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A Practical Approach to Pharmaceutical Commissioning and Qualification

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A Practical Approach to Pharmaceutical Commissioning and Qualification – A Symbiotic Relationship

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INTRODUCTION

An initial response to the recommendation to do Commissioning in the Pharmaceutical industry is that it is just an additional step – another roadblock to engineering success and something repeated during Qualification. However, effective Commissioning supports engineering *and* Qualification success. This course addresses efficient Commissioning techniques and synergizing with Qualification. Examples presented are not all definitive, and documentation may exceed or not include certain elements – Commissioning (and Qualification) must be structured for the project.

This course contains much of the material included in the basic Commissioning course, but focuses on the Pharmaceutical industry and recent initiatives with Commissioning. The Author has been a leader in the Pharmaceutical industry in the application of documented Commissioning to minimize the regulated paperwork required for Validation/Qualification. He shares his learned experiences in this course in the practical application of commissioning as it specifically relates to Pharmaceutical projects. (Note: Also see the course entitled "Commissioning Fundamentals and a Practical Approach" for a cost efficient method to apply Commissioning.)

COURSE CONTENT

Commissioning is an important aspect of any project, and is especially important in the Pharmaceutical industry in that it supports Validation (more accurately described as Qualification for the application described in this course.) Actually, Commissioning streamlines Qualification.

Commissioning Streamlines Qualification

Effective commissioning results in a focused and better first-time-success Validation effort. There are many ways Commissioning can benefit Qualification – Reduce costs (but don't overstate), a less rigorous documentation regimen (except for Enhanced commissioning requirements below), tests are closer to the source (suppliers, contractors, etc.) and therefore are often more meaningful, debugging/trouble shooting is minimized during Qualification, faster Qualification, catch problems Qualification might miss, better schedule attainment, better project quality attainment, and better customer satisfaction (when they finally realize the value of commissioning).

There are good reasons formal Commissioning is needed, many of which are directly related to more efficient Qualification. The following are a few examples:

1. Ratcheting Validation Costs – Each project has the tendency to "one up" the previous one and Qualification success may be graded by the weight of the paper generated.
2. Validation, a debugging exercise – Due to a lack of proper commissioning, problems may be discovered during Qualification that add cost, schedule duration, and undo stress. Validation should be a *one-shot* exercise and successfully completed as much as possible on the first try.

3. Overly extensive Validation, undue lifecycle burden – There is a tendency to over-Qualify due to a lack of confidence in the installation (actually due to a lack of adequate commissioning), which not only adds initial cost, but unnecessary lifecycle maintenance of a validated state. This over-qualification may extend to areas not associated with product quality, and is not necessary when effective commissioning is applied.
4. Repeating informal Commissioning activities – Most projects include some level of Commissioning, which are often repeated during Qualification

Validation/Commissioning: the Distinctions

It is important to understand the definitions of Validation/Qualification and Commissioning to determine the distinction and how each can effectively work together. First, Validation is "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes"[i] Qualification is a subset of Validation including IQ/OQ/PQ, and is "The documented verification that all aspects of a facility, utility or equipment that can affect product quality . . .

- . . . adhere to approved specifications" (Installation Qualification or IQ)
- . . . operate as intended throughout all anticipated ranges" (Operational Qualification or OQ)
- ". . . perform as intended meeting predetermined acceptance criteria"[ii] (i.e.: over time. Performance Qualification or PQ)

Commissioning is "A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder expectations."[iii] That is, Commissioning verifies what was specified was installed, that it functions properly, and it was successfully turned over to the user, *and* reasonably ensures Qualification success (avoid Qualification becoming a troubleshooting exercise). For cGMP, formal commissioning provides necessary documentation to verify and record commissioning was done and supports Qualification documentation.

Note the distinction between the two definitions. The Validation/Qualification definition emphasizes *product*; the Commissioning definition emphasizes *equipment*. Validation/Qualification is primarily concerned with and verifying aspects that could affect product quality. Commissioning is concerned with GEP (Good Engineering Practice) and Qualification success, and is an equipment/system/facility focus. When Commissioning is properly implemented, Qualification can focus on what is important – aspects that could affect product quality. Defining Qualification and Commissioning early in a project also allows Commissioning to emphasize Direct Impact elements to ensure Qualification success.

