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RESEARCH ARTICLE

Determination of the Confidence Interval of the Relative Standard Deviation Using Convolution

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Abstract Coefficient of variation is a widely used measure of dispersion and is important in comparing variables with different units or average values. In pharmaceutical industry, it is termed as the relative standard deviation (RSD) and is used widely to describe blend concentration variability, finished dose variability, dissolution q point variability, etc. Although theoretical formula and simulation methods for the estimation of the RSD confidence interval have been developed in previous literature, they are not well known, and they are either too complex to apply easily or require intensive computation. As a result, the statistical reliability of RSD estimates are rarely evaluated, which increases process risk as well as consumer risk. In this paper, we introduce a novel convolution numerical method for the quick and straightforward estimation of RSD confidence intervals. A standard statistical distribution group is developed, denoted as the Chi-on-Mu-square distribution, which is similar to the widely used Chi-square distribution. Results indicate the Chi-square distribution itself can be a good approximation in the RSD confidence interval calculation, especially when small RSD is expected or large number of samples is involved. The effect of deviations from the normal distribution populations is also discussed.

Keywords Coefficient of variation · Confidence interval · Relative standard deviation · Quality by design

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Introduction

The coefficient of variation estimate is the ratio between the standard deviation and the mean in a sampled population [1]. It is a unit-free measurement of the dispersion of samples. It has been widely applied in many scientific and technical fields (instead of the standard deviation) due to its merit in facilitating scaled dimensionless comparison of variation in variables having different units of measurement and average values [2]. In the pharmaceutical industry, the absolute value of the coefficient of variation is usually termed as the relative standard deviation (RSD), and it is used for multiple purposes, including to describe the variability of the total dose (potency) of active pharmaceutical ingredient (API) in unit dose products, the variability in API concentration in blend samples (blend uniformity), the variations in drug dissolution and bioavailability, etc. For drug safety control purpose, Food and Drug Administration (FDA) regulation sets up limit of 5 % as the target RSD value of the API blend concentration, and 6 % in finished products [3], which makes it one of the most critical performance indices on the manufacturing of solid dosage forms. No standard limit has been adopted for dissolution response, but FDA often uses RSD estimates to examine this issue in modified release formulations. Moreover, standardized confidence intervals are also used in bioequivalence analysis in most of the world.

Despite of the critical application of the RSD in pharmaceutical industry, the reliability of such estimates is rarely examined. Specifically, confidence intervals of RSD estimates are seldom calculated. While it is well known that the confidence interval of the RSD is a function of the number of samples, i.e., that accurate RSD estimates with narrow confidence intervals will be