

RISK ANALYSIS IN PHARMACY FOR PROCESS OF MASS DETERMINATION

Criteria for assessment of weighing instruments



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Balance estimation criteria

For estimation of balance parameters while their operation, most metrological supervision departments adopt their own criteria. They result from evaluation of complete manufacturing process, substance control and consideration of precision with which sample mass is to be determined. It is the first approach that requires good knowledge of production, control process and quality.

Another approach can be focusing on regulations specified in norm **PN-EN 45501**, "Metrological matters in non-automatic weighing instruments". The standard defines volume of maximal permissible errors (MPE) that may occur in a balance. It should be mentioned that operating errors are double as big as those specified in the standard. The errors division is presented in the table below.

| Maximal Permissible Error (MPE) | Load m expressed in verifying units | | | |
|---------------------------------|---------------------------------------|-----------------------------|---------------------------|---------------------|
| | I | II | III | IV |
| $\pm 0,5e$ | $0 \leq m \leq 50\,000$ | $0 \leq m \leq 5\,000$ | $0 \leq m \leq 500$ | $0 \leq m \leq 50$ |
| $\pm 1e$ | $50\,000 < m \leq 200\,000$ | $5\,000 < m \leq 20\,000$ | $500 < m \leq 2\,000$ | $50 < m \leq 200$ |
| $\pm 1,5e$ | $200\,000 < m$ | $20\,000 < m \leq 100\,000$ | $2\,000 < m \leq 10\,000$ | $200 < m \leq 1000$ |

Chart 1. Maximal permissible errors while conformity evaluation process performed according to basic requirements of directive 90/384/EEC and norm PN-EN 45501

In practice, it is not practical to base only on the standards in balance evaluation – balance can indicate too significant error and it is still treated as well-functioning. It is possible to accept more strict criteria for balance operation in one's own evaluation system. Such assumption is obligatory during balance control procedure in RADWAG Control Department – it has been assumed that a balance is working correctly if its errors during control are lower than $\frac{1}{3}$ of maximal permissible error defined in PN-EN 45501.

$$I_{TEST} \leq \frac{1}{3} Mpe$$

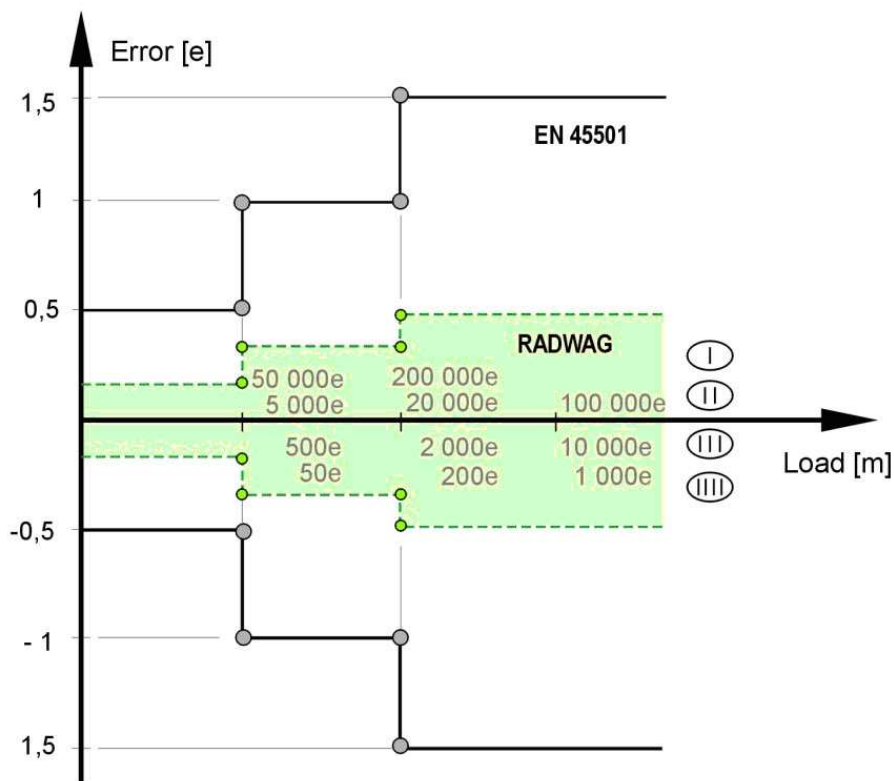


Fig 1. Graphic interpretation of MPE according to PN-EN 45501

Instances of balance estimation process according to standard requirements are presented in tables below. The first one contains MPE for balance PS 510/C/2.