The "W" Model

Commissioning supports Qualification relationally; for example, Inspection activities support and are similar to IQ, and testing activities support and are related to OQ/PQ. Factory Acceptance Tests (FAT) and Site Acceptance Tests (SAT) support and are similar to the overall Qualification effort. See Figure 2, a "W" Model, which illustrates the relationship between Design, Commissioning, and Qualification. This is similar to the familiar "V" model, except a center portion is added to illustrate the Commissioning relationship. The primary User Requirement Specification (URS) or similar document

defines the high level, low detail fundamental requirements of the project. Certain Commissioning Functionality Tests should verify the URS was complied with, which leads in to PQ. Commissioning Testing activities should also sufficiently verify the installation complies with the Functional Requirement Specification (a somewhat more detailed document than the URS), which leads in to OQ. Commissioning Inspection activities should sufficiently address the detailed spec, which leads in to IQ. FAT/SAT documents may include most Commissioning Testing/Inspection elements for some projects, and therefore be relational to all the design documents and lead in to related Qualification.

InVEST Wisely in Commissioning

When establishing Commissioning requirements, it is important to remain focused on commonsense objectives to make the effort meaningful and cost effective. The acrostic "InVEST" is helpful in establishing the focus:

- Integrate: Integrate Commissioning with Qualification. Don't automatically do things twice.
- Verify: Ask: does the Commissioning activity adequately verify the equipment or system is what was specified and works as it should?
- Ensure Qualification Success: Ask: does the commissioning effort sufficiently ensure Qualification will be successful – first time?
- Sensible: Do enough but don't over do it
- Traceable: Document it. Remember the saying, "If you don't document it, you didn't do it."

Establishing Commissioning and Documentation Requirements

Before developing Commissioning Documentation, establish the extent of Commissioning needed, and design efficient and effective Commissioning around the needs of the project (hopefully as expressed in a well-written URS/FRS.) Effective commissioning documentation defines the commissioning process (with signatory approval when needed), defines setting to work verifications, inspections, and tests; may confirm training completion (the project is not complete until users know how to use it); and may confirm documentation turnover (the project is not complete until drawings, specs, and O&M manuals are turned over to record/as-built condition and enable users to operate/maintain).

Typical Commissioning Documents may include the following, depending on project complexity. (See Figure 1 for an example hierarchy of Commissioning Documentation).

- Overall Commissioning Plan – for large and more complex projects – this is a masterplan for Commissioning when the approach needs preplanning and structure. On smaller projects/single equipment, consider relying on Standard Operating Procedure (SOP) requirements rather than a separate overall Plan.
- Pre Commissioning: Includes Factory Acceptance Test (FAT), Site Acceptance Test (SAT), and possibly other early inspection/test activities. These are usually structured for individual systems, and can be included in or required by Commissioning Plan. These could be stand alone for individual equipment/systems, and/or include essential elements of the Commissioning Test/Inspection Plans

- Commissioning Test and Inspection Plans: These could be stand alone for individual equipment/systems. These may also supplement areas not covered by FAT's/SAT's. Further, self-contained Commissioning Checklists can be used for simple/small work. Don't create unnecessary volumes of documentation.

Enhanced Commissioning

Certain commissioning activities need not be repeated during Qualification. It is possible to do Commissioning activities that satisfy elements of Qualification. This is called "Enhanced Commissioning." Documentation created by Enhanced Commissioning is considered sufficient for a related Qualification aspect and not repeated during Qualification. Enhanced Documentation may require more extensive and/or a more rigorous test/inspection regimen, as well as additional signatures. Essentially, Enhanced Documentation must satisfy all the requirements of Qualification documentation.

Note that Commissioning never replaces Qualification for Direct Impact systems. The Commissioning process can cover only elements of Qualification, and is not a substitute. Qualification should link back to properly documented Enhanced elements. Consider the impact of change control (formal or project) that could affect decisions as to when to use Enhanced commissioning.

