GENERAL GUIDANCE
ON “HOLD-TIME” STUDIES

REVISED DRAFT FOR COMMENT
(August 2014)

Should you have any comments on the attached text, please send these to
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## SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/13.521

**GENERAL GUIDANCE ON “HOLD-TIME” STUDIES**

<table>
<thead>
<tr>
<th>Step</th>
<th>Date</th>
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<tr>
<td>Preparation of draft by Dr A.J. van Zyl, South Africa, based on need identified by the WHO Prequalification Programme inspectors</td>
<td>November-December 2012</td>
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<tr>
<td>Preliminary internal review of draft</td>
<td>January 2013</td>
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<tr>
<td>Draft mailed for comments</td>
<td>February 2013</td>
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<td>Collation of comments</td>
<td>April 2013</td>
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<td>Review by inspectors collaborating with the WHO Prequalification Programme</td>
<td>May 2013</td>
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<tr>
<td>Discussion during the joint informal consultation with Prequalification Inspection team and inspectors from national inspectorates</td>
<td>30 May 2013</td>
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<tr>
<td>Follow-up of e-Discussion of Subgroup with expert inspectors to finalize new draft of working document for comments</td>
<td>June 2013</td>
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<td>July 2013</td>
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<td>September 2013</td>
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<td>Review of feedback received with Prequalification Inspection team</td>
<td>September 2013</td>
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<td>Presentation to forty-eighth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>14-18 October 2013</td>
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<td>Further follow-up action as required</td>
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<tr>
<td>Recirculation of working document for comments</td>
<td>February 2014</td>
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<tr>
<td>Compilation of comments</td>
<td>April 2014</td>
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<tr>
<td>Discussion of feedback during informal consultation on medicines quality: GXP, inspection guides and risk management</td>
<td>28-30 April 2014</td>
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<tr>
<td>Recirculation of updated working document</td>
<td>August 2014</td>
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<tr>
<td>Compilation of comments and evaluation of feedback received</td>
<td>End September 2014</td>
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<tr>
<td>Presentation to forty-ninth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>October 2014</td>
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<td>Further follow-up action as required</td>
<td>…</td>
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Manufacturers should ensure that the products that they manufacture are safe, effective and of the quality required for their intended use. Products should be consistently manufactured to the quality standards appropriate to their intended use and as required by the marketing authorization. Systems should ensure that pharmaceutical products are produced according to validated processes and to defined procedures. Manufacturing processes should be shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.

Arrangements should exist to ensure that the dispensed raw materials and packaging materials, intermediate products, bulk and finished products are stored under appropriate conditions. Storage should not have any significant negative effect on the processing, stability, safety, efficacy or quality of the materials, intermediate products and bulk products prior to final packing. Good manufacturing practices (GMP) require that a maximum acceptable holding period should be established to ensure that intermediates and bulk product can be held, pending the next processing step, without any significant
adverse effect to the quality of the material. Such a holding period should be underwritten by data, but need not be extended to find the edge of failure.

2. GLOSSARY

Bulk product
Any pharmaceutical product which has completed all processing stages up to, but not including, final packaging.

Intermediate
Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

3. SCOPE

This guideline focuses primarily on aspects that should be considered in the design of the hold-time studies during the manufacture of solid dosage forms. Many of the principles herein also apply to other dosage forms such as liquids, creams and ointments. This guideline does not cover aspects for hold times in cleaning validation or the manufacturing of active pharmaceutical ingredients (APIs).

This guideline is intended as a basic guide for use by pharmaceutical manufacturers and GMP inspectors. This document does not intend to prescribe a process for establishing hold times, but reflects aspects that should be considered in the design of the hold-time study.

Manufacturers should gather scientific and justifiable data to demonstrate that the dispensed raw materials and packaging materials, intermediate and bulk products:

- remain of appropriate quality before processing to the next stage;
4. ASPECTS TO BE CONSIDERED

Hold time can be considered as the established time period for which materials (dispensed raw materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified conditions and will remain within the defined specifications.

Data to justify the hold time can be collected, but not limited to:

- during development on pilot-scale batches,
- during scale up,
- during process validation, or
- as part of an investigation of a deviation that occurred during manufacture.

Hold-time studies establish the time limits for holding the materials at different stages of production to ensure that the quality of the product does not deteriorate significantly during the hold time. The design of the study should reflect the holding time at each stage. Hold times should normally be determined prior to marketing of a product and following any significant changes in processes, equipment, starting and packaging materials and represent actual processing. Hold time studies should be included during process validation (Ref: Process validation guideline).

Manufacturers may use a flow chart to review the manufacturing procedure of a product and then break up the critical stages of manufacturing process on the basis of time duration required for the particular storage and processing stages, typical pauses in the manufacturing campaign, and the potential impact of storage with reference to environmental and storage conditions. An example for a flow chart is given below.

