



1
2
3
4
5 **GENERAL GUIDANCE FOR INSPECTORS**
6 **ON “HOLD-TIME” STUDIES**

7
8 *REVISED DRAFT FOR COMMENT*
9

10
11
12 Should you have any comments on the attached text, please send these to
13 Dr Sabine Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance
14 and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland;
15 e-mail: kopps@who.int; fax: (+41 22) 791 4730 (kopps@who.int) and to
16 Ms Marie Gaspard (gaspardm@who.int), by 15 September 2013.

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

21
22 © World Health Organization 2013

23 All rights reserved.

24 This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The
25 draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in
26 whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned
27 staff and member organizations) without the permission of the World Health Organization. The draft should not be
28 displayed on any web site.

29 Please send any request for permission to:

30 Dr Matthias Stahl, Prequalification of Medicines Programme, Medicines Quality Assurance Programme, Quality
31 Assurance and Safety: Medicines, Department of Essential Medicines and Pharmaceutical Policies, World Health
32 Organization, CH-1211 Geneva 27, Switzerland; e-mail: stahlm@who.int.

33 The designations employed and the presentation of the material in this draft do not imply the expression of any opinion
34 whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or
35 area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent
36 approximate border lines for which there may not yet be full agreement.

37 The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or
38 recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.
39 Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

40 All reasonable precautions have been taken by the World Health Organization to verify the information contained in
41 this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied.
42 The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health
43 Organization be liable for damages arising from its use.

44 This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.
45

46 **SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/13.521**
47 ***GENERAL GUIDANCE FOR INSPECTORS ON “HOLD-TIME” STUDIES***
48

	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
Preliminary internal review of draft	January 2013
Draft mailed for comments	February 2013
Collation of comments	April 2013
Review by inspectors collaborating with the WHO Prequalification Programme	May 2013
Discussion during the joint informal consultation with Prequalification Inspection team and inspectors from national inspectorates	30 May 2013
Follow-up of e-Discussion of Subgroup with expert inspectors to finalize new draft of working document for comments	June 2013
Recirculation of working document for comments	July 2013
Compilation of comments and feedback	September 2013
Review of feedback received with Prequalification Inspection team	September 2013
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	...

49

50

CONTENTS

51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82

Introduction and background

Scope

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.

83 **Scope**

84

85 This document does not intend to prescribe a process for establishing hold times, but
86 reflects aspects that should be considered in the design of the hold-time study.

87

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

90

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

94

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

97

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

103

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

111

112 Manufacturers may use a flow chart to review the manufacturing procedure of a product
113 and then break up the critical stages of manufacturing process on the basis of time
114 duration required for the particular processing stage and the impact of time period with
115 reference to environmental conditions and storage conditions.

116

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

118

- 119 - binder preparation to granulation;
- 120 - wet granulation to drying;
- 121 - dried granules to lubrication/blending;
- 122 - lubrication/blending to compression;
- 123 - compression to coating;
- 124 - coating solution preparation to coating;
- 125 - coating to packing.

126

127 A written protocol, procedure or programme should be followed which includes the
128 activities to be performed, test parameters and acceptance criteria appropriate to the
129 material or product under test. The protocol and report should include but not be limited
130 to the following: a title, reference number, version, date, objective, scope, responsibility,
131 procedure, description of the material/product, sample quantities, sampling method and
132 criteria, acceptance limits, frequency for sampling, sampling locations, pooling of
133 samples, storage conditions, type of container, methods of analysis, results, conclusion,
134 recommendation, signatures, dates

135

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

138

139 Typically one or more batches of a material, intermediate or product can be used for
140 determining hold times. A risk-based approach can be used to determine the appropriate
141 number of batches. A representative sample of the batch of material or product subjected

142 to the hold-time study should be held for the defined hold period. The maximum storage
143 period for each category of material should be established on the basis of the study by
144 keeping the material in either the originator or simulated container used in production.
145 The containers used in which hold-time samples are stored should be of the same material
146 of construction as those used in manufacturing/quarantine. Hold-time samples should
147 have head space in proportion to bulk stored in manufacturing/quarantine. The sample
148 storage environmental conditions should be same as that of the quarantine
149 area/manufacture stage. *(Note: Where appropriate, a sampling plan should be established
150 and followed for taking samples for testing at the different intervals. The required sample
151 amount should be calculated based on the batch size, the intervals and tests to be
152 performed.)* At the test points a sample should be taken from the storage container and
153 tested. Results obtained should be compared with the initial baseline data of the control
154 sample results. Samples may be pooled for analysis where appropriate. Where necessary,
155 individual samples may be tested and compared statistically. Statistical calculations
156 should be done and trends identified and discussed to prove a reliable hold time.

157

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

160

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

165

166

167 Table 1. Example of maximum storage times without hold-time data
168

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

169
170 Hold times should be established where materials, intermediate, bulk or finished products
171 are stored for extended periods. Risk assessment (product specific) may further assist
172 manufacturers to determine which stage, tests, intervals and storage periods should be
173 considered for a hold time study. The accumulated hold time should be scientifically
174 justified. Table 2 below provides examples of stages and tests that may be considered.

175
176 Table 2. Examples of stages and tests that may be considered, based on risk assessment
177 and specific product needs
178

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

179
180
181
182
183
184

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