



**World Health
Organization**

GUIDELINES ON VALIDATION

(May 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 (kopps@who.int) with a copy to Ms Marie Gaspard (gaspardm@who.int) by **12 July 2016**.

Medicines Quality Assurance working documents will be sent out electronically only and will also be placed on the Medicines website for comment under “Current projects”. If you do not already receive our draft working documents please let us have your email address (to bonnyvw@who.int) and we will add it to our electronic mailing list.

© World Health Organization 2016

All rights reserved.

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

Please send any request for permission to:

Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms, Regulation of Medicines and other Health Technologies, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland.

Fax: (41-22) 791 4730; email: kopps@who.int.

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

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

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

This draft does not necessarily represent the decisions or the stated policy of the World Health

34 Organization.

35 SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT
36 QAS/16.666:
37 Guidelines on validation

38
39

Discussion of proposed need for revision in view of the current trends in validation during informal consultation on data management, bioequivalence, GMP and medicines' inspection	29 June– 1 July 2015
Preparation of draft proposal for revision of the main text and several appendices by specialists in collaboration with the Medicines Quality Assurance Group and Prequalification Team (PQT)-Inspections, based on the feedback received during the meeting and from PQT-Inspections, draft proposals developed on the various topics by specialists, as identified in the individual working documents.	July 2015– April 2016
Presentation of the progress made to the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	12–16 October 2015
Discussion at the informal consultation on good practices for health products manufacture and inspection, Geneva,	4–6 April 2016
Preparation of revision by Dr A.J. van Zyl, a participant at the above-mentioned consultation, based on his initial proposal and the feedback received during and after the informal consultation by the meeting participants and members of PQT-Inspections.	May 2016
Circulation of revised working document for public consultation	May 2016
Consolidation of comments received and review of feedback	August–September 2016
Presentation to the fifty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	17–21 October 2016
Any other follow-up action as required	...

40

41 **Background information**

42

43

44 The need for revision of the published *Supplementary guidelines on good*
45 *manufacturing practices: validation* (WHO Technical Report Series, No.
46 937, 2006, Annex 4) (1) had been identified by the Prequalification of
47 Medicines Programme and a draft document was circulated for comment in
48 early 2013. The focus of the revision was the Appendix on non-sterile
49 process validation (Appendix 7), which had been revised and was adopted
50 by the Committee at its forty-ninth meeting in October 2014.

51

52 The main text included in this working document constitutes the
53 **general principles of the new guidance on validation.**

54

55 The draft on the specific topics, the appendices to this main text, will
56 follow.

57

58 The following is an overview on the appendices that are intended to
59 complement the text in this working document:

60

61

Appendix 1

62

Validation of heating, ventilation and air-conditioning systems

63

→ will be replaced by cross-reference to WHO Guidelines
64 on GMP for HVAC systems for considerations in
65 qualification of HVAC systems

66

(update - working document QAS/15.639/Rev.1) (2)

67

68

Appendix 2

69

Validation of water systems for pharmaceutical use

70

→ will be replaced by cross-reference to WHO Guidelines on
71 water for pharmaceutical use for consideration in qualification of
72 water purification systems (3)

73

74

Appendix 3

75

Cleaning validation – consensus to retain

76

77

Appendix 4

78

Analytical method validation – update in process

79

80 *Appendix 5*
81 *Validation of computerized systems – update in process*

82
83 *Appendix 6*
84 *Qualification of systems and equipment – update in process*

85
86 *Appendix 7*
87 *Non-sterile process validation – update already published as Annex*
88 *3, WHO Technical Report Series, No. 992, 2015*

Draft for comment

Guidelines on validation

89

90

91

92 1. Introduction

93 2. Scope

94 3. Glossary

95 4. Relationship between validation and qualification

96 5. Validation

97 6. Documentation

98 7. Validation master plan

99 8. Qualification and validation protocols

100 9. Qualification and validation reports

101 10. Qualification

102 10.1 User requirement specifications

103 10.2 Factory acceptance test (FAT) and site acceptance test
104 (SAT)

