1200 G Street NW, Suite 400
Washington, DC 20005-3814
Tel: 202 783 8700
Fax: 202 783 8750
www.AdvaMed.org

AdvaMed
Advanced Medical Technology Association

February 15, 2005

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

Re: Docket No. 2004N-0234– Comments on Annual Guidance Agenda

Dear Sir or Madam:

AdvaMed respectfully submits the attached draft guidance document "Guidance for Industry and FDA Staff: MDR Reporting Self-Monitoring Blood Glucose Devices" for FDA's consideration as a proposed new guidance document. This proposal is being submitted in response to the July 9, 2004 *Federal Register Notice* request for possible topics for guidance documents.

The purpose of this document is to provide guidance for identifying medical device report (MDR) reportable events for self-monitoring of blood glucose (SMBG) devices. Our hope is that the guidance will improve the consistency of MDR reporting among manufacturers of self-monitoring blood glucose devices, thus increasing the usefulness of these reports to FDA.

Thank you for providing the opportunity to submit suggestions for consideration as new guidance. If you have any questions regarding the content of the document, please contact me.

Respectfully submitted,

Carolyn D. Jones
Associate Vice President
Technology and Regulatory Affairs

2004N-0234 C1

Guidance for Industry and FDA Staff:
MDR Reporting
for
Self-Monitoring Blood Glucose Devices

Prepared by
The Advanced Medical Technology Association's
Blood Glucose Monitoring Working Group
December 2004

Table of Contents

I. Purpose

The purpose of this document is to provide guidance for identifying medical device report (MDR) reportable events for self-monitoring of blood glucose (SMBG) devices. These devices provide *episodic* blood glucose results to assist patients and their caregivers in managing diabetes. The results are not to be used to diagnose diabetes. This guidance is intended to increase the usefulness of MDR reporting to FDA and to increase the consistency of reporting among SMBG device manufacturers.

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

The Least Burdensome Approach

We believe we should consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, please contact us so we can consider your point of view. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at http://www.fda.gov/cdrh/resolvingdisputes/ombudsman.html.

II. Background

A. The Intended Use and Risks of SMBG Devices

SMBG devices are *in vitro* medical devices that provide information, the quantitative measurement of glucose in capillary blood samples, enabling patients and their caregivers to monitor the effect of diabetes treatment and to help manage diabetes. In general, the use of such devices does not create a risk of direct harm to the patient because the devices are not applied in or on the human body. Therefore, the potential risks (and benefits) associated with these devices are limited to providing information that may impact treatment decisions. This is not to minimize the risk associated with an inaccurate reading. Since insulin is an inherently dangerous medication and the readings from SMBG devices are used to make decisions about insulin doses, the devices must be accurate.

The specific risks associated with currently marketed SMBG devices are that the device will not work as intended and either (1) the user will recognize that the device is not working and will need to employ other means to evaluate glycemic status and treatment or (2) the user will not recognize that the device is not working and will receive inaccurate results. Harm can occur if a delayed or inappropriate treatment decision results from inadequate or inaccurate information. However, as will be discussed below, the likelihood and severity of harm are considerably less in cases in which the user receives a non-quantitative result rather than an inaccurate one. Non-quantitative results include error messages and issues such as failure of the device to power on. Non-numeric results (e.g., "LO" and "HI") indicating that a glu-

cose result is, respectively, less than or greater than the lowest or highest value displayable by the system, are considered quantitative results.

Most SMBG devices are designed with some level of safeguards to reduce the probability of providing inaccurate information. For example, many SMBG devices are programmed to provide an error message rather than a glucose result under certain circumstances (e.g., insufficient blood applied to the test strip). The device labeling describes the error messages and identifies the conditions under which the error messages may occur. Other error conditions may not be detected by built-in safeguards.

B. The MDR System

The MDR system assists FDA in protecting the public health by helping to ensure that devices are not adulterated or misbranded and are safe and effective for their intended use. MDR requirements were purposefully couched in very general terms to encompass the vast range of medical devices and potential adverse events. In practice, however, to have meaning, reporting requirements must be interpreted with regard to the intended use and performance of each specific type of device.

