How to use your EQA data to support Risk Assessment within your ISO 15189:2022 accreditation

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Introduction

ISO15189:2022 puts an emphasis on a risk-based approach within the laboratory. Laboratories are responsible for ensuring that they are using assays that are fit for the purpose that the laboratory intends to use them for, and that if there are any changes in assay performance these are taken into consideration and communicated to users.

External Quality Assessment (EQA) has two very important roles — a retrospective assessment of an individual laboratory's quality and post market surveillance of all assays that are in use. There are differences in Scheme design between EQA providers. The laboratory should not assume that just because an assay is commercially available that it is fit for the purpose that they are using it for. Likewise, laboratories should not assume all EQA Schemes are the same.

Review of data to show how EQA data can be used to show how laboratories can use their EQA data to support choice of assay, ongoing verification and overall assay fitness for purpose. An example is shown for Serum Cortisol.

Methods

The UK NEQAS for Steroid Hormones Scheme distributes individual specimens, monthly, to ~480 participants in the UK and worldwide. Specimens are predominantly non-manipulated patient serum; however, in some cases exogenous steroid (hydrocortisone) is added to increase concentration and is a method of assessing recovery. Specimens are for Cortisol analysis only. Data for Cortisol from 2021–2023 has been reviewed. The Target Value is the Mass Spectrometry method mean (validated by a reference method).

Results

Figure 1 shows data and histograms for two different specimens, of similar concentration, for the same laboratory. Both specimens are pooled human serum with no added analytes.

- The %CV for all methods is similar for both specimens, as is also the case for all methods except OCD (J&J) VITROS.
- For the Siemens Atellica user shown, the scoring is very different – a positive bias of ~+10% for 511A and ~+30% for 512A, one month later. This could lead to investigation into a possible laboratory or EQA issue when in fact the difference is due to the analytical method.
- The serum used for Specimen 511A was from female donors and the serum for Specimen 512A was from male donors.

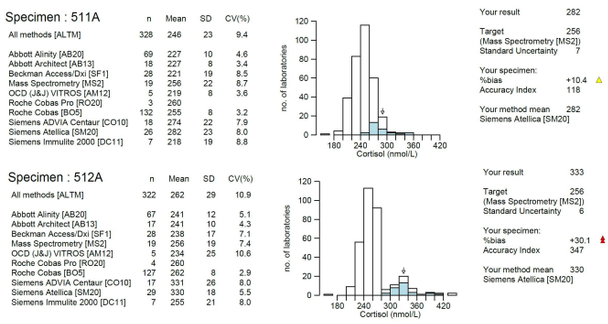

Figure 1. Histograms of reported Cortisol results on Specimens 511A and 512A for the same user, using a Siemens Atellica:
Pooled human serum with no added analyte (511A – Female, 512B – Male)

Due to the specimens being predominantly native pooled serum and if exogenous material is added this is only hydrocortisone (cortisol), it is possible to accurately assess individual manufacturer relative method biases, using the validated mass spectrometry field method mean as the Target Value. Figure 2 shows box and whisker plots for the B-score, which is the average specimen % bias of 18 data points over the last 6 months for all methods. It is clear to see that at the end of 2023, on average, there is a ~35% difference between the Abbott and the Siemens results.

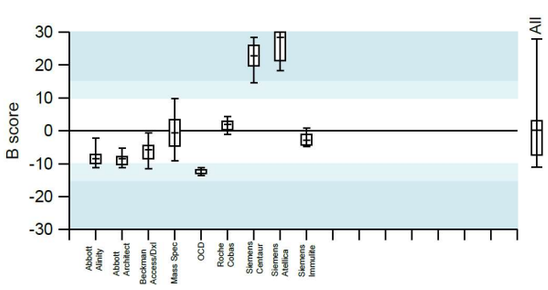

Figure 2. Box and Whisker plot of average bias (B-score) calculated from 18 data points over previous 6 months, for Cortisol, by manufacturer (Data Dec 2023)

