# *Process Validation: Batch Size Increase in the Downstream Process*

*Louise Burgos Reyes*
*Master in Manufacturing Competitiveness*
*Rafael Nieves, Pharm D.*
*Industrial and Systems Engineering Department*
*Polytechnic University of Puerto Rico*

***Abstract*** — The worldwide demand for the drug substance has increased by 30%. The drug substance is an ingredient used in the final product formulation, which later becomes the medicine that will reach the patients. The challenge that is faced is production limitations, which is driven by customer demand increased compared to previous years. Engineering uses historical data from the process to analyze and forecast the impact of the improvement. Then, the team captured key metrics to measure the impact of the implementation to validate if it was providing the planned yield. As a result of the implementation and validation strategy, the findings showed that flexibility to change different parameters and equipment functionality by reducing the amount of testing to confirm that the process fulfills the acceptance criteria included in the testing protocols, which includes Operation Verification, Performance Verification and Process Validation.

***Key Terms*** — Batch Size, Capacity increase, Drug Substance (DS), Process Validation (PV).

## PROBLEM STATEMENT

The current state of the downstream process was established in the first Process Validation (PV) that was conducted. The validated batch size is approximately 25 kg, which translates to one week of production. Functionally, the final step combines upstream batches of different upstream processes into a single batch. The demand for the Drug Substance (DS) has increased, hence the need to identify different areas for improvements. The Process Validation (PV) will allow the system to increase the batch size from 25 kg to 400 kg. This will allow the company to achieve the production target, but more importantly, support new patients, which is the main goal. The Validation approach for these improvements is simplified by testing only critical parameters and not all the parameters for each process step. This approach simplifies the validation process significantly. The proposed changes in the different steps and the risk to the patient's safety and regulatory affairs have been evaluated. Based on the risk evaluation, it was determined that conducting three Operation Verification (OV), one Performance Verification and a total of three GMP batches to complete the Process Validation.

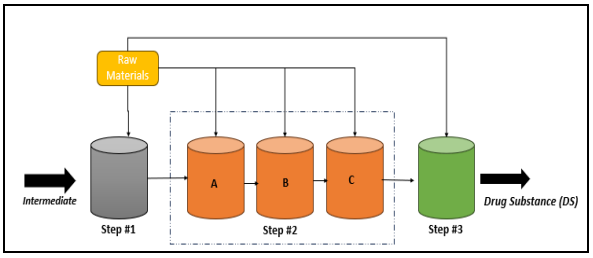


**Figure 1**
**Downstream Process Overview**

### Research Description

The pharmaceutical company's main goal is to manufacture different types of medicine to improve, extend and/or cure diseases for patients. This is a daunting goal that requires different types of processes and systems to be able to manufacture a lot of medicine. This process needs to be precise and controlled since a human person will be consuming the medicine and it could do more harm than good if not controlled correctly.

The United States (US) government has the goal to make sure all companies operating are following current Good Manufacturing Practices (cGMP) to protect the civilians. The agency that is dedicated to maintaining control and assuring that the product is manufactured per guidelines is the Food and Drug Administration (FDA). The FDA focuses to control all companies that make human consumption items are manufacturing per standards and there are systems in place to make sure there are little to no

deviations from the process that if not controlled could be life threating to the patient. The FDA has implemented guidelines that manufactures need to adhere by to be allowed to produce in the US with the highest quality possible [1], one of the guidelines is hard requirement of conducting process validations for any new product or major changes.

Process Validation (PV) is "documented evidence that provides a high degree of assurance that process will consistently operate or produce a product meeting its predetermined specifications and quality attributes" [2]. This step is one of the most critical steps in the implementation of a new product, process, or major change, since the company needs to show that they can produce the product and replicate the same results based on the pre-established parameters following a cGMP strategy and guideline to develop procedures, systems and how everything will be tracked. At this step of the process, the company must be able to collect all data that's required for the process and that will be maintained as part of the process approval by the FDA. The intent of the data is to assure that the system is in control and within the approved established parameters that were approved as part of the FDA review and approval. The PV can be broken down into three main stages "Process Development, Process qualification, and continued process verification" [2]. Each of these steps drive a different action in the process. The process development is the foundation of PV since it establishes the needed requirements, systems and data that need to be set and the system will be tested against in the next step. The process qualification will set the protocols and testing requirements, the data capturing by lot and capture any potential deviations that may be in the process. Then, the continued process verification verifies that the system continues to be in control per the established parameters and metric.

