

A CONSENSUS GUIDELINE

Performance Requirements

for **Continuous Glucose
Monitoring Systems**

2026 VERSION 1.0

Organized By



DIABETES TECHNOLOGY SOCIETY

CONSENSUS GUIDELINE ON PERFORMANCE REQUIREMENTS FOR CONTINUOUS GLUCOSE MONITORING SYSTEMS

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Purpose

This consensus guideline establishes a risk-based, totality-of-evidence framework for evaluating the performance of continuous glucose monitoring (CGM) systems across their intended uses and throughout the product life-cycle. Its architecture spans ten principal content areas, including 1) intended use and risk, 2) target populations and special conditions, 3) measurement traceability, comparators, and calibration, 4) interferences and environmental robustness, 5) analytical accuracy, 6) trend accuracy and rate of change performance, 7) alerts and clinical interpretation, 8) system reliability, software, interoperability, and cybersecurity, 9) study design and statistical methodology, and 10) usability, quality systems, labeling, and postmarket surveillance. See the Table of Contents for the complete structure.

Developed By

An international, multidisciplinary consensus panel convened by the Diabetes Technology Society, with stakeholders spanning clinical medicine, laboratory medicine, engineering, regulatory science, informatics, and patient representation.

Development at a Glance

77 experts from 20 countries across six continents.

Funding and Independence

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Foreword

Continuous glucose monitoring (CGM) systems have become central to diabetes management. They provide glucose values, trends, and alerts that support insulin-dosing decisions and automated insulin delivery (AID) systems. When performance falls short, patients may face serious harm, including life-threatening hypoglycemia, diabetic ketoacidosis (DKA), or hyperosmolar hyperglycemic state. Inaccurate, delayed, or unavailable information can also undermine confidence in treatment decisions.

To address this safety-critical need, Diabetes Technology Society convened a global panel spanning 20 countries. Regulators, public health officials, clinical investigators, bioengineers, and people living with diabetes developed a harmonized framework for evaluating CGM performance and lifecycle.

This consensus guideline provides an end-to-end framework for CGM evaluation, addressing clinical and measurement considerations, including target populations, measurement traceability, and comparator procedures. Covered topics also include analytical and clinical performance, study design, and system considerations, including reliability, interoperability, and cybersecurity. The guideline extends beyond conventional static-device evaluation frameworks to review adaptive, artificial intelligence/machine learning (AI/ML)-enabled CGM functions and connected systems, specifically addressing lifecycle governance including predetermined change-control plans, version control, and validation.

The guideline is grounded in a totality-of-evidence philosophy, meaning that device safety cannot rest on a single accuracy statistic. Evaluation instead requires an integrated assessment of interdependent factors. These include point and trend accuracy, alert performance, and reliability. Other factors include usability and human factors, cybersecurity, and biocompatibility. Data availability should also be considered.

The guideline harmonizes established international standards with emerging technologies, including AI/ML and cloud-connected ecosystems. It provides manufacturers, regulators, investigators, and clinicians with a shared, rigorous framework to help ensure that CGM systems support safe and reliable diabetes care.

Abstract

Continuous glucose monitoring (CGM) systems are increasingly used to guide diabetes management, yet approaches to evaluating their performance remain heterogeneous. Existing standards and regulatory requirements provide important foundations but do not fully address the expanding technical, clinical, and connected-system capabilities of contemporary CGM systems. This guideline provides a comprehensive, risk-based, totality-of-evidence framework for evaluating CGM performance across the device lifecycle. It evaluates analytical and clinical performance and study methodology to establish evidence of CGM performance. It assesses system reliability and cybersecurity and supports usability and quality management to promote safe, reliable operation, as well as the postmarket surveillance required to provide ongoing lifecycle monitoring. The framework was developed by a multidisciplinary international expert panel representing CGM development, evaluation, regulation, and clinical use. Its development incorporated published literature, performance standards, and regulatory requirements, complemented by expert consensus. The intended audience spans manufacturers, regulators, and investigators, who can use the framework to support development and evaluation. Clinicians and standards organizations can

also apply it to clinical use and standards development.

Executive Summary

Introduction

This guideline provides a risk-based, totality-of-evidence framework for evaluating CGM systems throughout their lifecycle. It is intended for organizations and professionals who develop, evaluate, or regulate CGM technologies.

CGM performance should not be characterized by a single accuracy metric. CGM systems provide glucose measurements and trend information that can support clinical decisions. They also provide rates of change and alerts that may influence connected system responses. Safe and effective use therefore depends on the performance of the sensor and other components of the intended system.

Guiding Principles

The guideline is based on six principles:

1. **Totality-of-evidence.** Evaluation should consider analytical, clinical, system, and lifecycle evidence, rather than relying on a single performance measure.
2. **Risk-based evaluation.** The level and type of evidence should account for the intended use and clinical risk. Requirements should also consider the target population and care setting. The potential consequences of error should further shape the evidence needed.
3. **Multidimensional performance evaluation.** CGM evaluation should address multiple performance measures, including accuracy and alerts. It should also capture operational characteristics, such as timeliness and data completeness. When relevant, it should assess resilience characteristics, including failure and recovery.
4. **Complete-system evaluation.** The intended CGM configuration should be evaluated as a complete system. This includes software and connectivity that may affect performance. Other relevant components should also be evaluated when they influence system function or safety.
5. **Population- and setting-specific evaluation.** Evidence should reflect the intended populations and clinical settings, including special populations or higher-risk environments when applicable.
6. **Lifecycle evaluation.** Evaluation should extend from development through postmarket use. It should encompass quality and risk management and verification and validation. Change and version control should govern system modifications, while labeling should communicate appropriate use. Surveillance and reassessment should support ongoing lifecycle oversight.

Stakeholder Application

Stakeholders have distinct responsibilities for generating, evaluating, and applying evidence. Manufacturers should provide evidence for the complete relevant system and maintain appropriate lifecycle controls. Investigators can design studies that reflect the intended use, populations, and settings, while regulators assess whether evidence is complete and proportionate to the intended claims and risks. Standards organizations promote consistent evaluation approaches. Beyond accuracy metrics, clinicians, health systems, and payers require evidence that medical device systems are appropriate for clinical use, focusing on aspects of reliability and usability, as well as data availability, connected-system performance, and clinical relevance.

Connected Systems

It is important that connected CGM functions are evaluated according to their intended use and configuration. Interoperability evaluation should address data exchange and semantic integrity, while system validation should address software and connected components. Where relevant, time synchronization, latency, and data availability should be evaluated, and cybersecurity and configuration management should consistently support reliable operation of connected systems. Changes in software or configuration should undergo risk-based reassessment when warranted. Connected systems can create hazards that are not evident when components are tested separately, so it is critical that the evaluation demonstrate that the system can fail safely, keep essential local functions available, and never silently pass along corrupted or misleading data.

Interpretation

Expectations should be tailored to the intended use and target population of the CGM. The clinical setting and level of risk should also guide the evaluation. System configuration should determine additional requirements when relevant. The terms “shall,” “should,” and “may” have specific meanings defined in How to Use This Guideline. This guideline complements, but does not replace, applicable laws, regulations, recognized standards, or regulatory guidance.

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How to Use This Guideline

The guideline is organized into 14 chapters that collectively cover the evaluation of CGM systems. The chapters encompass intended use and risk classification, as well as analytical and clinical performance and system reliability. Interoperability, quality systems, and emerging technologies receive additional attention. Chapter 13 provides a sample study protocol that translates the study-design principles described in Chapter 10 into a practical framework for CGM performance studies. Individual chapters may be consulted for specific evaluation questions, but the guideline is intended to be applied as an integrated framework.

Regarding normative language, “shall” indicates a requirement that the panel considers necessary to meet an established standard or regulatory expectation and is accompanied by the applicable supporting reference. “Should” denotes a recommended practice that is supported by scientific evidence, consensus, or risk-based considerations but is not intended as an absolute requirement. “May” identifies a permissible or optional approach. Requirements should be interpreted in the context of the device’s intended use and target population, as well as its connected-system configuration and regulatory pathway.

Scope

This guideline applies to CGM systems that measure interstitial glucose using subcutaneous or intradermal sensors. It does not cover noninvasive monitoring, intravascular monitoring, or devices providing semiquantitative or non-numeric results.

This guideline applies to individuals with diabetes across personal, professional, and remote-monitoring contexts, as well as to general wellness tracking. It includes pediatric patients, pregnant women, and people with kidney disease when these populations require specific evaluation. Higher-risk clinical environments, including inpatient, emergency, and intensive-care settings, are also within scope.

The system boundary encompasses the CGM measurement system and its software, with connected components that acquire or process CGM data. It extends to connected components that transmit or provide access to CGM data. It also addresses components that preserve CGM data integrity or support timely data delivery. The guideline does not establish independent performance or clinical-effectiveness requirements for insulin-delivery

systems, other therapeutic systems, or stand-alone clinical decision-support systems, except to the extent that their interaction with CGM data affects the performance, safety, or intended use of the CGM system.

Intended Users of This Guideline

This guideline is intended for four broad groups of users involved in CGM development, evaluation, regulation, clinical use, and financing: (1) technology developers and evaluators; (2) regulatory and standards stakeholders; (3) clinical and healthcare stakeholders; and (4) healthcare financing and policy stakeholders. Technology developers and evaluators include manufacturers, evaluation investigators, and researchers who develop, test, and validate CGM systems and their components. Regulatory and standards stakeholders span regulatory authorities and standards organizations responsible for establishing, interpreting, or applying requirements for CGM performance, safety, and quality, while clinical and healthcare stakeholders encompass clinicians, hospitals, and healthcare delivery organizations that use CGM systems in patient care and assess their performance and integration into clinical workflows. Finally, healthcare financing and policy stakeholders include payers and other organizations that evaluate the evidence, value, and appropriate use of CGM technologies. Across these groups, the guideline supports consistent evaluation of CGM performance, facilitates comparison across systems and studies, and helps translate technical and clinical evidence into regulatory, clinical, and payment decisions.

Guideline Evaluation Philosophy

This guideline adopts a totality-of-evidence, risk-based approach to evaluating CGM systems. Clinical performance should not be judged by a single accuracy metric or isolated technical characteristic. Rather, evaluation should consider analytical and clinical performance together. It should also consider system reliability, human factors, and software. Interoperability and cybersecurity may further affect system performance and safety. Other factors should be considered when they may influence the safety or effectiveness of a CGM system in its intended use.

The appropriate evidence should be determined by the intended use, target population, and risk profile of the system. Performance should therefore be evaluated across clinically relevant glucose ranges and conditions. Where appropriate, evaluation should also account for variability across wear periods, manufacturing lots, and sensor sites. Connected-system configurations should be evaluated when they are part of the intended system. Study design and statistical analysis should be sufficiently rigorous to distinguish meaningful performance differences from variability arising from the comparator system, study procedures, or other sources.

Regulatory and Standards Alignment

Whereas the preceding section describes the panel's evaluative philosophy, this section addresses how the guideline relates to existing external standards and regulatory frameworks. It builds on and harmonizes established regulatory requirements, consensus standards, and technical guidance relevant to CGM performance. The guideline incorporates core concepts from Clinical and Laboratory Standards Institute (CLSI) POCT05, relevant International Organization for Standardization (ISO) standards, and the Food and Drug

Administration (FDA) integrated continuous glucose monitoring (iCGM) regulatory framework (21 Code of Federal Regulations [CFR] 862.1355). It extends these foundations to contemporary CGM systems and connected technologies, complementing rather than replacing applicable regulatory requirements and recognized standards. The guideline also addresses risk management and quality management, as well as software lifecycle processes. In addition to usability, interoperability, and cybersecurity, postmarket surveillance and regulatory considerations are also addressed. Examples incorporated throughout the guideline include ISO 14971 for medical-device risk management and ISO 13485 for quality management systems. International Electrotechnical Commission (IEC) 62304 addresses medical-device software lifecycle processes, and relevant FDA requirements and guidance are incorporated where applicable.

When multiple standards or regulatory frameworks address the same aspect of CGM performance, the guideline seeks to identify areas of convergence and provide a coherent approach rather than establish competing requirements. For example, the guideline identifies consistent principles across CLSI POCT05, FDA iCGM special controls, and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) guidance regarding measurement uncertainty, traceability, and comparator measurement procedures. Regulatory requirements and standards may differ across jurisdictions and change over time. For this reason, applicable laws, regulations, recognized standards, and regulatory guidance remain controlling for individual products and submissions. This guideline provides a scientific and technical framework to support their application and promote greater consistency in evaluating CGM performance across devices, studies, and regulatory settings.

Guideline Development Methodology

Panel Composition and Guideline Development Process

In February 2026, the Diabetes Technology Society convened an international consensus panel to develop a guideline on technical performance requirements for CGM systems. The project was organized as a 14-chapter guideline intended to address the analytical, clinical, regulatory, and lifecycle considerations relevant to CGM performance evaluation.

The panel comprised 77 experts from 20 countries across six continents, with expertise spanning clinical medicine, laboratory medicine, engineering, regulatory science, informatics, epidemiology, industry, and patient representation. Full details on panel composition, including specific institutional and specialty representation, are provided in Section 1.1.2.

Each panelist was assigned to at least one group devoted to a chapter and could participate in additional groups. Each technical and regulatory chapter had a chair, and each chapter had one or more primary authors. The chapter authors were selected for subject-matter expertise, and chairs were responsible for facilitating balanced discussion, cross-disciplinary input, and consensus development.

Chapter groups met remotely three times between February and April 2026 to prepare initial drafts. Most panelists then met in person in Herndon, Virginia, on April 22–23, 2026, to review the draft, resolve areas of uncertainty, and identify topics requiring further discussion. Subsequent work was conducted remotely. Selected top-

ics required additional meetings to resolve technical and methodological questions, and an integrated draft was completed in June 2026. Between June and August 2026, the panel developed a sample protocol and harmonized the guideline's structure, terminology, and cross-chapter recommendations. The document was completed in September and voted on in late September and early October 2026.

Evidence Identification and Evaluation

The evidence base for this guideline drew on four complementary sources: published scientific literature, existing performance standards, applicable regulatory requirements, and expert consensus. The panel identified relevant evidence through expert review, and a formal systematic literature search was not performed. Particular attention was given to standards and regulatory documents addressing CGM performance.

Where the literature or standards did not sufficiently address an issue, the panel combined the available evidence with expert opinion. When differing viewpoints or evidence were identified, the panel sought to refine recommendations through discussion and chapter-level review. Recommendations were subsequently subject to formal consensus voting.

Governance, Consensus, and Voting Process

The guideline was developed through multiple rounds of review, iterative chapter revisions, and structured multidisciplinary discussion of the final integrated document. Each eligible voting panelist had one vote. Approval required both (1) at least 80% of votes cast in favor, excluding abstentions and recusals, and (2) a quorum of at least 50% of eligible panelists. Nonvoting advisors and observers did not participate in consensus voting. Voting took place in late September and early October 2026, followed by publication on October 26, 2026. All 77 panelists voted in favor of approval, representing 100% agreement among the voting panelists.

Review and Quality Assurance

The writing committee consisted of 16 authors. The additional 61 members of the guideline panel reviewed the document in multiple stages during video discussions and an in-person meeting in Herndon, Virginia, on April 22–23, 2026. The authors incorporated ideas from discussions and working meetings with officials from the FDA, the National Institutes of Health (NIH), the U.S. Department of Commerce, National Institute of Standards and Technology (NIST), the Centers for Disease Control and Prevention (CDC), and the American Diabetes Association. The authors are responsible for the substantive content of the guideline, which was reviewed by the full guideline panel and approved through the consensus voting process. The guideline reflects the consensus of the panel and represents the views of the Diabetes Technology Society. Feedback was collected through inline comments and structured remote-review processes. Contested items were put to a vote among the relevant chapter members prior to the in-person meeting or the full writing committee after the in-person meeting, with approval requiring a majority. An artificial intelligence (AI)–assisted tool was used solely to organize and route comments to the relevant chapter authors. It was not used to generate recommendations, evaluate evidence, or adjudicate comments.

Funding and Conflicts of Interest

This guideline development project received financial support from Abbott Diabetes Care, Dexcom, MiniMed, Radiometer, Roche, Sinocare, and Trinity Biotech. Funding supported administrative and logistical activities related to panel meetings, literature review, and manuscript preparation. Funders had no role in the selection of panelists other than the participation of panelists representing their respective companies. They did not direct the guideline agenda, control evidence reviews, or have an organizational role in consensus voting. Individual employees of funding organizations participated as disclosed panel members and were permitted to vote.

All panelists completed disclosure-of-interest forms in accordance with the Diabetes Technology Society policy. Relevant disclosures were reviewed during panel formation and managed throughout guideline development. Panelists with relevant conflicts of interest could contribute to drafting and discussion but could not chair a chapter group. Recommendations were developed through multidisciplinary discussion within chapters that included multiple panelists. The panel included 16 industry members and 61 non-industry members. We defined an industry member as a panelist employed by or primarily contracted to a company that manufactures or sells CGM systems, connected diabetes devices, or comparator analyzers. The final content reflects the panel's independent consensus judgment and does not necessarily represent the views of any individual panelist, project advisor, funding organization, or other organization whose employees or members contributed to its development.

Disclosures

AAA is affiliated with and a shareholder of Apex Medical AI Inc. and Thirdwayv Inc.

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DTA has received speaker and/or consulting fees from Abbott, Ascensia, Dexcom, Insulet, Lilly, MannKind,

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ES receives grant support (to Johns Hopkins) for her research from the American Heart Association and the National Institutes of Health. ES is a Deputy Editor of Diabetes Care. ES receives an honorarium from the American Diabetes Association for that work. ES receives royalties from Wolters Kluwer for her authorship of chapters and laboratory monographs in UpToDate on measurements of glycemic control and screening tests for type 2 diabetes. In 2025, ES received payment for an educational webinar (content her own) sponsored by Siemens Healthineers and hosted by the Association for Diagnostics & Laboratory Medicine.

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ML has received research grants from Eli Lilly and Novo Nordisk and has received honoraria from or has been a consultant for Bayer, Boehringer Ingelheim, Eli Lilly, Nordic Infucare, Novo Nordisk, and Rubin Medical, all outside the submitted work.

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TB served on advisory panels of Abbott, AstraZeneca, Eli Lilly, Medtronic, Novo Nordisk, Roche, Sanofi, and Tandem. TB received honoraria for participating in the speakers' bureaux of Abbott, AstraZeneca, Aventis, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, Pfizer, Roche, and Sanofi. TB's institution received research grant support from Abbott, Medtronic, Novartis, Novo Nordisk, Sandoz, Sanofi, and Tandem, and from Breakthrough T1D, the European Union, the Helmsley Charitable Trust, the National Institutes of Health, and the Slovenian Research and Innovation Agency.

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AFS, AHBW, BSa, BSh, BVH, CCC, CM, CMR, DBS, EG, EMB, ER, EYZ, GAA, HLi, HV, IN, JEC, JGC, KH, KMT, KYC, MBP, MLC, MM, MMS, MPr, MTK, SNS, SY, WAC, and WMR have nothing to disclose.

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HWV and CYT contributed to the discussions and provided technical expertise but were not part of the writing team and did not vote on the document. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, and the U.S. Department of Health and Human Services.

Limitations

Where potential use cases lack high-quality prospective clinical evidence, performance criteria necessarily relied on expert consensus, particularly regarding optimal study-protocol features. The panel included substantial industry expertise, although multiple measures were used to maintain editorial independence. Some topics lacked sufficient evidence to establish quantitative performance thresholds. The guideline may be revised when substantial new evidence, regulatory changes, or emerging technologies warrant reconsideration of its recommendations.

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Abbreviations

Abbreviation	Definition
15/30 minutes	15 or 30 minutes
AAMI	Association for the Advancement of Medical Instrumentation
AC	Acetaminophen
ACE	Alternate Controller Enabled
ADLM	Association for Diagnostics & Laboratory Medicine
AE	Adverse Event
AI	Artificial Intelligence

Abbreviation	Definition
AID	Automated Insulin Delivery
ALCOA	Attributable, Legible, Contemporaneously Recorded, Original (or a True Copy), and Accurate
ANSI	American National Standards Institute
APACHE	Acute Physiology and Chronic Health Evaluation
API	Application Programming Interface
ASTM	ASTM International
BG	Blood Glucose
BGM	Blood Glucose Monitor
BLE	Bluetooth Low Energy
BMI	Body Mass Index
CAPA	Corrective and Preventive Action
CDC	Centers for Disease Control and Prevention
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CKD	Chronic Kidney Disease
CLSI	Clinical and Laboratory Standards Institute
CMP	Comparator Measurement Procedure
corrF	Correction Factor
CRF	Case Report Form
CRM	Certified Reference Material
CSII	Continuous Subcutaneous Insulin Infusion
D50	Dextrose 50%
DKA	Diabetic Ketoacidosis
EHR	Electronic Health Record
EMC	Electromagnetic Compatibility
ESD	Electrostatic Discharge
EU	European Union
EU MDR	European Union Medical Device Regulation
FDA	U.S. Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources

Abbreviation	Definition
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GCP	Good Clinical Practice
GDM	Gestational Diabetes Mellitus
GDPR	General Data Protection Regulation
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HL7	Health Level Seven International
HRUS	Hazard-Related Use Scenarios
iCGM	Integrated Continuous Glucose Monitoring
ICH	International Council for Harmonisation
iCoDE	Integration of Continuous Glucose Monitoring Data into the Electronic Health Record
iCoDE-2	Integration of Connected Diabetes Device Data into the Electronic Health Record
ICU	Intensive Care Unit
IEC	International Electrotechnical Commission
IEEE	Institute of Electrical and Electronics Engineers
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFU	Instructions for Use
IRB	Institutional Review Board
ISF	Interstitial Fluid
ISO	International Organization for Standardization
IT	Information Technology
IV	Intravenous
IVD-MD	In Vitro Diagnostic Medical Device
LOC	Loss of Consciousness
MAD	Mean Absolute Difference
MARD	Mean Absolute Relative Difference
MARSI	Medical Adhesive-Related Skin Injury
ML	Machine Learning
MP	Measurement Procedure
MRD	Mean Relative Difference
NIH	National Institutes of Health

Abbreviation	Definition
NIST	National Institute of Standards and Technology
OAuth	Open Authorization
OGTT	Oral Glucose Tolerance Test
OHRP	Office for Human Research Protections
OS	Operating System
OTA	Over-the-Air
PCCP	Predetermined Change Control Plan
PMA	Premarket Approval
PMS	Postmarket Surveillance
QC	Quality Control
QMP	Qualified Medical Professional
QMS	Quality Management System
QMSR	Quality Management System Regulation
RG	Reference Glucose
RMP	Reference Measurement Procedure
ROC	Rate of Change
SAE	Serious Adverse Event
SBOM	Software Bill of Materials
SDC	Service-Oriented Device Connectivity
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
STU	Standard for Trial Use
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TDD	Total Daily Insulin Dose
Tmax	Time to Maximum Plasma Concentration
UADE	Unanticipated Adverse Device Effect
UI	User Interface
U.S.	United States
V&V	Verification and Validation

Chapter 1

Introduction, Scope, Terminology, and Regulatory Positioning

Included in this section:

- 1.1 PURPOSE AND CONTEXT
- 1.2 SCOPE
- 1.3 REGULATORY POSITIONING AND COMPATIBILITY WITH RECOGNIZED STANDARDS
- 1.4 DEVICE EVALUATION PHILOSOPHY
- 1.5 GLOSSARY
- 1.6 SUMMARY

Section 1.1

Purpose and Context

1.1.1 Purpose

This guideline provides a framework for evaluating the performance of continuous glucose monitoring (CGM) systems used in diabetes care. It covers clinical and measurement considerations, including target populations, comparator methods, and environmental robustness. Analytical performance factors, including accuracy metrics and interferences, are addressed, as are evaluation approaches such as clinical study design and total product lifecycle performance. The guideline focuses on CGM systems designed for people with diabetes, used either independently or with automated insulin delivery (AID) systems, as well as for wellness tracking by people without diabetes. It is intended to inform regulatory assessments, professional society guidelines, coverage determinations, and industry development practices.

1.1.2 Composition and Representation of the Consensus Panel

This panel consisted of 77 stakeholders from 20 countries across six continents, which reflected diverse regulatory and clinical practice environments. Members included former United States (U.S.) government regulators from the Food and Drug Administration (FDA); current officials from the National Institutes of Health (NIH), the U.S. Department of Commerce, National Institute of Standards and Technology (NIST), and the Los Angeles County Department of Health Services; industry representatives from six CGM manufacturers and four technology companies; organization representatives from the Association for Diagnostics & Laboratory Medicine (ADLM, formerly the American Association for Clinical Chemistry), the Canadian Society of Clinical Chemists, and the Institute of Electrical and Electronics Engineers (IEEE); people with diabetes; and academic CGM experts in adult endocrinology, pediatric endocrinology, internal medicine, clinical chemistry, clinical investigation, hospital medicine, nephrology, pregnancy care, diabetes education, bioengineering, epidemiology, informatics, and computer science.

1.1.3 Clinical Background

CGM systems play a critical role in diabetes management, enabling frequent assessment of glucose levels, thresholds, and trends, typically with alert options. These systems provide real-time glucose monitoring, which can assist patients, clinicians, and caregivers with determining insulin doses, preventing hypoglycemia and hyperglycemia, and operating AID systems. They also affect a user's sense of personal safety, confidence, and trust in their diabetes management. As CGM technologies increasingly inform direct therapeutic decisions, there is a critical need for a rigorous framework to evaluate their performance, safety, and reliability across clinical contexts.

1.1.4 Technology Overview

CGM devices are generally either inserted just beneath the skin or attached directly to the skin through an adhesive patch. Most commonly, these devices are designed to continuously sample glucose levels in interstitial fluid (ISF). The CGM system software then converts those levels to equivalent plasma glucose values, which are reported at defined intervals (e.g., every 5 minutes). CGM systems may also include notifications or data visualizations (e.g., alerts, alarms, and trends), as well as wireless data transmission and cloud connectivity. They are also frequently interoperable with external connected devices such as insulin pumps and AID systems, and/or integrated with decision-support software.

1.1.5 Risk Context

Clinical risks of inaccurate glucose measurements include severe hypoglycemia, diabetic ketoacidosis (DKA), coma, and death. These clinical risks associated with CGM performance can result from analytic performance issues or from system and use failures. These risks are increased in nonadjunctive use cases and in AID systems, where CGM data directly inform insulin dosing. Accordingly, CGM safety should be evaluated within a comprehensive risk context that reflects the intended use over the full sensor life.

Section 1.2

Scope

This guideline provides a complete and comprehensive framework for the evaluation of CGM performance, including:

- Intended use, use cases, and risk classifications;
- Target populations and special conditions;
- Measurement traceability, comparator systems, and calibration;
- Interferents and environmental robustness;
- Analytical performance (point accuracy, precision);
- Trend accuracy, rate of change (ROC), and lag characterization;
- Alert detection, clinical accuracy, and event interpretation;
- System reliability, stability, security, and biocompatibility;
- Study design, data processing, and statistical framework; and

- Usability, labeling, quality systems, and postmarket surveillance (PMS).

Many of the considerations presented here are relevant to other glucose-measuring technologies, such as non-invasive monitors, intravascular CGM systems, and devices providing semiquantitative or non-numeric results. However, such devices may require additional validation that is not discussed in this guideline, and they are out of scope.

Section 1.3

Regulatory Positioning and Compatibility with Recognized Standards

This guideline integrates and harmonizes core concepts from recognized consensus documents, including Clinical and Laboratory Standards Institute (CLSI) POCT05 and relevant International Organization for Standardization (ISO) frameworks, as well as FDA integrated continuous glucose monitoring (iCGM) regulation 21 Code of Federal Regulations (CFR) 862.1355. It extends these foundations to address emerging technologies, including adaptive algorithms, machine learning (ML)-based systems, and cloud-connected data ecosystems. The objective of the guideline is to promote international convergence toward a shared set of scientifically grounded expectations for CGM performance and safety across jurisdictions. For reference, lists of aligned standards are provided in each of the 11 technical and regulatory chapters; they are omitted from the Introduction, Protocol, and Conclusion chapters.

Section 1.4

Device Evaluation Philosophy

CGM safety and effectiveness should be determined through a totality-of-evidence approach, because no single accuracy statistic alone is sufficient. This approach should involve a combined assessment of the following factors:

- Analytical precision and reproducibility;
- Specificity and interference;
- Point and trend accuracy;
- Alert accuracy and performance;

- Sensor stability and survival;
- Data availability;
- Usability;
- Cybersecurity;
- Human factors; and
- Biocompatibility across the entire wear period.

Section 1.5

Glossary

Acute Physiology and Chronic Health Evaluation (APACHE): A scoring system used in intensive care units (ICUs) to measure the severity of a patient's illness.

Adaptive Algorithms: Algorithms that adjust their internal logic or parameters, either in real time or periodically, based on incoming patient data (e.g., personalizing prediction models to individual glycemic patterns).

Adjunctive Use: CGM use that requires confirmatory blood glucose monitoring values before treatment decisions are made.

Adverse Event (AE): Any unfavorable medical occurrence that develops or worsens during study participation, regardless of its relationship to the device.

Agreement Rates: The percentage of CGM-comparator measurement pairs that fall within predefined limits.

Alert Fatigue: Desensitization of clinicians or patients caused by redundant, unprioritized, or excessive alerts, which can lead to critical alerts being missed or ignored.

Ambulatory Glucose Profile: A standardized, clinically validated visual display of glucose patterns over time.

Analysis Window: The time interval used to determine whether a CGM alert corresponds to a reference-confirmed glycemic event. For each event, the window begins a fixed interval (15 or 30 minutes) before the event's start time and ends the same fixed interval after the event's end time.

Analytical Interference: An effect of a substance or condition that alters sensor output independently of glucose concentration and results in measurement error.

Analytical Performance: The ability of a measurement procedure or measuring system to correctly detect or

measure a particular measurand. It encompasses accuracy, including trueness (bias) and precision, as well as measuring range, selectivity, detection capability, and stability.

Atmospheric Pressure: The ambient air pressure surrounding the CGM system, which may influence sensor or device performance during operation.

Attributable, Legible, Contemporaneously Recorded, Original, and Accurate (ALCOA) Principles: A framework for data quality that requires data to be attributable, legible, contemporaneously recorded, original (or a true copy), and accurate.

Attrition: Loss of participants or study data due to withdrawal, discontinuation, or incomplete participation.

Audit Trail: A secure record that documents the creation, modification, and deletion history of study data.

Automated Insulin Delivery (AID) System: A system that automatically adjusts insulin delivery based on continuous glucose monitoring data and embedded control algorithms.

Automation Bias: The tendency of clinicians or users to rely excessively on automated or artificial intelligence outputs, leading to uncritical acceptance of those outputs even when they are wrong.

Bias: The systematic difference between a measured value, such as a CGM glucose value, and the corresponding reference value.

Biocompatibility: The ability of a device or material to perform as intended without causing unacceptable biological responses when in contact with the human body.

Calibration: The process of establishing or adjusting the relationship between a measurement system and a known reference value to support accurate measurement results.

Calibration Adherence: The extent to which users perform required calibration procedures according to device instructions.

Calibration Hierarchy: A sequence of calibrations from a reference to the final measuring system, in which the outcome of each calibration depends on the outcome of the preceding one.

Caregiver Receiver Error: A failure in which data transmission or alert escalation to a remote caregiver fails or is delayed, even though the primary connection to the patient's local receiver remains stable.

Cascading Failure: A systemic hazard in which a localized failure or transmission error in one component triggers a broader loss of coordinated function across connected components.

Case Report Form (CRF): The paper or electronic document used to collect protocol-required data for each study participant.

Certified Reference Material (CRM): A reference material characterized by a metrologically valid procedure for one or more specified properties and accompanied by a certificate specifying the property value, its associated

uncertainty, and a statement of metrological traceability.

Change Control: A documented process for evaluating, approving, implementing, and verifying modifications to a product, process, software component, or associated documentation.

Chemical Interferent: An endogenous or exogenous substance capable of affecting sensor performance or glucose measurement accuracy.

Chronic Kidney Disease (CKD): A condition characterized by impaired kidney function, commonly classified into five stages, with Stage 5 representing kidney failure and/or the need for dialysis or transplantation.

Clinic Sampling Window: A predefined interval during which comparator glucose measurements are obtained for performance assessment.

Clinically Significant Interference: An interference effect large enough to potentially affect clinical interpretation or treatment decisions.

Clinician-Platform Interoperability: Workflows in which clinicians access, review, and act on compiled and filtered CGM data within a clinical data platform or EHR for patient care and billing.

Clock Drift: Gradual divergence of local clock settings among system components over time, which can cause timing misalignment unless an authoritative time source is established.

Cloud-to-Cloud Interoperability: Secure data transmission between cloud-based platforms, such as routing glucose data from a CGM manufacturer's cloud to a third-party clinical analytics platform.

Command Conflict: A state in which multiple software components or devices attempt overlapping or contradictory control actions, resulting in unpredictable or unsafe device behavior.

Commutability: A property of a reference material, demonstrated by the closeness of agreement between measurement results for that material and those for representative clinical samples.

Comparator Measurement Procedure: The measurement procedure used to obtain values against which CGM results are compared. A comparator measurement procedure is not necessarily a reference measurement procedure.

Comparator Method: The analytical method used to obtain measurements for evaluating performance.

Concurrence: The rate of agreement between CGM and comparator values across defined glucose ranges.

Confidence Interval: A statistical range that quantifies the uncertainty around an estimated performance measure.

Continuous Glucose Monitoring (CGM) System: A system that measures glucose in interstitial fluid (ISF) at frequent intervals and reports glucose values, trends, and alerts.

Corrective and Preventive Action (CAPA): A quality system process used to investigate nonconformities, identify root causes, implement corrections and preventive measures, and verify their effectiveness.

Data Integrity: The completeness, consistency, accuracy, and reliability of data throughout their lifecycle.

Data Provenance: The documented origin and processing history of data elements, including their transformation and reconciliation status, as they are exchanged across system interfaces.

Dataset Provenance: The documented lineage, traceability, and demographic composition of datasets used to train, validate, and test artificial intelligence (AI) and machine learning (ML) models, to support data integrity and the assessment of algorithmic bias.

Design Controls: Quality system practices used to ensure that device design requirements are appropriately defined, reviewed, verified, validated, and maintained throughout development.

Device-Related Adverse Event: An adverse event determined to be caused by, or reasonably related to, the investigational CGM system.

Device-to-Cloud Interoperability: Transmission of CGM data from a local device, such as a receiver, smartphone, insulin pump, or computer, to a remote cloud service, either directly or through one or more intermediary components.

Device-to-Device Interoperability: Direct communication between physical hardware components, such as a CGM communicating with an insulin pump or automated insulin delivery controller.

Diabetes Technology Society Error Grid: An error grid developed by the Diabetes Technology Society to classify the clinical risk of glucose measurement errors into distinct risk zones.

Diabetic Ketoacidosis (DKA): A life-threatening emergency caused by insulin deficiency, in which elevated glucose and ketone production result in acidosis.

Difference Measures: The numerical difference between CGM and comparator values, expressed in absolute or relative terms.

Discrete Event Prediction: A predictive task that forecasts specific categorical glycemic events rather than continuous glucose concentrations.

Dose-Response Characterization: A study that evaluates the relationship between interferent concentration and the magnitude of sensor measurement error.

Electrochemical Sensor: A glucose sensor that measures glucose through an electrochemical reaction at the sensing electrode.

Electrochemically Active Compound: A substance capable of oxidation or reduction at the sensor electrode, which may produce false glucose signals.

Electronic Data Capture System: A computerized system used to collect, manage, and maintain clinical study data.

Endogenous Interferent: A substance produced within the body, such as uric acid or another metabolite, that may affect sensor performance.

Environmental Exposure: The environmental conditions a CGM system may encounter during normal use, including temperature, humidity, and atmospheric pressure.

Environmental Robustness: The ability of a CGM system to maintain acceptable performance under expected environmental conditions throughout its intended use.

Exogenous Interferent: A substance originating outside the body, including a medication, vitamin, mineral, or supplement, that may affect sensor performance.

Expanded Measurement Uncertainty: The product of a combined standard measurement uncertainty and a coverage factor greater than one, defining an interval around the measured value with a specified coverage probability.

Factory Calibration: Calibration performed by the manufacturer during production, allowing the CGM to operate without routine user-entered calibration values.

Failure Modes and Effects Analysis (FMEA): A structured, inductive risk analysis method used to identify potential failure modes, evaluate their effects, and prioritize risk control measures.

Fault Tree Analysis (FTA): A structured, deductive risk analysis method used to identify combinations of events or failures that may lead to a defined hazardous outcome.

Formative Evaluation: An iterative assessment performed during development to identify usability issues and improve the design before final validation.

Gestational Diabetes Mellitus (GDM): Diabetes first diagnosed during pregnancy in a person whose glucose metabolism was not previously known to be abnormal.

Glucose Manipulation: A controlled study procedure that intentionally raises or lowers glucose levels to evaluate CGM performance across a broad glycemic range.

Glucose Monitoring System: A device or system intended to measure glucose concentrations and provide glucose information to users or healthcare professionals.

Glycemic Alerts: Notifications triggered when a measured or predicted glucose value meets a predefined alert criterion. Threshold alerts are triggered when the measured glucose value crosses a predefined threshold, whereas predictive alerts are triggered when the CGM predicts that glucose will cross a predefined threshold within a specified time.

Glycemic Events: Events that occur when a comparator glucose crosses a predefined threshold that may be used for CGM alerts.

Glycolysis: The metabolic breakdown of glucose by cells. In collected blood samples, ongoing glycolysis lowers measured glucose over time.

Hematocrit: The volume fraction of erythrocytes in blood.

Hemolysis: The rupture of erythrocytes, releasing intracellular contents into the surrounding plasma or other fluid.

Human Factors Engineering: The application of knowledge about human capabilities, limitations, and behaviors to device design to improve safety, effectiveness, and usability.

Humidity: The amount of moisture in the environment, which may affect device operation or performance.

Identity/Authentication Failure: A security failure arising from weak endpoint authentication, spoofed devices, or compromised credentials that may allow unauthorized endpoints to inject false data or commands.

Imprecision: Variation among replicate indications or measured values obtained under specified conditions, commonly expressed as a standard deviation, variance, or coefficient of variation.

In-Clinic Session: A scheduled study visit, during which participants undergo supervised CGM performance testing and comparator glucose sampling.

In Silico Validation: Computational evaluation of device logic, control algorithms, or glucose predictions using simulated physiological models, performed before or alongside human clinical studies.

In Vitro Testing: Testing conducted outside the body under controlled laboratory or benchtop conditions.

In Vivo Testing: Testing conducted in human participants under physiological conditions.

Independent Observation: A data point that does not depend on or duplicate information from another observation in the analysis dataset.

Institutional Review Board (IRB): A committee that reviews research involving human participants to help protect their rights, safety, and welfare.

Instructions for Use (IFU): Written information provided by the manufacturer that describes intended use, setup, operation, maintenance, limitations, warnings, and precautions.

Integrated CGM (iCGM): A CGM system regulated by the U.S. Food and Drug Administration as a Class II device with special controls, designed to securely and reliably transmit glucose data to digitally connected devices, including AID systems.

Intended Use: A general statement of what a product is designed to do, for which population, and under what

conditions.

Intended-Use Population: The population for whom the CGM system is intended, as defined by the device labeling and indications for use.

Intended Wear Site: The anatomical location, specified in labeling, where a sensor is designed to be worn.

Interference Assessment: The process of determining whether an interferent affects glucose measurement accuracy.

Interferent: Any chemical substance, environmental factor, or physical condition that has the potential to alter sensor performance.

International System of Units Traceability: Metrological traceability to a unit of the International System of Units through a documented, unbroken calibration hierarchy.

Interoperability: The ability of connected components to exchange data, preserve meaning, and maintain clinically coherent function across devices, software, and services through technical connectivity, semantic consistency, and temporal integrity.

