

PROPOSED VALIDATION STANDARD VS-1

Nonaseptic Pharmaceutical Processes

Introduction and Preamble

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Introduction

This Preamble introduces the first in a series of new proposed validation standards by the **Institute of Validation Technology Standards Committee (IVT/SC)**. The purpose of the Preamble is to explain the rationale behind the proposed standard.

The Process Validation Standard VS-1 itself is intended to help practitioners worldwide who develop, implement, control, and validate processes that produce APIs (Active Pharmaceutical Ingredients – a.k.a. drug substances) and drug products. All of the new validation standards will also be used by reviewers of manuscripts intended for publication in the *Journal of Validation Technology (JVT)*.

Readers are encouraged to offer comments, questions, and recommendations. Such feedback should be useful to the **IVT/SC** and *JVT* editors updating this document and in developing future standards. Technologies are continually changing, sometimes in ways that can influence the way validation is best conducted. Therefore, the **IVT/SC** plans to periodically update each validation standard, including its corresponding Preamble and reference list. **IVT/SC** also plans to make all standards electronically available in order to be dynamically responsive to changing industrial practices and regulatory requirements, and make it easier for readers to cut and paste the contents for their use.

A fundamental need the **IVT/SC** intends to meet with its new standards stems from the fact that most GMP regulations today call for numerous written procedures; for example, more than 100 different kinds of written procedures are required to comply with current Good Manufacturing Practice (cGMP) Regulations in the United States. Many firms find it helpful to issue written policies in order to coordinate and reduce the number and length of required Standard Operating Procedures (SOPs). Thus, the *IVT* Validation Standards format includes statements that can be excised and used directly or with minor editing in a firm's policies and SOPs.

Regulations, Guidance Documents, and Standards

There are marked differences between regulations, guidance documents, and standards. In the United States, cGMP regulations evolve only through due process and are considered binding and legally substantive. Food and Drug Administration (FDA) guidance documents do not usually involve due process and are no more legally binding than are industrial guidance documents. (At one time, FDA Guidelines and Compliance Policy Guides were considered legally binding on FDA itself, but that ruling was reversed by FDA General Counsel in August 1990.) Rules Governing Medicinal Products in the European Community, counterpart of U.S. cGMPs, are also portrayed as nonbinding; however, such rules in the European Union (E.U.) and, within a few years, many FDA Guidance

Documents in the U.S., although technically nonbinding, often become regarded as de facto law.

In a somewhat related area of software validation, professional organizations like the Institute of Electronic and Electrical Engineers (IEEE) have demonstrated the value of setting standards. The rapid evolution of computer technology in today's pharmaceutical operations calls for focus on validation of computer-related systems. As with process validation, numerous guidance documents, published articles, and even regulations have appeared in recent years on the subject of computer-related system validation, most of which rely on IEEE standards for the software portion of this important subject.

Style of the IVT Validation Standard

Most pharmaceutical firms like to have lists of succinct, unambiguous, and explicit rules about quality assurance against which to audit. It is preferable for such rules to contain unambiguous, imperative verbs like "shall," "will," and "must," rather than passive verbs like "should," "may," and "can" to avoid interpretive debates with auditees, including suppliers and contract vendors. Standards usually satisfy this need, whereas guidance documents often do not. However, it is also important for those who are to follow the rules to have access to some kind of interpretive documents that accompany and explain the rules. FDA provides a preamble to each of its regulations for that purpose. Similarly, the **IVT/SC** plans to preface each validation standard with a Preamble like this one to explain the subjective rationale behind some of the more complex rules offered in the standard.

Validation has proven to be a complex subject, clear understanding of which depends largely on use of a common language by everyone concerned. Thus, the **IVT/SC** has attempted to provide a glossary that reflects the clearest and most accurate contemporary definitions possible. Moreover, each definition is developed in ways that will enable that term to have the same meaning when used in any *IVT* validation standard. With time and sustained effort, this approach is expected to help improve worldwide harmonization of validation terminology.

Contents of the Validation Standard

Each *IVT* validation standard will include the following five sections after the Preamble and list of contemporary references:

- I. Policy Statements – Standards that indicate what is required
- II. Procedural Statements – Standards that describe how to meet requirements
- III. Acronyms – Meaning of each acronym used in the document
- IV. Glossary – Definition of key terms, which are highlighted and asterisked (*) when first used in the validation standard
- V. Regulatory Excerpts – Regulatory language (United States, Australia, Canada, World Health Organization [WHO], Japan, and European Union) related to each Standard

Future Validation Standards by IVT/SC

The **IVT/SC** authors hope to deliver several new sets of *IVT* validation standards for publication in the *JVT* over the next few years. Future standards under consideration include the following (not necessarily in the order of proposed publication):

- Validation of Analytical Test Methods
- Aseptic Pharmaceutical Process Validation
- Biopharmaceutical Process Validation
- Medical Device Process Validation
- Equipment Cleaning Validation
- Computer-Related System Validation
- Water Treatment System Validation
- Terminal Sterilization Validation

Preamble

In recent years, several worldwide guidance documents and some regulations have been published that address pharmaceutical process validation. Not all such documents are harmonized and, in fact, some diametrically contradict each other. The Global Harmonization Task Force (GHTF)¹ appears to be making good progress, especially with regard to standardizing process validation for medical devices. Corresponding worldwide efforts to harmonize process validation for nonaseptic pharmaceuticals are at present less advanced, less consistent, and less comprehensive. In fact, significant confusion seems to exist about the subject. A primary objective of VS-1 is to help alleviate such confusion.

Frequently Encountered Questions

- When does process validation begin, and when does it end?
- What is a Validation Master Plan (VMP)?
- What kind of validation data can be created in the lab or pilot plant, and when must data be created at commercial scale?
- How important are statistical methods, and when must they be employed?
- What are the purposes of Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ)?
- When and why must three consecutive, commercial-size lots be run?
- How do requirements for existing (legacy) processes differ from those for new processes?
- What is revalidation, and when must it be conducted?

