Annex 4

General guidance on hold-time studies

1. Introduction and background

Manufacturers should ensure that the products that they manufacture are safe, effective and of the quality required for their intended use. Systems should be in place to 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 that are of the required quality and that comply with their specifications.

Good manufacturing practices (GMP) require that arrangements should be made to ensure that the dispensed raw materials and packaging materials, intermediate products, bulk and finished products are stored under appropriate conditions. Storage arrangements should not have deleterious effects on the subsequent processing, stability, safety, efficacy or quality of starting materials, intermediate products and bulk products prior to final packing. Maximum acceptable holding periods should therefore be established to ensure that intermediates and bulk product can be held, pending the next processing step, without producing results outside the acceptance criteria for the quality of the material. Normally, intermediate and bulk products should not be stored beyond the established hold time.

The choice of maximum holding period should be supported by relevant data. Studies may extend beyond the chosen maximum but it is not necessary to extend testing to determine the extreme limits at which failure occurs.

2. Glossary

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

Bulk product. Any pharmaceutical product that 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

These guidelines focus primarily on aspects that should be considered in the design of the hold-time studies during the manufacture of non-sterile solid dosage forms. Many of the principles described here also apply to other dosage forms such as liquids, creams and ointments. These guidelines do not cover aspects for hold times in cleaning validation, or the manufacturing of active pharmaceutical ingredients (APIs) or biologicals.

These guidelines are intended as a basic guide for use by manufacturers of pharmaceuticals and by GMP inspectors. This document is not intended 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;
- meet the acceptance criteria.

The finished product should meet the release specifications.

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.

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 produce results outside the acceptance criteria 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. The risk assessment of changes in processes, equipment, storage conditions, starting or packaging materials should include an assessment of whether further hold-time studies should be performed. Hold-time studies may be included during development on pilot-scale batches or during scale-up, and should be confirmed during process validation of commercial-scale processing (*1*). Further data can also be collected as part of an investigation of a deviation that occurred during manufacture.

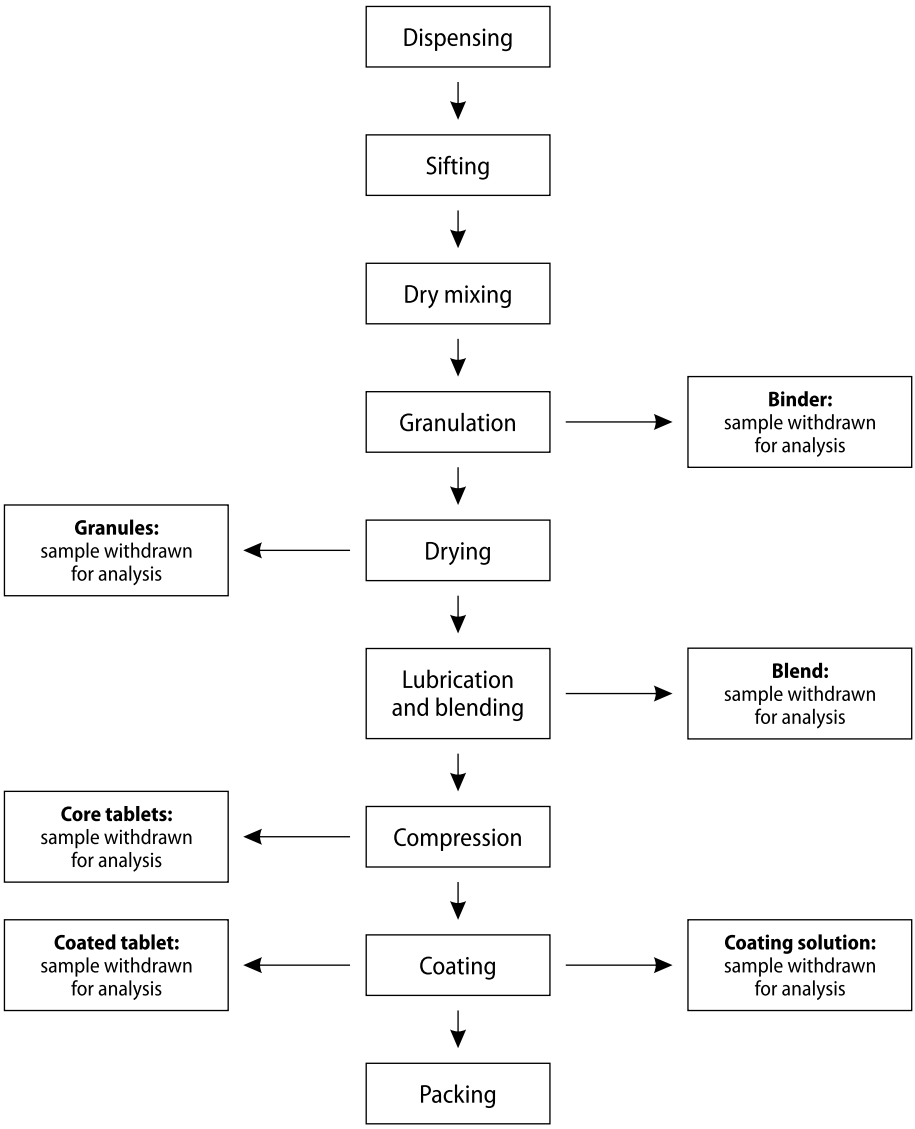
Manufacturers may use a flow chart to review the manufacturing procedure for a product and then break up the critical stages of the manufacturing process on the basis of the time period required for the particular storage and processing stages, typical pauses in the manufacturing campaign, and the potential impact of storage with reference to environmental and storage conditions. An example of a flow chart is given in Figure A4.1.

