

GUIDELINES ON VALIDATION – APPENDIX 4 ANALYTICAL METHOD VALIDATION (June 2016)

DRAFT FOR COMMENTS

Should you have any comments on the attached text, please send these to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms (<u>kopps@who.int</u>) with a copy to Ms Marie Gaspard (<u>gaspardm@who.int</u>) by **30 July 2016**.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/16.671:

GUIDELINES ON VALIDATION – APPENDIX 4

ANALYTICAL METHOD VALIDATION

90 91	Background information
92	The need for revision of the published Supplementary guidelines on good manufacturing
93	<i>practices: validation</i> (1) was identified by the Prequalification of Medicines Programme and a
94	draft document was circulated for comment in early 2013. The focus of the revision was the
95	Appendix on non-sterile process validation (Appendix 7), which had been revised and was
96	adopted by the Committee at its forty-ninth meeting in October 2014.
97	
97 98	The main text was sent out for consultation as <i>Working document QAS/15.639</i> entitled
99	"Guidelines on Validation" which constitute the general principles of the new guidance on
100	validation.
101	
102	The draft on the specific topics, the appendices to this main text, will follow. One of them, i.e. e
103	Analytical method validation, constitutes this working document.
104	
105	The following is an overview on the appendices that are intended to complement the general text
106	on validation:
107 108	Appendix 1
108	Validation of heating, ventilation and air-conditioning systems
110	\rightarrow will be replaced by cross-reference to WHO Guidelines on GMP for HVAC systems
111	for considerations in qualification of HVAC systems
112	(update - working document QAS/15.639/Rev.1)
113	
114	Appendix 2
115	Validation of water systems for pharmaceutical use
116	\rightarrow will be replaced by cross-reference to WHO Guidelines on water for pharmaceutical
117	use for consideration in qualification of water purification systems
118 119	Appendix 3
120	Cleaning validation – consensus to retain
121	
122	Appendix 4
123	Analytical method validation – updated text proposed in this working document
124	
125	Appendix 5
126	Validation of computerized systems – (update – see working document QAS/16.667)
127 128	Appendix 6
128	<i>Qualification of systems and equipment – update in process</i>
130	znanjeomon oj systems ana equipment — upadie in process
131	Appendix 7
132	Non-sterile process validation – update already published as Annex 3, WHO Technical Report
133	Series, No. 992, 2015

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134		APPENDIX 4
135		ANALYTICAL METHOD VALIDATION
136		
137	1.	Principle
138	2.	General
139	3.	Pharmacopoeial methods
140	4.	Non-pharmacopoeial methods
141	5.	Method validation
142	6.	Method verification
143	о. 7.	Method transfer
144	8.	Revalidation
145	9.	Characteristics of analytical procedures
146	<i>.</i>	
147	1.	PRINCIPLE
148	1.	
149	1.1	This appendix presents some information on the characteristics that should be considered
150		y validation of analytical methods. Approaches other than those specified in this appendix
151		e followed and may be acceptable. Manufacturers should choose the validation protocol
152	•	ocedures most suitable for testing of their product.
153	und pi	occures most surmore for testing of men product.
154	1.2	The manufacturer should demonstrate (through validation) that the analytical procedure is
155		le for its intended purpose.
156	Sultuo	
157	1.3	Analytical methods, whether or not they indicate stability, should be validated.
158	1.5	That yield methods, whether of not mey maleate stability, should be variated.
159	1.4	The analytical method should be validated by research and development before being
160		erred to the quality control unit when appropriate.
161	uunon	the quality control and when appropriate.
162	1.5	The recommendations as provided for in good laboratory practices and guidelines for
163		er of technology should be considered, where applicable, when analytical method
164		tion is organized and planned.
165	, and	
166	2.	GENERAL
167		
168	2.1	There should be specifications for both materials and products. The tests to be performed
169		be described in the documentation on standard test methods.
170	5110 011	
171	2.2	Specifications and standard test methods in pharmacopoeias ("pharmacopoeial
172		ds"), or suitably developed specifications or test methods ("non-pharmacopoeial methods")
173		proved by the national regulatory authority (NRA) may be used.
174	- PP	
175	2.3	Well-characterized reference materials, with documented purity, should be used in
176	analys	
177		
178	2.4	The most common analytical procedures include identification tests, assay of drug
179		nces and pharmaceutical products, quantitative tests for content of impurities and limit

tests for impurities. Other analytical procedures include dissolution testing and determination ofparticle size.

183 2.5 The results of analytical procedures should be accurate, legible, contemporaneous,
184 original, reliable and reproducible. All results should be archived for an appropriate period of
185 time as defined by the laboratory and be in compliance with NRA requirements.

