Monte Carlo Simulation for Evaluation of Measurement Uncertainty of pharmaceutical certified reference materials

Werickson Fortunato de Carvalho Rocha [1], *Raquel Nogueira*[2]

[1] INMETRO, Duque de Caxias, Brazil, wfrocha@inmetro.gov.br
[2] INMETRO, Duque de Caxias , Brazil, rnogueira@inmetro.gov.br

Abstract: The Supplemental Guide to the Expression of Uncertainty Measurement (2004), which deals with the propagation of distributions, emphasizes the use of the Monte Carlo simulation (MCS) for estimating the uncertainty of measurands. This paper describes the application and validation of a methodology, as recommended by the ISO GUM supplement, to evaluate the measurement uncertainty of the active pharmaceutical ingredient (API) content for two certified reference materials (CRMs): metronidazole and captopril. The Monte Carlo results complied with the GUM results for a critical value δ of 0.005 for metronidazole and δ 0.05 for captopril. Therefore, the GUM methodology was validated by the Monte Carlo method with expression of the API content with at least two decimal digit numbers.

Key words: Monte Carlo Simulation; Evaluation of Measurement Uncertainty; Certified Reference Materials; Active Pharmaceutical Ingredients.

1. Introduction

Metrological activities are fundamental to ensure the quality of scientific and industrial activities. Measurement results must be valid, comparable, and reproducible, and their uncertainties are the quantitative expression of their quality. In accordance to the ISO/IEC 17025:2005 standard, all calibration or testing laboratories must have and apply procedures to evaluate uncertainty in measurements as a guarantee of their technical competence.

In order to establish an international consensus for the estimation of measurement uncertainties, the International Standardization Organization (ISO) has developed and published the Guide to the Expression of Uncertainty in Measurement (GUM) , which has been widely accepted and followed . The GUM is based on sound theoretical principles and supports a fully consistent and transferable estimation of measurement uncertainty and traceability to the International System of Units (SI). However, this approach exhibits some important limitations mainly derived from the use of the law of propagation of uncertainty and from the application of the central limit theorem.

To avoid these limitations, the working group 1 of the Joint Committee for Guides in Metrology (JCGM-WG1) ‘‘Expression of Uncertainty in Measurements’’ promotes the use of the GUM and prepares supplemental guides. The first supplemental guide ‘‘The propagation of distributions’’ (2004) considers the propagation of distributions for general probabilistic basis for uncertainty evaluation from the direct use of the probability density function (PDF) of the input quantities rather than just their means and standard uncertainties. It also recognizes the Monte Carlo method as the most efficient numerical implementation for the propagation of distributions.

2. Instrumentation, measurement procedures and software

The instrumental and experimental procedures used for the certification of metronidazole and captopril reference materials were previously described [1,2] and were based on the ISO Guides 34:2009 and 35:2006. They consisted basically on material characterization (determination of organic impurities by high performance liquid chromatography according to eq. 4-5, determination of inorganic impurities by residue on ignition test, and determination of volatiles by loss on drying test), between-bottle homogeneity testing, short- and long-term stability studies, calculation of the API content using the mass balance approach, and uncertainty estimation of the property value for both CRMs.

$$[org] = \frac{A_{imp} \; x\, 100}{\left(A_{analyte\ dil}\ DF\right) + \sum A_{imp}} \qquad (1)$$

where $[org]$ is content of each organic impurity (%); A_{imp} is peak area of each organic impurity (concentrated solution); $A_{analyte\ dil}$ is the analyte peak area (diluted solution); DF is the dilution factor from the concentrated to the diluted solution, and ΣA_{imp} is the sum of peak areas of organic impurities.

$$[org]_{tot} = \sum \, [org] \qquad (2)$$

where $[org]$ is the total organic impurities content.

2. Results and discussion

2.1 Application of the GUM Method

Initially the combined standard uncertainties of the contents of organic impurities (u_{org}), inorganic impurities (u_{inorg}) and volatiles (u_{vol}) were determined by the traditional method. The uncertainties due to between-bottle (in)homogeneity (u_{bb}) and long-term stability (u_{lts}) studies were estimated according to the ISO Guide 35:2006 . The combined standard uncertainty of each CRM (u_{CRM}) was calculated according to the law of propagation of uncertainties, which consists of “the square root of the total variance obtained by combining all the uncertainty components”. Finally the expanded uncertainty of the certified property value (U_{CRM}) was obtained by multiplying u_{CRM} by the coverage factor (k = 2).

2.2 Application of the Monte Carlo method

For the Monte Carlo simulation, the variables of eq. 5 (mass balance) and the results of the homogeneity and stability studies were taken into account. First it was necessary to define the types of the probability density functions (PDF) of each of these input parameters.

3. CONCLUSION

The compatibility of the results obtained by the Monte Carlo method and the conventional method (GUM) has been demonstrated for two pharmaceutical CRMs. The Monte Carlo simulation is a practical tool for application of the principle of propagation of distributions and does not depend either on the assumptions or on the limitations related to the law of propagation of uncertainties (GUM uncertainty framework). Therefore, the risk of unreliable measurement uncertainties estimation, particularly in cases of complicated measurement models, can be reduced, and there is no need to evaluate partial derivatives.

The study showed that the agreement between the Monte Carlo and GUM results are valid until a determined number of decimal digits and, in the case of the two studied CRMs, these numbers were compatible to the BIPM recommendations to express the certified property values and their measurement uncertainties.