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Scientific rationale for sampling regimen and acceptance criteria of blend uniformity based on Monte Carlo simulation

Shuichi Tanabe [a,b,*], Takuya Miyano [a], Jin Maeda [a], Hiroshi Nakagawa [a], Tomoyuki Watanabe [a], Hidemi Minami [a], Nora A. Urbanetz [b]

[a] Formulation Technology Research Laboratories, Daiichi Sankyo Co., Ltd., Hiratsuka 2540014, Japan
[b] Pharmaceutical Development, Daiichi Sankyo Europe GmbH, Pfaffenhofen 85276, Germany

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ABSTRACT

This study proposes an alternative sampling regimen (number of sampling points, number of samples from each sampling point) and setting of the acceptance criteria for blend uniformity based on a statistical rationale. Currently, the sampling regimen and the acceptance criteria for the blend uniformity test of powder blends are determined according to the withdrawn guidance for industry by the Food and Drug Administration (FDA) and the proposal of the International Society for Pharmaceutical Engineering (ISPE)-sponsored Blend Uniformity and Content Uniformity (BUCU) Group to substitute the withdrawn guidance. However, both approaches lack scientific rationale in their publications. Herein this study addresses the scientific background based on the simulations utilizing the Monte Carlo method, in order to provide a scientific rationale for the sampling regimen and acceptance criteria. False positive probability, defined as the probability of failure to meet the minimum necessary requirement in future samples even when the tested sample satisfies the acceptance criteria in fact were used to evaluate the adequacy of the sampling regimen and acceptance criteria. This study aims at stimulating the discussion about blend uniformity that may ensure a higher quality of pharmaceutical products finally.

1. Introduction

The blending process is one of the common critical manufacturing processes to assure the quality of finished products such as uniformity of active ingredients content in the finished dosage units, defined as content uniformity. In general, samples taken from various points of bulk powder blend are evaluated to estimate the homogeneity of the active ingredients in the powder blend; i.e., blend uniformity. The sampling regimen, which is the combination of sampling points and the number of samples from each sampling point, and the acceptance criteria are the key factors in blend uniformity test. This is because usually the quality of the bulk powder is assured based on the test results of the samples. In the pharmaceutical industry, the discussion for the sampling regimen and the acceptance criteria for the blend uniformity test have been raised recently, initiated by the Food and Drug Administration (FDA). In August 2013, the FDA announced the withdrawal of its draft guidance for industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [1]. FDA's major concern was that Sections V and VII of the withdrawn draft guidance, which had been used as a basis for the sampling regimen and the acceptance criteria of blend uniformity test, no longer represented the agency's current thinking. The agency's recommendation to address the concerns is twofold. First, between- and within-location variability in the powder blend is a critical component of finished product quality and therefore should be evaluated. Second, the procedures and acceptance criteria in USP <905> are not a statistical sampling plan and so the results of the procedures should not be extrapolated to larger populations [1,2]. Considering these points, a systematic sampling regimen for the blend uniformity test is required taking the between- as well as the within-location variability into account, since the within-location variability; i.e., sampling bias, may bias the between-location variability which reflects the true variability of the active ingredient's content in the bulk powder blend. Regarding the acceptance criteria for the samples, the statistical rationale is desired to assure the homogeneity of the bulk powder blend considering the applied sampling regimen.

In 2014, the Blend Uniformity and Content Uniformity Group (BUCU Group) of the International Society for Pharmaceutical Engineering (ISPE) published two papers to propose the modifications to the withdrawn FDA draft guidance [3,4]. The statistical rationale for the proposed sampling regimen and the acceptance criteria for the content uniformity test of finished dosage units are provided in the publications and the ASTM E2709-12 and ASTM E2810-11 [5,6]. However, there is little scientific or statistical rationale for the proposal of the sampling

* Corresponding author at: Daiichi Sankyo Europe GmbH, Pharmaceutical Development, Luitpoldstrasse 1, 85276 Pfaffenhofen, Germany.
E-mail address: tanabe.shuichi.h3@daiichisankyo.co.jp (S. Tanabe).

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regimen and the acceptance criteria of the blend uniformity compared to the content uniformity. In addition, the BUCU Group encouraged other statistical, science and risk-based approaches in their publication. Application of process analytical tools such as in-line monitoring of the blend uniformity throughout the blending process would be one of the alternative modern approaches they had described for example [7,8]. However, not only PAT offering continuous monitoring of blend uniformity but also traditional endpoint controls with higher quality assurance could be beneficial to reduce research and development cost. The aim of this study is to evaluate the usefulness of the Monte Carlo simulation for the statistical rationale of the alternative sampling regimen and acceptance criteria following the BUCU Group's call for other statistical, science and risk-based approaches.