Current regulations require manufacturers to file MDRs when they become aware of information that reasonably suggests that their marketed device (1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and that device or a similar device marketed by the manufacturer would be likely to cause a death or serious injury if the malfunction were to recur (21 CFR § 803.20).

Since the use of *in vitro* diagnostic devices does not create a risk of direct harm to the patient, SMBG devices can "contribute to," but not "cause," a death or serious injury.

"Reasonably suggests" means that the information is internally consistent and credible to a person qualified to make medical judgments.

According to 21 CFR § 803.3, *Serious injury* means an injury or illness that:

- Is life-threatening;
- Results in permanent impairment of a body function or permanent damage to body structure; or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

For purposes of this guidance, *life–threatening*, *permanent*, and *medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure* have the following meanings. (The definitions of *permanent* and *medical or surgical intervention* are from 21 CFR § 803.3.)

Life–threatening means (1) clinical signs and symptoms of severe hypoglycemia that are reasonably attributable to the blood glucose concentration; (2) a blood glucose concentration $\leq$50 mg/dL in an individual with hypoglycemia unawareness; (3) a diagnosis of diabetic ketoacidosis; or (4) a diagnosis of nonketotic hyperosmolar state. Evidence of severe hypogly-

cemia includes confusion, obtundation, loss of consciousness, or seizure, with the inability to self-treat hypoglycemia.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure means treatment by a healthcare professional (including emergency response personnel) or a layperson of an acute hypo- or hyperglycemic complication of diabetes that the patient cannot self-treat due to the complication. The definition of *life-threatening* above includes examples of acute complications of hypoglycemia. Confusion, marked weakness, and loss of consciousness are examples of acute complications of hyperglycemia. Medical treatment includes parenteral therapy (e.g., parenteral fluids or a glucagon injection) but does not include the mere provision of orange juice or other form of oral glucose unless the patient was unable to self-treat as a consequence of hypoglycemia.

III. Reportable and Non-reportable Complaints

Regardless of reportability, all complaints should be documented as complaints under the Quality System Regulation (21 CFR Part 820). A flow diagram of the MDR filing process appears in Attachment 3.

A. Adverse Event MDRs

1. What is reportable

If an SMBG device provides an inaccurate or non–quantitative result (e.g., an error message), and if this result is the basis for a delayed or inappropriate treatment decision that causes a death or serious injury, the death or serious injury is attributable to the SMBG device and is reportable. For purposes of an adverse event MDR, an inaccurate result is one that falls outside zones A and B of the Consensus Error Grid (discussed below).

Use error (discussed below) rather than a device malfunction may be responsible for an inaccurate or non-quantitative result that contributes to a death or serious injury, and such use error is also reportable.

2. Discussion of what is reportable and not reportable

The allegation of a layperson that an SMBG device provided an inaccurate result that contributed to a death or serious injury must be internally consistent and such as not to cause a person qualified to make medical judgments to doubt the credibility of the information. The allegation requires corroboration by any of the following: (1) the SMBG device result was grossly inconsistent with the cause of death or serious injury to which the alleged inaccuracy contributed (e.g., a meter result of 120 mg/dL a few minutes before the patient experienced severe hypoglycemia); (2) the device result was inaccurate as defined in Attachment 1; or (3) the device results were imprecise as defined in Attachment 1.

Attachment 1 provides recommendations for determining inaccuracy and imprecision by reference to an error grid. The error grid represents a generally accepted method of assessing the potential clinical impact of a glucose meter result as a function of its deviation from a laboratory standard. "[T]he importance (i.e., the clinical consequence) of any particular error [in SMBG] depends on the absolute value of both the reference and measured values and not just on the percentage of deviation. Moreover, this dependence is not easily described by any simple mathematical relationship."[1]

The error grid is adapted here to apply to the comparison of two or more same-meter results to assess imprecision. Of the two error grids in common usage for SMBG devices, this guidance recommends the Consensus Error Grid[2] (see Attachment 2) rather than the Clarke[3]. The Consensus Error Grid is the successor to the Clarke Error Grid and differs from the latter (a) in representing a consensus of 100 endocrinologists rather than a consensus of a small number of clinicians and (b) in changing risk boundaries based on advances in knowledge acquired in the 15 years intervening since the original publication by Clarke and his colleagues.[4] The Consensus Error Grid eliminates the discontinuities of risk levels (i.e., skipping risk categories in crossing from one zone boundary to another) of the Clarke Error Grid.