The PV is a subset of the full FDA approval but is the process step that serves as foundation for the next steps toward approval. The typical cycle of a product line validation and qualification includes commissioning, equipment qualification, performance qualification, process qualification, and process performance qualification. All these follow a continuous cycle that needs to be conducted on every process change.

The commissioning process is the verification that the equipment ordered was received with no validation conducted. The equipment validation process will verify that the commissioned equipment works as indented. The performance qualification is the process that equipment works with the different manufacturing systems and that it shows data on the parameters. Process qualification is the process of qualifying the process with little to no raw materials, mostly water used at this step. Lastly, the process performance qualification is the process that emulates the real production run to show that the product can be made per the required controls.

## Research Objectives

The purpose of the validation activities is to:

- demonstrate that the manufacturing process, under the given conditions, performs as expected, and is robust and reproducible.
- all acceptance criteria are met.
- the produced batches meet the specifications.
- the purpose of process steps is fulfilled.
- Ensure proper documentation for validation activities.

## Research Contribution

The PV will support increasing the DS output in the manufacturing site. Several parameters' updates will support continuous improvement in all the process steps to achieve a stable process. Automation settings for equipment were optimized to prevent equipment breakdown (critical for the process). Also, parameter tuning was performed to optimize controllers at different process steps. New functionalities were added as a preventive measure to avoid scraping material when the process encounter challenges. This will allow operations to keep the product on a storage tank and continue running the process simultaneously. This means that if there is a deviation or parameter exceedances in previous process step, the material will not be transferred to the last step before having results to ensure the material is within specification. Yield increased is expected in one of the process steps. There are no

changes to supporting systems, raw materials, or utilities associated with this validation.

### System Design and Design Risk Assessment

During design development, the potential risks from changes associated with the changes are evaluated by a cross functional team consisting of process and automation engineers with input from the development resources. Potential risks for each change are recorded and assessed in the validation documentation. To further evaluate the changes, OV testing will be performed in a series of test batches run under the planned change conditions. To mitigate any potential impact to product quality during the evaluation of changes, all test batches will be either restricted for technical use only or rejected. Potential risk to tank cleaning process due to the increased concentration, as well as the resulting increased downstream batch sizes, has been evaluated and addressed. Verification of the impact to user requirements and process performance will be further documented in the execution of a Design Risk Assessment performed during the Design Review (DR).

### Design Review

The purpose of the Design Review is to ensure the design fulfils the overall intent of the changes and ensure all applicable user requirements are met. The design review must cover fulfilment of both critical aspects and other requirements.

### Design Qualification

There is no Design qualification required for this validation since no changes being made impact requirements identified as critical aspects.

### System Verification and Validation Strategy

The process steps in the downstream processes are currently in a Validated State. Process equipment modules and supporting systems have been deemed Fit-for-Intended Use as indicated by the approved System Acceptance and Release Reports. The changes planned for this validation will be implemented and verified then established as the new validated state using PV.

### Operational Verification

OV Test Plans will be performed to verify the changes are implemented correctly and perform as expected. The System Acceptance and Release Report will be approved before releasing the system for PV.

### Performance Verification

There will be one performance verification testing performed as part of the validation activities. The verification will be performed focusing on changes implemented in one of the process steps. This will be completed in parallel with the OVs to maximize the use of downtime.