105 10.3 Design qualification

106 10.4 Installation qualification

107 10.5 Operational qualification

108 10.6 Performance qualification

109 10.7 Requalification

110 10.8 Revalidation

111 10.9 Process validation

112 11. Change management

113 12. Deviation management

114 13. Calibration and verification

115 References

116

117

118

119 1. INTRODUCTION

120

121 1.1 Validation is an essential part of good practices including good
122 manufacturing practices (GMP) (4) and good clinical practices (GCP). It is
123 therefore an element of the pharmaceutical quality system. Validation, as a
124 concept, incorporates qualification and should be applied over the life
125 cycle of, e.g. the applicable product, process, system, equipment or utility.
126

127 1.2 These guidelines cover the general principles of validation and
128 qualification. In addition to the main part, appendices on validation and
129 qualification (e.g. cleaning, computer and computerized systems,

equipment, utilities and systems, and analytical methods) are included.

1.3 The following principles apply:

- the execution of validation should be in compliance with regulatory expectations;
- quality, safety and efficacy must be designed and built into the product;
- quality cannot be inspected or tested into the product;
- quality risk management principles should be applied in determining the need, scope and extent of validation;
- ongoing review should take place to ensure that the validated state is maintained and opportunities for continuing improvement are identified.

1.4 The implementation of validation work requires considerable resources such as:

- *time*: generally validation work is subject to rigorous time schedules;
- *financial*: validation often requires the time of specialized personnel and expensive technology.
- *human*: validation requires the collaboration of experts from various disciplines (e.g. a multidisciplinary team, comprising quality assurance, engineering, information technology, manufacturing and other disciplines, as appropriate.).

2. SCOPE

2.1 These guidelines focus mainly on the overall concept of validation and are not intended to be prescriptive in specific validation requirements. This document serves as general guidance only and the principles may be considered useful in its application in the manufacture and control of starting materials and finished pharmaceutical products (FPPs), as well as other areas. Validation of specific processes and systems, for example, in sterile product manufacture, requires much more consideration and a detailed approach that is beyond the scope of this document.

2.2 There are many factors affecting the different types of validation and it is, therefore, not intended to define and address all aspects related to one particular type of validation here.

171

172 2.3 The general text in the main part of these guidelines may be
173 applicable to validation and qualification of premises, equipment, utilities,
174 systems, processes and procedures.

175

176 3. GLOSSARY

177

178 The definitions given below apply to the terms used in these guidelines.
179 They may have different meanings in other contexts.

180

181 **calibration.** The set of operations that establish, under specified
182 conditions, the relationship between values indicated by an instrument or
183 system for measuring (for example, weight, temperature and pH),
184 recording, and controlling, or the values represented by a material
185 measure, and the corresponding known values of a reference standard.
186 Limits for acceptance of the results of measuring should be established.

187

188 **change control (including change management).** A formal
189 system by which qualified representatives of appropriate disciplines review
190 proposed or actual changes that might affect a validated status. The intent
191 is to determine the need for action that would ensure that the system is
192 maintained in a validated state (reference working document
193 QAS/15.639/Rev.1 - unpublished).

194

195 **cleaning validation.** Documented evidence to establish that
196 cleaning procedures are removing residues to predetermined levels of
197 acceptability, taking into consideration factors such as batch size, dosing,
198 toxicology and equipment size.

199

200 **commissioning.** The setting up, adjustment and testing of
201 equipment or a system to ensure that it meets all the requirements, as
202 specified in the user requirement specification, and capacities as specified
203 by the designer or developer. Commissioning is carried out before
204 qualification and validation.

205

206 **computer validation (including computerized system
207 validation).** Confirmation by examination and provision of objective
208 documented evidence that computerized system specifications conform to
209 user needs and intended uses, and that all requirements can be consistently
210 fulfilled.

211

212

213 **concurrent validation.** Validation carried out during routine
214 production of products intended for sale.

