Analytical imprecision goals for immunosuppressive drugs: A retrospective study and comparison of four alternative approaches. Wieland E[1], Schütz 2[1], Röhrich W[1], Shipkova M[1]. [1]Bioscientia Healthcare GmbH, Ingelheim, Germany, [2]Oncocyte Corporation, Nashville, TN, USA

Background: For application to patient care analytical methods need to demonstrate performance that meets the clinical needs. Different approaches for setting up permissible analytical imprecision goals (pCVa%) for the quantification of immunosuppressive drugs (ISDs) have been reported. This study determined pCVa% for 5 ISDs using routine results generated in 2023 and compared them to results from 4 alternative calculation approaches.

Methods: pCVa% for the quantification of cyclosporine A (CsA), tacrolimus (TAC), everolimus (EVR), sirolimus (SIR), and mycophenolic acid (MPA) were derived from the within-subject biological variation (CVi) based on 3 consecutive measurements (LC-MS/MS) per patient according to Harris (1). These pCVa% was then compared to the pCVa% calculated according to Fraser (2) (based on terminal elimination half time and dosing interval) and further to $Glick_{modif}$ as well as Haeckel et al. (3,4) both based on the width of the therapeutic range (TR), where the narrowest TRs for each drug at the authors' institution were used.

Results: pCVa% calculated by the different approaches:

Drug	TR	Patients	CVi%	Harris*	Fraser	$Glick_{modif}$	Haeckel
CSA	100-150 µg/L	55	13,8	6.9	5.4	3.3	3.2
EVR	3-8 µg/L	180	12,8	6.4	3.4	6.3	5.0
MPA	1.9 – 4.0 mg/L	107	24,2	12.1	7.7	5.3	4.4
SIR	3-6 µg/L	49	14,4	7.2	3.4	5.0	4.2
TAC	4-9 µg/L	216	13,3	6.6	5.4**	5.0	4.2

*pCVa=0.5*CVi; **prolonged release; extended release 6.4; immediate release 8.3

Conclusion: There is currently no consensus about the best approach to establish pCVa% for ISDs. Comparison of 4 different approaches demonstrated comparable goals wherein the pCVa% based on the CVi approach according to Harris was the least stringent. As far as attainment to the TR is still the most frequent objective for clinical decisions, we are in favor of extrapolating pCVa% from the width of the TR following the establishment of pCVa% based on reference ranges of endogenous biomarkers.

[1]Harris AmJClinPathol 1979;72:374, [2]Fraser, ClinChem 1987,33:387, [3]Glick, ClinChem 1976,22:475, [4]Haeckel et al. CCLM 2015,53:1161.

Key Words: immunosuppressive drugs, analytical performance specifications, analytical imprecision, biological variation, measurement uncertainty