Interstitial Fluid (ISF): The fluid in the spaces surrounding tissue cells, in which subcutaneous CGM sensors measure glucose.

Labeling: All written, printed, electronic, or graphic information accompanying a medical device, including labels, instructions for use, manuals, and promotional materials.

Lifecycle: The sequence of phases through which a product progresses, including conception, development, manufacture, distribution, use, maintenance, retirement, and disposal.

Lot-to-Lot Variability: Differences in performance between sensors produced in different manufacturing lots.

Manufacturing Lot: A defined production batch of sensors manufactured under similar conditions.

Masked CGM: A CGM configuration in which glucose data are collected continuously but are not displayed to the user during the monitoring period and are reviewed after the wear period ends.

Matched Pair: A CGM reading and a comparator glucose measurement collected within a predefined time window and used for performance evaluation.

Matrix: The material or biological medium in which the measurand is present and the measurement is performed, such as plasma, arterial whole blood, venous whole blood, or interstitial fluid.

Mean Absolute Difference (MAD): The average absolute difference between paired values, which is particularly relevant at low glucose levels.

Mean Absolute Relative Difference (MARD): The average absolute difference between paired values ex-

pressed as a percentage of the comparator value and used as a summary measure of relative point accuracy.

Measurand: The quantity intended to be measured. For CGM systems, the measurand is glucose concentration, specified according to the reporting unit.

Measurement Procedure: A detailed description of a measurement according to one or more measurement principles and a given measurement method, including the calculations required to obtain a result.

Measurement Uncertainty: A non-negative parameter characterizing the dispersion of quantity values attributed to a measurand, based on the information used.

Mechanical Stress: Physical forces, such as compression, bending, tension, or movement, that may influence sensor function.

Medical Adhesive-Related Skin Injury (MARSI): Skin damage caused by the application or removal of medical adhesives, including blistering, skin tearing, excoriation, and maceration.

Medical Device Reporting: The process of reporting device-related adverse events, deaths, serious injuries, or reportable malfunctions to regulatory authorities.

Metrological Traceability: A property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.

Modified Bland–Altman Plot: A scatter plot of the differences between CGM and comparator values across the system's glucose range.

Multianalyte Sensing: Biosensor technology capable of measuring glucose together with other metabolic biomarkers, such as ketones or lactate.

Nonadjunctive Use: CGM use that supports direct treatment decisions without routine confirmation by self-monitoring of blood glucose, except in specified circumstances.

Nonconformance: A failure to meet a specified requirement.

Offline Buffering: Temporary local storage of data during connectivity outages, followed by reconciliation on reconnection without data duplication, timeline oscillation, or inappropriate retrospective alerts.

Optical Sensor: A sensor that measures glucose using optical principles, including spectroscopy, absorbance, or fluorescence.

Optional Calibration: A CGM feature that allows the system to operate without routine user-entered blood glucose calibrations, while permitting the user to enter one or more blood glucose values to adjust sensor performance when desired.

Paired-Difference Testing: An interference screening method that compares sensor responses before and after exposure to a potential interferent.

Patient-Mediated Interoperability: Workflows in which patients actively export, share, or route their own health data through consumer devices or digital health tools.

Performance Drift: The gradual decline in the predictive accuracy of a sensor glucose model over time due to changes in patient behavior, physiology, or environment relative to the original training data.

Personal CGM: A CGM system intended for use by an individual with diabetes, or their caregiver, to continuously monitor glucose and support diabetes management outside a healthcare setting.

Physiological Lag: The delay between a change in circulating blood glucose and the corresponding CGM output, resulting from physiological glucose transport.

Physiological Variability: Natural biological variation among or within individuals that may affect sensor performance.

Pivotal Study: A clinical study intended to provide the primary evidence of safety and effectiveness needed to support a regulatory submission.

Plasma Glucose Concentration: The concentration of glucose in the plasma phase of blood, expressed in an appropriate unit such as mg/dL or mmol/L.

Platform-to-EHR Interoperability: Workflows in which CGM data are compiled, filtered, and securely integrated into an electronic health record (EHR) system for clinical review and billing.

Point Accuracy: The closeness of a CGM glucose value to the corresponding comparator glucose value at a specific time point.

Post-Dose Bias: The average difference between sensor glucose and reference glucose measurements after administration of an interferent.

Postmarket Surveillance (PMS): The systematic collection and analysis of information on device performance after commercial release to identify safety or effectiveness issues.

Power (Statistical Power): The probability that a study will detect a true difference or effect when one exists.

Pre-Analytical: Relating to processes that occur before measurement, including patient preparation, specimen collection, transport, cooling, storage, centrifugation, and other specimen preparation.

Pre-Dose Bias: The baseline difference between sensor glucose and reference glucose measurements before administration of an interferent.

Precision: Closeness of agreement among replicate indications or measured values obtained on the same or similar objects under specified conditions.

Predictable Localized Autonomous Mode (Fallback Mode): A fail-safe state in which safety-critical components transition to a predictable local operating mode when communication with external devices or cloud

services fails.

Prediction Horizon: The future time window over which an algorithm predicts glycemic trends or discrete events.

Prespecified Analysis: An analysis defined in the protocol or statistical analysis plan before study data are reviewed.

Primary Endpoint: A prespecified outcome used to evaluate whether the study objective has been achieved.

Primary Objective: The main question a study is designed to answer, typically focused on demonstrating CGM safety and performance.

Product Lifecycle Management: The coordinated management of a device through all phases of its lifecycle, from concept through retirement.

Professional CGM: A CGM system prescribed, applied, and managed by a healthcare professional to collect glucose data over a defined period for clinical assessment and treatment optimization.

Quality Control (QC): Operational procedures used to monitor whether a measurement system continues to operate within specified performance limits and whether its results are suitable for their intended use.

Quality Management System (QMS): A formal system of policies, processes, procedures, and responsibilities used to direct and control an organization with regard to quality.

Rate of Change (ROC): The speed at which glucose concentration increases or decreases over time, typically expressed in mg/dL/min.

Real-Time CGM: A CGM device that continuously measures glucose in interstitial fluid and automatically transmits glucose values, trends, and alerts to the user in near real time.

Real-World Device Performance: CGM functionality and reliability during normal use outside a controlled clinical environment.

Reference Glucose Measurement: A glucose value obtained using a validated comparator or reference method and used as the benchmark for CGM performance analyses.

Reference Measurement Procedure (RMP): A measurement procedure accepted as providing results fit for assessing the trueness of values obtained from other measurement procedures for quantities of the same kind.

Repeatability: Measurement precision under conditions that include the same measurement procedure, operator, measuring system, operating conditions, and location, with replicate measurements performed over a short period.

Risk Acceptability Criteria: Predefined thresholds used to determine whether a risk is acceptable, requires further mitigation, or is unacceptable.

Root Cause Analysis: A structured investigation used to identify the fundamental underlying cause of a problem or nonconformity.

Sample Size: The number of participants required to adequately evaluate study endpoints with the desired statistical power.

Semantic Consistency: The preservation of meaning during data exchange, ensuring that raw values, events, annotations, and alerts are interpreted consistently by sender and receiver.

Sensor Blinding: A study condition in which CGM glucose values are not visible to participants or study personnel, preventing clinical decisions based on investigational data.

Sensor Discontinuation: Permanent cessation of sensor use before the end of the intended wear period.

Sensor Failure: Any event that leaves the sensor unable to continue operating as intended before the end of the labeled wear period.

Sensor Glucose (SG): The glucose concentration reported by the CGM sensor.

Sensor Survival: The proportion of sensors that remain functional through their intended wear period.

Sequential Organ Failure Assessment: A scoring system used in intensive care units to track organ function, degree of organ failure, and risk of death.

Serious Adverse Event (SAE): An adverse event that results in death, is life-threatening, requires hospitalization, results in significant disability, or meets other regulatory seriousness criteria.

Signal Loss: Temporary interruption of CGM data transmission or glucose reporting.

Software Interoperability: Workflows in which CGM data are ingested directly by digital analytics platforms, artificial intelligence forecasting tools, or clinical decision-support algorithms.

Source Data: Original records, or certified copies, from which study findings are derived.

Stale-Data Hazard: The risk of clinical or automated therapeutic decisions being made on outdated or cached glucose values or alerts because of delayed uploads, connectivity buffering, or missing data-age indicators.

Stopping Criteria: Prespecified conditions requiring withdrawal of a participant or termination of part or all of a study to protect participant safety.

Subcutaneous Sensor: A sensor inserted beneath the skin to continuously measure glucose in interstitial fluid.

Synchronization Failure: Temporal misalignment caused by clock drift or inconsistent time authority, resulting in mismatched timelines for glucose values, insulin dosing, alerts, or other system events.

System Agreement: The percentage of CGM-comparator pairs that fall within specified agreement limits.

Systematic Measurement Error: A component of measurement error that produces a consistent or predictable deviation from the true value across repeated measurements.

Technical Connection: The physical and protocol-level communication channel that allows hardware and software components to exchange data.

Temperature Exposure: The temperature conditions encountered during storage, wear, or operation of the CGM system.

Temporal Integrity (Time Synchronization): A system property ensuring that sensors, receivers, applications, cloud services, and decision-support systems share a coherent timeline, so that glucose values, insulin dosing, alerts, and annotations are associated with the correct time point.

Time to Maximum Plasma Concentration (Tmax): The time required after administration for a substance to reach its maximum plasma concentration.

Trend Accuracy: The ability of a CGM system to accurately characterize the direction and rate of glucose change over time.

Trueness: Closeness of agreement between the average of an infinite number of replicate measured values and a reference quantity value.

Unanticipated Adverse Device Effect (UADE): A serious adverse effect, safety issue, or device-related problem that is unexpected in nature, severity, or frequency relative to known risks.

Usability Engineering File: A collection of records that demonstrates compliance with the usability engineering process and documents activities performed to identify and mitigate use-related risks.

Use-Related Risk Analysis: A systematic assessment of hazards and risks arising from interactions between users and a device.

User Calibration: Calibration performed by the user by entering one or more blood glucose values into the CGM system.

Validation: Confirmation through objective evidence that a device fulfills its intended use and user needs.

Vasoactive-Inotropic Score: A score that quantifies the amount of vasoactive and inotropic medication support given to critically ill patients.

Verification: Confirmation through objective evidence that specified design inputs or requirements have been fulfilled.

Version Governance: The policies and processes used to identify, control, track, and maintain released product versions throughout the device lifecycle.

Wear Duration: The intended period of continuous CGM sensor use before replacement.

Zero Trust Security: A security architecture that requires verification of every device and endpoint attempting to access an interoperable network, regardless of its location or previous pairing history.

Section 1.6

Summary

Chapter 1 provides a framework for evaluating the safety, effectiveness, and performance of minimally invasive CGM systems across the entire product lifecycle. The guideline covers analytical performance, clinical performance, and alert functionality, which characterize CGM measurement and its clinical use. It also considers reliability, usability, and cybersecurity, which support safe and dependable system operation. Study design follows established frameworks, including CLSI POCT05, applicable ISO standards, and U.S. FDA iCGM regulations. Because no single metric can be used to characterize CGM performance, a totality-of-evidence approach should be used, as outlined within the rest of the guideline.

Chapter 2

Intended Use, Use Cases, and Risk Classification

Included in this section:

- 2.1 INTRODUCTION
- 2.2 INTENDED USE
- 2.3 USE CASES
- 2.4 RISK CLASSIFICATION
- 2.5 REGULATORY CLASSIFICATION
- 2.6 MANUFACTURER CHECKLIST
- 2.7 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 2.8 SUMMARY

Section 2.1

Introduction

CGM systems operate across a wide range of clinical contexts, use environments, device configurations, intended users, and target populations. Consequently, the intended use and use case(s) of a CGM system define its risk profile, performance expectations, and the level of evidence required to support safety and effectiveness. Manufacturers should clearly define the intended use and target populations for each CGM system. Risk management, performance characterization, labeling, and validation activities should be appropriate and commensurate with the highest-risk claimed use case.¹

Section 2.2

Intended Use

A CGM system is typically intended to continuously measure and display interstitial glucose concentrations in people over a specified wear period, and to provide real-time or near-real-time glucose values, glucose trends, and alerts to support glucose management. In some cases, a CGM system is intended to support glucose management decisions, including insulin dosing and treatment adjustments, when used in accordance with the device labeling.

The CGM system may also be intended for self-management of daily activities, diet, physical activity, and medication management. Continuous glucose values, trends, and alerts can inform decisions about these activities.

Additional intended use statements may be included as appropriate to describe specific use cases. These may include professional use, remote monitoring, and interoperability with AID systems. Wellness-only uses may be specified when applicable, although it is important that such claims be supported by labeling, risk controls, and appropriate verification and validation (V&V) evidence.

Section 2.3

Use Cases

CGM use can be categorized into several distinct use cases, each associated with different clinical risks and performance requirements.

2.3.1 Personal Use

Personal CGM systems are used directly by patients to inform self-management decisions related to daily activities, diet, physical activity, and medication management. These systems typically provide real-time or near-real-time glucose values, trend information, and alerts to support ongoing glucose awareness.²

Populations using personal CGM systems include:

- Individuals with type 1 diabetes (T1D);
- Individuals with type 2 diabetes (T2D); and
- Women with gestational diabetes mellitus (GDM).

In these populations, CGM systems are used to support routine glucose management and, when indicated in labeling, decision-making related to therapeutic interventions.

Some over-the-counter CGM systems are marketed or used for non-medical or wellness purposes, including use by individuals without a diagnosis of diabetes. Such uses include monitoring glucose patterns to support exercise or optimize recovery, education, or general informational purposes. For wellness-only use cases, manufacturers and regulators should clearly define the intended use and limitations, and ensure that labeling, risk controls, and performance expectations are appropriate for non-clinical decision-making.

2.3.2 Professional Use

Beyond personal use, CGM systems may be deployed by healthcare professionals for monitoring and assessment in clinical or supervised ambulatory settings. Professional CGM use is comparable to other forms of extended physiologic monitoring (e.g., long-term blood pressure monitoring) and can include:

- Masked CGM, where data are collected and reviewed retrospectively;³ and
- Real-time CGM, where glucose values and trends are visible during the monitoring period.

Professional CGM use can support clinical assessment or therapy optimization under the supervision of trained healthcare professionals.

2.3.3 Higher-Risk Clinical Use

CGM systems may also be used by healthcare professionals in higher-risk or complex procedural environments, which can impose additional performance, reliability, and validation requirements. Such use cases include:

- Inpatient monitoring, including use in general wards or intensive care units (ICUs), where patients may experience unstable physiological conditions;⁴

- Intraoperative glucose monitoring during surgical procedures; and
- Deployment in emergency medical services environments.

These settings often involve increased clinical risk and different assumptions about user training. They may also require more stringent standards for accuracy, latency, and alarms. Additional requirements may apply to reliability and overall system robustness. Healthcare professionals should evaluate the capabilities of existing CGM products against the requirements for use prior to deploying CGM systems in higher acuity settings.

Section 2.4

Risk Classification

The overall risk profile of a CGM system is determined by the combination of:

- Intended use (e.g., lifestyle monitoring, routine insulin-dosing decisions, inpatient monitoring, or intraoperative glucose control);
- Intended user (e.g., trained healthcare professional, lay user, caregiver);
- Target population (e.g., individuals with or without diabetes, children, pregnant women, elderly users); and
- Use environment (e.g., home healthcare, ambulatory monitoring, hospital wards, critical care settings).

These factors influence the device's regulatory risk classification, the required rigor of clinical evidence, and the stringency of accuracy and performance specifications. They also impact the depth of cybersecurity, reliability, and interoperability validation required for regulatory submission.

Section 2.5

Regulatory Classification

The regulatory classification of CGM systems varies across jurisdictions and depends on the device's intended use, target population, and clinical application. In the U.S., CGM systems are regulated either as Class III (high risk) devices requiring Premarket Approval (PMA) or as Class II (moderate risk) devices subject to the 510(k) Premarket Notification pathway, depending on compliance with FDA iCGM (21 CFR 862.1355 integrated continuous glucose monitoring system). Under the European Union Medical Device Regulation (EU MDR

2017/745), CGM systems are classified as Class IIa (medium risk) or Class IIb (medium to high risk) depending on intended use. CGM systems used to guide treatment decisions are generally Class IIb. Manufacturers of CGM systems are responsible for determining the regulatory classification and evidentiary requirements prior to market introduction.

Table 2.1 below summarizes a partial list of risk class and regulatory classification by jurisdiction.

Table 2.1 Product Risk and Regulatory Classification by Jurisdiction

Jurisdiction	Regulatory Classification	Risk Class/Pathway
U.S. Food and Drug Administration	PMA based on product configurations — invasive, user/factory calibrated, personal/professional, and/or adjunctive/nonadjunctive CGMs	Class III Device: CGMs that do not meet the iCGM special controls, and are not intended for interoperable integration, are regulated as high-risk Class III medical devices.
U.S. Food and Drug Administration	iCGM, 21 CFR 862.1355, intended to be used alone or integrated interoperably with digitally connected medical devices	Class II. Original classification established via De Novo (Dexcom G6, 2018); subsequent iCGM devices are cleared via 510(k) citing this predicate, with special controls.
European Union Medical Device Regulation	Active device for monitoring/diagnosis; classification depends on intended use under Rule 10	Class IIa or IIb, depending on intended use and risk — nonadjunctive CGMs used for treatment decisions are generally IIb; monitoring-only configurations without immediate-danger potential can be IIa.
Health Canada	Medical device; classification depends on device characteristics and intended use per Schedule 1 rules	Typically, Class III for CGM systems in practice (glucose monitors are named as a Class III example in Health Canada guidance); Class II or IV are possible in principle for other device characteristics, but not commonly seen for CGMs specifically.

Section 2.6

Manufacturer Checklist

Section	Task
2.2 Intended Use	Define the intended use of the CGM product, with each claim supported by labeling, risk controls, and appropriate V&V evidence.
2.3 Use Cases	For each use case, define intended use and limitations, and ensure that the labeling, risk control measures, and performance expectations are appropriate for the use case.
	For wellness-only use cases, define the intended use and limitations, and ensure that labeling, risk controls, and performance expectations are appropriate for non-clinical decision-making.
2.4 Risk Classification	Align the required level of cybersecurity, reliability, and interoperability validation with the risk profile based on intended use, intended user, target population, and use environment.

Section 2.7

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
U.S. Food and Drug Administration	21 CFR 862.1355 — Integrated continuous glucose monitoring system	Provides performance expectations for an iCGM system.
European Union	The European Union Medical Device Regulation	Governs the clinical investigation, production, and distribution of medical devices in the European Union.

Organization	Document	Relevance
British Standards Institution	PAS 2600:2025 — Continuous glucose monitoring systems. Design verification and validation of performance	Establishes minimum design verification, validation, and performance requirements for CGM — a voluntary Publicly Available Specification.

Section 2.8

Summary

CGM systems are used across diverse populations, environments, and clinical applications, ranging from well-ness monitoring and diabetes self-management to professional and inpatient settings. The intended use, intended user, target population, and use environment collectively determine the device’s risk profile, performance requirements, regulatory classification, and the level of clinical and validation evidence needed to demonstrate safety and effectiveness. Manufacturers should ensure that labeling, risk controls, performance specifications, and validation activities are aligned with the intended use.

Chapter 3

Target Populations and Special Conditions

Included in this section:

- 3.1 PIVOTAL STUDY POPULATION DEFINITION
- 3.2 SPECIAL POPULATIONS
- 3.3 MANUFACTURER CHECKLIST
- 3.4 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 3.5 SUMMARY

Section 3.1

Pivotal Study Population Definition

This section outlines the considerations relevant to selection of target population(s) for CGM performance studies. The guiding principle in addressing the target population(s) and special condition(s) for studies assessing the accuracy and safety of CGMs is to identify the intended use of the device *a priori* by the sponsor, since CGM information is safety-critical for insulin dosing and hypoglycemia avoidance. Adult and pediatric insulin-treated populations, and predominantly those with T1D, should usually be included because T1D patients experience the widest glycemic excursions and are a core user population for studies of devices intended for diabetes patients. Additionally, these patients should be prioritized for testing because they experience frequent hypoglycemia and hyperglycemia episodes. If a CGM manufacturer is planning to obtain regulatory approval for specific high-risk populations, such as those with chronic kidney disease (CKD), pregnant women, or hospitalized patients, then studies should be done in those populations, as discussed below.

Participants in the primary study population for studies of devices intended for diabetes patients should have a clinical diagnosis of diabetes⁵ as stipulated according to the following age groups:

- **Age 10 years and below:** Has a clinical diagnosis of diabetes for 6 months or more, as documented in the medical record or other source documentation by an individual qualified to make a medical diagnosis. Participants should predominantly have T1D; however, non-autoimmune forms of diabetes, such as monogenic diabetes, may be included but should constitute no more than 10% of this age group; and
- **Age 11 years and above:** Has a clinical diagnosis of T1D or insulin-treated T2D for 6 months or more, as determined via medical record or source documentation by an individual qualified to make a medical diagnosis. Participants who are not using insulin may also be included in the study, depending on the intended-use population.

Other study participant eligibility considerations include comorbid clinical conditions and the ability to understand and consent to study procedures. In compliance with ISO 14155:2026, study materials shall be provided in layperson, non-technical language understandable to the participant or their legally designated representative. If a participant or representative is unable to read or write, then informed consent should be obtained through a supervised oral process in the presence of an independent witness. If venous blood is used, then participants should have adequate venous access to accommodate frequent sample testing of this source matrix.

If the study design requires one or more hyper- or hypoglycemic challenges, then the risks and inconveniences associated with these procedures shall be disclosed in the clinical investigation plan and informed consent materials (ISO 14155:2026). The principal investigator or authorized designee shall ensure participants are informed of the procedures and voluntarily consent to engage in them (ISO 14155:2026). For participant safety, the protocol should define specific exclusion criteria (see Section 13.2.2).

Section 3.2

Special Populations

3.2.1 General Considerations

Vulnerable or special populations such as children, pregnant women, patients with comorbidities, hospitalized patients, or critically ill individuals can also benefit from CGM, but if an indication is being sought, then it is critical that these populations are specifically studied. Trial designs often require adaptation, including modified protocol elements, designated analytical expectations, specific justification, extensive data collection to account for interfering substances, and/or stratified analyses. Each special-population study should include a rationale for the adapted approach, modified acceptance criteria supported by clinical and technical justification, and a risk assessment specific to the vulnerabilities of that population.

3.2.2 Pediatrics

For pediatric populations, accuracy and ROC performance should be comparable to those demonstrated in the adult population (21 CFR 862.1355(b)(1)(vi)). Because clinical data should represent performance throughout the intended-use population and measuring range (21 CFR 862.1355(b)(1)(iii)), pediatric study analysis should calculate performance by age group, recognizing that younger children may exhibit greater glycemic variability, higher rates of rapid glucose change, and tissue characteristics that may influence interstitial glucose dynamics.⁶

Because hypoglycemia risk and rapid glucose excursions are particularly safety-critical in pediatric populations, sponsors should ensure adequate representation of hypoglycemic values (<70 mg/dL [<3.9 mmol/L]) and rapid ROC conditions (≥ 1 mg/dL/min [≥ 0.06 mmol/L/min]) sufficient to evaluate performance under these circumstances.⁶

Glucose manipulation should be limited to participants 11 years of age or older. Venous plasma should be used for children 7 years of age or older. Either venous plasma or capillary (fingerstick) blood may be used for children between the ages of 6 and 7. Capillary blood should be used for children younger than 6 years old. The frequency of fingerstick testing should be optimized for adequate comparison pairs, safety, and tolerability in in-clinic and/or outpatient settings.⁶

3.2.3 Pregnancy

CGM use in pregnant women with T1D is now the standard of care based on randomized controlled trial evidence showing significant reductions in large-for-gestational-age infants, neonatal intensive care admissions >24 hours, and neonatal hypoglycemia requiring intravenous glucose therapy.^{7–10} CGM is also frequently used in pregnant women with T2D and GDM.

A sponsor seeking an indication for use in pregnancy should demonstrate analytical accuracy while accounting for glycemic considerations relevant to pregnancy management, including tighter therapeutic targets (target time in range 63–140 mg/dL [3.5–7.8 mmol/L]) and increased clinical sensitivity to mild hyperglycemia and hypoglycemia. The sample collection period in studies of pregnant women should be ≥ 6 hours and ≤ 9 hours. Hypo- and hyperglycemia challenges should not be performed, but data from a clinically indicated oral glucose tolerance test (OGTT), such as for GDM screening, may be used. The sensor wear site for the pregnancy indication should be carefully considered to avoid any impact from anatomical changes that may happen during pregnancy.

Pregnancy studies should include stratified reporting within pregnancy-relevant glucose ranges and should demonstrate that device accuracy supports clinical decision-making within those ranges. Clinical data should fully represent pregnant women within the intended-use population and should characterize performance across the device measuring range (21 CFR 862.1355(b)(1)(iii)). Because physiological changes during pregnancy may affect ISF dynamics, tissue perfusion, and metabolic variability, sponsors should demonstrate that analytical accuracy, trend accuracy, and alert performance remain clinically reliable across trimesters.

3.2.4 Chronic Kidney Disease

Patients with CKD and diabetes have a high burden of hyper- and hypoglycemia.¹¹ In patients with advanced CKD on dialysis, sponsors should demonstrate CGM analytical accuracy across dialysis modalities, as each modality can present unique conditions, including altered fluid balance, hematocrit variation, and acute metabolic changes in glucose, creatinine, free fatty acids, and potassium.¹¹

The performance analyses should evaluate CGM metrics during and between hemodialysis sessions.¹² Additionally, study designs should evaluate potential effects of hematocrit variation, changes in pH/acidemia, and the ultrafiltration volume and rate both during and between hemodialysis sessions. For use in patients on peritoneal dialysis, analytical accuracy should be ascertained in dialysate with or without icodextrin.

Hemoglobin A1c (HbA1c) may be unreliable in some populations, such as people with advanced CKD (Stages 4–5) who are not on dialysis. Where CGM is intended for these populations, sponsors should ensure that the device's analytical accuracy supports clinical decisions based on CGM metrics. These metrics include time in range, alerts and alarms, and trend information.

3.2.5 Hospital Use

Regulatory status for inpatient CGM varies by jurisdiction. In the United States, no CGM devices are FDA-approved specifically for inpatient care. In the European Union (EU), regulatory scope depends on the manufacturer's intended purpose, CE-marked indications, and instructions for use (IFU). Practice outside the intended purpose may constitute off-label use and is subject to national law, institutional policies, and informed-consent requirements.¹³

The standard outpatient inclusion criteria should therefore be appropriately adapted. The study population may include not only patients with a history of diabetes, but also patients exhibiting acute stress-induced hyperglycemia who require subcutaneous or continuous intravenous insulin therapy. Every effort should be made to collect accurate data throughout the measuring range of the device and with sufficient frequency to allow meaningful calculation of trend data and/or ROC. Data should be collected in the lower and higher ends of the reportable ranges, when possible, although explicit hyper- and hypoglycemic challenges in these patients should not be performed because of their medical fragility.

Sponsors should demonstrate that agreement rates, bias, trend accuracy, alert detection, signal availability, and stability across the intended wear duration support safe glycemic management within the intended hospital use context.

If CGM is intended to inform insulin dosing or other therapeutic decisions in hospitalized patients, then sponsors should demonstrate that device performance supports safe treatment decisions in the intended care environment (Table 3.1).¹⁴

Since a hospital stay may be shorter than one day, characterizing and reporting performance right after sensor insertion and throughout the first day of wear is critical for hospital use. If clinically significant performance degradation is observed prior to the standard outpatient end-of-life of the CGM system, then the approved wear duration for inpatient use should be explicitly shortened and reflected in the device labeling to maintain a safe margin for clinical decision-making. To account for localized hypoperfusion and prolonged pressure-induced artifacts (which are common in bedridden patients), anatomical site(s) should be carefully chosen and systematically evaluated.

For any study evaluating CGM performance in hospitalized patients, sponsors should include patients with multiple medical conditions and concurrent medication use, and data should be collected and analyzed to identify potential interferences or conditions where the CGM is not appropriate for use. Further research is needed to evaluate CGM accuracy in the hospitalized non-ICU setting. Patients hospitalized in this environment differ clinically from those in intensive care because they are hemodynamically stable and generally do not have life-threatening conditions known to affect CGM accuracy.¹⁴

ICU data should therefore not be pooled with data from patients on stable general medical-surgical wards. Sponsors seeking a specific indication for critically ill populations should establish a distinct, separately powered, and independently analyzed ICU cohort. For critically ill or perioperative populations where patients are frequently sedated, intubated, or otherwise incapacitated, the requirement for direct patient literacy is waived, and informed consent should be permitted via a legally authorized representative.

Table 3.1 ICU Scenarios That Can Affect CGM Accuracy

ICU Scenario	Effect on CGM Accuracy
Altered tissue perfusion, including vasopressor therapy	Widens lag between interstitial and plasma glucose
Hemodynamic instability	Compounds perfusion-related lag and noise
Acid-base balance instability	Potential accuracy drift with pH shifts
Oxygenation changes	Potential accuracy decay with hypoxia
Anemia or hematocrit variation	Complicates accuracy comparisons and calibration
Exposure to interferent medications (such as high-dose [>4 grams/day], intravenously administered acetaminophen)	Falsely elevates glucose reading without interference correction
Rapid fluid shifts as may be seen in severe sepsis, major trauma, or aggressive diuretic therapy	Transient discordance between interstitial and plasma glucose until compartments re-equilibrate
Generalized edema	Increases lag by increasing the diffusion time between capillary and interstitial compartments
Targeted temperature management for heat stroke or survivors of cardiac arrest	Shifts local blood flow at sensor site
Dialysate content	Alters local and systemic glucose kinetics near sensor site
Fluid resuscitation with blood or plasma	Transient discordance between interstitial and plasma glucose from dilution or glucose load until compartments re-equilibrate
Extracorporeal organ support (e.g., Continuous Renal Replacement Therapy, Extracorporeal Membrane Oxygenation)	Complex impacts relate to perfusion alteration, fluid shifts, temperature effects, and possible direct interference with sensor electronics/circuit proximity

To prevent selection bias, the clinical severity and tissue perfusion status of an ICU cohort should be objectively characterized and reported using validated global scoring systems (e.g., Sequential Organ Failure Assessment or Acute Physiology and Chronic Health Evaluation II [APACHE II] scores). Currently, APACHE II remains the most universally feasible and globally recognized tool, making it the most practical choice across diverse clinical settings.

Dynamic markers of shock and fluid shifts (e.g., peak arterial lactate, Vasoactive-Inotropic Score or norepinephrine equivalent dose, and cumulative fluid balance) should also be used. Use of these scores to characterize study sub-populations enables sponsors to demonstrate CGM applicability across a clinically diverse range of ICU patients.

Section 3.3

Manufacturer Checklist

Section	Task
3.1 Pivotal Study Population Definition	If seeking CGM regulatory approval, then conduct all studies in the population for which the device will be indicated.
3.2.1 General Considerations	Consider the need for adapted study designs, modified protocol elements, prespecified outcomes, and specific justification if conducting studies in vulnerable populations such as those with CKD, pregnant women, and hospitalized patients. Evaluate whether hypo- and hyperglycemic challenges are required, recognizing exceptions for young children, pregnant women, and those in critical care units.
3.2.2 Pediatrics	Ensure that analytical accuracy in children is similar to that demonstrated for adult populations.
3.2.3 Pregnancy	For pregnancy studies, include stratified reporting within pregnancy-relevant glucose ranges, and demonstrate that device accuracy supports clinical decision-making within those ranges across trimesters.
3.2.4 Chronic Kidney Disease	Assess analytical accuracy in patients with advanced CKD under conditions associated with altered fluid balance, hematocrit variation, and metabolic changes.
3.2.5 Hospital Use	Demonstrate that device performance remains consistent under physiological and environmental conditions commonly encountered in hospital care, including medical-surgical inpatient wards, perioperative settings, and ICUs when regulatory approval is required for use in hospitalized patients. Demonstrate that device performance supports safe treatment decisions in the intended care environment if CGM is intended to inform insulin dosing or other therapeutic decisions in hospitalized patients. Evaluate data from patients in critical care environments and general hospital settings separately.

Section 3.4

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
American Diabetes Association	Standards of Care in Diabetes—2026: Management of Diabetes in Pregnancy ⁹	Provides evidence and recommendations for the use of CGM in pregnant women.
Endocrine Society and European Society of Endocrinology	Preexisting Diabetes and Pregnancy: An Endocrine Society and European Society of Endocrinology Joint Clinical Practice Guideline ⁸	Provides joint U.S. and European professional society recommendations for use of CGM and CGM-driven automated insulin delivery systems.
National Institute for Health and Care Excellence	Diabetes in pregnancy: management from preconception to the postnatal period ⁷	Recommends consideration of the accuracy of the device and its provision of alerts and alarms in selecting a CGM system.
American Diabetes Association	Standards of Care in Diabetes—2026: Children and Adolescents ¹⁵	Emphasizes that children and adolescents are a unique population, and recommendations for adults do not necessarily apply. CGM accuracy during exercise is addressed.
International Society for Pediatric and Adolescent Diabetes	Clinical Practice Consensus Guidelines 2024 Diabetes Technologies: Glucose Monitoring ⁶	Provides updated information on technical aspects of CGM systems and how they are best utilized.
U.S. Food and Drug Administration	21 CFR 862.1355(b)(1)(vi)	Requires data demonstrating similar accuracy and ROC performance in the pediatric population.
U.S. Food and Drug Administration	21 CFR 862.1355(b)(1)(iii)	Requires that clinical data fully represent the performance of the device throughout the intended-use population and throughout the measuring range of the device.

Organization	Document	Relevance
Diabetes Technology Society	Diabetes Technology Society Expert Panel on Continuous Glucose Monitoring in People with Chronic Kidney Disease ¹¹	Provides accuracy metrics of widely available CGM systems and the effect of various substances that can impact sensor accuracy.
Endocrine Society	Advances in Glucose Monitoring and Automated Insulin Delivery: Supplement to Endocrine Society Clinical Practice Guidelines ¹⁶	Describes the use of CGM in non-critical care and critical care settings.
European Union	(EU) 2017/745, Article 2(12) and Annex I, Chapter III, Section 23 ¹⁷	Defines the requirements for the labeling and IFU regarding the safety and performance of medical devices such as CGM systems.

Section 3.5

Summary

Identification and characterization of the patient population for study in pivotal clinical trials is a critical step in determining the safety and effectiveness of CGM. Age, gestational status, the presence of diabetes complications, and the intended site of use (outpatient vs. inpatient) of trial participants are important considerations for the design of the study and the regulatory pathway.

Chapter 4

Measurement Traceability, Comparator Measurement Procedures, and Calibration

Included in this section:

- 4.1 CONCEPTUAL FRAMEWORK FOR TRACEABILITY IN CONTINUOUS GLUCOSE MONITORING
- 4.2 COMPARATOR MEASUREMENT SYSTEMS: GENERAL REQUIREMENTS
- 4.3 SELECTION OF COMPARATOR BLOOD MATRIX
- 4.4 PRE-ANALYTICAL CONTROL OF COMPARATOR MEASUREMENTS
- 4.5 CALIBRATION STRATEGIES IN CONTINUOUS GLUCOSE MONITORING SYSTEMS
- 4.6 IMPLICATIONS FOR ACCURACY ASSESSMENT AND REGULATORY EVALUATION
- 4.7 MANUFACTURER CHECKLIST
- 4.8 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 4.9 SUMMARY

Section 4.1

Conceptual Framework for Traceability in Continuous Glucose Monitoring

This chapter describes the activities required by CGM manufacturers to establish and document metrological traceability in the evaluation of CGM systems, including the validation of the ISF-to-blood glucose (BG) mapping algorithm, and the selection and characterization of comparator measurement procedures (CMPs), building on the methods outlined in ISO 17511:2020 for in vitro diagnostic medical devices. The goal of correctly establishing metrological traceability is to achieve comparable results across devices and technologies. End-user verification of CGM accuracy in routine clinical use is outside the scope of this chapter. CGM systems measure glucose in subcutaneous ISF and use signal-processing and calibration algorithms to estimate and report values intended to reflect blood plasma glucose concentrations. Importantly, although ISF is the sampled physiological compartment, the measurand, or the quantity intended to be measured, is the volumetric plasma glucose concentration rather than the ISF glucose concentration. Regardless of sample type or measurement technique, results should be expressed as plasma glucose concentration.¹⁸

Because CGMs are intended to report plasma glucose, not ISF glucose, metrological traceability for CGM systems needs to be established indirectly, by demonstrating agreement between CGM-reported values and validated CMPs that measure glucose in recognized blood matrices. Such CMPs could, in principle, serve as plasma reference measurement procedures (RMPs). However, practical limitations often necessitate the use of non-reference CMPs that are traceable and verified to the International System of Units through higher-order reference standards. Requirements for RMPs and certified reference materials (CRMs) are stated in ISO 15193 and ISO 15194, respectively.

Figure 4.1 illustrates, schematically and using a commonly applied approach, how metrological traceability for CGM systems may be established indirectly through a calibration hierarchy that links ISF sensor signals to clinically actionable plasma glucose values. Other approaches to establishing such indirect traceability may also be acceptable. As recognized in CLSI POCT05 and in guidance from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Selective Electrodes and Point-of-Care Testing, metrological traceability is a property of the entire CGM measurement system, including the ISF-to-BG mapping algorithm and the CMP.

The effect of ISF-to-BG mapping algorithms on combined measurement uncertainty and fitness for purpose of the reported CGM result should be evaluated. The study design described in Chapter 10 represents a method to evaluate this effect. The performance should be documented in accordance with the requirements in Chapter 6. Measurement uncertainty is an analytical performance parameter determined by combining relevant uncertainty contributions associated with the metrological traceability chain, including those observed as bias and imprecision. Because this contribution is already captured in the overall CGM performance evaluated against the CMP, separating the uncertainty attributable to the algorithm or other components of the CGM system is not required. Such separation is challenging and does not provide insights beyond the overall CGM performance

typically reported by manufacturers.

