SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Sensor, glucose, invasive, non-adjunctive, factory-calibrated, user-initiated

Device Trade Name: FreeStyle Libre Flash Glucose Monitoring System

Device Procode: PZE

Applicant's Name and Address: Abbott Diabetes Care Inc.
1360 South Loop Road
Alameda, CA 94502

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160030

Date of FDA Notice of Approval: September 27, 2017

II. INDICATIONS FOR USE

The FreeStyle Libre Flash Glucose Monitoring System is a continuous glucose monitoring (CGM) device indicated for the management of diabetes in persons age 18 and older. It is designed to replace blood glucose testing for diabetes treatment decisions.

The System detects trends and tracks patterns aiding in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. Interpretation of the System readings should be based on the glucose trends and several sequential readings over time. The System is intended for single patient use and requires a prescription.

III. CONTRAINDICATIONS

The FreeStyle Libre Flash Glucose Monitoring System must be removed prior to Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or high-frequency electrical heat (diathermy) treatment. The effect of MRI, CT scans, or diathermy on the performance of the system has not been evaluated. The exposure may damage the Sensor and may impact proper function of the device to detect trends and track patterns in the user's glucose values during the wear period.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Freestyle Libre Flash Glucose Monitoring System labeling.

V. DEVICE DESCRIPTION

The FreeStyle Libre Flash Glucose Monitoring System (FreeStyle Libre System, System, or Libre) uses an electrochemical sensor to monitor glucose levels in interstitial fluid (ISF). The sensor is held in place by an adhesive and incorporates both the subcutaneously implanted sensor and associated electronics. The sensor uses a glucose oxidase enzyme to oxidize glucose and transfer electrons to a metal electrode, producing a current. The strength of the current is proportional to the amount of glucose present in the subcutaneous space. The system converts the electrical current signal to a glucose value for display to the user on a handheld Reader.

The system is distinct from other currently marketed CGM devices in the following ways:

- It is calibrated at the point of manufacture (i.e., factory-calibrated) and does not require or accept any user-entered calibration
- It can be worn for up to 10 days following the initial 12 hour warm-up period
- It does not provide any glucose information, alarms, messages, or alerts to users unless the user initiates a scan of the sensor (e.g., no passive alerts for hypo- or hyperglycemia)

The FreeStyle Libre System consists of three primary components:

Sensor
The disposable Sensor can be worn for up to 10 days following the initial 12-hour warm-up period and consists of three primary elements:

- An outer casing that contains the electronics required to power the Sensor, measure temperature, maintain a memory of Sensor data, and facilitate wireless transmission of Sensor data to the Reader via radiofrequency communication.
- A medical grade adhesive layer that adheres the Sensor to the surface of the skin for the duration of wear.
- A sensor tail that is inserted into the subcutaneous tissue on the back of the patient's upper arm and generates an electrical current via the oxidation of glucose from the interstitial fluid. The sensor tail is electrically connected to the Sensor electronics to allow measurement of Sensor data.

Sensor insertion device
The Sensor insertion device consists of two secondary disposable single use components (Sensor Pack and Sensor Applicator) that require user assembly prior to Sensor application. The Sensor Pack is sterilized and is preloaded with the sensor tail loaded into an introducer needle while the Sensor Applicator is preloaded with the Sensor outer casing, internal electronics, and skin adhesive. To assemble these

components, the Sensor Applicator is aligned and pressed firmly into the Sensor Pack, which results in an assembled Sensor contained within the Sensor Applicator. After Sensor application the introducer needle is automatically retracted into the Sensor Applicator, which serves as a container for disposal.

Reader

The Reader is a small hand-held device that contains an antenna and the associated electrical circuitry to receive raw Sensor measurement data from up to 1.5" (4cm) away through wireless radiofrequency (RF) communication. The Reader collects glucose data from the Sensor and can store up to 90 days of information including glucose readings and notes. The Reader employs signal processing algorithms to convert the measurement data into glucose results. The Reader supports functionality of the single front button and a touchscreen color display for user interface navigation, user settings, power management, and a micro-USB port for battery charging and data upload to a computer installed with the FreeStyle Libre data management software. The Reader incorporates a built-in blood glucose meter, which can be used in combination with FreeStyle Precision Neo Blood Glucose Test Strips (K171941) to test blood glucose in a whole blood sample drawn from the fingertip or to test a control solution to assess functionality of the built-in blood glucose meter and compatible test strips.

