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GENERAL GUIDANCE FOR INSPECTORS ON "HOLD-TIME" STUDIES

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr Sabine Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; e-mail: kopps@who.int; fax: (+41 22) 791 4730 (kopps@who.int) and to Ms Marie Gaspard (gaspardm@who.int), by 15 September 2013.

Working documents are sent out electronically and they will also be placed on the Medicines web site for comment. If you do not already receive directly our draft guidelines please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

46 **SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/13.521**

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	Date
Preparation of draft by Dr A.J. van Zyl, South Africa, based on need identified by the WHO Prequalification Programme inspectors	November-December 2012
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Presentation to forty-eighth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	14-18 October 2013
Further follow-up action as required	…

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Introduction and background

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 starting and packaging materials used, intermediate products, bulk and finished products are stored under appropriate conditions. Storage should not have any 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 require that the maximum allowable hold time should be established to ensure that in-process and bulk product can be held, pending the next processing step, without any adverse effect to the quality of the material. These time periods must be supported by adequate data to demonstrate that the product will be stable throughout the approved shelf-life.

Normally intermediate and bulk products should not be stored for extended periods of time and are tested with stability-indicating methods.

Scope

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 starting and packaging materials, intermediate and bulk products:

- remain stable before processing to the next stage;
- meet the acceptance criteria and stability specification for the finished product.

The quality and stability of starting materials, intermediate products, bulk and finished products should be ensured at all stages of manufacture.

Maximum allowable hold times should therefore be established for starting materials, intermediate products, bulk and finished products on the basis of tests related to storage conditions. Data to justify the hold time can be collected during development on pilot scale batches, during process validation, or as part of the investigation that occurred during manufacture.

Hold-time studies establish the time limits of holding the materials at different stages of production by assuring that the quality of the product does not deteriorate during the hold time. To validate the hold time under the specified hold-time condition, results obtained should be within the limits of acceptance criteria throughout the hold time. Hold times should normally be determined prior to marketing of a product and following any significant changes in processes, equipment, starting and packaging materials. For products already marketed hold-time studies should be performed.

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 processing stage and the impact of time period with reference to environmental conditions and storage conditions.

Generally, as an example for oral tablets, the following stages should be considered:

- binder preparation to granulation;
- wet granulation to drying;
- dried granules to lubrication/blending;
- lubrication/blending to compression;
- compression to coating;
- coating solution preparation to coating;
- coating to packing.

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 include but not be limited to 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, dates

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. 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 storage period for each category of material should be established on the basis of the study by keeping the material in either the originator or simulated container used in production. The containers used in which hold-time samples are stored should be of the same material of construction as those used in manufacturing/quarantine. Hold-time samples should have head space in proportion to bulk stored in manufacturing/quarantine. The sample storage environmental conditions should be same as that of the quarantine area/manufacture stage. *(Note: Where appropriate, 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.)* At the test points a sample should be taken from the storage container and tested. Results obtained should be compared with the initial baseline data of the control sample results. Samples may be pooled for analysis where appropriate. Where necessary, individual samples may be tested and compared statistically. Statistical calculations should be done and trends identified and discussed to prove a reliable hold time.

Batches of products subjected to a hold-time study should also be subjected to long-term stability testing.

In general the following table provides examples of generally accepted hold times for materials, intermediate, bulk or finished products packed and stored in suitable containers, based on product knowledge. However, specific cases may necessitate other storage periods based on data.

Table 1. Example of maximum storage times without hold-time data

Stage	Suggested maximum storage period
Dispensed materials storage	5 to 30 days[1]
Solutions prepared (including granulating pastes, coating solutions and coating suspensions)	8 to 24 hours
Granules	2 to 30 days[2]
Blend	1 to 2 days
Core tablets – uncoated (in bulk containers)	30 days
Coated tablets (in bulk containers)	30 days

Hold times should be established where materials, intermediate, bulk or finished products are stored for extended periods. Risk assessment (product specific) may further assist manufacturers to determine which stage, tests, intervals and storage periods should be considered for a hold time study. The accumulated hold time should be scientifically justified. Table 2 below provides examples of stages and tests that may be considered.

Table 2. Examples of stages and tests that may be considered, based on risk assessment and specific product needs

Stage	Examples of tests to be considered[3]
Dispensed materials storage	Microbial test
Solutions prepared (including granulating pastes, coating solutions and coating suspensions)	Physical appearance Specific gravity Viscosity Sedimentation pH Microbial test

[1] Dispensed materials stored in containers similar to those in which material was supplied from the original manufacturer and under the same controlled conditions.
[2] Appropriate to the formulation of the granule.
[3] These parameters are examples. Manufacturers have to identify and justify the selection of stages and parameters selected or excluded from a hold-time study.

Granules	Description Assay Moisture content (loss on drying) Water content Particle size distribution Bulk density Tap density Angle of repose
Blend	Microbial test Moisture content (loss on drying) Blend uniformity Particle size Bulk/tapped density
Core tablets – uncoated (In bulk containers)	Description Hardness Thickness Friability Appearance Dissolution Disintegration Assay Degradation products/related substances (where applicable) Uniformity of dosage units Microbial test
Coated tablets (in bulk containers)	Description Hardness Thickness Friability Appearance Dissolution/dissolution profile Disintegration Assay Degradation products/related substances (where applicable) Uniformity of dosage units Moisture content Microbial test

Hold-time data under specified conditions should demonstrate comparable stability to the dosage form in the marketed package.

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