Figure 4.1 Calibration Hierarchy for Metrological Traceability of CGM Systems

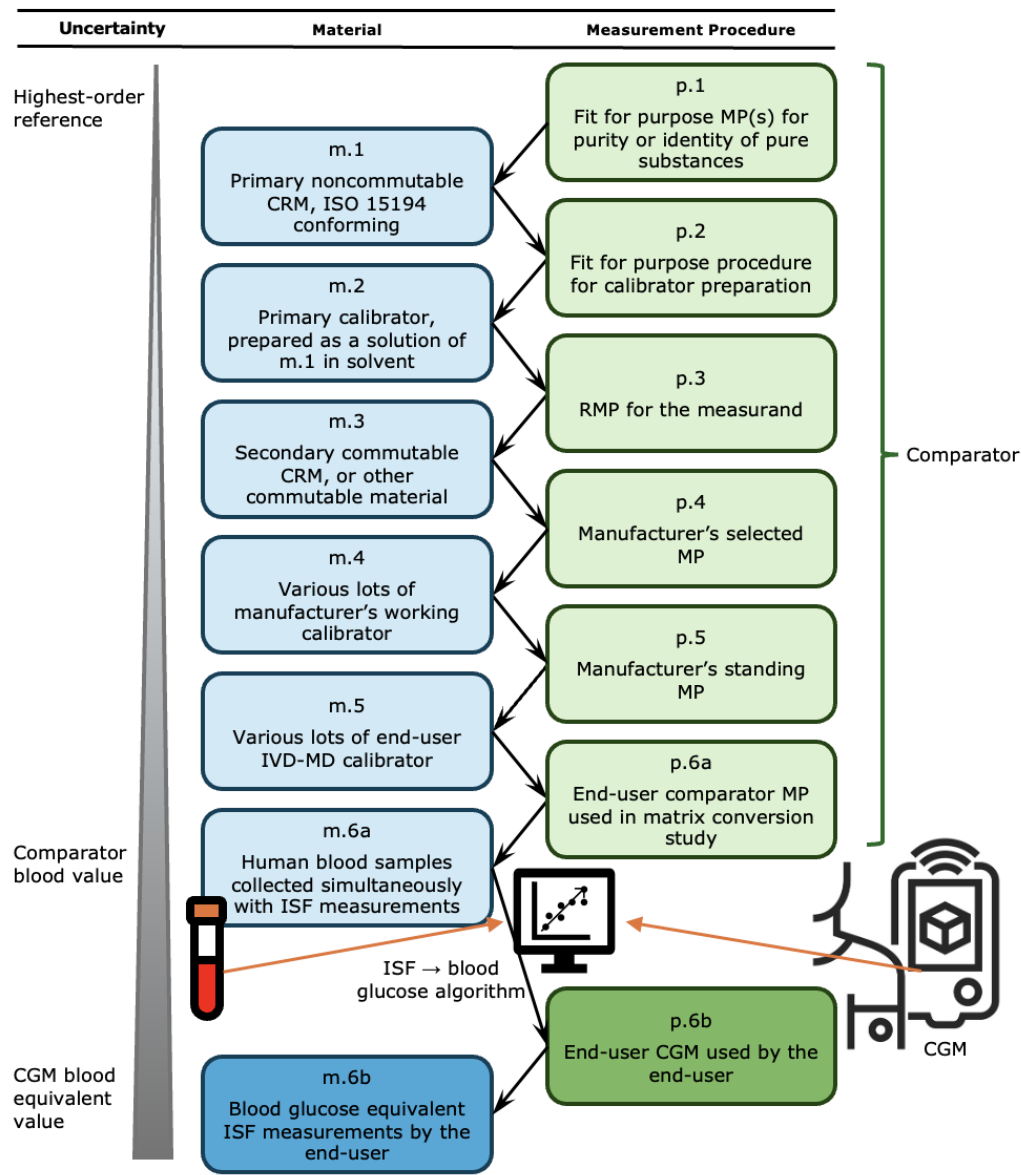


Figure 4.1 Schematic illustration of calibration hierarchy by which CGM systems relate ISF sensor signals to clinically actionable BG values. The leftmost column indicates increasing measurement uncertainty moving downward through the hierarchy. The middle column indicates test materials (m.*) shown in blue. The rightmost column indicates measurement procedures (indicated as p.*) shown in green. Nomenclature is aligned with ISO 17511:2020. Leftward arrows indicate assignment of values to materials by MPs, and rightward arrows indicate calibration of MPs using materials. The portion of the calibration hierarchy related to the CMP is shown in

light colors and indicated by a green curly bracket (}), and its details might deviate from the model hierarchy displayed. The portion of calibration hierarchy adapted from ISO 17511:2020 is shown in light colors, and that unique to the CGM is shown in dark colors. Human blood samples (m.6a) are collected and measured (p.6a) simultaneously with ISF measurements (p.6b). An ISF-to-BG algorithm is generated to align ISF sensor signals to blood-glucose-equivalent values (orange arrows). BG-equivalent ISF measurements (m.6b) are used for clinical decision-making. Abbreviations: Blood Glucose (BG), Certified Reference Material (CRM), Comparator Measurement Procedure (CMP), Continuous Glucose Monitoring (CGM), In Vitro Diagnostic Medical Device (IVD-MD), International Organization for Standardization (ISO), Interstitial Fluid (ISF), Measurement Procedure (MP), Reference Measurement Procedure (RMP).

The validity of this ISF-to-BG mapping function should be demonstrated across the range of physiological conditions, rates of glucose change, sensor wear phases, and patient-specific characteristics expected in intended use, because its robustness directly determines the clinical reliability of CGM-reported values (CLSI POCT05, 2nd ed., Chapters 4 and 9; 21 CFR 862.1355(b)(1)(iii)–(vi)). Accordingly, the CMP needs to demonstrate appropriate accuracy and reliability across the glucose concentration range being used. An example of a validation study design is described in Chapter 13.

Notably, trueness (the ability to measure the absolute glucose concentrations) and trend detection (the ability to detect changes in glucose over time) represent distinct performance characteristics. The former requires metrological traceability to a higher-order reference, whereas the latter depends primarily on repeatability precision and linearity, and can be achieved independently of metrological traceability.

Section 4.2

Comparator Measurement Systems: General Requirements

The CMP shall report plasma glucose metrologically traceable to higher-order references, in accordance with ISO 17511:2020. Calibration accuracy of the selected CMP should be verified independently, preferably by split-sample comparison with an established RMP using commutable clinical samples. Verification of calibration accuracy for the selected CMP is the responsibility of the CGM manufacturer, whereas establishment of metrological traceability of the CMP method itself is the responsibility of the comparator manufacturer (21 CFR 862.1355(b)(1)(ii); ISO 17511:2020, clauses 4.1 and 4.4–4.7; CLSI EP09c, 3rd ed., measurement-procedure comparison and bias-estimation sections).

The primary intended use of the CMP is to support establishment of manufacturer-level calibration hierarchy and CGM performance evaluation. Therefore, the CMPs used in a CGM calibration hierarchy should exhibit analytical performance sufficient to ensure that the total combined measurement uncertainty of the CGM, including contributions from the CMP, is consistent with the clinically acceptable CGM measurement uncer-

tainty (CLSI POCT05, 2nd ed., Chapters 4 and 9; ISO 17511:2020, 4.3). Therefore, the suitability of a CMP for establishing metrological traceability depends on its analytical performance, specifically accuracy and precision, as well as its metrological traceability and intended sample matrix. This suitability is independent of the type or technology of the CMP.

An implication of CMP-dependent CGM calibration is that bias between CMPs propagates directly into differences between CGM-reported values. This is especially relevant when different manufacturers align their systems to different CMPs. Even when each CGM system individually meets its measurement uncertainty specifications relative to its designated CMP, inter-CMP bias can render the resulting CGM values non-interchangeable across manufacturers. This limitation is especially important for applications where point accuracy is required or where data from multiple devices or batches need to be combined. Standardization of CMPs across manufacturers is therefore a prerequisite for CGM data to be used interchangeably.

While self-monitoring of blood glucose (SMBG) systems are required to meet the accuracy limits defined in ISO 15197, CGM systems are recognized to have additional sources of uncertainty, such as those arising from physiological differences between ISF and BG, temporal lag, and algorithmic estimation. If a CGM system is intended to serve as a functional replacement for plasma glucose measurement in clinical decision-making, then its measurement uncertainty should be assessed to be acceptable for that clinical use (ISO 17511:2020, 4.3).

Where the CMP uses sample preparation steps that alter the measured matrix (e.g., dilution, centrifugation, or hemolysis), the impact on reported glucose values should be declared and incorporated into the analysis. In particular, CMPs that hemolyze the sample measure whole-BG, which includes glucose in both plasma and erythrocytes. This may introduce a hematocrit-dependent bias that should be characterized and included in the CMP uncertainty assessment (ISO 17511:2020, 4.7.3 and 4.7.4).

Across CLSI POCT05, guidance from the IFCC Working Group on Continuous Glucose Monitoring, and FDA iCGM special controls (21 CFR 862.1355),¹⁹ several consistent principles emerge:

- **Measurement Uncertainty.** CMPs should demonstrate low imprecision and minimal bias across the clinically relevant glucose interval. Further information on allowable bias is provided in Chapter 6. CMP performance characteristics and their suitability should be evaluated in the context of the specific study design and incorporated into the overall measurement uncertainty assessment (ISO 17511:2020, 4.3, 4.7.3, 4.7.4).
- **Traceability Documentation.** The calibration hierarchy of the CMP should be documented, including higher-order reference standards (ISO 17511:2020, 4.1(a), 4.4, 4.6.1–4.6.3). At a minimum, this includes the analyzer model, the calibration materials used, calibration frequency, and the documented link to higher-order reference standards, such as CRMs fulfilling the requirements of ISO 15194 and RMPs conforming to ISO 15193. Correct implementation of traceability should be verified through split-sample comparison studies to an established RMP (ISO 17511:2020, 4.8.1–4.8.3).

Quality control (QC) procedures should also be described and documented. QC procedures serve to demonstrate that the CMP continues to operate within the specified performance characteristics.

- **Stability.** CMP performance should be demonstrably stable. Any systematic changes should be quantitatively accounted for within the CMP uncertainty budget (ISO 17511:2020, 4.6.4, 4.7.3, 4.8; ISO 23640). By ensuring that values assigned to calibrators are traceable to higher-order references, recalibration serves as the primary mechanism by which long-term changes in the measurement system are controlled and maintained in alignment with the reference system.
- **Timeliness of Results.** In CGM performance evaluation studies, ISF and BG measurements should be obtained simultaneously within the same individual, because the objective is to evaluate the in vivo relationship between these compartments. Accordingly, glucose manipulation should occur through controlled interventions in the participant, not in vitro. CMP turnaround time should be sufficiently short to support safe in vivo glucose manipulation and ensure that CMP results reflect the participant's physiological state at the time of sampling, particularly during periods of rapid glucose change. Short turnaround times also reduce pre-analytical glucose loss from in vitro glycolysis, which can introduce systematic negative bias unrelated to CGM performance. CMPs that provide faster, well-controlled results may therefore offer greater overall validity than analytically superior methods with prolonged turnaround, provided their measurement uncertainty is appropriately characterized. Where the designated study CMP cannot deliver results fast enough for real-time participant safety management, a separate marketed glucose-monitoring device may be used for that purpose, but it should not replace the designated CMP for traceability and accuracy assessment.

Section 4.3

Selection of Comparator Blood Matrix

Different blood matrices have been proposed to establish the relationship between ISF and plasma glucose. No matrix is intrinsically “more correct” from a physiological standpoint; observed differences in CGM performance metrics largely reflect matrix selection, calibration alignment, and comparator characteristics rather than true superiority of one physiological compartment over another. The following items should be considered when selecting the comparator blood matrix.

4.3.1 Physiological Considerations

Glucose volumetric concentrations differ systematically across blood compartments. Because erythrocytes have a lower water fraction than plasma, hemolysis dilutes plasma glucose with intracellular contents that have a lower volumetric glucose concentration. Hematocrit variation therefore influences the quantitative relationship between plasma glucose and glucose measured in hemolyzed whole blood. The CMP should provide accurate and reliable plasma glucose results for the specified blood matrix and sample preparation procedure. Metrological traceability of CMP results should be established in accordance with ISO 17511:2020.

Capillary, venous, and arterialized venous blood samples also differ physiologically, particularly during periods of rapid glucose change, but also for patients with edema or poor circulatory status. Capillary glucose more closely approximates arterial glucose, whereas venous glucose reflects glucose concentrations after tissue uptake and is generally lower than capillary glucose, particularly following meals. These differences are well documented and have measurable effects on observed CGM accuracy depending on the chosen comparator matrix.^{20–24}

Arterialization of venous blood by heating the arm is a technique used to obtain venous blood samples that more closely resemble arterial blood. Local warming of the hand or forearm (e.g., with a heating pad or heated air box) causes vasodilation and increases blood flow through capillaries and arteriovenous connections.^{20,22,25} Arterialization as a methodology employed during CGM performance studies requires standardization and training to ensure reproducible results are obtained.

4.3.2 Venous Versus Capillary Blood as Comparator Matrices

Both venous and capillary blood are acceptable comparator matrices in CGM performance studies when appropriately controlled, although they differ in experimental reproducibility, physiological behavior, and practical implementation. Selection of the comparator matrix therefore has direct implications for traceability, observed CGM performance metrics, and interpretability of results.

The majority of members of the IFCC Working Group on CGM recommended capillary blood in standardized performance studies, citing alignment with SMBG practice and clinical familiarity.^{26,27} Other expert groups and regulatory frameworks have emphasized the analytical robustness, traceability, and stability of venous plasma as the primary comparator matrix.²⁸

Because laboratory reference procedures, diagnostic standards, and regulatory performance requirements are defined in terms of plasma glucose, venous plasma represents the most appropriate primary matrix for establishing and maintaining metrological traceability of CGM devices.

Venous blood, typically analyzed as plasma using laboratory-grade analyzers, offers several advantages that have led to its widespread use in CGM pivotal trials and regulatory submissions, including studies supporting iCGM designation.²⁸ These advantages include:

- Direct metrological traceability to higher-order reference standards, as plasma-based RMPs and CRMs are well established;
- Lower pre-analytical variability when glycolysis is controlled through rapid cooling, appropriate anticoagulants, prompt centrifugation where applicable, and timely analysis;
- Larger sample volumes, enabling replicate measurements, assessment of analytical precision, and multi-analyte testing from a single draw; and
- Reduced risk of artifactual hypoglycemia, particularly during symptomatic hypoglycemia, where peripheral vasoconstriction can lead to falsely low capillary glucose readings.

Venous plasma is therefore the preferred comparator matrix for establishing calibration hierarchies and supporting robust analytical evaluation of CGM systems. However, venous plasma measurements are sensitive to pre-analytical handling, particularly in the interval between collection and plasma separation.

Capillary blood does retain important historical and practical relevance in diabetes care and CGM evaluation:

- It is the matrix used for SMBG, which remains integral to assessing CGM calibration where applicable and to verifying CGM readings in routine clinical use; and
- Current clinical targets for CGM-derived metrics, such as time in range, were largely established using CGM systems calibrated against capillary BG values. Where plasma is used as the chosen compartment, clinical study designs will need to be modified to establish the relationship between ISF and plasma. This design difference may introduce systematic offsets in CGM-reported values and related clinical targets.

However, capillary sampling, compared to venous sampling, has greater pre-analytical variability because, unlike venous sampling, its results can be affected by tissue fluid contamination, variable squeezing pressure, and inconsistent sampling technique. Limited sample volume is also a challenge for capillary-based measurements. A fingerstick can yield enough blood for strip-based blood glucose monitors (BGMs) but often not enough for laboratory-grade analyzers or replicate measurements. Venous plasma should therefore be used except in specific populations.

For specific populations where venous access is not feasible (e.g., young children), capillary blood may serve as the primary comparator, with appropriate justification and documentation. However, whole blood capillary measurements are more difficult to harmonize to higher-order reference standards, as CRMs for whole blood do not exist, which complicates formal traceability.^{29,30}

The selection of the blood matrix in the comparator method primarily affects the design of the study used to establish the relationship between CGM-ISF measurements and plasma glucose reported by the comparator method. Because the study design affects the accuracy and measurement uncertainty of the plasma glucose value reported by the CGM, the design needs to be well documented and executed consistently to ensure appropriate traceability and comparability across devices.

Section 4.4

Pre-Analytical Control of Comparator Measurements

Pre-analytical handling of comparator samples is a critical determinant of glucose measurement accuracy. Procedures for collection, processing, storage, and handling should be controlled to minimize changes in glucose concentration and other sources of pre-analytical variability, consistent with applicable CLSI recommendations

(CLSI PRE02 and PRE04, as appropriate). CMP results should maintain metrological traceability established in accordance with ISO 17511:2020.

The pre-analytical recommendations described in this section apply primarily to CGM manufacturer activities, specifically the establishment of metrological traceability and the derivation and validation of the ISF-to-BG mapping algorithm. Pre-analytical control in these contexts is critical because errors at this stage propagate directly into the calibration hierarchy and can be erroneously attributed to CGM sensor performance.

Key elements of pre-analytical control include the following:

- **Specimen Handling and Glycolysis Control:**

- Dilutional artifacts (e.g., dead space) in specimen acquisition should be controlled through adequate pre-sample discard volume;
- Immediate cooling of venous blood samples and rapid processing should be utilized to minimize in vitro glycolysis, which can reduce glucose concentrations by approximately 5–7% per hour at room temperature if left unmitigated;³¹
- Where a plasma-based CMP is available near the blood collection site, immediate centrifugation with plasma separation is an effective approach, as removal of erythrocytes eliminates the primary source of ongoing glucose consumption;
- Appropriate anticoagulants and glycolysis inhibitors (e.g., fluoride-based or citrate-buffered systems) may be used when immediate processing is not feasible;^{31–33}
- Any modification of the sample, including the addition of glycolysis inhibitors or use of alternative collection tubes, should be demonstrated to not adversely affect commutability of the sample with native clinical specimens. This requirement is essential to preserve valid metrological traceability and is consistent with ISO 17511; and
- QC procedures should be implemented to minimize analyzer artifacts (e.g., the classic “short sip,” in which an insufficient specimen volume is aspirated by a benchtop glucose analyzer, potentially compromising assay accuracy).

- **Timing of Processing and Analysis:**

- Maximum allowable time intervals between sample collection, processing (e.g., centrifugation), and analysis should be predefined and justified; and
- Time limits should be selected such that any residual sample instability introduces uncertainty that is negligible relative to the maximum allowable expanded measurement uncertainty of the CGM-reported values.

- **Environmental Control During Transport and Analysis:**

- Temperature conditions during transport (ISO 15189:2022, clause 7.2.5), storage, and analysis shall be controlled and monitored (CLSI PRE04:2023); and
- Samples exposed to unvalidated conditions should be excluded or analyzed separately with appropriate justification.

- **Documentation and Deviation Management:**

- All pre-analytical conditions, including collection tube type, anticoagulants, inhibitors, timestamps, temperature conditions, and processing steps, shall be documented (CLSI PRE04:2023); and
- Any deviations from the prespecified pre-analytical protocol shall be recorded, assessed for impact, and transparently reported (CLSI PRE04:2023).

Section 4.5

Calibration Strategies in Continuous Glucose Monitoring Systems

4.5.1 Overview of Calibration Approaches

Calibration is the process by which a CGM system translates the sensor signal derived from the ISF to estimates of BG concentration for clinical decision-making. Because CGM results are intended to represent clinically actionable BG values, the calibration strategy, including its design, implementation, and validation, is a core safety-critical element of the CGM system and remains the sole responsibility of the manufacturer, irrespective of whether calibration steps are performed at the factory, by the user, or automatically by the device.

Contemporary CGM systems employ one of three broad calibration strategies:

- **Factory Calibration:** Calibration parameters are established during manufacturing and are not updated by the user during routine operation. Factory-calibrated systems should demonstrate that calibration remains valid across the full labeled sensor lifetime, across manufacturing lots, and under the range of storage conditions, environmental exposures, and physiological conditions expected in real-world use (21 CFR 862.1355(b)(1)(iv) and (b)(3); CLSI POCT05).
- **User-Involved Calibration Adjustment:** In some systems, calibration parameters are periodically updated based on BG readings entered by users from an external BGM. Regardless of the source of the BG value, manufacturers should specify feasible adjustment schedules, define conditions under which adjustment is permitted or prohibited, and identify the required analytical performance characteristics of the external BG measurement procedure (MP) used for adjustment.

Although the user performs the adjustment step, the manufacturer retains full responsibility for the validity, safety, and robustness of the adjustment strategy. Manufacturers should demonstrate that CGM accuracy after adjustment is not unduly sensitive to known sources of BG measurement error, user technique variability, or physiological lag between blood and ISF. Adjustment during periods of rapid glucose change shall be explicitly addressed, limited, or discouraged in device labeling, and the impact of such conditions should be evaluated in performance studies (CLSI POCT05).

- **Hybrid or End-User-Free Adjustments:** Some CGM systems incorporate internal calibration, self-adjustment, or drift-correction algorithms that reduce or eliminate the need for end-user calibration. These systems shall demonstrate robustness against sensor aging, biofouling, tissue response, and lot-to-lot variability (21 CFR 862.1355(b)(1)(iv) and (b)(3); CLSI POCT05).

4.5.2 Calibration Stability and Lot-to-Lot Consistency

Regardless of calibration strategy, CGM systems should demonstrate calibration stability across the entire labeled in-use lifetime and consistency across manufacturing lots. For iCGM systems, consistent analytical and clinical performance throughout the sensor wear period is required under 21 CFR 862.1355(b)(1)(iv). Calibration performance should be evaluated under conditions representative of intended clinical use, including early, mid, and late lifetime phases, and across the full claimed glucose measuring interval (CLSI POCT05).

Manufacturers shall establish and document appropriate manufacturing and product-release controls in accordance with applicable regulatory and quality management system requirements to ensure that released CGM systems meet predefined performance specifications. These controls should address lot-to-lot variability and be capable of detecting clinically meaningful shifts in calibration or performance (21 CFR 862.1355(b)(3); ISO 13485:2016, clause 8.2.6).

Calibration performance should be evaluated in clinical studies using the same calibration strategy, rules, and schedules intended for real-world use. Optional, ad hoc, or unscheduled calibrations that are not part of the labeled use should be excluded from primary performance analyses or analyzed separately with clear justification (CLSI POCT05).

Section 4.6

Implications for Accuracy Assessment and Regulatory Evaluation

CGM bias and agreement metrics are directly dependent on CMPs, matrix selection, calibration strategy, and related study designs. Differences in these elements across CGMs can lead to substantial variability in accuracy, measurement uncertainty, and other analytical performance parameters that can limit the intended use of the device, affect patient care, or constrain broad use of research data. Current differences in measurement uncertainty, bias, or agreement rates between CGM systems may reflect differences in comparator traceability, pre-analytical control, or calibration methodology rather than clinically meaningful differences in sensor performance. Alignment of CMPs across studies through formal standardization programs is both feasible and beneficial and should be pursued.

Regulatory and consensus frameworks accordingly place strong emphasis on explicit definition, traceability, and documentation of CMPs and calibration hierarchies. Calibration strategies shall be prespecified, consistently applied, and validated within this same traceability framework (ISO 17511:2020, 4.1, 4.4, 4.6, 4.8; CLSI EP32).

Robust evaluation of CGM performance, therefore, requires a totality-of-evidence approach in which analytical accuracy, trend accuracy, calibration stability, sensor in-use lifetime performance, and clinical risk are interpreted in the context of CMPs with defined calibration hierarchies and documented measurement uncertainty. Only within such a framework can performance metrics be meaningfully compared across studies and systems.

Section 4.7

Manufacturer Checklist

Section	Task
4.1 Conceptual Framework for Traceability in Continuous Glucose Monitoring	Define the intended measurand explicitly as volumetric plasma glucose concentration.
	Establish indirect metrological traceability via CMPs traceable to higher-order RMPs/CRMs.
	Document the calibration hierarchy in accordance with ISO 17511:2020.

Section	Task
4.2 Comparator Measurement Systems: General Requirements	Select a CMP with sufficiently low and well-characterized uncertainty relative to the desired CGM uncertainty.
	Document the complete CMP calibration hierarchy: analyzer, calibrators, calibration frequency, link to higher-order reference (ISO 15193/15194).
	Select a CMP for which trueness has been verified by direct comparison with an established RMP using commutable samples.
	Select a CMP for which stability has been demonstrated across lot changes, recalibration cycles, and maintenance events.
	Select a CMP with documented QC procedures adequate to verify ongoing performance.
	Ensure comparator turnaround time supports safe in vivo glucose manipulation in study participants.
4.3 Selection of Comparator Blood Matrix	Select venous plasma as the primary comparator matrix.
	Establish the traceability and pre-analytical variability of the comparator used for capillary blood.
	Document the clinical and metrological rationale for matrix selection.
	Address physiological differences between venous, capillary, and arterialized venous matrices in study design, if applicable.
	Prespecify any matrix conversion equations in the study protocol, if applicable.
	Derive ISF-to-blood conversion algorithm from rigorously designed parallel clinical samples.
	Validate conversion algorithm independently using a separate dataset.
	Prohibit post hoc recalibration or adjustment of comparator data.
	Avoid capillary-to-venous conversion unless it is essential; document limitations explicitly if used.

Section	Task
4.4 Pre-Analytical Control of Comparator Measurements	Define collection tube type, anticoagulant, and glycolysis inhibitor requirements.
	Define and justify maximum allowable time intervals for collection, processing, and analysis.
	Control sample temperature during transport and storage.
	Demonstrate that sample modifications do not adversely affect commutability.
	Document all pre-analytical conditions and any deviations.
4.5 Calibration Strategies in Continuous Glucose Monitoring Systems	Define and prespecify the calibration strategy (factory, user-involved, or hybrid).
	Validate ISF-to-BG algorithm robustness across sensor wear phases, rates of glucose change, physiological conditions, and patient-specific characteristics.
	Demonstrate lot-to-lot calibration consistency.
	Evaluate calibration performance using the intended real-world calibration schedule.
	Exclude from primary performance analyses or analyze separately with clear justification ad hoc or unscheduled calibrations that are not part of the labeled use.
	Address in labeling conditions under which calibration is permitted, limited, or discouraged (e.g., rapid glucose change), if applicable.
4.6 Implications for Accuracy Assessment and Regulatory Evaluation	Document pre-analytical conditions in all study reports.
	Interpret CGM performance within a totality-of-evidence framework.
	Standardize CMPs and pre-analytical protocols across study sites.

Section 4.8

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
Clinical and Laboratory Standards Institute	CLSI POCT05 — Performance Metrics for Continuous Interstitial Glucose Monitoring	Provides an anchor for principle-based comparator requirements for CGM performance.
Clinical and Laboratory Standards Institute	CLSI EP09 — Measurement Procedure Comparison and Bias Estimation Using Patient Samples	Directly applies to method comparison study design and may be applied for matrix conversion validation.
Clinical and Laboratory Standards Institute	CLSI EP32 — Implementation of Metrological Traceability in Laboratory Medicine	Provides practical guidance on the core traceability framework according to ISO 17511.
Clinical and Laboratory Standards Institute	CLSI PRE04:2023 — Handling, Transport, Processing, and Storage of Blood Specimens for Routine Laboratory Examinations	Establishes standards for pre-analytical control of comparator samples, including temperature control during transport and storage, documentation of pre-analytical conditions, and management of deviations.
Clinical and Laboratory Standards Institute	CLSI PRE02-ED8:2025 — Collection of Diagnostic Venous Blood Specimens	Directly applies to pre-analytical control section (glycolysis, tube types, timing).
U.S. Food and Drug Administration	21 CFR 862.1355 — Integrated continuous glucose monitoring system	Establishes regulatory comparator and traceability expectations.
International Organization for Standardization	ISO 17511:2020 — In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples	Functions as the core traceability framework for calibration hierarchy and uncertainty propagation.

Organization	Document	Relevance
International Organization for Standardization	ISO 15193:2026 — In vitro diagnostic medical devices — Requirements for reference measurement procedures	Defines what constitutes an RMP for the measurand.
International Organization for Standardization	ISO 15194:2026 — In vitro diagnostic medical devices — Requirements for certified reference materials and the content of supporting documentation	Defines what constitutes a CRM for the measurand.
International Organization for Standardization	ISO 15197:2013 — In vitro diagnostic test systems — Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus	Establishes standards for SMBG test systems.
International Organization for Standardization	ISO 15189:2022 — Medical laboratories — Requirements for quality and competence	Governs quality management, comparator laboratory operations, and pre-analytical control requirements discussed throughout the chapter.
International Organization for Standardization	ISO 5725, Parts 1–6 — Accuracy (trueness and precision) of measurement methods and results	Defines accuracy, trueness, and precision, and provides methods for estimating and applying them.

Section 4.9

Summary

Metrological traceability for CGM systems is established indirectly by linking ISF sensor signals to plasma glucose values obtained using appropriately characterized CMPs. Traceability applies to the complete CGM measurement system, including the comparator procedure and calibration hierarchy. It also encompasses pre-analytical processes and the ISF-to-BG mapping algorithm. Comparator selection and blood-matrix choice should be supported by verified accuracy, documented traceability, and controlled sample handling appropriate for the intended CGM application. Calibration strategies should remain valid across sensor wear, manufacturing lots, relevant physiological conditions, and rates of glucose change. Standardized and transparent comparator and calibration practices are therefore essential for credible CGM performance evaluation and meaningful comparison across studies and systems.

Chapter 5

Interferents and Environmental Robustness

Included in this section:

- 5.1 INTRODUCTION
- 5.2 IN VITRO CHARACTERIZATION OF INTERFERENCE
- 5.3 IN VIVO CHARACTERIZATION OF INTERFERENCE
- 5.4 EXOGENOUS INTERFERENTS AND MEDICATIONS
- 5.5 ENVIRONMENTAL EXPOSURE
- 5.6 MANUFACTURER CHECKLIST
- 5.7 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 5.8 SUMMARY

Section 5.1

Introduction

Subcutaneous CGM systems operate at the interface between biological tissue and an electrochemical or optical sensing element over a defined wear duration. Performance can be influenced by physiological variability, tissue response, chemical interferents, environmental exposure, and/or mechanical stress. This chapter covers interferences from endogenous and/or exogenous compounds that could potentially affect sensor performance, depending on sensing modality, use environment, and user interaction. Manufacturers should perform a thorough assessment of the potential for interference from various medications, vitamins, minerals, and supplements (ISO 14971). For electrochemical sensors, electrochemically active compounds should be assessed, while for optical sensors, compounds that could interfere at the measurement wavelength should be considered. Compounds that could inhibit the biochemical reaction should additionally be considered in the evaluation.

Interference testing should generally begin with controlled in vitro methods that isolate the mechanism of interference. In vivo testing may be considered when in vitro methods cannot adequately characterize clinically relevant interference or when physiological processes such as absorption, metabolism, distribution, or tissue interactions cannot be reasonably simulated (CLSI EP07, CLSI EP37).

Examples of potential interferents include acetaminophen (AC), aspirin, hydroxyurea, ibuprofen, uric acid, vitamin C (ascorbic acid), and other compounds relevant to the intended-use population and sensing technology.

Section 5.2

In Vitro Characterization of Interference

5.2.1 Paired Difference Testing for Interference Assessment

Paired difference testing should be used for initial screening of potential interferents. Testing should be performed at concentrations equal to or exceeding expected therapeutic levels in accordance with CLSI EP07, CLSI EP37, ISO 14971, and FDA iCGM special controls (i.e., 21 CFR 862.1355).

The interferent should be added to a test solution containing a known glucose concentration, and sensor response should be measured before and after exposure. Testing should be performed at a minimum of two glucose concentrations representing clinically relevant low and high glucose conditions. Before testing, manufacturers should prespecify clinically justified allowable interference limits at each glucose concentration evaluated, considering the potential effects of measurement bias on clinical interpretation and treatment decisions (CLSI EP07).

If no clinically significant interference (which is interference that could alter clinical interpretation or treatment) is observed, then additional characterization is generally not required.

5.2.2 Dose-Response Method

When initial screening does not demonstrate that interference falls within the prespecified allowable limits, a dose-response assessment should be performed to characterize the relationship between interferent concentration and interference magnitude (21 CFR 862.1355).

Multiple interferent concentrations should be evaluated while maintaining a fixed glucose concentration. The resulting data should be used to determine whether interference is concentration dependent and to characterize clinically relevant exposure levels.

Published studies have demonstrated concentration-dependent bias for compounds such as AC, hydroxyurea, ascorbic acid, N-acetylcysteine, and uric acid.^{34–37}

Section 5.3

In Vivo Characterization of Interference

5.3.1 Indications for In Vivo Testing

In vivo testing may be considered when clinically significant interference is observed, and additional characterization is needed to assess its impact under expected use conditions.

Examples include situations where:

- Physiological processes cannot be adequately modeled in vitro;
- Metabolism or tissue distribution may influence interference; and
- Clinical relevance cannot be established through laboratory testing alone.

5.3.2 Study Design

When performed, in vivo interference studies should administer the labeled therapeutic dose or maximum anticipated therapeutic dose of the interferent while participants wear the CGM system. The number of participants should be statistically justified (ISO 14155).

- **Pre-dose Assessment:** Comparator samples should be collected at 15-minute intervals for at least one hour prior to interferent administration. Pre-dose bias is calculated as the mean or median difference between sensor glucose (SG) and reference glucose (RG) measurements during this period.
- **Post-dose Assessment:** Following interferent administration, RG measurements should continue at 15-minute intervals. The evaluation period should extend through the anticipated peak exposure period and should generally continue for at least one hour beyond the expected time to maximum plasma concentration (Tmax). Longer observation periods may be appropriate for compounds with delayed absorption, extended-release formulations, or prolonged elimination profiles.

Repeat-dose studies may be considered when cumulative interference is anticipated.

5.3.3 Bias Assessment

Bias attributable to the interferent should be calculated by comparing pre-dose and post-dose sensor performance. An example of a bias computation is presented in Table 5.1:

Table 5.1 Bias Computation Summary (e.g., Acetaminophen)

Bias Type	Formula	Description
Pre-dose bias	Mean or Median (SG – RG) during pre-dose period	Central tendency of the difference between SG and RG measurements, calculated over the entire pre-dose period
Post-dose bias	Mean or Median (SG – RG) during selected post-dose period	Calculated using the 1-hour window with the maximum bias, identified within the larger post-dose period
Acetaminophen (AC) bias	Post-dose bias – Pre-dose bias	Captures the change in bias attributable to AC, computed per sensor

Post-dose bias here uses the 1-hour sub-window with the maximum bias within the 3-hour post-dose period, not a simple average over the full 3 hours. AC bias is computed per sensor. Each sensor has its own pre-dose and post-dose bias values before the subtraction is applied. Any potential interferent has its own testing time windows, depending on its pharmacokinetics.

- **Metrics computation across the study:** The mean, median, and one-sided 95% confidence bound of interferent bias should be computed across all sensors in the study, with 95% confidence bound for the expected direction of bias to demonstrate no clinically significant changes in glucose measurements.

Section 5.4

Exogenous Interferents and Medications

Manufacturers should evaluate whether identified interferents require specific labeling, warnings, precautions, contraindications, or risk mitigation measures.

Examples include:

- Advising users regarding medications known to affect sensor performance;
- Identifying concentrations or dosing conditions associated with clinically relevant interference;
- Providing instructions for confirmatory glucose testing when interference may be present; and
- Describing limitations applicable to specific clinical settings or patient populations.

When clinically significant interference cannot be adequately mitigated through device design, appropriate residual risks should be communicated through labeling and risk management documentation consistent with ISO 14971. Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (2020) and Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use (2020) are guidance documents written for blood glucose monitoring systems and provide FDA-recommended approaches to interference testing, environmental (flex) studies, and labeling of limitations that may inform CGM interference and robustness evaluation.

Section 5.5

Environmental Exposure

Environmental robustness testing should demonstrate that system components function as intended under temperature, humidity, and atmospheric pressure conditions reasonably expected during use. Additional performance testing may be warranted when environmental conditions are expected to affect clinically relevant CGM outputs (International Electrotechnical Commission [IEC] 60601-1, IEC 60601-1-11, IEC 60068).

Examples include:

- Temperature extremes;
- Humidity extremes;
- Atmospheric pressure changes;
- Mechanical stress;³⁸

- Compression effects;³⁸ and
- Changes in tissue perfusion.

Section 5.6

Manufacturer Checklist

Section	Task
5.1 Introduction	Identify and document endogenous and exogenous compounds that may interfere with CGM performance based on intended use, target population, sensing technology, and use environment.
	Evaluate medications, vitamins, minerals, supplements, and other foreseeable compounds that may affect sensor performance.
	For electrochemical sensors, assess electrochemically active compounds and substances that may alter sensor chemistry or inhibit biochemical reactions.
	For optical sensors, assess compounds that may interfere at the measurement wavelength through absorption, fluorescence, scattering, or other optical mechanisms.
	Justify the selection of in vitro and/or in vivo interference testing methods based on interference mechanism and clinical relevance.
5.2.1 Paired Difference Testing for Interference Assessment	Conduct initial interference screening using paired-difference testing in accordance with CLSI EP07 and CLSI EP37.
	Test interferents at concentrations equal to or exceeding expected therapeutic levels.
	Evaluate interference at a minimum of two clinically relevant glucose concentrations representing low and high glucose conditions.
	Document whether clinically significant interference is observed and determine whether additional characterization is warranted.

Section	Task
5.2.2 Dose-Response Method	Perform dose-response characterization when clinically significant interference is identified during initial screening.
	Evaluate multiple interferent concentrations and characterize the relationship between interferent concentration and interference magnitude.
	Determine whether observed interference is concentration dependent and identify clinically relevant exposure levels.
5.3.1 Indications for In Vivo Testing	Consider in vivo testing when physiological processes, metabolism, tissue distribution, or clinical relevance cannot be adequately characterized in vitro.
5.3.2 Study Design	Administer the therapeutic or maximum anticipated therapeutic dose of the interferent during in vivo studies.
	Provide statistical justification for the in vivo study sample size.
	Collect pre-dose RG measurements at 15-minute intervals for at least one hour before interferent administration.
	Continue post-dose reference sampling through the anticipated peak exposure period and at least one hour beyond the expected T _{max} .
	Consider repeat-dose studies when cumulative interference is anticipated.
5.3.3 Bias Assessment	Calculate pre-dose bias, post-dose bias, and interferent-attributable bias using predefined analysis methods.
	Report study-level summary statistics, including mean, median, and one-sided 95% confidence bound of interferent-attributable bias for the expected direction of bias.
	Assess whether observed interference results in clinically meaningful impact on glucose measurement performance.

Section	Task
5.4 Exogenous Interferents and Medications	Determine whether identified interferents require labeling, warnings, precautions, contraindications, or other risk-mitigation measures.
	Identify medications or exposure conditions associated with clinically relevant interference and communicate these limitations in product labeling when appropriate.
	Provide instructions for confirmatory glucose testing when interference may affect sensor performance.
	Document residual interference risks and risk-control measures in accordance with ISO 14971.
	Ensure that clinically significant interference that cannot be mitigated through device design is appropriately disclosed through labeling and risk management documentation.
5.5 Environmental Exposure	Establish operational temperature, humidity, and atmospheric pressure ranges for intended use.
	Demonstrate environmental robustness under reasonably foreseeable storage, transport, and use conditions.
	Evaluate the impact of environmental conditions, including temperature, humidity, atmospheric pressure, mechanical stress, compression, and tissue perfusion changes, when these factors may affect clinically relevant CGM outputs.

Section 5.7

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
Clinical and Laboratory Standards Institute	CLSI EP07 — Interference Testing in Clinical Chemistry	Serves as the primary reference for the identification, characterization, and statistical evaluation of analytical interference; supports paired-difference and dose-response testing methodologies.
Clinical and Laboratory Standards Institute	CLSI EP37 — Supplemental Tables for Interference Testing in Clinical Chemistry	Provides recommended concentrations for endogenous and exogenous interferents to support clinically relevant interference testing.
International Organization for Standardization	ISO 14971 — Medical devices — Application of risk management to medical devices	Provides the overall framework for identifying, assessing, controlling, and communicating interference and environmental risks associated with CGM systems.
International Electrotechnical Commission	IEC 60601-1 — Medical electrical equipment — Part 1: General requirements for basic safety and essential performance	Establishes general safety and environmental operating requirements applicable to CGM systems and associated components.
International Electrotechnical Commission	IEC 60601-1-2 — Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic disturbances — Requirements and tests	Defines requirements for evaluating device performance under electromagnetic disturbances that could affect CGM operation.
International Electrotechnical Commission	IEC 60601-1-11 — Medical Electrical Equipment Used in the Home Healthcare Environment	Addresses environmental conditions, user interactions, and foreseeable exposures encountered during home use of CGM systems.

Organization	Document	Relevance
International Organization for Standardization	ISO 10993 Series — Biological Evaluation of Medical Devices	Provides requirements for assessing tissue-device interactions and biocompatibility that may influence sensor performance throughout wear.
U.S. Food and Drug Administration	Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use (2020)	Provides FDA-recommended approaches to interference testing, environmental (flex) studies, and labeling of limitations for prescription blood glucose monitoring systems; may inform CGM interference and robustness evaluation.
U.S. Food and Drug Administration	Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (2020)	Provides FDA-recommended approaches to interference testing, environmental (flex) studies, and labeling of limitations for over-the-counter blood glucose monitoring systems; may inform CGM interference and robustness evaluation.
U.S. Food and Drug Administration	Special Controls for Integrated Continuous Glucose Monitoring Systems (iCGM) (21 CFR 862.1355)	Defines performance, safety, interoperability, interference characterization, and risk communication expectations for iCGM systems.
International Electrotechnical Commission	IEC 62366-1 — Application of Usability Engineering to Medical Devices	Supports identification and mitigation of use-related risks, including user instructions, warnings, precautions, and communication of interference limitations.
Clinical and Laboratory Standards Institute	CLSI POCT05 — Performance Metrics for Continuous Interstitial Glucose Monitoring	Provides CGM-specific performance concepts and supports interpretation of interference-related impacts on sensor accuracy and clinical performance.
International Organization for Standardization	ISO 15189 — Medical laboratories — Requirements for quality and competence	Establishes quality and competence requirements for medical laboratories performing comparator measurements in interference studies.
International Organization for Standardization	ISO 15197 — In vitro diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus	Provides performance requirements for SMBG systems that may serve as comparator devices in interference evaluations, provided their suitability for the intended evaluation is established.