215
216 **design qualification.** Documented verification that the proposed
217 design of facilities, systems and equipment is suitable for the intended
218 purpose.

219
220 **good engineering practices.** Established engineering methods and
221 standards that are applied throughout the project life-cycle to deliver
222 appropriate, cost-effective solutions.

223
224 **installation qualification.** Documented verification that the
225 installations (such as machines, computer system components, measuring
226 devices, utilities and manufacturing areas) used in a processor system are
227 appropriately selected and correctly installed in accordance with
228 established specifications.

229
230 **operational qualification.** Documented verification that the
231 system or subsystem operates as intended over all anticipated operating
232 ranges.

233
234 **performance qualification.** Documented verification that the
235 equipment or system performs consistently and reproducibly within
236 defined specifications and parameters in its normal operating environment
237 (i.e. in the production environment). (In the context of systems, the term
238 “process validation” may also be used.)

239
240 **process validation.** The collection and evaluation of data,
241 throughout the product life cycle, which provides documented scientific
242 evidence that a process is capable of consistently delivering quality
243 products.

244
245 **prospective validation.** Validation carried out during the
246 development stage on the basis of a risk analysis of the production
247 process, which is broken down into individual steps; these are then
248 evaluated on the basis of past experience to determine whether they may
249 lead to critical situations.

250
251 **qualification.** Documented evidence that premises, systems or
252 equipment are able to achieve the predetermined specifications properly
253 installed, and/or work correctly and lead to the expected results.

254 Qualification is often a part (the initial stage) of validation, but the
255 individual qualification steps alone do not constitute process validation.
256

257 **revalidation.** Repeated validation of a previously validated system
258 (or a part thereof) to ensure continued compliance with established
259 requirements.
260

261 **standard operating procedure.** An authorized written procedure
262 giving instructions for performing operations not necessarily specific to a
263 given product or material but of a more general nature (e.g. equipment
264 operation, maintenance and cleaning; validation; cleaning of premises and
265 environmental control; sampling and inspection). Certain standard
266 operating procedures may be used to supplement product-specific master
267 batch production documentation.
268

269 **validation.** Action of proving and documenting that any process,
270 procedure or method actually and consistently leads to the expected
271 results.
272

273 **validation master plan.** The validation master plan is a high-level
274 document that establishes an umbrella validation plan for the entire
275 project and summarizes the manufacturer's overall philosophy and
276 approach, to be used for establishing performance adequacy. It provides
277 information on the manufacturer's validation work programme and
278 defines details of and timescales for the validation work to be performed,
279 including a statement of the responsibilities of those implementing the
280 plan.
281

282 **validation protocol.** A document describing the activities to be
283 performed during a validation, including the acceptance criteria for the
284 approval of a process or system – or a part thereof – for intended use.
285

286 **validation report.** A document in which the records, results and
287 evaluation of validation are assembled and summarized. It may also
288 contain proposals for the improvement of processes and/or systems and/or
289 equipment.
290

291 **verification.** The application of methods, procedures, tests and
292 other evaluations, in addition to monitoring, to determine compliance with
293 established requirements and specifications.
294

295 **worst case.** A condition or set of conditions encompassing the upper

296 and lower processing limits for operating parameters and circumstances,
297 within SOPs, which pose the greatest chance of product or process failure
298 when compared to ideal conditions. Such conditions do not necessarily
299 include product or process failure.

300

301 **4. RELATIONSHIP BETWEEN VALIDATION AND** 302 **QUALIFICATION**

303

304 4.1 Qualification and validation are essentially the same. The term
305 qualification is normally used for equipment and utilities, and validation
306 for systems and processes. In this sense, qualification can be seen as part
307 of validation.

308

309 4.2 Where the term “validation” is used in the document, the same
310 principles may be applicable for “qualification)

311

312 **5. VALIDATION**

313

314 **Approaches to validation**

315

316 5.1 Manufacturers should organize and plan validation in a manner
317 that will ensure product quality, safety and efficacy throughout its life
318 cycle.

319

320 5.2 The scope and extent of qualification and validation should be
321 based on risk management principles.