---

[1] Parkes JL, Slatin SL, et al. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care* 2000;23(8):1143-1148.

[2] *Ibid.*

[3] Clarke, WL, Cox D, et al. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 1987;10(5):622-628.

[4] Cox, DJ, Clarke WL, et al. Accuracy of perceiving blood glucose in IDDM. *Diabetes* Care 1985;8(6):529-536.

The definitions of the zones in both systems appear in the table below.

Risk Level (Zone)	Clarke Error Grid	Consensus Error Grid
A	Measured blood glucose <20% deviation from true blood glucose or both measured blood glucose and true blood glucose <70 mg/dL.	No effect on clinical action.
B	Deviation from true blood glucose >20% but leads to no treatment or benign treatment.	Altered clinical action—little or no effect on clinical outcome.
C	Overcorrection of acceptable blood glucose levels.	Altered clinical action—likely to effect [sic] clinical outcome.
D	Dangerous failure to detect and treat blood glucose errors.	Altered clinical action—could have significant medical risk.
E	Erroneous treatment (i.e. treatment contradictory to that actually required).	Altered clinical action—could have dangerous consequences.

This guidance recognizes that reasonable individuals might assign a given pair of meter/laboratory results to a different zone than that assigned by the grid; however, the benefit of the consistency inherent in the general use of an expert-derived Consensus Error Grid clearly outweighs the creation of an alternative grid by each manufacturer.

This guidance recommends reporting as adverse event MDRs complaints of glucose meter measurements that fall outside zones A and B of the Consensus Error Grid and corroborate the claim that an inaccurate result or imprecise results contributed to a death or serious injury.

"Use error" is an "[a]ct, or omission of an act, that has a different result to that intended by the manufacturer or expected by the operator. ... Use error includes slips, lapses, mistakes and reasonably foreseeable misuse."[5] Examples of use error are failure to store the product according to labeling, failure to use the product as directed, and failure to maintain the product as directed. The use of the product despite a labeled (usually technology-driven) contraindication, such as severe dehydration, hematocrit out of labeled range, and use of a known interfering substance, are other examples. Use error, although not technically due to a malfunction, is reportable if it contributes to a death or serious injury.

[5] Proposal for Reporting of Use Errors with Medical Devices by their Manufacturer or Authorized Representative. GHTF/SG2/N31R8:2003. Study Group 2 – Final Document, § 3.1.

"Abnormal use" is an "[a]ct or omission of an act by the operator or user of a medical device as a result of conduct that is beyond any means of reasonable risk control by the manufacturer or expected by the operator. ... Foreseeable misuse that is warned against in the instructions for use is considered abnormal if all other reasonable means of risk control have been exhausted."[6] An example of abnormal use is a user recognizing that LCD segments are missing but nevertheless guessing at what the result might be. Abnormal use is not reportable even if it contributes to a death or serious injury.

B. Malfunction MDRs

1. What is reportable

If an SMBG device malfunctions and provides an inaccurate or imprecise result, but a death or serious injury is not a consequence, the malfunction is reportable if a repeat of the situation would be expected to cause a death or serious injury. Even if a manufacturer concludes that a particular malfunction is not reportable, the manufacturer is expected to use valid statistical techniques (e.g., trending) to assess complaints and take corrective and/or preventive action as appropriate. (See 21 CFR § 820.250.)

2. Discussion of what is reportable and not reportable

If an SMBG device malfunctions and provides a non-quantitative result or a result that the user realizes is not credible (e.g., a result of 2 mg/dL in a conscious individual), but death or serious injury is not a consequence, the malfunction is not reportable. In the case of error messages, the meter functioned properly by identifying the problem, and, in some of these cases, the reported problem probably does not represent a malfunction (e.g., error messages indicating not enough blood or test strip movement). In all cases of non-quantitative (or noncredible) results, the malfunction is not reportable because the complaint does not constitute "information that reasonably suggests" the malfunction "*would be likely* [emphasis added] to cause or contribute to a death or serious injury if the malfunction were to recur."