186

182

187 2.6 The procedure should become part of a continuous verification procedure to demonstrate
that it meets the predefined criteria over the life of the procedure.
189

190 2.7 Trend analysis and risk assessment should be considered at intervals to ensure that the191 method is appropriate for its intended application.

192

193 2.8 Changes to methods should be managed in accordance with the authorized change control 194 procedure. The variability of reference materials and other factors such as changes in the process 195 for synthesis of the drug substance, changes in the composition of the finished product, changes 196 in the analytical procedure, when analytical methods are transferred from one laboratory to 197 another (when method transfer is not possible) or when major pieces of equipment instruments 198 change should be considered. These should be understood, controlled and, where possible, 199 reduced. Verification or revalidation should be considered where appropriate.

200
201 2.9 The scope of verification or degree of revalidation depend on the nature of the change(s)
202 and the outcome of risk assessment.

203

204 2.10 There should be evidence that the analysts, who are responsible for certain tests, are
205 appropriately qualified to perform those analyses ("analyst proficiency").
206

207 2.11 The data obtained during method validation and verification should be considered
208 covered by good anything practices (GxP) requirements and are expected to follow the principles
209 of good data and record management practices (2). Their associated metadata are also expected
209 to be retained and subjected to good data and record management practices.

211
2.12 When computerized systems are used to obtain and process data relating to method
validation and verification, they should comply to the principles enunciated in Appendix 5 –
Validation of computerized systems.

215
2.13 Adequate attention should be paid to the method of sample preparation. The description
of this step should be as detailed as possible, especially if it can have a significant impact on tests
results (e.g. particular attention should be paid to details such as sonication time, sonication bath
temperature and mixing and to samples where demixing is known to occur).

220

221 2.14 Failures occurring during method validation, and how these were overcome, should be
222 included in the method validation report – it is not acceptable to present only the passing results
223 as it will give a biased imaged on the reliability of the method and on how it should be applied.
224

225

PHARMACOPOEIAL METHODS

3.

226 227

When pharmacopoeial methods are used, evidence should be available to prove that such 3.1 228 methods are suitable for routine use in the laboratory (verification). 229 230 3.2 Pharmacopoeial methods used for determination of content or impurities in 231 pharmaceutical products should also have been demonstrated to be specific with respect to the 232 233 substance under consideration (no placebo interference). 234 235 4. NON-PHARMACOPOEIAL METHODS 236 237 4.1 Non-pharmacopoeial methods should be appropriately validated. 238 239 5. **METHOD VALIDATION** 240 Validation should be performed in accordance with the validation protocol. The protocol 241 5.1 should include procedures and acceptance criteria for all characteristics. The results should be 242 243 documented in the validation report. 244 5.2 Justification should be provided when non-pharmacopoeial methods are used if 245 pharmacopoeial methods are available. Justification should include data such as comparisons 246 with the pharmacopoeial or other methods. 247 248 Standard test methods should be described in detail and should provide sufficient 249 5.3 information to allow properly trained analysts to perform the analysis in a reliable manner. As a 250 minimum, the description should include the chromatographic conditions (in the case of 251 252 chromatographic tests), reagents needed, reference standards, the formulae for the calculation of results and system suitability tests. 253 254 255 6. **METHOD VERIFICATION** 256 Method verification consists of partial validation. It should be performed for already 257 6.1 validated analytical methods under the following circumstances: 258 259 when an already validated method is used on a product for the first time (e.g. in (a) case of a change in active pharmaceutical ingredient (API) supplier, change in the method 260 of synthesis or after reformulation of a drug product); 261 when an already validated method is used for the first time in a laboratory (in 262 (b) some cases, method transfer may be preferable). 263 264 6.2 Method verification may include only the validation characteristics of relevance to the 265 particular change. For instance, in the case of a change in API supplier, the only expected 266 difference would be in the impurity profile or solubility of the API, and therefore, for a related 267 substances method, there should be an appropriate verification that the method is able to detect 268 and quantitate all potential impurities, even the late eluting ones. Specificity should be among the 269 tests considered (see sections 9 and 10 below for more detail). 270 271

6.3 Method verification is suitable in lieu of method validation for pharmacopoeial methods.

273274 7. METHOD REVALIDATION

275 7.1 Methods should be maintained in a validated state over the life of the method (see point

- 2.6 above). Revalidation of an analytical procedure should be considered whenever there arechanges made to the method, including:
- 278 changes to the mobile phase (please refer to *The International Pharmacopoeia* and other
- pharmacopoeias for the acceptance limits beyond which revalidation must be performed);
- 280 changes to the column;
- 281 changes to the temperature of the column;
- 282 changes to the concentration/composition of the sample and standards;
- 283 changes to the detector (change in detector type, e.g. if going from ultraviolet (UV)-
- visible detection to fluorimetry, or wavelength of detection).

