

# **Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use**

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## **Guidance for Industry and Food and Drug Administration Staff**

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Office of In Vitro Diagnostics and Radiological Health  
Division of Chemistry and Toxicology Devices**

# **Preface**

## **Public Comment**

You may submit electronic comments and suggestions at any time for Agency consideration to <http://www.regulations.gov> . Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2013-D-1445. Comments may not be acted upon by the Agency until the document is next revised or updated.

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## Guidance for Industry and Food and Drug Administration Staff

1 *This guidance represents the current thinking of the Food and Drug Administration (FDA*  
2 *or Agency) on this topic. It does not establish any rights for any person and is not binding*  
3 *on FDA or the public. You can use an alternative approach if it satisfies the requirements*  
4 *of the applicable statutes and regulations. To discuss an alternative approach, contact the*  
5 *FDA staff or Office responsible for this guidance as listed on the title page.*

### I. Introduction

6 This guidance document describes studies and criteria that FDA recommends be used when  
7 submitting premarket notifications (510(k)s) for blood glucose monitoring systems (BGMs)  
8 which are for prescription point-of-care use. FDA intends for this document to guide  
9 manufacturers in conducting appropriate performance studies and preparing 510(k)  
10 submissions for these device types.

11  
12 This guidance is not meant to address self-monitoring blood glucose test systems (SMBGs)  
13 for over-the-counter (OTC) home use by lay-users. FDA is issuing another guidance titled  
14 “Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use” to address those  
15 device types.

16 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM380327.pdf>)

17  
18  
19 For the current edition of FDA-recognized standards referenced in this document, see the  
20 FDA Recognized Consensus Standards Database Web site at  
21 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>.

22  
23 FDA's guidance documents, including this guidance, do not establish legally enforceable  
24 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and  
25 should be viewed only as recommendations, unless specific regulatory or statutory

26 requirements are cited. The use of the word *should* in Agency guidances means that  
27 something is suggested or recommended, but not required.

28

## 29 **II. Background**

30

31 Portable blood glucose meters that measure blood glucose values are used by millions of  
32 people every day as an aid in diabetes self-management. These types of devices are also used  
33 by healthcare professionals in a variety of clinical settings including acute and chronic care  
34 facilities, general hospital wards and intensive care units, physicians' offices, assisted living  
35 facilities and nursing homes.

36

37 Historically, the FDA has not recommended different types of information in premarket  
38 submissions (510(k)s) for BGMSs intended to be used by healthcare professionals as  
39 compared to over-the-counter self-monitoring blood glucose test systems (SMBG) intended  
40 for home use by lay-users. However, it has become increasingly clear that these different use  
41 settings comprise distinct intended use populations with unique characteristics that can  
42 impact device design specifications, and that manufacturers should take these unique  
43 characteristics into account when designing their devices. In order to distinguish between  
44 FDA recommendations for prescription use blood glucose meters, which are intended for use  
45 in point-of-care professional healthcare settings, and those intended for OTC self-monitoring  
46 by lay-users, the Agency is issuing two separate guidances for (i) BGMSs intended for use in  
47 point-of-care professional healthcare settings, and (ii) SMBGs intended for home use for self-  
48 monitoring by lay-users. The FDA believes that by making this distinction, each of the  
49 devices can be better designed to meet the needs of their intended use populations, thereby  
50 providing greater safety and efficacy.

51

52 In recent years, concerns have been raised related to infection control issues involving blood  
53 glucose meters and lancing devices. According to the Centers for Medicare and Medicaid  
54 Services (CMS) and the Centers for Disease Control and Prevention (CDC), blood glucose  
55 meters can transmit bloodborne pathogens if these devices are contaminated with blood  
56 specimens and are shared between users without effective cleaning, disinfecting, and  
57 appropriate infection control measures.<sup>1</sup> Because BGMSs used in professional healthcare  
58 settings are more likely to be used on multiple patients, this type of use requires certain  
59 design features and capacity for cleaning and disinfection to prevent the spread of bloodborne  
60 pathogens.<sup>2</sup>

61

62 In addition, concerns have been raised regarding the inability of currently cleared BGMSs to  
63 perform effectively in professional healthcare settings because these devices have not been  
64 adequately evaluated in some of the populations in which they are being used. Patients in  
65 professional healthcare settings are often fundamentally different than lay-users using these

---

<sup>1</sup> See information at <http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html>.

<sup>2</sup> Thompson, N.D. and Perez, J.F. (2009) Eliminating the blood: Ongoing outbreaks of hepatitis B virus infection and the need for innovative glucose monitoring technologies. *Journal of Diabetes Science and Technology*. 3(2), 283-288.

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66 devices at home. Patients in professional healthcare settings can be acutely ill and medically  
67 fragile and are more likely to present physiological and pathological factors that could  
68 interfere with glucose measurements relative to lay-users. Errors in BGMS device accuracy  
69 can lead to incorrect insulin dosing, which, when combined with other factors, can lead to  
70 increased episodes of hypoglycemia. For hospitalized patients who may be seriously ill,  
71 glucose meter inaccuracies could further increase risk to health.

72  
73 Previously, most blood glucose meters, even those intended to be used by healthcare  
74 professionals, were submitted to FDA with claims for OTC home use by lay-users. Sponsors  
75 evaluated these devices for self-use by healthy people with diabetes or by healthcare  
76 professionals on healthy people with diabetes; however, they were actually being used by  
77 healthcare professionals as point-of-care (POC) devices to monitor blood glucose levels in  
78 diabetic and non-diabetic patients in various states of health. Scientific and clinical issues  
79 specific to the professional healthcare setting which could affect glucose meter performance  
80 were never evaluated for these devices. Use of BGMSs in professional healthcare settings on  
81 patients in various states of health and receiving intensive medical intervention and therapy,  
82 when they were evaluated and cleared based on studies performed in healthy subjects, can put  
83 patients at risk. Therefore, when devices are intended for use in professional healthcare  
84 settings, the intended use population should be accurately defined, distinct performance  
85 parameters should be met, and sponsors should demonstrate substantial equivalence of the  
86 device for that particular use.

87  
88 The intent of this guidance is to describe the studies that should be conducted to demonstrate  
89 BGMS performance for devices which are intended to be used in diverse professional  
90 healthcare settings on subjects in various states of health. Intended use populations for a  
91 BGMS may include patients in all professional healthcare settings, patients in specific  
92 healthcare settings (e.g., in emergency response vehicles), patients in long-term care  
93 facilities, or patients at a physician's office. The Agency expects that not all sponsors will  
94 seek clearance for their device to be used across all professional healthcare settings. BGMSs  
95 intended for POC use in specific professional healthcare settings should be studied in those  
96 specific populations according to the recommendations in this guidance, and labeled  
97 appropriately. For BGMSs intended for use in many or all professional healthcare settings, it  
98 may be necessary to identify sub-populations in which the BGMS may function differently  
99 than in the broader intended use population. The identification and study of patient  
100 subpopulations is described in greater detail in Section VI.C below. In all cases, performance  
101 studies should account for factors such as disease state, patient condition, physiological state  
102 and medications that might affect device performance in the intended use population for that  
103 BGMS.

104  
105 *CLIA waiver of professional use meters*

106  
107 FDA's clearance of a 510(k) submission for SMBGs intended for OTC home use allows  
108 automatic CLIA waived categorization (*see* 42 U.S.C. 263a(d)(3)). As described above, most  
109 blood glucose meters on the market today, even those used in healthcare professional

110 settings, were previously submitted to FDA with claims for OTC use by lay-users and were  
111 therefore given CLIA waived categorization pursuant to regulation (see 42 CFR 493.15). The  
112 use of blood glucose meters cleared for OTC use in professional healthcare settings poses a  
113 number of additional risks to patients, as described above. By contrast, clearance of BGMSs  
114 as prescription use devices intended for point-of-care use in professional healthcare settings  
115 as described in this guidance means that FDA expects that clearance of BGMSs for  
116 prescription point-of-care use will be categorized upon clearance as moderate complexity.  
117 However, FDA recognizes the importance of having CLIA-waived BGMSs in point-of-care  
118 professional healthcare settings and intends, through the studies described in this guidance, to  
119 facilitate CLIA waiver for these devices by recommending that the information described  
120 below be submitted in a dual 510(k)/CLIA waiver submission or an associated application for  
121 CLIA Waiver, and enabling BGMSs to be CLIA waived concurrently with their 510(k)  
122 clearance.<sup>3</sup>

123  
124 FDA has proposed several studies in this guidance that can be performed in a way that will  
125 allow sponsors to request both FDA review of their 510(k) submission clearance and CLIA  
126 waiver for their BGMSs concurrently. For example, the recommended number of samples  
127 (for each sample type: arterial, venous, capillary blood) requested in the Method  
128 Comparison/User Evaluation (Section VI-C below) is specifically recommended to allow  
129 results from this study to be used to support a CLIA waiver application. The sponsor should  
130 plan to conduct these studies using untrained intended users in a CLIA waived setting. Based  
131 on feedback from the clinical community, we understand that because of the settings in which  
132 these devices are used, and the types of users who use them in clinical practice, it is  
133 beneficial to patients and the healthcare community that BGMSs be CLIA waived; therefore,  
134 sponsors should design their studies with CLIA-waiver in mind. We recommend that  
135 sponsors refer to FDA’s guidance entitled “Recommendations: Clinical Laboratory  
136 Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In  
137 Vitro Diagnostic Devices”  
138 (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm079632.htm>) to further  
139 understand how the studies described and recommended in this guidance can be performed to  
140 support CLIA waived status We also encourage sponsors to contact the Agency with  
141 questions prior to starting their studies to ensure that the studies they plan to perform are  
142 designed to support CLIA waived use of their device.<sup>4</sup>

### 144 **III. Scope**

145  
146 This guidance document is limited to BGMSs which are regulated under 21 CFR 862.1345.

147  
148 The following product codes are within the scope of this guidance document:

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<sup>3</sup> For information on FDA’s CLIA administrative procedures, see FDA’s guidance entitled “Administrative Procedures for CLIA Categorization – Guidance for Industry and Food and Drug Administration Staff”.  
(<http://www.fda.gov/RegulatoryInformation/Guidances/ucm070762.htm>).

<sup>4</sup> Requirement for a Pre-Submission for a Dual 510(k) Waiver by Application  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm393233.htm>

149 CGA (glucose oxidase method)  
150 CFR (hexokinase method)  
151 LFR (glucose dehydrogenase method)

152

153 This document is **not** meant to address the following types of devices:

154

- 155 • SMBGs intended for home use by lay-users (product code NBW). Additional  
156 considerations (labeling or other) may be needed for OTC devices.
- 157 • Devices used to screen for and/or to diagnose diabetes (such as clinical chemistry  
158 analyzers).
- 159 • Continuous glucose sensors, implanted or external (e.g., continuous glucose  
160 monitoring systems (CGMs) or sensors within catheters).
- 161 • Non-invasive glucose measurement devices (i.e., devices that do not require removal  
162 of a blood sample from a fingerstick or other anatomical site).
- 163 • Blood glucose test technologies labeled for specialized use (e.g., for automated  
164 monitoring to aid in glycemic control protocols).

165

166 While FDA recommends that the information described in this guidance be included in  
167 premarket submissions for BGMSs, submissions containing alternative information may be  
168 sufficient if able to demonstrate substantial equivalence to a legally marketed predicate  
169 device.

170

171 We recommend that you contact the Division of Chemistry and Toxicology Devices in the  
172 Office of In Vitro Diagnostics and Radiological Health (OIR) if you have questions regarding  
173 alternative intended uses or similar technologies.