Organization	Document	Relevance
International Electrotechnical Commission	IEC 60068 Series — Environmental Testing	Provides methodologies for environmental stress testing, including temperature, humidity, vibration, and other environmental challenges relevant to CGM performance.
ASTM International	ASTM D4169 — Performance Testing of Shipping Containers and Systems	Supports evaluation of transportation and distribution conditions to ensure sensor performance after shipping and handling.

Section 5.8

Summary

Interferents and environmental factors can affect the accuracy of subcutaneous CGM systems, and manufacturers should evaluate these risks based on the sensor technology, intended use, and operating environment. Potential endogenous and exogenous interferents, including medications, vitamins, minerals, supplements, and other compounds, should be assessed primarily through in vitro testing, with in vivo studies performed when clinical relevance cannot be adequately established in vitro. A stepwise approach consisting of interference screening, dose-response characterization, and, when necessary, clinical evaluation should be used to determine the magnitude and clinical significance of interference. When clinically significant interference or environmental limitations are identified, manufacturers should implement appropriate risk controls and communicate residual risks through labeling, warnings, precautions, contraindications, and other risk mitigation measures consistent with ISO 14971. Ultimately, manufacturers should demonstrate that the CGM system maintains acceptable performance under reasonably foreseeable conditions of use and that users are adequately informed of any limitations that could affect sensor performance or clinical decision-making.

Chapter 6

Analytical Accuracy Evaluation (Point and Trend Accuracy)

Included in this section:

- 6.1 INTRODUCTION
- 6.2 DATA PAIRING RULES
- 6.3 RATE OF CHANGE CALCULATION
- 6.4 SYSTEM AGREEMENT AND DIFFERENCE MEASURES EVALUATION
- 6.5 CONCURRENCE ANALYSIS
- 6.6 INTEGRATED CONTINUOUS GLUCOSE MONITORING PERFORMANCE REQUIREMENTS
- 6.7 PRECISION EVALUATION
- 6.8 GENERAL CONSIDERATIONS FOR STATISTICAL REPORTING
- 6.9 MANUFACTURER CHECKLIST
- 6.10 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 6.11 SUMMARY

Section 6.1

Introduction

Point accuracy is defined as the numerical agreement between a CGM reading and a comparator value at a given time point. Point accuracy is influenced by sensor performance, physiological lag, and algorithm performance, while metrological traceability, as described in Chapter 4, supports the reliability and comparability of the measurements used to evaluate it. Trend accuracy refers to how well a CGM system captures the direction, ROC, and timing of glucose excursions over time, rather than the absolute glucose value at a single point.

Analytical accuracy is not a single metric but a system-level performance characteristic. For iCGMs, this property shall be validated across the intended-use population, the full measuring range, the sensor wear period, and changing glucose levels (21 CFR 862.1355(b)(1)). Trend data are used to inform diabetes treatment decisions, such as timing and the amount of carbohydrates or insulin to take to avoid hypoglycemia or hyperglycemia, respectively. Therefore, trend accuracy at the high and low ends of glucose ranges, as well as during periods of rapid glucose ROCs at any glucose concentration, is especially critical for decision-making. Because no single metric fully characterizes performance, evaluation requires a panel of complementary measures.

Section 6.2

Data Pairing Rules

Protocols should prespecify the method for pairing CGM readings with comparator measurements (i.e., determining “matched pairs”). Pairing is typically performed by matching each comparator measurement to the temporally closest CGM reading within a predefined window. Primary analyses (e.g., point accuracy of the CGM) should include all matched pairs within the CGM’s reportable range, and any out-of-range values should be summarized separately.

Section 6.3

Rate of Change Calculation

CGM systems provide a series of glucose values and therefore can provide time-dependent characteristics of glucose fluctuation, which include the rate and direction of change in glucose. The most common method for calculating the ROC is by determining the change in glucose concentration over a defined time interval, where CGM values are paired with the RG results. The ROC of the comparator measurements is calculated from the

sequential reference values divided by the time interval between them, and the ROC of the CGM measurements is calculated from the sequential CGM values paired with the reference values, divided by the time interval between them. Baseline mathematical equations for the ROC calculations are provided in CLSI POCT05, 2nd ed., Section 6.1.

Reference BG measurements collected during accuracy studies are typically obtained at longer and less frequent time intervals than with CGM. To enable comparison between CGM and reference ROCs, a best-fit least-squares linear regression may be applied to the CGM glucose values occurring between two consecutive reference measurements as described in CLSI POCT05, 2nd ed., Section 6.1. The resulting slope of the fitted line represents the CGM-derived ROC over that interval, which can be compared directly with the RG ROC.

Section 6.4

System Agreement and Difference Measures Evaluation

Sponsors should report agreement rates, which are defined as the percentage of CGM-comparator pairs falling within specified accuracy limits. Three criteria apply: the 15/15 criterion requiring values within ± 15 mg/dL (± 0.8 mmol/L) when glucose is below 70 mg/dL (3.9 mmol/L) and within ± 15 percent when glucose is 70 mg/dL (3.9 mmol/L) or higher, the 20/20 criterion requiring values within ± 20 mg/dL (± 1.1 mmol/L) or ± 20 percent, and the 40/40 criterion requiring values within ± 40 mg/dL (± 2.2 mmol/L) or ± 40 percent. The value of 70 mg/dL (3.9 mmol/L), below which absolute differences are calculated, applies to comparator values, when results are stratified by comparator glucose levels (Table 6.1), and to CGM values, when results are stratified by CGM glucose levels (Table 6.2).

Sponsors should report the mean absolute relative difference (MARD), mean absolute difference (MAD), mean relative difference (MRD), mean bias, and mean absolute bias between CGM and comparator values.

Tables 6.1 and 6.2 present results stratified by comparator and CGM glucose ranges, respectively. Thresholds may be adjusted for CGM devices with a dynamic range different from 40–400 mg/dL (2.2–22.2 mmol/L).

Table 6.1 Accuracy Within Comparator Value Ranges

Comparator Glucose Level (mg/dL [mmol/L])	No. Pairs	% Within ±15 mg/dL (±0.8 mmol/L)	% Within ±20 mg/dL (±1.1 mmol/L)	% Within ±40 mg/dL (±2.2 mmol/L)	% Within ±15%	% Within ±20%	% Within ±40%	MARD (%)	Mean Bias (mg/dL [mmol/L])	Mean Absolute Bias (mg/dL [mmol/L])
<54 (<3.0)	x	xx.x	xx.x	xx.x	N/A	N/A	N/A	x.x	x.x	x.x
54–69 (3.0–3.8)	x	xx.x	xx.x	xx.x	N/A	N/A	N/A	x.x	x.x	x.x
70–180 (3.9–10.0)	x	N/A	N/A	N/A	xx.x	xx.x	xx.x	x.x	x.x	x.x
181–250 (10.1–13.9)	x	N/A	N/A	N/A	xx.x	xx.x	xx.x	x.x	x.x	x.x
>250 (>13.9)	x	N/A	N/A	N/A	xx.x	xx.x	xx.x	x.x	x.x	x.x
Overall	x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x

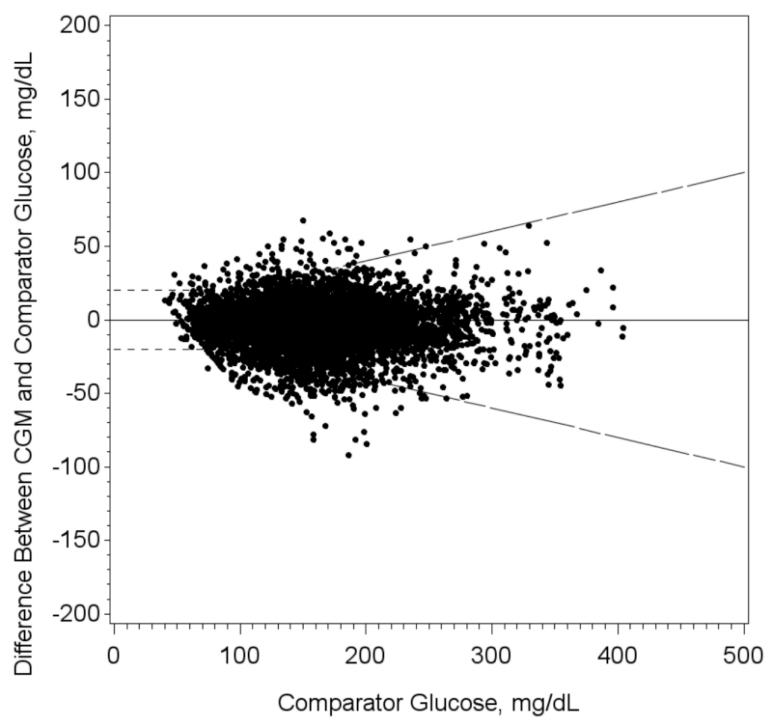
Table 6.2 Accuracy Within CGM Glucose Ranges

CGM Glucose Level (mg/dL [mmol/L])	No. Pairs	% Within ±15 mg/dL (±0.8 mmol/L)	% Within ±20 mg/dL (±1.1 mmol/L)	% Within ±40 mg/dL (±2.2 mmol/L)	% Within ±15%	% Within ±20%	% Within ±40%	MARD (%)	Mean Bias (mg/dL [mmol/L])	Mean Absolute Bias (mg/dL [mmol/L])
<54 (<3.0)	x	xx.x	xx.x	xx.x	N/A	N/A	N/A	x.x	x.x	x.x
54–69 (3.0–3.8)	x	xx.x	xx.x	xx.x	N/A	N/A	N/A	x.x	x.x	x.x
70–180 (3.9–10.0)	x	N/A	N/A	N/A	xx.x	xx.x	xx.x	x.x	x.x	x.x
181–250 (10.1–13.9)	x	N/A	N/A	N/A	xx.x	xx.x	xx.x	x.x	x.x	x.x
>250 (>13.9)	x	N/A	N/A	N/A	xx.x	xx.x	xx.x	x.x	x.x	x.x
Overall	x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x.x	x.x	x.x

MARD is a summary of the overall analytical agreement between measured and comparator glucose values, but it has limitations. Any single accuracy metric across the entire measuring range can obscure region-specific and dynamic errors, including hypoglycemia, rapid rises in postprandial glycemia, and insulin-driven declines. The consensus panel recommends that if regulatory decisions are made using MARD, then they should use MARD in the hypo-, eu-, and hyperglycemic ranges.

Graphical presentations should include modified Bland–Altman plots (Figure 6.1) displaying CGM-comparator differences plotted against comparator values with agreement boundaries, along with per-sensor agreement distributions showing heterogeneity of sensor performance. Additional evaluation methods such as the Diabetes Technology Society Error Grid and Trend Accuracy Matrix³⁹ may be utilized to assess the clinical effects of point and trend inaccuracy.

Figure 6.1 An Example of a Modified Bland–Altman Plot Showing the Difference Between CGM and Comparator Glucose Measurements vs. Comparator Glucose Measurement



Abbreviation: Continuous Glucose Monitoring (CGM).

Metrics should be reported for the entire dataset and stratified by glucose ranges, including below 54 mg/dL (3.0 mmol/L), 54 to below 70 mg/dL (3.0 to below 3.9 mmol/L), 70–180 mg/dL (3.9–10.0 mmol/L), 181–250 mg/dL (10.1–13.9 mmol/L), and above 250 mg/dL (13.9 mmol/L).⁴⁰ Metrics should also be stratified by wear-period segment, by insertion site where multiple sites are indicated, and by manufacturing lot to capture lot-to-lot variability. An example table for reporting metrics across different wear periods is shown in Table 6.3 below for a 15-day sensor. This table should be adjusted for sensors with different wear lengths.

Table 6.3 Sensor Accuracy Relative to Comparator Over the Wear Duration

Wear Period	No. Pairs	Within ±15%/ ±15 mg/dL (±0.8 mmol/L)	Within ±20%/ ±20 mg/dL (±1.1 mmol/L)	Within ±40%/ ±40 mg/dL (±2.2 mmol/L)	MARD (%)	Mean Bias (mg/dL [mmol/L])
Beginning days	x	xx.x	xx.x	xx.x	xx.x	xx.x
Early Middle days	x	xx.x	xx.x	xx.x	xx.x	xx.x
Late Middle days	x	xx.x	xx.x	xx.x	xx.x	xx.x
End days	x	xx.x	xx.x	xx.x	xx.x	xx.x

Section 6.5

Concurrence Analysis

The percentage of concurring glucose values in each comparator’s glucose range should be presented for each corresponding CGM range, and the concurrence matrix should include both CGM- and comparator-stratified results (Table 6.4). The cutoff values for glucose ranges may be adjusted based on the dynamic range of the CGM.

Table 6.4 Concurrence Matrix of CGM and Comparator Glucose Values by Glucose Range

Comparator (mg/dL [mmol/L])	CGM (mg/dL [mmol/L])										N	
		40–60	61–80	81–120	121–160	161–200	201–250	251–300	301–350	351–400		
	<40	(2.2–	(3.4–	(4.5–	(6.7–	(8.9–	(11.2–	(14.0–	(16.7–	(19.5–		
	(<2.2)	3.3)	4.4)	6.6)	8.8)	11.1)	13.9)	16.6)	19.4)	22.2)		
<40 (<2.2)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x
40–60 (2.2–3.3)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x
61–80 (3.4–4.4)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	x

Comparator (mg/dL [mmol/L])	CGM (mg/dL [mmol/L])											N
		40–60	61–80	81–120	121–160	161–200	201–250	251–300	301–350	351–400		
	<40	(2.2–	(3.4–	(4.5–	(6.7–	(8.9–	(11.2–	(14.0–	(16.7–	(19.5–	>400	
	(<2.2)	3.3)	4.4)	6.6)	8.8)	11.1)	13.9)	16.6)	19.4)	22.2)	(>22.2)	
81–120 (4.5–6.6)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X
121–160 (6.7–8.8)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X
161–200 (8.9–11.1)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X
201–250 (11.2–13.9)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X
251–300 (14.0–16.6)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X
301–350 (16.7–19.4)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X
351–400 (19.5–22.2)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X
>400 (>22.2)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	X

For trend accuracy, a commonly used method for evaluating the accuracy of CGM trend information is the ROC concurrence matrix, which assesses the agreement between sensor-derived glucose ROCs and RG ROCs. Table 6.5 provides an illustrative example of an ROC concurrence matrix. In this matrix, the gray diagonal cells represent correct classification of glucose trends, while off-diagonal cells represent misclassification errors. The magnitude of error increases as counts occur farther from the diagonal; cells farthest from the diagonal correspond to the largest trend errors.

Errors are of particular clinical concern when the RG exhibits an ROC greater than ± 2 mg/dL/min (± 0.11 mmol/L/min), and the CGM reports an ROC in the opposite direction (e.g., rising versus falling). Such directional disagreement during periods of rapid glucose change may result in clinically significant errors, as it can lead to inappropriate treatment actions, including inappropriate insulin dosing or delayed carbohydrate intake.

Therefore, CGM trend performance reporting should include the percentage of observations in which:

- The reference ROC is < -2 mg/dL/min (< -0.11 mmol/L/min) while the sensor-reported ROC is > 1 mg/dL/min (> 0.06 mmol/L/min); and
- The reference ROC is > 2 mg/dL/min (> 0.11 mmol/L/min) while the sensor-reported ROC is < -1 mg/dL/min (< -0.06 mmol/L/min).

These categories represent large directional misclassifications during rapid glucose excursions and are critical for assessing the clinical safety of CGM trend information.

Table 6.5 Concurrence Matrix for ROC

Reference ROC (mg/dL/min [mmol/L/min])	CGM ROC (mg/dL/min [mmol/L/min])					N
		-2 to <-1	-1 to ≤1	>1 to ≤2		
	<-2 (<-0.11)	(-0.11 to <-0.06)	(-0.06 to ≤0.06)	(>0.06 to ≤0.11)	>2 (>0.11)	
<-2 (<-0.11)	xx.x	xx.x	xx.x	xx.x	xx.x	x
-2 to <-1 (-0.11 to <-0.06)	xx.x	xx.x	xx.x	xx.x	xx.x	x
-1 to ≤1 (-0.06 to ≤0.06)	xx.x	xx.x	xx.x	xx.x	xx.x	x
>1 to ≤2 (>0.06 to ≤0.11)	xx.x	xx.x	xx.x	xx.x	xx.x	x
>2 (>0.11)	xx.x	xx.x	xx.x	xx.x	xx.x	x
N	x	x	x	x	x	x

Section 6.6

Integrated Continuous Glucose Monitoring Performance Requirements

For iCGM devices, statistical testing shall demonstrate that lower one-sided 95% confidence bounds meet specified analytical thresholds within defined glucose ranges and overall agreement limits while preventing extreme discordances (see Table 6.6) (21 CFR 862.1355). Because of autocorrelation in continuous glucose measurements (where current values are influenced by previous ones), the 95% lower confidence limit should be estimated using appropriate methods that address the dependence in individual paired CGM-comparator points. Evaluation of CGM systems that are not seeking iCGM designation should follow a multidimensional risk-based totality-of-evidence approach in which compliance is not determined solely by any single analytical metric

or threshold.

Table 6.6 Minimum System Accuracy Requirements for iCGM Devices

Assessment Type	CGM Value	Accuracy Criteria
Analytic accuracy (lower one-sided 95% confidence bound)	Entire measuring range	>87% of all points within $\pm 20\%$
	<70 mg/dL (<3.9 mmol/L)	>85% within ± 15 mg/dL (± 0.8 mmol/L) >98% within ± 40 mg/dL (± 2.2 mmol/L)
	70–180 mg/dL (3.9–10.0 mmol/L)	>70% within $\pm 15\%$ >99% within $\pm 40\%$
	>180 mg/dL (>10.0 mmol/L)	>80% within $\pm 15\%$ >99% within $\pm 40\%$
Discordant reading	<70 mg/dL (<3.9 mmol/L)	No true value >180 mg/dL (>10.0 mmol/L)
	>180 mg/dL (>10.0 mmol/L)	No true value <70 mg/dL (<3.9 mmol/L)
	ROC accuracy	$\leq 1\%$ of glucose ROC >1 mg/dL/min (>0.06 mmol/L/min) if true ROC <–2 mg/dL/min (<–0.11 mmol/L/min) $\leq 1\%$ of glucose ROC <–1 mg/dL/min (<–0.06 mmol/L/min) if true ROC >2 mg/dL/min (>0.11 mmol/L/min)

Sponsors shall explicitly tabulate extremely discordant pairs, defined as CGM values below 70 mg/dL (3.9 mmol/L) paired with comparator values above 180 mg/dL (10.0 mmol/L), or CGM values above 180 mg/dL (10.0 mmol/L) paired with comparator values below 70 mg/dL (3.9 mmol/L) (21 CFR 862.1355). For iCGM devices, regulatory special controls require that such extreme discordances do not occur.

Section 6.7

Precision Evaluation

Sponsors should evaluate sensor precision and repeatability. This evaluation should quantify inter-sensor variability using a relevant study design, such as the simultaneous wear of two sensors at the same anatomical location (e.g., arm, abdomen). Reported metrics should demonstrate that sensor-to-sensor variability does not introduce clinically significant treatment risk across glucose ranges and wear periods.

Section 6.8

General Considerations for Statistical Reporting

Per-sensor performance should be evaluated by calculating sensor-level agreement metrics and presenting the distribution to reveal the tail (extreme values) for poorly performing sensors. All studies should present standardized tables showing the distribution of paired comparator values across the full glycemic ranges, the distribution across both CGM and comparator ROC categories, and total paired values per category to ensure interpretability and prevent biased reporting.

Statistical reports should include point estimates for all performance metrics together with 95% confidence intervals for key measures. Clearly documented statistical methods should be used for calculating the 95% confidence interval, and sample size justifications should be supported by power calculations. They should also describe a prespecified multiplicity control strategy unless all co-primary endpoints independently meet their acceptance criteria. Only the prespecified primary sensor should be included in the accuracy evaluation when two sensors are worn concurrently by the same participants for precision analysis.

Reports should provide, at a minimum, the following analyses:

- **Primary Endpoint Analyses:**
 - Reports should present point estimates and lower one-sided 95% confidence bounds for primary endpoints using an appropriate statistical method to account for within-subject correlation. Analyses should clearly state whether performance goals are met.
- **Secondary Endpoint Analyses:**
 - Sensor concurrence: Reports should provide concurrence agreement between CGM and comparator measurements.
 - Trend accuracy: Reports should provide agreement between CGM ROC and comparator ROC,

including the frequency of extreme mismatches during rising and falling glucose conditions.

- Sensor life and data availability: Reports should present Kaplan–Meier analysis of sensor survivability, percent data availability, and documented reasons for early end of life, including firmware-determined ends.

• **Additional Analyses:**

- Percent accuracy: Reports should provide percent accuracy (% within 15/15, 20/20, and 40/40) stratified by glucose ranges, wear day, or wear location.
- Point accuracy: Reports should include summaries of mean difference (mean bias) and MARD, stratified by comparator glucose range, CGM glucose range, and wear period, as illustrated in Tables 6.1–6.3.
- Precision: Reports should include precision analysis based on concurrent dual sensors, using measures such as coefficient of variation and paired absolute relative difference.
- Subgroup analyses: To assess heterogeneity, reports should summarize performance by age, sex, and body mass index (BMI) category. They should also evaluate baseline HbA1c quartile, diabetes type, treatment regimen, and clinical site. Of note, if the study is not designed to be powered to detect heterogeneity across subgroups, then it is likely that only large differences will be detected.

If sensors used in the study require calibration, then the calibration should be performed per study protocol and be consistent with the intended use. The protocol should also define the circumstances under which calibration is required, the frequency of calibration, and details of calibration method (e.g., the SMBG system used and test strip lot information). Calibration frequency during the study should be consistent with the intended product labeling, and the average number of calibrations per subject should be reported.

Section 6.9

Manufacturer Checklist

Section	Task
6.1 Introduction	Define the point accuracy and trend accuracy, and their relevance to evaluating CGM performance.
6.2 Data Pairing Rules	Document the data pairing rule in clinical study protocol and/or statistical analysis plan.

Section	Task
6.3 Rate of Change Calculation	Define the method used for ROC calculation for both CGM and comparator values.
	Justify the choice of ROC calculation method if it is different from the ones specified in CLSI POCT05, 2nd ed.
6.4 System Agreement and Difference Measures Evaluation	Define the method used for system agreement and difference measures evaluation.
	Specify the glucose range over which these analytical accuracy metrics will be evaluated.
	Include both tables and figures to illustrate the overall analytical agreement between CGM and comparator glucose values, as well as whether outliers are present.
	Perform subgroup analyses by glucose range, wear-period segment, insertion site (where multiple sites are indicated), and manufacturing lot.
6.5 Concurrence Analysis	Present a concurrence matrix for both glucose values and glucose ROC.
6.6 Integrated Continuous Glucose Monitoring Performance Requirements	Define statistical method for calculating lower one-sided 95% confidence bound.
	Tabulate extreme discordant CGM-comparator pairs for both glucose values and glucose ROC.
6.7 Precision Evaluation	Define the method used for between-sensor precision evaluation.
6.8 General Considerations for Statistical Reporting	Provide details of the endpoints that need to be evaluated in the clinical study report.
	Present standardized tables for the endpoint analyses.

Section 6.10

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
Clinical and Laboratory Standards Institute	CLSI POCT05, 2nd ed. — Performance Metrics for Continuous Interstitial Glucose Monitoring ⁴¹	Serves as the anchor for principle-based comparator requirements for CGM performance.
U.S. Food and Drug Administration	21 CFR 862.1355 — Integrated continuous glucose monitoring system ⁴²	Establishes special controls, including accuracy and discordance criteria, for iCGM systems.
Diabetes Technology Society	The Diabetes Technology Society Error Grid and Trend Accuracy Matrix for Glucose Monitors ³⁹	Evaluates the clinical effect of CGM point and trend inaccuracy.

Section 6.11

Summary

CGM analytical accuracy should be evaluated using both point accuracy (agreement between CGM and comparator glucose values at a specific time) and trend accuracy (how well the CGM captures the direction and rate of glucose changes over time). Study designs require predefined data-pairing methods, standardized ROC calculations, and reporting of multiple performance metrics, including system agreement rates and difference measures. Accuracy endpoints should be stratified across clinically important glucose ranges, wear periods, and manufacturing lots, and accuracy results should be presented in standard tables, graphical methods, and concurrence matrices. Analyses should also include evaluation of clinically significant errors, particularly during periods of hypoglycemia, hyperglycemia, and rapid glucose ROC excursions. For iCGM devices, sponsors shall demonstrate compliance with predefined analytical accuracy thresholds, confidence-bound requirements, and the absence of extreme discordant readings (21 CFR 862.1355). Precision testing using concurrent sensor wear, sensor-level performance assessments, comprehensive statistical reporting, and subgroup analyses should be included to provide a complete, risk-based evaluation of CGM performance.

Chapter 7

Alert Detection, Clinical Accuracy, and Event Interpretation

Included in this section:

- 7.1 INTRODUCTION
- 7.2 ALERT TYPES
- 7.3 GLYCEMIC ALERT EVALUATION
- 7.4 GLYCEMIC EVENT EVALUATION
- 7.5 REPORTING
- 7.6 MANUFACTURER CHECKLIST
- 7.7 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 7.8 SUMMARY

Section 7.1

Introduction

Alerts and alarms, two terms used interchangeably in CGM systems, are core safety features, designed to notify users of current or impending hypoglycemia, hyperglycemia, and rapid glucose change. The utility of alerts has been extensively studied in the literature.^{43–47} Many CGM systems support two types of alerts:

- Threshold alerts (required): triggered when the CGM crosses a predefined threshold (e.g., $SG \leq 70$ mg/dL [≤ 3.9 mmol/L] for hypoglycemia). Threshold alerts should be evaluated when they are part of the device's intended use. These requirements do not apply to masked professional CGM systems or wellness devices that do not provide alerts as part of their intended use; and
- Predictive alerts (optional): triggered when the CGM forecasts that SG will cross a predefined threshold within a user-selected time horizon.^{48,49}

This chapter addresses two categories of performance metrics, applicable to both alert types:

- Glycemic alert evaluation: Glycemic alerts are triggered when a measured or predicted glucose value meets a predefined alert criterion. Alerts are evaluated by checking whether the comparator crossed the corresponding glucose threshold within the applicable analysis window. If the comparator crossed the threshold within that window, the alert is classified as a true alert; otherwise, it is classified as a false alert.
- Glycemic event evaluation: Glycemic events occur when the comparator crosses a predefined threshold. Events are confirmed by checking whether the CGM has crossed that same threshold within a defined window around the event time. If the CGM has crossed the threshold within the window, then the event is classified as a confirmed event; otherwise, it is classified as a missed event.

Alert performance shall be evaluated across a range of clinically relevant threshold settings appropriate to the intended use of the device and shall be stratified across glycemic ranges (CLSI POCT05). Performance metrics should also be evaluated within a prespecified window (e.g., within 15 or 30 minutes of the alert or event).

Manufacturers shall design CGM systems to minimize unnecessary alert burden and mitigate the risk of alert fatigue, while preserving clinically meaningful notifications, as described in American National Standards Institute (ANSI)/Association for the Advancement of Medical Instrumentation (AAMI) HE75:2009 (R2018) and IEC 60601-1-8.

Section 7.2

Alert Types

7.2.1 Threshold Alerts

High and low SG alerts (threshold alerts) notify the user when SG is at or above the high limit, or at or below the low limit.

7.2.2 Predictive Alerts

Predictive alerts are optional and notify users when their SG level may soon reach a high or low limit. Manufacturers should design their device so that users may select how early they would like to be notified before their SG level reaches a high or low limit. Depending on the manufacturer's design, notification settings can range from as little as 5 minutes to greater than 60 minutes before the limit is reached.

Section 7.3

Glycemic Alert Evaluation

7.3.1 True and False Alert Rate — Threshold Alerts

The true alert rate is the rate at which the comparator confirmed that the CGM alert was triggered correctly, whereas the false alert rate is the rate at which the CGM alert is triggered without confirmation from the comparator. These rates are important because users need to be notified when their BG is low or high so that they can take corrective action. A high true alert rate or low false alert rate indicates that when the CGM indicates that glucose is at, or will reach, a specified threshold, the user's BG is likely to be at or approaching that threshold.

A typical approach for calculating true and false alert rates for threshold alerts is outlined below:

- **Data Point Identification:** All SG data points equal to or below the predefined low threshold (e.g., SG ≤ 70 mg/dL [≤ 3.9 mmol/L] for hypoglycemia), or equal to or above the predefined high threshold (e.g., SG ≥ 180 mg/dL [≥ 10.0 mmol/L] for hyperglycemia), are identified.
- **Candidate Alert Definition:** Qualifying SG points are grouped together to form a single alert. Any two qualifying points that are at most 30 minutes from each other should be grouped together. As a result, a single alert may include multiple points, as long as each point is no more than 30 minutes into the future from the previous one.

- The alert start time is defined as the timestamp of the first qualifying point.
- The alert end time is defined as the timestamp of the last qualifying point in the grouped sequence.
- **Analysis Window Definition:** For each alert, an analysis window is constructed by extending 15 or 30 minutes (15/30 minutes) prior to the alert's start time and 15/30 minutes after the alert end time.
- **Alert Performance Classification:** For comparator values available within the analysis window:
 - If at least one comparator value meeting the same threshold criterion (e.g., ≤ 70 mg/dL [≤ 3.9 mmol/L]) falls within the analysis window, then the alert is classified as a true alert.
 - If there is no comparator value meeting the threshold in question (e.g., ≤ 70 mg/dL [≤ 3.9 mmol/L]) within the analysis window, then the alert is classified as a false alert.
 - If there are no available comparator values within the analysis window, then the corresponding alert is not evaluable and is not included in alert rate calculations.
- **Alert Rate Calculations:**
 - The true alert rate is defined as the number of alerts that are classified as a true alert divided by the number of evaluable alerts.
 - The false alert rate is defined as the number of alerts that are classified as a false alert divided by the number of evaluable alerts. The false alert rate is also equal to 1 minus the true alert rate.

7.3.2 True and False Alert Rate — Predictive Alerts

As with threshold alerts, the true alert rate for optional predictive alerts is the rate at which the comparator confirmed that the CGM alert was triggered correctly, whereas the false alert rate is the rate at which the CGM alert is triggered without confirmation from the comparator. Predictive alerts are triggered before a threshold is crossed; specifically, a user receives a predictive alert when their SG level is predicted to reach their high or low limit in the time horizon setting they select. In general, the earlier the warning, the more time a user will have to react to a potential high or low, but this also increases the risk of false alerts. The true alert rate at a given horizon setting indicates how often the forecast is a reliable basis for early action, whereas the false alert rate at that same horizon indicates how often that early warning may be erroneous.

A typical approach for calculating true and false alert rates for predictive alerts is outlined below:

- **Data Point Identification:** All SG data points equal to or below the predefined low threshold (e.g., SG ≤ 70 mg/dL [≤ 3.9 mmol/L] for hypoglycemia), or equal to or above the predefined high threshold (e.g., SG ≥ 180 mg/dL [≥ 10.0 mmol/L] for hyperglycemia), are identified.
- **Candidate Alert Definition:** Qualifying SG points are grouped together to form a single alert. Any two qualifying points that are at most 30 minutes from each other should be grouped together. As a result, a single alert may include multiple points, as long as each point is no more than 30 minutes into the future from the previous one.

- The alert start time is defined as the timestamp of the first qualifying point.
- The alert end time is defined as the timestamp of the last qualifying point in the grouped sequence.
- **Analysis Window Definition:** For a predicted SG value of x minutes into the future, the alert start time and alert end time are shifted by x minutes into the future. The value of x is typically 30 minutes. For each alert, the analysis window is then constructed by extending 15/30 minutes prior to the alert start time and 15/30 minutes after the alert end time.
- **Alert Performance Classification:** For comparator values available within the analysis window:
 - If at least one comparator value meeting the same threshold criterion (e.g., ≤ 70 mg/dL [≤ 3.9 mmol/L]) falls within the analysis window, then the alert is classified as a true alert.
 - If there is no comparator value meeting the threshold in question (e.g., ≤ 70 mg/dL [≤ 3.9 mmol/L]) within the analysis window, then the alert is classified as a false alert.
 - If there are no available comparator values within the analysis window, then the corresponding alert is not evaluable and is not included in alert rate calculations.
- **Alert Rate Calculations:**
 - The true alert rate is defined as the number of alerts that are classified as a true alert divided by the number of evaluable alerts.
 - The false alert rate is defined as the number of alerts that are classified as a false alert divided by the number of evaluable alerts. The false alert rate is also equal to 1 minus the true alert rate.

Section 7.4

Glycemic Event Evaluation

7.4.1 Confirmed and Missed Event Detection Rates — Threshold Alerts

The confirmed event detection rate is the rate at which the device alerted when it should have alerted, such as when the comparator was at or below the hypoglycemic threshold. Conversely, the missed event detection rate is the rate at which the device fails to alert when it should have done so at a specified comparator threshold. These rates are clinically meaningful because users need to be notified when their glucose is low or high so that they can act accordingly. High confirmed event detection rates and low missed event detection rates indicate that users can have confidence that they will be notified by the device if their glucose is low or high.

A typical approach for calculating confirmed and missed event detection rates for threshold alerts is outlined below:

- **Data Point Identification:** All comparator data points equal to or below the predefined low threshold (e.g., comparator ≤ 70 mg/dL [≤ 3.9 mmol/L] for hypoglycemia), or equal to or above the predefined high threshold (e.g., comparator ≥ 180 mg/dL [≥ 10.0 mmol/L] for hyperglycemia), are identified.
- **Candidate Event Definition:** Qualifying comparator points are grouped together to form a single event. Any two qualifying points that are at most 30 minutes from each other should be grouped together. As a result, a single event may include multiple points, as long as each point is no more than 30 minutes into the future from the previous one.
 - The event start time is defined as the timestamp of the first qualifying point.
 - The event end time is defined as the timestamp of the last qualifying point in the grouped sequence.
- **Analysis Window Definition:** For each event, an analysis window is constructed by extending 15/30 minutes prior to the event's start time and 15/30 minutes after the event's end time.
- **Event Performance Classification:** For SG values available within the analysis window:
 - If at least one SG value meeting the same threshold criterion (e.g., ≤ 70 mg/dL [≤ 3.9 mmol/L]) falls within the analysis window, then the event is classified as a confirmed event.
 - If no such SG value is observed within the analysis window, then the event is classified as a missed event.
 - If there is no available SG within the analysis window, then the corresponding event is not evaluable and is not included in event detection rate calculations.
- **Event Detection Rate Calculations:**
 - The confirmed event detection rate is defined as the number of events that are classified as a confirmed event divided by the number of evaluable events.
 - The missed event detection rate is defined as the number of events that are classified as a missed event divided by the number of evaluable events. The missed event detection rate is also equal to 1 minus the confirmed event detection rate.

7.4.2 Confirmed and Missed Event Detection Rates — Predictive Alerts

For optional predictive alerts, the confirmed event detection rate is the rate at which a comparator-defined event was preceded by an SG predictive alert within the prespecified time horizon, whereas the missed event detection rate is the rate at which the comparator reached a designated alert threshold without being preceded by an SG alert. Event detection rates are directly tied to the clinical value proposition for predictive alerts, as patients rely on these alerts to accurately forecast glycemic excursions. High confirmed event detection rates and low missed event detection rates for predictive alerts indicate that users can be confident they will receive early, accurate notifications from the device for clinically significant changes in glucose values.

A typical approach for calculating confirmed and missed event detection rates for predictive alerts is outlined below:

- **Data Point Identification:** All comparator data points equal to or below the predefined low threshold (e.g., comparator ≤ 70 mg/dL [≤ 3.9 mmol/L] for hypoglycemia), or equal to or above the predefined high threshold (e.g., comparator ≥ 180 mg/dL [≥ 10.0 mmol/L] for hyperglycemia), are identified.
- **Candidate Event Definition:** Qualifying comparator points are grouped together to form a single event. Any two qualifying points that are at most 30 minutes from each other should be grouped together. As a result, a single event may include multiple points, as long as each point is no more than 30 minutes into the future from the previous one.
 - The event start time is defined as the timestamp of the first qualifying point.
 - The event end time is defined as the timestamp of the last qualifying point in the grouped sequence.
- **Analysis Window Definition:** For a predicted SG value of x minutes into the future, the event start time and event end time are shifted backwards by x minutes. The value of x is typically 30 minutes. For each event, the analysis window is then constructed by extending 15/30 minutes prior to the event start time and 15/30 minutes after the event end time.
- **Event Performance Classification:** For SG values available within the analysis window:
 - If at least one SG value meeting the same threshold criterion (e.g., ≤ 70 mg/dL [≤ 3.9 mmol/L]) falls within the analysis window, then the event is classified as a confirmed event.
 - If no such SG value is observed within the analysis window, then the event is classified as a missed event.
 - If there is no available SG within the analysis window, then the corresponding event is not evaluable and is not included in event detection rate calculations.
- **Event Detection Rate Calculations:**
 - The confirmed event detection rate is defined as the number of events that are classified as a confirmed event divided by the number of evaluable events.
 - The missed event detection rate is defined as the number of events that are classified as a missed event divided by the number of evaluable events. The missed event detection rate is also equal to 1 minus the confirmed event detection rate.

Section 7.5

Reporting

Table 7.1 can be used for reporting alert rates and event detection rates as described above, for a specific insertion location. For example, a True Alert Rate Table for arm insertion would report true alert rates as a percentage, typically for both a ± 30 -minute time window and a ± 15 -minute time window.

Table 7.1 Sample Table for Reporting Alert Rates or Event Rates

Alert Type	Glucose (mg/dL [mmol/L])	Alert Rate % (±30 min window)	Alert Rate % (±15 min window)
Low Alerts	Urgent low (if applicable)	xx%	xx%
	54 (3.0)	xx%	xx%
	60 (3.3)	xx%	xx%
	70 (3.9)	xx%	xx%
	80 (4.4)	xx%	xx%
	90 (5.0)	xx%	xx%
High Alerts	180 (10.0)	xx%	xx%
	220 (12.2)	xx%	xx%
	250 (13.9)	xx%	xx%
	300 (16.7)	xx%	xx%

The format used in Table 7.1 should be included in the regulatory submission packages for adult and pediatric patients. The same format should be used for confirmed event detection rates, missed event detection rates, true alert rates, and false alert rates. Each performance metric should be presented in a separate table.

Section 7.6

Manufacturer Checklist

Section	Task
7.1 Introduction	Define glycemic alerts and events, and their relevance to evaluating CGM performance.
7.2 Alert Types	Define threshold alerts and optional predictive alerts.
7.3 Glycemic Alert Evaluation	Define true and false alert calculations for threshold and optional predictive alerts.
7.4 Glycemic Event Evaluation	Define confirmed and missed event calculations for threshold and optional predictive alerts.
7.5 Reporting	Define glycemic alert and event reporting requirements for manufacturers.

Section 7.7

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
Clinical and Laboratory Standards Institute	CLSI POCT05 — Performance Metrics for Continuous Interstitial Glucose Monitoring	Defines metrics for evaluating CGM alert and event performance, including true, false, and missed alert rates.
Association for the Advancement of Medical Instrumentation	ANSI/AAMI HE75:2009 (R2018) — Human Factors Engineering — Design of Medical Devices	Provides human factors guidance for designing alerts that users can notice, understand, and act on.