322

323 5.3 Statistical calculations should be applied, where appropriate, and
324 provide scientific evidence that the process, system or other related aspect
325 is appropriately validated.

326

327 5.4 Qualification and validation should be done in accordance with
328 predetermined protocols, and the results appropriately documented, e.g. in
329 reports.

330

331 5.5 There should be an appropriate and effective quality system
332 ensuring the organization and management of validation.

333

334 5.6 Senior management should ensure that there are sufficient
335 resources to perform validation in a timely manner. Management and
336 persons responsible for quality assurance should be actively involved in

337 the process and authorization of protocols and reports.
338

339 5.7 Personnel with appropriate qualification and experience should
340 be responsible for performing validation.
341

342 5.8 There should be a specific programme or schedule to support
343 planning and execution of validation activities.
344

345 5.9 Validation should be performed in a structured way according to
346 the documented protocols and procedures.
347

348 5.10 Qualification and validation should be performed:

- 349 – for new premises, equipment, utilities and systems, and processes
350 and procedures;
- 351 – when changes are made, depending on the outcome of risk
352 assessment;
- 353 – where necessary or indicated based on the outcome of periodic
354 review.
355

356 5.11 A written report on the outcome of the validation should be
357 prepared.
358

359 5.12 The scope and extent of validation should be based on knowledge
360 and experience, and the outcome of quality risk management principles as
361 described in the *World Health Organization (WHO) guidelines on quality
362 risk management*. Where necessary worst-case situations or specific
363 challenge tests should be considered for inclusion in the validation, for
364 example, stress load and volume verification in computer system
365 validation.
366

367 **6. DOCUMENTATION** 368

369 6.1 --Qualification and validation should be done according to written
370 procedures.
371

372 6.2 Documents associated with qualification and validation include:
373

- 374 – validation master plan (VMP);
- 375 – standard operating procedures (SOPs);
- 376 – specifications;
- 377 – protocols and reports;

- 378 – risk assessment outcomes;
- 379 – process flow charts;
- 380 – operator manuals;
- 381 – training records;
- 382 – calibration procedures and records;
- 383 – sampling plans;
- 384 – testing plans and methods;
- 385 – statistical methods and results;
- 386 – history of qualification or validation;
- 387 – plan for ensuring review of validation status;
- 388 – plan for ensuring maintaining a validated state.

391 **7. VALIDATION MASTER PLAN**

392
393 7.1 A manufacturer should have a VMP which reflects the key
394 elements of validation. It should be concise and clear and contain at least
395 the following:

- 396 – title page and authorization (approval signatures and dates);
- 397 – table of contents;
- 398 – abbreviations and glossary;
- 399 – validation policy;
- 400 – philosophy, intention and approach to validation;
- 401 – roles and responsibilities of relevant personnel;
- 402 – resources to ensure validation is done;
- 403 – outsourced services (selection, qualification, management through
404 life cycle);
- 405 – deviation management in validation;
- 406 – change control in validation;
- 407 – risk management principles in validation;
- 408 – training;
- 409 – scope of validation;
- 410 – documentation required in qualification and validation such as
411 procedures, certificates, protocols and reports;
- 412 – premises qualification;
- 413 – utilities qualification;
- 414 – equipment qualification;
- 415 – process validation;
- 416 – cleaning validation;
- 417 – personnel qualification such as analyst qualification;
- 418

- 419 – analytical method validation;
- 420 – computerized system validation;
- 421 – establishing acceptance criteria;
- 422 – life-cycle management including retirement policy;
- 423 – requalification and revalidation;
- 424 – relationship with other quality management elements;
- 425 – validation matrix;
- 426 – references.

427
428 7.2 The VMP should be reviewed at regular intervals and kept up to
429 date according to current GMP.

430 **8. QUALIFICATION AND VALIDATION PROTOCOLS**

431
432
433 8.1 There should be qualification and validation protocols describing
434 the qualification and validation to be performed.