Factory Acceptance Tests (FAT) and Site Acceptance Tests (SAT) may include Enhanced elements. However, be careful when using FAT especially for Enhanced, in that changes may be made at the factory in an uncontrolled setting that affect other outcomes.

FAT/SAT Considerations

For many projects (especially single equipment) the SAT may constitute the majority of the Commissioning activities. When FAT's (usually a business decision) are provided, SAT's can have a reduced regimen; however, this must be carefully thought out when Enhanced elements are included.

Typical FAT/SAT considerations may include the following, many of which are good candidates for Enhanced classification. (Note: Prime potential candidates to include Enhanced documentation are noted by (E))

- Functionality –operate equipment/system during testing (E)
- Alarms and safeties
- PLC/Control thorough checkout/challenge (E)
- Utilities (E)
- Maintenance needs
- Calibration (E)
- Labeling
- Training and turnover (E)

Commissioning Test Plans

Commissioning Test Plans may be needed to supplement SAT's and to Commission in an integrated setting, many elements of which may be good candidates for Enhanced designation. This is not to be confused with a Commissioning Plan, which is the umbrella or overall document. First, the following are *Inspection* (Supporting IQ) questions that must be answered as applicable and included in a Commissioning Test Plan:

- Was specified equipment/systems installed? (E)

- Installed correctly?
- Proper utilities? (E)
- Appropriate human interface?
- Safety/environmental/ergonomics?
- Documentation (user manuals) and other closeout needs completed? (E)
- Training of user personnel completed? (E)

The Commissioning Test plan also includes *Testing* Considerations that support OQ, which may answer the following questions as applicable:

- Does the equipment or system perform as specified? (E)
- Does it deliver URS/FRS or BOD (Basis of Design) requirements (or other Acceptance Criteria)? (E)
- Does it operate safely and produce safe results? (E)
- Does it properly function in an integrated setting? (E)
- Calibration (E)

Self-Contained Commissioning Checklists are useful for small projects where Commissioning Plans and Test Plans are not warranted. These are useful for small work where the complete Commissioning exercise can be accomplished on a succinct document. Again, *InVEST* wisely – don't do more than is needed. These checklists can be enhanced, and may include the following:

- Verify item specified was installed (E)
- Utility connection (E)
- Functionality checkout (E)
- Verify calibration completed (E)
- Verify closeout documentation completed (E)
- Verify training or orientation completed (E)
- CMMS entry (E)
- Other internal requirements (E)

Impact Assessments

Before drafting the Commissioning or final Qualification documentation, it is essential to perform an Impact Assessment. This process is well defined in ISPE materials. An Impact Assessment is crucial because it enables Qualification and Commissioning to focus on what is important. This focus also allows Commissioning to minimize Qualification while supporting its success. Qualification is minimized both by breadth of coverage, and benefits from Commissioning Enhanced documentation. Only cGMP Direct Impact equipment/systems require validation, and other aspects (Indirect Impact and No Impact) can be Commissioned in accordance to Good Engineering Practice in lieu of an overstated Qualification protocol.

***SMART* Commissioning and Qualification Acceptance Criteria/Ranges**

Also important in synergizing Commissioning and Qualification and increasing the likelihood of success in both is to assign *SMART* acceptance criteria. The acrostic *SMART* is as follows:

- Sensible: Be practical in assigning Validated ranges. Is the range really needed to ensure product quality? What does the product really require? Can

the equipment deliver this range consistently? Do the ranges also meet business/payback objectives?

- Maintainable: Will the range be maintained over time?
- Accurate: Is the range measurable? Are realistic tolerances considered? Can equipment consistently meet this target?
- Range: Is a reasonable range assigned? Rarely can point values be maintained. Design values must be well within Validated ranges to minimize nuisance alarms and Quality intervention.
- Traceable: Has/can the attainment of the range be verified and documented? Can it be verified later?

