

Testing for Biotin Interference in In Vitro Diagnostic Devices

Draft Guidance for Industry

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., WO71, Room 3128
Silver Spring, MD 20993
Phone: 800-835-4709 or 240-402-8010
ocod@fda.hhs.gov*

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or

*Office of Policy
Guidance and Policy Development
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., WO66, Room 5431
Silver Spring, MD 20993
Phone: 301-796-5900*

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I. INTRODUCTION

The Food the Drug Administration (FDA) 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, as well as 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.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

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 in patient samples can cause falsely high or falsely low results, depending on the test. Incorrect test results may lead to inappropriate patient management or misdiagnosis (Ref. 1). FDA's concern regarding biotin interference was expressed in a Safety Communication on November 28, 2017 (Ref. 2) and manufacturers of currently marketed devices have been working with FDA to address interference when it occurs. Historically, devices using

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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. 3-5) 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, consistent with recent advice we have been providing manufacturers and sponsors. These recommendations should not be interpreted to mean that FDA considers that labeling alone will be sufficient to mitigate the risk of incorrect results from biotin interference in all cases.

III. BIOTIN TESTING RECOMMENDATIONS

- Sponsors should contact the appropriate CBER or CDRH review division if biotin interference at clinically relevant analyte and biotin concentrations 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. 6)
- Consistent with the recommendations in the CLSI standard, concentrations of biotin that reflect current trends in biotin consumption should be evaluated, up to 3500 ng/mL.
- The test 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.
- The results of the testing should be communicated to end-users, including clinical laboratories and clinicians. Therefore, information on biotin interference should be included in the labeling¹ of the device, including 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.

¹ More information regarding IVD labeling requirements is available at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/InVitroDiagnosticDeviceLabelingRequirements/default.htm>.

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IV. REFERENCES

1. Biotin: Fact Sheet for Consumers, accessed March 20, 2019. <https://ods.od.nih.gov/factsheets/Biotin-Consumer/>
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6. Clinical Laboratory Standards Institute. (2018) *Interference Testing in Clinical Chemistry*, 3rd Edition: April. <https://clsi.org/standards/products/method-evaluation/documents/ep07/>