Division of Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852


Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we respectfully submit these comments in response to the Food and Drug Administration’s (FDA’s or Agency’s) Draft Guidance for Industry: “Testing for Biotin Interference in In Vitro Diagnostic Devices” (hereinafter Biotin Draft Guidance).

AdvaMedDx member companies produce advanced, in vitro diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing in vitro diagnostic companies in the United States and abroad.

GENERAL COMMENTS

AdvaMedDx is committed to high-quality, accurate tests and appreciates the opportunity to provide our comments in response to the draft guidance. The draft guidance describes FDA’s recommendations for testing for biotin interference on devices that use biotin/avidin technology and communicating the results of such testing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. Biotin, also known as vitamin B7, is a water-soluble vitamin often found in multi-vitamins, prenatal vitamins, dietary supplements marketed to improve hair, skin, and nail health and cosmetics. It also has been used in high doses as part of experimental treatment, e.g., in clinical trials, of Multiple Sclerosis (MS) patients.

FDA should change the recommended biotin testing levels from 3500 ng/mL to 1200 ng/mL. FDA previously recommended that manufacturers evaluate up to at least a 1200 ng/mL threshold in the November 2017 safety communication.1 The draft guidance does

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not explain why the 3500 ng/mL level was selected but the level appears to have been based on the 3500 ng/mL level in Clinical Laboratory Standards Institute (CLSI) EP37: Supplemental Tables for Interference Testing in Clinical Chemistry, 1st Edition (FDA Recognition # 7-284). The Supplemental Tables provide recommended interference testing concentrations and are intended for use with the evaluation procedures in CLSI EP07: Interference Testing in Clinical Chemistry, 3rd Edition (FDA Recognition # 7-275). We support the use of voluntary consensus standards, including EP07 and EP37. However, for this particular substance, we do not believe the 3500 ng/mL level reflects current science or adds value for patients. CLSI acknowledges that the science can evolve and stated in EP37 that it removed the table of recommended concentrations from the EP07 into a separate document as recommended thresholds need to change frequently to reflect updates in scientific thinking.

We note that 1160 ng/mL is the highest serum concentration observed in literature with a single 300 mg dose. A dose of up to 300 mg per day (30 times the over-the-counter higher dose available of 10 mg), is an extremely high biotin level. Therefore, testing to 1200 ng/mL is sufficient to cover the highest concentration observed in the literature.

The 3500 ng/mL concentration may be based on calculating 3 times the 1160 ng/mL peak observed in literature. We believe such a safety factor exceeds what is necessary. The 1160 ng/mL peak reported in literature was a result of an experiment and does not reflect an approved treatment. A multiple sclerosis (MS) patient administered the therapeutic treatment (clinical trial) 3 times daily of 100 mg and had a concentration of 694 ng/mL. This level is well below the 1200 ng/mL we recommend be tested pursuant to this guidance. Furthermore, in 2018 two clinical trials testing high-dose, pharmaceutical-grade biotin in MS patients were halted due to poor efficacy results. With the halting of those trials, current trends for high-dose biotin use may have shifted. For all these reasons, we do not believe a safety factor of three times the 1160 ng/mL concentration adds value for patients and would recommend using a level of 1200 ng/mL.

**Manufacturers should have the ability to select medically meaningful biotin levels for inclusion in the labeling.** The draft guidance recommends that the manufacturer include in the labeling information regarding each concentration level tested. However, we think there is an appropriate distinction between what is appropriate for testing and what is appropriate for inclusion in labeling. We note that EP07 recommends labeling of medically meaningful concentration levels. The universe of levels tested is much broader than the universe of levels that are medically meaningful. What constitutes a medically meaningful level will turn on several factors, including intended use. For instance, the medically meaningful levels for an assay intended for monitoring may occur over a broader range than one intended for screening. An expectation to provide all levels tested may result in a very large amount of information in the Instructions for Use if many levels were tested, making it difficult for the end-user to discern the important ones.

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FDA should clarify that in most instances, labeling would be sufficient to mitigate the risk of potentially incorrect results from biotin interference. We would propose clarifying that mitigations in addition to labeling should be reserved for specific and limited cases where the risk of potentially incorrect results from biotin interference could significantly affect patient health. In instances where FDA believes mitigations beyond labeling are needed, educational outreach to audiences other than laboratorians should be considered as a mitigation.

AdvaMedDx thanks FDA for its consideration of these general comments and the specific comments that follow. We provide a line-numbered version of the draft guidance for ease of reference. Please do not hesitate to contact me at 202-434-7230 or jwolszon@advamed.org if you have any questions.