The user assembles and applies the Sensor to the back of the upper arm, and uses the Reader to activate the Sensor. Twelve hours after the Sensor is successfully activated, the Reader can be used to check glucose. The FreeStyle Libre System is factory calibrated and does not require, or allow, calibration with blood glucose values, for example as obtained from a blood glucose monitoring system (glucose meter) typically used for glucose self-monitoring for diabetes management.

The FreeStyle Libre System allows the user to wirelessly query glucose data from the Sensor by bringing the handheld Reader in close proximity (within 1.5" or 4cm) of the Sensor; i.e., scanning a Sensor. The act of scanning a Sensor initiates Reader calculations of real-time glucose measurements (glucose values) accompanied by trend information (glucose arrows) and historic eight-hour glucose results (glucose graph) that are presented on the Reader display. The Reader does not passively capture glucose information in the absence of a scan. Therefore, glucose values, trend information, and system messages are completely dependent on user-initiated action (a scan). In the absence of a scan; for example, when a user is sleeping, or otherwise occupied or distracted, and unable to scan their Sensor, the Reader is not able to alert users to high or low glucose levels, or changing glucose levels. Users must scan the sensor in order for the Reader to display current glucose levels and trends and provide any appropriate glucose-level or trend related messages. However, users can configure the Reader to provide reminders at specific times of the day, or on a timer (e.g., a specific amount of time after the current time). Reminders will be activated even if the Reader is turned off.

The FreeStyle Libre System is intended for single patient use and the Reader can only pair with one Sensor at a time. If the Reader activates a Sensor it cannot activate a second Sensor without discontinuing interaction with the first.

The Sensor may be scanned by the Reader as frequently as a user desires, and a current glucose value will be displayed in one minute increments. If consecutive scans occur within one minute, the same glucose result may be displayed as the previous scan.

The Sensor automatically stores glucose data every fifteen minutes. During a scan, the preceding eight hours of glucose data are transferred to the Reader, where those data are logged and may be viewed by the user. The Sensor has an eight-hour memory capacity and must be scanned every eight hours to ensure complete data capture by the Reader. If the Sensor is not scanned every eight hours then only the most recent eight hours of data will be captured and any data generated outside of an eight-hour period covered by a scan will be lost and not available to the user. For example, if a user scans their Sensor before going to sleep, and then sleeps for ten hours before scanning the Sensor again, historic glucose information during the first two hours of sleep will be lost. The Sensor is disposable and may be worn for up to ten days before it must be replaced.

The Reader stores up to about ninety total days of information including glucose readings and notes and provides several options to review the information. The user also has the option to review the information by connecting the Reader USB port to a computer with appropriate software to generate and print additional reports.

The Reader also incorporates a built-in blood glucose meter, which uses a hardware and software design based on the FreeStyle Precision Neo Blood Glucose Monitoring System (K142928). Use of the Freestyle Precision Neo test strips with the Freestyle Libre built-in glucose meter was reviewed concurrently with this PMA, in K171941. The built-in test strip port can be used to test blood glucose or to test the meter and strip functionality using a control solution.

Additional information about the device components and their function can be found in the Freestyle Libre Flash Glucose Monitoring System User's Manual.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the control of diabetes. Control of diabetes can be achieved through a combination of methods and behaviors. Self-behaviors include healthy eating, taking medications as appropriate, and being active. Methods of controlling glucose levels (glycemic control) have been shown to reduce severe diabetes-related complications. Methods of monitoring glycemic control include periodic measurement of Hemoglobin A1c (HbA1c), which reflects average blood glucose levels over a three month period. Self-monitoring of blood glucose using glucose meters and test strips provides quantitative measurements of fingerstick blood glucose at a single point in time for patients and their healthcare providers to monitor the effectiveness of glycemic control and make more immediate treatment modifications. Continuous glucose