174

## 175 **IV. Reducing the Risk of Bloodborne Pathogen** 176 **Transmission**

177

178 Since BGMSs use blood specimens for glucose measurement, their design and instructions  
179 for use are very important factors in reducing the risk of bloodborne pathogen transmission  
180 during use. This is especially important for blood glucose meters used in professional settings  
181 which may be used in the care of multiple patients. According to the Centers for Medicare  
182 and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC),  
183 blood glucose meters can transmit bloodborne pathogens such as viral hepatitis, if these  
184 devices are contaminated with blood and are shared between users without effective cleaning  
185 and disinfection.<sup>5</sup> To minimize the risk of bloodborne pathogen transmission you should  
186 address the following in your device design and labeling:

187

---

<sup>5</sup> “Infection Prevention during Blood Glucose Monitoring and Insulin Administration”  
<http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html>.



- 188 • Meters should be designed such that all external materials can be cleaned (removal of  
189 organic soil) and disinfected (microbicidal process).  
190 • All external surfaces of the meter, including seams and the test strip port, should be  
191 designed for both ease of use and ease of cleaning and disinfection.  
192 • You should develop an effective disinfection method and provide the validated  
193 cleaning and disinfection procedures for your BGMS device in your 510(k)  
194 submission as well as in the labeling. Cleaning and disinfection are different  
195 processes and need separate validation procedures and specifications.  
196 • You should validate the efficacy of any disinfectant you recommend for use with your  
197 device, as described below. We recommend you consult the Environmental Protection  
198 Agency’s (EPA) list of disinfectants that are registered for use against infectious  
199 bacteria and viruses in choosing disinfectants to validate for use with your device.<sup>6</sup>  
200 • Your BGMS device should be intended for use with only auto-disabling, single use  
201 lancing devices. Single use lancing devices are designed to be used only once, after  
202 which the blade is retracted, capped, or otherwise made unusable. The auto-disabling,  
203 single use lancing device you recommend for use with your BGMS device should be  
204 specified in your labeling. You should emphasize in the labeling that lancing devices  
205 are for single patient use and should NEVER be used for more than one person. Your  
206 labeling should instruct users to discard lancing devices in designated sharps  
207 containers.  
208 • Labeling concerning safe device use can reduce the risk of user error, therefore,  
209 instructions for cleaning and disinfection should be clear and detailed. The various  
210 test system components should be named in such a way that they are recognized as  
211 belonging to the same system or family of products, and to distinguish them from  
212 similar devices intended for single-patient use only (e.g., ABC blood glucose test  
213 system, ABC blood glucose meter, ABC blood glucose test strips, etc.). See Section X  
214 Labeling below for detailed labeling recommendations. For additional information  
215 on labeling your reusable medical device, see FDA’s guidance entitled “Reprocessing  
216 Medical Devices in Health Care Settings: Validation Methods and Labeling”  
217 ([http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidan  
219 cedocuments/ucm253010.pdf](http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidanc<br/>218 cedocuments/ucm253010.pdf)).

220 Validation of cleaning and disinfection procedures involves both validation that the cleaning  
221 and disinfection products are effective against the primary viruses of concern (Human  
222 Immunodeficiency Virus (HIV), Hepatitis B, Hepatitis C) and validation that the cleaning and  
223 disinfection procedures do not deteriorate the device or alter device performance. FDA’s  
224 recommendations for such validation procedures are outlined in the following Subsections.

### 225 **A. Validated cleaning and disinfection procedures**

226 You should select cleaning and disinfection products that do not result in physical  
227 deterioration of the device overall, or any device component such as the housing, touch

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<sup>6</sup> Selected EPA-registered Disinfectants available at <http://www.epa.gov/oppad001/chemregindex.htm>.

228 pad, or buttons. You should make note of any physical indicators of deterioration during  
229 your validation study and provide this information for our review in your 510(k)  
230 submission. The disinfectant product you choose should be effective against HIV,  
231 Hepatitis B, and Hepatitis C viruses. Of these viruses, Hepatitis B virus is the most  
232 difficult to kill and prior outbreak episodes associated with blood glucose meters have  
233 been due to transmission of Hepatitis B viruses. Therefore, disinfection efficacy studies  
234 should be performed to demonstrate effectiveness of the chosen disinfectant against  
235 Hepatitis B virus. Please note that 70% ethanol solutions are not effective against viral  
236 bloodborne pathogens, and the use of 10% bleach solutions may lead to physical  
237 degradation of your device.

238  
239 To demonstrate that your disinfection procedure is effective against Hepatitis B virus, you  
240 should perform disinfection efficacy studies to demonstrate that your procedure is  
241 effective with the external meter materials (e.g. case, display, buttons, etc.). Studies have  
242 demonstrated that viruses can remain infective for different time periods, depending on  
243 the surface. Viral survival may increase or decrease with the number of microbes present  
244 on a surface. Increasing amounts of microbes can protect viruses from disinfection, and  
245 damaging effects may also result from microbial proteases and fungal enzymes. Factors  
246 that influence survival on surfaces include fomite properties, initial viral titer, virus strain,  
247 temperature, humidity and suspending media. The simplest disinfection method would be  
248 the use of towelettes pre-saturated with a selected disinfectant. Disinfection with a  
249 towelette will reduce the risk of liquid getting into the meter, therefore minimizing the  
250 chance of affecting the glucose meter function. However, you should choose a  
251 disinfectant that is effective against Hepatitis B Virus and is compatible with your device.  
252 If you intended to claim that your disinfection protocol is effective against other  
253 pathogens you should consider submitting a pre-submission to discuss this with the  
254 Agency prior to conducting your testing. For information about the pre-submission  
255 process, see FDA's guidance entitled "Requests for Feedback on Medical Device  
256 Submissions: The Pre-Submission Program and Meetings with Food and Drug  
257 Administration Staff  
258 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>).

260  
261 We recommend you refer to the following standards:

- 262 • ASTM standard ASTM E1053-11: *Standard Test Method for Efficacy of Virucidal*  
263 *Agents Intended for Inanimate Environmental Surfaces*
- 264 • ASTM standard ASTM E2362-09: *Standard Practice for Evaluation of Pre-saturated*  
265 *or Impregnated Towelettes for Hard Surface Disinfection.*

266 **B. *Demonstration that the device is robust to cleaning and disinfection***  
267 ***procedures***

268 You should demonstrate through bench studies that your BGMS device is robust to  
269 cleaning and disinfection procedures after multiple cleaning and disinfection cycles. You  
270 should describe in your 510(k) submission the study design and results demonstrating that

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271 the analytical performance of the BGMS is not impacted by the cleaning and disinfection  
272 procedures.

273  
274 You should address the following in your study design:

- 275  
276 • You should choose worst case scenarios with regards to cleaning and disinfection  
277 frequency and end user environment to determine the number of cleaning and  
278 disinfection cycles that should be tested. For example, the number of times you clean  
279 and disinfect the meter should be representative of the cleaning and disinfection that  
280 the meter will be exposed to during its use life (typically 3-5 years). A cleaning step  
281 should precede the disinfection step for each cleaning and disinfection cycle.
- 282 • The disinfection contact time used in the robustness study should be identical to the  
283 contact time used in the disinfection efficacy testing and described in your cleaning  
284 and disinfection instructions in the labeling.
- 285 • We recommend using the same disinfectant product for both cleaning and  
286 disinfection. The effects of using multiple cleaning products on the efficacy of  
287 disinfectant products are not well understood.
- 288 • You should demonstrate that the test strip port and all other openings which are  
289 susceptible to blood contamination and could either directly or indirectly be contacted  
290 during use are able to withstand your cleaning and disinfection procedures. You  
291 should ensure that you test parts of the meter that are particularly susceptible to blood  
292 contamination, such as the test strip port and material seams. It is important to be able  
293 to clean and disinfect all parts of your meter to reduce the risk of bloodborne  
294 pathogen transmission.
- 295 • When you evaluate your device after the cleaning and disinfection phase, you  
296 should ensure that the procedure does not cloud or deface the display of the meter and  
297 does not corrode or erode the plastic housing or buttons. You should note all these  
298 physical indicators of deterioration throughout your study and include these results in  
299 your 510(k) submission. You should evaluate the accuracy of the meter using blood  
300 samples compared to results obtained by a comparator method (please refer to Section  
301 VI below for the definition of comparator method) to ensure that accuracy is not  
302 affected by repeated cleaning and disinfection. You should also evaluate the  
303 functionality of meter features (as appropriate), for example, touch screen function,  
304 USB port function, speaking functions, etc., to ensure they are not affected by  
305 repeated cleaning and disinfection.
- 306 • You should include infection control in your risk analyses and incorporate your  
307 validated cleaning and disinfecting procedures into your risk assessment.

308  
309 You should include a description of the protocols and acceptance criteria for all studies in  
310 your 510(k) submission.

311

## V. Device Description

You should provide the following information in the device description portion of your 510(k) submission:

- Description of physical components of the system (including diagrams where appropriate).
- Manufacturer's performance specifications.
- Description and explanation of the test principle, including chemical reactions.
- Description of the format of results, including units of measurement and whether results are reported in whole blood or plasma equivalents<sup>7</sup>.
- Description of the composition and levels of control material recommended for use with your system.
- User maintenance needs (e.g., batteries).
- Features of the device, such as data transmission capabilities or features designed to enhance robustness and ease of use.
- Features designed to minimize the risk of bloodborne pathogen transmission among patients.

Description of features controlled by the software, which should describe the following:

- Displays and user messages: This includes how the BGMS determines and displays the glucose concentration, messages or displays that appear while a user is taking a measurement, and features such as how a user can retrieve past results from storage in the device.
- User prompts: You should describe prompts that the BGMS provides to the user, expected user responses, and timing issues (e.g., how quickly does the user need to respond, what happens if they respond after the allowed time). Examples of a user prompt include messages to the user to add specimen to the test strip, insert the test strip into the meter, calibrate the meter, or store a result, etc.
- Error messages and alerts: This includes any error messages or alerts that the BGMS displays. You should describe how the system responds to errors in user action, user inaction, or system status. Suggested examples of error messages or alerts include when a test strip is inserted incorrectly or removed prematurely, too small a sample is applied to the test strip, damaged, incorrect or deteriorated test strips are used, or when there is a low battery or excessively high ambient temperature. This should also include the methods by which the BGMS detects and alerts the user when glucose levels are outside of the linear range of the system. You should describe at what point each message is triggered and describe any self-diagnostic routines that the system

---

<sup>7</sup> Note that BGMSs intended for use in the U.S. should report results in mg/dL and in plasma equivalents.

353 performs.

354

- 355 • It is important that you identify the expected responses by the user to the error  
356 messages or alerts. This includes whether and how the user should input information  
357 or press certain buttons to correctly set up the meter or respond to an error message or  
358 alert.

359

## 360 **VI. Performance Evaluation for Prescription-Use** 361 **BGMSs**

362

363 Subsections A-F below indicate the types of device performance information that you should  
364 include in a 510(k) submission for a BGMS. Although many manufacturers design their  
365 BGMS validation studies based on the International Standards Organizations document  
366 15197: *In vitro diagnostic test systems—Requirements for blood glucose monitoring systems*  
367 *for self-testing in managing diabetes mellitus*, FDA believes that the criteria set forth in the  
368 ISO 15197 standard do not adequately protect patients using BGMSs in professional settings,  
369 and does not recommend using the criteria in ISO 15197 for BGMSs.

