Total combined global risk assessment applied to pharmaceutical equivalence of medicines

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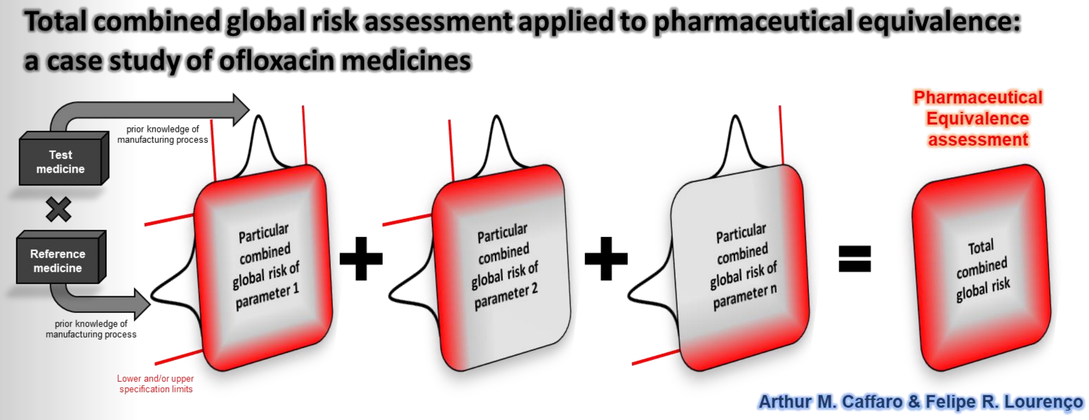
GRAPHICAL ABSTRACT



INTRODUCTION

Pharmaceutical equivalence is an important step in determining the interchangeability between medicines, particularly when bioequivalence is not required or applicable. Pharmaceutical equivalence study ensures that test and reference medicines gave the same active ingredient, strength, dosage form, and quality, which indicate they are identical in terms of their chemical and physical properties. Usually, pharmaceutical equivalence is assessed using a single batch of generic medicine and a single batch of reference medicine. However, the regulatory agency may require ongoing monitoring of the generic medicine's quality to ensure that it continues to meet the standards set by the regulatory body. To the best of our knowledge, there is no work in the literature that allow one to assess the total combined risk of a pharmaceutical equivalence study not yet performed (e.g. what are the risk of a false pharmaceutical equivalence decision for two medicines – test and reference – that will be manufactured in the future?) [1]. This risk of false decision for a future batch that will be tested is defined as global risk, which is estimated using Bayesian statistics [2]. The aim of this work was to assess the total combined global risk of false decisions regarding the pharmaceutical equivalence (non-equivalence) of test and reference medicines.

MATERIALS AND METHODS

Test and reference medicines of ofloxacin ophthalmic solution were subjected to assay (HPLC), pH determination, potency (agar diffusion), identification (HPLC and TLC), volume, and sterility test. In addition, test and reference medicines of ofloxacin tablets were subjected to assay for ofloxacin content (HPLC), friability test, potency (agar diffusion microbiological assay), identification (HPLC and UV), hardness, appearance, disintegration test, uniformity of dosage unit test, and weight.

RESULTS AND DISCUSSION

Particular and total global risks were estimated using Monte Carlo method (MCM) implemented in a MS-Excel spreadsheet. The consumers' risk values were calculated as function of the historical mean for quantitative analysis (e.g. assay, pH, potency, volume, friability, etc.) or the probability of a compliant batch for qualitative analysis (e.g. identification, sterility test, appearance, etc.). For quantitative analysis, the risk values differ for tests with interval specification limits (e.g. assay, potency, etc.) when compared to those tests with minimum or maximum specification limits only (e.g. volume, friability test, hardness, etc.). For qualitative analysis, the higher the probability of a compliant batch the lower the consumers' risk values. The total combined global risk of a false pharmaceutical equivalence decision can be significantly high (above of 5%) for some of the simulated conditions.

