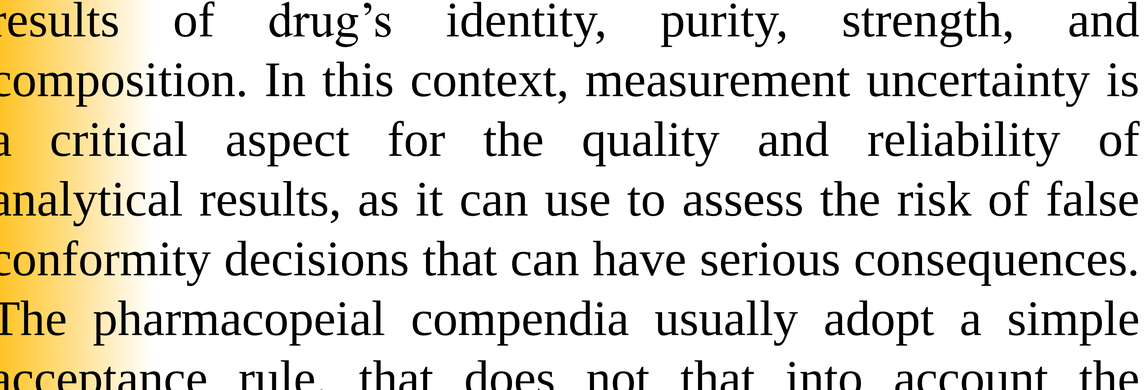
Multivariate guard-bands applied on multiparameter evaluations of medicines

Felipe R. Lourenço, Cintia M. da Silva
University of São Paulo (Av. Prof. Lineu Prestes, 580, São Paulo/SP, Brazil, feliperl@usp.br)

GRAPHICAL ABSTRACT



INTRODUCTION

Medicines are essential for maintaining good health and treating diseases and illnesses. The quality, efficacy, and safety of medicines are usually verified by analytical results of drug's identity, purity, strength, and composition. In this context, measurement uncertainty is a critical aspect for the quality and reliability of analytical results, as it can use to assess the risk of false conformity decisions that can have serious consequences. The pharmacopeial compendia usually adopt a simple acceptance rule, that does not that into account the information from measurement uncertainty. In this work, we compared the decision making using simple acceptance rule and decision rule with the use of guard-band (that takes into account the use of measurement uncertainty information) for multiparameter evaluation of ofloxacin ophthalmic solution and acyclovir topical cream.

MATERIALS AND METHODS

Ciprofloxacin ophthalmic solution medicines were subjected to volume measurements, pH determination, density determination, assay (HPLC), potency (agar diffusion) and drop test. Acyclovir topical cream samples were subject to weight measurements, bacterial and fungal enumeration tests, and assay (UV). Multivariate guard-band widths were calculated by multiplying the standard uncertainty (u) by an appropriate multivariate coverage factor (k') [1]. The multivariate coverage factor (k') was obtained by Monte Carlo method and Goal Seek tool implemented in a MS-Excel spreadsheet [2].

RESULTS AND DISCUSSION

According to the simple acceptance rule (that do not take into account the measurement uncertainty information), all the results obtained for ciprofloxacin ophthalmic solution and acyclovir topical cream are within the specification limits. However, there is an increased risk of false conformity decisions for assay of ciprofloxacin and drop test. In other words, when considering a decision rule with the use of guard-bands (that takes into account the measurement uncertainty information), assay and drop test results are not compliant (are out of the acceptance limits obtained using guard-bands). Decisions made using simple acceptance rule and decision rules with the use of guard-band may differ. Therefore, the use of information of measurement uncertainty in conformity (non-conformity) assessment is highly recommended to ensure the proper efficacy, safety, and quality of medicines.

Table 1. Measured values and its standard uncertainties, specification limits, acceptance limits (univariate guard-band obtained using $k = 1.64$), multivariate acceptance limits (multivariate guard-band obtained using $k' = 2.35$ and 2.04), and risk assessment (consumer's risk values) for ciprofloxacin ophthalmic solution medicines from lab A (generic) and B (reference) and for acyclovir topical cream medicines from lab A (generic), B (similar), and C (reference).

