Summary

The purpose of this document is to provide the facts about the accuracy of self-monitoring of blood glucose (SMBG) systems.

Accuracy can be defined as the closeness of agreement of a test result with an accepted reference value. There are multiple drivers of accuracy, including manufacturing processes, environmental factors and patient use.

All SMBG systems approved by the U.S. Food and Drug Administration (FDA) must meet the minimum 15/20 requirements of ISO 15197. While multiple studies assert accuracy claims, one manufacturer has proven the ability to exceed this standard across all lots of product produced.
Defining Accuracy

SMBG system accuracy is defined as the closeness of agreement of a test result with an accepted reference value.¹

- There are multiple drivers of accuracy, including manufacturing processes, environmental factors and individual patient use.

- System accuracy is independent from system precision. An SMBG system that delivers precise, or consistent, results is not necessarily guaranteed to be accurate.

- System accuracy is important, as SMBG readings may affect clinical decisions. A blood glucose reading is often referred to as “clinically accurate” if it would allow for a correct clinical decision to be made.
**FDA Requirements for Accuracy of SMBG Systems**

The FDA requires all manufacturers of SMBG systems to meet the ISO 15197 standard set by the International Organization for Standardization (ISO) in 2003. It states that the minimum acceptable accuracy for results produced by a glucose monitoring system shall be as follows:

- 95% of individual glucose results shall fall:
  - Within ±15 mg/dL of the results of the manufacturer’s measurement procedure at glucose concentrations <75 mg/dL
  - And within ±20% at glucose concentrations ≥75 mg/dL

SMBG manufacturers must submit test results from one lot of product to the FDA to demonstrate adherence to these standards. A *lot* is defined as a batch of product manufactured under uniform conditions during a set period of time. Most lots consist of several thousand vials of test strips.
Roche’s Commitment to Quality

Roche, the maker of ACCU-CHEK products, is committed to manufacturing quality products that provide accurate results.

In fact, the ACCU-CHEK Aviva Plus test strip was developed to meet an even higher accuracy specification that is consistent with what AdvaMed, the association of companies that produce medical device and diagnostic products, advocates. With this tighter specification, patients can have even more confidence in the accuracy of their blood glucose results.

<table>
<thead>
<tr>
<th>Acceptance criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Standard—ISO 15197: 2003</td>
<td>95% of individual glucose results shall fall within ±15 mg/dL of the reference results at glucose concentrations less than 75 mg/dL and within ±20% at glucose concentrations greater than or equal to 75 mg/dL.</td>
</tr>
<tr>
<td>ACCU-CHEK Aviva Plus test strip</td>
<td>95% of individual glucose results shall fall within ±15 mg/dL of the reference results at glucose concentrations less than 100 mg/dL and within ±15% at glucose concentrations greater than or equal to 100 mg/dL.</td>
</tr>
</tbody>
</table>

The ACCU-CHEK Aviva Plus test system was tested against and meets an accuracy specification that is 23% tighter than the current ISO standard. This means that a smaller bias is expected between the meter’s blood glucose result and the reference value when using the ACCU-CHEK Aviva Plus test strip versus systems that only meet the ISO standard.

Accuracy comparison

The ACCU-CHEK® Aviva Plus test strip results cover an area 23% smaller than the area defined by the ISO standard.
As the following chart depicts, a 15/15 standard at a 100 mg/dL breaking point is tighter than the current standard for blood glucose values >75 mg/dL. By changing the break point to 100 mg/dL, the accuracy level is maintained at blood glucose values ≤75 mg/dL, and accuracy is increased at >75 mg/dL.

<table>
<thead>
<tr>
<th>bG Value (mg/dL)</th>
<th>Current Standard (15/20% with 75 mg/dL break point)</th>
<th>Tighter Specification (15/15% with 100 mg/dL break point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>±15 mg/dL</td>
<td>±15 mg/dL</td>
</tr>
<tr>
<td>75</td>
<td>±15 mg/dL</td>
<td>±15 mg/dL</td>
</tr>
<tr>
<td>80</td>
<td>±16 mg/dL</td>
<td>±15 mg/dL</td>
</tr>
<tr>
<td>90</td>
<td>±18 mg/dL</td>
<td>±15 mg/dL</td>
</tr>
<tr>
<td>100</td>
<td>±20 mg/dL</td>
<td>±15 mg/dL</td>
</tr>
<tr>
<td>110</td>
<td>±22 mg/dL</td>
<td>±16.5 mg/dL</td>
</tr>
</tbody>
</table>

We believe that while accuracy is an extremely important factor in the use of blood glucose monitors, it is only one component in the total performance of a blood glucose system. We focus on each of the following areas to ensure our testing supplies are safe, accurate and effective.