ISPE Baseline Guides present Design, Normal Operating, and Operating Ranges. (Also see Figure 3 for a graphical illustration.) *Design* is the value to which the equipment or system is designed. Normal Operating is the range, wider than Design, at which a pre-alert could occur for maintenance notification – this could be the Commissioned range (in some instances you might want to make the Commissioning range even narrower.) Even wider is the Operating or Validated Acceptance range. It is crucial to have a less stringent Validated (Operating) range than the Commissioned (Normal Operating) range, both of which should be less stringent than the design range or value. For example, if the desired Validated (Operating) range of a filler may be 300 vials or bottles per minute, the Commissioned (Normal Operating) might be 320, and the Design 340. If the Operating range was set at the design value or range, occasional failures would likely occur. (For this example, don't forget to also check at the lower speed during Commissioning – some equipment may not operate properly at slow speeds.) Buffers should be provided. Remember, once Operating or Validated ranges are assigned, there could be a Quality intervention required when there are excursions – obviously, this should be avoided. Ideally, acceptance criteria should be determined early, and be a part of the FRS against which final Commissioning and Qualification documents are drafted.

Specific Examples

This course to this point has argued the need for Commissioning, the need to *InVEST* wisely and set *SMART* acceptance criteria, and utilize Enhanced commissioning documentation in the Qualification effort. The remainder of the course will cover examples of typical Commissioning considerations and approaches for GMP Technology and GMP Utility systems. Obviously, any application could differ, requiring more or less of the listed considerations.

Technology systems include Computer/Control Systems, Packaging/Fill, and Process/Manufacturing. Typical cGMP Direct Impact Utilities could include HVAC, Purified (or WFI) Water, Compressed Air, and others (site/product specific). As before, prime potential candidates for Enhanced elements are marked with (E). URS/FRS (or Acceptance Criteria) elements commissioning verification are indicated, as well as possible Commissioning vehicles (i.e. documents). Given the complexity of the various systems or with some combinations of systems, overall Commissioning Plans should also be considered where needed.

Computer/Controls

- URS/FRS Elements or Acceptance Criteria Commissioning Verification
  - Hardware/Software verification and testing (E)
  - Security (E)

  - Part 11 issues (E)
  - Functionality/challenge (E)
  - Alarms (E)
  - Trends (E)
  - Data verification and integrity (E)
  - Human interface/graphics (E)
  - Backup (E)
  - Input/output verification (E)
- Include verification of items being controlled - somewhere! (E)
- Commissioning vehicle: Most commissioning activities (inspections/tests) can be captured in FAT/SAT (E)

Packaging/Fill

- URS/FRS Elements or Acceptance Criteria Commissioning Verification
  - Verify specified equipment installed (E)
  - Utility connections (E)
  - Instrumentation/calibration (E)
  - Controls interface (E)
  - Proper installation/alignment (E)
  - Materials of fabrication (E)
  - Safeties/ergonomics
  - Additional for sterile (E)
  - Run product!
    - Line Speeds (E)
    - Labeling (E)
    - Tolerances (E)
    - Proper Product Encapsulation (E)
    - Finish Form Acceptance Criteria (E)
    - Cartoning
- Commissioning vehicle:
  - Most commissioning activities (inspections/tests) may be captured in FAT/SAT (E)
  - Supplement with Commissioning Test Plans (E)
  - Great opportunity for Qualification synergy (E)

Process/Manufacturing

- URS/FRS Elements or Acceptance Criteria Commissioning Verification
  - Verify specified equipment installed (E)
  - Utility connections (E)
  - Proper installation/alignment (E)
  - Materials of fabrication, passivation (E)
  - Operating parameters (flow rates, mixing, heating, cooling, vacuum, reactions) (E)
  - Adjustments, balancing, tests (pressure, etc.) (E)
  - Instrumentation/calibration (E)
  - Safeties/ergonomics
  - Acceptable product (E)

- Commissioning vehicle: Commissioning Plan, Commissioning Test Plans, and FAT/SAT on individual major equipment when needed. If project essentially consists of a single equipment, FAT/SAT could satisfy most of (if not all) the Commissioning Test/Inspection activities. (E)