370

371 In this guidance, the term “comparator method” refers to a laboratory-based glucose  
372 measurement method that has been well-validated for precision and accuracy, and that is  
373 traceable to a higher order, e.g., an internationally recognized reference material and/or  
374 method. The traceability chain should include as few stages as possible to reduce bias. FDA’s  
375 current thinking on the recommended study designs and device performance criteria are  
376 discussed below in Subsections A-F.

377

### 378 **A. Precision Evaluation Study**

379 You should evaluate both within-run precision and intermediate precision for your BGMS  
380 and include these evaluations in your 510(k) submission. The following sections outline  
381 FDA’s current thinking on appropriate study design and analyses to evaluate within-run  
382 and intermediate precision for BGMSs.

383

#### 384 *Within-Run Precision Evaluation:*

385 Within-run precision studies are bench studies designed to evaluate imprecision under  
386 conditions of repeated measurement of the same sample with different meters and  
387 multiple test strip lots. In order to assess imprecision of the device across the claimed  
388 measuring range, you should evaluate samples containing glucose concentrations within  
389 each of the five intervals provided in Table 1 below.

390

391

**Table 1. Glucose Concentrations for Precision Evaluations**

<b>Interval</b>	<b>Glucose Concentration Range (mg/dL)</b>
1	30-50
2	51-110
3	111-150
4	151-250
5	251-400

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394

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You should determine within-run precision using venous whole blood samples. Altered venous whole blood samples such as those that are spiked, diluted, or allowed to glycolyze in order to obtain the appropriate glucose concentrations are acceptable in order to facilitate coverage of the entire claimed glucose measuring range. However, you should clearly identify all altered samples (spiked, diluted, or glycolyzed) in all submitted data. A minimum of 500 test strips from at least 10 vials and 3 manufacturing lots should be used in this study. For each sample concentration, a minimum of 10 meters should be used, with at least 10 measurements taken by each meter (i.e., at least 100 measurements per concentration). Test strips should be taken from the same vial and/or package for each meter.

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We recommend you present the results as the mean value of all measurements per meter for each glucose concentration with the corresponding standard deviation (SD) and percent coefficient of variation (CV). In addition, for each glucose concentration range in Table 1, you should also provide the mean value, standard deviation (with 95% confidence intervals) and percent CV for data combined over all meters. You should describe the statistical procedures used in the analysis. You should provide the results based on all data, and if you wish to exclude any data points (outliers), you should provide a separate, additional data analysis with those points excluded and fully describe the method of outlier identification and the results of your investigations into those outliers.

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*Intermediate Precision Evaluation:*

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Intermediate precision measurement studies are bench studies designed to evaluate imprecision under simulated normal use conditions; for example, measurement by multiple operators over multiple days using multiple reagent system lots. These studies may be performed with prepared control solutions rather than whole blood samples.

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The total number of meters and individual operators in these studies is at the discretion of the sponsor; however, a minimum of 10 meters should be used for each glucose concentration. Intermediate precision should be evaluated over a minimum of 10 days, taking at least 1 measurement per meter per day of a sample from each glucose concentration interval listed in Table 1. This should produce a minimum of 10 measurements per meter for each glucose concentration and 100 total measurements per glucose concentration. You should use a minimum of 500 test strips from a minimum of

428 10 vials or packages that cover a minimum of 3 manufacturing lots. These test strips  
429 should be taken from the same vial and/or package for each meter.

430

431 For each glucose concentration in Table 1, you should present data for each test strip lot  
432 and also for pooled lots including the mean value of the measurements for each meter  
433 with the corresponding standard deviation (SD) and percent coefficient of variation (CV).  
434 You should also present the mean value, standard deviation (with 95% confidence  
435 intervals) and percent CV for data combined over all meters. You should describe the  
436 statistical procedures you use. You should provide results based on all data, and if you  
437 wish to exclude any data points, you should provide a separate, additional data analysis  
438 with those points excluded and fully describe the method of outlier identification and the  
439 results of your investigations into those outliers.

440

## 441 **B. *Linearity Evaluation Study***

442 You should evaluate the linearity of your BGMS across the entire claimed measuring  
443 range. We recommend that studies include an evaluation of at least 11 evenly spaced  
444 concentrations tested and analyzed according to the guideline “Evaluation of the  
445 Linearity of Quantitative Measurement Procedures: A Statistical Approach”, CLSI  
446 document EP6-A. Linearity studies should be performed using venous whole blood  
447 samples. Altered venous whole blood samples such as those that are spiked, diluted, or  
448 glycolyzed are acceptable in order to facilitate coverage of the entire glucose  
449 concentration range. You should clearly identify the number of altered samples (spiked,  
450 diluted, or glycolyzed) within your 510(k) submission.

451

452 You should submit a detailed description of the study design, target concentrations, a list  
453 of all data collected in this study, summary of the results and conclusions drawn from the  
454 study, and a description of the statistical analysis used.

455

## 456 **C. *Method Comparison/User Evaluation***

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### 458 **1. *General Study Design***

459 When testing samples from the intended patient population, you should design your study  
460 to accurately reflect system performance in the hands of the intended user. You should  
461 perform a set of comprehensive clinical evaluations to assess system accuracy to support  
462 the professional use of these devices in the intended use population.

463

464 FDA recognizes that most study evaluations performed for 510(k) submissions occur in  
465 idealized conditions, thereby potentially overestimating the total accuracy of the BGMS,  
466 even when performed in the hands of the intended user. Nonetheless, it is important that  
467 you design your study to most accurately evaluate how the device will perform in the  
468 intended use population. Therefore, the study should be conducted in conditions that  
469 reflect the expected use of the device. This study should be performed under  
470 environmental conditions that are consistent with the validated environmental conditions

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471 of the device (e.g., temperature, humidity, altitude, etc.). You should fully describe the  
472 conditions of your study in your 510(k) submission.

473  
474 You should evaluate device accuracy for each claimed sample type (e.g., arterial, venous,  
475 capillary, heelstick whole blood, etc.) when the device is used by a POC operator.  
476 Evaluation of each sample type should include a minimum of 350 patients (e.g., samples  
477 from at least 350 patients for an arterial study, samples from at least 350 patients for a  
478 capillary study, samples from at least 350 patients for a venous study, etc.). FDA  
479 recommends sponsors perform their studies to support concurrent CLIA waiver at the  
480 time of clearance by performing the studies as described in this guidance with  
481 consideration to the aspects of study design described in FDA’s guidance entitled  
482 “Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA)  
483 Waiver Applications for Manufacturers of In Vitro Diagnostic Devices”  
484 (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm079632.htm>).<sup>8</sup> Different  
485 sample types (e.g., arterial and venous) can be acquired from the same patient and be used  
486 in the different studies. Each sample should be fresh and measured on both the candidate  
487 device (i.e., new device) and the comparator method. Samples do not have to be  
488 collected specifically for your studies; however, to obtain CLIA waiver, the tests should  
489 be done per the labeling instructions by untrained users typical of CLIA-waived users.  
490 Note that patient information should be available for each sample to aid in the  
491 identification of potential interfering factors. More than one measurement may be taken  
492 with the comparator method and averaged for each sample in order to allow a better  
493 estimate of the true glucose value of that sample. However, no measurements should be  
494 excluded from the data analysis. It is not necessary that POC operators perform the  
495 comparator method measurements in the study.

496  
497 For each claimed sample type, the samples tested should adequately span the claimed  
498 glucose measuring range of the BGMS device. Though it may be difficult to obtain  
499 samples at the extreme ends of the measuring range, the study for each sample matrix  
500 should contain at least 10 unaltered samples < 80 mg/dL and at least 10 unaltered samples  
501 between 300 mg/dL and the upper limit of the claimed measuring range of the device. It  
502 may be necessary to enroll more than 350 patients for each sample type in order to obtain  
503 at least 10 unaltered samples < 80 mg/dL and at least 10 unaltered samples between 300  
504 mg/dL and the upper limit of the claimed measuring range of the device. Testing should  
505 be performed by the intended POC operators (e.g., nurses, nurse assistants, etc.) to  
506 accurately reflect device performance in POC settings; at least 9 operators should  
507 participate in each study (e.g., capillary, venous, and arterial studies). Different operators  
508 may be used for each study. You should submit data from all subjects; no data or subjects  
509 should be excluded from your analysis.

510  
511 The subjects you enroll in the method comparison/user study should accurately reflect the  
512 intended use population of your device. In your 510(k) submission, you should describe

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<sup>8</sup> For example, users should be untrained, and the studies should be performed in intended use settings in the midst of normal working conditions. Please note that we intend to accept 350 patient samples for each sample type for the purposes of CLIA waiver studies for these devices.



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513 the inclusion and exclusion criteria for enrolling study subjects, as well as the  
514 demographics of the subjects that participated in the study. If your intended use  
515 population is broad but includes patient sub-populations that might be particularly  
516 vulnerable to potential interferences and/or health risks resulting from meter inaccuracy,  
517 you should identify and include patients from these specific vulnerable sub-populations in  
518 your study. You should define these sub-populations and provide a rationale for your  
519 definitions. For example, vulnerable sub-populations could be defined as patients in  
520 specific hospital wards, units, or departments— medical, neonatal, pediatric or surgical  
521 intensive care units (ICUs). Vulnerable subpopulations could, for example, also be  
522 defined as categories of patients with general types of medical conditions—cardiac,  
523 surgical, pulmonary, or oncology patients. These sub-populations are provided as an  
524 example for common patient groups found in a hospital setting, however, if you would  
525 like to discuss other sub-populations or other aspects of your study with the Agency, we  
526 recommend that you submit a request for a Pre-Submission meeting prior to conducting  
527 your testing. For information about the pre-submission process, see FDA’s guidance  
528 entitled “Requests for Feedback on Medical Device Submissions: The Pre-Submission  
529 Program and Meetings with Food and Drug Administration Staff  
530 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>).

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532  
533 Your study should include at least 50 patients from each vulnerable patient sub-  
534 population you have defined in order to collect sufficient performance data to support the  
535 use of your device in these populations. Please note that in some instances, in order to  
536 fully characterize your device in your intended use population, FDA suggests that you use  
537 more than 50 patients per subpopulation to ensure all conditions and medications have  
538 been evaluated. Furthermore, if you intend for your study to also support a broad  
539 intended use population, then you should ensure that your study population includes  
540 sufficient numbers of patients outside of the vulnerable subpopulations you identified to  
541 support the use of your device in the broader intended use population. This broader  
542 population might include in-patients dispersed throughout various hospital departments.  
543 Depending on the number of specific vulnerable sub-populations you identify, the  
544 collection of samples from more than 350 subjects for each sample type (venous, arterial,  
545 capillary) may be indicated to support the use of your device in your intended use  
546 population. Your results should clearly indicate the specific patient population associated  
547 with each sample and you should present the combined results for your entire intended  
548 use population and separately for each vulnerable patient subpopulation (if present).

549  
550 If you wish to claim suitability of your device with anti-coagulants, then within the 350  
551 (minimum) samples you collect for each sample type you should include at least 50 to 75  
552 patient samples per claimed anti-coagulant.

553  
554 In your study, you should include a minimum of 10 test strip vials or packages that cover  
555 a minimum of 3 test strip lots. All test strips used in the study should have undergone  
556 typical shipping and handling conditions from the site of manufacture to a U.S. user prior

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557 to the study. You should describe these shipping and handling conditions in your 510(k)  
558 submission.