There are several bases for this assertion. First, SMBG devices were not available until the 1980's. These devices are not the sole source of information for diabetics, who are trained to recognize signs and symptoms of hypo- and hyperglycemia, and to respond to them appropriately. Therefore, even if the SMBG device were to produce a non-quantitative or noncredible result, the likely response would not be progression to acute metabolic decompensation but rather treatment, if appropriate, to prevent a significant deterioration in glycemic control. Furthermore, many diabetics have back-up meters so that they are not solely reliant on the malfunctioning meter.

Another rationale for not reporting non-quantitative or noncredible results as malfunction MDRs is that, historically, most users complaining of non-quantitative results have not reported an injury. Most non-quantitative results reflect error-trapping mechanisms. As discussed in section II. A., most SMBG devices include error-trapping to reduce the likelihood of providing an inaccurate result in case of use error (e.g., temperature out of

[6] Proposal for Reporting of Use Errors with Medical Devices by their Manufacturer or Authorized Representative. GHTF/SG2/N31R8:2003. Study Group 2 – Final Document, § 3.2

range) or malfunction (e.g., a test strip problem). Many complaints of malfunction (including inaccurate and imprecise results) are resolved by troubleshooting over the telephone. Many manufacturers of SMBG devices have customer service departments available 24 hours per day, seven days per week, to assist in troubleshooting and to rapidly replace, at no cost to the user, meters that have allegedly malfunctioned. Finally, investigation does not confirm a malfunction in the vast majority of meters returned to SMBG manufacturers. In many cases of confirmed malfunction, the malfunction is due to use error (e.g., improper cleaning techniques leading to damage of the display or intrusion of water into the device).

"Use error" and "abnormal use" are defined in the preceding section. As noted, use error technically does not represent a malfunction and is not reportable absent a resultant death or serious injury.

ATTACHMENT 1

Recommendations for Determining Whether an SMBG Device is Inaccurate or Imprecise

Inaccuracy for Adverse Event MDR Reporting

To determine whether an SMBG device result is inaccurate and, as such, contributed to a death or serious injury, compare the result to the laboratory result of a blood sample obtained within no more than 10 minutes of the device sample. Plot the results on a Consensus Error Grid for type 1 diabetes, which is more stringent than the version for type 2. The SMBG device result will be considered inaccurate if the result falls outside zones A and B of the Consensus Error Grid. For meter results reported as "low" because they exceed the meter's lower limit, use the glucose value corresponding to 1 mg/dL (0.06 mmol/L) less than the meter's lower limit. For meter results reported as "high" because they exceed the meter's upper limit, use the glucose value corresponding to 1 mg/dL (0.06 mmol/L) greater than the meter's upper limit, but not greater than 550 mg/dL, the upper limit of the Consensus Error Grid. Likewise, assume reference values greater than 550 mg/dL are equal to 550 mg/dL.

The same standard should be used regardless of the site from which the blood sample was obtained; that is, whether the sample is from the commonly used fingertip site or alternative sites such as the palm or forearm.

Imprecision for Adverse Event MDR Reporting

Imprecision is defined as a device result falling outside zones A and B of the Consensus Error Grid when the result is plotted against the mean of two or more same-device results. All of the results to be compared must have been obtained within no more than 10 minutes of each other. For purposes of the Consensus Error Grid, the mean is considered the laboratory method result. For meter results reported as "low" or "high," follow the instructions for Inaccuracy, above.

For example, consider the following same-meter results: 110 mg/dL at 3:00 p.m., 150 mg/dL at 3:10 p.m., and 180 mg/dL at 3:20 p.m. The first two results and the last two results can be compared to each other, but all three results cannot be compared because more than 10 minutes elapsed between the first and last samples. Plot each individual result against the appropriate average on the Consensus Error Grid. For example, the average of the 3:00 p.m. and 3:10 p.m. results is 130 mg/dL. The values of 110 and 150 mg/dL are plotted on the Consensus Error Grid as meter results, 130 mg/dL as the laboratory result. The SMBG device results are considered precise because neither falls outside zones A and B of the Consensus Error Grid.

