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Sample Size for Tablet Compression and Capsule Filling Events During Process Validation

Naseem Ahmad Charoo [1, *], Mark Durivage [2], Ziyaur Rahman [3], Mohamad Haitham Ayad [4]

[1] Zeno Therapeutics FZ LLC, Alpha Towers, Dubai Internet City, Dubai, UAE
[2] Quality Systems Compliance LLC, Lambertville, Michigan 48144
[3] Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, College Station, Texas 77843
[4] Johnson & Johnson, Dubai Health Care City, Dubai, UAE

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ABSTRACT

During solid dosage form manufacturing, the uniformity of dosage units (UDU) is ensured by testing samples at 2 stages, that is, blend stage and tablet compression or capsule/powder filling stage. The aim of this work is to propose a sample size selection approach based on quality risk management principles for process performance qualification (PPQ) and continued process verification (CPV) stages by linking UDU to potential formulation and process risk factors. Bayes success run theorem appeared to be the most appropriate approach among various methods considered in this work for computing sample size for PPQ. The sample sizes for high-risk (reliability level of 99%), medium-risk (reliability level of 95%), and low-risk factors (reliability level of 90%) were estimated to be 299, 59, and 29, respectively. Risk-based assignment of reliability levels was supported by the fact that at low defect rate, the confidence to detect out-of-specification units would decrease which must be supplemented with an increase in sample size to enhance the confidence in estimation. Based on level of knowledge acquired during PPQ and the level of knowledge further required to comprehend process, sample size for CPV was calculated using Bayesian statistics to accomplish reduced sampling design for CPV.

Introduction

Process validation is establishing evidence that the process consistently produces a product meeting its predetermined specifications.[1] During solid dosage manufacturing, the uniformity of dosage units (UDU) is ensured by testing samples at 2 stages, that is, blend stage and tablet compression or capsule/powder filling stage as these 2 stages represent the potential high risk to this critical quality attribute.

It would be in the best interest of the patient to perform 100% inspection of the entire manufactured lot. However, often 100% inspection is not feasible due to the destructive nature of the testing procedure. Furthermore, 100% inspection would incur very high cost besides being a time-consuming affair. In such cases, the Food and Drug Administration (FDA) recommends that if the results of a process cannot be fully verified by subsequent inspection/test, the process shall be validated with a high degree of assurance.[2] The recent guidance document dissects the process validation activity into 3 stages as shown in Table 1.[1] The tests to be performed and their specifications must be developed during process design stage and must be known before process performance qualification (PPQ).

The sampling plan assumes high importance in that it must demonstrate with certain confidence that a required performance level is achieved by the process. For example, 95% confidence statement would imply that there is only 5% chance that the specifications would exclude the mean of the lot. However, the risks associated with the sampling must be taken into consideration and sample size should be commensurate with the risk to the homogeneity of finished product due to formulation or process parameters. Furthermore, the therapeutic index of the drugs should also be given due consideration. For instance, narrow therapeutic index drugs might warrant stringent process qualification criteria and large sample size.

The United States Pharmacopeia (USP) chapter on UDU <905> mandates sampling 30 dosage units during tablet compression or capsule filling at different time intervals.[3] Note that although this test is a quality control test, it is not uncommon to find companies

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* *Correspondence to:* Naseem Ahmad Charoo (Telephone: +971-4-4310694; Fax: +971-4-3684806).
E-mail address: naseem102@yahoo.com (N.A. Charoo).

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Table 1
Process Validation Stages

Process Stage	Process Design	Process Qualification	CPV
Objective	Define commercial manufacturing process	Design of the facility and qualification of the equipment and utilities and PPQ	Ongoing program to collect and analyze data to assure that process remains in a state of control (the validated state) during commercial manufacture
Execution strategy	Building and capturing process knowledge and understanding • Design of experiments to obtain knowledge on multivariate interactions • Pilot scale to predict performance of commercial manufacturing process	• Effect of the scale-up • Higher level of sampling and testing	Collecting and statistically analyzing quality attributes
Outcome	Establishing a strategy for process control • Material analysis • Equipment monitoring • In-process monitoring	A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected	Data gathered during this stage might suggest ways to improve and optimize the process

using this sample size for process validation. In the first stage, 10 samples are assayed. The acceptance value of these 10 units should be $\leq$L1%. In an event of acceptance value higher than L1%, remaining 20 units are analyzed. The lot passes the uniformity of dosage test if the acceptance value of 30 units is $\leq$L1% and all the individual results fall within the range calculated using L2 factor. For a target mean drug concentration within 1.5% of label claim, the individual units should fall within the 75%-125% range of label claim. However, the USP sampling plan requires no less than 30 samples, which is relatively small and may not provide a confident estimation of the batch in comparison to larger sample sizes in meeting acceptance criteria. Moreover, the acceptance criterion is too wide and might subject patient to high risk in case of narrow therapeutic index drugs.