HVAC

- BOD/URS/FRS Elements or Acceptance Criteria Commissioning Verification
  - Temperature (E)
  - Relative Humidity (E)
  - Particle Counts (E)
  - Differential Pressure (E)
  - Air Change Rate (E)
  - Laminar flow issues (E)
  - Room Classifications (E)
- Commissioning vehicles
  - Pre-Commissioning Activities (FAT/SAT): Airhandler (AHU) and Building Management System (BMS) (E)
  - Major equipment factory start-up (Setting-to-work, etc.) (E)
  - Commissioning Test Plan (E)
    - Sequence of Operation Challenge (E)
    - Standard Tests and Inspections (such as IO verification, Calibrations, etc.) (E)
    - Test and balance (E)
    - HEPA Filter certifications (E)
    - Trends (E)
    - Viable/Non-viable counts (E)
    - Inspection activities (E)

Purified Water

- URS/FRS Elements or Acceptance Criteria Commissioning Verification:
  - TOC's (E)
  - Conductivity (E)
  - Production rates (E)
  - Micro (E)
  - Other (E)
- Commissioning vehicles
  - FAT/SAT of equipment (E)
  - Commissioning Test Plan:
    - Challenge installed system to meet acceptance criteria, alarms, safeties, automatic operation, etc. (E)
    - SCADA/PLC checkout (E)
    - Trends (E)
    - Inspection activities (E)

Compressed Air

- BOD/URS/FRS Elements or Acceptance Criteria Commissioning Verification:
  - Viable and non-viable particle counts (E)
  - Moisture (dew point) (E)

- Flow rate/Pressure (E)
- Oil free? (E)

- Commissioning vehicles
  - Pre-commissioning: SAT's of major equipment (E)
  - Commissioning Test Plan (E)
    - Challenge installed system to meet acceptance criteria, alarms, safeties, automatic operation, etc.
    - Trends
    - Inspection activities

COURSE SUMMARY

Commissioning Documentation and Qualification are symbiotic when properly applied. Qualification helps define what is important for Commissioning to emphasize, while Commissioning minimizes the Validation effort and supports its success. Remember to "*InVEST*" wisely (Integrate Commissioning with Qualification, Verify, Ensure Qualification Success, Sensible, Traceable/Document it) and set *SMART* Acceptance Criteria in the beginning (Sensible, Maintainable, Accurate, Range, Traceable). To get more information, see various trade organizations (ISPE, ASHRAE, etc.). Tried and tested GEP approaches and documents are available, and translate easily into documented GEP Commissioning and Enhanced Commissioning. Of course, ISPE has many publications available, including the excellent "Commissioning and Qualification" Baseline guide. But mostly, learn by doing it!

