Testing for Biotin Interference in In Vitro Diagnostic Devices

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Guidance for Industry

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U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
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I. INTRODUCTION

The Food the Drug Administration (FDA or we) is providing recommendations on the testing for interference by biotin on the performance of in vitro diagnostic devices (IVDs). This guidance is intended to help device developers and clinicians understand how FDA recommends biotin interference testing be performed, and how the results of the testing should be communicated to end-users, including clinical laboratories and clinicians. The recommendations apply to IVDs, including devices that are licensed under section 351 of the Public Health Service Act (42 U.S.C. 262) and used in donor screening, that use biotin technology. This guidance finalizes the draft guidance of the same title dated June 2019.

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II. BACKGROUND

FDA has become aware of potential biotin interference with IVDs that use biotin/avidin interactions as part of the device technology. Many IVDs use biotin technology due to its ability to bond with specific proteins which can be measured to detect certain health conditions. For example, biotin is used in hormone tests and tests for markers of cardiac health like troponin. Biotin, also known as vitamin B7, is a water-soluble vitamin often found in multi-vitamins, prenatal vitamins, and dietary supplements marketed for hair, skin, and nail growth (Ref. 1). Biotin levels in samples from patients who consume more than the recommended daily intake for biotin can cause falsely high or falsely low results, depending on the test principle. Incorrect test results may lead to inappropriate patient management or misdiagnosis (Ref. 1). FDA's concern regarding biotin interference was expressed in Safety Communications on November 28, 2017 (Ref. 2) and November 5, 2019 (Ref. 3) and manufacturers of currently marketed devices have been working with FDA to address interference when it occurs. Historically, devices using

biotin/avidin technology have been assessed for biotin interference at the normal recommended daily doses of biotin (30 µg per day, which results in plasma/serum biotin levels of < 1 ng/mL). However, several recent reports (Refs. 4-6) have described unanticipated biotin interference with the performance of some IVDs due to consumer use of dietary supplements that result in plasma/serum biotin levels of > 1 ng/mL. In addition, extremely high biotin doses also have been observed (up to 300 mg per day, which results in plasma/serum biotin levels of > 1000 ng/mL).

This guidance describes FDA's recommendations for testing for biotin interference on devices that use biotin/avidin technology and communicating the results of such testing to the end-users, including via labeling. The recommendations in the guidance are consistent with recent advice we have provided to individual manufacturers and sponsors that have consulted with the agency. They reflect FDA's thinking that labeling alone may not be sufficient to mitigate the risk of incorrect results from biotin interference in all cases. Additional mitigation strategies may be considered when the risk of potentially incorrect results from biotin interference could significantly affect patient or public health.

III. RECOMMENDATIONS

- Sponsors should contact the appropriate CBER or CDRH review division if biotin interference at clinically relevant analyte and biotin concentrations in patient samples is demonstrated.

- We recommend that studies designed to test for biotin interference follow designs similar to those included in the most current version of Clinical Laboratory Standards Institute (CLSI) *EP07, Interference Testing in Clinical Chemistry; Approved Guideline* (Ref. 7).

- Concentrations of biotin that reflect current trends in biotin consumption should be evaluated. Biotin should be evaluated up to 3500 ng/mL, three times the maximum expected clinical concentration.
  The evaluation of biotin at this level is consistent with the recommendations in the CLSI standard and appropriate for minimizing the risk to patients from incorrect test results.

- The samples should include analyte levels near the medical decision point(s) of the device.

- For assays that are susceptible to biotin interference at concentrations less than 3500 ng/mL, the concentration of biotin at which no interference is detected should be determined.

- Information on biotin interference should be communicated to end users such as clinical laboratories and clinicians, including via the labeling[1] of the device. Relevant

[1] Under 21 CFR 809.10(b)(10), the labeling accompanying an in vitro diagnostic product shall state known extrinsic factors or interfering substances affecting results. More information regarding IVD labeling requirements is available at https://www.fda.gov/medical-devices/device-labeling/vitro-diagnostic-device-labeling-requirements.

information to include in the labeling may be the percent difference or bias at each concentration tested for both qualitative and quantitative assays and the consequence of biotin interference (e.g., falsely elevated, falsely depressed), if observed.

IV. REFERENCES

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