### Process Validation

Following the conclusion of verification testing, manufacture of at least three consecutive DS PV batches will be performed at an increased feed rate. All batches will be produced using qualified equipment in accordance with approved standard operating procedures. Batches will be executed at setpoints expected to be used for future production. The PV will demonstrate that the manufacturing process is suitable for routine operation by confirming that the process as designed and implemented is robust, performs as expected and consistently can produce a product of the required quality.

### Technical Runs

Run 1 technical batch in all the process steps to confirm that the results are within specifications and the change implementation was successful prior to start Good Manufacturing Practices (GMP) production.

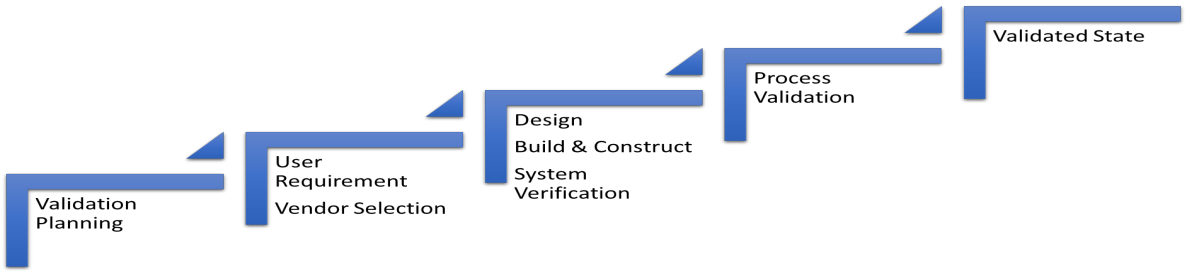


**Figure 2**

**Validation Strategy**

## METHODOLOGY

This process validation covers the validation of three consecutive batches of the DS, using the manufacturing method described in the process validation in manufacturing procedure. The target batch size is increased from one storage tank (approximately 25 kg) to ten (approximately 400 kg) that then constitute a single batch.

### Number of Batches

Three batches are considered sufficient to demonstrate reproducibility and to confirm that the process performs as expected. The production process is well known from production site in China that produces batches up to 500 kg.

### Batch Release

The DS produced during the PV is intended for commercial production and will be released as described in the procedure for batch release. As such, PV batches must be produced in a manner that allows them to be released. The purpose of each step must be fulfilled and all the specification samples must be within specification according to Table 1.

**Table 1**

**Drug Substance Release Specifications**

| Component | Samples | Acceptance Criteria |
|---|---|---|
| Content [mg/mg] | 3 samples per batch | Passed |
| Sum of Impurities | | Passed |
| Water Content (%) | | Passed |
| Total Aerobic Microbial Count (TAMC) | | Passed |
| Total Yeast and Mold Count (TYMC) | | Passed |
| Particle Size Distribution | | Passed |

### Validation Strategy

The scope of the project includes different change requests (CR) in the system, a Validation Plan (VP) was developed to plan the validation activities covering the batch size increase. Change control is handled according to internal procedures. The CR cases for the changes related to the VP must be approved for execution before starting production of PV batches. The Validation Report (VR) must be part of the CR Execution Plan.

### Verification Activities

To test all the changes, a Solvent Run was executed in all the process steps. This allows the engineers to conduct the OVs without using the product. The worst-case scenario was selected, operating close to the upper and lower limits (when applicable). The batch reports and automation parameters were reviewed to ensure compliance with specifications. The results were as expected with exceptional process parameter control. An approved PV protocol is required to continue into GMP production.

### Process Validation

Following the conclusion of verification testing, manufacture of at least three consecutive PV batches will be performed at increased Feed Rate. Up to Ten batches (intermediate from step #2) will be used as input for the final step (step #3). All batches will be produced using qualified equipment in accordance with approved standard operating procedures. Batches will be executed at setpoints expected to be used for future production. The PV will demonstrate that the manufacturing process is suitable for routine operation by confirming that the process as designed

and implemented is robust, performs as expected and consistently can produce a product of the required quality (reproducibility). Specification sampling will be performed in accordance with the approved PV Protocol. Validation activities will be concluded on the PV report.

