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## Developing a Sound Process Validation Strategy

David M. Fetterolf

### ABSTRACT

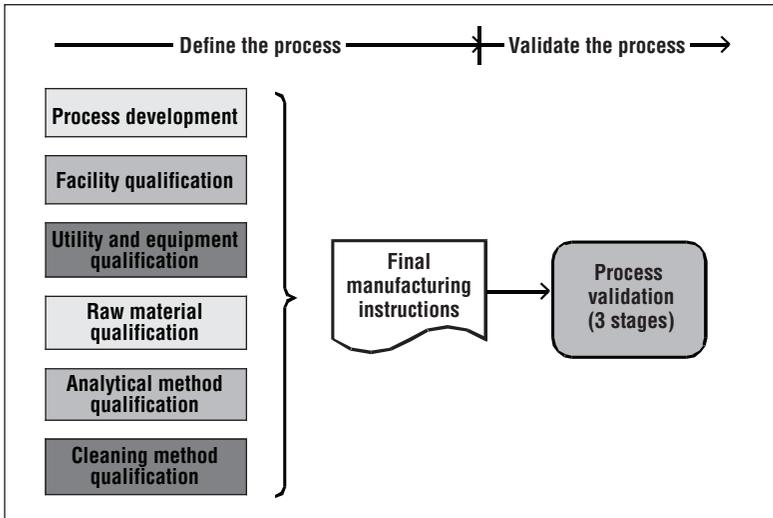
The amount of development and supporting activities leading to process validation requires the allocation of an enormous amount of both internal and external resources. Consequently, time and budgetary constraints rarely allow for repeating any portion of the required activities. Development of a sound process validation strategy, a major portion of which involves defining the process to be validated, will help define the path, focus the resources, and drive the prevalidation exercise to meet every milestone.

**D**eveloping a comprehensive process validation strategy early in clinical development is critical to the execution of a successful validation program, and should also be consistent with the FDA's Quality by Design initiative.<sup>1</sup> Development and process support activities leading to process validation require the allocation of internal and external resources. Because of the nature of validation requirements, partnering with external experts in this area can prove to be an important decision to complete the program successfully. Time and

budgetary constraints do not allow for repeating required activities, so all external resources need to be proven in their experience. Development of the validation strategy, mainly by defining the process to be validated, will help define the development path, focus the resources to execute the key studies, and drive the validation exercise.

The validation strategy is captured in a document that defines the process and activities related to each stage of process validation.<sup>2</sup> The requirements of the strategy are defined in the following sections.

**David M. Fetterolf** is the associate director of manufacturing at BioTechLogic, Inc., Glenview, IL, 919.854.0785, dfetterolf@biotechlogic.com.

**Figure 1.** Process definition and validation flow

## PROCESS DEFINITION

The key to executing a successful validation is defining the exact process to be validated. Each parameter included in the manufacturing instructions must have a documented control space that has been established based on experimental or manufacturing data, as well as the quality of the starting materials and the capability of the operators, facility, equipment, and utilities. This requires an evaluation of historical data, deviations, and planned experiments during clinical batches. Figure 1 depicts the flow of the process definition and validation activities.

To ensure that validation activities do not need to be repeated, the areas listed in Figure 1 should be defined and qualified by a parallel path.

The activities related to utility and equipment qualification can be summarized in a high-level list of utilities and equipment specific to the manufacturing process.

## FACILITY

The facility should be qualified for manufacturing the intended product and appropriate for the respective phase of development.<sup>3</sup> Before implementation of a process in any developmental phase, it should be verified that procedures are in place for quality systems management such as facility cleaning; gowning; the flow of personnel, equipment, and material; environmental monitoring; calibration; change control; and preventive maintenance. A strategy for open versus closed processing steps should be developed so that appropriate environmental and process controls can be established. More stringent environmental requirements are implemented as the product moves from the fermentation and cell culture