435
436 8.2 As a minimum the protocols should include the following
437 significant background information:

- 438
439 – the objectives;
- 440 – the site;
- 441 – the responsible personnel
- 442 – description of the standard operating procedures (SOPs) to be
443 followed;
- 444 – equipment or instruments to be used;
- 445 – standards and criteria as appropriate;
- 446 – the stage of validation or qualification;
- 447 – the processes and/or parameters;
- 448 – sampling, testing and monitoring requirements;
- 449 – stress testing where appropriate;
- 450 – calibration requirements;
- 451 – predetermined acceptance criteria for drawing conclusions;
- 452 – review and interpretation of results;
- 453 – change control, deviations;
- 454 – archiving and retention.

455
456 8.3 There should be a description of the way in which the results will
457 be analysed, including statistical analysis where appropriate.

458
459 8.4 The protocol should be approved prior to use. Any changes to a

460 protocol should be approved prior to implementation of the change.
461

462 **9. QUALIFICATION AND VALIDATION REPORTS** 463

464 9.1 There should be written reports on the qualification and validation
465 performed.
466

467 9.2 Reports should reflect the protocols and procedures followed and
468 include at least the title and objective of the study; make reference to the
469 protocol; reference to the appropriate risk assessment; details of materials,
470 equipment, programmes and cycles used; procedures and test methods
471 with appropriate traceability.
472

473 9.3 Results should be recorded and be in compliance with good data
474 and record management practices.
475

476 9.4 Results should be reviewed, analysed and compared against the
477 justified predetermined acceptance criteria, interpreted and statistically
478 analysed where appropriate.
479

480 9.5 Results should meet the acceptance criteria. Deviations, out-of-
481 specification and out-of-limit results should be documented and
482 investigated according to appropriate procedures. If these deviations are
483 accepted, this should be justified. Where necessary, further studies should
484 be performed.
485

486 9.6 The conclusion of the report should state whether or not the
487 outcome of the qualification and/or validation was considered successful,
488 and should make recommendations for future monitoring and setting of
489 alert and action limits where applicable.
490

491 9.7 The departments responsible for the qualification and validation
492 work should approve the completed report.
493

494 9.8 The quality assurance department should approve the report after
495 the final review. The criteria for approval should be in accordance with the
496 company's quality assurance system.
497

498 9.9 Any deviations found during the validation process should be
499 managed and documented. Corrective actions should be considered.
500

501 **10. QUALIFICATION**

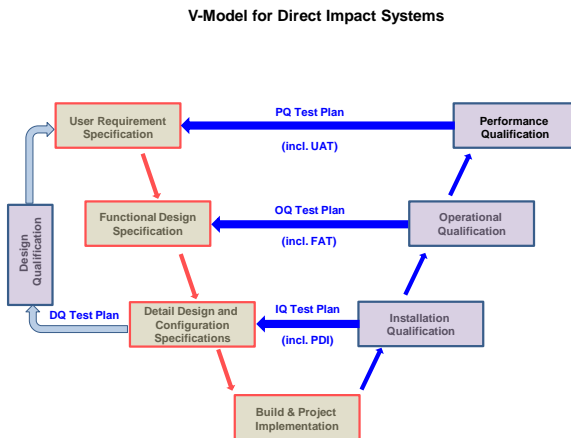
502

503 10.1 There are different approaches in qualification and validation. The
504 manufacturer should select an appropriate approach for the conduct
505 thereof.

506

507 Figure 1.The V-model as an example of an approach to qualification and
508 validation.

509



510

511 **Note. See text below for clarification on terms and stages*

512

513 10.2 All relevant SOPs for operation, maintenance and calibration
514 should be prepared during qualification.

515

516 10.3 Training should be provided to operators and training records
517 should be maintained.

518

519 10.4 Normally, qualification should be completed before process
520 validation is performed.

521

522 10.5 The process of qualification should be a logical, systematic process
523 and should follow a logical flow from the premises, followed by utilities,
524 equipment, to procedures and processes.