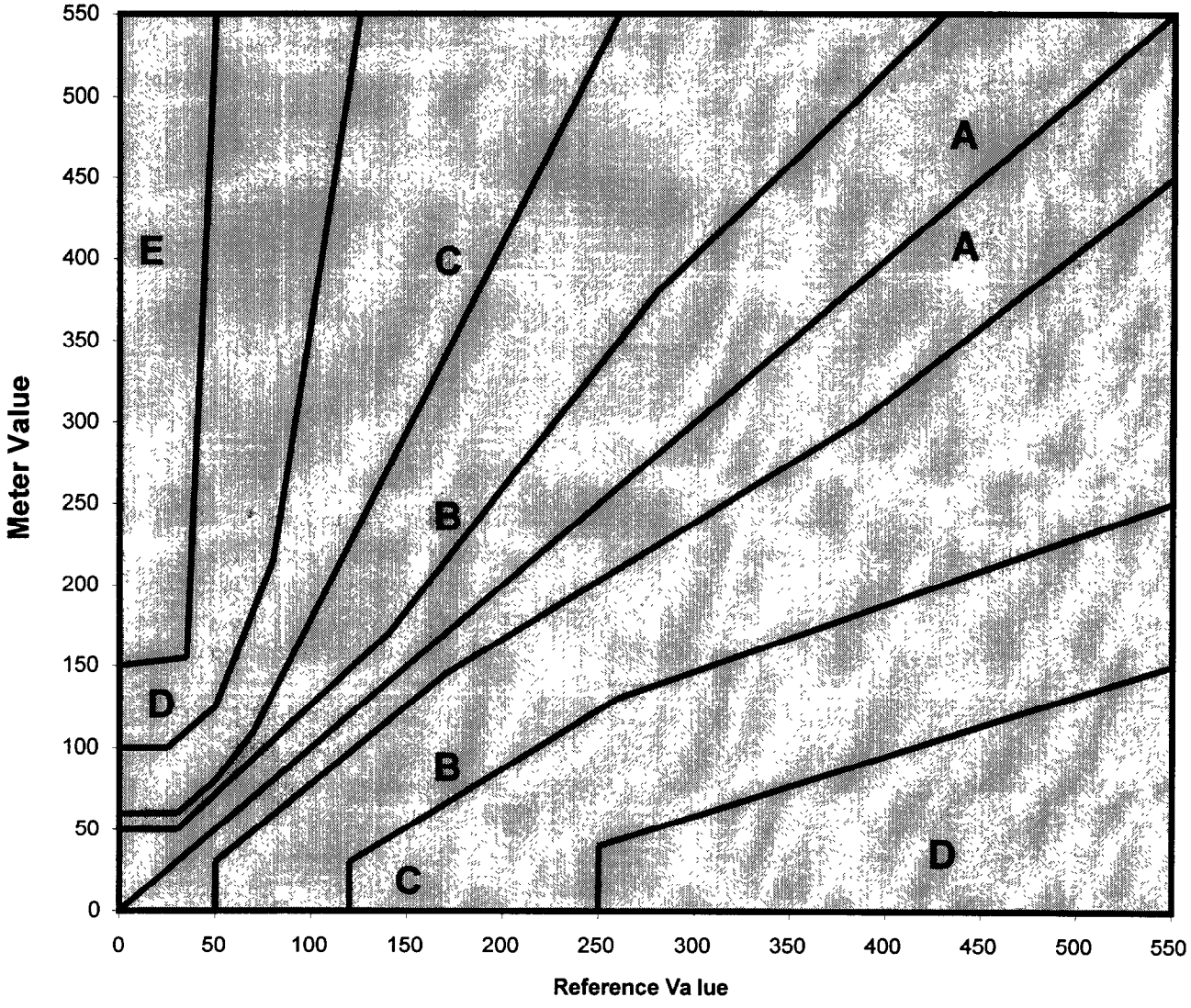
To determine the precision of an alternative site (i.e., non-fingertip) result, compare the result to the same-meter result as described above if the same-meter result was from a similar site. If the same meter result was a finger test, compare the two results as described in the section on inaccuracy, where the finger test result is considered the laboratory result, provided that the comparison is consistent with the product labeling.