The Validation Master Plan (VMP)

The Validation Master Plan (VMP) is a master document that begins with the initiation of any validation project and is regularly updated as needed, at least until the product becomes commercial. Although the VMP is specifically called for by most contemporary draft and approved validation guidelines, it has become a confusing term because two basic definitions exist; both are used by different (and sometimes even the same) regulatory officials. One definition calls for the VMP to be project-oriented, as in this standard, VS-1 (Sec. IV – Glossary). The other definition describes a more global document embracing a firm's overall validation philosophy.

Most pharmaceutical firms use policies and/or procedures (SOPs) to address such global matters individually. **IVT/SC** finds the second (global) VMP definition workable, but cumbersome and inefficient. To minimize confusion, a firm should clearly define its use of the term VMP (e.g., by written policy or SOP), while ensuring that global and project-related matters are both adequately covered in some way. For firms preferring the global VMP, a term such as Validation Project Plan can be used in place of the VMP defined in VS-1.

A Brief History and Status of Process Validation Guidelines

FDA made available its first draft Guideline on Process Validation in March 1983, shortly after which the Pharmaceutical Manufacturers' Association (PMA, now PhRMA – Pharmaceutical Research and Manufacturers of America) appointed its Validation Advisory Committee (VAC) to respond. FDA's guideline² was not finalized until May 1987. During the intervening four years, three PMA Committees (VAC, the Deionized Water Committee, and the Computer System Validation Committee) each published an industrial validation guideline.^{3,4,5} Prior to each publication, PMA/FDA meetings were held and draft documents discussed at length until regulatory and industrial experts reached basic agreement on all major issues. Nonetheless, in subsequent years, some misunderstandings and contradictory interpretations have evolved, the majority of which are based on semantics, rather than technical differences.

Two recent guidance documents, one by FDA⁶ (Guidance for Industry – Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients – Mar 1998), and the other by the European Agency for the Evaluation of Medicinal Products (EMA)⁷ (Note for Guidance on Process Validation – 30 Sep 1999), describe the importance of

Research & Development (R&D) roles in process validation and offer a full life-cycle approach that begins with R&D. Two other draft guidance documents by Pharmaceutical Inspection Convention (PIC)⁸ (Mar. 1999) and by the EC⁹ (Validation Master Plan Design Qualification, Installation, and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation – 30 Oct. 1999), one a minor modification of the other, seem out of harmony with the life-cycle approach, suggesting that "...three consecutive batches/runs within the finally agreed upon parameters... would constitute a proper validation of the process." The same two documents also contain certain terminology that is outdated, contradictory, or otherwise in need of global harmonization.

Process Validation Life Cycle (Time Line)

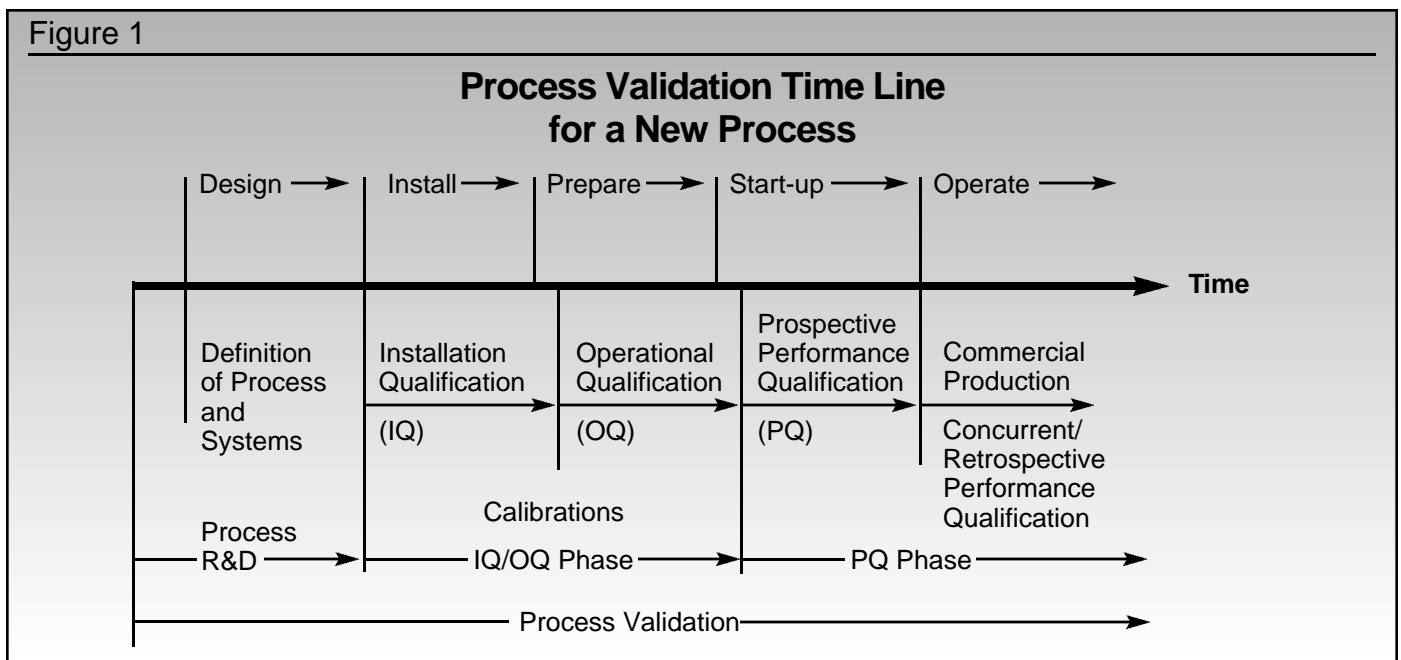
VS-1 Policy Statement 1.3 lists 12 steps in the process validation life cycle, starting with definition of the product and the process. *Figure 1* provides a validation time line embracing this life cycle. Critical pharmaceutical product specifications are determined chiefly by safety (animal and human) studies. Critical process operating parameters are a function of process capability and are determined by process development, which includes process validation.