Figure 1 – A Commissioning Documentation Hierarchy

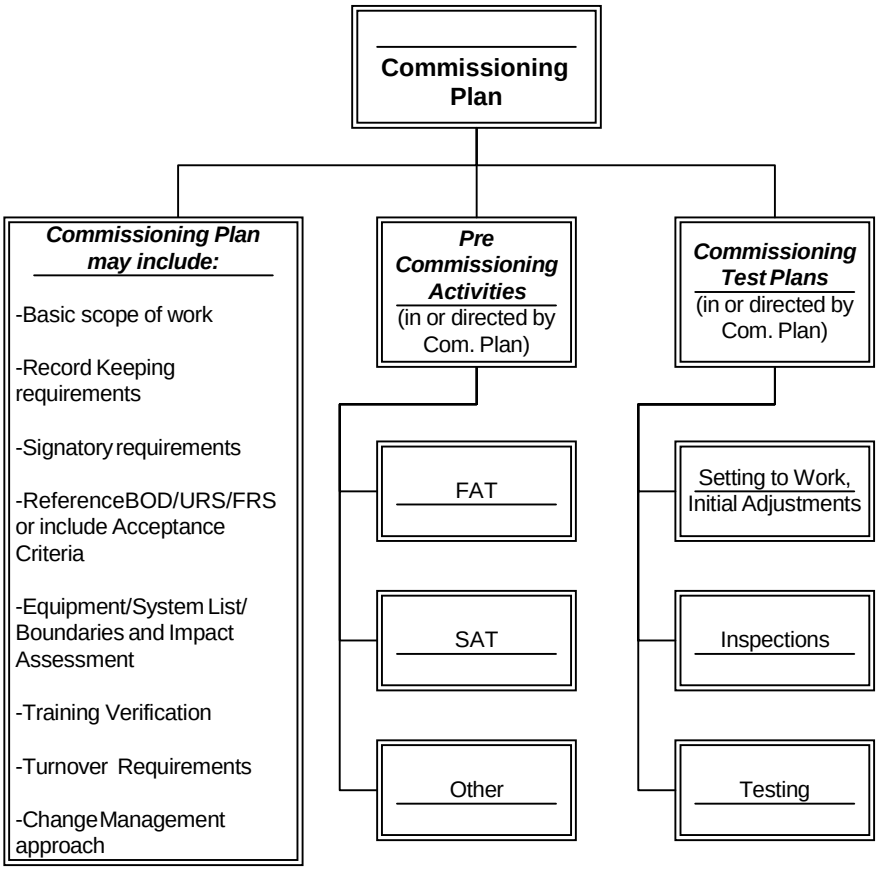
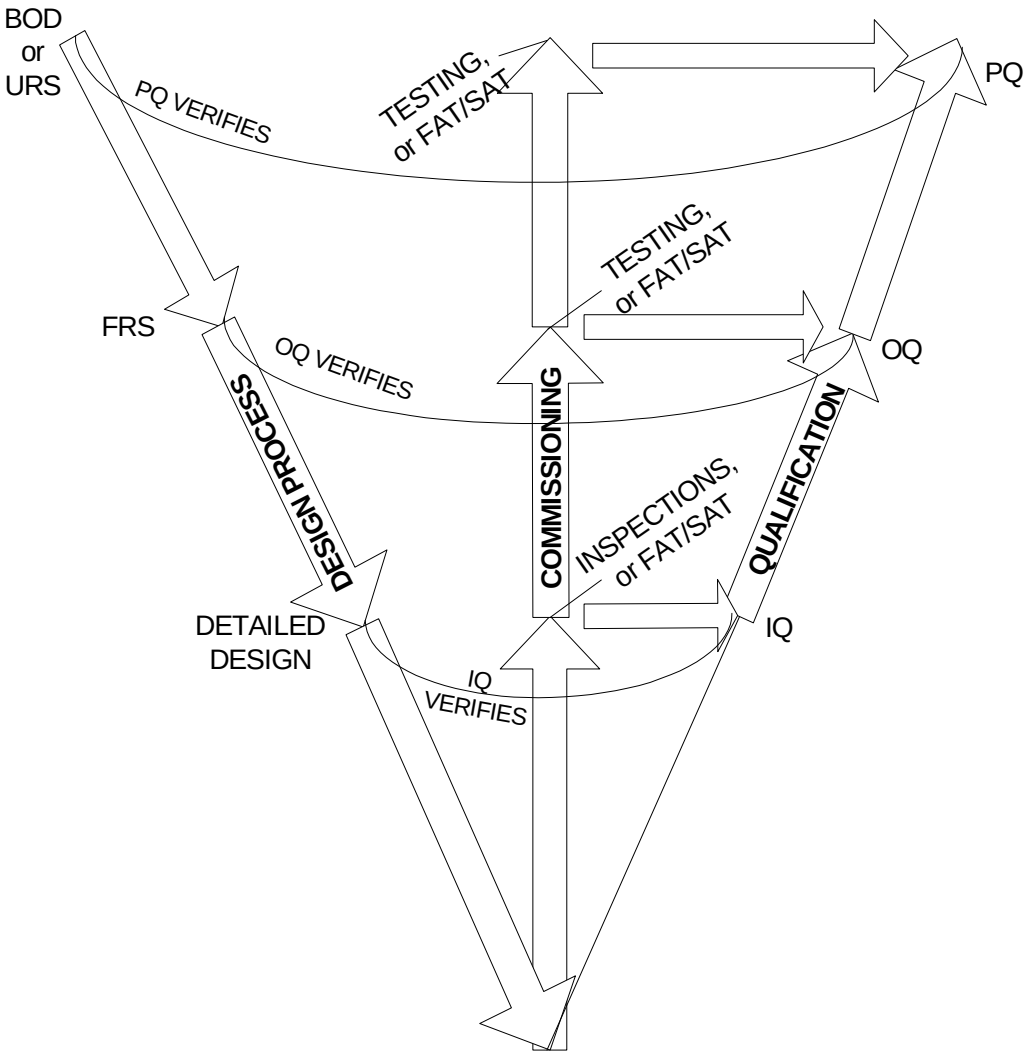