2. Methods

2.1. Acceptance criteria of population blend uniformity—lower probability bound (LB)

In general, content uniformity of the finished dosage units such as tablets and capsules is affected by the four factors: mean concentration of the active ingredients in the powder blend used, uniformity of the active ingredient amount in the powder blend used, mean weight of unit dosage forms, and the weight variation of unit dosage forms. Segregation of the active ingredients content during the unit dosing process such as tableting and capsule filling will be also a factor affecting content uniformity. Therefore, the acceptance criteria of the blend uniformity should be equal to or lower than the acceptance criteria for the content uniformity of unit dosage forms in order to ensure that the tablets manufactured using the powder blend meet the content uniformity test. In addition, since the blend uniformity test is conducted for the samples taken from the population, i.e., bulk powder blend, the acceptance criteria for the samples should be set considering the estimated probability density distribution of the population. Based on this consideration, the minimum necessary requirement for the population blend uniformity, and the acceptance criteria for the samples taken from the powder blend were set as follows:

The minimum necessary requirement for the population powder blend was set such that it will assure that the future samples taken from the population will meet the USP <905> acceptance criteria with the predefined probability at least (lower probability bound (LB)). This is the same requirement for the population drug product content uniformity provided in ASTM E2810, which is the upper limit of the standard deviation (SD) of the assay with respect to the mean assay value. Note that the assay is defined as a percentage of active ingredients' label claim in powder blend, tablets, and finished dosage units. LB = 95% was selected in this study because it is provided in the ASTM E2810 as an example, and commonly used in the regulatory area. At LB = 95%, the upper limit of the assay SD, i.e., homogeneity of the active ingredients, at the mean assay value of 100% is 6.0% [9]. Generally, the target assay value in the blending process is 100%, therefore, the minimum necessary requirement for the population assay SD was set to not >6.0%.

2.2. Estimation of false positive probability based upon Monte Carlo simulation

To compare the adequacy of the sampling regimen and acceptance criteria of samples to assure the population blend uniformity, false positive probability, defined as the probability of failure to the minimum requirement in future samples even when the tested sample satisfies the acceptance criteria, were calculated. The false positive probabilities of the various sampling regimen and acceptance criteria were calculated based upon probability density distributions. As pointed out by the agency, two individual variations, between- and within-location variability, should be considered to estimate the probability density distributions, however, it is difficult to establish the mathematical estimation model of the probability density distribution that has two independent variabilities. Alternatively, the distribution was calculated using the Monte Carlo method. Monte Carlo simulation is widely applied in science and engineering with experiments on random numbers

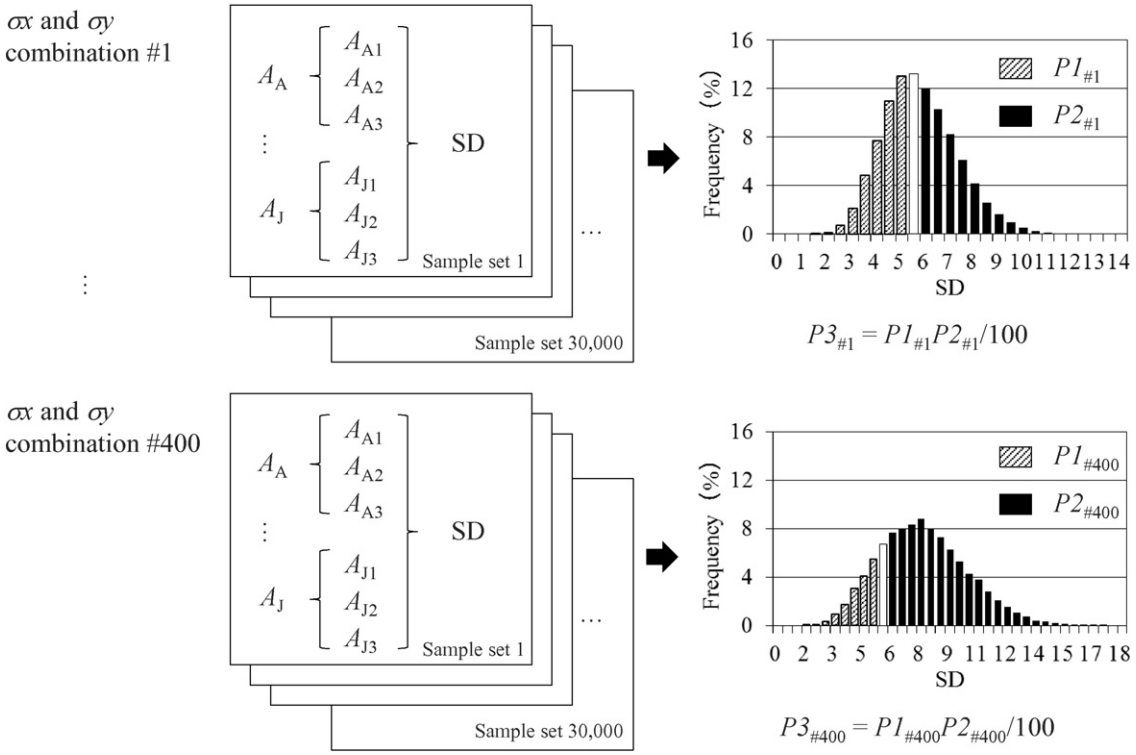

Fig. 1. Algorithm of the Monte Carlo simulation in the case of sampling regimen 10 × 3, acceptance criteria of not >5.0% SD.