A significant semantics issue today involves two different perceptions of the scope and definition of the term process validation. The leading perception, to which **IVT/SC** subscribes, is that process validation embraces an entire life cycle, beginning in R&D, including IQ, OQ, and PQ, and ending only when the related product is no longer commercial. The other, now outdated, perception is that process validation starts after IQ and OQ; in fact, some authors^{8,9} equate process validation exclusively with PQ.

Unfortunately, the three PMA guidelines^{3,4,5} of the early 1980s failed to recognize the future semantic problem by portraying validation as something following IQ and OQ. FDA had included performance qualification in its 1983 draft guideline, but associated the term with medical devices, and not with pharmaceutical processes.

In the early 1990s, PDA's Committee on the Validation of Computer-Related Systems recognized the importance of the life cycle, since good software design and development are essential to ultimate system validation and must start at the beginning of the life cycle. PDA defined computer-related system validation as all-embracing, with PQ representing a late stage of the validation life cycle. The GAMP Forum^{10,11} soon thereafter adopted a similar approach.

Practitioners and regulators have learned that, just as "quality must be built into a product" (i.e., "it cannot be tested in") robustness also has to be built into a process. The analogy between process validation and validation of computer-related systems is apt; in both cases, considerable interaction by multiple disciplines throughout the life cycle, including effective technology transfer from R&D to Production and Quality Control, have proven essential.



The Three Lot Controversy

During 1983 – 1984, representatives of FDA and Industry debated at length over the value of positioning three consecutive, commercial-sized lots as pivotal evidence of process validation. Industry agreed that FDA's argument for three lots might be suitable for medical devices, but argued successfully that it was not appropriate for pharmaceutical processes for several reasons:

1. Unnecessarily costly and risky to perform prior to regulatory submission;
2. Limited statistical benefit from three lots; and
3. Establishing critical process parameter ranges and probable adverse consequences of exceeding range limits¹² represents a better investment of resources and contributes more to process robustness and reliability, while the three-lot requirement can detract from such efforts.

In 1990, when FDA launched its Pre-Approval Inspections (PAI) program, the three-lot issue again arose. PAI's chief architects (Richard Davis and Joseph Phillips, FDA, Newark District Directors) announced they would require evidence of three consecutive, successful lots of commercial size prior to shipment of a new product across state lines, as "final" evidence of process validation, even when the firm had already received its New Drug Application (NDA) Approvable Letter.

This time, Industry did not protest the requirement. Several reasons made the requirement logical:

- Three commercial lots add some degree of assurance that the process works and at least a limited indication of reproducibility.
- Three lots can be made in a practical period of time, compared with the number of lots required to gather statistical evidence of reproducibility.
- The overall approach forces focus of validation emphasis on process development measures that occur earlier in the life cycle and, thus, do not jeopardize market launch timing.

Since 1990, most firms have found the predistribution three-lot requirement practical and useful. Some have made the mistake of believing that critical parameters should be varied during the three runs in order to develop new validation evidence, usually of the kind that can be developed in the laboratory or pilot plant more economically and with less risk of failure.

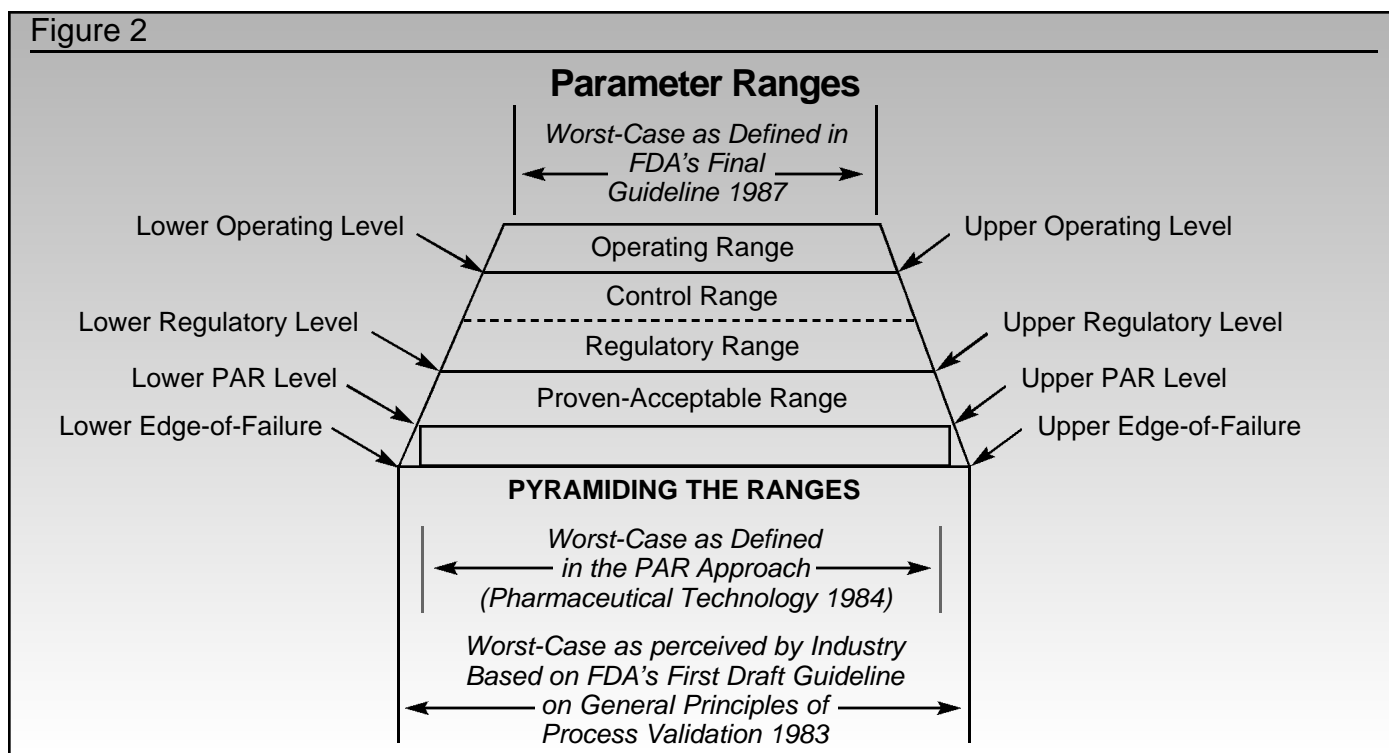
Critical Operating Parameters and the Pyramid

Another concept that appears ambiguous in most current guidance documents is whether a process should be validated against regulatory or "internal" process parameters and product specification limits. The pyramid portrayed in *Figure 2* should help clarify this matter.