Figure 2: The "W" Model



THE "W" MODEL

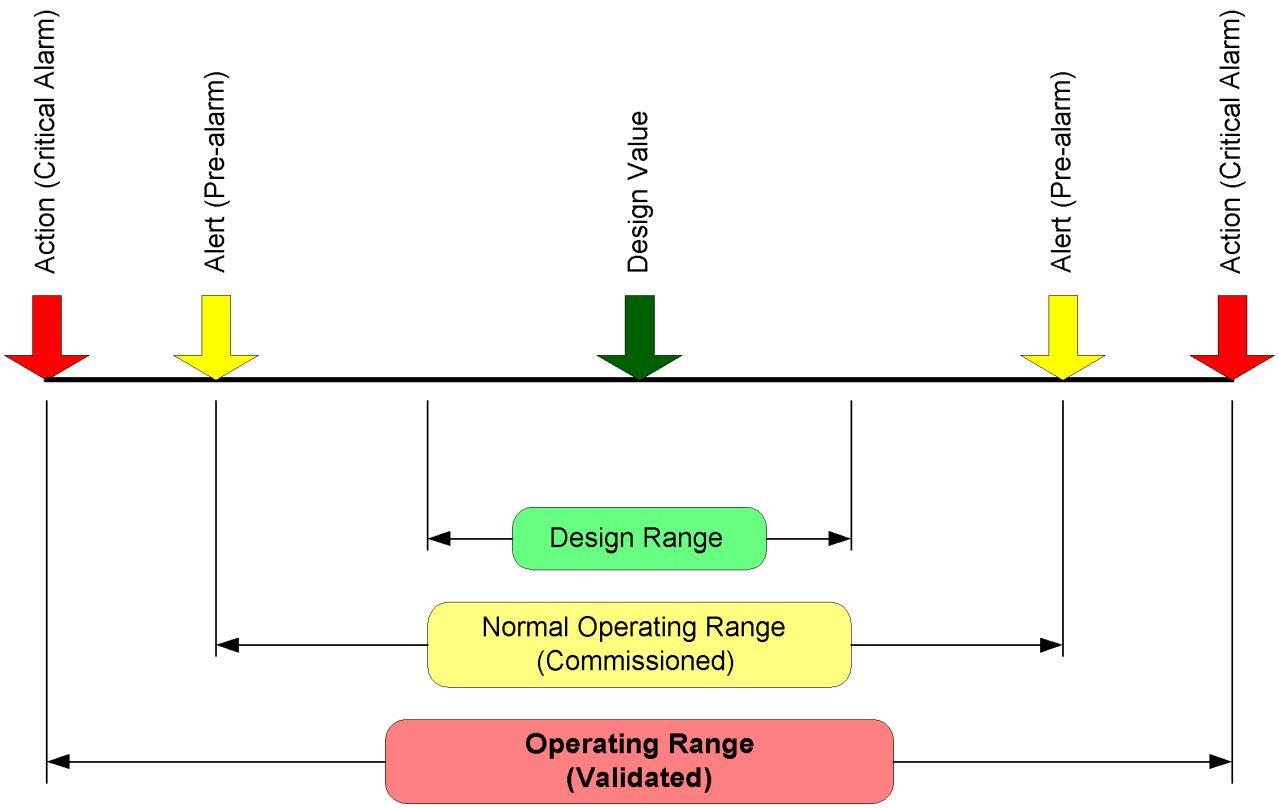


Figure 3: Design Conditions Chart

References

[i] FDA Guidelines on General Principles of Process Validation, May 1987

[ii] Reference: "Pharmaceutical Engineering Guides for New and Renovated Facilities – Volume 5 – Commissioning and Qualification," Glossary

[iii] Reference: "Pharmaceutical Engineering Guides for New and Renovated Facilities – Volume 5 – Commissioning and Qualification," Page 127