In Reply to A Comment about Analytical Performance Specifications for the Combined Measurement Uncertainty Budget in the Implementation of Metrological Traceability of Parathyroid Hormone

We would like to thank Dr Panteghini for his kind words on the contribution of our work toward the standardization of parathyroid hormone (PTH) measurements (1) and for his lucid and thorough explanation of concepts related to the setting of analytical performance specifications (APS) endorsed by the Joint Committee on Traceability in Laboratory Medicine Task Force on Reference Measurement System (RMS) Implementation. However, as Dr Panteghini clearly notes in his letter, APS are only theoretical targets which might not be achievable due to technical limitations. As models, they possess their own advantages and disadvantages, which are relevant to all biomarkers, whatever their concentration, the complexity of their measurement, the state of the art of the technology available at the time, and the uncertainty of the reference material available.

In our study, we used the PTH WHO 95/646 International Standard (IS). Notably, the uncertainty associated with this standard was not provided and had to be estimated, as delineated in our supplementary materials. The estimated uncertainty of the IS substantially consumed a major portion of the allowable uncertainty for a reference method, leaving no budget for other uncertainties, including those inherent to the procedure. Consequently, we opted for a less stringent APS for the RMS (set at half the total budget for measurement uncertainty, TBmu), to allocate more budget for the uncertainties linked to the reference measurement procedure (RMP), aligning with the considerable uncertainty budget associated with the WHO 95/646 IS. This approach was pragmatic, rather than "dogmatic," and was based on the current state of the art of the currently available standard. However, we are confident that when a new standard, presenting a lower uncertainty, is made available, our method will comply with the performance required to fulfil the requested 1/3 of the total uncertainty budget for an RMP.

We would also like to thank Dr Panteghini for his question on the uncertainty type we used. In this paper, we used the "Standard Uncertainty" as we did not apply the coverage factor $k = 2$, and indeed did not mention it in our manuscript.

While it is true that our approach may not be perfect, we have recently shown that the in silico recalibration of 5 immunoassays (comprising 2 second-generation and 3 third-generation PTH assays) against our candidate LC-MS/MS reference method has yielded notable results (2), including a considerable improvement in harmonization of PTH results in patients afflicted with chronic kidney diseases and those undergoing hemodialysis. In current daily practice, an overestimation of more than 200% can be observed with some frequently used second-generation PTH immunoassays which is unacceptable and can lead to potential medical errors. The data we recently presented do not only open the door to complete standardization of PTH assays but also hold the potential for significantly improving patient care. In conclusion, even if the ideal APS were not met at this stage, mainly due to the uncertainty attributed to the WHO IS used to calibrate the RMP, the results we obtained demonstrate that our candidate RMP is fit for purpose to successfully standardize PTH assays.

Nonstandard Abbreviations: PTH, parathyroid hormone; APS, analytical performance specifications; IS, International Standard; RMP, reference measurement procedure.

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