We employ quality checks to ensure that every single lot of ACCU-CHEK® Aviva Plus test strips meets this tighter accuracy specification.

For every ACCU-CHEK Aviva Plus test strip lot produced:

- We test 1 out of every 100 vials for homogeneity or consistency of performance. As each lot has thousands of vials, this process is quite labor intensive.
- We test vials that are representative of the entire lot a second time. Some are tested in a lab; others are tested with capillary blood from actual patients with diabetes to reflect a real-world environment.

Only those lots that achieve the acceptance criteria based on the tighter accuracy specification are released into the market. These quality checks ensure that ACCU-CHEK Aviva Plus test strips are safe, accurate and dependable.

All SMBG systems cleared by the FDA must meet the ISO 15197 standard.
Ensuring Adherence to Accuracy Requirements

Manufacturers must calibrate SMBG systems against a lab reference method to ensure adherence to the ISO 15197 accuracy standard. Three different types of lab reference methods exist:

- Glucose oxidase
- Glucose dehydrogenase
- Glucose hexokinase

All three methods detect glucose without suffering greatly from interfering substances. The primary differences between them are the enzyme system and the technique used for detecting glucose.

The most commonly used methods—glucose oxidase and glucose hexokinase—are examined below.

<table>
<thead>
<tr>
<th>Lab Reference*</th>
<th>Enzyme System Used</th>
<th>Technique for Detecting Glucose</th>
<th>Popular Brand of Analyzer</th>
</tr>
</thead>
<tbody>
<tr>
<td>glucose oxidase</td>
<td>glucose oxidase</td>
<td>electrochemical</td>
<td>YSI 2300 STAT Plus™</td>
</tr>
<tr>
<td>glucose hexokinase</td>
<td>hexokinase and glucose-6-phosphate dehydrogenase</td>
<td>spectrophotometric (optical)</td>
<td>Roche Hitachi 917</td>
</tr>
</tbody>
</table>

* Most SMBG systems in the U.S. are calibrated using a glucose oxidase lab reference method. ACCU-CHEK products are calibrated using a glucose hexokinase reference method.

While SMBG systems must be calibrated against a lab reference method, variations between different reference methods exist.
Guidelines for Accuracy Evaluations

In addition to stating the minimum standard for SMBG system accuracy, ISO 15197 also outlines requirements for accuracy evaluations. Examples include:5

1. Scope and Setting
System accuracy should be evaluated with at least 100 different subjects over at least 10 days. Ideally, measurement should take place in a diabetes outpatient clinic or hospital setting.

2. Appropriate Reference Methods
SMBG readings should be compared to reference values “determined by the manufacturer’s measurement procedure.” In other words, an ideal evaluation would use the lab reference method that the SMBG system was designed to be calibrated with as a point of comparison. This information can be found on an SMBG manufacturer’s product labeling.

3. Range of Glucose Samples
Accuracy evaluations should use capillary blood and should include glucose samples that are representative of a wide range of meter operation. The table below illustrates the percentage of glucose samples that should fall within each glucose concentration range.

<table>
<thead>
<tr>
<th>Percentages of samples %</th>
<th>Glucose concentrations mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&lt;50</td>
</tr>
<tr>
<td>15</td>
<td>50–80</td>
</tr>
<tr>
<td>20</td>
<td>80–120</td>
</tr>
<tr>
<td>30</td>
<td>120–200</td>
</tr>
<tr>
<td>15</td>
<td>201–300</td>
</tr>
<tr>
<td>10</td>
<td>301–400</td>
</tr>
<tr>
<td>5</td>
<td>&gt;400</td>
</tr>
</tbody>
</table>

4. Lot Inclusion
A single lot may be evaluated if data demonstrates that variability across lots is minor. However, many manufacturers choose to examine multiple lots in order to demonstrate robustness of product performance.

Manufacturers should adhere to ISO guidelines when conducting accuracy evaluations for SMBG systems.
Examining Accuracy Claims

A variety of SMBG accuracy studies have been published. Five critical questions must be asked when evaluating these studies and the subsequent claims they have produced.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study conducted by an objective third party?</td>
<td>• Use of an objective third party prevents manufacturers from tailoring a study to demonstrate favorable performance. For example, a specific lot may be selected to provide better-than-expected performance.</td>
</tr>
</tbody>
</table>
| How many lots were tested? (Some manufacturers refer to lots as “batches.”) | • Use of only one lot allows for tailoring a study toward favorable performance.  
• Using multiple samples across various lots provides a better indication of actual manufacturing output. |
| Did the study follow ISO 15197 requirements for proper use of lab reference methods? | • ISO 15197 requires that accuracy evaluations use the lab reference method indicated on an SMBG manufacturer’s labeling. This ensures consistency with how the system was designed. |
| Did the study follow ISO 15197 requirements for correct glucose concentrations of samples? | • ISO 15197 requires that capillary evaluations of system accuracy include glucose samples that range from <50 mg/dL to >400 mg/dL. |
| Does the accuracy claim represent all lots being manufactured?  | • Accuracy claims are valid for the specific lots tested within a particular study. But unless a manufacturer aligns its quality control process accordingly, it cannot ensure that all lots produced meet the claim. |
External Factors That Affect Accuracy