Lab A (Generic medicine)	**Measured value and its standard uncertainties**	**Specification limits**	**Acceptance limits (Univariate guard-bands)**	**Multivariate acceptance limits (Multivariate guard-bands)**	**Risk assessment (consumers' risk values)**
Volume (mL)	5.2 ± 0.1	Min. 5.0	Min. 5.16	Min. 5.23	2.25 %
pH	4.5 ± 0.2	3.5 to 5.5	3.83 to 5.17	3.97 to 5.03	0.00 %
Density (g/mL)	1.015 ± 0.002	1.000 to 1.020	1.003 to 1.017	1.004 to 1.016	0.51 %
Assay (mg/mL)	3.28 ± 0.04	2.70 to 3.30	2.77 to 3.23	2.79 to 3.21	30.72 %
Potency (%)	97.4 ± 3.5 %	90.0 to 110.0	95.8 to 104.2	98.2 to 101.8	1.79 %
Drop Test (mg/drop)	119 ± 4	95 to 123	102 to 116	104 to 114	16.01 %
TOTAL					40.78 %
Lab B (Reference medicine)	**Measured value and its standard uncertainties**	**Specification limits**	**Acceptance limits (Univariate guard-bands)**	**Multivariate acceptance limits (Multivariate guard-bands)**	**Risk of false decision (consumers' risk values)**
Volume (mL)	5.5 ± 0.1	Min. 5.0	Min. 5.16	Min. 5.23	0.00 %
pH	4.4 ± 0.2	3.5 to 5.5	3.83 to 5.17	3.97 to 5.03	0.00 %
Density (g/mL)	1.005 ± 0.002	1.000 to 1.020	1.003 to 1.017	1.004 to 1.016	0.43 %
Assay (mg/mL)	3.26 ± 0.05	2.70 to 3.30	2.78 to 3.22	2.82 to 3.18	21.17 %
Potency (%)	100.4 ± 3.5 %	90.0 to 110.0	95.8 to 104.2	98.2 to 101.8	0.46 %
Drop Test (mg/drop)	177 ± 6	142 to 185	152 to 175	156 to 171	9.12 %
TOTAL					26.36 %
Lab A (Generic medicine)	**Measured value and its standard uncertainty***	**Specification limits**	**Acceptance limits (Univariate guard-bands)**	**Multivariate acceptance limits (Multivariate guard-bands)**	**Risk of false decision (consumers' risk values)**
Weight (g)	10.56 ± 0,11	Min. 10	10.17	10.22	0.000 %
Bacteria Count (CFU/g)	< 10	Max. 10^3	$10^{2.51}$	$10^{2.39}$	0.000 %
Fungal Count (CFU/g)	< 10	Max. 10^2	$10^{1.51}$	$10^{1.39}$	0.024 %
Assay (%)	104.8 ± 0.7	90.0 to 110,0	91.2 to 108.8	91.4 to 108.6	0.000 %
TOTAL					0.024 %
Lab B (Similar medicine)	**Measured value and its standard uncertainty***	**Specification limits**	**Acceptance limits (Univariate guard-bands)**	**Multivariate acceptance limits (Multivariate guard-bands)**	**Risk of false decision (consumers' risk values)**
Weight (g)	10.35 ± 0,10	Min. 10	10.17	10.21	0.030 %
Bacteria Count (CFU/g)	< 10	Max. 10^3	$10^{2.51}$	$10^{2.39}$	0.000 %
Fungal Count (CFU/g)	< 10	Max. 10^2	$10^{1.51}$	$10^{1.39}$	0.044 %
Assay (%)	98.3 ± 0.8	90.0 to 110,0	91.3 to 108.7	91.6 to 108.4	0.000 %
TOTAL					0.074 %
Lab C (Reference medicine)	**Measured value and its standard uncertainty***	**Specification limits**	**Acceptance limits (Univariate guard-bands)**	**Multivariate acceptance limits (Multivariate guard-bands)**	**Risk of false decision (consumers' risk values)**
Weight (g)	10.34 ± 0,10	Min. 10	10.17	10.21	0.036 %
Bacteria Count (CFU/g)	< 10	Max. 10^3	$10^{2.51}$	$10^{2.39}$	0.000 %
Fungal Count (CFU/g)	< 10	Max. 10^2	$10^{1.51}$	$10^{1.39}$	0.042 %
Assay (%)	102.1 ± 0.5	90.0 to 110,0	90.8 to 109.2	91.0 to 109.0	0.000 %

References

[1] M.Lombardo, C.M.da Silva, F.R. Lourenço, *Regulatory Toxicology and Pharmacology*, **2022**, *136*, 105279.

[2] C.M. da Silva, F.R. Lourenço, *Journal of Pharmaceutical and Biomedical Analysis*, **2023**, *222*, 115080.

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