559

560 Method comparison and user performance studies for a BGMS should include multiple  
561 users and multiple blood glucose meters. Only auto-disabling, single use lancing devices  
562 should be used in these studies. You should incorporate your labeling instructions for  
563 cleaning and disinfection in your user study protocol to ensure that the meters are  
564 appropriately cleaned and disinfected during the course of this study and any additional  
565 measures in place to mitigate the risk of potentially transmitting disease between  
566 healthcare providers and subjects during the study (for example use of disposable gloves  
567 or other physical barriers). The study protocol should also include details on how often  
568 and when gloves worn by the trained health professionals should be changed between  
569 subjects. Meters should be cleaned and disinfected after each subject, using validated  
570 procedures for all studies performed. Refer to Section IV, above (Reducing the Risk of  
571 Bloodborne Pathogen Transmission) for additional information regarding the validation  
572 of cleaning and disinfecting of BGMSs.

573

574 BGMS test results are used by healthcare professionals to make critical decisions about  
575 treatment; therefore, it is important that the results are accurate so that medical decision  
576 errors are better avoided. In order to demonstrate that a BGMS is sufficiently accurate for  
577 use by health care professionals, you should demonstrate that 95% of all values are within  
578 +/- 12% of the comparator method for glucose concentrations,  $\geq 75$  mg/dL, and within +/-  
579 12 mg/dL at glucose concentrations  $< 75$  mg/dL, and 98% of values should be within +/-  
580 15% of the comparator method for glucose concentrations  $\geq 75$  mg/dL, and within +/- 15  
581 mg/dL at glucose concentrations  $< 75$  mg/dL. The BGMS should be as accurate as  
582 possible to avoid critical patient management errors. Though we expect that BGMSs will  
583 be able to meet this criteria, there may be instances where meters may be determined to  
584 be substantially equivalent when performance does not meet these criteria because, for  
585 example, other features of the meter or its setting of use provide benefits that compensate  
586 for different performance. In instances where your BGMSs is unable to meet this criteria,  
587 you should provide a clinical justification for all test results, including those that exceed  
588 the above mentioned criteria, and describe why the potential for that error would not  
589 affect patient safety when extrapolated to the intended use setting (e.g., when extrapolated  
590 to the volume of testing performed in the intended use setting). FDA will review your  
591 justification to determine whether the data suggest that patients may be put at risk or  
592 whether your justification and any proposed mitigations are adequate.

593

594 Hematocrit and sodium values should be measured and recorded for each study subject to  
595 help identify potential interference with the device and to inform investigations into  
596 outlier results. Similarly, blood oxygen levels should be measured and recorded for each  
597 patient for any arterial blood study. You should present these individual values in the  
598 510(k) submission along with the BGMS and comparator method results. It is not  
599 necessary that hematocrit, sodium and blood oxygen measurements be made by POC  
600 operators.

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We expect that the measuring range of the meter will meet the clinical needs of the intended use population. BGMSs intended for prescription-use in the hospital setting should be able to measure blood glucose accurately down to 10 mg/dL and up to 500 mg/dL, or a clinical justification should be provided for alternate measuring ranges. BGMSs intended for use outside a hospital setting and which will not reasonably be used to test neonatal samples should be able to measure blood glucose accurately down to 20 mg/dL. The BGMS device should identify and provide an error code in situations where the measured glucose level falls outside of the device's stated measuring range. For example, if BGMS XYZ has a measuring range that can detect glucose concentrations down to 10 mg/dL, then blood samples with glucose concentrations below 10 mg/dL should provide an appropriate error code (e.g., "LOW - Less than 10").

You should describe the following in your 510(k) submission:

- Study setting including the size, type, and location of each site and a justification of how the selected study conditions simulate intended use conditions. Study sites should be representative of where BGMSs are used in the U.S. and you should include an explanation of why you believe each site is representative.
- Criteria used to select study subjects.
- Description of the patient demographics including age, disease states, and all medications for each patient.
- Sample types collected (arterial, venous, capillary).
- Number of test strip lots, number of test strip vials, and number of meters used in the study.
- Description of the shipping and handling conditions of the test strips prior to use in the study.

*Accuracy at Extreme Glucose Values:*

Because the study described above using real patient samples may not provide a robust evaluation of BGMS performance in the extreme upper and lower ends of the measuring range, you should perform additional studies using blood samples altered to achieve glucose concentrations of less than 80 mg/dL and greater than 300 mg/dL. This additional extreme glucose value study should be performed separately from the method comparison/user evaluation described above and may be performed in a laboratory setting, though untrained intended users typical of users in a CLIA waived setting should perform the testing to support CLIA waiver of the device.

Your study of accuracy at extreme glucose values should include a minimum of 50 prepared samples with glucose concentrations < 80 mg/dL and a minimum of 50 prepared samples with glucose concentrations > 300 mg/dL. These samples should evenly cover the lower and upper limits of the claimed measuring range. Samples may be altered by spiking or allowing the samples to glycolyze in order to obtain appropriate glucose concentrations. Samples should be measured on both the BGMS device and the comparator method. You should analyze this data separately from the user evaluation data

646 but using the same methods described below for the user evaluation. FDA will apply the  
647 same review criteria to both studies.

648  
649 *Neonatal Studies:*

650 If your intended use population includes neonates, you should perform studies to support  
651 performance in neonatal samples (defined as samples from subjects less than 28 days  
652 old). Neonatal blood is known to differ from adult blood and these differences may have  
653 a direct impact on the safety of blood glucose monitoring in that population. For example,  
654 neonatal blood often has higher hematocrit levels (51 to 65 %) and lower blood glucose  
655 concentrations (20 to 80 mg/dL) compared to adult blood.

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657 You should evaluate device performance with neonatal samples in direct comparison to  
658 the comparator method by testing 100 -150 fresh neonatal blood specimens, including  
659 samples from neonates less than 24 hours old. Samples should be collected and measured  
660 by at least three POC users in a POC setting. Glucose concentrations should be measured  
661 with the BGMS and the comparator method, and the hematocrit levels for each patient  
662 should also be measured and reported in the study. You should present your results as  
663 described below in the Data Analysis Subsection. Data from all subjects in the study  
664 should be submitted in your 510(k), and no subjects should be excluded from the data  
665 analysis.

666  
667 Since it may be difficult to obtain samples at the extreme low end of the measuring range  
668 using real neonatal patient samples, you should perform additional studies using blood  
669 samples (either adult blood or maternal cord blood) altered to achieve glucose  
670 concentrations between 10 and 50 mg/dL. Blood specimens used in these additional  
671 studies should be adjusted to at least two levels of hematocrit at or near 40% and 65%, in  
672 order to simulate the high hematocrit levels of neonatal blood. This will allow you to  
673 provide a robust evaluation of device performance in the extreme lower end of the  
674 measuring range for simulated neonatal blood. These additional studies should be  
675 performed separately from the neonatal studies described above and may be performed in  
676 a laboratory setting (e.g., at the manufacturer's facility), however, untrained users typical  
677 of CLIA-waived users should perform the testing to support CLIA waiver of the device.

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680 **2. Data Analysis**

681 *Data exclusion and outliers:*

682 You should present all data in the 510(k) submission, including cases in which the meter  
683 displays an error code, a 'High' or 'Low' message, or no result. All outliers (e.g., data  
684 points that do not conform to minimum accuracy criteria) should also be included in your  
685 510(k) submission. You should investigate all outlier results and describe the results of  
686 these investigations, providing explanations for the occurrence of outliers when possible.  
687 To help inform your investigations into outlier results, you should collect information  
688 regarding patient medications, hematocrit measurements, oxygen, and sodium levels  
689 during your study. You should include the following in your description of the results:

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*Analysis of Results:*

You should present the difference between individual study subject results and results of the comparator method (or mean of the comparator measurement, if multiple replicates are measured using the comparator method) by plotting the data on an X-Y graph. The plot should include the regression line and line of identity, as well as the 99% confidence regions. Your summary of results should include the slope and y-intercept, calculated using a suitable analysis procedure (e.g., Linear Regression, Deming regression) and the estimate of the deviation (standard error). Bland-Altman analysis may also be presented. You should describe all statistical methods used and clearly identify and describe any outliers in the analysis.

*Tabular data presentation:*

You should present results in the following tabular format for each sample matrix. In Table 2 and Table 3 below, X= the number of samples within the specified difference from the comparator method, and Y= total number of samples.

**Summary of data within specified mg/dL of the comparator method.**

**Table 2. For glucose concentrations <75 mg/dL:**

Within +/- 5 mg/dL	Within +/- 10 mg/dL	Within +/- 12 mg/dL	Within +/- 15 mg/dL	Exceeds +/- 15 mg/dL
X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)

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**Table 3. For glucose concentrations ≥75 mg/dL:**

Within +/- 5%	Within +/- 10%	Within +/- 12%	Within +/- 15%	Within +/- 20%	Exceeds +/- 20%
X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)

**D. Interference Evaluation**

You should evaluate the effect of potentially interfering endogenous and exogenous substances and conditions, such as icterus, lipemia, and varying hematocrit levels, as well as the effect of common medications on your device’s performance. Conditions that are known to interfere with glucose monitoring test systems, such as ketoacidosis, should be included in the labeling as limitations unless you have provided data demonstrating that these conditions do not interfere with your device.

**1. Endogenous/Exogenous Substances**

*Study design:*

You should perform interference testing using samples containing glucose concentrations across the range of the device. Specifically, testing should be performed in samples with

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target glucose values of approximately between 50 - 70 mg/dL, 110-130 mg/dL, and 225-270 mg/dL to evaluate clinically relevant decision points.

You should evaluate each potentially interfering substance at clinically relevant concentrations. When performing your studies, you should test all substances at the highest concentration that could potentially be observed in a whole blood sample; if interference is observed, you should perform dilutions of the interferent to determine the concentration at which interference begins to occur. For example, if interference is observed with 20 mg/dL acetaminophen, additional testing should be performed with samples containing lower concentrations of acetaminophen, such as 15 mg/dL, 10 mg/dL and 5 mg/dL, to determine the lowest concentration of acetaminophen where interference is first observed. If the results from the additional testing determine that interference is not observed in the sample containing 5 mg/dL acetaminophen and interference is observed in the sample containing 10 mg/dL acetaminophen, then 10 mg/dL is the lowest concentration of acetaminophen where interference begins to occur.

The substances listed below in Table 4 below represent known or potential interferents for current blood glucose measurement technologies and comprise the minimal list of substances that should be tested for interference.

**Table 4. List of Known or Potential Interferents for BGMSs.**

<b>Interferent</b>	<b>Recommended Test Concentration</b>
Acetaminophen	20 mg/dL
Ascorbic acid	3 mg/dL
Conjugated Bilirubin	50 mg/dL
Unconjugated Bilirubin	40 mg/dL
Cholesterol	500 mg/dL
Creatinine	10 mg/dL
Dopamine	20 mg/dL
EDTA**	200 mg/dL
Galactose	15mg/dL
Gentisic acid	1000 mg/dL
Reduced Glutathione	92 mg/dL
Hemoglobin	20 g/dL
Heparin**	500 IU/dL
Ibuprofen	50 mg/dL
Icodextrin	1094.4 mg/dL
L-Dopa	0.5 mg/dL
Maltose	10,000 mg/dL
Methyldopa	1000 mg/dL
Salicylic acid	60 mg/dL
Sodium	414 mg/dL
Tolbutamide	100 mg/dL

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Tolazamide	40 mg/dL
Triglycerides	1500 mg/dL
Uric acid	24mg/dL
Xylose	200 mg/dL
Sugar Alcohols**	0.09 mg/dL

\*The inclusion of EDTA and Heparin in this table refers to their use as therapeutic substances and not as anticoagulants for sample preparation. Separate studies should be performed to validate the use of these substances as anticoagulants used for sample preparation (as described in Section C, above).