It is important that the proven-acceptable, regulatory, and operating ranges all be recognized and considered when writing validation protocols. Many firms also use control ranges that lie between operating and regulatory ranges for added insurance against, and control over, minor plant deviations. Regulatory range limits represent those that a firm includes in its registration (e.g., NDA). The firm's basic commitment is that product safety and efficacy will be ensured when all regulatory limits are met. Regulatory range limits must fall within the upper and lower edges-of-failure. In order to define edges-of-failure, it is essential to identify what the probable adverse consequences are of exceeding the edges-of-failure in each direction. For example, exceeding the upper edge-of-failure for tablet hardness might cause an unacceptable dissolution rate, while exceeding the lower edge-of-failure could lead to friability problems. Overheating an API solution may cause predictable degradation reactions, while underheating could cause premature crystallization or failure to complete a desired reaction.

Many firms employ more than one range of internal limits, such as control ranges for quality monitoring and approvals, as well as the usual, and somewhat tighter, operating ranges for shop-floor directions. As seen in *Figure 2*, each internal range must lie within the corresponding regulatory range for compliance. Control ranges are often

Figure 2



found to be convenient, especially for in-process control test limits, but need not be regarded as essential.

In its initial 1983 draft guideline, FDA proposed that process validation should be based on FDA's definition of "worst-case," which, at that time, extended from one edge-of-failure value to the other (*Figure 2*). The industry objected to the proposal and pointed out in a 1984 article¹² that it is unnecessary to have either edge-of-failure value available, so long as one can establish a Proven-Acceptable Range (PAR) that embraces the regulatory range. In its final 1987 guideline, FDA redefined worst-case (*Figure 2*) to equate with the operating range, a move that facilitated future process validation planning.

Establishing the End Values

The major objective of process validation is to ensure development of a robust process that will produce a product having the intended quality every time the process is run. The first five steps of the Process Validation Life Cycle (VS-1 Policy 1.3) involve establishing end values of regulatory and internal ranges.

Although not absolutely essential, it is also useful to identify edges-of-failure, since the difference between edge-of-failure ranges and regulatory ranges helps determine sensitivity of the process as to causing product rejections. Edge-of-failure data, as well as all other limit values, can frequently be determined in the laboratory or pilot plant (using aliquot samples) long before the process is fully scaled up.

For APIs, reaction kinetics are often used to predict thermal and pH end values. Other studies that help ensure robustness can be created in the early stages of API process development; for example:

1. Determining conditions under which API polymorphs, isomers, hydrates, solvates, and degradation products might form (also important for process patent reasons);
2. Isotherms of pH and temperature versus API solubilities, degradation rates, and other variables; and
3. Similar studies involving major impurities specific to the API process.

In the case of drug products, developmental pharmaceuticals, which include physicochemical profiles and excipient interaction studies, similarly provide information that is needed to determine edges-of-failure and reliable end values. Stability studies and behavior of various lots of clinical supplies contribute further insight to drug product end value design.

Final determination or confirmation of operating ranges for some unit operations, such as blending, will require exploratory studies in larger equipment. In the case of blending, such studies should be preceded by particle size measurements and crystal morphology studies in the laboratory, since the tendency to blend or deblend is often predictable. Blending also represents a case where commercial-scale experiments can usually be run at low risk, for example, to optimize rotational speed and time periods by testing aliquot samples taken at various time intervals.

Use of Statistics in Process Validation

Some current publications address process validation from an almost exclusively statistical approach. The effect of such articles on non-statisticians occasionally ranges from dismay to panic and, unfortunately, drives them away instead of toward use of statistics. Statistical Process Control (SPC) can be especially valuable when applied to process validation, both before and after the validated process enters commercial use. By statistically analyzing critical process parameter data throughout a batch or continuous process, SPC provides the opportunity to predict problems (trend analysis) and even take corrective action (trend control) before the problems occur. Yet today relatively few firms actually appear to be implementing SPC universally across all processing. Diagnosing reasons for this apparent anomaly is beyond the scope of this Preamble. Nonetheless, all firms need to be aware of where statistical tools are and are not needed in process validation work and to have statistical expertise available, regardless of whether SPC itself is broadly used.

Statistical analysis is routine and taken for granted in most laboratory work, including the validation and implementation of analytical test methodology, and in the design of most sampling plans. A question that frequently arises is when statistical tools need to be applied to determine adequacy of operating and regulatory ranges (i.e., process capability.) A glance at *Figure 2* might help answer this question. If a proven-acceptable range exists for a given parameter that is 20% wider than the regulatory range, and if the regulatory range is 20% wider than the operating range, the process is likely to be robust enough to obviate need for statistical analysis for the given parameter. Conversely, if the same ranges appear to be within 2% of each other, the process may or may not require more development, but statistical analyses should certainly be considered. Between those two extremes, judgment is needed of the kind that can usually be provided only by statistical experts.

Another common situation in which statistical analyses may be essential occurs when multiple critical process operating parameters display interactive effects and none of the parameters can be analyzed in isolation. Factorial design experiments may be needed, design and interpretation of end results of which are likely to demand statistical analyses.

The bottom line is that most process validation teams should include or have access to a statistics expert. Because use of SPC offers many opportunities to improve costs and quality through trend analyses and trend control, SPC is highly recommended as a measure to be included in a process validation program.