Inaccuracy and Imprecision for Trending

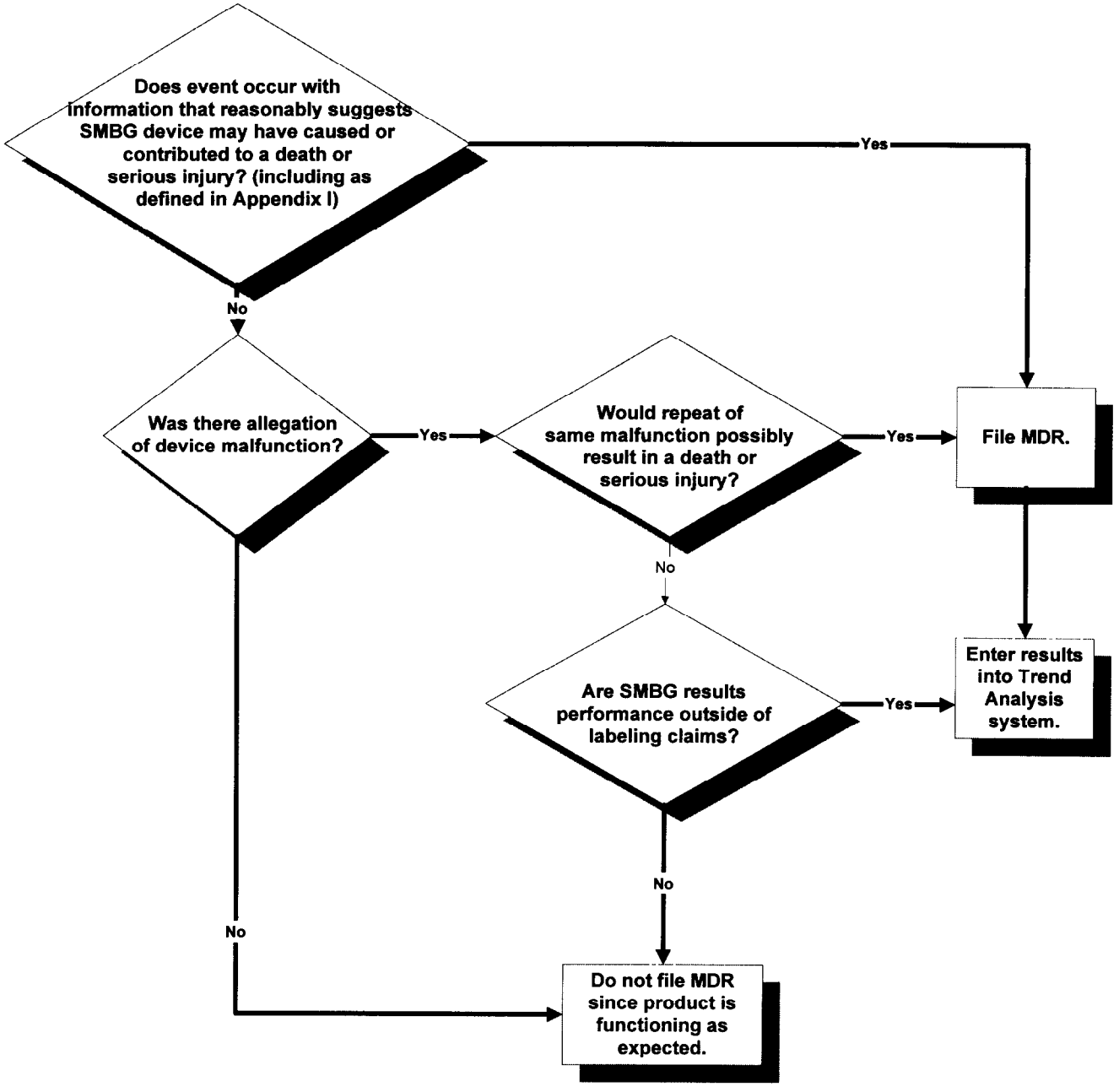
Glucose test results that meet the criteria for inaccuracy or imprecision, as discussed above, should be evaluated by valid statistical techniques according to the manufacturer's quality system regardless of whether the inaccuracy or imprecision was associated with a death or serious injury (21 CFR Part 820 and, in particular, 21 CFR § 820.250).

ATTACHMENT 2

THE CONSENSUS ERROR GRID



ATTACHMENT 3



No