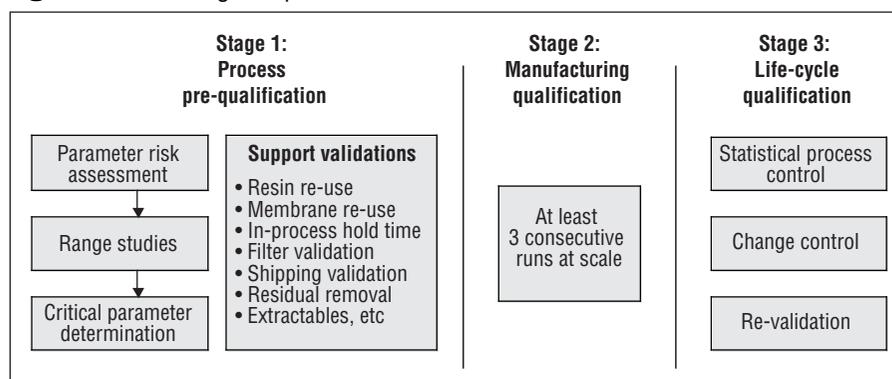
area through isolation and purification. For example, whole cells and viruses are typically manipulated in the upstream areas and completely removed from the product stream before entering the purification area. Often, this is ensured by adding a filtration step between the isolation and purification suites. Additionally, controls are increased throughout the course of purification. For example, during a final chromatography step, additional environmental monitoring can be performed, and all connections, fraction collection, sampling, and container closure can be performed under a laminar flow hood.

These facility prevalidation activities are documented in reports and outlined in facility flow diagrams that can be used to show control of the environment, product, personnel, material, and contamination. A comprehensive list of supporting information related to facility control can be used for regulatory submissions and as references during pre-approval inspection (PAI) readiness activities and the PAI.

## UTILITIES AND EQUIPMENT

The installation and operation of all utilities should be qualified before use in the process through commissioning, design qualification (DQ), installation qualification (IQ), and operational qualification (OQ) studies. When the actual process is transferred to production, a detailed engineering review ensures that all of the processing ranges are specified

**Figure 2.** Three stages of process validation



in the user requirements, commissioning documents, and those qualified during the IQ and OQ studies. Acceptability of utility performance through points of use should be confirmed through performance qualification (PQ) studies. Although changes are made throughout the course of development and process optimization, documentation reviews can be continually performed as part of the change control program to ensure the process is operated in the previously qualified ranges.

All processing equipment should have the appropriate level of installation and operational qualification performed. All processing ranges are verified to be in the qualified ranges of the equipment and all contact surfaces are compatible with product or process solutions.<sup>4</sup> Documentation reviews can be continually performed as changes are made to ensure the process is operated in the previously qualified ranges. During process validation (or sooner if resources allow) PQ studies on critical pieces of equipment are performed to ensure the equipment is appropriate for the

specific product being manufactured.

The activities related to utility and equipment qualification can be summarized in a high-level list of utilities and equipment specific to the manufacturing process, which includes references to equipment and system numbers, calibration, and preventive maintenance schedules and qualification reports. As with facility prevalidation, this list can be used for regulatory

submissions and used as references during PAI readiness and the PAI.

## RAW MATERIALS

Multicompendial grades for raw materials should be used and in-house specifications should be put in place as early as possible in the development process. Raw materials should be sourced from approved vendors or testing should be performed according to the Certificate of Analysis (C of A) until vendor qualification is complete.<sup>5</sup> Animal-derived materials should not be used. For critical raw materials, it is beneficial to qualify two sources to ensure supply, unless these materials are commonly used and readily available.