IQ, OQ, and PQ

Rather widespread confusion seems to have accompanied the great variety of definitions that have evolved for the three “qualification” terms, Installation Qualification, Operational Qualification, and Performance Qualification. Here are a few basics that may help clarify the terms (all definitions can be found in the VS-1 Section IV Glossary):

- Systems and processes are validated; equipment and materials are qualified; persons are trained and qualified.
- IQ is intended to ensure that all critical equipment has been purchased and installed correctly.
- OQ is intended to ensure that all critical equipment works as intended for the process in which it is to be used.
- It is not unusual for some IQ and OQ activities to overlap, an occurrence that presents no problem as long as it is recognized and addressed systematically.
- IQ and OQ data records must be adequate to support ongoing and future change control and revalidation requirements.
- PQ is intended to demonstrate that the process will function correctly in its normal operating environment. The demonstration may involve pilot lots, commercial-scale lots, or carefully designed simula-

tions of either. PQ protocols often involve individual modules (i.e., steps, unit operations) of a new process prior to pilot or commercial scale-up of the full process. When a given critical process parameter cannot be simulated at less than commercial scale, all other process parameters are often established first to avoid potential interference with the first commercial batch that must involve the sensitive parameter. The three commercial lots required to authorize future distribution can theoretically represent the final PQ experiments; however, there is no limit to the number of subsequent commercial lots that can continue to be considered part of the PQ step in the validation life cycle.

Instrument calibration is an example of an activity that overlaps IQ, OQ, and other steps in the life cycle. In validation work, instruments frequently need more extensive calibration (e.g., concerning linearity) than in subsequent process control applications. The step in which the records are included is unimportant as long as the records are available and consistently documented.

Nonresearch-Based Firms

The question may be raised, "How do nonresearch-based firms, such as those that produce off-patent generic products rather than proprietary drugs, develop basic developmental pharmaceuticals, such as physicochemical profiles?" **IVT/SC**'s response is that such firms have the same responsibility for understanding and providing robust, reliable processes as do the larger, research-based firms. By the time proprietary products are off patent, they have often become compendial (e.g., United States Pharmacopoeia [USP], BP), with much of the required basic information readily available. However, minor differences in processing equipment or materials can affect process robustness. Contract development work may be necessary if the firm lacks process development resources.

Legacy Processes

A validation life cycle for an established (legacy), or altered process (revalidation) will be the same as for a new process, except for those steps already adequately completed and directly applicable. Legacy processes should have created numerous batch records which, with appropriate retrospective statistical review, can be translated into a series of PQ experiments, provided that a well-defined process and adequate change control measures are in effect. □

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Suggested Reading

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PROPOSED VALIDATION STANDARD VS-1

Nonaseptic Pharmaceutical Processes

The following standards are intended to reflect desirable contemporary practices, are not binding in any way, and can be modified to suit a firm's specific needs. The standards incorporate imperative verbs (e.g., shall, will, must) to provide users with unambiguous quality assurance auditing tools and are prefaced by a preamble that provides rationale for several of the more complex concepts. The Standards are also directed toward users located at a given plant site that may or may not be part of a larger corporation.

Terms that are **bold** and asterisked (*) the first time they are used are defined in Section IV – Glossary.

I. POLICY STATEMENTS

POL 1.1

Every manufacturing process used for producing an **Active Pharmaceutical Ingredient (API)***, a critical **Intermediate***, a **Drug Product***, or **In-Process Material*** shall be validated.

POL 1.2

Primary **Process Validation*** administrative responsibility shall be assigned to a **Site Validation Steering Committee (SVSC)***, which must minimally include representation by the site **Quality Authority*** and the site **Production Authority***. The SVSC shall adjudicate validation issues and appoint project-specific validation teams as needed that include principal(s) having expertise in the processes involved. Such SVSC responsibilities extend to processes used by contract vendors and suppliers of the firm's drug products and/or APIs, as well as to those processes employed on-site.

POL 1.3

The validation life cycle of a new process involves the following steps:

- 1.3.1 Define each module (step, unit operation) of the process.
- 1.3.2 Define **Critical Product Specifications***.
- 1.3.3 Define the **Critical Process Operating Parameters***.
- 1.3.4 Develop the **Critical Process Operating Parameter Ranges***, based initially on laboratory studies of manufacturing material behavior under normal and stress conditions, and later on results of producing products under varied conditions.
- 1.3.5 Define the **Probable Adverse Consequences*** of exceeding the critical process operating parameter ranges in each direction (end values).
- 1.3.6 Implement comprehensive **Change Control*** and **Revalidation*** procedures.
- 1.3.7 Qualify equipment (**Installation Qualification*** and **Operational Qualification***).
- 1.3.8 Train and qualify operational and supervisory laboratory and plant personnel in product-specific validation principles.
- 1.3.9 Ensure that interrelated systems (e.g., LIMS, environmental controls, utilities) are all validated;
- 1.3.10 Conduct **Performance Qualification***.
- 1.3.11 Assemble and document evidence of **process robustness*** and reproducibility.
- 1.3.12 Provide for retention of archived validation files for required periods following last commercial lot expiration date.

A validation life cycle for an established (legacy) or altered process (requires revalidation) will be the same as above, except for those steps that apply and can be shown by **Retrospective Process Validation*** to have been already satisfactorily completed.

POL 1.4

A **Validation Master Plan (VMP)*** shall be used to define and coordinate validation activities related to any new, existing, or revised production process.

POL 1.5

Validation Protocols* shall be used to define individual validation experiments and practices.

POL 1.6

Validation Task Reports* shall be used for documenting and summarizing results of validation studies. Definitive statements must be used, especially in describing objectives, conclusions, and product or process definitions. Collectively, project validation task reports are to support acceptability of all critical process operating parameter ranges, corresponding acceptance limits, and evidence of process robustness and reproducibility.

POL 1.7

All validation master plans, protocols, and task reports must be approved and available to the SVSC. All such validation documents created on-site must be approved by the site quality authority and, when production is involved, also by the site production authority.

POL 1.8

Concurrent Process Validation* techniques can be employed only with site management approval, in such exceptional cases as rework lots or orphan drug products.