Basic balance characteristics:

- Precision class II
- Max 510 g
- Min 20mg
- d 1 mg
- e 10 mg

| Load m | Capacity | MPE | MPE | Real indication error |
|--------------------------|-------------|------------------|---------------------|-----------------------|
| [verifying unit] | [g] | [verifying unit] | [reading unit] | [reading unit] |
| $0e \leq m \leq 5000e$ | 0 – 50 g | $\pm 0,5 e$ | $\pm 5 \text{ mg}$ | $\pm 10 \text{ mg}$ |
| $5000 e < m \leq 20000e$ | 50 – 200 g | $\pm 1 e$ | $\pm 10 \text{ mg}$ | $\pm 20 \text{ mg}$ |
| $20000e < m \leq 51000e$ | 200 – 510 g | $\pm 1,5 e$ | $\pm 15 \text{ mg}$ | $\pm 30 \text{ mg}$ |

Chart 2. MPE according to norm PN-EN 45501 for balance model PS 510/C/2

The second table contains balance-sheet for microbalance MYA 5. Basic balance characteristics:

- precision class I
- Max 5 g
- Min 1mg
- d 1 µg
- e 1 mg

| Load m | Capacity | MPE | MPE | Real indication error |
|--------------------------|----------|------------------|----------------------|-----------------------|
| [verifying unit] | [g] | [verifying unit] | [reading unit] | [reading unit] |
| $0e \leq m \leq 5\,000e$ | 0 – 5 g | $\pm 0,5 e$ | $\pm 500 \text{ mg}$ | $\pm 3 \mu\text{g}$ |

Chart 3. MPE according to norm PN-EN 45501 for microbalance MYA 5

If one's criteria are based on acceptance criteria according to standard PN-EN 45501 it should be taken into account that M are twice increased in balance operation. In case of microbalances and ultra-microbalances, so-called verification is quite problematic because of drastic difference between permissible errors accepted by the standard and real errors of balances.

Obviously, as for the range of examination methodology, the standard provides clear instructions that can be commonly used or corrected up to individual needs.

The third attitude for evaluation of balances is connected with requirements of American Pharmacopoeia. This approach defines what precision a balance should have in order to be put into operation:

If it is not specified . . . , a substance is correctly weighed (taking random and systematic error into account), if device measurement uncertainty does not exceed 0,1% of readout.

USP, General Chapter 41 „Weights and Balances”

Measurement uncertainty is satisfactory if 3-times standard deviation from series of at least 10 repetitions divided by series average value does not exceed 0,001.

USP, General Chapter 41 „Weights and Balances”

Such approach is used by American market product manufacturers, that are a part of global concerns which are subordinated to periodical controls by FDA.

The fourth approach is directed to Risk Analysis in accordance to document EMEA* ICH Q9** "Quality Risk Management". The document is of general nature and shows how to manage risk. Obviously, it is necessary to adapt the assumptions to balances. How should risk be defined?, How to reduce it? How to manage it? It requires defining. Risk area will depend on the weighing procedures that are performed.

**EMEA – European Drugs Agency, EU agency for medical products estimation and supervision coordination.*

***ICH Q9 – Guide elaborated by a group of experts for pharmaceutical industry*

Irrespective of adapted balance estimation criteria, following 4 parameters should be subject to examination:

- repeatability
- linearity error
- centricity
- sensitivity change

The frequency of controlling balance parameters and choosing the appropriate ones for control depends on weighing range in which the balance is used.