Organization	Document	Relevance
International Electrotechnical Commission	IEC 60601-1-8 — Medical Electrical Equipment — Part 1-8: General Requirements, Tests and Guidance for Alarm Systems	Specifies requirements for alarm systems, including alarm priority levels and auditory and visual signal characteristics.

Section 7.8

Summary

Alerts are a core safety feature of CGM systems, designed to notify users of current or impending hypoglycemia, hyperglycemia, and rapid glucose change. This chapter provides calculation methods for true alerts, false alerts, confirmed event detections, missed event detections, and their respective rates, which can be used to evaluate the alert performance of the CGM system, as well as reporting requirements for manufacturers.

Chapter 8

System Reliability, Stability, Cybersecurity, and Biocompatibility

Included in this section:

- 8.1 INTRODUCTION
- 8.2 SENSOR STABILITY
- 8.3 GLUCOSE DATA AVAILABILITY
- 8.4 SENSOR SURVIVAL
- 8.5 DATA RELIABILITY AND CYBERSECURITY
- 8.6 ELECTROMAGNETIC COMPATIBILITY
- 8.7 BIOCOMPATIBILITY
- 8.8 STERILITY
- 8.9 SOFTWARE VALIDATION
- 8.10 MANUFACTURER CHECKLIST
- 8.11 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 8.12 SUMMARY

Section 8.1

Introduction

The long-term safety and effectiveness of a CGM system depend on more than analytical accuracy alone. At the level of measurement, the system should deliver accurate glucose readings and maintain reliable sensor performance throughout the wear period. At the level of data and software, it should ensure continuous data availability and rely on validated software functionality to process and display those readings correctly. With respect to external threats, it should be protected against cyberattacks and resistant to electromagnetic interference that could corrupt or disrupt its operation. Finally, because the sensor is worn in contact with the body, it should be biologically safe and remain sterile until use.

Manufacturers should demonstrate that the CGM system performs consistently throughout the labeled wear period, maintains reliable communication and data delivery, protects against cybersecurity threats, operates safely in expected electromagnetic environments, and utilizes biocompatible and sterile components. Comprehensive V&V of these characteristics provides assurance that the CGM system remains safe, reliable, and effective for its intended use and users.

Section 8.2

Sensor Stability

Sensor signal stability across the labeled wear period is a critical component of CGM system performance. Manufacturers should evaluate and present performance across the full wear duration by segmenting the wear period into clinically meaningful time intervals, such as early, middle, and late phases, or into day-based groupings, as appropriate for the labeled sensor wear duration. Performance evaluation should include both the first day of wear and the final day of the labeled wear duration to adequately characterize performance over time.

For each defined time interval, system agreement across medically relevant glucose ranges (e.g., <54 mg/dL [<3.0 mmol/L], 54–69 mg/dL [3.0 – 3.8 mmol/L], 70–180 mg/dL [3.9 – 10.0 mmol/L], 181–250 mg/dL [10.1 – 13.9 mmol/L], and >250 mg/dL [>13.9 mmol/L]) should be presented to characterize performance. This analysis should enable assessment of whether accuracy and reliability are maintained throughout the entire wear period. In addition, performance on the first day of sensor wear should be reported separately, given the potential for transient variability during sensor insertion and initialization.

For CGM systems requiring user calibration, it is important to evaluate how time since the last calibration impacts point accuracy. Accuracy metrics should be stratified across predefined post-calibration time and glucose concentration intervals to assess potential temporal degradation in performance following calibration. If accuracy is shown to degrade significantly as a function of time since the user's most recent calibration, then man-

Manufacturers should investigate whether modifications to the calibration scheme are warranted. Any calibration scheme modifications derived from study results should be evaluated using an independent dataset or other appropriately justified validation approach before being used to support performance claims. The calibration methodology employed in the study should reflect intended clinical use. This includes calibration timing, conditions, and user procedures. Calibration should be performed using accurate, traceable SMBG devices with appropriate user techniques consistent with labeling and IFU.

For CGM systems that support optional calibration, the impact of calibration on system performance should be characterized. This evaluation should include the effect of calibration on accuracy, as well as any recommended calibration timing and the number of calibrations advised, if applicable. Calibration should be performed under stable glucose conditions to minimize confounding effects from rapid glucose changes. A stable glucose condition is recommended to be defined as a rate of glucose change within ± 1 mg/dL/min (± 0.06 mmol/L/min).

Sensors should also incorporate effective mechanisms that prevent continued use beyond the labeled wear duration. Such mechanisms could include automatic shutoff or lockout functions. These measures are necessary to ensure the device is not used beyond its validated performance period and to mitigate the risk of degraded accuracy or reliability from extended use.

Section 8.3

Glucose Data Availability

Glucose data availability is defined as the ratio of the number of glucose readings presented to the user in comparison to the number of readings expected based on device specifications. Manufacturers should calculate overall glucose data availability across sensor wear days for the full wear period. For interoperable CGM systems, manufacturers should demonstrate the absence of any clinically significant data gaps, defined as those that could prevent connected devices from achieving their intended functions. Labeling should clearly describe any limitations related to data availability, including known conditions or operational states that could reduce glucose data delivery.

When the CGM system is integrated into a closed-loop or interoperable AID system, it is particularly important to report CGM data delivery performance as part of the overall system's performance characterization. One acceptable reporting approach is to enumerate missed CGM data in each operational hour, including associated timestamps and wear-day identifiers, and to extrapolate these data (e.g., median or distribution) across the full sensor wear period.

Missed CGM data should be separately analyzed and reported during periods of hypoglycemia. For example, manufacturers should report the number or percentage of missed data points during hypoglycemia across the wear period.

Section 8.4

Sensor Survival

The sensor survival rate is the probability that a sensor remains operational for the full duration of the labeled wear period. Sensor survival probability should be estimated using the Kaplan–Meier product-limit method⁵⁰ to appropriately account for censored observations, such as elective sensor removal or discontinuation for reasons unrelated to device performance. Estimated sensor survival rates should be substantially similar to those of other currently marketed CGM products, considering differences in labeled wear duration and intended use. Survival analyses should be performed across the full sensor wear period to identify any time-dependent changes in operational reliability.

All sensor discontinuations should be systematically classified by failure mode and quantitatively summarized. Failure mode categories should include device or component failures and failures to initialize. They should also include adhesive-related failures and algorithm-based terminations. Connectivity failures and other system-initiated or user-independent causes of sensor discontinuation should also be included. The frequency and timing of device failure over the sensor wear period should be recorded to identify potential patterns or trends that could affect clinical performance or labeling claims. This analysis should support a comprehensive assessment of overall system reliability and inform risk management activities.

Section 8.5

Data Reliability and Cybersecurity

Modern CGM systems communicate wirelessly with manufacturer-developed smartphone applications, cloud-based services, third-party applications, and AID systems, and may support remote software and firmware updates. As CGM systems become increasingly integrated with AID systems, cybersecurity considerations extend beyond data privacy and confidentiality and represent a critical patient-safety risk. Manufacturers should establish and maintain a comprehensive cybersecurity risk management program that identifies, assesses, and mitigates risks associated with cybersecurity vulnerabilities throughout the entire product lifecycle. This program should address risks related to wireless communications, cloud connectivity, and interoperable system interfaces. It should also address remote monitoring and software update mechanisms. Cybersecurity risk controls should be commensurate with the potential impact of exploitation on patient safety, data integrity, and system availability.

Wireless communication protocols used by CGM systems, including but not limited to Bluetooth Low Energy and Near Field Communication, should incorporate risk-appropriate authentication and encryption mechanisms to maintain data privacy, integrity, and system performance. Manufacturers should implement appropriate mitigation controls and maintain documented processes for vulnerability detection, coordinated vulnera-

bility disclosure, and timely remediation, including deployment of security updates when necessary. For interoperable CGM and AID systems, CGM and AID manufacturers should establish and implement appropriate functional, performance, and interface requirements to support safe and effective operation. These requirements should include, at a minimum:

- Defined communication interfaces used to communicate with the sensor and connected systems;
- Specified CGM data update intervals (e.g., 1-minute or 5-minute updates);
- Requirements for generation, transmission, and display of glucose values, trend information, and alerts; and
- Identification and control of risks related to electronic interfaces, including data integrity, communication security, latency, and data loss.

Because many CGM systems support remote monitoring and telehealth workflows, including home-to-cloud-to-caregiver data transmission and real-time viewing by caregivers, communication latency, data availability, and security should be explicitly validated for these common use scenarios where relevant. Validation should demonstrate that remote users and caregivers receive timely, accurate, and complete information comparable to that available on primary displays, with appropriate safeguards against unauthorized access and data loss. Manufacturers should demonstrate that transmitted glucose data are preserved without corruption or truncation across all system components. V&V activities should confirm correct display of glucose values, trend indicators, and alerts on all receiving devices, and should verify time synchronization across the sensor, receiver, cloud services, and connected systems.

Input-data quality-control mechanisms should be implemented to detect corrupted, implausible, or noisy signals and prevent unreliable data from being displayed or propagated to connected systems, including AID controllers, where receipt of incorrect glucose results could be fatal. Manufacturers should also validate interference use cases in environments where multiple CGM systems may be activated concurrently, such as hospitals, clinics, or group settings (e.g., summer camps). Validation should demonstrate that CGM data are transmitted only to the intended user and authorized follower caregivers, and that cross-pairing, data misrouting, or incorrect data association does not occur under conditions of radio-frequency congestion or high device density.

Adherence to recognized cybersecurity standards, such as IEC 81001-5-1, AAMI SW96, and IEEE 2621, is strongly recommended. Programs such as the IEEE 2621 Medical Device Cybersecurity Certification Program provide assurance for connected diabetes devices. This helps support consistent implementation of secure connectivity practices.

Manufacturers should implement a documented secure development lifecycle for CGM software and connected components, aligned with recognized security standards and integrated with existing software lifecycle processes. Cybersecurity risk management should incorporate formal threat modeling at the system and component level. Threat modeling should identify attack paths, trust boundaries, and high-risk functions, and should also describe the resulting security controls. Manufacturers should document a security architecture that describes trust boundaries and key data flows, including authentication and authorization mechanisms, cryptographic protections, and segregation of safety-critical functions from non-critical components.

CGM systems rely on third-party software and services. Manufacturers should maintain a software bill of materials (SBOM) that inventories third-party components and platforms. The SBOM should support vulnerability monitoring, impact assessment, over-the-air (OTA) software update procedures where applicable, and remediation. Manufacturers should also define governance for third-party dependencies, including mobile devices, operating systems (OSs), and companion applications. Cloud services should also be included. This governance should include criteria for supported configurations and handling for end-of-life platforms.

V&V for cybersecurity should include risk-based security testing such as static and dynamic analysis, as well as independent penetration testing of device, mobile, and cloud components. Expectations related to the scope and timing of remediation actions for identified vulnerabilities should be clearly defined. Vulnerability-handling processes should use a structured approach to scoring and prioritization, such that issues with the greatest potential impact on patient safety, data integrity, or system availability are addressed first.

To support regulatory and third-party review, manufacturers should provide a minimum set of cybersecurity evidence artifacts. These may include threat-model documentation, security architecture diagrams, SBOMs, and summaries of security testing. They should also include evidence of secure deployment, patching, and update processes. For most connected devices, updates can occur either OTA or on-site. Regardless of the chosen method for software updates, the software patch should undergo rigorous testing prior to market deployment to ensure no impact on the safety, security, or effectiveness of the function of the system. V&V testing of the planned software patch, including both protocols and results, should be documented as part of the Quality Management System (QMS) for the specific manufacturer.

For digital health applications, including telehealth workflows, integration of CGM and AID data into the patient's electronic health record (EHR) is of critical importance. Manufacturers are encouraged to adopt established CGM and AID data-integration standards, such as Integration of Continuous Glucose Monitoring Data into the Electronic Health Record (iCoDE)⁵¹ and Integration of Connected Diabetes Device Data into the Electronic Health Record (iCoDE-2),⁵² to facilitate interoperability, clinical usability, and longitudinal patient care.

Section 8.6

Electromagnetic Compatibility

CGM systems should be evaluated for electromagnetic compatibility (EMC) and electrical safety to ensure safe and effective performance under expected use conditions. EMC is defined as the ability of the CGM system to limit electromagnetic emissions such that it does not interfere with other equipment, while maintaining safe and effective performance when exposed to electromagnetic disturbances. The manufacturer shall define the Essential Performance of the CGM system according to IEC 60601-1. At a minimum, the manufacturer should evaluate whether loss or degradation of measurement accuracy, processing or communication of interstitial glucose values or glucose trend information, or generation or transmission of alerts and alarms for hypoglycemic or hyperglycemic conditions could result in unacceptable risk. CGM systems should be designed such that electro-

magnetic disturbances do not result in clinically misleading glucose information, missed or delayed alerts, loss of trend data, or other conditions that could adversely affect patient safety.

Manufacturers shall evaluate EMC immunity and emissions in accordance with recognized consensus standards, including IEC 60601-1-2, using test levels appropriate for the home healthcare environment unless a different intended use environment is justified. Additional EMC testing may be required depending on the device design, sensor architecture, wireless communication technologies, or intended use conditions.

Electrostatic discharge (ESD) represents a specific electromagnetic disturbance that can adversely affect CGM performance, reliability, and safety. CGM systems are particularly susceptible to ESD because of the use of low-power analog front-end circuitry, sensitive integrated circuits, and body-worn form factors. ESD events can result in incorrect glucose readings, data corruption, loss of communication, or unintended device reset or shutdown. Manufacturers shall evaluate ESD immunity in accordance with IEC 60601-1-2 and IEC 61000-4-2, using test setups and stress levels representative of the intended use environment. Because CGM systems are wearable medical devices, ESD testing should reflect real-world handling scenarios while the device is operational. Testing should demonstrate that ESD events do not compromise essential performance or result in unsafe system behavior.

Manufacturers should document EMC and ESD risks and their mitigations as part of the device risk management process. The associated test methods, acceptance criteria, and results should be included as supporting evidence in the premarket submission.

Section 8.7

Biocompatibility

CGM systems should be designed and manufactured to minimize the risk of adverse local or systemic biological responses throughout their intended duration of use. All patient contact materials should be demonstrated to be biologically safe and suitable for their specific contact type and exposure duration.

Biocompatibility evaluation shall be conducted in accordance with recognized international standards, such as ISO 10993, and should consider the nature of device contact, including prolonged skin contact and subcutaneous implantation, as applicable. Evaluations should assess local biological effects, including cytotoxicity, sensitization, and skin irritation. They should also assess systemic and material-mediated safety risks, including systemic toxicity. Manufacturers should demonstrate that the selected materials, device design, and intended use do not result in unacceptable biological risk over the claimed duration of use. Biocompatibility risks, mitigations, and supporting test evidence should be documented as part of the device risk-management process.

Section 8.8

Sterility

CGM sensors and insertion needles should be supplied in sterile, sealed packaging. The moment the sensor is inserted, sterility is lost. The sensors are designed for single use only and therefore should not be reused, reinserted, or re-sterilized. With proper use, infection risks are low. However, manufacturers should communicate to users about the best practices to maintain sterility, including cleaning the skin with alcohol or an antiseptic wipe prior to insertion. Users should also be advised to remove the sensor and seek medical care if an infection is observed.

Section 8.9

Software Validation

CGM software shall be validated as a medical device software system (21 CFR Part 820, IEC 62304, ISO 14971). Validation shall encompass the following software components of the CGM system, including:

- Embedded software in the sensor/transmitter, used for functions including signal acquisition and calibration;
- Software in the mobile app/receiver used for display of glucose results, alerts, and trend arrows;
- Cloud backend software for functions including data storage, analytics, and caregiver monitoring; and
- Algorithms for data transformation, including glucose estimation and alert logic.

Each of these components should be covered in the validation strategy, beginning with clear, testable requirements tied to user needs. Manufacturers should use the IEC 62304-style process for planning, design, implementation, verification, and maintenance, focusing on producing objective evidence that the entire ecosystem operates safely and effectively for the intended purpose.

Section 8.10

Manufacturer Checklist

Section	Task
8.2 Sensor Stability	Report performance for the full wear period across both clinically meaningful time intervals and medically relevant glucose intervals.
8.3 Glucose Data Availability	Compute glucose data availability across sensor wear days, and show the absence of any clinically significant data gaps.
8.4 Sensor Survival	Document primary sensor survival, premature failure rates, and categorized failure modes.
8.5 Data Reliability and Cybersecurity	Implement secure wireless communication protocols that incorporate risk-appropriate authentication and encryption mechanisms to maintain data integrity, privacy, and performance.
	For interoperable systems, establish and implement appropriate functional, performance, and interface requirements.
8.6 Electromagnetic Compatibility	Evaluate CGM systems for EMC and electrical safety to ensure reliable performance under expected use conditions.
8.7 Biocompatibility	Evaluate and document biocompatibility using recognized standards.
8.8 Sterility	Supply CGM sensors to the user in a sealed, sterile package.
8.9 Software Validation	Validate CGM software as a medical device software system using recognized standards.

Section 8.11

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
U.S. Food and Drug Administration	21 CFR 862.1355 — Integrated continuous glucose monitoring system	Establishes requirements for data throughout the claimed sensor life without clinically significant gaps in sensor data availability.
Clinical and Laboratory Standards Institute	CLSI POCT05 — Performance Metrics for Continuous Interstitial Glucose Monitoring	Provides consensus standards for evaluating accuracy, reliability, and data presentation in CGM systems.
International Organization for Standardization	ISO 14971 — Medical devices — Application of risk management to medical devices	Defines international standards for applying risk management to medical devices.
International Electrotechnical Commission	IEC 62304 — Medical device software — Software life cycle processes	Establishes an international standard that specifies the life cycle requirements for medical device software.
International Electrotechnical Commission	IEC 81001-5-1:2021 — Health software and health IT systems safety, effectiveness and security — Part 5-1: Security — Activities in the product life cycle	Defines the life cycle requirements for development and maintenance of health software.
International Electrotechnical Commission	IEC 82304-1 — Health software — Part 1: General requirements for product safety	Provides general safety and security requirements for health software products designed to run on general-purpose computing platforms without dedicated hardware.

Organization	Document	Relevance
International Electrotechnical Commission	IEC 80001-1 — Application of risk management for IT networks incorporating medical devices	Establishes an international standard that guides healthcare and information technology (IT) groups on managing risks when connecting medical devices to IT networks.
Institute of Electrical and Electronics Engineers	IEEE 2621.1-3 — Standard for wireless diabetes device security	Defines a secure framework for evaluating wireless diabetes devices like insulin pumps and CGMs.
Association for the Advancement of Medical Instrumentation	ANSI/AAMI SW96:2023 — Standard for Medical Device Security — Security Risk Management for Device Manufacturers	Establishes requirements for managing security risks throughout the medical device lifecycle, integrated with the ISO 14971 safety risk management process.
International Organization for Standardization/International Electrotechnical Commission	ISO/IEC 29147 — Information technology — Security techniques — Vulnerability disclosure	Provides guidelines for vendors on how to responsibly receive, handle, and disclose information about potential vulnerabilities in products and online services.
International Organization for Standardization/International Electrotechnical Commission	ISO/IEC 30111 — Information technology — Security techniques — Vulnerability handling processes	Provides requirements and recommendations for vendors on how to process, investigate, and remediate potential security vulnerabilities in products or online services.
International Electrotechnical Commission	IEC 60601-1-2 — Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic disturbances — Requirements and tests	Specifies EMC requirements, test methods, and allowable emission limits for medical electrical equipment and systems to ensure basic safety and essential performance.
International Electrotechnical Commission	IEC 61000-4-2 — Electromagnetic compatibility — Part 4-2: Testing and measurement techniques — Electrostatic discharge immunity test	Specifies the international standard for testing electrical and electronic equipment against ESD from human operators or nearby objects.

Organization	Document	Relevance
International Electrotechnical Commission	IEC 60601-1 — Medical Electrical Equipment — Part 1: General Requirements for Basic Safety and Essential Performance	Establishes standards for the basic safety and essential performance of medical electrical equipment.
U.S. Food and Drug Administration	Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices	Outlines key design considerations, labeling suggestions, and premarket submission recommendations for devices using electronic interfaces to exchange data.
U.S. Food and Drug Administration	Cybersecurity in Medical Devices: Quality Management System Considerations and Content of Premarket Submissions	Integrates security into QMS via a Secure Product Development Framework.
International Organization for Standardization	ISO 10993-1 — Biological Evaluation of Medical Devices — Part 1: Evaluation and Testing Within a Risk Management Process	Provides guidelines and requirements for manufacturers to appropriately assess the biological safety of a medical device, including testing.
U.S. Food and Drug Administration	21 CFR Part 820 — Quality Management System Regulation	Sets current good manufacturing practice rules for designing, making, packaging, labeling, storing, installing, and servicing medical devices intended for human use.

Section 8.12

Summary

This chapter outlines the key requirements for ensuring the long-term reliability, safety, and performance of CGM systems throughout their lifecycle. Manufacturers should demonstrate consistent performance across the entire wear period with reliable operation in both stand-alone and interoperable AID systems. Many CGM systems connect with other medical devices. These systems rely on dependable wireless connectivity, cloud services, and mobile applications. Comprehensive cybersecurity guards their connections. Software validation and data integrity controls confirm reliable system performance. Together, these safeguards protect patient safety and en-

sure accurate glucose data. Manufacturers should demonstrate compliance with established standards for EMC, ESD, biocompatibility, and sterility, with V&V activities covering all hardware, software, and connected-system components. CGM systems should maintain accurate, secure, and dependable performance under real-world conditions, supported by rigorous testing, lifecycle risk management, and objective evidence demonstrating safety and effectiveness for their intended use.

Chapter 9

Interoperability

Included in this section:

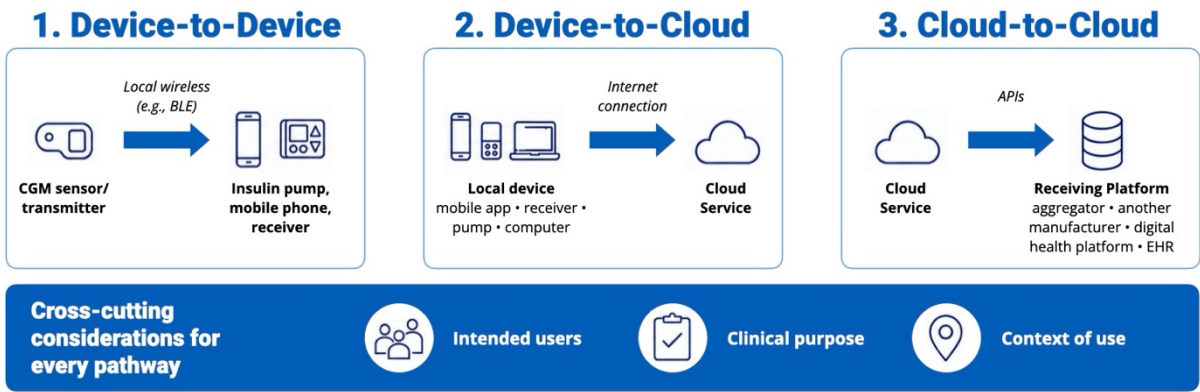
- 9.1 INTRODUCTION
- 9.2 TYPES OF INTEROPERABILITY
- 9.3 INTEROPERABILITY RISK MANAGEMENT
- 9.4 DATA EXCHANGE SPECIFICATIONS AND INTERFACE LIFECYCLE MANAGEMENT
- 9.5 TIME SYNCHRONIZATION AND CLOCK INTEGRITY
- 9.6 STRESS TESTING
- 9.7 ECOSYSTEM MANAGEMENT
- 9.8 INTEROPERABILITY ASSESSMENT
- 9.9 COMPATIBILITY AND CHANGE MANAGEMENT
- 9.10 MANUFACTURER CHECKLIST
- 9.11 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 9.12 SUMMARY

Section 9.1

Introduction

In CGM systems, interoperability is the ability of connected components to exchange data, preserve meaning, and maintain clinically coherent function across devices, software, and services.⁵³ This property has three dimensions: technical connection, semantic consistency, and temporal integrity. Where appropriate to the intended use and regulatory context, CGM interoperability may align with established health informatics and device communication standards, including ISO/IEEE 11073-10425:2024 (CGM-specific),⁵⁴ ISO/IEEE 11073-10101:2020, ISO/IEEE 11073-20601:2022, ISO/IEEE 11073-10201:2020 (supporting frameworks), Health Level Seven International (HL7) Fast Healthcare Interoperability Resources (FHIR),⁵⁵ HL7 CGM FHIR Implementation Guide, and the iCoDE and iCoDE-2 recommendations.^{51,52,55–57} ISO/IEEE 11073-10425:2024 specifies normative communication, term codes, formats, and behaviors between CGM devices (agents) and data managers such as smartphones or personal computers.⁵⁴ ISO/IEEE 11073-10101:2020 defines standardized nomenclature for point-of-care medical device communication, with primary emphasis on acute care devices and vital signs information. ISO/IEEE 11073-20601:2022 defines the optimized personal health data exchange protocol and application profile base architecture, and ISO/IEEE 11073-10201:2020 establishes the general domain information model used for point-of-care medical device communication. HL7 FHIR is a standard for electronic health data exchange, and the HL7 CGM FHIR Implementation Guide (Standard for Trial Use [STU] 1, v1.0.0, published September 2025) provides a standardized approach for exchanging CGM data, including summary reports and individual glucose observations, between systems. The iCoDE Report (2022) established the first consensus report for integrating CGM data into the EHR, and the iCoDE-2 Report (2025) extended this work to include insulin delivery data from connected pumps and pens. Section 9.11 provides a list of relevant standards, and Figure 9.1 illustrates the principal technical pathways for CGM interoperability and the cross-cutting considerations that inform the risk assessment of each interface.

Figure 9.1 Technical Pathways and Cross-Cutting Considerations for CGM Interoperability



Abbreviations: Application Programming Interface (API), Bluetooth Low Energy (BLE), Continuous Glucose Monitoring (CGM), Electronic Health Record (EHR).

Section 9.2

Types of Interoperability

For the purposes of this guideline, CGM interoperability interfaces should be classified according to the architecture of the primary technical pathway through which data are exchanged: device-to-device, device-to-cloud, or cloud-to-cloud. A single end-to-end workflow may include more than one pathway in sequence, and each interface should be evaluated separately as well as within the complete workflow.

Device-to-Device Interoperability: This type of interoperability refers to communication between local physical components. Examples include transmission of CGM data to an insulin pump, pod, or other AID component, as well as transmission to a dedicated receiver, smartphone, or other mobile device. These connections commonly use local wireless communication and may support real-time glucose display, alerting, or AID. Wireless device-to-device interoperability depends on several functional considerations. Devices should pair and authenticate before they exchange data. Communication range limits where devices can connect. Wireless interference and coexistence with other systems affect link reliability. Battery state affects connection stability. Connection handoffs and data latency should stay within clinically acceptable limits. Devices should behave safely during loss and restoration of communication.

Device-to-Cloud Interoperability: This type of interoperability refers to transmission of CGM data from a local device to a remote cloud service. The originating device may be a CGM receiver, smartphone, insulin pump, computer, or other gateway, and the connection may occur directly or through one or more intermediary components. Examples include a smartphone application uploading CGM data through Wi-Fi or cellular service, a receiver transferring data through an internet-connected computer, or a connected device uploading data directly to a manufacturer's cloud platform. Device-to-cloud interoperability depends on several functional considerations. Devices should authenticate and be authorized before uploading data. When internet access is unavailable, devices should buffer data until the connection returns. Upload latency and timestamp preservation determine whether data retain accurate timing. After connectivity is restored, reconciliation should ensure data completeness.

Cloud-to-Cloud Interoperability: This type of interoperability refers to data exchange between remote software services or platforms. Examples include transmission from a CGM manufacturer's cloud to an aggregator, another device manufacturer, a third-party digital health or clinical platform, a healthcare organization's integration environment, or an EHR.

Cloud-to-cloud interoperability depends on several functional considerations, including application programming interface (API) specifications and versioning, which define how services exchange data. Authentication and

authorization control which services may access the data. Semantic consistency should be preserved through any data transformation, while service availability and rate limits determine when and how often data can be requested. Latency affects how quickly data reach the receiving platform. Error handling and reconciliation allow services to recover from failed or inconsistent exchanges, while data provenance and allocation of responsibilities establish accountability between participating organizations.

CGM interoperability is also described by workflow: clinician-platform, platform-to-EHR, software, and patient-mediated interoperability. These categories describe who uses the data and for what purpose, as opposed to how the data travel. Each relies on one or more of the three pathways above. For example, platform-to-EHR integration is a cloud-to-cloud exchange, and patient-mediated sharing typically combines device-to-cloud and cloud-to-cloud steps. Each workflow should therefore be evaluated end to end, using the pathway requirements in this section.

The intended user, clinical purpose, and context of use should be treated as cross-cutting risk considerations for all interfaces. The intended user determines who will act on the data, the clinical purpose determines which decisions the data support, and the context of use defines the conditions under which the data are used.

Functional requirements should describe the interface's purpose, intended users, and the actions expected in response to the transmitted information. Data exchange requirements should identify the direction of data exchange and the required data elements. Performance requirements should establish acceptable limits for latency and availability.

Individual definition is important because the same type of interface can serve very different functions. For example, a cloud-to-cloud interface may support retrospective clinician review, real-time remote monitoring, clinical decision support (CDS), or patient-directed data sharing. These uses involve different users, timing requirements, and consequences of failure. Real-time remote monitoring, for example, generally requires much lower latency and higher availability than retrospective review. Accordingly, interface-specific requirements should be established based on the intended use and associated risks.

Although the technical pathway may be the same, the required controls and consequences of delayed, incomplete, or inaccurate data may differ substantially. Verification, validation, labeling, and risk controls should therefore be proportionate to the intended use and potential clinical consequences of each interface and the complete end-to-end workflow.

For CGM data integrated into hospital systems, such as EHRs or bedside monitoring networks, each interface should be evaluated within the same pathway and risk framework, recognizing that inpatient use may be outside the device's cleared or approved indications. Point-of-care device connectivity standards, such as the ISO/IEEE 11073 service-oriented device connectivity (SDC) family (-10207, -20701), may be relevant to such integrations.

Where applicable, interoperable components should align with relevant regulatory classifications and special controls. In the U.S., these may include iCGM systems under 21 CFR 862.1355, interoperable automated glycemic controllers under 21 CFR 862.1356, and alternate controller enabled (ACE) infusion pumps under 21 CFR 880.5730.

Section 9.3

Interoperability Risk Management

Interoperability risk management is a distinct component of CGM risk management, as connected systems create hazards that may not be evident when components are assessed separately. Risk analyses should address two levels of hazard. The first level covers risks within individual components, such as devices, software, networks, and cloud services. The second level covers hazards of the shared system as a whole. Some of these hazards arise because responsibility is distributed across components and no single component owns the outcome. Others are emergent failure modes, which arise from interactions between components even when each component works as intended. Specific categories of hazards relevant to interoperability risk management include:

- **Technical and Systemic Hazards:** Relevant hazards include cascading failures and command conflicts, as well as synchronization failures. Software and communication hazards include incompatible software versions and delayed transmissions. Temporal and contextual hazards include stale data, time-synchronization and clock-integrity errors, and loss-of-context errors. These concerns have heightened patient safety implications in AID ecosystems, remote monitoring workflows, and cloud-based analytics. They are also important when CGM data are utilized by artificial intelligence (AI)-enabled decision-support tools, or when CGM systems are used by pediatric populations.

In pediatric use in particular, the receiver is frequently split (e.g., the child wears the sensor, while parents or school nurses monitor telemetry remotely). Pediatric-specific hazards include remote-monitoring telemetry instability, latency, or errors in alert-escalation pathways when a primary connection (Bluetooth) is stable, but the secondary connection (cellular/cloud to caregiver) is lost. Multi-vendor and third-party dependencies should be considered, including the use of different versions of standards or implementation guides. These dependencies extend to visual displays of information. If a third-party app, EHR, or remote dashboard displays CGM trends using conflicting arrow directions or differing color-coded glycemic ranges compared to the primary display, then it could cause user confusion or medical errors. Standardized minimum design controls governing data visualizations, such as the design controls governing the Ambulatory Glucose Profile, should be applied by all receiving platforms.

- **Security and Identity Hazards:** Risk management should also address authentication integrity, authorization boundaries, and identity-management dependencies across interoperable components. The risk analysis should also consider security and identity hazards within connected ecosystems. Both device spoofing and credential compromise allow an attacker to impersonate a legitimate participant: device spoofing fakes a device's identity, and credential compromise uses stolen credentials to gain access. Unauthorized endpoints are connections that were never approved to exchange data with the system. Incorrect attribution occurs when data or commands are assigned to the wrong device, user, or patient. Such errors can lead to clinical decisions based on another person's data.
- **Third-Party Alerting:** An additional interoperability risk consideration relevant to CGM systems is third-party applications that re-present or re-alert on CGM data. Risk analyses and labeling should ex-

plicitly address hazards related to third-party alerting, including the potential for duplicate, conflicting, or misleading alerts.

For a more detailed analysis of representative interoperability hazards, illustrative causes, and example controls, see Table 9.1.

Because safe performance depends on the combined behavior of medical devices and the networks into which they are integrated, roles and responsibilities for network-related risk management should be clearly defined. These responsibilities should be allocated between the manufacturer and the responsible organization or deploying institution, with explicit risk controls, assumptions, and failure boundaries.

Labeling and technical documentation should describe intended interoperable uses (what the system is designed to do) and operational dependencies (what external conditions it requires). They should also disclose residual risks (hazards remaining after risk controls) and limitations (what the system does not support). Responsibility boundaries among manufacturers, software developers, cloud-service providers, and deploying institutions should be explicitly documented for interoperable workflows. Processes for coordinated investigations, communications, and remediations of interoperability-related incidents should also be defined.

Table 9.1 Interoperability Hazard-Control Matrix for Connected CGM Ecosystems

Hazard class	Typical underlying causes	Potential clinical or operational impact	Example risk controls	Primary responsible parties
Cascading failures across components	Tight coupling among CGM, pump, app, or cloud services; dependence on a shared service or data path	Loss of coordinated function, incorrect dosing context, missed alerts	Architectural isolation, fault containment, independent safety interlocks, degraded operating modes	CGM manufacturer, pump manufacturer, app developer, cloud-service provider
Synchronization failures	Clock drift, inconsistent time authority, missed synchronization events	Misaligned glucose and insulin timelines, incorrect trend interpretation, audit inconsistency	Defined authoritative clock, timestamp hierarchy, synchronization tolerances, validation under reconnection conditions	Device manufacturers, app developer, cloud-service provider

Hazard class	Typical underlying causes	Potential clinical or operational impact	Example risk controls	Primary responsible parties
Stale-data hazards	Delayed upload, buffering, offline operation, cached data displayed without age context	Decisions made on outdated glucose values or alerts	Data-age indicators, expiration rules, suppression of stale data for safety-critical use, clear user notification	CGM manufacturer, app developer, dashboard provider
Command conflicts	Multiple software components or devices attempting overlapping control actions	Unpredictable settings, inconsistent system behavior, unsafe automation interactions	Command arbitration rules, single-writer controls, conflict detection, audit logging	Device manufacturers, app developers
Incompatible software or standards versions	Asynchronous updates, mismatched APIs, unsupported profiles, deprecated interfaces	Partial interoperability, missing data elements, failed alerts or workflows	Semantic versioning, compatibility matrices, backward-compatibility policies, interoperability regression testing	All participating manufacturers and software developers
Identity and authentication failures	Weak endpoint authentication, credential compromise, spoofed devices, poor identity management	False data injection, unauthorized access, incorrect attribution of commands or data	Strong authentication, device identity controls, authorization boundaries, credential lifecycle management, Zero Trust principles	Device manufacturers, cloud-service provider, deploying institution
Alert overload and unfiltered data streams	Excessive raw data forwarded to health IT platforms, redundant alert pathways, poor prioritization	Clinician alert fatigue, missed critical events, reduced usability	Filtering rules, prioritization logic, aggregation, escalation policies, labeling of interoperability limitations	CGM manufacturer, EHR vendor, third-party app developer, deploying institution

Hazard class	Typical underlying causes	Potential clinical or operational impact	Example risk controls	Primary responsible parties
Third-party re-presentation or re-alerting	External applications re-displaying glucose data or generating duplicate alerts	Conflicting displays, duplicate alerts, user confusion, delayed action	Labeling, validation of supported apps, alert governance, consistency checks across display and alert pathways	CGM manufacturer, third-party app developer
Caregiver receiver errors	Data transmission or display on caregiver monitoring application (same manufacturer or external application) fails or is delayed	Conflicting displays, failed caregiver alerts, user/caregiver confusion, delayed action, decisions made on outdated glucose values or alerts	Connection status and data-age indicators on the caregiver application; notification to caregiver and patient when remote data transmission is interrupted; validation of end-to-end latency for home-to-cloud-to-caregiver pathways; escalation of critical alerts through an alternate channel; labeling of remote monitoring limitations	CGM manufacturer, third-party app developer

Table 9.1 provides illustrative examples of interoperability hazards, common causes, possible impacts, example controls, and primary responsible parties in connected CGM ecosystems. The table is intended to support structured risk analysis and allocation of responsibilities. The table is not exhaustive and should be adapted to the intended use, system architecture, and deployment environment.

Section 9.4

Data Exchange Specifications and Interface Lifecycle Management

In interoperable systems, data exchange specifications are critical to ensuring that data content and meaning are preserved across platforms. Interoperability specifications should be documented in interface documentation, implementation guides, or equivalent technical design documentation. These specifications should define standardized data elements, including timestamp conventions and units, as well as metadata expectations, event annotation structures, and synchronization semantics. Clear definitions ensure that glucose values, alerts, device states, and contextual events retain the same meaning across platforms. Where feasible, data structures and coding approaches should leverage established health informatics standards to promote consistent interpretation across connected health information technology (IT) environments. In addition to data exchange specifications, data provenance requirements should also be defined. Interoperable systems should preserve the origin and processing history of data elements exchanged across platform interfaces, so each value can be traced to its source and every change to it can be identified. They should also preserve reconciliation state, which shows whether discrepancies between data sources have been resolved. These requirements apply to AI-derived outputs where applicable.

Maintaining the interfaces across which data are exchanged is an ongoing lifecycle responsibility. Formal interface specifications and machine-readable documentation should be actively maintained, together with API version control and backward-compatibility policies. Deprecated interfaces should be actively managed. Even when a single named standard is not specified, interfaces should be defined precisely enough to support safe implementation and verification, which ensure the interface is built and confirmed to work as specified before release. The same precision supports maintenance and change control after release, keeping the interface functional and ensuring that any modifications to it are managed safely.

Interoperability requires appropriate privacy, security, and governance controls in addition to technical mechanisms for transmitting data. Each interoperable interface should implement appropriate safeguards for authentication, authorization, access control, and data protection. These safeguards should reflect the intended use, the systems and users involved, the type of data exchanged, and applicable legal and regulatory requirements (e.g., Health Insurance Portability and Accountability Act [HIPAA] and General Data Protection Regulation [GDPR]). Recognized technical specifications (e.g., Open Authorization [OAuth] 2.0 for authorization and HL7 FHIR for data exchange) should also be used where appropriate.^{51–53,55,56,58} Where supported by applicable law, policy, and implementation standards, systems should represent and exchange consent and authorization in machine-readable form, so that receiving systems can determine whether the patient has permitted sharing and which users or systems may access the data. Systems should also exchange purpose-of-use metadata, which states why the data are being accessed. These metadata may inform access-control and disclosure decisions but do not, by themselves, establish that a use or disclosure is legally permissible. Participating entities remain responsible for determining the applicable legal basis and enforcing relevant jurisdictional, contractual, organizational, and ethical requirements.