7.2 In case of repeated system suitability failures or when obtaining of doubtful results. In
such cases an investigation of the root cause should be performed, the appropriate changes made
and the method revalidated.

- 7.3 Periodic revalidation of analytical methods should be considered according to a periodthat is scientifically justifiable.
- 7.4 It is acceptable for revalidation to include only the validation characteristics of relevanceto the particular change and method.

292 8. METHOD TRANSFER

- 293
 294 8.1 During method transfer, documented evidence should be established to prove that a
- method has equivalent performance when used in a laboratory different from that where it has
 been originally validated.
- 8.2 Generally, it should be performed by comparing a set of results obtained by an analyst in
 one laboratory to that obtained by another analyst at the laboratory to which the method is being
 transferred.
- 301

304

- 302 8.3 The two sets of results should be statistically compared and the differences between the
 303 two sets of test results should be within an acceptable range.
- 8.4 Method transfer should be performed before testing of samples for obtaining critical data
 for a dossier, such as process validation or stability studies or applied for routine use.
- 307
 308 8.5 A predefined protocol should be followed which includes at least: a title, objective,
 309 scope, responsibilities of the sending unit (SU) and the receiving unit (RU); a specification of
 310 materials and methods; the experimental design and acceptance criteria; documentation

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- specificity;

- 311 (including information to be supplied with the results, and report forms to be used, if any);
- procedure for the handling of deviations; references; and details of reference samples (starting
- materials, intermediates and finished products). The protocol should be authorized and dated.
- 314

8.6 In the case of independent testing by a separate entity, such as a national quality control

testing laboratory that is testing samples on its market, method transfer is not always possible. It

is not considered an obligation but may be considered as an optional step when encountering

difficulties in applying any particular method. See *WHO guidelines on transfer of technology in*

319 *pharmaceutical technology* (3) for further reference.

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323 324

321 9. CHARACTERISTICS OF ANALYTICAL PROCEDURES

- 322 9.1 Characteristics that should be considered during validation of analytical methods include:
- linearity; 325 range; 326 327 accuracy; 328 precision; - detection limit; 329 330 – quantitation limit; - robustness. 331 332 This list should be considered typical but occasional exceptions should be dealt with on a case-333 334 by-case basis 335

9.1.1 *Accuracy* is the degree of agreement of test results with the true value, or the closeness of
the results obtained by the procedure to the true value. It is normally established on samples of
the material to be examined that have been prepared to quantitative accuracy. Accuracy should be
established across the specified range of the analytical procedure.

340

Note: It is acceptable to use a "spiked" placebo where a known quantity or concentration of areference material is used.

343

9.1.2 *Precision* is the degree of agreement among individual results. The complete procedure
should be applied repeatedly to separate, identical samples drawn from the same homogeneous
batch of material. It should be measured by the scatter of individual results from the mean (good
grouping) and expressed as the relative standard deviation (RSD).

- 348
- 9.1.2.1 *Repeatability* should be assessed using a minimum of nine determinations covering the
 specified range for the procedure, e.g. three concentrations/three replicates each, or a minimum
 of six determinations at 100% of the test concentration.
- 352
- 353 9.1.2.2 Intermediate precision expresses within-laboratory variations (usually on different days,
- different analysts and different equipment). If reproducibility is assessed, a measure of
- 355 intermediate precision is not required.

- 357 9.1.2.3 *Reproducibility* expresses *precision* between laboratories.

358
359 9.1.3 *Robustness* (or *ruggedness*) is the ability of the procedure to provide analytical
360 results of acceptable accuracy and precision under a variety of conditions. The results from
361 separate samples are influenced by changes in the operational or environmental conditions.
362 Robustness should be considered during the development phase and should show the reliability
363 of an analysis when deliberate variations are made in method parameters.