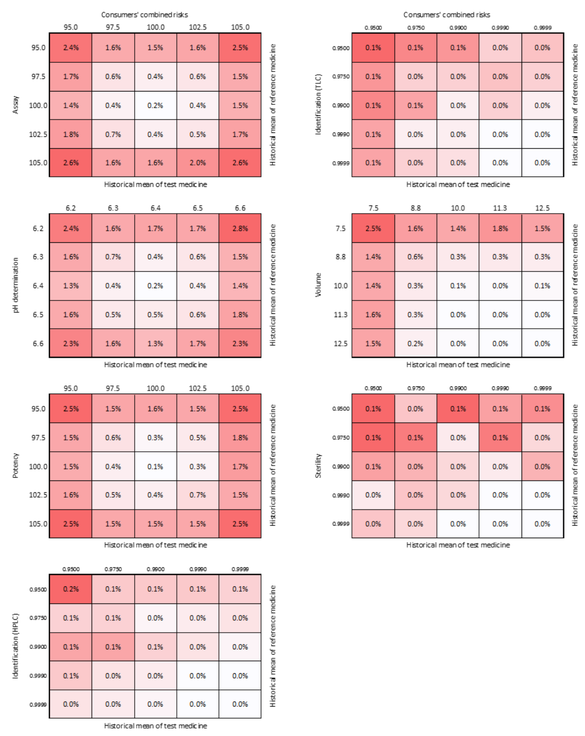


Figure 1. Particular and total combined global consumers' risks of ofloxacin ophthalmic solution as function of historical mean of manufacturing process.

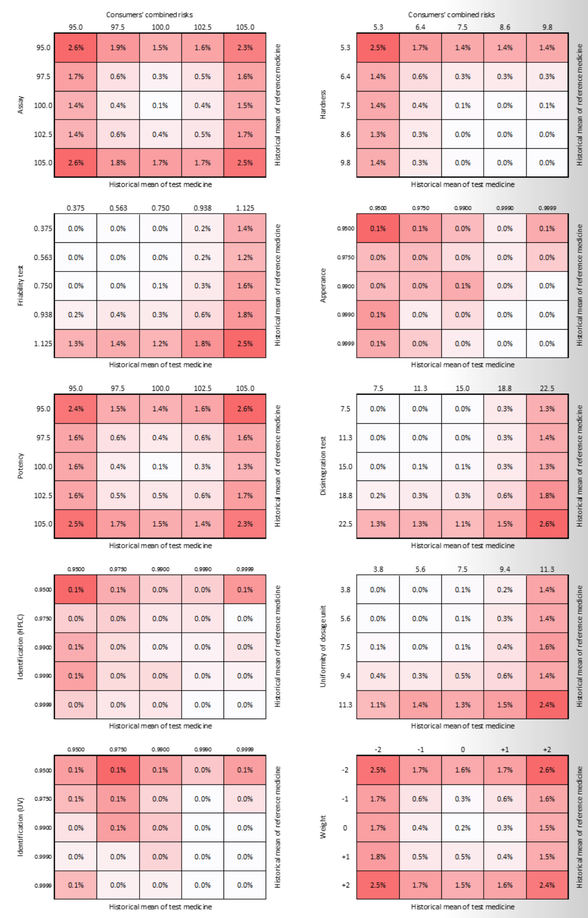


Figure 2. Particular combined global consumers' risks of ofloxacin tablets as function of historical mean of manufacturing process.

Reduced risk values were obtained when historical means were far from the specification limits and the probability of a compliant batch is high, or when the standard deviation values are low.

References
[1] M.L.G. Bertanha, F.R. Lourenço, *Journal of Pharmaceutical and Biomedical Analysis*, **2021**, *204*, 114269.
[2] R.J.N. Bettencourt da Silva, F.R. Lourenço, F.R. Pennecchi, D.B. Hibbert, I. Kuselman, *Chemometrics and Intelligent Laboratory System*, **2019**, *188*, 1-5.

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