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Justification of the criterion for the maximal permissible deviation of the average mass from the nominal value for solid dosage forms

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Introduction. During pharmaceutical development and routine production, the operator adjusts technological equipment to assure an acceptable average mass of a solid dosage form (SDF). The deviation of the average mass from the nominal value critically affects the deviation of assay results. Usually, the average mass is calculated from 20 dosage units, which causes additional uncertainty of the assay reportable value (Δ_{Oper}). We have not found any guidelines that propose a metrologically justified criterion for the deviation of the SDF average mass from the nominal value.

Aim of research. The research aimed to formulate requirements for the maximum permissible deviation of the SDF average mass from the nominal value and to assess their feasibility by verifying the actual uncertainty of the SDF average mass deviation based on the results of ongoing verification of the drug manufacturing process at Ukrainian pharmaceutical companies.

Materials and Methods. Results of critical quality parameters (average mass and assay) for routinely produced 391 batches of 14 SDFs from Ukrainian pharmaceutical companies assessed during ongoing process verification. All SDFs have an average mass of 80 mg to 250 mg.

Results. For the average content value of the active pharmaceutical ingredient (API) in SDFs, which is controlled by the assay test, the uncertainty ($\Delta_{\overline{x}}$) consists of the following components:

- Uncertainty of API assay standardization (Δ_S). For most APIs with content limits of 99.0–101.0 %, an assay is carried out by titration; therefore, $\Delta_S \leq$ 1%;

- 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 ($\Delta_{UDU,g} \leq 2.18\%$). To calculate this criterion, the approach from [1] was used;
- Maximum permissible uncertainty of the assay analytical procedure (Δ_{As}) in accordance with the State Pharmacopeia of Ukraine (SPhU) 5.3.N.2 ($\Delta_{As} \leq 1.6\%$);
- Uncertainty of the reference standard characterization (Δ_{Rs}), which shall not have a significant influence on assay results ($\Delta_{Rs} \leq 0.51\%$, SPhU 5.12^{N}).
- Uncertainty of the average mass adjustment (Δ_{oper}) that requires standardization.

The uncertainty components are independent; therefore:

$$\Delta_{\overline{X}}^2 = \Delta_S^2 + \Delta_{UDU,g}^2 + \Delta_{As}^2 + \Delta_{oper}^2 + \Delta_{Rs}^2.$$

Hence, the requirements for Δ_{oper}:

$$\Delta_{oper} = \sqrt{\Delta_{\overline{X}}^2 - \Delta_S^2 - \Delta_{UDU,g}^2 - \Delta_{As}^2 - \Delta_{RS}^2} = \sqrt{3.4^2 - 1^2 - 2.18^2 - 1.6^2 - 0.51^2} = 1.73\% \ (n = 20).$$

The actual deviation of the average mass varies for different SDF batches. Considering that the degrees of freedom for its determination are the same (n = 20; v = 19), Δ_{oper} is directly proportional to the standard deviation. This allows for the application of the Fisher criterion and the proposal of guard bands ($\Delta_{oper,\,g}$):

$$\Delta_{oper,g} = 1.17\% \ (n = 20).$$

For the evaluation, SDFs with low average masses were chosen since the operator pays attention to the absolute deviation in mg rather than the relative deviation in %, which can lead to a large deviation in %. The results of ongoing verification of the drug manufacturing process of 14 SDF for 391 batches demonstrated the following:

1. Deviation of the average mass is described by a normal distribution law, i.e. it is a random variable (Fig. 1), which was verified by the Pearson chi-square test (χ^2):

$$\chi^2(33{,}30) < \chi^2_{\alpha,k-c}(33{,}41).$$

2. The average mass adjustment (100.4 %) tends towards the nominal value since operators try to adjust the value close to 100 % and minimize deviation.

3. The uncertainty of the average mass adjustment is 3%, which confirms the need for a criterion for its permissible deviation. SDF production without deviation control makes it impossible to apply guard bands for assay.

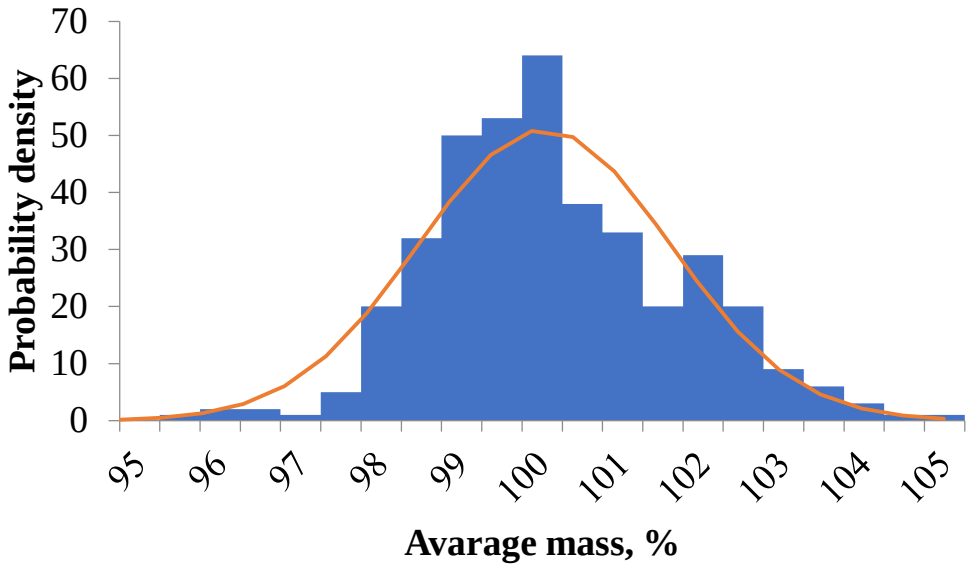

Fig. 1. Distribution of the SDF average mass deviations from the nominal value.

The deviation of the average mass from the nominal value meets the proposed criterion in 60% of cases. Consequently, the proposed criterion is achievable and can be implemented in routine practice.

Conclusions:

1. The results of ongoing verification of the drug manufacturing process of 14 SDFs for 391 batches demonstrate that the deviation of the average mass from the nominal value is described by a normal distribution law.
2. The uncertainty of the average mass adjustment is 3%, which indicates the need for control over the average mass adjustment during routine production.
3. Guard bands for the average mass adjustment have been proposed (n = 20): $\Delta_{oper,g}$ = 1,17%. It has been shown that the proposed criterion is achievable and can be implemented in routine production.
4. Once the successful achievement of the proposed criterion is confirmed in routine production at Ukrainian pharmaceutical companies, it would be rational to include it in the SPhU to standardize approaches.

Reference

1. *Gryzodub* O. *I. et al., J. Org. Pharm. Chem., 2005, 3, 1(9), 60-64.*