\*\* All common sugar alcohols, including but not necessarily limited to, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol should be independently tested.

In addition to the list of potential interferents provided in Table 4, you should conduct an interference risk analysis and carry out bench studies to evaluate interference from additional drugs commonly used in your intended use population. These bench studies from additional drugs should be conducted in the same manner described in this Section.

You should provide a reliable estimate of the interference predicted for each potential interferent. To do this, we recommend the following method of measuring and calculating interference. First, blood samples should be generated at each target glucose concentration described above. Each glucose sample should be tested in replicates with the comparator method (we suggest at least 4 replicates in order to reduce standard error) to establish the glucose concentration in the sample. The glucose samples should then be split into a test sample to which a specific amount of potential interferent is added and a control sample containing solvent/vehicle in lieu of the potential interfering substance. Both control samples and test samples should be measured in replicates on the BGMS. At least three test strip lots should be used for this evaluation. Each of the control and test samples should be tested on your BGMS in replicates of 30 across the three lots (10 replicates per lot of test strips for a total of 30 replicates per sample). The mean of replicates should be calculated for each control and test sample. The relative bias (mg/dL) and percent bias should be calculated using the results of the control sample relative to test sample for each concentration of potential interferent. These results should be submitted with 95% confidence intervals as part of your 510(k) submission.

For BGMSs, the degree of acceptable interference may vary by substance tested and the intended patient population of your device. Therefore, you should report in your 510(k) submission the interference testing data as well as the expected imprecision of the system at that glucose concentration. If interferences are observed, you should propose appropriate labeling to address any observed interferences; the labeling language appropriate for the observed interference will be discussed during the review of the 510(k) submission.

As new drugs are developed that could potentially interfere with your device, or new interfering substances are identified for other BGMSs, you should evaluate these new drugs or substances for potential interference with your device. For example, if a new drug intended to treat cardiac complications in diabetic patients is approved, you should

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791 conduct a careful evaluation to determine whether the new drug interferes with your  
792 device. You should report to FDA if significant new interferences are observed with your  
793 device or with any cleared glucose monitoring devices that are on the market. New  
794 drugs/potential interferents should also be evaluated when new or significantly modified  
795 technology is introduced.

796

797 *Data Analysis:*

798 You should provide raw data sets as well as a summary table for all interference results.  
799 Please note that the summary tables should be presented separately for each test strip lot  
800 and for all lots pooled for each glucose level tested. Table 5 below provides a sample  
801 format of a summary table.

802

803 **Table 5. Recommended Summary Table Format:**

804

*Test Strip Lot #(s)*

<b>Interferent</b>	<b>Mean Glucose Value (Comparator)</b>	<b>Interferent Concentration (mg/dL)</b>	<b>Control Sample Mean</b>	<b>Test Sample Mean</b>	<b>Bias (mg/dL)</b>	<b>% Bias</b>	<b>Confidence Interval around % Bias</b>
Acetaminophen	60 mg/dL	20 mg/dL					
	120 mg/dL	20 mg/dL					
	250 mg/dL	20 mg/dL					

805

806 In your 510(k) submission you should include a detailed description of the study design, a  
807 list of all data collected in this study, the summary tables indicated above, and a  
808 description of the conclusions drawn from the study.

809

810 **2. Hematocrit**

811 *Study design:*

812 Because a reasonably sized method comparison study may not include the full range of  
813 hematocrit values expected in the intended use population, you should perform a separate  
814 study to determine how much analytical error is contributed by varying hematocrit levels.  
815 This should constitute a bench study designed to evaluate the effect of hematocrit on the  
816 performance of your BGMS to assess whether your device can safely be used across the  
817 claimed hematocrit range in the intended use population. The observed hematocrit levels  
818 may be very broad in the intended use population for this type of device; the intended  
819 patient population may reasonably be expected to have hematocrit levels between 10 and  
820 65%. Therefore, we recommend a minimum hematocrit range of 10-65% as the claimed  
821 range for BGMSs.

822

823 You should evaluate hematocrit interference by measuring samples containing various  
824 glucose concentrations. The samples should be prepared to contain designated levels of  
825 hematocrit that span the claimed hematocrit range for the device. Blood samples may be  
826 altered by spiking or allowing them to glycolyze to obtain desired glucose concentrations.  
827 Specific percentages of hematocrit may be achieved for each sample by manipulating the



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828 plasma to packed cell ratio following centrifugation. Hematocrit levels tested should span  
829 the claimed range in 5% intervals. Testing across the hematocrit range in 5% intervals  
830 allows for a more accurate assessment of bias from hematocrit interference than using  
831 broader intervals. For example, if your claimed hematocrit range is from 10-65%, you  
832 should test samples at 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 and 65 % hematocrit. The  
833 samples should also span the claimed measuring range for blood glucose. Samples should  
834 include 5 different blood glucose concentrations evenly spread and targeted to the  
835 following ranges: 30 – 50, 51 – 110, 111 – 150, 151 – 250, and 251 – 400 mg/dL.

836

837 Each sample should be tested on the comparator method in multiple replicates (e.g., we  
838 recommend a minimum of 4 replicates). A mean of the comparator measurements should  
839 give greater confidence in the true glucose concentration of the sample.

840

841 You should test a minimum of 3 test strip lots to evaluate interference from hematocrit.  
842 Each sample should be tested on your new BGMS in replicates of 30 (10 replicates per lot  
843 of test strips for a total of 30 replicates per sample). Each replicate should be compared to  
844 the average comparator value for the sample and a bias and percent bias calculated. The  
845 percent bias for each replicate should be used to determine an average percent bias for the  
846 sample (with 95% confidence intervals).

847

848 Because hematocrit interference is only one of the variables that can contribute to the  
849 overall analytical error of the system, it is important that it represent only a portion of the  
850 allowable error for the system. For this reason, bias observed in this study for glucose  
851 concentrations greater than or equal to 75 mg/dL should be less than 5% on average, and  
852 no individual value should be greater than 10% of the comparator method. For samples  
853 less than 75 mg/dL glucose the absolute bias (mg/dL) should be reported (with 95%  
854 confidence intervals) and justified for clinical impact. For all results that are outside of  
855 the criteria described above, you should provide a clinical justification for the observed  
856 data and describe why the potential for that error due to hematocrit interference does not  
857 affect patient safety when extrapolated to the intended use setting.

858

859 *Data Analysis:*

860 You should provide raw data sets as well as a summary of the hematocrit interference  
861 study (see recommended summary formats in Table 6 and Table 7 below). Please note  
862 that the summary tables should be presented separately for each test strip lot and glucose  
863 level tested.

864

865 **Table 6. Sample summary format for hematocrit (Hct) results of samples with**  
866 **glucose concentrations <75 mg/dL:**

867 *Lot #; Glucose Level # (mg/dL)*

Mean Glucose Value (Comparator)	Hct (%)	Mean Glucose Value (Meter)	Bias (mg/dL)	95% Confidence Intervals around Bias	# of Measurements > +/- 10 mg/dL	Clinical Justification

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873

**Table 7. Sample summary format for hematocrit (Hct) results of samples with glucose concentrations  $\geq 75$  mg/dL:**

*Lot #, Glucose Level # (mg/dL)*

Mean Glucose Value (Comparator)	Hct (%)	Mean Glucose Value (Meter)	Bias (mg/dL)	% Bias	# of Measurements > +/- 15% Bias

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You should include in your 510(k) submission a detailed description of the study design, a list of all data collected in this study, the summary tables indicated above, and a summary of the conclusions drawn from the study.

### **3. Oxygen**

*Study design:*

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A typical professional use setting can include patients with a broad range of blood oxygen levels. If you intend for your BGMS to be used in patients with a broad range of blood oxygen levels you should conduct a study using a validated method appropriate to the sample type to demonstrate the range of blood oxygen levels that your device can be used with. You should supplement the results of this study by collecting data on the blood oxygen levels of patients in your Method Comparison/User Evaluation Study (Subsection C, above), as appropriate, and conducting an analysis for any oxygen effects on BGMS performance. If you believe that blood oxygen levels do not affect the performance of your device you should provide a comprehensive justification for this, which should be supported by any analysis of interference of blood oxygen levels on device performance as evaluated in your Method Comparison/User Evaluation Study (Subsection C, above).

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### **E. Flex Studies**

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Generally, the risk of an erroneous result may be greater for POC tests than laboratory-based tests. This is because there are fewer controls in place in POC settings to mitigate risks and the users may be untrained and may not know how to identify or address an incorrect result. You should demonstrate that your BGMS design is robust (e.g., insensitive to environmental and usage variation) and that all known sources of error have been assessed through a detailed risk assessment and are effectively controlled. In general, flex studies should be used to demonstrate robust design while risk management should be used to demonstrate the identification and effective control of error sources, although the two are not mutually exclusive.

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Most risk control measures should be fail-safe mechanisms or failure alert mechanisms. Examples of fail-safe mechanisms are lock-out functions to ensure that a BGMS does not provide a result when test conditions are inappropriate, such when there is a component malfunction or operator error. Other examples are measures within the BGMS to prevent operator error, such as guides or channels that prevent improper strip placement. We

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908 recommend that BGMS design incorporate fail-safe mechanisms whenever technically  
909 practicable. If fail-safe mechanisms are not technically practicable for some risks, failure  
910 alert mechanisms should be used. Failure alert mechanisms notify the operator of any  
911 BGMS malfunction or problem. They may include measures such as internal procedural  
912 controls or electronic controls. Devices with such mechanisms allow the operator to  
913 correct the error, or put the operator on notice that the results will be unreliable due to the  
914 error. For example, in cases where the result exceeds the reportable range (e.g., extremely  
915 high or low glucose result) and the result is a critical value, the device should give a  
916 message such as "high" or "low."

917

918 Flex studies, or studies that stress the operational boundaries of a BGMS, should be used  
919 to validate the insensitivity of the test system to performance variation under stress  
920 conditions. Where appropriate, flex studies should also be used to verify and/or validate  
921 the effectiveness of control measures at operational limits.

922

923 In order to identify all relevant flex studies for your BGMS device, we recommend that  
924 you conduct a systematic and comprehensive risk analysis that identifies all potential  
925 sources of error, including test system failures and operator errors, and identify which of  
926 these errors can lead to a risk of a hazardous situation. You should then identify control  
927 measures, including fail-safe mechanisms and failure alert mechanisms that will reduce  
928 risks for these sources of error. When the control measures have been implemented, you  
929 should (1) verify that each control measure has been properly implemented, and (2) verify  
930 and/or validate the effectiveness of each control measure. When appropriate, flex studies  
931 should be used to verify and/or validate the effectiveness of these control measures.

932

933 Below we have identified flex studies that we believe are important for you to perform  
934 and recommend including in the 510(k) submission of your BGMS. At the same time, we  
935 encourage you to continue to perform risk analyses to determine whether your device  
936 includes any unique or new features that should be validated through additional flex  
937 studies.

938

939 If your BGMS does not perform adequately in flex studies, we recommend that you either  
940 provide a justification, determined by means of thorough risk analysis, as to why adequate  
941 performance in that flex study is not necessary, or alternatively you should indicate an  
942 additional implemented validated control mechanism. FDA will review such  
943 justifications to determine whether the proposed mitigation strategies are adequate to  
944 protect patients.

945

946 In the case of the following flex studies, verification should include performance testing;  
947 however, it is sufficient if you provide information indicating that flex studies have been  
948 conducted in accordance with an FDA-recognized industry standard. We recommend you  
949 include information regarding the type of testing performed, the reference standard  
950 followed, the acceptance criteria, and whether the BGMS passed testing requirements.