Accuracy is inherent in SMBG systems, but it can also be driven by environmental factors, such as:

- Temperature
- Humidity
- Altitude

Human factors can also affect SMBG accuracy. These can often be corrected through proper patient training.

- Inadequate blood drop obtained
- Blood incorrectly applied to test strip
- Test strip inserted into meter incorrectly
- Alcohol, if used, not allowed to dry before testing
- Use of expired test strips
- Improper coding
- Ineffective hand washing
## Challenges in Comparing SMBG System Results

All SMBG systems must meet the ISO 15197 standard. However, when two different systems are compared, their test results may be different. The following two scenarios illustrate how this can occur.

### Scenario 1—System A and system B were both calibrated using the same lab reference method

<table>
<thead>
<tr>
<th>Reading from SMBG system A deviated from lab result by +10%</th>
<th>Reading from SMBG system B deviated from lab result by -10%</th>
<th>Results from two systems deviate from each other by 20 percentage points</th>
</tr>
</thead>
</table>

### Scenario 2—System A and system B were calibrated using different lab reference methods

<table>
<thead>
<tr>
<th>Reading from SMBG system A deviated from lab result by +10%</th>
<th>Reading from SMBG system B deviated from lab result by -10%</th>
<th>Results from two systems could deviate from each other by more or less than 20 percentage points because they were calibrated using two different lab reference methods</th>
</tr>
</thead>
</table>

These scenarios illustrate the challenge in directly comparing readings from one SMBG system to another.

Two SMBG systems can both meet the ISO 15197 accuracy standard but provide two different blood glucose readings.
Evaluating Clinical Impact

To help overcome the challenge of comparing two different systems, industry professionals often refer to clinical accuracy. A blood glucose reading is clinically accurate if it would allow for a correct clinical decision to be made.

A consensus error grid* can be used to assess the clinical accuracy of SMBG systems. This grid places SMBG-measured glucose results on the y-axis and actual glucose results as measured by a lab analyzer on the x-axis. The risk posed by discrepant readings is categorized by five zones, labeled A through E.

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**Zone A:** No effect on clinical action  
**Zone B:** Altered clinical action—little or no effect on clinical outcome  
**Zone C:** Altered clinical action—likely to affect clinical outcome  
**Zone D:** Altered clinical action—could have significant medical risk  
**Zone E:** Altered clinical action—could have dangerous consequences

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* Both the Parkes Error Grid and Clarke Error Grid are used to examine clinical accuracy. The Parkes grid is portrayed above, as it was developed more recently and is increasingly used by SMBG manufacturers in clinical studies. The primary difference between the grids is the placement of dividing lines between zones.
Recall that ISO 15197 requires that 95% of SMBG glucose results fall:

- Within ±15 mg/dL of the results of the manufacturer's measurement procedure at glucose concentrations <75 mg/dL.
- And within ±20% at glucose concentrations ≥75 mg/dL.

SMBG results that meet this criteria should fall within Zone A and allow for correct patient treatment.

**If two different SMBG readings both fall into Zone A, they are both clinically accurate.**
| **Interference and Use Limitation Testing** | • We test for more than 190 of the most common and known interferences.  
• We believe that this is roughly 7 times the number tested by other major manufacturers. |
| **System Safeguards** | • We employ system safeguards to warn patients of external factors that can impact system accuracy. These safeguards include underdose detection, test strip expiration warnings, damaged test strip detection, abnormal temperature warnings and low-meter battery warnings. |
| **Labeling** | • We support standardizing product labeling with a simple, easy-to-use format.  
• With the launch of the ACCU-CHEK Aviva Plus care kit, we have redesigned the labeling to be more user friendly. |
| **Quality Assurance** | • We support development of an industry standard for complaint handling, medical device reporting (MDR) of product malfunctions and consistent manufacturing processes. |
| **Patient Support and Education** | • Our call center is available 24/7/365 and offers patient support in over 150 languages. |
References


7. Manufacturer 510(k) product submission and internal Roche evaluation.
If you have any questions, please contact your local ACCU-CHEK® representative.