## Results And Discussion

During PV, samples were taken according to the DS specification. The product containers were sampled as described in the PV protocol. The results of the samples described in the protocol are presented in the sections below. The sampling strategy assesses the process steps by (1) Fulfilment of the acceptance criteria that includes the specification internal release limits (2) Fulfilment of the acceptance criteria that includes DS specification (3) Reproducibility that is shown by batches consecutively fulfilling the acceptance criteria.

The change tested in "step #2, Tank C" concentration allowed to operate an increased number of batches combined into step #3. The increased concentration provides a capacity increase to run 10 batches coming from step #2 per step #3 batch. The outcome will be that step #3 tank is filled close to the maximum working volume. There will be a higher concentration feed which will correspond to approximately 65% larger step #3 batches depending on yield losses and exact volumes.

Step #3 will process at a new target liquid feed rate to reduce batch processing time for the increased batch size.

### Sampling Specification

The specification acceptance criteria for the Drug Substance are shown in Table 2. The data captured the content, sum of impurities, water content, TAMC, TYMC and particle size which all meet specification. All analytical results have met the acceptance criteria. The batch-to-batch variation of process impurities is related to the incoming material to the final steps is consistent within the batches. The process parameter data is within operating range and supports that the incoming material is representative of routine manufacturing material and supports validity of the PV batches. The DS results variance within the batches are all within 3 standard deviations, ensuring the process is in control. Yield increased (Figure 3) after changing several parameters in step 2, the final process of this step performed as expected. The yield is consistent and within the expected range (90-95%). In terms of concentration, 2 samples were analyzed per batch (Figure 4). The results aligned with the yield data collected during and after the PV was conducted. The concentration increased corresponds to approximately 50% larger Step #3 Batches depending on yield losses and exact volumes. The batch will process at a new target feed Rate to reduce batch processing time for the increased batch size of ten batches (approximately 4000 kg).

