg and ≥ 5% of the weight of the dosage unit.
- Pharmacopoeial tests/limits would be accepted e.g. USP <905>
- Scored tablets: CU must also be demonstrated for half-tablets (one-time study) if CU is required for whole tablets and also if half-tablet contains < 5mg of the API. CU may be required for half-tablets for paediatric use even if ≥ 5 mg.
Dissolution

- Dissolution is considered product-specific: method and limits should be appropriate for the proposed product.

- Dissolution limits at release and shelf-life should be identical - provide confidence about release properties of the FPP
  - Expressed in terms of 'Q' – allows for 3 stage testing S1, S2 & S3

- Limits proposed should be meaningful – reflect dissolution profile results observed for biolot; must be in line with basis of biowaiver acceptance; & not too wide as to be irrelevant

- May have limits at > 1 time points e.g. Artemether dissolution limits NLT 40%(Q) in 1 hour and NLT 60% (Q) in 3 hours
Example specifications - FPP

- You have been provided with *Exercise 1 - Specifications* in your folder.

- Please review the specifications. What proposals for improvement would you make on these specifications?
Example specifications – Possible answers

- Description should include colour of tablets (full description of appearance)
- Related substances test and limits missing
- Dissolution limits should be expressed in terms of 'Q' – allows for 3 stage testing S1, S2 & S3 i.e. NLT 70% (Q) in 60 minutes
- Assay limits at release should be revised to 95.0-105.0%, unless justified
- Uniformity of weight should be amended to be in line with harmonized pharmacopoeial texts e.g. Uniformity of dosage units USP chapter <905>
- Disintegration limits should be revised to at least NMT 3 minutes
- Include an identification test for the API
Model dossier FPP specifications

- Please turn to section 2.3.P.5.1(a) on page 50/96 of the QOS of Model dossier for summary of specifications of Levonorgestrel 0.75 mg tablets.

- Please identify the positive aspects of these specifications.
Positive aspects

- Clear tablet appearance description
- More than one identification tests based on different principles
- Uniformity of dosage units by content uniformity in line USP <905> (API content 0.75 mg)
- Degradation products test with limit for unspecified impurities NMT 0.5% in line with ICH Q3B
- Assay limit at release 95.0-105.0%
- Dissolution limits expressed in terms of 'Q'
- Standard of the specifications declared
- Release and shelf life specifications separate & version-controlled
- Tests, reference to analytical procedures and appropriate acceptance criteria provided
Common deficiencies

- Specification not version-controlled, not dated, not signed and no standard claimed/declared
- Critical test parameters not included e.g. missing PSD limits for low solubility API, no identification test etc.
- Proposed limits not considered appropriate e.g. assay limits at release being too wide
- Officially recognized pharmacopoeial monograph exists and the proposed In House tests/limits do not meet minimum pharmacopoeial requirements
- Pharmacopoeial standard claimed not met by proposed tests/limits or equivalence of proposed In House test methods is not demonstrated
- References to test methods missing from the specifications
Thank you

Questions?