951 The flex studies we recommend performing in this manner are:

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- 953 • Mechanical Vibration Testing
- 954 • Shock Testing
- 955 • Electromagnetic compatibility (EMC) Testing
- 956 • Electrostatic Discharge/Electromagnetic Interference Testing

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We have also identified additional flex studies (described below) that manufacturers should perform in order to demonstrate adequate system performance in intended use settings. Unless otherwise indicated, we recommend that you clearly identify all flex studies performed on your device in your 510(k) submission. A detailed description of the following attributes should be included in your 510(k) submission for each study:

- 964 • Study goal
- 965 • Study protocol
- 966 • Methods used to apply samples to test strips
- 967 • Description of sample type and any anticoagulants used
- 968 • Study results
- 969 • Description of conclusions made from the study

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The recommended flex studies as well as recommended study designs are outlined below in Subsections 1-8. These flex studies should be performed using fresh venous or capillary whole blood samples, not control solutions.

975 **1. Test Strip Stability Testing**

976 You should perform studies that assess test strip performance throughout the test strip  
977 stability claims, including both closed and open vial claims. Three studies should be  
978 performed to support test strip stability: 1) closed vial stability (shelf life) should be  
979 performed to assess the recommended shelf life and conditions when the vial is stored  
980 closed throughout the claimed expiration dating, at different combinations of temperature  
981 and humidity spanning the recommended storage conditions; 2) open vial stability should  
982 be performed to mimic conditions under which an individual would actually use the strips  
983 where the vial is opened and closed throughout its claimed open vial life and stored at  
984 different combinations of temperature and humidity throughout the recommended storage  
985 conditions; and 3) extended open vial stability that mimics use of test strips from vials  
986 that have been left completely open for the duration of the claimed test strip open vial life  
987 when stored at different combinations of temperature and humidity throughout the  
988 recommended storage conditions. We suggest that you submit only the study protocols for  
989 these test strip stability assessments, the acceptance criteria, and the conclusions of any  
990 studies which have been completed.

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These studies (shelf life, open vial and extended open vial) should be designed to span both the claimed temperature range and humidity range at various time points throughout the duration of the respective claim. The time points that are assessed (e.g., 1 month, 3

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995 months, 2 years) should be specified in the protocol. Combinations of real-time and  
996 accelerated stability studies are acceptable. However, if accelerated studies are provided,  
997 real-time studies should be ongoing and the protocols and acceptance criteria should be  
998 provided for both study types.  
999

1000 Separate testing of test strip and meter shipping and storage conditions is not necessary if  
1001 the temperature and humidity studies outlined here use only packaged blood glucose  
1002 meters and blood glucose test strips that have undergone appropriate storage conditions  
1003 and the longest possible shipping duration (both as specified by the manufacturer).  
1004

1005 You should perform adequate precision and accuracy evaluations at each identified time  
1006 point. Examples of such studies are described below. Through these evaluations, you  
1007 should demonstrate that the CV and accuracy calculated in these studies are within the  
1008 labeled performance of the BGMS.  
1009

1010 *Precision Evaluation:*

1011 Precision with Control Materials

1012 This study should be completed over 5 days and use glucose controls. At least two  
1013 meters should be included in this study and at least 10 measurements should be taken  
1014 per glucose control level, per meter.  
1015

1016 Precision with Whole Blood Samples

1017 This study should use whole blood samples spanning the claimed measuring range of  
1018 the BGMS. Samples may be altered by spiking with glucose or allowing the samples  
1019 to glycolyze in order to evaluate the extreme end of the system's measuring range. At  
1020 least two meters should be included in this study and at least 10 measurements should  
1021 be taken per glucose level, per meter.  
1022

1023

1024 *Accuracy Evaluation:*

1025 This study should be performed using whole blood samples that span the claimed  
1026 measuring range of the BGMS. It is acceptable for samples to be spiked with a known  
1027 concentration of glucose or allowed to glycolyze to achieve the desired concentration in  
1028 order to evaluate the extreme ends of the system's measuring range. Glucose  
1029 concentrations (e.g. 30-50, 100-150, 200-300, 350-500 mg/dL) should be measured with  
1030 the BGMS and compared to values obtained with the comparator method.  
1031

1032 **2. System Operating Conditions Testing**

1033 You should perform a study to assess the performance of your BGMS when used under  
1034 various operating temperature and humidity conditions. These studies should be designed  
1035 to represent actual use conditions experienced by BGMS users. Tested temperature and  
1036 humidity ranges should not only cover the operating ranges that adequately reflect the  
1037 intended use environment, and that are specified in the device labeling, but should also  
1038 stress the BGMS by including ranges outside of the claimed operating range. Testing  
1039 should incorporate the four extreme temperature and humidity combinations (high

1040 temperature/low humidity; high temperature/high humidity; low temperature/low  
1041 humidity; low temperature/high humidity). Measurements made on whole blood samples  
1042 with your candidate device should be compared to values obtained with the comparator  
1043 method.

1044

1045 We also encourage manufacturers to consider ways in which temperature and/or humidity  
1046 detectors might be incorporated into test strip containers to alert users when strips have  
1047 not been handled correctly or stored according to recommended and validated conditions.

1048

1049

### **3. Altitude Effects**

1050 Relative to sea level, high altitude comprises a complex set of environmental differences  
1051 and can induce multiple physiological changes, any or all of which might interfere with  
1052 BGMS performance. For example, high altitude often involves extremes of temperature  
1053 and humidity and can result in changes to hematocrit and blood pressure. The intended  
1054 use environment of BGMSs in the United States includes high altitude conditions and  
1055 therefore manufacturers should conduct studies to assess the effects of altitude on their  
1056 BMGS or should provide a justification for why altitude does not have an effect on the  
1057 performance of their BGMS.

1058

1059 An altitude effects study should compare results from whole blood samples with your  
1060 candidate device relative to the comparator method. These studies should also include a  
1061 pressure change. Studies based on oxygen tension instead of pressure change are not  
1062 adequate, because oxygen tension is only one component that changes with altitude.  
1063 Altitude pressure changes can be accomplished by physically increasing altitude (e.g., in  
1064 an airplane, on a mountain), or by simulating increasing altitudes and atmospheric  
1065 conditions in a pressurized chamber. Results should support the altitude labeling claim  
1066 for your device. You should provide your definition for terms such as “sea level”. The  
1067 definition of sea level should not extend above 500 feet. You should test your BGMS at a  
1068 minimum of 10,000 feet above sea level.

1069

1070

### **4. Error Codes for Samples Outside the Measuring Range**

1071 You should perform adequate analyses to demonstrate that your meter provides the  
1072 appropriate error codes when measured glucose concentrations are outside of the BGMSs  
1073 claimed measuring range, and include these results in your 510(k) submission.

1074

1075

### **5. Short Sample Detection**

1076 Blood glucose measurement from short samples (samples of reduced sample volume) can  
1077 lead to inaccurate results. To avoid the risk of inaccurate results, BGMSs should be able  
1078 to detect that a short blood sample that has been applied to the test strip and should not  
1079 provide a result to the user. Short sample detection systems should not rely on visual  
1080 verification by the user.

1081

1082 The volume required to classify a test sample as a short sample is dependent upon your  
1083 BGMS. In your short sample detection studies you should include blood samples with

1084 known glucose concentrations in the following three ranges: 50-65, 100-120, and 200-250  
1085 mg/dL. You should test blood samples with your candidate device at each of the glucose  
1086 concentrations listed above. Results obtained from the candidate device should be  
1087 compared to the comparator method. Blood samples with serially reduced volumes  
1088 should be measured on the device until an error is either generated by the BGMS or the  
1089 test result falls outside of the device's stated performance range. In your 510(k)  
1090 submission you should describe the results from both the candidate device, and the  
1091 comparator method, as well as include the sample volumes tested for each glucose  
1092 concentration range.

1093  
1094 **6. Sample Perturbation Study**

1095 Sample perturbation occurs when a user has applied an appropriate volume of blood to  
1096 the test strip for glucose measurement but an event, such as wicking of blood away from  
1097 the test strip, flicking of the test strip, or flicking of the meter occurs during the start of  
1098 measurement and alters the volume of the initial sample application. You should  
1099 adequately demonstrate how your BGMS handles sample perturbation through a sample  
1100 perturbation study.

1101  
1102 In a sample perturbation study a sample should be applied to the test strip and after the  
1103 BGMS has begun to read the sample, but before the measurement is complete, the test  
1104 strip should be perturbed. The sample perturbation study should incorporate blood  
1105 samples with known glucose concentrations in the following three ranges: 50-65, 100-  
1106 120, and 200-250 mg/dL. In your 510(k) submission you should describe your protocol,  
1107 including your specific method of perturbing the test sample, as well as meter results  
1108 compared to the comparator method.

1109  
1110  
1111 **7. Intermittent Sampling**

1112 Intermittent sampling occurs when a short sample is applied to a test strip, a glucose  
1113 measurement begins, and the user adds more sample to the test strip before the glucose  
1114 measurement is complete. You should adequately demonstrate how your BGMS handles  
1115 intermittent sampling by conducting an intermittent sampling study.

1116  
1117 The intermittent sampling study should incorporate blood samples with known glucose  
1118 concentrations in the following three ranges: 50-65, 100-120, and 200-250 mg/dL. You  
1119 should perform intermittent sampling studies that are representative of actual events. For  
1120 instance, approximately one half of the sample should be applied to the test strip prior to  
1121 the start of sample measurement, then the other half of the sample should be applied to  
1122 the strip after a set period of time, such as once the sample starts reading. For systems that  
1123 allow a second sample of blood without producing an error message, different time delays  
1124 throughout the claimed period of second application should be tested once the sample  
1125 starts reading but before the measurement is complete. You should describe how the  
1126 device responds to this scenario, including whether a result is reported by the device,  
1127 whether the result is accurate (relative to the comparator method) and when an error code  
1128 is reported.

1130 **8. Testing with Used Test Strips**

1131 You should perform a study to demonstrate how your BGMS performs when a used test  
1132 strip is inserted. We recommend that BGMSs be designed to automatically recognize the  
1133 insertion of used test strips. Insertion of used test strips into a blood glucose meter should  
1134 not provide glucose measurement results to the user. If an automatic used test strip  
1135 recognition function has been incorporated into your BGMS, you should perform a study  
1136 to demonstrate the functionality of this recognition system. In your 510(k) submission  
1137 you should provide the study protocol, acceptance criteria and results of your used test  
1138 strip study.

1139 **F. *Meter Calibration and Quality Control Material***

1140 We recommend you review FDA’s guidance entitled “Guidance for Industry and FDA  
1141 Staff - Assayed and Unassayed Quality Control Material”  
1142 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocument/s/ucm079179.htm>) and submit the recommended information to support clearance of any  
1143 assayed glucose quality control material you choose to provide with your BGMS. For a  
1144 description of more points to consider regarding calibration and quality control materials,  
1145 please refer to FDA’s guidance entitled “Points to Consider for Review of Calibration  
1146 and Quality Control Labeling for In Vitro Diagnostic Devices”  
1147 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceeDocuments/UCM094139.pdf>). At least two levels of quality control material should be  
1148 available for use with your system.  
1149  
1150

1151  
1152 You should describe in your 510(k) submission how your BGMS recognizes and  
1153 distinguishes control materials from patient specimens, either automatically or manually  
1154 by the user, as well as explain how the system compensates for differences between test  
1155 strip lots (e.g., how the meter is calibrated or coded for each test strip lot).  
1156

1157 **VII. Test Strip Lot Release Criteria**

1158  
1159 Your test strip lot release criteria should be sufficient to ensure consistent quality of the  
1160 BGMS test strips. You should provide a description of the lot release criteria and a summary  
1161 of the sampling scheme in your 510(k) submission. In addition, you should explain how the  
1162 system compensates for differences between strip lots or strip types.  
1163

1164 We recommend that you select a sampling scheme appropriate for the operation of your  
1165 BGMS and test each outgoing test strip lot or batch using the precision and accuracy  
1166 evaluations described below. Your test strip lot release criteria should be designed to ensure  
1167 that all released lots conform to the labeled BGMS device performance *in the hands of the*  
1168 *intended user*. Therefore, these criteria should be more stringent than the criteria used to  
1169 evaluate total error in the performance studies. Estimates of the BGMS’s imprecision and  
1170 average bias may be used to determine appropriate lot release criteria. Examples of such  
1171 testing are described below.