POL 1.9

When a secondary manufacturing site is scheduled to produce with an established process using similar equipment, the primary site SVSC shall make the necessary process validation information, including the primary site validation task reports, available for use by the secondary site SVSC in preparing its VMP. The new VMP must then also include all site-specific information required to comply with these standards.

POL 1.10

Relevant process validation information from other divisions, departments, and production sites (including R&D) is to be gathered, used, and maintained by the SVSC.

II. PROCEDURAL STATEMENTS

PROC – 1.a [ref. POL-1.3.1 - 1.3.4]

Process definitions for validation purposes are to be based on the manufacturing master-instruction for APIs and the Dosage Form Monograph (DFM) for drug products. Such definitions are to also include at least the following information:

- Process flow diagrams where multiple steps are involved;
- Copy of, or reference to, regulatory and operating manufacturing instructions;
- Regulatory and operating acceptance criteria for in-process control tests;
- Regulatory and operating acceptance criteria for critical product characteristics of relevant

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- APIs, drug products, intermediates, and in-process materials;
 - A list of all critical process operating parameters;
 - Regulatory and internal acceptability limits for each critical process operating parameter range;
 - Identification of probable adverse consequences to be expected when acceptable critical process operating parameter ranges are not met.

PROC – 1.b [ref. POL-1.3.1- 1.3.11]

Documented evidence of process robustness shall be established prior to approval of the first production **batch*/lot***, and such evidence shall continue to be recorded and analyzed throughout the commercial life of the process and product.

PROC – 1.c [ref. POL-1.3.4]

Small-scale development studies and laboratory experiments must precede plant-scale process validation studies. Documented results of the studies and experiments shall be collected through technology transfer processes, reviewed, and included or referenced in the VMP. Such studies are to include at least the following:

1. Comprehensive process and product definitions, as listed in POLs 1.3.1-1.3.5;
2. **Developmental Pharmaceuticals*** and other preformulation studies conducted with the drug substance and relevant excipients;
3. Required analytical test methods and controls, including associated validation documentation;
4. Summaries of all pertinent process development and clinical supply batches produced prior to final scale-up; and
5. Summaries of pertinent control laboratory work-to-date.

PROC – 1.d [ref. POL-1.3.6]

Change control and revalidation measures shall be established and implemented to identify, document, and review changes to all variables that could alter the validated state of each manufacturing process.

PROC – 1.e [ref. POL-1.3.6]

Change control and revalidation measures include, and are not limited to, review of changes to the following:

- Product and manufacturing material specifications;
- Source of components;
- Product formula (drug products);
- Manufacturing process instructions;
- Test procedures;
- Equipment (automated and nonautomated);
- Support systems, including SOPs;
- Manufacturing location; and
- Utilities.

PROC – 1.f [ref. POL-1.3.6]

Results of annual record reviews of product complaints, adverse events, batch records, change controls, revised SOPs, and QA investigations are to be reviewed, analyzed for trends, and responded to as part of the ongoing change control and revalidation programs.

PROC – 1.g [ref. POL-1.3.7]

Installation Qualification (IQ) and Operational Qualification (OQ) are to be conducted and docu-

mented in a manner that ensures proper installation and functionality of all processing equipment and permits effective change control.

PROC – 1.h [ref. POL-1.3.7]

Installation Qualification is to include at least the following:

- List of all equipment, operation of which has potential bearing on product quality or process performance;
- As-built drawings and specifications for all purchased equipment, new or used;
- Verification that all such equipment and the installation thereof meets original intent, including applicable building, electrical, plumbing, and other such codes;
- Preventive maintenance plans and schedules for all such equipment.

PROC – 1.i [ref. POL-1.3.7]

Operational qualification is to include at least the following:

- A list identifying each module (step, unit operation, or stage) of the process;
- Process operating parameters for each module, including those designated as critical;
- An OQ protocol designed to demonstrate the equipment used in each module operates as intended throughout each process operating parameter range;
- Task report(s) describing the successful execution of each OQ protocol.

PROC – 1.j [ref. POL-1.3.10]

Performance Qualification (PQ)* shall be performed when the following steps are complete and production has been authorized. At least three consecutive, commercial scale lots shall be successfully produced and tested prior to market distribution of any product.

- Process fully defined, including definition of critical process operating parameters, potential adverse consequences, and critical process operating parameter ranges;
- Product specifications completed;
- IQ and OQ steps completed;
- Operating personnel trained and qualified; and
- Change control procedures in place.

PROC – 1.k [ref. POLs - 1.3.3; -1.4]

Critical process operating parameter data shall be collected for each commercial batch manufactured to provide ongoing evidence of process capability and robustness. Tabulations of data (e.g., spreadsheets) shall be maintained and periodically analyzed to ascertain that critical process operating parameter ranges are being consistently met.

PROC – 1.l [ref. POL-1.4]

The Validation Master Plan (VMP) is to include or identify at least the following (to avoid excessive detail in the VMP, cross references to relevant detailed documents may be used, including to validation protocols):

1. The plan for establishing process robustness, including use of results from development pharmaceuticals and other process development efforts, such as the number and sizes of PQ batches intended to be involved;

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2. Relevant task reports (e.g., from R&D or other sites);
 3. Identification of all test methods and analytical instruments to be used in the validation work, including calibration plans associated with each;
 4. IQ and OQ plans with identification of specific areas in which IQ and OQ are expected to overlap;
 5. Individual validation protocols for each validation study;
 6. Sampling and testing plans;
 7. Provisions for change control and document control to be executed throughout the validation project;
 8. Key SOPs and policies;
 9. Project team organization with training backgrounds, responsibilities, and authorities;
 10. Definition of resources required and allocated; and
 11. Validation schedules, including responsible party or parties associated with each line item.

PROC – 1.m [ref. POL-1.5]

Each Validation Protocol shall include, and is not limited to, the following:

1. Statement of experimental objectives;
2. Definition of what is to be qualified or validated;
3. Experimental plan to be executed, including number of trials and data to be gathered;
4. Detailed sampling plans, including sample sizes, sites, and methods;
5. Test plans with acceptance criteria to be met or established;
6. Descriptions of all testing instruments to be used and specific calibration plans (full details or reference to detailed instructions) for each; and
7. Description of all statistical analyses to be applied.