Respectfully submitted,

/s/

Jamie Wolszon
Associate Vice President
Technology and Regulatory Affairs
## Testing for Biotin Interference in In Vitro Diagnostic Devices

<table>
<thead>
<tr>
<th>Section</th>
<th>Line No</th>
<th>Proposed Change</th>
<th>Comment/Rationale</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>General comment</td>
<td>Since FDA believes that biotin consumption is an issue, FDA should recommend that any supplement or cosmetic containing biotin list the biotin quantity on the supplement or cosmetic labeling with a note for consumers to inform their physician that they are taking biotin and the dosage they are taking.</td>
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<tr>
<td>I</td>
<td>169 – 171</td>
<td>The recommendations apply to IVDs, including 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.</td>
<td>Clarifying edit. As currently drafted, the language could be read to suggest that donor screening devices licensed under Section 351 of the Public Health Service Act are not IVDs.</td>
</tr>
<tr>
<td>II</td>
<td>185 – 186</td>
<td>For example, biotin is used in hormone tests and tests for markers of cardiac health like troponin.</td>
<td>We believe that this example could cause readers to overly focus on the tests referenced and not the broader scope of tests that may be susceptible to biotin interference.</td>
</tr>
<tr>
<td>II</td>
<td>189</td>
<td>Excess biotin or biotin levels associated with usage of biotin beyond the recommended daily intake in patient samples can cause falsely high or falsely low results, depending on the test principle.</td>
<td>Revised to clarify that only “excess biotin” or “biotin levels associated with usage of biotin beyond the recommended daily intake” in patient samples can lead to analytically false results. We would also propose adding “principle” as it is the test principle that is determinative for false high or low results.</td>
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<td>II</td>
<td>199 – 201</td>
<td>In addition, extremely high biotin doses also have been observed (up to 300 mg per day, which results in plasma/serum biotin levels of &gt; 1000 ng/mL), in an experimental therapeutic setting in multiple sclerosis patients (peak plasma/serum biotin levels of &gt; 600 ng/mL and &gt; 1000 ng/mL can be observed after 3 doses of 100 mg and single-dose 300 mg biotin, respectively.)</td>
<td>As discussed in the cover letter, plasma/serum levels of 1160 ng/mL were observed in a study administering high-dose biotin to Multiple Sclerosis patients and healthy controls. Piketty et al., 2017. The 300 mg single dose was an investigational case where 1160 ng/mL were measured at peak time. The experimental therapeutic regimen used in the clinical trials of high-dose biotin in MS patients is three times daily of 100 mg, which leads to peak levels &lt; 1000 ng/mL. See Saint Paul et al., 2015.</td>
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<td>II</td>
<td>205 – 208</td>
<td>These recommendations should not be interpreted to mean that FDA considers that in most instances, labeling alone will be sufficient to mitigate the risk of potentially incorrect results from biotin interference in all cases. Mitigations in addition to labeling should be reserved for specific and limited cases where the risk of potentially incorrect results from biotin interference could significantly affect patient health. In instances where FDA believes mitigations beyond labeling are needed, educational outreach to audiences other than laboratorians should be considered as a mitigation.</td>
<td>See cover letter.</td>
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<td>III</td>
<td>220 – 221</td>
<td>Consistent with the recommendations in the CLSI standard, concentrations of biotin that reflect current trends in biotin consumption should be evaluated, up to 1200 3500 ng/mL.</td>
<td>See cover letter.</td>
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<td>III</td>
<td>223–224</td>
<td>The test samples should include analyte levels near the medical decision point(s) of the device.</td>
<td>Clarifying edit to remove possible ambiguity introduced by use of the word “test” in this sentence.</td>
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</tbody>
</table>
| III     | 226–228  | For assays that are susceptible to biotin interference at concentrations below the recommended concentration of 1200 ng/mL, less than 3500 ng/mL, the concentration of biotin at which no interference is detected should be determined; the lowest concentration of biotin at which medically meaningful interference (percent difference or bias) is detected should be determined. | See above and in cover letter supporting our recommendation to move the level to 1200 ng/mL.  
It is our understanding that FDA’s prior recommended approach to interference testing has been as follows: The manufacturer will evaluate the interference at the recommended concentration. If interference is found at that level, then the manufacturer will test at lower levels to determine the lowest concentration level at which there is medically meaningful interference. We would propose language consistent with this approach. |
| III     | 231–234  | Therefore, information on biotin interference should be included in the labeling of the device, including the percent difference or bias at each concentration tested; the bias at medically meaningful concentrations tested for both qualitative and quantitative assays and the consequence of biotin interference (e.g., falsely elevated, falsely depressed), if observed. | See cover letter.                                                                                                                                                                                                 |

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Testing for Biotin Interference in In Vitro Diagnostic Devices

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov/. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions on the content of this guidance, contact Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD) at 240-402-8010 or 800-835-4709, or email ocod@fda.hhs.gov. For questions about this document concerning products regulated by Center for Devices and Radiological Health (CDRH), contact the Office of In Vitro Diagnostics at 301-796-5900, or email CDRH-OIR-Policy@fda.hhs.gov.

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

June 2019
Draft Guidance for Industry

Additional copies are available from:
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

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
https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The Food and 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
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.
IV. REFERENCES

https://ods.od.nih.gov/factsheets/Biotin-Consumer/

https://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm586505.htm


