# Particular and total risks in the conformity assessment of paracetamol oral solutions

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## Introduction

Paracetamol (acetaminophen) is one of the most commonly prescribed painkillers and it's widely available and used as an over-the-counter medicine worldwide [1]. As a multiparameter product, this medicine has multiple quality parameters to attend to guarantee its safety and efficiency.

The measurement uncertainty associated with all measure values must be considered to provide traceability and reliable results. It enables the risk evaluation in conformity assessment, that plays an important role in the decision making process, reducing the probability of making an erroneous decision such as accept an out-of-specification medicine/batch or reject an within-the-specification medicine/batch [2].

When more than one quality parameter is considered for evaluation, all of them need to be in compliance regarding the quality specifications. The particular risks of the parameters can't solely influence the conformity decision, being necessary to consider the total risk. However, the evaluation of multiple quality parameters can generate metrological correlation due to the sharing of analytical steps. This correlation affects the total risk value, and therefore should be consider in the determination of the total risk [3].

Given the above, the aim of this work was to determine the measurement uncertainties and the particular and total risks regarding the quality parameters of relative density, active pharmaceutical ingredient (API) content, and dose per drop of paracetamol in oral solutions, considering the metrological correlation.

## Materials and Methods

Three brands of paracetamol oral solution 200 mg/mL were evaluated regarding the relative density, API content (by ultraviolet absorption spectrophotometry), and dose per drop, according to the Brazilian Pharmacopeia.

The individual uncertainty values were estimated by the analytical balance calibration, by repeatability studies of the glassware, and by ANOVA analysis of the relative density, absorbance and drop mass. The standard uncertainty of the drop volume, API content, and dose per drop were obtained by Monte Carlo Method (standard deviations of 50,000 simulations for each parameter) in a Microsoft Excel worksheet. The particular and total risks for each brand were also estimated by Monte Carlo Method, considering whether the 50,000 simulation values are within or out-of-specification.

## Results and Discussion

The total risk takes into account all quality parameters. Among the three brands evaluated, only brand C presented all its parameters within specification (Table 1). Brands A and B, on the other hand, presented out-of-specification dose/drop values (Table 1).

When one or more quality parameters are out-of-specification, the product cannot be considered adequate for use. Thus, brands A and B do not meet the specifications regarding conformity assessment, and should be rejected; therefore the particular risks for dose/drop and the total risk correspond to the producer risk, which is the probability of rejecting a batch within specification, considering the 50,000 Monte Carlo simulations (Table 2). On the other hand, the risks regarding brand C refer to consumer risk, which is the probability of approving an out-of-specification batch, considering the 50,000 Monte Carlo simulations (Table 2).

**Table 1**. Mean values and standard uncertainties of the evaluated quality parameters of paracetamol oral solution brands.

| Quality parameters evaluated | Specification limits | Mean value ± u | | |
|---|---|---|---|---|
| | | Brand A | Brand B | Brand C |
| relative density (g/mL) | 1.10-1.20 | 1.13 ± 0.03 | 1.15 ± 0.00 | 1.13 ± 0.03 |
| API content (mg/mL) | 180-220 | 189.34 ± 2.21 | 203.80 ± 2.27 | 204.89 ± 2.33 |
| dose/drop (mg/drop) | 11.3-15.3 | 9.49 ± 0.70 | 10.30 ± 0.28 | 12.00 ± 1.10 |
| Conformity assessment | | not comply | not comply | comply |

Mean values of 50,000 Monte Carlo simulations for each parameter; u: standard uncertainty

**Table 2.** Risks of false decision in the conformity assessment of the evaluated quality parameters of paracetamol oral solution brands.

| Quality parameters | Type of risk | Risk value (%) | | |
|---|---|---|---|---|
| | | Brand A | Brand B | Brand C |
| relative density | particular | 0.11[1] | 0.00[1] | 0.00[1] |
| API content | particular | 7.50[1] | 0.00[1] | 2.95[1] |
| dose/drop | particular | 2.03[2] | 0.57[2] | 31.56[1] |
| all considered | total | 1.98[2] | 0.57[2] | 32.84[1] |

[1] consumer risk; [2] producer risk

Although brands A and B are considered not-conforming, the risks of false decision related to them are relatively low. With the exception of the consumer risk regarding the API content of brand A, which was above the maximum permissible risk of 5% (7.5%), the producer's risks were below 5% (total risk 1.98% and 0.57% for brands A and B, respectively). The decision to accept brand C is inconclusive, since the consumer's total risk is considerably high (32.84%), much higher than 5%.

## Conclusions

The three brands of paracetamol oral solutions were evaluated regarding the risks of false conformity decisions, considering 50,000 Monte Carlo simulations. The risks were estimated using a frequentist approach, which takes into account the measured value, its measurement uncertainty, and the specification limits. Also, using the Monte Carlo method, the metrological correlation between the quality parameters measured values was considered in the risk estimations.

Regarding the evaluated quality parameters, brands A and B were considered non-conforming, yet presented low risk of rejecting a batch within specification. Brand C was considered conforming; however, it presented high risk of approving an out-of-specification batch. These results reinforce the importance of considering the total risk of false decisions in the conformity assessment along with the quality parameters evaluation.

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