525

526 10.6 Stages of qualification should normally start with the preparation

527 of user requirement specifications (URS). Depending on the function and
528 operation of the utility, equipment or system, this is followed by, as
529 appropriate, different stages in qualification such as a factory acceptance
530 test (FAT), site acceptance test (SAT), design qualification (DQ),
531 installation qualification (IQ), operational qualification (OQ) and
532 performance qualification (PQ).

533
534 10.7 One stage of qualification should be successfully completed before
535 the next stage is initiated, e.g. from IQ to OQ.

536
537 10.8 In some cases, only IQ and OQ may be required, as the correct
538 operation of the equipment, utility or system could be considered to be a
539 sufficient indicator of its performance.

540
541 Major equipment and critical utilities and systems, however, may require
542 URS, DQ, IQ, OQ and PQ.

543
544 10.9 Computerized systems, including equipment with software
545 component(s), require user and functional requirements specifications,
546 design and configuration specifications, development of SOPs, training
547 programmes for system use and administration, and an appropriate level of
548 IQ, OQ and PQ verification testing. This includes tests such as stress, load,
549 volume and other performance verification tests that mimic the live
550 production environment. It also includes user acceptance testing according
551 to draft SOPs and training as well as end-to-end business processes for
552 intended use.

553
554 *(Note: See WHO Guidelines on computerized system validation for*
555 *details)*

556 **User requirement specifications**

557
558 10.10 Manufacturers should prepare a document that describes, for
559 example, the utility or equipment to be sourced. The requirements and
560 specifications for the utility or equipment should be defined by the user
561 and documented in the URS.

562
563 10.11 The URS should be used when selecting the required utility or
564 equipment from an approved supplier, and to verify suitability throughout
565 the subsequent stages of qualification.

566
567

568 **Factory acceptance test and site acceptance test**

569 10.12 Where appropriate, FAT and SAT should be performed to verify
570 the suitability of the system at site, prior to the subsequent stages of
571 qualification. This should be appropriately documented.

572

573 **Design qualification**

574 10.13 DQ should provide documented evidence that the design
575 specifications were met and are in accordance with the URS.

576

577 **Installation qualification**

578 10.14 IQ should provide documented evidence that the installation was
579 complete and satisfactory.

580

581 10.15 The design specifications, including purchase specifications, drawings,
582 manuals, spare parts lists and vendor details should be verified during IQ
583 as should the configuration specifications for the intended operational
584 environment.

585

586 10.16 Components installed should be verified and documented evidence
587 should be provided that components meet specifications, are traceable and
588 are of the appropriate material of construction.

589

590 10.17 Control and measuring devices should be calibrated.

591

592 **Operational qualification**

593 10.18 OQ should provide documented evidence that utilities, systems or
594 equipment and all its components operate in accordance with operational
595 specifications.

596

597 10.19 Tests should be designed to demonstrate satisfactory operation over
598 the normal operating range as well as at the limits of its operating
599 conditions (including worst-case conditions).

600

601 10.20 Operation controls, alarms, switches, displays and other
602 operational components should be tested.

603

604 10.21 Measurements made in accordance with a statistical approach
605 should be fully described.

606

607 **Performance qualification**

608 10.22 PQ should be conducted prior to release of the utilities,

609 systems or equipment under conditions simulating conditions of intended use
610 to provide documented evidence that utilities, systems or equipment and
611 all its components can consistently perform in accordance with the
612 specifications under routine use.

613

614 10.23 Test results should also be collected over a suitable period of time
615 during continuous process verification and/or periodic review and
616 monitoring of the utilities, systems and equipment to prove consistency.

617

618 **Requalification**

619

620 10.24 Utilities, systems and equipment should be maintained in a validated
621 state. Any changes made to these should be managed through the change
622 control procedure. The extent of validation or qualification as a result of
623 such a change should be determined based on risk management principles.

624

625 10.25 Requalification should be done based on the identified need. The
626 requalification should be considered based on risk management principles.
627 Factors such as the frequency of use, breakdowns, results of operation,
628 criticality, preventive maintenance, repairs, calibration, verification may
629 be considered.