monitors can be used for detecting glycemic control trends and patterns when used as adjunctive devices to complement, not replace, information obtained from glucose meters; All other currently approved continuous glucose monitors can also provide real-time passive alerts and alarms to users in the absence of user initiated action. Information from some continuous glucose monitors can be used to make diabetes treatment decisions. Automated insulin delivery devices can be used to automatically adjust insulin delivery from an insulin pump based on glucose data generated from a continuous glucose monitor.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with their healthcare provider to select the method that best meets their needs, expectations and lifestyle.

VII. MARKETING HISTORY

The FreeStyle Libre System has not been marketed in the United States.

A different version of the FreeStyle Libre System has been marketed in the following countries – Australia, Austria, Belgium, Brazil, Chile, Finland, France, Germany, Greece, Japan, Kuwait, Israel, Italy, Netherlands, Norway, Saudi Arabia, Spain, Sweden, Switzerland, United Arab Emirates, and United Kingdom since September 2014. A different version has been marketed in Canada since July 2017.

The device has not been withdrawn from marketing in any of these countries for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects associated with the use of the device:

The following are possible adverse effects of inserting a sensor and wearing the adhesive patch: local erythema (redness), local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, and adhesive irritation. There is a remote risk of sensor or needle fracture during insertion, wear or removal, with fragments retained under the skin.

There are potential adverse effects associated with making diabetes treatment decisions when glucose values and rates of change provided by the device are inaccurate, as follows:

The risks of making treatment decisions based on falsely high readings include inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong existing hypoglycemia which can result in seizures, loss of consciousness, and rarely, death.

The risks of making treatment decisions based on falsely low readings include inappropriate administration of carbohydrates. These inappropriate treatments could increase the risk of hyperglycemia or prolong existing hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and acute diabetic ketoacidosis (DKA) which can result in weakness, seizures, and death.

Inaccurate calculation of the rate of change of glucose by the device could increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. Inaccurate calculation of the rate of change of glucose by the device could also prevent a patient from taking measures to prevent a sustained increase or decrease in glucose levels, which could lead to serious hypoglycemia or hyperglycemia.

There are potential adverse effects associated with making acute and long-term therapy adjustments when glucose values and rates of change provided by the device are inaccurate. The risks of making therapy adjustments based on inaccurate device information include inappropriate adjustment of diabetes medication regimens. This could increase the risk of hypoglycemia and corresponding risk of seizures, loss of consciousness, and rarely, death; it may also increase the risk of hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and risk of acute diabetic ketoacidosis (DKA) which can cause weakness, seizures, and death.

The device also provides glucose threshold and predictive messages (alerts) when the Sensor is scanned; these alerts may cause a user to take action to prevent potential future glycemic events (e.g., set reminders for future glucose checks or future action, or take immediate treatment-based action). Potential adverse events may therefore also result from inaccuracies that cause a failure to trigger alerts, or cause false alerts. This may cause users to take an inappropriate action, or incorrectly take no action, and result in increased risk or prolongation of hyperglycemia or hypoglycemia.

In the absence of a user-initiated action (scan) the system cannot provide glucose-related alerts, which could serve to notify users of an actual or impending glucose value above or below glucose thresholds. The lack, compared to currently approved continuous glucose sensors, of alerts in the absence of user-imitated action (scan) could increase the risk of severe hypoglycemia or diabetic ketoacidosis through decreased opportunities for detection of hypoglycemia or hyperglycemia relative to other similar currently marketed continuous glucose sensors.

For the specific adverse events that occurred in the clinical studies please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Bench Performance Testing

Non-clinical testing was conducted at the System level as well as on individual components of the Reader, Sensor insertion device, and sensor component.

