Drug interference in glucose measurement and its impact on patient safety

Oliver Hauss, PhD [1], Rolf Hinzmann , MD, PhD [2], Julia Rötschke, PhD[2], Brian Huffman, PhD [3]

[1]Dr. Hauss Training & Consulting, Maxdorf, Germany. [2]Roche Diabetes Care GmbH, Mannheim, Germany. [3]Roche Diabetes Care, Inc, Indianapolis, IN, USA.

Background

The accuracy of glucose measurements does not just depend on the general accuracy of the technology as such but can be confounded by the presence of interfering substances or conditions. These can range from abnormally high or low hematocrit to drugs taken by a patient due to comorbidities.

There is an extensive set of recommendations for the testing of interferences for SMBGs. For CGM, the situation is less concrete.

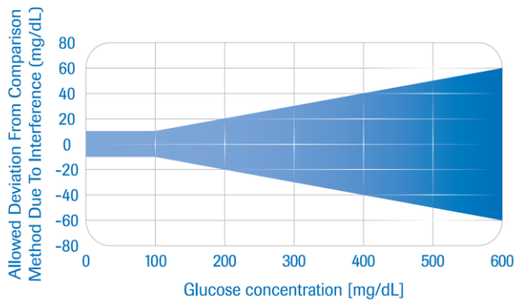
We review the specific regulations as well as the efforts made by manufacturers and researchers to identify interfering substances.

What is interference?

CLSI : **"a cause of medically significant difference in the measured test result due to the effect of another component or property of the sample"**.

ISO standard 15197:2013 for SMBG: an interfering substance requiring labelling is **any substance that causes a mean deviation by 0.55 mmol/L (10 mg/dL) or more for concentrations <5.55 mmol/L (<100 mg/dL) and of 10% or more above that concentration** (Fig. 1).

Such deviations can lead to missed hypo- or hyperglycemic events, or even cause them due to inappropriate insulin dosing. It is thus important to understand which situations can lead to erroneous glucose measurements and which measurements may thus be unreliable.



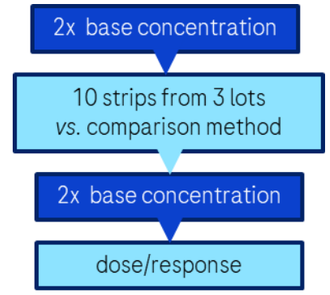
Abbreviations

CGM: Continuous Glucose Monitoring; CLSI: Clinical & Laboratory Standards Institute; FDA: Food and Drug Agency;
HCP: Healthcare Provider; ISO: International Standardization Organization.

How is interference measured so far?

ISO 15197:

- Test two glucose levels: between 2.8 – 5.5 mmol/L (50 – 100 mg/dL) and between 13.9 – 19.4 mmol/L (250 – 350 mg/dL).
- Prepare two samples for each: one spiked with the candidate substance and the other with an equivalent volume of diluent.
- Measure the blank twice, once before and once after the test series with the comparison method to ensure a stable glucose concentration.
- Compare 10 strips from 3 lots with the comparison method unaffected by candidate substance.
- If the average difference is larger than allowed, make dose/response series.
- Label substance and threshold concentration in product documents.



FDA: Guidance for interference testing prior to submitting premarket notification largely agrees with ISO.
CLSI: General interference testing independent of the specific application with similar protocol, suggests testing 3x maximum therapeutic concentration.

All guidances list substances to be tested, **but also expect manufacturers to engage in a continuous risk analysis of their own to identify potential other and/or new interfering factors and continuously expand testing with new candidate substances.** Roche, e.g., is testing a list of over 200 compounds for their Accu-Chek® Guide and Accu-Chek® Instant SMBG systems, including typical interferences, following hints from literature and customers, and including new drugs such as SGLT2-inhibitors. Beyond these official and mandatory (in case of SMBG) testing methods, complementary ones exist using real world data or patient samples. These methods account for the fact that interference may also be caused by metabolites or by effects only manifest in the presence of two or more substances. A patient sample method is also suggested as a complementary measure by CLSI, but not part of the standard testing regime.

What about interference in CGM?

Especially in countries with highly developed healthcare systems, more and more PwD use CGM rather than SMBG for their management of blood glucose concentrations.

- CGM uses measurement principles quite similar to SMBG systems – similar challenges regarding interference can be expected and have been demonstrated.
- Some CGM systems try to keep certain interferents off the sensor by a specially designed membrane cover.
- CGM measures interstitial fluid, not blood, and in-vivo, presenting the challenge of a highly dynamic environment.
- Established protocols – and, more importantly, results – thus cannot necessarily be transferred one-to-one.
- Interference tests adapted from the SMBG protocols have been done for some instruments.
- Protocols for testing under dynamic conditions have been suggested, but not formalized.
- CGM is still far from the routine and regulated interference testing procedures established for SMBG meters.
- CGM users and their HCPs have to anticipate potential sources of interference and consider them when evaluating CGM data.

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Conclusions

Interference testing for SMBG is well established and regulated, but still requires constant vigilance and expansion to new drugs entering the market. The effort a manufacturer puts into interference testing contributes to patient safety.

Interference testing for CGM is still in its infancy and a corresponding level of care needs to be considered when interpreting CGM results. More studies and formal guidelines are needed.

It is important that PwD and HCP familiarize themselves with the interferents of the SMBG and CGM systems they use or prescribe.