1172

1173 *Precision Evaluation:*

1174 Precision using Control Materials

1175 This study should be completed over 5 days and use glucose controls. At least two meters  
1176 should be included in this study and at least 10 measurements should be taken per control  
1177 level, per meter.

1178

1179 Precision using Whole Blood Samples

1180 This study should include at least 10 measurements using whole blood samples spanning  
1181 the claimed measuring range of the BGMS. Spiking samples with glucose, or including  
1182 samples in which glucose was allowed to glycolyze is acceptable in order to evaluate the  
1183 extreme end of the system's measuring range. At least two meters should be included in  
1184 this study and at least 10 measurements should be taken per glucose level, per meter.

1185

1186 *Accuracy Evaluation:*

1187 The accuracy evaluation should be performed using whole blood samples that span the  
1188 claimed measuring range of the BGMS. It is acceptable for samples to be spiked with a  
1189 known concentration of glucose, or to include samples in which the glucose was allowed to  
1190 glycolyze in order to evaluate the extreme ends of the system's measuring range. Glucose  
1191 concentrations should be measured on the BGMS meter and compared to the comparator  
1192 method.

1193

1194

## 1195 **VIII. Third Party Test Strips**

1196

1197 Third party test strips refer to test strips manufactured and distributed by a company other  
1198 than the company that manufactures and distributes the BGMS. Third party test strip  
1199 manufacturers should ensure that they are aware of any design changes to the meter because  
1200 such changes could affect compatibility of the strip with the meter. Because test strips and  
1201 meters work as integral systems, third party test strip manufacturers should sufficiently  
1202 address in their 510(k) submissions how they will mitigate the risk of incorrect results due to  
1203 meter design changes. One way to effectively ensure that the third party test strip  
1204 manufacturer is made aware of any design changes to the meter is by having in place an  
1205 agreement between the third party test strip manufacturer and the manufacturer.

1206

## 1207 **IX. Software**

1208

1209 For software descriptions of BGMSs, their components, and accessories, we recommend that  
1210 you follow FDA's guidance entitled "Guidance for the Content of Premarket Submissions for  
1211 Software Contained in Medical Devices"

1212 ([http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceD](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf)  
1213 [ocuments/ucm089593.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf)). Generally, we consider blood glucose meters to be moderate

1214 level of concern devices because glucose results will be the basis for treatment, including  
1215 determination of insulin dosage by the patient or health care provider. Incorrect glucose  
1216 results or failure of the software to detect an error could result in improper therapeutic  
1217 management. (Also see Section V, above, regarding software descriptions in your 510(k)  
1218 submission).  
1219

## 1220 **X. Labeling**

1221  
1222 The 510(k) submission must include labeling in sufficient detail to satisfy the requirements of  
1223 21 CFR 807.87(e). Final labeling must also satisfy the requirements of 21 CFR 809.10.  
1224 Distinct labeling (e.g. user manual, quick start guide (optional), package inserts for both test  
1225 strips and controls, and box and container labels for the meter, test strips and control  
1226 materials) appropriate for the intended user of the BGMS should be provided for each device  
1227 component.  
1228

1229 The following items are intended to further assist you in complying with the requirements of  
1230 21 CFR 809.10 for all labeling. You should refer to that regulation for the complete list of  
1231 labeling requirements for *in vitro* diagnostic devices.  
1232

- 1233 1. All device label and labeling must contain the proprietary and common names of the  
1234 device. 21 CFR 809.10(a)(1) and 21 CFR 809.10(b)(1). The various test system  
1235 components should be named in such a way that they are recognizable as belonging to  
1236 the same system, or family of products, and to distinguish them from those  
1237 components intended for single-patient use only (for example, ABC blood glucose  
1238 test system, ABC blood glucose meter, ABC blood glucose test strips, etc.) to aid in  
1239 identification of system components.
- 1240 2. You must include the intended use of the product in your label and labeling. 21 CFR  
1241 809.10(a)(2) and 21 CFR 809.10(b)(2).
- 1242 3. You must include the symbol statement “Rx only” or “**R** only” or the statement  
1243 “Caution: Federal law restricts this device to sale by or on the order of a \_\_\_”, the  
1244 blank to be filled with the word “physician”, “dentist”, “veterinarian”, or with the  
1245 descriptive designation of any other practitioner licensed by the law of the State in  
1246 which the practitioner practices to use or order the use of the device in your label and  
1247 labeling. 21 CFR 809.10(a)(4) and 21 CFR 809.10(b)(5)(ii).  
1248
- 1249 4. Labeling must include the chemical, physical, physiological, or biological principles  
1250 of the procedure as per 21 CFR 809.10 (b)(4). The discussion of these principles  
1251 should include identification and biological source of the enzyme and a description of  
1252 the reaction. Labeling should clarify whether results are determined in terms of whole  
1253 blood or plasma equivalents. BGMSs intended for use in the U.S. should report  
1254 results in terms of plasma equivalents.

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- 1255 5. The labeling must provide instructions for specimen collection and preparation,  
1256 including special precautions regarding specimen collection as per 21 CFR  
1257 809.10(b)(7). Instructions should include a statement to users on the importance of  
1258 thoroughly washing and drying the skin before taking a sample because contaminants  
1259 on the skin may affect results.
- 1260 6. You must include a statement of limitations of the procedure in your labeling (21  
1261 CFR 809.10(b)(10)). Labeling must state known extrinsic factors or interfering  
1262 substances affecting results as per 21 CFR 809.10(b)(10). This should include, but is  
1263 not limited to, the following:
- 1264 a. Labeling should include testing conditions that may cause clinically  
1265 significant errors (due to bias or imprecision) with your device (e.g., specific  
1266 drugs, oxygen therapy, testing with venous, arterial, or neonatal blood, high  
1267 altitude, or EMC interference). Sponsors should indicate the most extreme  
1268 conditions (e.g., the highest altitude, highest and lowest temperatures, etc.) at  
1269 which device should be used based on the results of performance testing.
- 1270 b. You should describe clinical situations, patient populations or conditions in  
1271 which the BGMS performance may not be acceptable. For example, FDA  
1272 recommends statements such as the following: inaccurate results may occur in  
1273 severely hypotensive individuals or in dehydrated patients or patients in shock;  
1274 inaccurate results may occur for individuals experiencing a hyperglycemic-  
1275 hyperosmolar state, with or without ketosis.
- 1276 c. Labeling should include limitations against alternative site testing and use for  
1277 tight glycemic control (unless appropriate studies are performed and included  
1278 in the 510(k) submission). Labeling should also state that results from  
1279 alternative sampling sites (if used) should not be used to calibrate continuous  
1280 glucose monitoring systems (CGMS) or entered into insulin dose calculators  
1281 for dosage recommendations.
- 1282 7. Labeling must provide appropriate storage instructions adequate to protect stability of  
1283 the product. 21 CFR 809.10 (b)(5)(iv). This type of information should be provided  
1284 for all components of the system including control solutions, test strips, etc.
- 1285 8. Labeling must describe details of calibration and quality control procedures. 21 CFR  
1286 809.10(b)(8)(v) and 21 CFR 809.10(b)(8)(vi). This is to help ensure optimal  
1287 performance of the system.
- 1288 9. Labeling must include expected values. 21 CFR 809.10(b)(11). FDA recommends  
1289 that the expected values in the package insert should be those for non-diabetics. FDA  
1290 does not recommend including additional ranges adjusted for diabetics because such  
1291 ranges are individually determined by a clinician. The expected values should be cited  
1292 from in-house studies or up-to-date reference sources.
- 1293 10. Labeling must include specific performance characteristics. 21 CFR 809.10(b)(12).  
1294 Sponsors should briefly describe all studies and summarize results in the package  
1295 inserts. FDA recommends that this include performance data summaries from in-  
1296 house and user studies. For presentation of accuracy in particular, see the suggested

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1297 representations below for an example. Performance should be presented separately for  
 1298 each anatomical site, matrix (arterial, capillary, etc.) and any additional specific  
 1299 claims (e.g. neonatal).

1300 We recommend the following types of presentations to show the results of your accuracy  
 1301 studies in user manuals and package inserts.

1302

1303 **Suggested Representation of Accuracy for Prescription-use Only Devices – Example:**

1304

1305 The [XYZ] meter and [XYZ] reagent strips for the [XYZ] monitoring system were tested on  
 1306 capillary blood samples from 350 patients, and the results were compared to the comparator  
 1307 method (e.g., YSI). The tables show differences in glucose values between the XYZ device  
 1308 and the comparator method. Table 8 below represents samples for glucose results lower than  
 1309 70 mg/dL (by the XYZ device). Table 9 below table represents samples for glucose results  
 1310 greater than or equal to 70 mg/dL.

1311

1312 **Table 8. Glucose results lower than 75 mg/dL**

Difference range between ABC laboratory comparator method and the XYZ device	Within +/- 5 mg/dL	Within +/- 10 mg/dL	Within +/- 12 mg/dL	Within +/- 15 mg/dL
The percent (and number) of samples for which the difference between the XYZ device and ABC laboratory comparator method were within the difference range shown in the top row.	90% (126/140)	95% (133/140)	96% (135/140)	98% (137/140)

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1314 **Table 9. Glucose results greater than or equal to 75 mg/dL**

Difference range between ABC laboratory comparator method and the XYZ device.	Within +/- 5%	Within +/- 10%	Within +/- 12%	Within +/- 15%	Within +/- 20%
The percent (and number) of samples for which the difference between the XYZ device and ABC laboratory method were within the difference range shown in the top row.	80% (168/210)	95% (199/210)	96% (202/210)	98% (206/210)	100% (210/210)

1315

1316 The tables above show that 347 (137+210) of the 350 samples met the defined acceptance  
 1317 criteria.

1318

1319 Note: When glucose meter results are compared to the laboratory results, differences below  
 1320 70 mg/dL are expressed in mg/dL, while those greater than or equal to 70 mg/dL are  
 1321 expressed in percent.

1322

*Contains Nonbinding Recommendations*

- 1323 1. You must describe the principles of operation for the instrument as well as service  
1324 and maintenance information. 21 CFR 809.10(b)(6). Labeling should include a list or  
1325 summary of error messages, descriptions of what those error messages mean, and  
1326 appropriate troubleshooting procedures for those error messages.
- 1327 2. Label and labeling must include statements of warning or precautions as appropriate  
1328 to the hazard presented by the product on the outer container and the insert. 21 CFR  
1329 809.10(a)(4) and 21 CFR 809.10(b)(5)(ii).