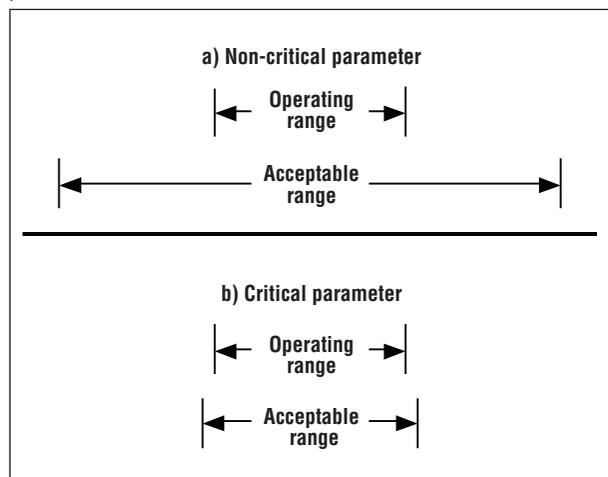
The details of all raw material qualifications are summarized in tables that include: where the raw materials are used in the manufacturing process, criticality, grade requirements, vendor information, and in-house specification references. This list can facilitate the generation of information included in the chemistry, manufacturing, and controls (CMC) section of the submission documents.

## ANALYTICAL METHODS

Although the development of analytical methods usually parallels process development, methods should be qualified (e.g., linearity, accuracy, precision) as early as possible to ensure the validity of results obtained during process optimization studies.<sup>6</sup> Understanding concentration and purity or impurity methods, such as ultra violet (UV) and high performance liquid chromatography (HPLC) at an early stage is important so that variability can be taken

**Although not necessary, analytical methods used in critical parameter determination studies such as design of experiments and one-factor-at-a-time should be validated.**

**Figure 3.** The differences between noncritical and critical parameters.



into account during the analysis of data from development studies.

Although not necessary, analytical methods used in critical parameter determination studies such as design of experiments (DOE) and one-factor-at-a-time (OFAT) should be validated.<sup>7</sup> At a minimum, these methods need to be qualified to ensure the data generated is meaningful for making decisions on the criticality of parameters. As mentioned above, this will give greater assurance in the results, and can sometimes reduce the amount of replicates needed during range-finding experiments. Similarly, these methods can also be used during many of the Stage 1 (Figure 2) supporting validation activities such as the in-process hold time study.

Once analytical method qualification and validation are complete, all changes are assessed for effect on the respective method as part of the change control program, and revalidation is performed as needed. A list of methods and qualification and validation report references is a useful tool that can be used during drafting of the submission.

### CLEANING METHOD QUALIFICATION

The same approach can be taken for cleaning equipment and components (e.g., resins, membranes) that is taken with cleaning of areas in the facility (i.e., floors, walls, ceilings). The cleaning agents used should be assessed for both compatibility and effectiveness. To assess compatibility, studies to show that the cleaning method do not adversely

affect the contact surfaces should be performed.<sup>4,8,9</sup> To evaluate cleaning effectiveness, the cleaning method should be challenged with various types of organisms (e.g., gram-negative, gram-positive, yeast, spore former,)—preferably environmental isolates—to show the objective of cleaning is met. Because it is practical to perform cleaning validation during the process validation batches, it is important to ensure that all cleaning methods are appropriate for use and qualified to appropriate limits.

### STAGES OF PROCESS VALIDATION

The three stages of process validation are shown in Figure 2. Stage 1 comprises pre-qualification activities used to generate the list of critical process parameters used in the manufacturing qualification protocol. Stage 2 is the execution of the manufacturing qualification and stage 3 is ongoing process monitoring through life-cycle qualification.

Stage 1 entails performing process understanding studies to establish the design space for all process parameters, determining which parameters are critical, and executing supporting validation studies. Because the pre-qualification activities involve the evaluation of process parameters and their ranges, they will not be meaningful until the manufacturing instructions are finalized. The key to meaningful pre-qualification studies is a process pre-qualification plan that is based on a well-defined manufacturing process. This is completed by a thorough analysis of the potential study and how it relates to the desired quality attributes in the finalized process. For example, chromatography resin re-use (lifetime) studies should only begin when the complete chromatography cycle (sanitization, equilibration, loading, elution, regeneration, cleaning, and storage) and the procedure for the manufacture of the starting material (i.e., load) are defined.