364

356

- 365 The verification of stability of analytical solutions is of particular importance.
- Other characteristics of robustness include extraction time. In the case of liquid chromatography,
 robustness testing may also include verification of the impact of changes in pH, temperature and
 flow rate (see ICH Q2 Validation of Analytical Procedures, Step 4, for further details).
- 9.1.3.1 Factors that can have an effect on robustness when performing chromatographic analysis
 include:
- 372 373
- stability of test and standard samples and solutions;
- 375 reagents (e.g. different suppliers);
- different columns (e.g. different lots and/or suppliers);
- 377 extraction time;
- 378 variations of pH of a mobile phase;
- 379 variations in mobile phase composition;
- 380 temperature;
- 381 flow rate.
 382

9.1.4 *Linearity* indicates the ability to produce results that are directly proportional to the
concentration of the analyte in samples. A series of samples should be prepared in which the
analyte concentrations span the claimed range of the procedure. If there is a linear relationship,
test results should be evaluated by appropriate statistical methods. A minimum of five
concentrations should be used.

- 9.1.5 *Range* is an expression of the lowest and highest levels of analyte that have been
 demonstrated to be determinable for the product. The specified range is normally derived from
 linearity studies.
- 392

388

9.1.6 Specificity (selectivity) is the ability to measure unequivocally the desired analyte in the
 presence of components such as excipients and impurities that may also be expected to be
 present. An investigation of specificity should be conducted during the validation of
 identification tests, the determination of impurities and assay.

- 397
- 9.1.7 Detection limit (limit of detection) is the smallest quantity of an analyte that can be
 detected, and not necessarily determined, in a quantitative fashion. Approaches may include
 instrumental or non-instrumental procedures and could include those based on:
- 401

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- 402 visual evaluation;
- 403 signal to noise ratio;
- 404 standard deviation of the response and the slope;
- 405 standard deviation of the blank;
- 406 calibration curve.
- 407

9.1.8 *Quantitation limit (limit of quantitation)* is the lowest concentration of an analyte in a
sample that may be determined with acceptable accuracy and precision. Approaches may include
instrumental or non-instrumental procedures and could include those based on:

- 411
- 412 visual evaluation;
- 413 signal to noise ratio;
- 414 standard deviation of the response and the slope;
- 415 standard deviation of the blank;
- 416 calibration curve.

417 9.2 Characteristics (including tests) that should be considered when using different types of

- analytical procedures are summarized in Table 1.
- 419

420 Table1. Characteristics to consider during analytical validation

Type of analytical procedure	Identification	Testing for impurities	Testing for impurities	Assay — dissolution (measurement only) — content/potency
Characteristics		Quantitative tests	Limit tests	
Accuracy	-	+	-	+
Precision Repeatability Intermediate precision ^a	- -	+ +	- -	+ +
Specificity	+	+	+	+
Detection limit	_	_b	+	_
Quantitation limit	-	+	-	_
Linearity	-	+	_	+
Range	-	+	_	+

Characteristic is normally not evaluated;

+ Characteristic should normally be evaluated.

^a In cases where a reproducibility study has been performed, intermediate precision is not needed.

- ^b May be needed in some cases.
- 421 422

423 Statistical analysis used to evaluate validation characteristics against predetermined acceptance
 424 criteria should be appropriate for the intended evaluation. Appropriately validated software

- should be used. An appropriate number of samples to provide adequate statistical power and
- 426 range should be considered.
- 427 9.3 System suitability testing
- 428

429 Note: System suitability testing is an integral part of many analytical procedures. The tests are

430 based on the concept that the equipment, electronics, analytical operations and samples to be

431 432 433 434 435	param procea	ed constitute an integral system that can be evaluated as such. System suitability test eters that need to be established for a particular procedure depend on the type of lure being evaluated, for instance, a resolution test for a high-performance liquid atography (HPLC) procedure.
436 437	9.3.1 validat	The suitability of the entire system should be confirmed prior to and during method tion tests as well as during the test of samples.
438		
439 440		System suitability runs should include only established standards or reference materials wn concentration to provide an appropriate comparator for the potential variability of the
441	instrun	nent.
442		
443		Where a sample is used for system suitability or a trial run, written procedures should be
444		shed and followed and the results of all such trial runs be included in the results and data
445		process. A sample can be used only if it is a well characterized material. Characterization
446		a case should be performed prior to the use of this sample as part of system suitability
447		. The sample material or product under test should not be used for trial run purposes or to
448		te suitability of the system (see WHO guidelines on good data and record management
449	practic	ces (2).
450 451		
452		
453	Refere	ences
454		
455	1.	Supplementary guidelines on good manufacturing practices: validation
456		(WHO Technical Report Series, No. 937, 2006, Annex 4).
457		
458	2.	WHO Guidelines on good data and record management practices (WHO Technical
459		Report Series, No. 996, 2016, Annex 5).
460		
461	3.	WHO guidelines on transfer of technology in pharmaceutical technology (WHO
462		Technical Report Series, No. 961, 2011, Annex 7).
463		
464		***
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