1330  
1331 You should clearly and prominently state the important warnings for your devices, for  
1332 example in a section titled **Important Safety Instructions**. You should stress the risk of  
1333 disease transmission when using BGMSs and reference any relevant public health  
1334 notifications, standard practice guidelines, or other resources available to users. At a  
1335 minimum, the following warnings should be included:

- 1336
- 1337 • Users need to adhere to Standard Precautions when handling or using this device.  
1338 All parts of the glucose monitoring system should be considered potentially  
1339 infectious and are capable of transmitting blood-borne pathogens between patients  
1340 and healthcare professionals. For more information, refer to “*2007 Guideline for  
1341 Isolation Precautions: Preventing Transmission of Infectious Agents in  
1342 Healthcare Settings*”,  
1343 <http://www.cdc.gov/hicpac/2007ip/2007isolationprecautions.html>.
  - 1344 • The meter should be cleaned and disinfected following the manufacturer’s  
1345 instructions after use on each patient. This Blood Glucose Monitoring System  
1346 may only be used for testing multiple patients when Standard Precautions and the  
1347 manufacturer’s cleaning and disinfection procedures are followed.
  - 1348 • Only auto-disabling, single use lancing devices may be used with this device.
- 1349

1350 In the section describing **how to obtain a blood sample** (see also item 4, above,  
1351 regarding sample collection), you should re-iterate the risk of bloodborne pathogen  
1352 transmission and state that only an auto-disabling, single use lancing device should be  
1353 used. We recommend that you incorporate Standard Precautions and practices in your  
1354 instructions. Include any graphics demonstrating correct blood draw procedures and  
1355 ensure that the pictures show users wearing gloves.

1356  
1357 In addition, we recommend that you refer users to the following practice guidelines:

1358  
1359 “*Biosafety in Microbiological and Biomedical Laboratories (BMBL)*”,  
1360 <http://www.cdc.gov/biosafety/publications/bmb15/>

1361  
1362 CLSI (Clinical Laboratory Standards Institute) Document M29-A3: *Protection of  
1363 Laboratory Workers From Occupationally Acquired Infections*.

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1365 You should stress that the operator should remove their gloves, clean their hands and  
1366 wear a new pair of clean gloves before testing each patient.

*Contains Nonbinding Recommendations*

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1. You must include a step-by-step outline of procedures 21 CFR 809.10(b)(8). Labeling must list any points that may be useful in improving precision and accuracy as per 21 CFR 809.10(b)(8).

FDA recommends that the user manual should contain detailed instructions for how users are to perform **cleaning and disinfection procedures** for the meter **between patients**. This information should be based on the validation studies performed as described above in Section IV. You should also include the following:

- An explanation of why the cleaning and disinfection should be performed.
- The recommended frequency of cleaning and disinfection, i.e., between each patient.
- The materials needed for cleaning and disinfection and how they can be purchased or prepared.
- A detailed procedure describing what parts of the device should be cleaned and disinfected, what should not be cleaned and disinfected (avoided), the amount of time the disinfectant needs to remain on the meter (contact time), etc. You should include graphics/photographs to assist the user. Again, be sure that all graphics show the user wearing gloves.
- A statement that after cleaning and disinfection, users' gloves should be removed, hands cleaned, and a new pair of clean gloves worn before proceeding to the next patient.
- A contact telephone number for technical assistance or questions should be prominently listed in the cleaning and disinfection section.

We recommend you also include the references below:

*"FDA Public Health Notification: Use of Fingertick Devices on More than One Person Poses Risk for Transmitting Bloodborne Pathogens: Initial Communication"*  
<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm224025.htm>

*"Infection Prevention during Blood Glucose Monitoring and Insulin Administration"*,  
<http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html>

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## Appendix 1. Sources of Error to Consider for BGMSs

Table 10 below lists sources of error associated with the design, production, and use of BGMSs. We do not intend for this to be a complete list. You should consider all sources of error based on your knowledge of your specific device. Documents such as CLSI EP-18A [7] and ISO 14971 [1] also provide lists of preanalytical, analytical, and post-analytical errors to consider.

**Table 10 – Examples of Sources of Error**

Category	Source of error or failure
Operator	<p>Failure to follow procedure correctly, for example:</p> <ul style="list-style-type: none"> <li>• Sample contamination</li> <li>• Incorrect specimen collection (e.g., poor lancing technique and incorrect volume)</li> <li>• Application of an insufficient amount of blood to the strip or incorrect application of blood to strip</li> <li>• Use of a sample from an alternate site not validated by the manufacturer</li> <li>• Application of the specimen to the strip more than once (for example, if the user believes not enough specimen was added the first time)</li> <li>• Incorrect insertion of strip into meter</li> <li>• Inaccurate timing</li> <li>• Use of contaminated, outdated, or damaged strips or reagents, including calibrators or quality control materials</li> <li>• Failure to understand or respond to meter output</li> <li>• Errors in meter maintenance or cleaning</li> <li>• Errors in calibration or failure to calibrate or otherwise adjust the meter or check performance with quality control materials, as directed by labeling</li> <li>• Incorrect saving or use of stored data</li> <li>• Improper storage or handling of the meter, calibrators, quality control materials or test strips, or maintenance of the meter</li> <li>• Inadvertent changes of parameters (such as units of measurement)</li> <li>• Incorrect incorporation of results into overall treatment plan (prescription-use)</li> <li>• Use of strips not validated for use on the meter</li> </ul>
Reagent	<ul style="list-style-type: none"> <li>• Expired strips or reagents</li> </ul>

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	<ul style="list-style-type: none"> <li>• <b>Damaged or contaminated strip</b></li> <li>• <b>Failure of strips, calibrators, or quality control materials to perform adequately</b></li> <li>• <b>Incorrect manufacturing; product fails to conform with specifications</b></li> <li>• <b>Incorrect dimensions of reagent strip</b></li> <li>• <b>Interference with chemical reaction on strip (e.g., reducing substances)</b></li> <li>• <b>Inadequate design of container for strips or other reagents; failure to prevent deterioration; failure of desiccant used to keep strips dry</b></li> </ul>
Environmental	<ul style="list-style-type: none"> <li>• <b>DEVICE EFFECTS</b> <ul style="list-style-type: none"> <li>• <b>Temperature</b></li> <li>• <b>Humidity</b></li> <li>• <b>Altitude; hyperbaric oxygen therapy conditions</b></li> <li>• <b>Electromagnetic radiation</b></li> <li>• <b>Visible light; sunlight</b></li> </ul> </li> <li>• <b>HUMAN FACTORS</b> <ul style="list-style-type: none"> <li>• <b>Lighting, glare off meter surfaces</b></li> <li>• <b>Distractions, visual and auditory</b></li> <li>• <b>Stressful conditions</b></li> <li>• <b>Limited manual dexterity</b></li> </ul> </li> </ul>
Software	<ul style="list-style-type: none"> <li>• <b>Confusing or obscure user prompts and feedback</b></li> <li>• <b>Incorrect mathematical algorithm</b></li> <li>• <b>Undetected or unrecognized signal errors</b></li> <li>• <b>Timing failure</b></li> <li>• <b>Incorrect storage of test results in memory, including matching result with correct patient or time of test</b></li> <li>• <b>Other software failures</b></li> </ul>
Hardware	<ul style="list-style-type: none"> <li>• <b>Electronic failure</b></li> <li>• <b>Physical trauma or vibration</b></li> <li>• <b>Damage to the device from incorrect strip dimensional tolerances (third party manufacturer)</b></li> <li>• <b>Electrostatic discharge</b></li> <li>• <b>Electromagnetic/radiofrequency interference</b></li> <li>• <b>Battery reliability, lifetime, and replacement</b></li> <li>• <b>Component(s) failure</b></li> <li>• <b>Incorrect manufacture</b></li> </ul>



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System	<ul style="list-style-type: none"><li>• <b>Physical trauma or vibration</b></li><li>• <b>Incorrect calibration/adjustment (between lots of strips)</b></li><li>• <b>Calibration failure, interference, instability or use beyond the recommended period of stability.</b></li><li>• <b>Labeling not geared to intended user.</b></li><li>• <b>Meter or operation complexity not geared to intended user</b></li><li>• <b>Inadequate training</b></li></ul>
Clinical	<ul style="list-style-type: none"><li>• <b>Interference from endogenous substances</b></li><li>• <b>Severe conditions (e.g., dehydration, hypoxia, hyperglycemic-hyperosmolar state, hypotension or shock, ketoacidosis)</b></li><li>• <b>Interference from other exogenous substances (e.g., maltose intravenous solutions)</b></li></ul>

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## Appendix 2. Special 510(k)s and BGMSs

### What is a special 510(k) and how does it apply to your blood glucose meter submission?

A special 510(k) submission is an alternative to the traditional method of demonstrating substantial equivalence for certain modifications that do not alter the intended use or fundamental scientific technology of the device. For such modifications, the Agency believes that the rigorous design control procedure requirements outlined in the Quality System Regulation (QS reg) [See 21 CFR 820] produce highly reliable results that can form, in addition to the other 510(k) content requirements, a basis for the substantial equivalence determination.

As such, under the special 510(k) option, a manufacturer who is intending to modify his/her own legally marketed device will perform and present the risk analysis and the necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements. Once the manufacturer has ensured the satisfactory completion of this process, a "Special 510(k): Device Modification" may be submitted.

#### Eligibility for a Special 510(k):

To determine whether a modified BGMS device is eligible to be submitted as a Special 510(k), you should consult the FDA guidance entitled "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance"

([www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm)). Sponsors should also consult the document on FDA's website "How to Prepare a Special 510(k)"

(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134573.htm>).

As noted above, to be eligible for a special 510(k), the manufacturer should be modifying their own legally marketed device. This usually means that the candidate device and predicate device are part of the same device design file. *Similarities* between the candidate and predicate devices alone do not necessarily mean that the candidate device is a modification of the predicate device.

FDA believes that to ensure the success of the Special 510(k) option, there should be a common understanding of the types of device modifications that may gain marketing clearance by this path. As such, it is critical that Industry and Agency staff can easily determine whether a modification is appropriate for submission as a Special 510(k). To optimize the chance that a Special 510(k) will be accepted and efficiently reviewed, 510(k) submitters should evaluate each modification to insure that the device modification does not: (1) affect the intended use or (2) alter the fundamental scientific technology of the device.

*Contains Nonbinding Recommendations*

1459 Based on FDA's experience with blood glucose meters, we can offer the following list of  
1460 modifications that may or may not be eligible for review as a Special 510(k). This list is not  
1461 intended to be all-inclusive.

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1463 **Modifications that are generally eligible for a Special 510(k):**

- 1464 • Minor changes in user interface
- 1465 • Change in memory capabilities (e.g., adding the ability to store additional results)
- 1466 • Elimination of strip coding requirements
- 1467 • Addition of a voice (speaking) feature if the device is not intended for visually  
1468 impaired users

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1470 **Modifications that are generally NOT eligible for a special 510(k):**

- 1471 • Significant change in the sample volume applied to the glucose test strip
- 1472 • Addition of alternative sampling sites (e.g., adding the palm in addition to the  
1473 fingertip)
- 1474 • Addition of sample matrices (e.g., adding venous blood in addition to capillary blood)
- 1475 • Change to the measuring algorithm used to calculate a glucose concentration
- 1476 • Change in enzyme used in the chemical reaction (e.g., from glucose dehydrogenase to  
1477 glucose oxidase)
- 1478 • Any other modification that affects the intended use of the device
- 1479 • Any other change in fundamental scientific technology

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1481 We recommend that you contact Office of In Vitro Diagnostics and Radiological Health  
1482 (OIR) to discuss any specific questions you have regarding your BGMS device's eligibility to  
1483 be submitted as a special 510(k).

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