The parameter risk assessment and range-finding studies should only begin when a complete list of parameter ranges from the manufacturing instructions is compiled. Therefore, the final manufacturing instructions must be in place for the assessment to be meaningful. Each parameter is assessed for its potential to affect (positively or negatively) the applicable process controls or

quality attributes. Each parameter is given a numerical rating based on the likelihood and potential magnitude of impact (e.g., failure modes and effects analysis, FMEA), which often includes an evaluation based on scientific rationale of the control mechanism.<sup>1,10</sup> The parameters that have the highest likelihood and potential to affect the process are entered into range-finding studies (e.g., DOE, OFAT) and the outcome for each studied parameter is the relationship between its normal operating range (control space) and its proven acceptable range (design space).<sup>11,12</sup> The normal operating range is the range at which the parameter is typically controlled during routine operations and is usually the range found in the manufacturing instructions. It takes into account the minimum and maximum values tested during initial development and a review of process history, which shows the capability of the operators, facility, equipment, and utilities. The proven acceptable range is defined by the minimum and maximum values for each parameter found during the range-finding studies. Range-finding studies are often designed such that the ranges studied are 2x or 3x the normal operating range.

The criticality of each process parameter is determined by analyzing the relationship among the operating range, acceptable range, and the failure limits. In general, if the acceptable range is more than 2x the operating range (Figure 3a), then the parameter is considered non-critical.<sup>12</sup> This suggests that the parameter can be controlled tightly by the operator or automation system, and even a significant deviation from the set point would not affect the manufacturing process. Conversely, if a parameter's operating range is less than 2x its acceptable range (Figure 3b), this indicates that a deviation to the normal operating range would likely result in a failure to meet an in-process control, in-process specification, or failure of the batch. This parameter would be deemed critical. This analysis is continued until the criticality of all parameters is evaluated, and their actual impact on the process has been determined.

Stage 1 is also the stage in which supporting validations are performed. In some circumstances, not all supporting validation studies are completed before stage 2; however,

these studies still fall in the category of process pre-qualification. For example, during shipping validation studies, the packaging and shipping processes are defined, qualified and validated. These studies could be performed after stage 2 and use the shipments of the material produced during the manufacturing process qualification to confirm shipping conditions. In this example, the packing configuration, procedures, laboratory simulations and study design would be completed in stage 1, but the actual shipment verification would be performed after stage 2 is complete.

Stage 2 entails the performance of three consecutive runs at the intended commercial scale.<sup>13</sup> The manufacturing process qualification is performed under a prospective protocol using the appropriate output and results from the stage 1 studies (i.e., critical parameters), in-process controls and specifications, and any additional criteria specific to the process.

Stage 3 is the ongoing assessment of process performance through life cycle qualification and management of process changes.<sup>14</sup> Criteria are outlined in a prospective life-cycle qualification protocol and appropriate standard statistical process control (SPC) techniques (control charts, ANOVA, Western Electric Tests, etc.) are used to confirm ongoing acceptability of process performance.<sup>15</sup> Critical process parameters are monitored routinely during batch release and compiled with the SPC data for annual reporting. After validation, all changes made to manufacturing procedures are assessed for impact to the validated process, and revalidation is performed as needed.

## CONCLUSION

Developing a process validation strategy early in clinical development is critical to the execution of a successful validation program because process validation is more than just running three consecutive batches under protocol. The magnitude of activities leading to the qualification batches requires resources and expertise that far exceed those in place for routine development and production. However, if a sound strategy is developed for process definition and completion of the commercial batch at an early stage, the risk of repeating the validation exercise is greatly reduced. With the proper resources put in place to execute the comprehensive strategy, there is the additional benefit of generating

complete and thorough lists of documents, reports, flow diagrams, and other references that will facilitate regulatory submission writing, pre-approval inspection readiness activities, and can be used to support the pre-approval inspection. ♦

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**BioTechLogic**  
Manufacturing Management

*For more information, contact:*

**David Fetterolf, Associate Director of Manufacturing**  
919.854.0785, [dfetterolf@biotechlogic.com](mailto:dfetterolf@biotechlogic.com)

**Peter Dellva, Head of Business and Finance**  
847.730.3475, [pdellva@biotechlogic.com](mailto:pdellva@biotechlogic.com)

[www.biotechlogic.com](http://www.biotechlogic.com)