For example, for oral tablets that are coated the following stages may be considered:

- binder preparation to granulation – consider the granulate;
- wet granulation to drying – the dried granulate;
- dried granules to lubrication/blending – the lubricated blend;
- blend to compression;
- compression to coating – the tablet cores;
- coating solution to preparation – the coating solution;
- coating to packing – consider the bulk coated tablets;
- coating to packing in bulk or FDF;
- packing in bulk to FDF.

Example for a flow chart:

- Dispensing
  - Sifting
  - Dry Mixing
  - Granulation
    - Drying
    - Lubrication & Blending
      - Core tablets: Sample withdrawn for analysis
      - Blend: Sample withdrawn for analysis
  - Compression
  - Coating
    - Coated tablet: Sample withdrawn for analysis
  - Packing
    - Drying

Binder: Sample withdrawn for analysis

Coating Solution: Sample withdrawn for analysis
A written protocol, procedure or programme should be followed which includes the activities to be performed, test parameters and acceptance criteria appropriate to the material or product under test. The protocol and report should generally include the following: a title; reference number; version; date; objective; scope; responsibility; procedure; description of the material/product; sample quantities; sampling method and criteria; acceptance limits; frequency for sampling; sampling locations; pooling of samples; storage conditions; type of container; methods of analysis; results; conclusion; recommendation; signatures and dates. Acceptance criteria are typically more stringent than registered specifications to provide assurance that the material is well within control. When setting the specifications any known stability trends will need to be taken into account.

For certain products microbiological aspects should also be considered and included where appropriate.

Typically one or more batches of a material, intermediate or product can be used for determining hold times. A risk-based approach can be used to determine the appropriate number of batches, considering inter alia the characteristics of the materials A representative sample of the batch of material or product subjected to the hold-time study should be held for the defined hold period. The maximum hold period for each category of material should be established on the basis of the study by keeping the material in either the original or simulated container used in production. The containers used in which hold-time samples are stored should be the same pack as used in production unless the pack is exceptionally large, in which case one that is equivalent (same material of construction and closure system to the production packaging system) may be used. Reducing the size of container when necessary for testing holding time, should be justified. Where head space is important the hold-time samples should represent the maximum possible head space (worst-case scenario) to bulk stored in manufacturing/quarantine. The sample storage environmental conditions should be same as that of the quarantine area/manufacture stage. A sampling plan should be established
and followed for taking samples for testing at the different intervals. The required sample amount should be calculated based on the batch size, the intervals and tests to be performed. Results should be compared with the initial baseline data of the control sample. Samples may be pooled for analysis where appropriate, e.g. when the analysis of a composite sample will not miss issues expected in the variation of the product.

Where appropriate, statistical analysis of the data generated should be performed to identify trends and to justify the limits and hold time set.

Batches of finished products made from intermediates or bulk products and subjected to a hold-time study should be considered for long-term stability testing if data show adverse trending or shifting patterns during the intermediate time points up to the end of the shelf-life. The shelf-life of the product – irrespective of hold times – should be measured from the time the active ingredients are mixed with other ingredients. Normally intermediate and bulk products should not be stored beyond the established hold time. All testing of bulk intermediates and product should be performed using validated stability-indicating methods.

The following table provides examples of stages and tests that may be considered.

Table: Examples of stages and tests that may be considered, based on risk assessment and specific product needs

<table>
<thead>
<tr>
<th>Stage</th>
<th>Test to be carried out as per specification</th>
<th>Study time</th>
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</thead>
<tbody>
<tr>
<td>Binder preparation</td>
<td>Microbial test</td>
<td>Initial, 2hrs, 5hrs, 8hrs. In case of starch: initial, 2hrs, 5hrs</td>
</tr>
<tr>
<td>Solution prepared (including granulation pastes, coating solution and coating suspensión)</td>
<td>Physical appearance, Specific gravity, Viscosity, Sedimentation, pH, Microbial test</td>
<td>Initial, 12, 24, 36, 48, 60, 72 hours</td>
</tr>
<tr>
<td>Granule</td>
<td>Description, Assay, Related substances, Loss on drying, Water content, Particle size distribution, Bulk density, Tap density, Angle of repose.</td>
<td>Initial, 30\textsuperscript{th} day, 45\textsuperscript{th} day</td>
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<tr>
<td>Blend</td>
<td>Microbial test, Loss on drying, Blend uniformity, Particle size, Bulk/Tapped density</td>
<td>Initial, 30\textsuperscript{th} day, 45\textsuperscript{th} day</td>
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<tr>
<td>Core tablets – uncoated (in bulk container)</td>
<td>Description, Hardness, Thickness, Friability, Disintegration, Dissolution or Dissolution profile, assay, Degradation products/related substance, Uniformity of dosage units, Microbial test.</td>
<td>Initial, 30\textsuperscript{th} day, 60\textsuperscript{th} day &amp; 90\textsuperscript{th} day</td>
</tr>
<tr>
<td>Coated tablets (in bulk container)</td>
<td>Description, Hardness, Thickness, Friability, Disintegration, Dissolution or Dissolution profile, Assay, Degradation products/related substance, Uniformity of dosage units, Moisture content, Microbial test.</td>
<td>Initial, 30th day, 60th day &amp; 90th day</td>
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