# ASSESSMENT OF THE INFLUENCE OF THE AVERAGE MASS VARIATION IN TABLETS ON THE FEASIBILITY OF ASSAY ACCEPTANCE CRITERIA

Petrus V.V. [1], Gryzodub O.I. [2], Leontiev D.A. [2], Volovyk N.V. [2]
*[1]National University of Pharmacy, Kharkiv, Ukraine*
*[2]Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines, Kharkiv, Ukraine*
petrus.vasyl@gmail.com

**Introduction**: The presence of variability sources from analysis and technology affecting the variability of assay results necessitates the need to use guard bands to reduce the frequency of false-negative decisions in analysis of finished drug products by an independent laboratory where API content meets the specification requirement but is close to the limits according to the results of the manufacturer's analysis. Such a factor is the variability of average mass (deviation from the nominal value – $\Delta_{oper}$) for the solid dosage form (SDF). The deviation of assay results from the nominal value is directly proportional to $\Delta_{oper}$. $\Delta_{oper}$ is not standardized in the guidance documents; therefore, based on the requirements for standardization of other variability sources, we proposed the maximum permissible value for $\Delta_{oper}$ as 1.17% [1]. It is crucial to evaluate the feasibility of introducing guard bands in practice, considering the proposed standardization for $\Delta_{oper}$.

**Aim of research**: Compile the variability budget for the proposed standardization of main factors influencing assay results. Based on the results obtained during the ongoing verification process at Ukrainian pharmaceutical companies, evaluate the feasibility of guard bands application for assay and the impact of $\Delta_{oper}$.

**Materials and Methods**: Results of critical quality parameters (average mass and assay) for routinely produced 391 batches of 14 SDFs routinely produced and assessed during ongoing process verification by Ukrainian pharmaceutical companies. All SDFs have an average mass ranging from 80 mg to 250 mg. Methods of mathematical statistics (SPhU, 5.3.N.1).

**Results**: It has been shown that the assay result ($\Delta_{\overline{X}}$) is influenced by the main sources of variability, which are standardized as follows [1]:

- Uncertainty of API assay standardization ($\Delta_S$): typically, $\Delta_S \leq 1.0\%$;
- Target uncertainty of the assay ($\Delta_{As}$) according to the State Pharmacopeia of Ukraine (SPhU) 5.3.N.2: $\Delta_{As} \leq 1.6\%$ for assay content limits ± 5%;
- Uncertainty of the reference standard characterization SPhU $5.12^{N}$: $\Delta_{Rs} \leq 0.51\%$.

*Technological variation:*

- Uncertainty of the average assay result, which is associated with technological variation in the API content between SDF units ($\Delta_{UDU,g}$), namely by averaging 20 units: $\Delta_{UDU,g} \leq 2.18\%$.
- Uncertainty of the average mass adjustment: $\Delta_{oper} \leq 1.17\%$.

Since these variability factors are independent, the overall variability budget for the assay result can be evaluated as follows:

$$max\Delta_{\overline{X}} = \sqrt{max\Delta_S^2 + max\Delta_{As}^2 + max\Delta_{RS}^2 + max\Delta_{UDU,guar}^2 + max\Delta_{Oper}^2};$$

$$max\Delta_{\overline{X}} = \sqrt{1.0^2 + 1.6^2 + 0.51^2 + 2.18^2 + 1.17^2} = 3.2\%.$$

It can be concluded that the proposed standardization of variability sources

ensures the release of SDFs within ± 5.0% for assay, where the analysis result will fall within the guard bands (95% confidence), since $max\Delta_{\overline{X}}$ < (5.0%-1.6%=3.4%). Therefore, the use of guard bands for assay (=1.6%) is theoretically feasible.

For individual SDF batches, due to random variability, there is a significant risk that the true API concentration value will be closer to the content limits than the guard bands, which may lead to an unacceptably high risk of rejecting these SDF batches upon reanalysis by the official laboratory. Therefore, a conscientious manufacturer is interested in implementing guard bands (SPhU 5.3.N.1), i.e. fulfilling the requirements for the assay result ($X$):

$$95\% + 1{,}6\%\ (96{,}6\%) \leq X \leq 105\% - 1{,}6\%\ (103{,}4\%),$$

To evaluate the actual variation for X, the results of ongoing verification of the manufacturing process of 14 SDFs for 391 batches were calculated. Preliminary, it was determined that $\Delta_{oper}$ (95% one-sided confidence interval) = 3%. This prevents the use of guard bands for assay without proper control over $\Delta_{oper}$. The data processing results showed that:

1. Assay results for 59 batches fall outside the guard bands, which is equivalent to 15% of all batches.

2. Non-compliance with guard bands is due to several factors. To evaluate the influence of $\Delta_{oper}$, the assay results of incompliant batches were recalculated to the nominal average mass. After that, the number of assay results not meeting the guard bands decreased from $n$ = 59 to $n$ = 36, i.e., by 39%. This demonstrates that the proper control over $\Delta_{oper}$ has a critical impact on compliance with guard bands requirements.

**Conclusions**:

1. The compiled variability budget for the assay results has shown that the accepted standardization in the pharmaceutical sector ensures the release of SDFs (assay content limits ± 5.0%), for which the analysis result should be within guard bands of 1.6% with 95% reliability, i.e. within ± 3.4%. Therefore, theoretically, the use of guard bands should not pose any issues for the manufacturers.
2. The analysis of the results of ongoing verification process of 14 SDFs out of 391 batches showed that only 15% of all batches (59 batches) had assay results that exceed the guard bands.
3. After recalculating assay results to the nominal average mass, the number of assay results that fell outside guard bands decreased from 59 to 36, i.e. by 39%.
4. The obtained results indicate the possibility of achieving the guard bands requirements for the assay in practice for SDFs with assay content limits ± 5.0%. However, for this to be achieved, the manufacturer must set the goal of meeting these requirements and ensure the proper control over variation for $\Delta_{oper}$.

**Reference**:

1. *Petrus V.V. et al.,* Justification of the criterion for the maximal permissible deviation of the average mass from the nominal value for solid dosage forms. *1st Scientific and Practical Internet Conference with international participation «Actual problems of quality, management and economics in pharmacy and health care»,* Kharkiv, Ukraine, 19th May, 2023. In-print.