For patient-directed sharing, systems should provide understandable and appropriate granular controls where technically feasible and consistent with the intended use and safety requirements of the interface. Controls may identify the recipient and the data types shared, which together define who receives what information. They may also specify the purpose and permitted uses, which define why the information is shared and what the recipient may do with it. Finally, controls may set a duration that limits how long the permissions remain in effect. When consent is the applicable legal basis, it should meet the requirements for valid consent. The person should give it freely, retain the right to withdraw it, and base it on a specific and informed understanding of what they are agreeing to. Their agreement should also be unambiguous.⁵⁸ Authorization processes should separately meet applicable legal and organizational requirements.

Section 9.5

Time Synchronization and Clock Integrity

Time synchronization is a core interoperability requirement, given that temporal alignment is fundamental to safe CGM operation. Glucose values, alerts, and insulin dosing depend on accurate timekeeping, as do exercise annotations, trend interpretation, time-dependent associations between variables, automated decisions, and time-dependent decision support prompts. Time integrity should therefore be addressed as a system property rather than a secondary implementation detail.

Time synchronization requires attention to erroneous local clock settings in the device, including clock drift, timestamp hierarchy, future-dated timestamps, and synchronization tolerances. Other relevant considerations include time-zone handling, daylight-saving transitions, and offline buffering. Delayed upload reconciliation should also be addressed. A timekeeping architecture should identify the authoritative source of time when timestamps differ across system elements. Validation should confirm preservation of timestamps through temporary disconnection, local storage, and transmission delays, even when later reconciled in the cloud. Finally, the system should clearly label future-dated timestamps when detected and provide a reconciliation mechanism.

Time integrity requirements apply across sensors, receivers, and mobile applications, as well as across cloud services, remote dashboards, and connected decision-support systems. These requirements aim to ensure that displayed glucose data, event and alert histories, and trend calculations remain clinically coherent throughout the ecosystem.

Section 9.6

Stress Testing

Interoperability validation should include stress testing under degraded and faulted conditions, including dropped packets, delayed transmission, and duplicated messages. Test scenarios should also include data faults, such as corrupted data and stale cached values. Potential connectivity problems should be evaluated, such as intermittent Bluetooth or Wi-Fi, partial cloud outages, and device handoffs. Testing should also consider device issues such as low battery, software-update mismatches, and intermittent sensor gaps.

Stress testing should evaluate degraded operating modes, performance of safe fallback behaviors, user notification expectations, and fail-safe transitions. The ecosystem should respond predictably when data become delayed, incomplete, or contextually invalid. It is critical that silent propagation of stale, corrupted, or misleading data does not occur. Testing should also evaluate resilience and recovery behavior following restoration of connectivity or synchronization. Recovery processes should preserve clinically coherent state transitions and should avoid oscillation, duplication, or unintended replay of data during reconnection. Testing shall verify that each component enters and maintains a defined, predictable, and risk-appropriate safe state or degraded operating mode consistent with its intended use. Such behavior may include continued local operation or transition to a preprogrammed fallback state, both of which keep the component functioning. It may also include suspending functions that depend on unavailable data while retaining that data for later synchronization. Appropriate user notification may accompany any of these responses (21 CFR 862.1356(b)(1)(vi); 21 CFR 862.1355).⁵⁹ Testing shall also verify that critical events occurring during the interruption are handled and logged appropriately and that normal operation can be restored without unsafe commands, duplicated actions, unintended replay, or loss of clinically relevant state (21 CFR 862.1356(b)(1)(vi), ISO/IEEE 11073-20601:2022).⁵⁹ Finally, testing shall verify that critical components can seamlessly transition into a predictable localized autonomous mode to ensure user safety when all interoperable communications fail completely (21 CFR 862.1356, 21 CFR 880.5730, 21 CFR 862.1355).^{59,60}

Beyond identifying hazards, interoperability should also be evaluated under representative failure and recovery conditions to verify that connected CGM ecosystems maintain safe and predictable operation during communication disruptions, software faults, and component failures. For a more detailed analysis of representative stress and recovery scenarios, expected system behaviors, and illustrative acceptance criteria, see Table 9.2.

Table 9.2 Representative Interoperability Stress and Recovery Scenarios for Connected CGM Ecosystems

Scenario	Injected condition or failure state	Expected system behavior	Illustrative acceptance criteria
Network latency	Artificial delay in transmission between CGM, app, or cloud	System identifies delayed data, preserves ordering, and avoids unsafe use of stale information	Delayed status is visible; values older than the defined threshold are flagged or restricted from safety-critical use
Packet loss	Intermittent or sustained dropped packets during transmission	System retries or degrades gracefully without creating false clinical signals	No silent corruption; no false critical alerts caused solely by packet loss; reconnection behavior is logged
Message duplication	Duplicate glucose or alert messages introduced in the data stream	System suppresses or reconciles duplicate data and preserves coherent event history	Duplicate messages do not generate duplicate alerts, duplicate trend artifacts, or duplicate downstream actions
Corrupted data payload	Altered or malformed transmitted values or metadata	System rejects, quarantines, or clearly flags invalid content	Corrupted data are not displayed as valid glucose values and do not trigger unsafe automated actions
Intermittent Bluetooth disconnection	Repeated loss and restoration of short-range connectivity	Automatic reconnection occurs when feasible; user is informed of degraded status	Connection state is visible; duplicate data or alerts do not occur during reconnection
Partial cloud outage	Loss of selected cloud functions while local device and app remain active	Local functions continue in a defined degraded mode; cloud-dependent features fail safely	Safety-critical local behaviors remain available; missing cloud services do not cause silent loss of critical user awareness
Device handoff	Transfer between receiver, phone, or other supported viewing platforms	Data continuity is preserved and time ordering remains coherent across platforms	No gaps, duplication, or misordered event history beyond predefined tolerances

Scenario	Injected condition or failure state	Expected system behavior	Illustrative acceptance criteria
Time shift or clock drift	Manual clock change, drift, or conflicting time sources	System re-establishes time coherence or flags the inconsistency for review	Misordered data are prevented or clearly identified; time correction events are traceable
Recovery after prolonged disconnection	Reconnection following extended offline operation with buffered data	Buffered data are reconciled without oscillation, replay, or misleading retrospective alerts	Reconciled data remain traceable; late-arriving data do not trigger unsafe retrospective actions
Total interoperability failure with local fallback	Complete loss of communications across interoperable components	Critical components enter a predictable localized autonomous mode with safe fallback behavior	Essential local safety functions remain available; fallback mode is clearly indicated to the user

Table 9.2 presents representative stress and recovery scenarios that can be used to structure interoperability validation in connected CGM ecosystems. The scenarios and acceptance criteria are illustrative rather than mandatory. They should be tailored to the system design, intended use, interface architecture, and safety significance of each interoperable function.

Section 9.7

Ecosystem Management

Modern CGM systems increasingly depend on a broader digital ecosystem that includes smartphones, OSs, and cloud vendors. Wearable platforms, middleware, APIs, and third-party applications are additional dependencies. Safe performance often therefore depends on components not fully controlled by a single manufacturer. Interoperability expectations should explicitly account for this broader ecosystem. Patient- and caregiver-facing materials should clearly explain which interoperable components are supported, how connections are established, and what behaviors to expect during degraded or disconnected operation.

Manufacturers should define the supported OSs and how unsupported configurations will be handled. They should specify compatibility-testing strategies and update qualification processes. Finally, they should establish change controls for app-store deployment and management of third-party dependencies. External changes that can affect safe performance should be monitored, including changes to OSs, cloud infrastructure, and external software services. Where CGM data are exchanged with an EHR or other health IT systems, ecosystem manage-

ment should also account for institutional deployment environments and standards-based interface dependencies.

When AI-enabled components participate in interoperable workflows, ecosystem management should govern model versioning and update coordination. It should also track validation dependencies and monitor AI outputs for clinically relevant changes. Distinctions between raw CGM data and AI-derived interpretations should remain transparent throughout interoperable exchanges.

Section 9.8

Interoperability Assessment

Verification should include bench testing, simulated interoperability testing, and fault-injection testing, which examine components under controlled conditions. Validation should include end-to-end workflow testing and human factors testing, which confirm that connected ecosystems work safely for their intended users. Defined minimum interoperability scenarios, prespecified acceptance criteria, and reporting expectations are core elements of interoperability assessments.

Assessment activities should be traceable to interface requirements, intended use conditions, and any relevant standards used. Where applicable, evaluation should include both intra-vendor and multi-vendor testing. Human factors activities should address interoperability tasks such as pairing, data routing, and alert interpretation. They should also assess how users reconcile delayed data, handle erroneous data (such as future-timestamped, misattributed, or corrupted data), and respond to degraded or failed connections. Preservation of clinically meaningful workflow behavior across interoperable systems should also be evaluated, with testing addressing alert escalation pathways, transitions of care, remote-monitoring workflows, and user understanding of degraded or disconnected system states. When an integrated workflow spans multiple organizations, the assessment should include joint validation and documented agreements that define roles, responsibilities, and escalation pathways. A formal joint steering committee is preferred to coordinate these activities.^{61,62}

Reporting should summarize conformance and interoperability test results, as well as known limitations that may affect safe integration or use. The assessment record should support understanding of interface-level performance and end-to-end workflow behavior. Postmarket monitoring processes should also evaluate real-world interoperability performance following deployment. Monitoring should include update-related failures, synchronization anomalies, and interoperability complaints. It should also identify emerging hazards in heterogeneous deployment environments.

Section 9.9

Compatibility and Change Management

Compatibility dependencies should be addressed explicitly, because interoperability failures often arise when ecosystem components update at different times. Some updates are under the manufacturer’s control, such as firmware, cloud backend, and AI model changes. Others come from outside parties, such as OS changes, third-party software modifications, and API revisions by partner systems. Either kind can leave components that once worked together mismatched. Compatibility hazards should be analyzed not only at the level of a single interface, but also at the level of the end-to-end clinical workflow.

Compatibility maintenance policies, semantic versioning principles, and interoperability regression testing should be established, together with expectations and delegated responsibilities for timely coordination of updates across ecosystem components. These controls complement cybersecurity and software lifecycle processes and reduce the likelihood that otherwise valid changes create unrecognized hazards in connected CGM systems. For standards-based interfaces, implementation guides, and external platform requirements, the impact of changes in underlying standards should be monitored and documented. To robustly protect the expanded attack surfaces introduced by these asynchronous changes, compatibility and security management should explicitly embed Zero Trust security principles and industry-standard authorization protocols such as OAuth 2.0.

Section 9.10

Manufacturer Checklist

Section	Task
9.2 Types of Interoperability	Define interoperability scope and interfaces: List all intended interoperable connections (device-device, device-cloud, cloud-cloud, clinician-platform, platform-EHR, software, patient-mediated). For each interface, specify purpose, intended users, and use conditions; map to iCGM/AID classifications where applicable.

Section	Task
9.3 Interoperability Risk Management	Perform interoperability-specific risk analysis: Analyze shared-system hazards, multi-component failures, and multi-vendor dependencies. Relevant hazards include cascading failures, synchronization failures, and stale data. They also include command conflicts, alert fatigue, and spoofing. Additional hazards include incorrect data attribution and credential compromise.
	Design identity, authentication, and authorization controls: Implement strong endpoint authentication and clear authorization boundaries. Address spoofed devices, unauthorized endpoints, and incorrect attribution of data/commands.
	Provide clear labeling and user-facing interoperability information: Describe intended interoperable uses, residual risks, dependencies, and limitations. List validated third parties and supported versions; explain expected behaviors in degraded/disconnected states.
9.4 Data Exchange Specifications and Interface Lifecycle Management	Specify interoperable data and interface contracts: Standardize data elements, units, and timestamps. Also standardize event annotations. Maintain interface specs, versioning, backward compatibility, deprecation, and change control.
	Implement consent and authorization metadata: Include machine-readable consent/authorization parameters with exchanged data. Use these metadata to support each participating entity's enforcement of applicable legal and ethical requirements (e.g., HIPAA, GDPR). Metadata alone do not establish legal permissibility.
9.5 Time Synchronization and Clock Integrity	Engineer time synchronization and clock integrity: Define authoritative time source and synchronization tolerances. Handle drift, time-zone changes, daylight saving, offline buffering, and delayed uploads; validate timestamp reconciliation.
9.6 Stress Testing	Conduct stress and recovery testing under conditions of increased latency, packet loss, and data corruption. Testing should also address intermittent connectivity, system outages, and communication handoffs. Low battery conditions and sensor data gaps should be evaluated. Verify degraded modes, safe fallback, and fail-safe transitions. User notifications and local autonomous operation should also be assessed.
9.7 Ecosystem Management	Define ecosystem dependencies and supported configurations: Declare supported OSs, devices, third-party components, and configurations. Plan compatibility testing, update qualification, and handling of unsupported configurations; monitor external changes.

Section	Task
9.8 Interoperability Assessment	Plan interoperability V&V: Develop a V&V plan, including bench, simulated, and workflow testing, plus fault-injection. Include human factors testing for pairing, routing, and alert interpretation. Testing should also assess user responses to delays and degraded states.
	Monitor interoperability postmarket and across organizations: Track interoperability failures, complaints, anomalies, and emergent hazards. Where workflows span organizations, maintain joint validation, incident management, and escalation agreements.
9.9 Compatibility and Change Management	Implement compatibility and change management: Use semantic versioning and interoperability regression testing. Coordinate updates across components; assess compatibility risks at interface and workflow levels.

Section 9.11

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
International Organization for Standardization/Institute of Electrical and Electronics Engineers	ISO/IEEE 11073-20701:2020 — Point-of-care medical device communication — Service-oriented medical device exchange architecture and protocol binding	Defines the service-oriented device connectivity (SDC) architecture for point-of-care device communication. Relevant when CGM data are integrated into hospital systems.
International Organization for Standardization/Institute of Electrical and Electronics Engineers	ISO/IEEE 11073-10207:2019 — Point-of-care medical device communication — Domain information and service model for service-oriented point-of-care medical device communication	Defines the information and service model for SDC. Relevant when CGM data are integrated into hospital systems.

Organization	Document	Relevance
International Organization for Standardization/Institute of Electrical and Electronics Engineers	ISO/IEEE 11073-10425:2024 — Personal health device communication — Device specialization — Continuous glucose monitor (CGM)	Specifies the normative communication protocols, data formats, terminology codes, and behaviors between CGM devices (agents) and data managers such as smartphones or personal computers.
International Organization for Standardization/Institute of Electrical and Electronics Engineers	ISO/IEEE 11073-10101:2020 — Point-of-care medical device communication — Nomenclature	Defines the standardized nomenclature and term codes for medical device communication. These codes support semantic consistency across device standards.
International Organization for Standardization/Institute of Electrical and Electronics Engineers	ISO/IEEE 11073-20601:2022 — Personal health device communication — Application profile — Optimized exchange protocol	Defines the optimized personal health data exchange protocol and application profile base architecture.
International Organization for Standardization/Institute of Electrical and Electronics Engineers	ISO/IEEE 11073-10201:2020 — Point-of-care medical device communication — Domain information model	Establishes the general domain information model used for point-of-care medical device communication.
Health Level Seven International	HL7 FHIR	Standardizes clinician-platform and software interoperability. It provides a fast, simple, and secure API-based approach to exchange electronic health data between medical computing systems and EHR platforms.
Health Level Seven International	HL7 FHIR Implementation Guide: Continuous Glucose Monitoring, STU 1 (v1.0.0), 2025	Specifies FHIR profiles for exchanging CGM summary reports and individual glucose observations between devices, apps, and EHRs.
Diabetes Technology Society	iCoDE Report: Integration of CGM Data into the EHR (2022)	Provides consensus recommendations for integrating CGM data into the EHR, including data elements, workflows, and governance.
Diabetes Technology Society	iCoDE-2 Report (2025)	Extends iCoDE to integrate data from connected insulin pumps and pens into the EHR and creates a platform for presenting both CGM and insulin pump data.

Organization	Document	Relevance
U.S. Department of Health and Human Services	HIPAA — Health Insurance Portability and Accountability Act of 1996 (Privacy Rule/Security Rule)	Establishes federal regulatory requirements for protecting the privacy, confidentiality, and security of individually identifiable health information.
European Union	GDPR (EU) 2016/679	Regulates the processing of personal data and privacy, establishing strict legal and ethical constraints on data protection across jurisdictions.
Internet Engineering Task Force	OAuth 2.0 (RFC 6749) — The OAuth 2.0 Authorization Framework	Serves as the industry-standard authorization and delegated access framework used to secure API-based access, enabling safe, patient-mediated data sharing.
U.S. Food and Drug Administration	Special Controls for Integrated Continuous Glucose Monitoring Systems (iCGM) (21 CFR 862.1355)	Defines performance, safety, interoperability, interference characterization, and risk communication expectations for iCGM systems.
U.S. Food and Drug Administration	Interoperable Automated Glycemic Controller (21 CFR 862.1356)	Defines special controls for interoperable automated glycemic controllers, including requirements for reliable data communication with connected devices.
U.S. Food and Drug Administration	Alternate Controller Enabled Infusion Pump (ACE Pump) (21 CFR 880.5730)	Defines special controls for ACE insulin pumps (product code QFG), which are designed to interact with external, digitally connected controllers, such as AID software or CGM systems, to deliver variable basal and bolus doses automatically.
British Standards Institution	PAS 2600:2025 — Continuous glucose monitoring systems. Design verification and validation of performance	Establishes minimum design verification, validation, and performance requirements for CGM — a voluntary Publicly Available Specification.

Section 9.12

Summary

CGM interoperability enables safe exchange of glucose data across devices, software, and clinical systems. It requires that data retain consistent meaning, accurate timing, and clinical integrity. Risk management should address stale data, connectivity failures, and cybersecurity threats. Manufacturers should define clear interface specifications, supported configurations, and responsibility boundaries. Validation should include end-to-end testing, stress testing, and postmarket monitoring.

Chapter 10

Study Design, Data Processing, and Statistical Framework

Included in this section:

- 10.1 STUDY POPULATION, SIZE, AND ENDPOINTS
- 10.2 MANUFACTURING LOT REPRESENTATION
- 10.3 SENSOR INSERTION AND WEAR-SITE EVALUATION
- 10.4 CLINIC SESSIONS
- 10.5 SAFETY EVALUATIONS AND STOPPING CRITERIA
- 10.6 DATA INTEGRITY
- 10.7 MANUFACTURER CHECKLIST
- 10.8 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 10.9 SUMMARY

Section 10.1

Study Population, Size, and Endpoints

10.1.1 Study Population

Pivotal accuracy and performance CGM studies intended to support regulatory submissions should enroll participants who adequately represent the heterogeneity of the intended-use population (e.g., demographic characteristics including age, sex, BMI, race, ethnicity), and these details should be reported in study documents. To ensure sufficient coverage of the claimed glucose range of the sensor, it is recommended that most study participants use insulin so that glucose can be effectively manipulated during in-clinic sessions (see Section 10.4).

All participants using insulin at baseline should have known or knowable insulin dosing parameters (e.g., insulin sensitivity/correction and carbohydrate factors) prior to enrollment, and investigators should use established methods to verify and optimize these dosing parameters to maximize participant safety and manipulation efficacy. It is best practice to confirm all planned insulin doses with participants prior to administration. Subcutaneous administration of insulin is preferred, with an appropriate experimental rationale prespecified in the protocol, although both intravenous (IV) and inhaled insulin use may be allowed where appropriate. While people with T1D are typically enrolled disproportionately to facilitate these manipulations, participants who are not using insulin may also be included in the study, depending on the intended-use population.

Table 10.1 identifies protocol decisions that should be established prospectively to ensure that a pivotal CGM performance study generates interpretable, clinically relevant, and regulatory-grade evidence.

Table 10.1 Core Design Decisions for a Pivotal CGM Performance Study

Design domain	Decision to prespecify	Purpose
Population and claims	Intended-use population, age groups, insulin use, wear sites, glucose range, and wear duration	Ensures that enrollment and analyses support the proposed indication and labeling
Reference and sampling	Comparator method, clinic-session timing, sampling frequency, and handling of rapid glucose excursions	Generates valid paired data across the reportable glucose range and rates of change
Sensor performance	Manufacturing-lot allocation, primary sensor designation, sensor-replacement rules, and wear-period analyses	Evaluates consistency, accuracy, survival, and stability over intended use

Design domain	Decision to prespecify	Purpose
Safety and conduct	Glucose-manipulation eligibility, safety monitoring, discharge criteria, adverse-event definitions, and stopping rules	Protects participants and enables consistent safety assessment
Analysis and data quality	Primary endpoints, correlated-data methods, missing-data rules, subgroup analyses, and audit-trail procedures	Produces credible, interpretable, and regulatory-grade evidence

10.1.2 Power and Sample Size

The statistical analysis plan should prespecify the success criteria and sample-size basis for each primary endpoint. Sample-size calculations should account for the applicable performance criterion or margin, expected variability, within-participant correlation among repeated matched measurements, the required distribution of observations across clinically relevant glucose ranges and wear periods, and any multiplicity or joint-success considerations. The study enrollment target should be based on the largest endpoint-specific sample-size requirement and then increased to account for anticipated attrition, missing data, and non-evaluable participants or matched observations. When study success requires all co-primary endpoints to meet their respective criteria, the probability of meeting all criteria should be considered rather than assuming that endpoint-specific power represents overall study power. The significance level, confidence level, and target power or precision should be prespecified and justified for the applicable endpoints and decision rules.

The enrolled population should be sufficient to represent the intended-use population and relevant sources of clinical and biological variability, including any age groups or other subgroups for which separate performance conclusions are planned. Applicable regulatory requirements and regulatory feedback may require enrollment or evaluable observations beyond the statistically calculated minimum. Additionally, in the U.S., studies supporting an iCGM submission shall provide robust clinical data representative of the intended-use population, measuring range, and sensor wear period (21 CFR 862.1355). For pediatric use, data should demonstrate similar accuracy and ROC performance compared with adults, unless the governing regulatory body accepts an appropriate clinical or technical justification for why pediatric data are not needed. The required study size and population composition should therefore be justified for the specific device, intended use, submission pathway, and applicable regulatory requirements and should be discussed with the relevant regulatory authority when appropriate.

10.1.3 Study Objective and Endpoints

The primary objective of a CGM pivotal study is to establish the performance (e.g., point and trend accuracy) and safety of the system. The performance of the CGM system should be evaluated by comparison to a laboratory-grade glucose measurement method that is accurate and traceable to a primary standard across

the system's claimed measuring range (typically 40–400 mg/dL [2.2–22.2 mmol/L]). In the U.S., the FDA has accepted several cleared laboratory and point-of-care instruments such as the YSI 2900c, Radiometer ABL90 FLEX PLUS, and the Nova Primary Glucose Analyzer as appropriate comparators. When these methods are not available, an appropriate near-patient analyzer with documented turnaround should be used to ensure that samples do not deteriorate before they are analyzed. A central laboratory method should be used only for traceability checks. Primary endpoints should support the intended performance claims and are generally performance and safety related. For performance endpoints, proportions of paired readings (i.e., by CGM glucose range and by comparator glucose range) meeting prespecified thresholds in clinically relevant glucose ranges should be reported (e.g., % within $\pm 20\%$ / ± 20 mg/dL [± 1.1 mmol/L] overall; % within ± 15 mg/dL [± 0.8 mmol/L] and % within ± 40 mg/dL [± 2.2 mmol/L] when < 70 mg/dL [< 3.9 mmol/L]; % within $\pm 15\%$ and % within $\pm 40\%$ when 70–180 mg/dL [3.9–10.0 mmol/L] and > 180 mg/dL [> 10.0 mmol/L]). See Chapter 6 for additional details.

Section 10.2

Manufacturing Lot Representation

Sensors used in CGM performance studies should adequately represent the full range of manufacturing release criteria for commercially distributed sensors. At least three manufacturing lots should be used for the study, with approximately equal distribution across participants, to allow for assessment of lot-to-lot variability.

Section 10.3

Sensor Insertion and Wear-Site Evaluation

10.3.1 Sensor Insertion and Blinding

CGM sensors should be inserted by the intended user according to the IFU. Study staff should provide only the same level of instruction or support that an end user would receive in typical use (e.g., help line, labeling). Any sensor insertion pain, discomfort, or bleeding should be documented. Sensors should be activated according to the IFU, and performance should be evaluated during the entire intended wear period. To minimize risks associated with taking medical action based on unknown sensor performance and to ensure participant safety, CGM systems should be blinded (i.e., glucose measurements are not available to participants or study staff throughout the study). Because CGM values are blinded, participants cannot act on CGM readings or alerts. Real-world measures collected in this study may therefore differ from unblinded use and should be interpreted with this limitation. Each participant should contribute sensor accuracy data from no more than one sensor per wear site. Sensors that fail early may be replaced if they fail before any paired accuracy data have been collected, but the tim-

ing and reason for replacement should be documented, and data from these sensors should be included in sensor survival and failure analyses. If a sensor falls off or fails after some paired accuracy data have been collected, then all paired data collected until the sensor fell off or failed should be included within the accuracy analysis and the sensor should not be replaced. If a participant has more than one device assigned for the same wear indication, then the primary device should be selected for the accuracy analysis. If the selected primary device is replaced, then the replacement sensor should become the primary device. For each comparator time point, only the designated primary device should be matched to the comparator measurement based on the blood draw time. For replacement sensors, wear time should be reset and calculated beginning at the replacement sensor's insertion time.

10.3.2 Intended Wear Sites

Because CGM performance can vary among anatomical sites, each intended wear site should be evaluated separately, and the sample size for each intended wear site should be adequate to support the validity of the data. For accuracy and survival performance analyses, only one sensor per participant per wear site should be used (i.e., a primary sensor determined *a priori*). Additional simultaneously worn sensors may be used for precision analyses but should not be treated as independent observations for primary accuracy endpoints. When multiple sensors are placed for precision measurements, sensors should be inserted to ensure appropriate time syncing for precision analyses. Additional sensors should also be included in safety analyses.

10.3.3 Sensor Removal and Insertion Site Evaluations

Sensor removals should be performed by the intended user during a designated sensor-removal visit, conducted either in-clinic or remotely. At this visit, sensor adhesion should be assessed (e.g., using a standardized scale defined within the study protocol indicating the percentage of sensor remaining adhered). Skin evaluation at each insertion site (e.g., the degree of erythema, edema, infection, pain, discomfort, or medical adhesive-related skin injury [MARSI]) should also be conducted at this visit. The clinical protocol should predefine irritation severity levels that qualify as device-related adverse events (AEs), and those events should be documented appropriately and accompanied by follow-up care when necessary. Additional recommendations related to skin evaluations are provided in Section 10.5.3.

Section 10.4

Clinic Sessions

10.4.1 In-Clinic Performance Evaluation

CGM system performance should be evaluated against a defined comparator reference method using in-clinic accuracy studies that are overseen by experienced study investigators (i.e., licensed healthcare professionals with extensive knowledge of diabetes and precise insulin dosing). At the time of enrollment, each study participant should be assigned to a fixed clinic session schedule, and study participants 6 years of age or older should be assessed for adequate venous access. Clinic sessions should be distributed across the entire intended wear period at a frequency sufficient to assess sensor stability and detect any potential drift or bias over time (e.g., the first 24 hours after warm-up, the mid-wear interval, and the end-of-wear period). Limited scheduling flexibility (e.g., ± 4 hours on the scheduled clinic day) may be allowed for participant scheduling purposes.

10.4.2 Clinic Session Safety Considerations

Vital signs (i.e., heart rate, blood pressure, and temperature) should be collected at the beginning of each clinic session to confirm that the participant can safely start the session. Baseline glucose assessment should also be obtained as part of the pre-session safety assessment. For participants undergoing glucose manipulation (described in more detail below), a ketone measurement using a point-of-care capillary beta-hydroxybutyrate meter should also be taken prior to initiating the clinic session if glucose is equal to or greater than 300 mg/dL (16.7 mmol/L) or there are symptoms of possible ketosis. Since patients typically arrive in the fasting state (where ketones are expected), the mere presence of ketones should not automatically be regarded as precluding glucose manipulation.

The facility should have the ability and training to promptly administer both oral glucose and IV glucose in the unlikely event of severe hypoglycemia. Using smaller, multiple doses of insulin can enhance both the safety and efficacy of the manipulations. Doing this safely requires investigator knowledge of insulin kinetics and experience in calculating “insulin-on-board” (i.e., residual insulin effect). Use of this methodology effectively mitigates concerns of “insulin stacking” (i.e., excessive insulin dosing). Protocols should specify safe discharge criteria for participants over a prespecified amount of time (e.g., stability of glucose levels and ketone checks if hyperglycemic).

10.4.3 Clinic Sampling Windows

Comparator measurements should be collected every 15 ± 5 minutes across the CGM system’s reportable glucose range, and sample collection should occur over periods long enough to allow for safe glucose manipulation and to ensure enough samples are collected to evaluate the sensor’s ability to accurately measure during ROCs. More

frequent sampling (e.g., every 5–7 minutes) during rapid glucose excursions or extremes (e.g., <70 mg/dL [<3.9 mmol/L] or ≥ 300 mg/dL [≥ 16.7 mmol/L]) may be appropriate to collect sufficient data to meet endpoints or to maintain participant safety, though variability in measurement frequency can limit comparability across studies. Accordingly, deviations should be minimized and documented, as sampling frequency will affect certain analyses (e.g., ROC).

10.4.4 Glucose Manipulation

To evaluate the CGM system trend accuracy over different ROCs, study participants' glucose should be manipulated during specified in-clinic sessions. Only participants on intensive insulin therapy should undergo glucose manipulation during a study; there should be no deliberate attempt to manipulate glucose levels for participants on non-intensive insulin therapy or non-insulin therapy, or for young pediatric participants (e.g., aged <11 years). Similarly, pregnant participants should not undergo glucose manipulation, but data from a clinically indicated oral glucose OGTT, such as for GDM screening, may be used.

Study investigators or qualified personnel should be present while study participants' glucose is manipulated, and study protocols should prespecify strategies to obtain a wide range of glucose values and different ROCs through controlled glucose manipulation (i.e., raising or lowering glucose through food with insulin delay or insulin with food delay, respectively). Study protocols should provide specific guidelines for the scope of glucose manipulation during clinic sessions. For example, study participants' glucose may be manipulated to either a hypoglycemic or a hyperglycemic range within one clinic session, or to both ranges within a clinic session, if safe.

Study protocols should specify criteria for safe start of manipulations, criteria for monitoring manipulations to ensure continued safety, and guidance for safe discharge (e.g., stability of glucose levels and ketone checks if hyperglycemic). In each safety scenario, protocols should specify required assays (i.e., glucose, ketones) and thresholds for action. Protocols should provide sufficient flexibility to the investigator both to ensure participant safety and to respect a participant's right to decline a glucose manipulation procedure or withdraw from study participation at any time. An example of a safe and effective glucose manipulation protocol is provided in Chapter 13.

For studies conducted in the United States, Category 2 of the 1998 Office for Human Research Protections (OHRP)/FDA Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure defines blood-collection criteria for expedited review. For healthy, nonpregnant adults weighing at least 110 lb (50 kg), collection may not exceed 550 mL per 8-week period. For other adults and children, it may not exceed the lesser of 50 mL or 3 mL/kg per 8-week period. Collection may not occur more than twice per week. These limits are not absolute maximums for all research. Expedited review also requires no more than minimal risk. Protocols exceeding these limits require review by a convened IRB and justification for the additional blood volume. More restrictive local IRB, ethics committee, or institutional requirements should be followed. For studies longer than 8 weeks, collection should be scheduled so that the applicable limits are not exceeded in any 8-week period.

10.4.5 Real-World Home-Use and Device Performance

Although at-home accuracy evaluation using SMBG as the reference method is not typically used to support regulatory decisions, it may be included to supplement in-clinic accuracy data. However, at-home SMBG data should be analyzed separately and not pooled with primary accuracy data pairs. One scenario in which at-home SMBG may be acceptable to include in a regulatory submission is for young pediatric participants under the age of 6.

Real-world device performance may also be characterized using data collected under intended-use conditions as part of the study protocol. Such characterization, if conducted, should include:

- Frequency and duration of signal loss;
- Adherence to calibration schedules (if applicable);
- Participant-initiated sensor replacements;
- Sensor discontinuation rates; and
- The influence of exercise, illness, sleep, and routine daily activities on signal reliability.

Section 10.5

Safety Evaluations and Stopping Criteria

10.5.1 Safety Monitoring Procedures

Study protocols shall specify study procedures for monitoring participant safety from enrollment through the protocol-defined safety follow-up period in accordance with applicable regulatory requirements (e.g., 21 CFR 812) and Good Clinical Practice (GCP) (International Council for Harmonisation [ICH] E6(R3)). Safety assessments should be prespecified within a study protocol and should include the collection, evaluation, documentation, and follow-up of AEs, device deficiencies, and other safety-related events. The protocol should also define methods for assessing event severity and causality (e.g., any relationship to the investigational device, study procedures, or underlying disease). Safety events should be reported by investigators, sponsors, and other responsible parties in accordance with applicable regulations, ethics committee/IRB requirements, sponsor procedures, and study-specific reporting plans.

Manufacturers should systematically document insertion-site-related AEs. Inflammatory and irritative events include irritation, inflammation, and discomfort or pain. Infectious and allergic events include infection and allergic responses. Traumatic and hemorrhagic events include bleeding and hematoma. Skin reactions should

be graded using standardized assessment scales, infections and allergic responses should be tracked and characterized, and the frequency and severity of all insertion-site AEs should be reported in clinical study reports and product labeling, as appropriate.

10.5.2 Definition and Scope of Adverse Events

The protocol shall define AEs and serious adverse events (SAEs) in accordance with applicable GCP and medical device investigation requirements (e.g., ICH E6(R3), ISO 14155, and applicable regulations). An AE is any unfavorable or unintended medical occurrence that arises or worsens during the study period, regardless of its relationship to the investigational device or study procedures. An SAE is an AE that meets predefined seriousness criteria, such as death, a life-threatening event, hospitalization, significant disability, or another medically important event. All AEs and SAEs should be documented and assessed for seriousness, severity, clinical significance, and causal relationships using methods defined in the protocol.

10.5.3 Device-Related Adverse Events

Device-related AEs include clinically meaningful local reactions at the sensor insertion or adhesive sites. Examples include:

- Excessive bleeding, hematoma, or significant insertion site pain;
- Erythema or edema meeting predefined severity thresholds (e.g., ≥ 3 on the Draize scale⁶³);
- MARSI, including skin tearing, maceration, blistering, or excoriation;
- Local infection, including cases with visible pus or large pustules; or
- Retained sensor fragments after removal.

Any device-related AEs shall be recorded, evaluated, and followed until they are resolved or determined stable by procedures defined within the study protocol (e.g., by the study investigator) (21 CFR 812).

10.5.4 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect is novel in nature, severity, or incidence compared with the investigational plan and known device profile. Study protocols shall also specify that if a UADE is determined to present an unreasonable risk to subjects, then the study or parts of the study presenting the identified risk shall be terminated as soon as possible (21 CFR 812).

10.5.5 Stopping Criteria

Study protocols shall include explicit stopping criteria both for individual participants and for the entire study and shall include a participant’s decision to exit the study (ICH E6(R3)).

Section 10.6

Data Integrity

The manufacturer is responsible for ensuring that all trial data are accurate, complete, consistent, and reliable throughout the trial data lifecycle. The data shall be attributable, legible, contemporaneously recorded, original (or a true copy), and accurate (ALCOA) (ICH E6(R3)).

The data reported on the Case Report Form (CRF) shall be derived from the source data. All discrepancies should be explained (ICH E6(R3)). Audit trails shall be maintained for change and correction to the data reported in the CRF or electronic systems (ICH E6(R3)). If electronic data systems are used, then attributability, reliability, consistency, and logic of the data entered shall be ensured, and any changes shall be documented, without deletion of entered data (ICH E6(R3)). A security system shall be used to prevent any unauthorized access to the data, and there should be adequate backup, retention, and retrievability of data (ICH E6(R3)).

Section 10.7

Manufacturer Checklist

Section	Task
10.1 Study Population, Size, and Endpoints	Ensure the study population is representative of the intended-use population, sample size is adequately powered for all primary endpoints, and primary performance endpoints are prespecified and supported by an appropriate comparator method.

Section	Task
10.2 Manufacturing Lot Representation	Include at least three manufacturing lots with approximately equal participant distribution to evaluate lot-to-lot variability; lots should adequately represent the full range of manufacturing release criteria for commercially distributed sensors.
10.3 Sensor Insertion and Wear-Site Evaluation	Evaluate sensor performance over the full intended wear period, document insertion/removal site outcomes, and assess each intended wear site separately.
10.4.1 In-Clinic Performance Evaluation	Conduct clinic sessions throughout the wear period using a validated laboratory-grade comparator method to assess accuracy, stability, and sensor drift.
10.4.2 Clinic Session Safety Considerations	Implement prespecified safety monitoring procedures, including vital signs, glucose assessment, ketone checks when appropriate, and safe discharge criteria.
10.4.3 Clinic Sampling Windows	Obtain comparator glucose measurements at predefined intervals sufficient to evaluate performance across the reportable glucose range and during glucose excursions.
10.4.4 Glucose Manipulation	Use protocol-defined glucose manipulation procedures to achieve a broad range of glucose values and ROCs while maintaining participant safety.
10.4.5 Real-World Home-Use and Device Performance	Characterize real-world device performance, including signal loss, calibration adherence, and sensor replacements. Also assess sensor discontinuations and the effects of daily activities.
10.5.1 Safety Monitoring Procedures	Monitor, classify, document, and report all AEs, SAEs, and UADEs throughout the study.
10.5.3 Device-Related Adverse Events	Evaluate and document insertion-site and adhesive-related AEs, including severity, causality, and resolution status.
10.5.4 Unanticipated Adverse Device Effects	Establish procedures for identifying, reporting, and responding to UADEs, including study termination if unacceptable risk is identified.
10.5.5 Stopping Criteria	Define participant-level and study-level stopping criteria within the protocol before study initiation.

Section	Task
10.6 Data Integrity	Ensure all study data comply with ALCOA principles, maintain complete audit trails, and implement controls for data security, backup, retention, and traceability.

Section 10.8

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
U.S. Department of Health and Human Services (Office for Human Research Protections [OHRP]) and U.S. Food and Drug Administration (FDA)	Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure, Category 2 (63 FR 60364; November 9, 1998)	Defines blood-collection volume and frequency criteria for eligibility for expedited IRB review.
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	ICH E6(R3) — Good Clinical Practice	Details the ethical, scientific, and quality standards for the conduct of clinical trials involving human participants.
U.S. Food and Drug Administration	21 CFR 812 — Investigational Device Exemptions	Establishes requirements for investigational device studies, including safety monitoring and reporting of UADEs.
International Organization for Standardization	ISO 14155:2026 — Clinical investigation of medical devices for human subjects — Good clinical practice	Specifies the design, conduct, recording, and reporting of clinical investigations to assess the safety and performance of medical devices in human subjects.

Section 10.9

Summary

This chapter provides guidance for designing and conducting CGM clinical studies, including participant selection, sample size, study endpoints, and use of appropriate RG methods. This chapter recommends evaluating sensor performance across the full wear period, using different manufacturing lots, characterizing all intended insertion/wear sites, and utilizing controlled in-clinic glucose challenges (i.e., glucose manipulation) to characterize the full range of the CGM. The chapter also emphasizes participant safety, accurate AE reporting, and strong data integrity practices to ensure reliable and trustworthy study results.