630

631 10.26 Requalification should also be considered after cumulative /
632 multiple changes.

633

634 10.27 Changes of equipment which involve the replacement of
635 equipment on a “like-for-like” basis will require requalification.
636 Replacement of parts may not require full requalification.

637

638 10.28 Where a system, utility or equipment has not been used for an
639 extended period of time, requalification may have to be considered.

640

641 10.29 Where appropriate, periodic requalification may be performed.

642

643 **Revalidation**

644

645 10.30 Systems should be in place to ensure that procedures remain in a
646 validated state, e.g. such as through verification in cleaning validation and
647 analytical method validation.

648

649 10.31 Revalidation should be done when the need is identified.

650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690

10.32 Where periodic revalidation is done, this should be done in accordance with a defined schedule to ensure that the validated state is maintained.

10.33 Periodic revalidation should be considered as some process changes may occur gradually over a period of time, or because of wear of equipment.

10.34 The frequency and extent of revalidation should be determined using a risk-based approach together with a review of historical data.

Process validation

“New approach”

10.35 It is recommended that manufacturers implement the new approach in process validation. See *Guidelines on process validation*.

“Traditional approach”

10.36 Where the “traditional approach” in process validation is followed, the need for validation should be considered, e.g. through product quality review.

11. CHANGE MANAGEMENT

11.1 Changes should be controlled in accordance with an SOP as changes may have an impact on a qualified utility or piece of equipment, and a validated process, system and/or procedure.

11.2 When a change is initiated, consideration should be given to previous changes and whether requalification and/or revalidation is needed as a result of the cumulative effect of the changes.

11.3 The procedure should describe the actions to be taken, including the need for and extent of qualification or validation to be done.

12. DEVIATION MANAGEMENT

12.1 Deviations during validation and qualification should be documented and investigated, through the deviation management procedure

691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731

13. CALIBRATION AND VERIFICATION

13.1 Calibration and verification of equipment, instruments and other devices, as applicable, should be initiated during installation qualification to ensure that the system operates according to the described specifications and because the calibration status could have been affected during transport and installation.

13.2 Thereafter, it should be performed at regular intervals in accordance with a calibration programme and SOPs.

13.3 Personnel who carry out calibration and preventive maintenance should have an appropriate qualification and training.

13.4 A calibration programme should be available and should provide information such as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.

13.5 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration. A valid certificate of calibration should be maintained which is dated and includes reference to and traceability to, e.g. standards used, acceptance limits, uncertainty where applicable, range, calibration due date.

13.6 Calibrated equipment, instruments and other devices should be labelled, coded or otherwise identified to indicate the status of calibration and the date on which recalibration is due.

13.7 When the equipment, instruments and other devices have not been used for a certain period of time, their function and calibration status should be verified and shown to be satisfactory before use.

13.8 Equipment, instruments and other devices should be calibrated before or on the due date for calibration to ensure that they remain in a calibrated state.

13.9 Where instruments and devices are identified as critical or non-critical, or impacting and non-impacting for the purpose of calibration, documented evidence of the decision making process should be available.

732 This should include impact and or risk assessment.
733

734 **References**
735

- 736 1. Supplementary guidelines on good manufacturing practices:
737 Validation. *WHO Technical Report Series, No. 937, 2006,*
738 Annex 4.
739
- 740 2. Supplementary guidelines on good manufacturing practices for
741 heating, ventilation and air-conditioning systems for non-
742 sterile pharmaceutical dosage forms (working document
743 QAS/15.639/Rev.1) (*Appendix 1*).
744
- 745 3. Water for pharmaceutical use. *WHO Technical Report Series, No.*
746 *970, 2012, Annex 2 (Appendix 2).*
747
- 748 4. Good manufacturing practices: Quality assurance of
749 pharmaceuticals. WHO guidelines, good practices, related
750 regulatory guidance and GXP training materials. CD-ROM, update
751 2016.
752

753
754 ***
755
756