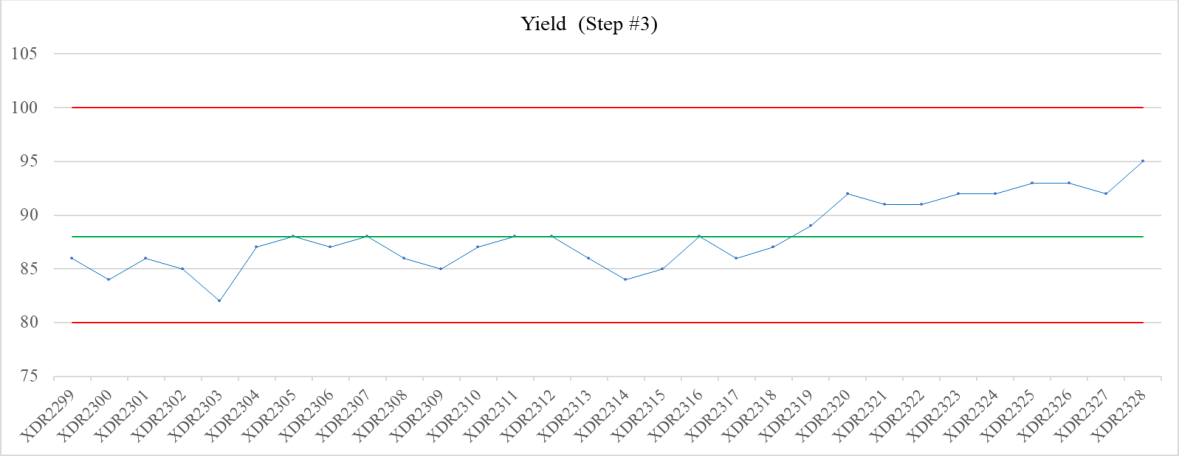


**Figure 3**
**Yield per Batch**

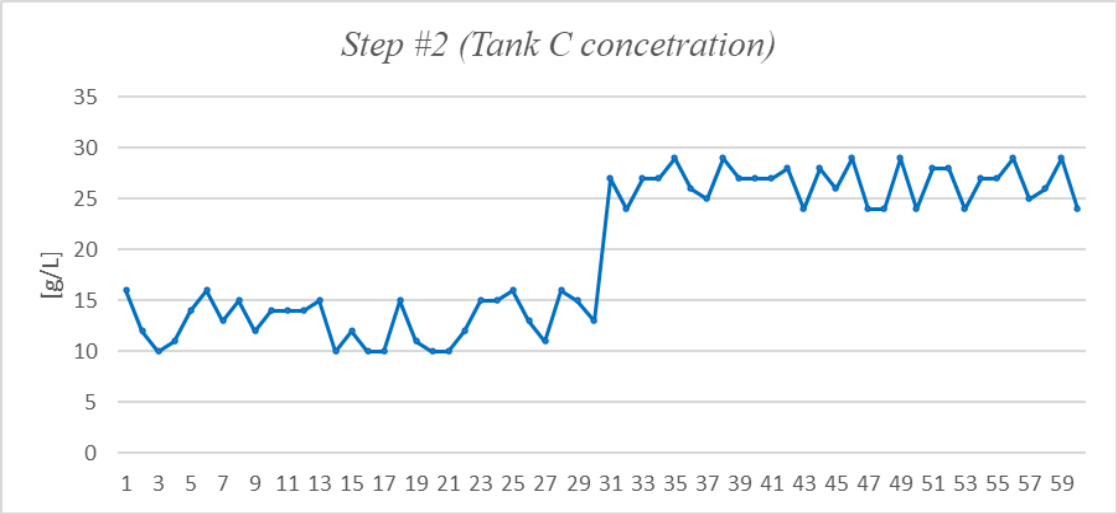


**Figure 3**

**Concentration Increases After Change**

**Table 2**

**Release Specification PV Results**

| | | Results (Passed-1 or Fail-0) | | | | | |
|---|---|---|---|---|---|---|---|
| **Batch IDs for PV** | **Sample #** | **Content [mg/mg]** | **Sum of Impurities** | **Water Content (%)** | **Total Aerobic Microbial Count (TAMC)** | **Total Yeast and Mold Count (TYMC)** | **Particle Size Distribution** |
| XDR2321 | 1 | Passed | Passed | Passed | Passed | Passed | Passed |
| | 2 | Passed | Passed | Passed | Passed | Passed | Passed |
| | 3 | Passed | Passed | Passed | Passed | Passed | Passed |
| XDR2322 | 1 | Passed | Passed | Passed | Passed | Passed | Passed |
| | 2 | Passed | Passed | Passed | Passed | Passed | Passed |
| | 3 | Passed | Passed | Passed | Passed | Passed | Passed |
| XDR2323 | 1 | Passed | Passed | Passed | Passed | Passed | Passed |
| | 2 | Passed | Passed | Passed | Passed | Passed | Passed |
| | 3 | Passed | Passed | Passed | Passed | Passed | Passed |

### Reproducibility

All results are within the specified limit to demonstrate reproducibility according to internal procedures. There is minimal variation from batch to batch as well as within a batch for all analyzed test results. Sampling data is consistent within each batch and across all three batches which demonstrates that the process performs in a robust and reproducible manner capable of producing the DS.

## Conclusion

The three PV batches (XDR2321, XDR2322, XDR2323) were executed successfully and according to the PV protocol. Analytical data was collected from the product containers and met all acceptance criteria listed in the PV protocol. Similar results at expected levels are seen within the batches and between the batches. The results of the specification analyses are within the internal release limits in the DS. Further, the increased concentration in "step #2, Tank C" and parameter values increased yield by 3% and provided operational stability/repeatability. The comparison of the produced DS data proves that product produced at the manufacturing is comparable to product produced at the existing validated facility in China.

## References

[1] US Food and Drug Administration (FDA), "*Current Good Manufacturing Practice (CGMP) Regulations,"* May 19, 2023 [Online]. Available: https://www.fda.gov/drugs/pharmaceutical-quality-

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