Chapter 11

Quality Systems, Usability, Labeling, and Lifecycle Management

Included in this section:

- 11.1 INTRODUCTION
- 11.2 QUALITY MANAGEMENT SYSTEM
- 11.3 RISK MANAGEMENT
- 11.4 DESIGN CHANGE CONTROL AND CONFIGURATION MANAGEMENT
- 11.5 TOTAL LIFECYCLE ACTIVITIES
- 11.6 HUMAN FACTORS AND USABILITY
- 11.7 LABELING
- 11.8 END-OF-LIFE PLANNING
- 11.9 MANUFACTURER CHECKLIST
- 11.10 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 11.11 SUMMARY

Section 11.1

Introduction

This chapter defines the foundational expectations for establishing and maintaining a robust, lifecycle-based framework for CGM systems, including iCGM systems marketed in the U.S. under 21 CFR 862.1355. It draws on internationally recognized standards, including ISO 13485, ISO 14971, IEC 62304, and IEC 62366-1. Where U.S. requirements apply, the chapter also addresses the Quality Management System Regulation (QMSR; 21 CFR Part 820), which incorporates ISO 13485 requirements. It outlines how manufacturers should implement and integrate quality system processes, usability engineering, and labeling controls to ensure that iCGM devices are safe, effective, and fit for their intended use across diverse user populations and real-world conditions (QMSR). References to iCGM special controls apply to devices seeking or holding iCGM classification in the U.S.; all other requirements in this chapter apply to CGM systems generally.

In addition to core regulatory expectations, this chapter addresses total product lifecycle management, including disciplined change control, continuous risk evaluation, and the incorporation of real-world performance data to sustain compliance over time.

Section 11.2

Quality Management System

A QMS is a structured framework of policies, processes, and procedures that ensures the consistent design, development, production, and maintenance of a CGM in compliance with regulatory requirements, as outlined in FDA's QMSR and ISO 13485:2016. For CGM systems, software is a safety-critical part of sensing and alerting.⁶⁴ Manufacturers shall establish and maintain software lifecycle processes in accordance with QMSR/ISO 13485 and IEC 62304. Software lifecycle activities should include the following six activities: 1) development, 2) verification, 3) validation, 4) release, 5) maintenance, and 6) retirement.

For CGM manufacturers, a robust QMS is critical to ensure that patients with diabetes can safely and effectively interact with the device across the breadth of use environments. These can include extreme temperatures, moisture, and lighting variability.^{65,66}

Core components of a QMS should include:

- Document and Record Control: Systems to create, approve, change, and archive controlled forms and data;
- Risk Management: Ongoing process (per ISO 14971) to identify, evaluate, and mitigate device risks throughout the lifecycle;

- Design and Development Controls: Formal planning, verification, validation, and design transfer stages;
- Supplier Quality Management: Evaluation, qualification, and monitoring of external vendors and components; and
- Production and Process Controls: Validated manufacturing processes, environmental controls, and equipment calibration.

A well-designed QMS supports compliance with applicable global medical device regulations. It also delivers broader operational value by safeguarding patient safety, enhancing product quality, and fostering trust among stakeholders.

Section 11.3

Risk Management

Risk management activities are tightly integrated with the QMS to ensure that the CGM system performs safely and reliably across its lifecycle. Activities should follow a structured process consistent with ISO 14971, including a documented risk management plan that defines risk acceptability criteria for the development, manufacturing, and postmarket phases.

Risk management shall address:

- Product design;
- Manufacturing and assembly processes; and
- User workflows and interactions (ISO 14971).^{67,68}

Activities include identifying hazards and their associated harms. Mitigations are then implemented to reduce risk.

11.3.1 Hazard Identification and Control

Hazard identification should be conducted early and iteratively using a multidisciplinary team (e.g., engineering, human factors, clinical, quality, regulatory). Analysis shall consider intended use and user workflows to identify potential hazards and prioritize risks (ISO 14971).

Risk control shall follow a hierarchical approach:

- Inherently safe design (eliminate hazards where possible);

- Protective measures (e.g., system safeguards, alerts); and
- Information for safety (labeling, instructions, training) (ISO 14971).

Outputs from risk analysis should inform:

- Product design;
- Labeling and training content;
- V&V activities;
- Manufacturing processes;
- Post-production activities (ISO 14971); and
- PMS activities.

11.3.2 Risk Analysis Methods

Structured methods such as Failure Modes and Effects Analysis (FMEA) and Fault Tree Analysis (FTA) can be used to identify harms and define mitigations. FMEA is an inductive method used to identify potential failure modes, evaluate their effects on system performance and patient safety, and prioritize risk controls. Within the ISO 14971 framework, FMEA supports:

- Identification of failure modes at component, subsystem, and system levels;
- Analysis of cause-effect relationships leading to hazardous situations;
- Estimation of risk based on severity and probability; and
- Prioritization and verification of risk controls.

When utilized, FMEA should be initiated during early design and maintained throughout the product lifecycle, with outputs documented in the risk management file. Table 11.1 summarizes how FMEA supports each phase of the ISO 14971 risk management process, from early hazard identification through PMS.

Table 11.1 Role of FMEA in Risk Management Phases

Risk Management Phase	Role of FMEA
Risk Analysis	Identify failure modes and associated hazards
Risk Evaluation	Support estimation of risk (severity × probability)

Risk Management Phase	Role of FMEA
Risk Control	Drive identification and prioritization of mitigations
V&V	Confirm effectiveness of implemented controls
Production/Post-Launch	Update with field data and emerging failure modes

FTA is a deductive method used to identify and evaluate combinations of faults that may lead to a defined hazardous event. Within the framework of ISO 14971, FTA complements inductive methods by enabling:

- Identification of multi-point failures and latent conditions;
- Evaluation of system-level interactions (hardware, software, usability);
- Estimation of hazardous event probability (quantitative or semiquantitative); and
- Verification of risk control effectiveness, particularly for critical safety functions.

FTA is particularly suited for complex, software-driven, and interconnected systems, including AI-enabled and networked devices. Guidance on data quality for quantitative analysis may be referenced in ISO/TR 24971.

11.3.3 Risk Control Measures

Risk control measures shall be defined and implemented throughout the product lifecycle. Their effectiveness shall be verified in the product’s design and software, in the labeling and training provided to users, and in the manufacturing processes (ISO 14971, ISO 13485, IEC 62304, IEC 62366-1). Key risk-control domains include cybersecurity, wear-site considerations, and biocompatibility. Safe integration with AID systems should also be addressed.

Any user-facing controls identified through use-related risk analysis classified as critical tasks should be validated in the human factors validation study (IEC 62366-1, FDA Human Factors Guidance).^{67,68} All risk controls shall be traceable from the risk management file to design-related controls and verified or validated to demonstrate effective risk mitigation, appropriate to the safety classification defined in risk management activities and inclusive of end-to-end software performance (ISO 14971).

11.3.4 Risk Management Report

The Risk Management Report provides a comprehensive summary of the CGM risk management process in accordance with ISO 14971, integrating hazards related to hardware, software, cybersecurity, and usability. For iCGM systems, it should demonstrate alignment with iCGM special controls, including impacts on accuracy, alerts, data integrity, and interoperability. In accordance with ISO 14971, the Risk Management Report shall:

- Confirm completion of planned risk management activities;
- Summarize hazard identification, risk evaluation, and risk controls;
- Justify overall residual risk relative to intended use and clinical benefit; and
- Define postmarket monitoring activities.

Section 11.4

Design Change Control and Configuration Management

During product development activities, change control and version governance shall be maintained as part of QMS adherence (ISO 13485). This is inclusive of configuration management to control software versions, released configurations, and traceability between requirements, risk controls, verification activities, and releases. Manufacturers should maintain an SBOM, manage software anomalies through risk-based processes, and implement appropriate supplier controls contributing to and maintaining any aspects of the product software system.

All postmarket modifications to a CGM system shall be governed by a documented design and change-control process within the QMS (ISO 13485, ISO 14971, IEC 62304). Each modification shall be formally specified, risk-assessed, and reviewed prior to release (QMSR, ISO 13485). The manufacturer shall evaluate the potential impact of the change on analytical performance (including accuracy, precision, and bias), ROC calculations, alert generation and timing, data integrity, interoperability, cybersecurity, and clinical interpretation, in accordance with CGM performance and safety requirements (QMSR, ISO 13485).⁶⁹

Verification and, as applicable, validation activities shall be predefined based on change impact and shall demonstrate continued compliance with applicable iCGM special controls (ISO 13485, QMSR, 21 CFR 862.1355). Methods may include software verification, bench and in vitro testing across the intended glucose range, evaluation using characterized datasets, and clinical performance assessment, as appropriate.

Any modification with a reasonable likelihood to affect glucose values, trend information, or alert behavior shall be evaluated across intended use conditions and demonstrate that performance meets applicable CGM acceptance criteria (QMSR).⁶⁹ Comparative analyses to the previously cleared version should use prespecified statistical methods to support conclusions of equivalence, non-inferiority, or improvement.

All changes shall be documented within the design and development file with traceability to design inputs and risk controls (QMSR). Version-specific documentation should include the change description, risk classification, V&V evidence, and assessment of impacts to labeling and user-facing functionality. This documentation may support ongoing compliance and regulatory submissions, as required.

Section 11.5

Total Lifecycle Activities

To ensure continued safety and effectiveness, the manufacturer shall implement PMS, systematically analyzing complaints, nonconformance, and real-world performance (QMSR, ISO 13485). For iCGM systems, this includes monitoring performance relative to iCGM special controls (e.g., accuracy, alerts, data integrity, interoperability, cybersecurity). Identified signals shall be evaluated using a risk-based approach to determine the need for Corrective and Preventive Action (CAPA), with implementation and effectiveness verification to ensure sustained product quality and performance (QMSR, ISO 13485).

11.5.1 Postmarket Surveillance

PMS shall be implemented in accordance with QMSR to systematically collect and analyze real-world data and detect safety signals (QMSR, ISO 13485).^{65,66} For iCGMs, PMS shall demonstrate continued compliance with iCGM special controls (21 CFR 862.1355).

PMS shall integrate complaint handling and nonconformance control as primary inputs. Events shall be risk-triaged, investigated, and trended using statistically valid methods, with linkage to iCGM accuracy criteria in Table 6.6 (QMSR, 21 CFR 862.1355(b)(1)(v)). Where applicable, safety signals should be communicated as specified under the Medical Device Reporting regulations.

PMS activities shall include:

- Evaluating real-world performance (e.g., field studies, registries as applicable);
- Monitoring for changes in performance across lots, versions, and time;¹⁹
- Maintaining version control, with risk-based re-verification and revalidation for updates;
- Trending complaints and nonconformances statistically;
- Implementing CAPA and escalation processes; and
- Tracking AEs and deficiencies. These may include inaccurate readings, missed alerts, and connectivity issues. They may also include wear-site or biocompatibility reactions and cybersecurity incidents (QMSR).

PMS outputs shall feed into risk management and change control, with reassessment of risks and implementation of corrective actions as needed (QMSR). Activities can be defined in a PMS Plan, and findings can be captured in a periodic PMS Report, with full traceability to support regulatory review and continuous improvement.

11.5.2 Corrective and Preventive Action and Effectiveness Assessments

CAPA shall be implemented to correct existing issues and prevent recurrence (ISO 13485, QMSR).

Quality data should be evaluated using a risk-based approach to determine whether CAPA is required. CAPA shall be initiated when that evaluation identifies the need for systemic corrective action, recurrence prevention, or verification of effectiveness (ISO 13485, QMSR). Quality data evaluated may include:

- Complaint trends (ISO 13485:2016, clause 8.2.2);
- Nonconformances (ISO 13485:2016, clause 8.3);
- PMS signals (ISO 13485:2016, clauses 8.2.1 and 8.4);
- Audit findings or process deviations (ISO 13485:2016, clauses 8.2.4, 8.2.5, and 8.4); and
- Field performance issues (e.g., accuracy drift, missed alerts, connectivity failures).

Triggers include repeated events, high-severity risks, and systemic issues. They also include any signal indicating potential degradation of iCGM performance or safety. CAPA outputs should be traceable to risk management, design controls, and iCGM performance requirements. Regulatory reporting and field actions (e.g., corrections or recalls) shall be conducted as required (21 CFR 803, 21 CFR 806).

Section 11.6

Human Factors and Usability

Human factors engineering should be integrated throughout product development in accordance with IEC 62366-1, ANSI/AAMI HE75, and FDA Human Factors Guidance. These activities should ensure the CGM supports safe and effective use and aligns with CGM special controls, particularly for usability, labeling, and alert performance.⁷⁰

Human factors engineering systematically evaluates user perception, cognition, and physical interaction with the CGM system to identify and mitigate use-related risks across all stages of use.^{67,68} This includes consideration of diverse user populations, such as children, pregnant women, and older adults, who may have varying cognitive, physical, sensory, and situational needs that influence safe and effective device use.⁷¹

Usability risks and potential hazards should be identified at key product-user interaction boundaries (e.g., sensor insertion, activation, calibration where applicable, data interpretation, and response to alerts) and documented within the usability engineering file. These risks should be addressed through a combination of design solutions, labeling, and user training. Inherently safe design should take priority where feasible. Use-related risk analysis should define critical tasks associated with higher-severity hazards, which should be evaluated and validated to

ensure that all intended users can correctly understand system outputs and safely interact with the device across realistic use conditions (FDA Human Factors Guidance).

Table 11.2 below shows examples of interaction boundaries and the user experience risks associated with them. It also indicates where these risks should be documented within the design and development file.

Table 11.2 Usability Risks and Documentation

No.	Interaction Boundary	Human Factors Risk	Risk Documentation
1	Human–Device	Insertion, Wear	Use-Risk and Clinical Risk
2	Human–Software Interface	Interpretation, Action	Use-Risk
3	Human–Algorithm	Trust, Reliance	Use-Risk
4	System–System	Interoperability	Use-Risk and System Failure Modes

Use-related risk analysis shall evaluate potential use errors such as misinterpretation of data, missed or inappropriate response to alerts, incorrect calibration, and insertion errors (IEC 62366-1, FDA Human Factors Guidance). Tasks associated with high-severity hazards shall be defined as critical tasks (FDA Human Factors Guidance).^{72,73} A critical task is a user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care.

Use-related risk analysis is a core integration point between human factors engineering and risk management. Table 11.3 below highlights the human factors activities specified in IEC 62366-1, use-related risk outputs, and alignment with ISO 14971.

Table 11.3 Human Factors Integration with Risk Management

Usability Engineering Phase	ISO 14971:2019		
	IEC 62366-1 Subclauses	Mapping	Primary Deliverable
1. Context and Use Error Identification	Prepare Use Specification (5.1), Identify User Interface (UI) characteristics related to safety and potential Use Errors (5.2)	Intended use (5.2), Safety characteristics (5.3)	CGM System Use Specification, list of potential Use Errors

Usability Engineering Phase	IEC 62366-1 Subclauses	ISO 14971:2019 Mapping	Primary Deliverable
2. Hazard Analysis and Scenario Mapping	Identify known or foreseeable Hazards and Hazardous Situations (5.3), Identify and describe Hazard-Related Use Scenarios (HRUS) (5.4)	Hazards (5.4), Sequences of events (5.4), Severity (5.5)	Use-Related Hazards, HRUS
3. Scenario Prioritization and Planning	Select HRUS for Summative Evaluation (5.5), Establish UI Evaluation plan (5.7)	Risk evaluation (5.5, 6), verification and validation planning	HRUS Selection, UI Evaluation Plan
4. User Interface Specification and Iterative Design	Establish UI Specification (5.6), Perform UI design, implementation, and Formative Evaluation (5.8)	Risk control design, implementation, and verification (7.1, 7.2)	UI Specification, Formative Evaluation Records
5. Final Validation and Residual Risk	Perform Summative Evaluation of UI Usability (5.9)	Residual risk evaluation (7.3), Overall residual risk (8)	Summative Evaluation Records, Residual Risk Assessment

Formative studies should identify and evaluate safety-critical tasks (e.g., sensor insertion, activation, calibration if applicable, data interpretation, alert response, and error handling) and overall usability across representative use environments.^{67,68} Studies should include intended user populations with diverse physical, cognitive, and sensory capabilities and assess whether design, algorithms, alerts, and instructions adequately mitigate use-related risks.

Summative (validation) testing shall evaluate the final design and labeling, confirming that critical tasks can be performed safely and that information is correctly understood (IEC 62366-1, ANSI/AAMI HE75). Testing should demonstrate that mitigations are effective and that observed use errors do not result in unacceptable clinical risk. Residual risks identified during validation shall be documented in the risk management file and addressed in labeling, warnings, and user instructions (ANSI/AAMI HE75).

Section 11.7

Labeling

Labeling shall be designed for safe and effective use (21 CFR 801, IEC 62366-1). Content should use clear, concise language, appropriate health literacy, readable formatting, and visual aids, with reinforcement in device interfaces where applicable.^{67,68}

Labeling should include:

- Intended use and user populations;
- Contraindications, warnings, and precautions;
- Setup, operation, and calibration (if applicable);
- Interfering substances;
- Safe use conditions (e.g., wear duration, storage, handling); and
- Key performance characteristics.

Additional elements may include troubleshooting, customer support, cybersecurity instructions, and EMC information. Devices should include manufacturer identification and a unique device identifier. Standardized symbols (e.g., ISO 15223-1) may be used with appropriate references.

Patient-facing labeling content shall include IFU and CGM performance characteristics, including a description of the sensor performance data for each intended-use population and an overview of the study design (21 CFR 801). For iCGMs, the following is required per special controls listed in 21 CFR 862.1355:

- A description of the accuracy in the following BG concentration ranges: less than 54 mg/dL (3.0 mmol/L), 54 mg/dL to less than 70 mg/dL (3.0 to 3.9 mmol/L), 70 to 180 mg/dL (3.9 to 10.0 mmol/L), greater than 180 to 250 mg/dL (10.0 to 13.9 mmol/L), and greater than 250 mg/dL (13.9 mmol/L);
- A description of the accuracy of positive and negative ROC data;
- A description of the frequency and duration of gaps in sensor data;
- A description of the true, false, missed, and correct alert rates and a description of the available glucose concentration alert settings, if applicable; and
- A description of the observed duration of CGM life for the device, including sensor wear duration.

Additional summaries of clinical studies may be provided in labeling where appropriate. Human factors engineering should address labeling and IFU that function as risk controls, consistent with FDA Human Factors Guidance, IEC 62366-1, and ANSI/AAMI HE75. Labeling associated with critical tasks should be included in

human factors validation, as applicable. Structured usability evaluation of CGM systems can identify labeling-related use errors and inform improvements to the user interface (UI), IFU, and training.^{67,68} Observed use errors and comprehension failures should be analyzed to determine their causes and whether changes to the device design, UI, labeling, or training are needed. Changes affecting critical tasks should be evaluated, with additional validation performed where warranted and remaining risks documented through the applicable risk management process.

Section 11.8

End-of-Life Planning

A CGM manufacturer should develop a plan to manage the end-of-life phase for a device, considering decommissioning, disposal, and environmental impact of hardware and software components. Key considerations include:

- Ensuring the safe removal and disposal of components (e.g., biohazardous sensors), with controls to prevent patient harm and maintain data integrity;
- Evaluating the environmental impacts of materials, packaging, and disposal;
- Evaluating impact and notification of any cloud and supplier services; and
- Notifying users and regulators of device retirement, residual risks, and any updates to labeling/IFU with traceability maintained in QMS records.

ISO 14040 can be referenced for further environmentally responsible end-of-life planning considerations.

Manufacturers should define and communicate support periods for product versions, including anticipated end-of-support and end-of-life dates. Retired and unsupported versions should be clearly identified, and users should be informed of any limitations on software updates, cybersecurity support, technical support, or other manufacturer services. End-of-support planning should address vulnerability monitoring and risk assessment, user notification, migration or replacement options, secure decommissioning, and appropriate controls for devices that remain in service. Although routine updates and support may cease after the communicated end-of-support date, newly identified vulnerabilities should be evaluated and addressed in accordance with their potential safety impact, applicable regulatory requirements, and the manufacturer's established cybersecurity risk-management procedures. Appropriate actions may include security updates where feasible, compensating controls, safety communications, migration or replacement, or other corrective actions.

Section 11.9

Manufacturer Checklist

Section	Task
11.2 Quality Management System	Establish, document, and implement a QMS with defined management responsibility, roles, and oversight.
	Integrate and consistently apply design, production, and process controls.
	Implement and conduct risk-based CAPAs and verify the outcomes.
	Demonstrate audit readiness with complete and traceable documentation (e.g., medical device file, design and development file).
11.3 Risk Management	Follow ISO 14971, a recognized risk management framework.
	Identify and address CGM-specific hazards, including accuracy, alerts, data integrity, interoperability, and cybersecurity.
	Implement risk controls through design, safeguards, and labeling.
	Justify any residual risk relative to the clinical benefit.
11.4 Design Change Control and Configuration Management	Maintain configuration management of software versions, released configurations, and the SBOM.
	Specify, risk-assess, and review every postmarket change before release.
	Evaluate change impact on accuracy, ROC, alerts, data integrity, interoperability, cybersecurity, and clinical interpretation.
	Predefine V&V based on change impact to show continued compliance with iCGM special controls.
	Document changes in the design and development file with traceability to design inputs and risk controls.

Section	Task
11.5 Total Lifecycle Activities	Define the CAPA process.
	Ensure that CAPA inputs include complaints, nonconformances, and PMS signals.
	Monitor and trend real-world performance to detect issues (e.g., accuracy, drift, alert failures, connectivity).
	Document root cause analysis and effectiveness verification.
	Ensure that CAPA actions are traceable to design/process updates and validated, and that compliance is maintained.
11.6 Human Factors and Usability	Identify critical tasks through use-related risk analysis (e.g., insertion, calibration, alert response).
	Conduct formative studies and make design improvements based on findings.
	Evaluate the final design through summative validation in realistic environments with representative users.
	Demonstrate through summative validation that critical tasks are performed safely and effectively, including correct interpretation of glucose values, trends, and alerts.
	Confirm during summative validation that foreseeable use errors, including those involving interoperable system interactions, do not create unacceptable risk.
11.7 Labeling	Clearly define intended use and user populations (21 CFR 801).
	Disclose iCGM performance: accuracy by range, trend accuracy, alert performance, data gaps, and sensor wear duration.
	Validate critical tasks mitigated with labeling through human factors summative testing to ensure correct understanding and safe user action.

Section	Task
11.8 End-of-Life Planning	Plan for the safe removal and disposal of components (e.g., biohazardous sensors).
	Identify environmental impacts of materials and processes.
	Notify users and regulators of device retirement, residual risks, and any updates to labeling/IFU.

Section 11.10

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
Association for the Advancement of Medical Instrumentation	ANSI/AAMI HE75 — Human Factors Engineering — Design of Medical Devices	Provides practical human-factors design guidance for safe and effective CGM user interactions.
U.S. Food and Drug Administration	Applying Human Factors and Usability Engineering to Medical Devices (FDA, 2026)	Provides FDA recommendations for use-related risk analysis, critical tasks, and usability testing of CGM systems.
U.S. Food and Drug Administration	21 CFR 820 — Quality Management System Regulation	Establishes QMS requirements supporting controlled CGM design, production, CAPA, complaint handling, and records.
U.S. Food and Drug Administration	21 CFR 803 — Medical Device Reporting	Establishes requirements for reporting qualifying CGM adverse events and malfunctions to FDA.
U.S. Food and Drug Administration	21 CFR 822 — Postmarket Surveillance	Provides FDA authority to require postmarket surveillance for certain devices.
U.S. Food and Drug Administration	21 CFR 801 — Medical Device Labeling	Establishes U.S. labeling requirements for CGM intended use, instructions, warnings, and performance information.

Organization	Document	Relevance
U.S. Food and Drug Administration	21 CFR 862.1355 — Integrated continuous glucose monitoring system	Establishes iCGM classification and device-specific special controls for safety, performance, labeling, and interoperability.
International Electrotechnical Commission	IEC 62304 — Medical device software — Software life cycle processes	Defines lifecycle requirements for the development and maintenance of medical device software.
International Electrotechnical Commission	IEC 62366-1 — Medical devices — Application of usability engineering to medical devices	Defines a usability-engineering process for identifying and mitigating CGM use-related risks.
International Organization for Standardization	ISO/TR 24971 — Guidance on the application of ISO 14971	Provides practical guidance on how to develop risk-management documentation.
International Organization for Standardization	ISO 13485 — Quality Management Systems	Specifies QMS requirements for CGM design, production, and validation. It also addresses supplier controls and CAPA.
International Organization for Standardization	ISO 14040 — Life Cycle Assessment	Provides a framework for considering environmental impacts across the CGM product lifecycle, including disposal.
International Organization for Standardization	ISO 14971 — Application of risk management to medical devices	Provides a framework for identifying, controlling, and monitoring CGM risks throughout the product lifecycle.

Section 11.11

Summary

This chapter provides a framework for the development, maintenance, and retirement of CGM systems. It sets requirements for quality management, risk management, and software lifecycle processes. It also addresses human factors engineering and labeling, which help users operate the device safely and effectively. It also requires PMS, CAPA, and change management to maintain product performance over time. Finally, it establishes expectations for device retirement, disposal, and continued regulatory compliance.

Chapter 12

Emerging Considerations

Included in this section:

- 12.1 INTRODUCTION
- 12.2 CLINICAL DECISION SUPPORT
- 12.3 ARTIFICIAL INTELLIGENCE/MACHINE LEARNING AND ADAPTIVE ALGORITHMS
- 12.4 OTHER TECHNOLOGIES
- 12.5 MANUFACTURER CHECKLIST
- 12.6 RELEVANT STANDARDS, GUIDANCE, AND REGULATORY REQUIREMENTS
- 12.7 SUMMARY

Section 12.1

Introduction

As iCGM systems become more software-driven and integrated with connected diabetes technologies, manufacturers should evaluate functions that extend beyond glucose sensing, including 1) CDS, 2) AI/ML-enabled features with adaptive algorithms, and 3) other technologies. Analogous to the iCGM provision for current CGM systems, similar provisions may eventually become available for IV and noninvasive measurement systems. Any new functionality should be addressed within the manufacturer's quality system, risk management, design validation, cybersecurity, and change-control processes.

Section 12.2

Clinical Decision Support

When a manufacturer incorporates CDS functionality into an iCGM system or makes interoperability claims involving a CDS function, each function should be evaluated separately. The evaluation should identify the function's intended user and intended use, as well as the inputs it receives and the outputs it produces. It should also consider the urgency of those outputs and the function's level of automation, since both affect whether a user can independently review a recommendation before acting. In the U.S., software functions that acquire, process, or analyze CGM signals or patterns; provide patient-specific or time-critical insulin-dosing recommendations or therapeutic alerts; or control or adjust an AID system generally remain regulated device functions subject to applicable device requirements. As described in FDA's 2026 Clinical Decision Support Software: Guidance for Industry and Food and Drug Administration Staff, a function may qualify as non-device CDS under section 520(o)(1)(E) of the Federal Food, Drug, and Cosmetic Act only when it satisfies all four statutory criteria.⁷⁴ Regulated CDS functions should be clinically appropriate, validated for their intended users and context of use, and transparently labeled. Labeling should describe the function's intended purpose, inputs, outputs, performance, limitations, and the degree of reliance that users may appropriately place on its recommendations.

Section 12.3

Artificial Intelligence/Machine Learning and Adaptive Algorithms

For medical software incorporating AI and ML used in the U.S., manufacturers may leverage the FDA Marketing Submission Recommendations for a Predetermined Change Control Plan (PCCP) for AI-Enabled Device Software Functions (FDA-2022-D-2628). PCCPs are optional and enable manufacturers to make predetermined changes in their device without necessitating additional marketing submissions for implementing each modification described in the PCCP. Without a PCCP, significant updates, including new training data or major retraining, generally require a new submission. With a PCCP, predefined modifications may be implemented within approved boundaries. This process enables controlled iteration. PCCPs shall be integrated with ISO 14971, ISO 13485, and IEC 62304 and supported by clear change-control and versioning practices.

In any device utilizing AI or ML technology, manufacturers shall define model inputs and outputs, intended functions, prediction horizons, and associated clinical actions (IEC 62304:2006, ISO 14971:2019). They should document dataset provenance and should also maintain strict separation of training datasets, validation datasets, and test datasets.

Predictive algorithms that generate CGM alerts or forecast glycemic threshold crossings should be evaluated using the applicable methods described in Chapter 7. Other AI/ML-enabled predictive functions should be validated using methods appropriate to the function's intended use, intended users, intended population, prediction horizon, expected clinical action, and the potential consequences of erroneous, incomplete, or delayed output. Comparators, endpoints, datasets, performance metrics, and acceptance criteria should be prespecified and clinically justified because no single validation method or set of metrics is appropriate for all predictive functions. The types of evidence and testing environments used should be proportionate to the intended use and associated risk.

Manufacturers should identify and implement risk controls appropriate to the intended use and potential clinical consequences of AI/ML-enabled functions in accordance with applicable risk-management and software-lifecycle processes (ISO 14971:2019; IEC 62304:2006). Some functions produce outputs that can affect clinical decisions, alerts, or automated insulin dosing. When these outputs may be erroneous, delayed, or uncertain, then risk controls are needed, which may limit or suppress the output or shift to a fallback state. They may also notify users of uncertainty and incorporate human oversight. Controls should match the function and its risk. UIs and labeling should communicate clinically relevant limitations, uncertainty, and appropriate user responses in a manner suited to the intended users and context of use.

Because regulatory expectations for AI-enabled medical device functions continue to evolve, manufacturers should monitor applicable regulatory requirements and guidance throughout the product lifecycle. Table 12.1 summarizes selected recent U.S. and international regulatory and policy developments relevant to AI-enabled medical device functions.

Table 12.1 Selected Regulatory and Policy Developments Relevant to AI-Enabled Medical Device Functions

Issuing body	Date and status	Document	Relevance to CGM and AI-enabled device functions
U.S. Food and Drug Administration	January 2026; final guidance	Clinical Decision Support Software: Guidance for Industry and Food and Drug Administration Staff	Clarifies the four statutory criteria for non-device CDS under section 520(o)(1)(E) of the Federal Food, Drug, and Cosmetic Act. Software that processes CGM signals or patterns, provides specific time-critical treatment outputs, or is intended for patients or caregivers may remain a regulated device function.
U.S. Food and Drug Administration	January 2026; final guidance	General Wellness: Policy for Low Risk Devices: Guidance for Industry and Food and Drug Administration Staff	Clarifies the boundary between low-risk general-wellness products and regulated device functions. The policy does not apply when a function is intended for the diagnosis, cure, mitigation, prevention, or treatment of diabetes or another disease or condition.
U.S. Food and Drug Administration	January 2025; draft guidance (not for implementation)	Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations	Provides nonbinding draft recommendations regarding marketing-submission content and lifecycle management for AI-enabled device software functions, including risk management, data management, performance evaluation, transparency, and postmarket performance monitoring.

Issuing body	Date and status	Document	Relevance to CGM and AI-enabled device functions
U.S. Food and Drug Administration	August 2025; final guidance	Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence-Enabled Device Software Functions	Describes recommendations for proposing planned AI-enabled device modifications, the methods used to develop and validate them, and assessment of their potential effects. Modifications described in an FDA-authorized PCCP may be implemented without an additional marketing submission.
International Medical Device Regulators Forum	April–July 2026; proposed document for public consultation (not final)	N93 Technical Framework for Artificial Intelligence Life Cycle Management	Proposes an internationally harmonized lifecycle framework for AI-enabled medical devices. It may inform future expectations but should not be presented as current final International Medical Device Regulators Forum guidance or a binding requirement.
European Union	Adopted 2024; binding regulation with phased applicability; subsequently amended	Regulation (EU) 2024/1689 — Artificial Intelligence Act	Establishes a horizontal, risk-based legal framework for AI systems in the EU. Applicability to an AI-enabled medical device depends on the function, classification, and relevant conformity-assessment requirements; not every AI-enabled CGM function is automatically classified as high risk.

Expanding use of CGMs in non-prescription and wellness contexts, along with concerns about oversimplified interpretation of glucose data, product reliability, and cybersecurity, heightens the need for clearly defined intended use, accurate and non-misleading claims, robust data protection, and active surveillance for misuse, misunderstanding, and real-world performance drift.

Section 12.4

Other Technologies

Manufacturers should also account for emerging technologies that are outside the scope of this guideline (e.g., noninvasive and intravascular sensing) and evolving regulatory expectations. This includes evaluating performance under real-world conditions (e.g., compression effects, extended wear), supporting long-term use validation, and ensuring continued alignment with safety and performance requirements. As regulatory pathways expand for lower-risk or wellness-oriented applications, adoption of consistent performance standards and cross-platform comparability will be important to support user safety, usability, and effective glucose management outcomes.

Section 12.5

Manufacturer Checklist

Section	Task
12.2 Clinical Decision Support	Evaluate whether extended functions constitute regulated medical device functions, CDS, or non-device CDS, and apply appropriate controls.
	Ensure treatment-impacting CDS outputs are clinically appropriate, rigorously validated, and transparently labeled.

Section	Task
12.3 Artificial Intelligence/Machine Learning and Adaptive Algorithms	Validate the accuracy and timing of outputs from AI/ML-enabled functions used by AID systems, and verify fail-safe behavior, including an appropriate fallback state.
	Apply software lifecycle controls appropriate to the device and applicable regulatory framework (e.g., IEC 62304) and manage planned modifications through applicable change-control processes, including an FDA-authorized PCCP where appropriate.
	Define and explicitly document AI/ML model inputs, outputs, intended functions, prediction horizons, and resulting clinical actions.
	Document the origin of all data and enforce strict separation between training, validation, and test datasets.
	Validate AI/ML-enabled functions using independent data, comparators, endpoints, performance metrics, and evidence sources appropriate to the intended use, prediction horizon, intended users, and potential clinical consequences, consistent with Chapter 7 where applicable.
	Distinguish validation against the algorithm's specified prediction target from evaluation of clinical risk. Depending on the intended use, predictions may be compared with subsequent CGM readings to assess sensor-trajectory prediction and with glucose measurements obtained using an appropriate laboratory reference method to assess clinical accuracy and safety.
	Implement AI-specific safeguards.
	Implement risk controls for low-confidence outputs where clinically relevant, such as suppressing the output or notifying intended users or receiving systems.
	Offer AI/ML model explainability where clinically relevant, tailored to the intended user's technical background and clinical risk level.
12.4 Other Technologies	Maintain awareness of applicable FDA and international regulatory requirements and guidance concerning AI-enabled medical devices.
	Implement data integrity controls and monitor real-world use informing updates.
	Validate emerging technologies under real-world and long-term use conditions to maintain ongoing compliance with safety and performance requirements.

Section 12.6

Relevant Standards, Guidance, and Regulatory Requirements

Organization	Document	Relevance
U.S. Food and Drug Administration	Artificial Intelligence-Enabled Medical Devices List	Provides a public, noncomprehensive list of AI-enabled medical devices authorized for marketing in the United States.
U.S. Food and Drug Administration	Clinical Decision Support Software (2026)	Defines when CDS software is not a device. Software that analyzes CGM signals or patterns remains regulated.
U.S. Food and Drug Administration	General Wellness: Policy for Low Risk Devices (2026)	Covers low-risk wellness products. Invasive products or those making disease-related claims remain regulated devices.
U.S. Food and Drug Administration	Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices	Provides nonbinding recommendations concerning the design, testing, risk management, and interface information for interoperable medical devices, including interfaces relevant to iCGM and AID systems.
U.S. Food and Drug Administration	Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence-Enabled Device Software Functions	Provides recommendations for describing planned modifications, the methodology for developing and validating those modifications, and their impact assessment in a PCCP. Modifications included within an FDA-authorized PCCP may be implemented without an additional marketing submission.

Organization	Document	Relevance
International Electrotechnical Commission	IEC 62304:2006+AMD1:2015 — Medical device software — Software life cycle processes	Specifies software lifecycle processes for medical device software. Its regulatory applicability depends on the device, jurisdiction, and applicable conformity or submission requirements.
International Electrotechnical Commission	IEC 62366-1:2015+AMD1:2020 — Medical devices — Part 1: Application of usability engineering to medical devices	Specifies a usability-engineering process for medical devices and may be applied to alarm safety, foreseeable use errors, automation bias, and interpretation of predictive outputs.
International Electrotechnical Commission	IEC/TR 80002-1 — Medical device software — Part 1: Guidance on the application of ISO 14971 to medical device software	Provides guidance on applying ISO 14971 to medical device software, including software failure modes, data-pipeline hazards, and software-related risk controls.
International Medical Device Regulators Forum	Draft — Technical Framework for Artificial Intelligence Life Cycle Management	Proposes an internationally harmonized framework for AI-enabled medical-device lifecycle management, including data management, performance evaluation, monitoring, and change management. Released as a draft for public consultation in April 2026; not final at the time of publication.
International Organization for Standardization	ISO 14971:2019 — Medical devices — Application of risk management to medical devices	Specifies a risk-management process for medical devices and may be applied to hazards involving algorithm performance, dataset limitations, sensor latency, and false or delayed alerts.
International Organization for Standardization/U.S. Food and Drug Administration	ISO 13485:2016/FDA Quality Management System Regulation, 21 CFR Part 820	ISO 13485 specifies QMS requirements for medical devices. FDA's QMSR incorporates ISO 13485:2016 by reference, together with applicable FDA-specific requirements, for manufacturers subject to 21 CFR Part 820.

Organization	Document	Relevance
International Organization for Standardization/International Electrotechnical Commission	ISO/IEC 42001:2023 — Information technology — Artificial intelligence — Management system	Specifies requirements for an organizational AI management system. It may complement medical-device quality and risk-management processes but is not itself a medical-device product standard.
International Electrotechnical Commission	IEC 81001-5-1:2021 — Health software and health IT systems safety, effectiveness and security — Part 5-1: Security — Activities in the product life cycle	Specifies secure product-lifecycle activities for health software and health IT systems. Applicability depends on the product, system architecture, jurisdiction, and applicable regulatory framework.
U.S. Congress	21st Century Cures Act (Pub. L. No. 114-255)	Amends section 520 of the Federal Food, Drug, and Cosmetic Act by adding subsection (o), which excludes specified software functions from the statutory definition of a device. These are certain administrative, wellness, electronic-record, data-transfer, and clinical decision support (CDS) functions when the applicable statutory criteria are satisfied.

Section 12.7

Summary

As the integration of AI and ML into CGM systems accelerates, these features need to be evaluated through robust quality, cybersecurity, and risk management frameworks. The performance of algorithms that influence clinical decisions or automated insulin dosing should be evaluated during a CGM system's regulatory review process. To support safe model updates without triggering a new regulatory submission for every iteration, manufacturers can leverage PCCPs to predefine boundaries for algorithmic changes. Rigorous validation of AI/ML-based medical functions further demands strict dataset separation and should ideally employ a multi-tiered testing approach, combining *in silico* (when justifiable), retrospective, and prospective clinical data. Finally, manufacturers should incorporate conservative fail-safes during high-risk scenarios and maintain active real-world surveillance to protect against algorithm drift and misuse.

Chapter 13

Sample Protocol for Continuous Glucose Monitoring Performance Evaluation

Included in this section:

13.1 PURPOSE

13.2 STUDY PROCEDURES

13.3 SAFETY CONSIDERATIONS

13.4 EXAMPLE HYPOGLYCEMIA MANAGEMENT PROTOCOL (OUTSIDE OF MANIPULATION PERIOD)

13.5 EXAMPLE HYPERGLYCEMIA AND KETONEMIA MANAGEMENT PROTOCOL (OUTSIDE OF MANIPULATION PERIOD)

Section 13.1

Purpose

This sample protocol template is provided as a framework to support the standardized conduct of clinical trials and operationalize the study-design principles described in Chapter 10 for evaluating CGM systems. It is intended to serve as a framework that should be adapted by investigators, sponsors, and research sites for evaluating CGM system accuracy. Alternate safety measures may be used according to the specific objectives of a study, the specific participant population, and applicable regulatory or institutional requirements.

The procedures described herein reflect current best practices for participant preparation, glucose challenge methodologies, RG sampling, safety monitoring, and clinic visit conduct. While not intended to supersede study-specific protocols or local requirements, the template is designed to promote safety and consistency in trial execution and to facilitate the collection of high-quality, comparable CGM performance data across studies and research settings. The study sponsor may refine specific participant eligibility criteria as needed, within this guideline's safety limits.

The overarching priorities of this template are to enhance participant safety, support effective and efficient study conduct, and minimize participant burden and discomfort while maintaining scientific rigor. Adoption of standardized procedures, where appropriate, may improve the reliability, reproducibility, and interpretability of study results and contribute to greater consistency in the evaluation of CGM technologies.