PROC – 1.n [ref. POL-1.6]

Validation task reports shall be used for documenting and summarizing results of validation studies. Five illustrative categories of task reports are listed and are not necessarily all-inclusive. Collectively, the validation task reports must support acceptability of all critical process operating parameter ranges, corresponding acceptance limits, and evidence of process robustness:

1. Product development summary (e.g., as one of several technology transfer measures);
2. Lot summary report (e.g., identification and size of development and production lots, yields, failures if any, major conclusions);
3. Process performance report (e.g., tables detailing lots versus actual critical process parameter data);
4. In-process control report (e.g., tables detailing lots tested versus results, including actual product attribute data); and
5. Validation protocol completion report (could cover any subject for which a protocol is executed).

III. ACRONYMS

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
BPC	Bulk Pharmaceutical Chemical
cGMPs	Current Good Manufacturing Practice (U.S.)

DFM	Dosage Form Monograph
EC	European Community (now, EU)
EMA	European Agency for the Evaluation of Medicinal Products
EU	European Union
FDA	Food & Drug Administration (U.S.)
GAMP	Good Automated Manufacturing Practice (Forum)
GHTF	Global Harmonization Task Force
IEEE	Institute of Electronic and Electrical Engineers
IQ	Installation Qualification
IVT/SC	Institute of Validation Technology/Standards Committee
NDA	New Drug Application
OQ	Operational Qualification
PAI	Pre-Approval Inspection
PDA	Parenteral Drug Association
PIC	Pharmaceutical Inspection Convention
PMA	Pharmaceutical Manufacturers Association (now Pharmaceutical Research and Manufacturers of America [PhRMA])
PQ	Performance Qualification
QA	Quality Assurance
R&D	Research & Development
SOP	Standard Operating Procedure
SPC	Statistical Process Control
SVSC	Site Validation Steering Committee
USP	United States Pharmacopoeia
VAC	Validation Advisory Committee
VMP	Validation Master Plan

IV. GLOSSARY

*Reference
Standard
Number*

POL-1.1 **Active Pharmaceutical Ingredient (API)** – (synonymous with drug substance and bulk pharmaceutical chemical.) A substance that is represented for use in a drug and, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished drug product. Such substances are intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body of humans or other animals.

PROC-1.b **Batch** – A specific quantity of a drug product, an intermediate, an API, or other material that is intended to have uniform character and quality within specified limits and produced according to a single manufacturing order during the same cycle of manufacture.
(Note: see also **Lot**.)

POL 1.3.6 **Change Control** – A procedure for:

(a.) Identifying all modifications or alterations that are potentially significant to a state

- of control, qualification, or validation;
- (b.) implementing corrective action, such as repair, readjustment, requalification, and/or revalidation;
- (c.) implementing interim measures to be taken until effective corrective actions are complete; and
- (d.) documenting all of the above.

POL-1.8 **Concurrent Process Validation** – a subset of prospective validation in which batches are released for distribution based on extensive testing and data generated during actual implementation of the process. Used only in special cases and with approval of the quality authority.

POL-1.3.3 **Critical Process Operating Parameter** – an operating variable that is assigned a required control range with acceptability limits, outside of which exists potential for product or process failure. A critical process operating parameter is determined via process development and investigational work.

POL-1.3.4 **Critical Process Operating Parameter Range** – a range of values for a critical process operating parameter that lie statistically at or below a specified maximum value and/or at or above a specified minimum operating value.

POL-1.3.2 **Critical Product Specifications** – limitations assigned to specific product characteristics, control of which is important to product safety, efficacy, or other significant fitness-for-use product attributes.

PROC-1.c **Developmental Pharmaceutics** – preformulation studies of the physical, chemical, and (possibly) morphological properties of a drug substance (API) and its interactions with other excipients to be used in a pharmaceutical drug product formulation. Objectives are to provide predictive information leading to a robust product and process.

POL-1.1 **Drug Product** – a finished dosage form (e.g., tablet, capsule) that contains an API, generally in association with excipients. Synonymous with finished drug product.

POL-1.1 **In-Process Material** (as applied to drug product manufacture) – any material manufactured, blended, compacted, coated, granulated, encapsulated, tableted, or otherwise processed that is produced for and used in the preparation of a drug product. (Corresponding materials used in the preparation of APIs are referred to as intermediates.)

POL-1.3.7 **Installation Qualification (IQ)** – documented verification that equipment, system, or subsystem has been properly installed and adheres to applicable codes and approved design intentions and that supplier recommendations have been suitably addressed.

POL-1.1 **Intermediate** – a material produced during steps in the synthesis of an API that must undergo further molecular change or processing before it becomes an API. The degree to which a given intermediate should be rated “critical” must be determined by a firm’s experts based on such criteria as:

- potential toxicity or other physiological activity;
- degree to which equipment used is dedicated to the process, as opposed to having multiple uses; and
- ease or difficulty of removing process residuals when cleaning equipment.

(Note that the term “intermediate” is also occasionally used in relation to certain drug products in regulatory documents.)

PROC-1.b **Lot** – a batch or a specific identified portion of a batch having uniform character and quality within specified limits.

Lot (for an API produced by continuous process) – a specific, identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.

Note: Although lot and batch are considered synonymous, “lot” is often used with packaged APIs or drug products and with purchased raw materials and packaging materials. “Batch” is commonly used for intermediates and in-process materials.

POL-1.3.7 **Operational Qualification (OQ)** – documented verification that equipment, system, or process performs as specified throughout representative or anticipated operating ranges. OQ frequently includes investigational work and statistical analysis for reduction of nonrandom variation and optimization. (Note: Overlap between IQ and OQ often occurs and is considered allowable, but should be addressed in the VMP.)

POL-1.3.10 **Performance Qualification (PQ)** – documented evidence that each step in the defined process or system functions as intended and produces intended results under normal operating conditions.