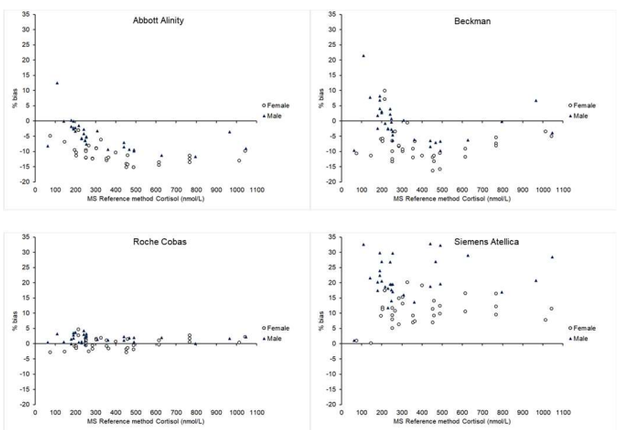

Figure 3: Bias plots for Cortisol by Manufacturer:
Data shown by sex for four major manufacturers

Figure 3 shows bias plots by method during 2021−2023. Variation is observed both within and between manufacturers. There are sex related differences in the Cortisol method for Abbott Alinity, Beckman and Siemens Atellica assays (the Siemens Atellica being the most pronounced) and a concentration dependent bias for Abbott Alinity and Beckman. The Roche Cobas Cortisol assay shows negligible bias and no sex differences.

Figure 4 is a review of the box and whisker data shown in Figure 2, but over a five-year time period, for four of the major manufacturers. Time is on the x-axis, data is shown for 5-years, with a data point notionally monthly. Some methods, for example the Roche Cobas, show very tight spread of B-score (Bias score) which is consistent for a long period of time. Other methods show changes in the spread of data (length of box), which is likely to be attributed to different Lot numbers of reagent/calibrator being in circulation at the same time. There may also be shifts in bias, over time, as seen for the Siemens Atellica, which once again could be due to changes in reagent/calibration.

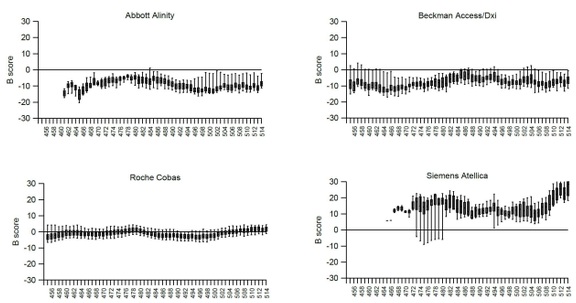

Figure 4: Seismograph plots of B-score (average specimen % bias of 18 data points over 6 months), over previous 5 years (2019-2023) for Cortisol for four major manufacturers

Conclusions

Laboratories need to be aware of the shortcomings of each and every assay and the benefits of probing with challenging EQA. Using individual specimens with minimal or no manipulation has shown that there are significant assay and sex specific differences for a defined analyte such as Cortisol. These differences not only impact interpretation of clinical results, but also EQA data. From an EQA perspective this is very important as laboratories could use resource investigating apparent EQA issues which are solely related to specificity issues of the assay.

Laboratories need to be aware of assay limitations at the point of assay selection not only so that they can take into account any differences in their reference ranges but also for risk assessment of service provision. Cortisol results are often reviewed following a Short Synacthen test where specific hard cut-off values are used to determine whether the patient has demonstrated an adequate response in cortisol production after synthetic ACTH stimulation. It may be necessary to use assay dependent cut-offs.

Long term assay stability can be assessed by longitudinal repeat distributions of pools over time. Assay stability is important for biological markers that are monitored over time and for markers that have defined cut-offs (as in the case of cortisol). EQA data must be used alongside patient data to assess the impact of any changes in bias with this being communicated to the end user.

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