Section 13.2

Study Procedures

13.2.1 Responsibilities

The investigator and research study team are responsible for the monitoring of participants throughout the duration of each clinic session visit to ensure safety. Research staff will be responsible for conducting visit procedures and recording all data into source documentation. Any medications (including insulin) will be administered by licensed nursing or medical professionals with experience managing diabetes or self-administered by the participant. These licensed nursing or medical professionals will be responsible for insertion and maintenance of IV catheters. Investigators are responsible for overseeing all study procedures to ensure participant safety. Investigators or qualified designees are responsible for all insulin dosing decisions and meal intake decisions during glucose manipulation periods. Investigational CGM devices should be blinded to study staff and participants. If any data were to become available, then study participants should be instructed not to use them and report the data disclosure to study staff immediately.

Outside of the manipulation period, participants and/or their guardians will manage their glucose as they normally would, using their routine glucose monitoring practices and medication regimen.

13.2.2 Inclusion and Exclusion Criteria

These are the **minimum** inclusion and exclusion criteria that should be used for the study. Additional criteria may be included depending on the study.

- Study participants should require insulin therapy, specifically continuous subcutaneous insulin infusion (CSII) or multiple daily injections to participate in glucose manipulation.
- Participants aged 11 years and older should be willing to have their glucose manipulated.
- Participants should have been diagnosed with diabetes for at least 6 months prior to enrollment and should have had a known or knowable insulin sensitivity factor for at least 1 month prior to enrollment to participate in glucose manipulation.
- Participants with a history of hypoglycemia unawareness should not be enrolled for glucose manipulation.
- Participants who are known to be pregnant or attempting to conceive or are not using a reliable form of contraception should not participate in glucose manipulation.
- Participants with T1D who are using sodium-glucose co-transporter 2 inhibitor therapy should not participate in glucose manipulation.
- Participants with a history of myocardial infarction or with significant coronary artery disease as assessed by the investigator should not participate in glucose manipulation.
- Participants with end-stage renal disease or on hemodialysis should not participate in the accuracy study unless they are the intended patient population of the study.
- Participants with a hemoglobin or hematocrit level that is 10% or more below the normal range (normal range may differ by sex and method of measurement) should not be enrolled in venous blood collection studies.
- Participants who had an episode of severe (Level 3) hypoglycemia requiring intervention from a healthcare professional or requiring assistance from a non-healthcare professional during the 3 months prior to the screening visit should not participate in hypoglycemic challenges.
- Participants who had an episode of DKA within the last 3 months should not participate in hyperglycemic challenges.

13.2.3 General Requirements

These are the **minimum** requirements that should be incorporated into the protocol to maintain study participants' safety and integrity of the data.

13.2.3a Sensor Application

- The study participant and/or parent/legal guardian prepares each application site and applies the sensor to the intended location following the instructions provided without additional assistance from study staff (as would be expected to happen when the device is marketed).
- If the study participant wears two sensors (to enable precision evaluation) at a given physiological location, then the sensor used for accuracy evaluation should be defined at the time of sensor application (for example, first applied sensor).
- A sensor may not be replaced after a paired sensor-reference data point is generated. If the sensor is replaced for any failure, then the failed sensor should be included in the sensor survival analysis.
- If there is an over-patch required, then it should be part of the accuracy evaluation, and the over-patch should be applied by the intended user or caregiver.

13.2.3b System Use

- Sensors should be blinded to the study participants and the investigator(s). Therefore, no therapy/management decisions can be made by the participant or the site using the results obtained from the sensor. Study participants are required to adhere to their previously established diabetes management plans, including use of their personal BG management device for routine glucose monitoring.

13.2.3c Reference Sample Collection and Glucose Manipulation

- Participants aged 7 years and older should have venous samples collected as reference samples, and the reference measurements should be performed using a laboratory analyzer traceable to higher standards.
- Venous blood sampling frequency is nominally every 15 ± 5 minutes. Frequency should increase to every 5–7 minutes when glucose is less than 70 mg/dL (3.9 mmol/L) or equal to or greater than 300 mg/dL (16.7 mmol/L). These are performed in one or more in-clinic settings, each lasting 8–10 hours (for pregnant participants, see Section 3.2.3).
- The amount of blood that can be collected from each participant should be estimated, and the duration of their participation in an in-clinic setting should be determined based on their age and body weight.

- For studies conducted in the United States, follow the Category 2 blood-collection criteria described in Section 10.4.4. For healthy, nonpregnant adults weighing at least 110 lb (50 kg), collection may not exceed 550 mL per 8-week period; for other adults and children, collection may not exceed the lesser of 50 mL or 3 mL/kg per 8-week period. Collection sessions may not occur more than twice per week. Protocols exceeding these limits require review by a convened IRB and justification for the additional blood volume. More restrictive local or institutional requirements should be followed.
- For studies longer than 8 weeks, collection should be scheduled so that the applicable limits are not exceeded in any 8-week period.

13.2.3d Reference Sample Collection Schedule

- Performance should be evaluated across the full sensor wear duration by segmenting the wear period into clinically meaningful time intervals, such as early, middle, and late phases, or into day-based groupings, as appropriate for the labeled sensor wear duration. Performance evaluation should include both the first day of wear (including immediately after sensor application, segmenting it into the first 12 hours and the second 12 hours with data collected across the entire 24 hours) and the final day of wear, including up to the end of the sensor wear period to adequately characterize performance over time.
- Avoid sensor removal at the last sampling clinic visit if it occurs prior to the full sensor wear period (i.e., a sensor intended for 7 days of wear should not be removed prior to 168 hours even if the last sampling clinic visit occurred early on the 7th day).

13.2.4 In-Clinic Visit Procedures

Intake procedures on the day of clinic visits should include the following:

- Collection of vital signs;
- Review of medications, changes in health status, most recent insulin bolus or meal intake (time and number of units and/or grams of carbohydrates taken), assessment of AEs if present;
- Fingerstick glucose assessment;
- Ketone assessment if BG ≥ 300 mg/dL (≥ 16.7 mmol/L); and
- IV catheter placement.

Once arrival procedures are complete, participants will proceed with clinic visit sampling and glucose manipulation procedures, if applicable. Participants who have had severe hypoglycemia within the past 24 hours cannot participate in hypoglycemic manipulation at that clinic visit. Participants who arrive with hyperglycemia ≥ 300

mg/dL (≥ 16.7 mmol/L) and with ketone values of ≥ 0.6 mmol/L cannot participate in hyperglycemic manipulation at that clinic session. However, in both instances, participants may participate in the other manipulation per investigator discretion (see Table 13.4).

13.2.5 Glucose Manipulation Eligibility and Preparation

Age-related permission to manipulate and blood sample sources for a glucose reference are presented in Table 13.1.

Table 13.1 Age Thresholds for Different Reference Sampling and Glucose Manipulations

Age (Years)	Permission to Manipulate	Source of Blood Sample
<6	No	Capillary
6 to 7	No	Venous or capillary
≥ 7 to 11	No	Venous
≥ 11	Yes	Venous

13.2.5a Pre-Clinic Visit Preparation

If the participant is required to undertake glucose manipulation, then the following steps may be performed to improve the success of glucose manipulation.

- Participants planned to undergo glucose manipulations will be advised to take their insulin doses as they normally would, unless otherwise advised by the investigator.
 - Dose adjustments may be recommended to promote stable BG levels overnight per investigator discretion.
 - Participants should disclose their carbohydrate factor (insulin-to-carbohydrate ratio) and correction factor (corrF; insulin sensitivity factor). To confirm these values, investigators should estimate both ratios from the total daily insulin dose (TDD) using established rules. The 500 rule ($500 \div \text{TDD}$) yields a conservative carbohydrate factor in grams per unit. The 1800 rule ($1800 \div \text{TDD}$) estimates the correction factor in mg/dL per unit, and the 100 rule ($100 \div \text{TDD}$) provides the mmol/L equivalent.
- Participants should be reminded to bring all medications with them to their clinic visit. Participants should expect to take all their medications at their usual times, but these may also be adjusted or withheld

at the discretion of the investigator.

- Example: Participants with T2D planned to undergo hyperglycemic manipulation may be advised to hold their oral antihyperglycemic medications until the manipulation is completed.
- Participants should be encouraged to abstain from eating carbohydrates or taking rapid-acting insulin in the morning prior to arrival at the clinic, unless the participant's BG requires intervention:
 - BG is <70 mg/dL (<3.9 mmol/L) and decreasing:
 - * Participants should be encouraged to treat with rapid-acting carbohydrates as per their usual routine, recommending no more than 20 g of carbohydrate when possible.
 - * Participants who experience severe (Level 3) hypoglycemia within 24 hours of the scheduled clinic session should reschedule the clinic session (if possible to do within window per study protocol) or they may participate in a hyperglycemic manipulation or participate in the clinic session under observation only (i.e., no glucose manipulations per investigator discretion).
 - BG is ≥ 300 mg/dL (≥ 16.7 mmol/L) and/or significant ketones present (≥ 0.6 mmol/L):
 - * If a correction bolus is needed, then participants should be advised to use a higher BG target of 150 mg/dL (8.3 mmol/L) to avoid hypoglycemia prior to their arrival or during transit to the research site.
 - * If the ketone level is 0.6 mmol/L or higher, then the participant cannot participate in hyperglycemic manipulation at that clinic session, but may participate in hypoglycemic manipulation or in the clinic session under observation only (i.e., no glucose manipulations).
 - * Participants who experience DKA or symptoms of illness with ketosis within 24 hours of the scheduled clinic session should reschedule the clinic session (if possible to do within window per study protocol) or they may participate in the clinic session under observation only (i.e., no glucose manipulations).
- Participants may freely eat protein prior to arrival if desired. No bolus insulin is required for protein intake.
- Participants using an insulin pump should be advised to bring additional pump supplies in case of failure during the clinic session (e.g., spare infusion set). All participants should be advised to bring their own insulin to the clinic session.

13.2.6 Glucose Manipulation Procedures and Targets

Adults and adolescents (age ≥ 11 years) receiving intensive insulin therapy should undergo hypoglycemic and/or hyperglycemic manipulations targeting specific glucose ranges during designated clinic visits.

The initiation of a glucose manipulation period is defined as the administration of carbohydrates or insulin with the intention of inducing hyperglycemia or hypoglycemia. Specifically,

- Hyperglycemic manipulation is initiated when:
 - Oral carbohydrate is administered to induce hyperglycemia.

- Example: Participant is provided a meal and insulin is withheld.
- Hypoglycemic manipulation is initiated when:
 - Insulin is administered through subcutaneous injection or CSII to induce hypoglycemia.
 - Example: Participant is given a bolus of insulin to achieve a target glucose of <70 mg/dL (<3.9 mmol/L), and food is withheld.

Glucose manipulations may be initiated via the administration of carbohydrates or insulin to induce hyperglycemia or hypoglycemia per the discretion of the investigator or qualified designee. The following guidelines in Table 13.2 may be considered to aid in achieving target glucose values.

Table 13.2 Guidelines for Initiating Glucose Manipulations

Glucose and Trend	Suggested Manipulation	Actions and Considerations
<180 mg/dL (<10.0 mmol/L) and stable or trending down >180 mg/dL (>10.0 mmol/L) and dropping	Hypoglycemia	• Calculate insulin dose to a target of <70 mg/dL (<3.9 mmol/L) for up to 90 minutes and no more than 25 minutes ≤55 mg/dL (≤3.1 mmol/L), based on the participant's known or optimized (based on investigator assessment/calculations) insulin sensitivity factor or corrF. The low target to be used for calculations should be determined by the expected indications of the product and participant characteristics. • It is mandatory to consider any recently administered insulin boluses (i.e., subtract “insulin on board”) when calculating additional bolus amounts to achieve the target during a hypoglycemic manipulation.
>180 mg/dL (>10.0 mmol/L) and stable or rising <180 mg/dL (<10.0 mmol/L) and rising	Hyperglycemia	• Administer a mixed meal of approximately 40–55 g of carbohydrates to target a glucose of ≥300 mg/dL (≥16.7 mmol/L) for approximately up to 75 minutes and no more than 30 minutes ≥400 mg/dL (≥22.2 mmol/L).

Glucose and Trend	Suggested Manipulation	Actions and Considerations
		• The exact type of food, quantity of carbohydrate, and timing of consumption should be adjusted at the discretion of the investigator, taking into consideration the diabetes type, the starting glucose value, and timing/quantity of recent insulin taken or meals consumed prior to arrival at the clinic session.
		• Strategic use of foods/beverages with variable rates of carbohydrate absorption is encouraged. For example, incremental administration of liquid carbohydrates (e.g., 2 oz of a meal replacement drink every 15 minutes) followed by foods with slower carbohydrate absorption will help control ROC while safely achieving target hyperglycemia.
		• Initiating a hyperglycemic manipulation with a meal high in fat (>35%) and protein is not advised, as this can result in delayed and sustained hyperglycemia, prolonging the clinic session and possibly resulting in extended monitoring at discharge.

13.2.7 Safety Monitoring

This section provides general guidance for clinical staff to ensure participant safety during standardized glucose manipulation procedures in CGM clinical trials. All interventions should be conducted under investigator oversight and in accordance with protocol-specific procedures, institutional policies, and applicable regulatory requirements.

Frequent glucose monitoring (preferably venous, but capillary glucose can be used when maximum blood volume for sampling is an issue, or venous access is not available) should be used during all manipulation periods. Participants with insulin pumps should continue to wear them during manipulations. However, AID functionality should be paused, and all insulin doses should be reviewed and approved by the investigator.

13.2.7a Pre-Manipulation Safety Assessment

Prior to initiation of any glucose manipulation:

- Verify participant eligibility for the scheduled clinic session and confirm readiness for study procedures. Participants should have adequacy of venous access assessed at screening. While distal cannulation is preferred, cannulation of the antecubital vein is permissible.
- Determine the maximum allowable blood volume for each participant across all clinic sessions based on the participant's age, weight, health status, and applicable regulatory and institutional requirements, as specified in Section 10.4.4.
- IV access and study-related blood sampling may be initiated once an investigator or qualified designee has confirmed that a participant can safely proceed.
- AID systems should remain active until the manipulation period begins, unless otherwise specified in the protocol or at the discretion of the investigator.
- **Hypoglycemia at intake:** If glucose is below 70 mg/dL (3.9 mmol/L), then notify the investigator to assess if the participant can safely initiate sampling for hypoglycemic manipulation.
- **Hyperglycemia at intake:** If glucose is equal to or above 300 mg/dL (16.7 mmol/L), then measure capillary beta-hydroxybutyrate (ketones) with a point-of-care device and notify the investigator to assess if the participant can safely initiate sampling for hyperglycemic manipulation.
- **Significant hyperglycemia or ketosis:** If marked hyperglycemia (greater than 400 mg/dL [22.2 mmol/L]) is accompanied by elevated ketones and symptoms consistent with metabolic decompensation, immediately engage the investigator to ensure hydration and administration of appropriate insulin. The participant should not undergo glucose manipulations during that session.

Calculation of Maximum Blood Collection Under Category 2 Limits

Category 2 is one of nine categories of minimal-risk research that an IRB may approve through expedited review, rather than review by the full convened IRB; it covers blood collection by fingerstick, heelstick, earstick, or venipuncture within specified volume and frequency limits. For each 8-week period, the applicable blood-volume limits for eligibility for expedited review are:

- Healthy, nonpregnant adults weighing at least 110 lb (50 kg): 550 mL.
- Other adults and children: the lesser of 50 mL or 3 mL/kg.

For other adults and children:

Maximum blood volume (mL) = the lesser of 50 mL or $[3 \text{ mL/kg} \times \text{body weight (kg)}]$.

Estimated maximum number of additional blood draws within an 8-week period:

Total number of additional draws = $[\text{applicable maximum blood volume (mL)} - \text{other planned study-related blood collection during the same 8-week period (mL)}] \div \text{blood volume per draw (mL)}$.

Include waste blood in the volume per draw and round the result down to a whole number. If no blood volume remains, then no additional draws are available within these limits.

Notes:

- Blood collection should not occur more than twice per week.
- For studies longer than 8 weeks, repeat the calculation for each applicable 8-week period to ensure that the limits are not exceeded.
- These limits determine eligibility for expedited review under Category 2; they are not absolute maximums for all research. Protocols exceeding these limits require review by a convened IRB and justification for the additional blood volume, as described in Section 10.4.4.

13.2.7b Safety Monitoring During Manipulation

It is critical that all manipulation procedures be conducted under investigator supervision. Glucose should be assessed at frequent, protocol-defined intervals, with attention to absolute glucose levels, direction of change (trend), and ROC. Sampling frequency is nominally every 15 ± 5 minutes. Frequency should increase to every 5–7 minutes when glucose is less than 70 mg/dL (3.9 mmol/L) or equal to or greater than 300 mg/dL (16.7 mmol/L). The hypoglycemic manipulation should be terminated and therapy to raise glucose administered immediately if glucose declines below 40 mg/dL (2.2 mmol/L). After a maximum of 25 minutes between 40–55 mg/dL (2.2–3.1 mmol/L), therapy to gradually increase glucose should be administered. A limit of 55 mg/dL (3.1 mmol/L) is used during manipulation to provide a safety margin above the 54 mg/dL (3.0 mmol/L) threshold for clinically significant hypoglycemia. Glucose values above 400 mg/dL (22.2 mmol/L) will not be targeted; treatment will be administered at or before the time glucose reaches 400 mg/dL (22.2 mmol/L), and a maximum of 30 minutes duration in this glucose range (≥ 400 mg/dL [≥ 22.2 mmol/L]) will be allowed. If glucose values remain in severe low or high ranges beyond the specified maximum limits, then the manipulation should be terminated and glucose-treating therapy administered. Sampling may continue while glucose levels are being treated.

The comparator measurement (e.g., a venous sample measured on a YSI analyzer) should be used for all clinical decision making. However, capillary point-of-care glucose measurements may be used if:

- More frequent sampling is determined to be needed for safety by the investigator;
- Venous sampling access is not available; or
- Maximum permissible sample volume is in danger of being exceeded.

Investigators should remain immediately available for real-time clinical decision making during active manipulation periods.

Hypoglycemic Manipulation — General Principles

- Insulin dosing or other glucose-lowering strategies should be determined by the investigator in advance or in real time, as applicable.
- Participants should be closely monitored for both absolute glucose thresholds and rapid downward trends.
- Rapid-acting carbohydrates should be administered in small, titrated amounts based on predefined glucose thresholds and rate of decline.
- Escalation of carbohydrate administration should occur if glucose continues to fall or fails to respond appropriately.
- Investigator notification is required for any rapid decline, severe hypoglycemia, or failure to respond to treatment.
- The investigator should target maintaining <70 mg/dL (<3.9 mmol/L) for up to 90 minutes, with no more than 25 minutes spent between 40–55 mg/dL (2.2–3.1 mmol/L).

Once the manipulation period is complete, glucose should be supported toward recovery using standardized carbohydrate administration until safe euglycemia ($BG \geq 70$ mg/dL [≥ 3.9 mmol/L] and stable or rising) is achieved, after which oral intake may resume per protocol. Participants may bolus for any meals post-hypoglycemic challenge as they normally would.

For participants using insulin pumps or AID systems:

- Before the participant leaves, the investigator should confirm, together with the participant, that the participant's insulin pump has been restored to its usual settings, including resumption of AID for participants who arrived using this feature.
- Resumption of basal insulin delivery may be contingent on confirmation of glucose recovery and clinical stability.

Hyperglycemic Manipulation — General Principles

- Ketones should be tested when glucose is ≥ 300 mg/dL (≥ 16.7 mmol/L).
 - Hyperglycemic manipulation should not be initiated if ketones are ≥ 0.6 mmol/L.
 - Ketones should be monitored hourly when ≥ 0.6 mmol/L and/or when glucose is ≥ 300 mg/dL (≥ 16.7 mmol/L).
 - Hyperglycemic manipulation should be terminated if ketones are >3.0 mmol/L. Insulin will be administered to target euglycemia (approximately 120 mg/dL [6.7 mmol/L] using the participant's or an alternative insulin corrF as determined by the investigator) and the participant will enter free-range glucose control. Sampling may continue for the remainder of the visit.
- Initial carbohydrate dosing to induce hyperglycemia, and any insulin dosing, should be determined by the investigator.

- Participants should be monitored for sustained hyperglycemia, upward trends, and rapid increases in glucose.
- In cases of moderate hyperglycemia with downward trends, observation without intervention may be appropriate if clinically stable.
- In cases of persistent or rising hyperglycemia, investigator-directed corrective insulin dosing should be used, typically based on prespecified correction algorithms.
- Investigator notification is required for severe hyperglycemia, rapid upward trends, or when ketones exceed protocol-defined thresholds.

At completion of the manipulation period, corrective insulin dosing may be administered per investigator guidance or standardized calculation methods to facilitate return to target glycemic range of above 70 mg/dL (3.9 mmol/L) and below 300 mg/dL (16.7 mmol/L). A target glucose of approximately 120 mg/dL (6.7 mmol/L) will be used. Additional insulin may be administered for post-hyperglycemic challenge meal consumption. It is recommended that post-challenge meals are not initiated until BG is <250 mg/dL (<13.9 mmol/L) with a downward trend. Ketones will be monitored hourly until BG is <300 mg/dL (<16.7 mmol/L) and/or ketones are <0.6 mmol/L.

BG targets and duration of manipulation period are outlined in Table 13.3. Actions based on ketone monitoring values are outlined in Table 13.4.

Table 13.3 BG Targets and Duration of Manipulation Period (Total in One Clinic Session)

Blood Glucose* (mg/dL [mmol/L])	Duration	Action
<40 (<2.2)	N/A	• Stop manipulation. • Treat to euglycemia. • May continue sampling.
40–55 (2.2–3.1)	Up to 25 minutes	• Observe. • Treat to euglycemia after specified time.
<70 (<3.9)	Up to 90 minutes	• Observe. • Treat to euglycemia after specified time.
70–299 (3.9–16.6)	No limit	• Observe.

Blood Glucose* (mg/dL [mmol/L])	Duration	Action
≥300 (≥16.7)	Up to 75 minutes	• Check ketones within 15 minutes of first sample ≥300 mg/dL (≥16.7 mmol/L).
≥400 (≥22.2)	Up to 30 minutes	• Treat to euglycemia. • Consider initiating treatment prior to glucose reaching 400 mg/dL (22.2 mmol/L).

*Venous blood should be used for decision-making when available; otherwise, capillary BG values may be used.

Table 13.4 Ketone Monitoring

Ketones (mmol/L) (when BG ≥300 mg/dL [≥16.7 mmol/L])	Action
<0.6	• Check hourly until BG <300 mg/dL (<16.7 mmol/L). • May initiate hyperglycemic manipulation.
0.6–3.0	• Check hourly until <0.6 mmol/L. • Monitor for symptoms of DKA. • May initiate hypoglycemic manipulation per investigator discretion.
>3.0	• Stop hyperglycemic manipulation. • Administer insulin to target euglycemia (e.g., 120 mg/dL [6.7 mmol/L]). • May continue sampling. • Check hourly until <0.6 mmol/L.

13.2.7c Post-Manipulation Management

Following completion of glucose manipulation procedures, participants may resume oral intake once clinically stable and glucose values are within a safe range as defined by the protocol.

Meals should be provided in a manner that minimizes postprandial glycemic variability (e.g., avoiding high-fat meals unless specified for study purposes).

Insulin dosing following manipulation should be individualized based on participant-specific parameters (e.g., insulin-to-carbohydrate ratio and corrF) and investigator guidance.

In general:

- Insulin bolusing for post-manipulation meals may be divided or staged in situations where residual glucose instability is anticipated.
- Timing of insulin administration should consider current glucose levels, direction of change, and recent carbohydrate or insulin exposure.
- Additional carbohydrate intake without insulin may be appropriate in cases of borderline or low glucose during recovery, per protocol-defined thresholds.

For hyperglycemic recovery, initiation of meals and insulin administration should be delayed until glucose trends demonstrate stability or improvement.

13.2.7d Correctional Management

Correctional carbohydrate or insulin dosing after manipulation should be guided by:

- Current glucose level relative to target range;
- Direction and ROC;
- Recent insulin or carbohydrate exposure; and
- Participant-specific insulin sensitivity parameters.

In general:

- Mild deviations from target range may be managed with observation or small carbohydrate intake without insulin.
- Moderate hyperglycemia may be managed with investigator-directed correction insulin dosing.
- Participants should return to AID or baseline insulin delivery settings once clinically stable, unless otherwise specified in the protocol.

13.2.7e General Safety Considerations

- All interventions should prioritize participant safety over strict adherence to target glucose trajectories.
- Rapid glucose changes warrant increased monitoring frequency and investigator notification.
- Clinical judgment should be exercised in all cases where protocol guidance does not fully address the observed scenario.
- AEs, including severe hypo- or hyperglycemia, should be documented and managed according to institutional and regulatory reporting requirements.

13.2.8 Discharge Procedures and Guidelines

Upon completion of clinic session procedures, participants should undergo standardized discharge procedures to ensure clinical stability and safety prior to leaving the study site.

Typical discharge assessments may include:

- Measurement of vital signs;
- Assessment of BG (see BG discharge guidelines below);
- Ketone assessment;
- Removal of IVs; and
- Device downloads.

Before discharge, study staff will confirm with the participant that all insulin pump settings, including any AID features, have been restored to the participant's usual configuration.

A general "safe range" for discharge may be defined as a BG value (capillary or venous as applicable) between 70 mg/dL (3.9 mmol/L) and 300 mg/dL (16.7 mmol/L).

Participants may be considered eligible for discharge once glucose values have been confirmed to be within a safe range and stable. Discharge to home, continued observation, or transfer to an emergency or inpatient service should be determined by the investigator according to the participant's condition and documented recovery criteria. Home discharge should occur only after clinical stability is established. Any later intentional glucose manipulation following a serious metabolic event should require documented investigator reassessment and any protocol-required sponsor or ethics review.

General Glucose-Based Discharge Considerations

The following guidance may be used to support standardized decision-making; however, investigator judgment should take precedence in all cases.

Participants will be allowed to leave the clinic after their final two consecutive glucose values, measured on a reference analyzer or SMBG and taken over the last 30 minutes, show a BG level above 70 mg/dL (3.9 mmol/L) and below 300 mg/dL (16.7 mmol/L) and the investigator feels that they are stable and that it is safe for them to leave.

Section 13.3

Safety Considerations

13.3.1 Treatment of Hypoglycemia and Hyperglycemia (Outside of Manipulation Period)

Outside of the manipulation period, maintenance of euglycemia should be the target. Treatment of hypoglycemia or hyperglycemia outside of manipulation periods should be initiated in the event of a hypoglycemic or hyperglycemic event, or per investigator discretion (e.g., participant is symptomatic, or to prevent the occurrence of severe events).

Treatment of hypoglycemia may include oral carbohydrates, IV dextrose, or glucagon. In participants who are unable to take oral carbohydrates safely or reliably, IV dextrose should be administered. In participants unable to take oral carbohydrates and without adequate IV access, glucagon (intramuscular, subcutaneous, or intranasal) should be administered.

Treatment of hyperglycemia may include subcutaneous, inhaled, or IV insulin, per the site standard operating procedures and/or investigator discretion.

Specific treatment for hypoglycemia or hyperglycemia will be administered according to site-specific standard operating procedures and/or per the discretion of the treating investigator. Reasons for initiating treatment and specific actions taken will be documented by study staff.

13.3.2 Clinic Session and/or Glucose Manipulation Stopping Criteria

Eligible participants are expected to undergo glucose manipulations at clinic session visits per protocol. For safety reasons, glucose manipulations may be stopped at any time during the clinic session even if sampling in glucose target ranges has not occurred or been completed.

The glucose manipulation will be stopped if any of the following occur:

- Participant requests to end the manipulation due to discomfort;
- Participant ketone measurement is >3.0 mmol/L; or
- Participant shows symptoms of DKA.

These participants may continue with clinic session sampling under observation after manipulation has been terminated if determined safe by the investigator.

Participants who end their glucose manipulation period early will be expected to attempt glucose manipulations at subsequent clinic session visits, unless otherwise determined by the investigator.

Participation in the clinic session visit will be ended, and the participant will be discharged if:

- Participant develops an acute illness that would prevent ongoing study participation;
- Participant experiences an SAE;
- Participant requires medical intervention to treat severe hypoglycemia (Level 3);
 - Those who experience severe (Level 3) hypoglycemia during a glucose manipulation will not attempt hypoglycemic manipulations at subsequent visits but may participate in hyperglycemic manipulations.
- Participant is unwilling or unable to participate in study procedures (e.g., having IV catheter placed, enduring frequent SMBG measurements, or other necessary study procedures); and
- Other events occur requiring discharge, as determined by the investigator.

Participation in the clinic session visit will be ended, and the participant may be discharged if the participant develops severe hyperglycemia.

- Those who experience DKA during a glucose manipulation will not attempt hyperglycemic manipulations at subsequent visits but may participate in hypoglycemic manipulations.

Participants who are discharged prematurely from any clinic session for elevated ketones may not participate in hyperglycemic manipulation at future clinic sessions. Similarly, participants who are discharged prematurely from any clinic session for hypoglycemia may not participate in hypoglycemic manipulation at future clinic sessions.

A manipulation period is considered to be stopped when an intervention is made to bring a participant out of the manipulation period target glucose range (e.g., carbohydrates or insulin administered), irrespective of the participant's comparator analyzer or SMBG value.

- Comparator analyzer and/or SMBG values may continue in target glucose range for a period of time after a manipulation has ended due to individual physiologic response to glucose and/or insulin.

- Example: A participant undergoing a hyperglycemic manipulation has had a BG value of >300 mg/dL (>16.7 mmol/L) for 30 minutes.
 - The participant complains of nausea and requests to stop the glucose manipulation.
 - A correction bolus of insulin is administered, which ends the glucose manipulation.
 - The participant should be provided ad libitum hydration, continue to be monitored, and may continue to undergo frequent sampling (including 5–7-minute intervals while glucose is within range to achieve target number of values) if determined to be safe by the investigator.
- Reasonable efforts should be made to provide timely intervention to end glucose manipulations in order to avoid extended duration of hypo- or hyperglycemia beyond target manipulation duration.

13.3.3 Hypoglycemia and Hyperglycemia as Adverse Events

Mild symptoms of hypoglycemia or hyperglycemia are expected, as these are inherent risks associated with having diabetes and with use of insulin, in addition to being deliberately manipulated as part of the protocol.

Therefore, only severe hypoglycemia or hyperglycemia should be considered AEs and classified according to criteria outlined below:

- Severe hypoglycemia is defined as a BG value which is <54 mg/dL (<3.0 mmol/L), AND which results in altered mental status such as severe confusion, loss of consciousness (LOC), or seizure, requiring external help for treatment. Seizure or LOC without associated hypoglycemia should be reported as separate AEs.
- Severe hyperglycemia is defined as a BG value ≥ 300 mg/dL (≥ 16.7 mmol/L), and:
 - Ketones >3.0 mmol/L and/or
 - Symptoms of DKA (e.g., nausea, vomiting, abdominal pain).

Asymptomatic or mild hypoglycemia or hyperglycemia will not be considered AEs.

Severe hypoglycemia or hyperglycemia may be treated according to the guidelines described above.

Previous definitions of severe hypoglycemia relate to clinical care and eligibility criteria for study participation. The definition provided in this section includes a glucose threshold specifically to define severe hypoglycemia for AE reporting purposes.

Section 13.4

Example Hypoglycemia Management Protocol (Outside of Manipulation Period)

13.4.1 Purpose

To promptly reverse hypoglycemia in a consistent and therapeutic manner.

13.4.2 Definitions

Hypoglycemia is a BG that is <70 mg/dL (<3.9 mmol/L) even in the absence of obvious signs and symptoms.

13.4.3 Signs and Symptoms of Low Blood Glucose

- Shakiness;
- Sweating, chills, clamminess;
- Irritability, confusion, lightheadedness, or dizziness;
- Altered state of consciousness or personality change;
- Weakness or lack of energy; and
- Tingling or numbness in the lips, tongue, or cheeks.

13.4.4 Procedures

- If hypoglycemia is detected at any time during study procedures or while a participant is on site, then notify the supervising investigator immediately.
- Proceed with treatment according to participant status as indicated below while awaiting further instruction from supervising investigators or other qualified medical professionals (QMPs).

Conscious Participant without Intravenous Access

1. Treat with 15–20 g of fast-acting oral carbohydrate (the American Diabetes Association’s “15-15 Rule”).

- a. For participants <200 lb, use 15 g carbohydrates (CHO);
- b. For participants ≥200 lb, use 20 g CHO;
- c. OR use the formula:

Carb dose (g) = (Target BG [mg/dL] – Current BG [mg/dL]) / (430 / Weight [lb]). Examples of simple carbohydrate are displayed in Table 13.5.

Table 13.5 Examples of Simple Carbohydrate for a Participant <200 lb

Carbohydrate Type	Grams	Quantity to Administer
Glucose tablets	1 tablet = 4 grams CHO	Give 3–4 tablets
Apple juice	30 mL = 3.5 grams CHO	Give about 130 mL of juice
Regular cola beverage	30 mL = 3.25 grams CHO	Give about 140 mL of cola

- 2. Repeat BG in 15 minutes and document.
- 3. If BG remains below 70 mg/dL (3.9 mmol/L) after treatment, then repeat the above procedure.
- 4. Continue to perform BG testing and treatment every 15 minutes until BG reaches the target of ≥70 mg/dL (≥3.9 mmol/L).

Participant Unable to Take Oral Carbohydrate, with Intravenous Access

(Registered Nurse or QMP only)

For adults: Two examples of three-step treatment regimens.

Example 1:

- 1. BG 41–69 mg/dL (2.3–3.8 mmol/L): give 25 mL dextrose 50% (D50) (12.5 g) by IV push, followed by a saline flush.
- 2. BG ≤40 mg/dL (≤2.2 mmol/L): give 50 mL D50 (25 g) by IV push, followed by a saline flush.
- 3. Recheck BG in 15 minutes and repeat the dose for the current BG until BG is ≥70 mg/dL (≥3.9 mmol/L).

Example 2:

- 1. For BG <60 mg/dL (<3.3 mmol/L), treat with D50:

a. To determine dose, use the following formula:

$$(100 - \text{BG}) \times 0.3 = \text{number of mL of D50 to administer via IV bolus ("push").}$$

2. Recheck BG in 15 minutes and document.
3. If BG remains <60 mg/dL (<3.3 mmol/L), then repeat D50 using the same dosing formula and the most recent BG result.

For children <50 kg: Use a weight-based dose of IV dextrose according to the site's pediatric protocol rather than a fixed adult D50 dose.

Unconscious Participant without Intravenous Access

1. Treat with glucagon (dose and route according to label).
2. Glucagon may cause nausea and vomiting. Turn the participant on their side to avoid aspiration.
3. Establish IV access and await further orders from the supervising investigator or QMP.
4. Recheck BG in 15 minutes after glucagon injection.

Section 13.5

Example Hyperglycemia and Ketonemia Management Protocol (Outside of Manipulation Period)

13.5.1 Purpose

To correct hyperglycemia and ketonemia in a consistent, safe, and therapeutically appropriate manner, with a QMP making all treatment decisions.

13.5.2 Procedure

Hyperglycemia: Definition — Glucose ≥ 300 mg/dL (≥ 16.7 mmol/L)

1. Check ketones.
2. Notify QMP promptly of any glucose ≥ 300 mg/dL (≥ 16.7 mmol/L).
3. QMP should provide appropriate medical treatment, including insulin and hydration.

Insulin will be administered using the participant's known or adjusted $\text{corrF}/\text{insulin}$ sensitivity factor (per investigator discretion) treating to a target of approximately 120 mg/dL (6.7 mmol/L). A more conservative (e.g., 150 mg/dL [8.3 mmol/L]) target may be used to avoid subsequent hypoglycemia if the participant has remaining insulin on board or there is concern for glucose instability.

Ketonemia: Definition — Ketones ≥ 0.6 mmol/L

1. Notify QMP of any ketones ≥ 0.6 mmol/L.
2. QMP should provide appropriate medical treatment, including insulin, hydration (oral or IV), and carbohydrates as appropriate.
3. Repeat ketones after 1 hour.
4. Ketones will continue to be monitored hourly until < 0.6 mmol/L.

Chapter 14

Conclusion

CGM performance cannot be captured by a single number. As the preceding chapters demonstrate, dependable CGM performance depends on the interaction of multiple evaluation domains. These include, first, analytical performance: measurement traceability, analytical accuracy, and trend accuracy. They also include clinical and system safety: alert reliability, system robustness, and cybersecurity robustness. Finally, they include ecosystem and evidentiary rigor: interoperability, usability, and study design. Each domain should be evaluated against the clinical risk of the intended use. This consensus guideline puts that principle into practice through concrete, actionable requirements rather than a general statement of intent.

Several elements of this framework extend beyond those emphasized in prior CGM guidance. Chapter 6 moves beyond single-metric accuracy to a stratified, multi-metric evaluation across the full glycemic range, including glucose and rate-of-change concurrence matrices. It also identifies the Diabetes Technology Society Error Grid and Trend Accuracy Matrix as tools that may be used to evaluate clinical consequences. Chapter 9 introduces a structured interoperability hazard taxonomy and a companion stress-testing matrix. These assessment tools extend performance evaluation beyond the sensor itself to the full connected ecosystem. The interconnected technologies include cloud services, companion applications, and receiving devices. Chapter 12 aligns AI/ML-enabled CGM functions with a predetermined change-control approach. This method reflects current FDA and international expectations, which continue to evolve. It addresses dataset provenance, validation-set independence, and the post-deployment review of adaptive algorithms. Chapter 13 goes a step further than principle alone. It presents, in full operational detail, a protocol template that embodies the study-design and safety-monitoring requirements set out earlier in this guideline. This fully worked template translates the guideline's requirements into an actual trial. The protocol is offered as a framework, rather than as a fixed prescription. Investigators, sponsors, and research sites should adapt it to the specific CGM system, intended use, and population under evaluation when designing studies of CGM performance. The Manufacturer Checklists closing most chapters translate the document's narrative requirements into auditable action items. Therefore, the guideline can function as a working reference rather than only a statement of principle.

Readers should apply these chapters as an integrated whole. No single chapter, metric, or checklist item independently establishes that a CGM system is safe or effective. Evaluation should weigh evidence in proportion to the clinical risk of the intended use, the target population, and the conditions of use.

Manufacturers should generate and maintain evidence for the complete CGM system, including connected applications and cloud services. They should also apply design, quality, and risk-management controls that sustain performance over the product lifecycle. Investigators should conduct studies that reflect target populations and intended wear periods. These studies should also reflect real-world conditions of use, including clinically relevant glycemic ranges and system configurations.

Regulatory authorities and standards organizations can apply this framework to support consistent, risk-proportionate evaluation across products and jurisdictions. Clinicians, diabetes care specialists, health systems, and payers should weigh the totality-of-evidence, rather than isolated accuracy figures, when evaluating CGM technologies. People with diabetes should remain central to these considerations, with continued attention by technology developers to usability, burden of use, and real-world safety.

This guideline complements, and does not replace, applicable laws, standards, and regulatory guidance. It should

be applied in the context of a device's intended use, risk classification, and connected-system configuration. It does not establish independent performance or clinical-effectiveness requirements for therapeutic systems, including AID systems, or stand-alone clinical decision-support systems, but it applies wherever interactions with CGM data affect CGM performance, safety, or intended use.

Periodic review and revision will be necessary as CGM technologies, clinical applications, and regulatory expectations evolve. Future work should extend evidence in underserved contexts, such as pediatric, pregnancy, CKD, and inpatient populations. By applying a comprehensive, risk-proportionate, and evidence-based framework across the CGM lifecycle, this guideline is intended to support more reliable glucose information and safer decision-making for people with diabetes, their care teams, and the health systems that serve them.

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