POL-1.3.5 **Probable Adverse Consequence** – most likely potential failure(s) that will occur to product quality attribute(s) or to process state of control by exceeding a specified control parameter range (in either direction.)

POL-1.3.11 **Process Robustness** – degree to which a process can function in a state of control under normal plant operating conditions, at commercial scale, with reproducibility from batch to batch.

POL-1.2 **Process Validation** – establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation involves activities that start early in the process development life cycle and continues throughout the commercial life of the product.

POL -1.2 **Production Authority** – counterpart of quality authority, sometimes referred to as production head or, in the case of FLP (Fill-Label-Pack) operations, packaging head.

POL-1.5 **Protocol** – a written plan of action designed to gather documented evidence that will support or refute a set of stated premises or meet predetermined objectives.

POL-1.2 **Quality Authority** – one or more persons who, collectively, have formal responsibilities for specified quality-related operations, such as approval of manufacturing materials, release of finished products, review and approval of documents, and adjudication of quality assurance investigations. titles of quality authority principals vary throughout the world; for example, in the U.S., one term “the q.c. unit,” is all-embracing; in the E.U. and Canada, the head of quality control has some of the responsibilities, while a qualified person has others; terms such as responsible head (or person) and quality assurance (and/or control) department are also used in other areas.

POL-1.3 **Retrospective Process Validation** – using historical data, such as batch records and trend analyses, to provide or augment documented evidence that a process does what it purports

to do and is stable. (*Note: Some regulatory agencies define the term to mean validating the process after the product has been commercialized.*)

- POL-1.3.6** **Revalidation** – repetition of the validation process or a specific portion of it. Revalidation may include a total process review and/or requalification of those portions of the process potentially affected by a change.
- POL-1.2** **Site Validation Steering Committee (SVSC)** – a standing committee with authority and responsibilities for validation policies, practices, and adjudication of issues. Must include quality authority and production authority representation, and often includes representatives of other involved disciplines. The name of the SVSC may vary from firm to firm.
- POL-1.4** **Validation Master Plan (VMP)** – a comprehensive, project-oriented action plan that includes or references all protocols, key SOPs and policies, existing validation task reports, and other relevant materials on which the specific system or process validation effort will be based. The Plan also identifies resources to be allocated, specific personnel training and qualification requirements of relevant, organizational structure and responsibilities of the validation team, and planned schedules. The VMP is subject to periodic revisions covered by change-control procedures.
- POL-1.5** **Validation Protocol** – a written plan of action designed to gather documented evidence that will support or refute a set of stated validation premises or meet predetermined validation objectives. (See **Protocol**.)
- POL-1.6** **Validation Task Report** – a written report that summarizes results and conclusions of executing all or any portion of a Validation Master Plan (often referred to as a final report if summarizing all activities of the VMP.)

V. REGULATORY EXCERPTS

Regulatory Reference

- AUS 611 When any new master formula and processing instruction is adopted, steps should be taken to
Validating demonstrate and document that...the defined process...will consistently yield a product of the
Processes required quality.
- AUS From time to time, processes and procedures should undergo critical appraisal to ensure that
612 they remain capable of achieving the intended results...
- AUS ...Repeat studies should be undertaken periodically and in any case whenever a significant
669 change in starting materials or method of manufacture is introduced. Records of validation
 should be available for inspection.
- AUS ...the quality assurance or quality control department should...carry out, coordinate or par-
805 ticipate in initial and periodic process validation studies
- CAN **C.02.011.**
C.02.011 [W]ritten procedures, prepared by qualified personnel [shall] ensure...the drug will meet...
[i 2, 3]

specifications...and each lot or batch of that drug shall be produced in compliance with those procedures.

INTERPRETATION

2. **All critical production processes are validated.**
3. **Validation studies are conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions is...evaluated, approved and maintained.**

CAN
C.02.014
[i 6]

C.02.014

...No lot or batch of a drug shall be reprocessed without the approval of the person in charge of the quality control department.

INTERPRETATION

6. **...Validation of reprocessing operations is required to demonstrate that the quality of the finished product is not affected.**

EC
1.3ii

1.3. [GMP requires]:

ii. critical steps of manufacturing processes and significant changes to the process are validated...

EC
4.26

4.26. There should be written procedures and... associated records of actions taken or conclusions reached...for...validation...

EC
5.22

5.22. [A]ny new manufacturing formula or method of preparation...should...(be suitable) for routine processing [which] should...yield a product consistently of...required quality.

EC
5.23

5.23. Significant amendments to...manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

EC
5.37

5.37 Critical processes should be validated...

ECA1
Ax1-43

43. Care should be taken that any validation does not compromise the processes.

JAPI.Ch.4,
Art.10(1-3)

I Ch.4, Art. 10

[The manufacturer shall]

(1) [Perform validation where]:

A. ...drug manufacturing is started at the manufacturing plant.

B. ...a change which might cause a serious effect on the quality of the drug is made.

C. Other cases required for the proper conduct of manufacturing control and quality control of drugs.

(2) [R]eport in writing to the product security pharmacist the results of validation.

(3) [R]etain...validation records for three years after the date of recording.

US .110(a)

§ 211.110 Sampling and testing of in-process materials and drug products.

(a) ...[W]ritten...control procedures shall...validate the performance of ...manufacturing processes that may be responsible for causing variability in the characteristics of in-process

material and the drug product...

- WHO 5.1 ...Processes...should...undergo periodic revalidation to ensure that they remain capable of achieving the intended results...
- WHO 5.2 Critical processes should be validated, prospectively or retrospectively.
- WHO 5.3 When any new master formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the material and equipment specified, should be shown to yield a product consistently of the required quality.
- WHO 5.4 Significant amendments to the manufacturing process, including any change in equipment or materials that may affect product quality and/or the reproducibility of the process, should be validated.
- WHO 17.52 The efficacy of any new processing procedure should be validated...
- WHO 18.34 Steps that are critical for the quality of the active pharmaceutical ingredient should be defined and the procedures applied should be validated. □