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

- binder preparation to granulation – consider the granulate;
- wet granulation to drying – consider the dried granulate;
- dried granules to lubrication/blending – consider the lubricated blend;
- blend to compression;
- compression to coating – consider the tablet cores;

- coating solution to preparation – consider the coating solution;
- coating to packing – consider the bulk coated tablets;
- coating to packing in bulk;
- packing of bulk to finished packed dosage form.

Figure A4.1
Example of a flow chart for reviewing the manufacturing procedure



A written protocol, procedure or programme should be followed, which includes, for example, 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 or product; sample quantities; sampling method and criteria; acceptance limits; frequency of 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.

All testing of bulk intermediates and product should be performed using validated stability-indicating methods.

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 the characteristics of the materials and other relevant aspects. 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 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 in which hold-time samples are stored should be the same pack as is used in production unless the pack is exceptionally large, in which case one that is equivalent (constructed of the same material and using the same closure system as the production packaging system) may be used. Reducing the size of container, when this is necessary for testing holding time, should be justified.

Where the headspace of containers used for bulk storage in manufacturing and/or quarantine is important, for example, because of a risk of potential degradation as a result of oxidation, then the hold-time studies should represent worst-case conditions. In such cases, the ratio of headspace to contents in the test containers should be at least as great as the maximum that is possible in routine production (especially taking into account part-filled containers). The environmental conditions for sample storage should be the same as those of the quarantine area/manufacture stage. A sampling plan should be established and followed for taking samples for testing at the different intervals. The amount of sample required should be calculated based on the batch size, the intervals, and the tests to be performed. Results should be compared with the initial baseline data on the control sample. Samples may be pooled for analysis where appropriate,

e.g. when the analysis of a composite sample will not lead to issues that would be detectable in single samples being missed when the samples are pooled.

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.

Table A4.1 provides examples of stages, study times and tests that may be considered for a coated tablet.

Table A4.1
Examples of stages, study times and tests that may be considered, based on risk assessment and specific product needs

Stage	Test to be carried out as per specification	Study time
Binder preparation	Microbial test, appearance, viscosity, if applicable	Initial, 2, 5, 8 hours. In case of starch: initial, 2, 5 hours
Dispersions prepared (including granulation pastes, coating solution and coating suspension	Physical appearance, specific gravity, viscosity, sedimentation, pH, microbial test	Initial, 12, 24, 36, 48, 60, 72 hours
Granule	Description, assay, related substances, loss on drying, water content, particle size distribution, bulk density, tap density, angle of repose	Initial, 15th day, 30th day, 45th day
Blend	Microbial test, loss on drying, blend uniformity, particle size, bulk/tapped density	Initial, 15th day, 30th day, 45th day
Core tablets – uncoated (in bulk container)	Description, hardness, thickness, friability, disintegration, dissolution or dissolution profile, assay, degradation products/ related substance, uniformity of dosage units, microbial test	Initial, 30th day, 45th day, 60th day and 90th day

Table A4.1 *continued*

Stage	Test to be carried out as per specification	Study time
Coated tablets (in bulk container)	Description, appearance or visual examination, hardness, thickness, friability, disintegration, dissolution or dissolution profile, assay, degradation products/ related substance, moisture content, microbial test	Initial, 30th day, 45th day, 60th day and 90th day

Reference

1. Supplementary guidelines on GMP: validation, non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992).