Recognizing this USP has revised general notices section to state that this test need not be used as a release test and performance of the batch cannot be referenced vis-a-vis this test as the standard applies only to the units tested.[4] However, when tested, the product must pass this test throughout its shelf life. Consequently, FDA also no longer supports USP <905> test for batch release.[5,6] Therefore, sampling plans must be based on statistically valid rationale. Many alternative strategies based on large sample sizes have been proposed that provide statistical assurance that a drug product would meet USP <905> criteria with a certain confidence.[5,7] Yet, most of these approaches do not assess the risk to the patient resulting from the nonhomogeneity of the dosage forms arising due to the formulation and process variables. The aim of this study is to review these alternative sampling strategies and additionally propose a sample size selection approach based on quality risk management principles for PPQ and continued process verification (CPV) stages by linking dosage uniformity to potential formulation and process risk factors. Furthermore, we will explore whether the knowledge acquired during the PPQ stage can be used to accomplish reduced sampling design for CPV.

Modifications to the Withdrawn Draft Stratified Sampling Guidance Document

In 2003, based on the recommendations of Product Quality Research Institute Blend Uniformity Working Group, FDA issued a draft guidance titled, "powder blends and finished dosage units—stratified in-process dosage unit sampling and assessment."[7] The draft guidance was judiciously followed by the pharmaceutical industry until its withdrawal in 2013 as sections V and VII did not represent the Agency's current thinking. Section V of the draft guidance though recommended sampling 3 replicate samples from 10 different locations of the blender, but required only 1 sample per location to be evaluated to assess blend uniformity at stage I. On the other hand, FDA currently prefers analysis of all 3 replicates for each location, allowing variance component analysis of the data for understanding between-location and within-location variability. In section VII, the number of samples and the acceptance criteria were based on the limits provided in USP <905> UDU and as explained previously the chapter provides limited assurance and lacks statistical sampling planning.[8]

To evaluate adequacy of blend uniformity and homogeneity of the finished product in accordance with the current good manufacturing practice, The International Society for Pharmaceutical Engineering (ISPE) blend uniformity and content uniformity group proposed modifications based on ASTM 2709 and ASTM 2810 to the withdrawn draft stratified sampling guidance document to assess the adequacy of blend homogeneity and content uniformity of finished dosage units.[5-9] ASTM 2810 applies the statistical aspects of the methodology prescribed in ASTM 2709 specifically to UDU test, providing thereby higher statistical confidence (e.g., 90%) that future samples will have a high probability (e.g., 95% coverage) of passing the USP <905> UDU test. Furthermore, the recommendations provided in the amendment, like the withdrawn draft guidance document, link blend homogeneity to the content uniformity. The modified approach proposes different sample size criteria for 2 stages, namely process design and qualification and CPV.[5]

During process design and qualification stage, the group recommended to sample 3 replicate samples from 10 different locations in the blender (phase I) and assay only 1 sample per location. The blend is deemed uniform if the blend assay of 10 locations exhibits standard deviation (SD) $\leq$3% of the target. Samples from locations 2 and 3 must be assayed if blend SD is greater than 3.0%. SD of $\leq$3% would qualify the blend as acceptable. If SD is greater than 5.0% of target and if the cause cannot be attributed to sampling or analytical error during investigation and it is likely that product or process is causing high variability, then blend is not considered uniform.[5]

In the second phase, that is, during compression or filling, the group recommended to take at least 3 samples from 40 different locations across the batch. Out of these, 3 samples from 20 locations must be assayed if the SD of blend in phase I is $\leq$3%. The individual values should lie between 75% and 125% of the label claim and comply with a statistical test to assure appropriate level of assurance to comply with USP <905>. If the results do not comply, then 3 units from additional 20 different locations must be analyzed. All the individual results must be within 75%-125% and comply with a