- System electrical safety, environmental, and functional testing demonstrated compliance to IEC 60601-1, IEC 60601-1-2, IEC 60601-1-11 and IEC 15693 while usability testing of the System in accordance with EN 62366 demonstrated that the System meets the needs of the intended use conditions (See Table 1).
- Reader mechanical and electrical testing met the design requirements (See Table 2).
- Sensor insertion device mechanical, electrical, and functional testing met the design requirements (See Table 3).
- Sensor component testing of sensitivity, variability, response time, linearity, and temperature sensitivity met the design requirements. Interfering substances testing has been conducted and appropriate labeling has been determined based on the testing results. Labeled operating temperatures were demonstrated to have no adverse impact on the Sensor performance (See Table 4).

Table 1: System Level Testing

Preclinical Test	Objective	Results
Safety Testing	Verify System compliance with IEC 60601-1.	Pass
EMC Testing	Verify Reader and Sensor compliance with the Radiated Immunity, Magnetic Immunity, Radiated Emissions, and Electrostatic Discharge requirements of IEC 60601-1-2 at elevated levels for home use following FDA guidance on Design Considerations for Devices Intended for Home Use (issued November 24, 2014) Verify Reader compliance with FCC Part 15.209 (General Requirements) and 15.225 (Operation within the band13.110-14.010 MHz) and with the Conducted Emissions and AC Line requirements of IEC 60601-1-2 and IEC CISPR 11. Verify System EMC coexistence ability to obtain Sensor glucose measurement in the presence of other RF wireless in-band devices based on FDA guidance.	Pass
Environmental Operation	Verify Reader and Sensor (excluding sensor component) meets Environmental Operation requirements of IEC 60601-1-11 and is functional over a temperature range of 10ºC to 45ºC and humidity range of 10% to 90% RH	Pass
Environmental Storage	Verify Reader meets Environmental Storage requirements of IEC 60601-1-11 and is functional after exposure to a temperature range of -20ºC to 60ºC and	Pass

	humidity range of 10% to 90% RH	
Altitude	Verify System meets the Altitude requirements of IEC 60601-1-11 subclause 4.2.2.	Pass
Reader RF Carrier Frequency Test	Verify Reader supports the wireless communication using a frequency of 13.56 MHz ± 7 KHz by directly measuring the radio's main carrier frequency.	Pass
Reader and Sensor Radio Communications Range Test	Verify Reader and Sensor can successfully wirelessly send and receive data within the specified distance.	Pass
Sensor Radio Communications Timing Test	Verify time required to transfer Sensor glucose information to the Reader from the Sensor meets the specification requirement.	Pass
System In-Band EMC Rejection Test	Verify System does not produce erroneous glucose data in the presence of RFID systems.	Pass
Human Factor / Usability	Validate System meets the needs of the intended use conditions in accordance to EN 62366 and EN 60601-1-6. A summative study in a simulated use environment evaluated at minimum 20 participants in each intended user group (Patients group and Caregiver group) representing the overall characteristics of the intended user populations. Participants were not provided System training, and were given typical use scenarios to complete.	Pass

Table 2: Reader Level Testing

Preclinical Test	Objective	Results
Physical Design	Verify Reader meets dimensional and mass design requirements.	Pass
Mechanical Stress Testing	Verify Reader meets the drop, shock, and vibration test requirements as specified in IEC 60601-1 and IEC 60601-1-11.	Pass
Button Cycling	Verify Reader button is capable to withstand the specified cycle requirements based on typical use assumptions	Pass
Micro USB Connector	Verify Reader has a micro-B USB connector that withstands a minimum of insertions	Pass
Strip Connector	Verify that the strip connector meets design and contact resistance requirements	Pass
Fluid Resistance	Verify that the Reader's capability to remain undamaged and fully operational after cleaning for a number of cycles based on the Reader's typical use assumptions for cleaning.	Pass
Cleaning and Disinfection	Verify that the Reader is capable to maintain undamaged and fully operational after cleaning cycles	Pass

Robustness and Efficacy Tests	based on typical use assumptions and that the Reader meets the cleaning and disinfection requirements set forth in the FDA Letter to Manufacturers of BGM Systems dated September 30, 2010	
Strip Connector Compatibility and Performance Testing	Verify that the Reader strip port is compatible with strips and verify that the strip connector is designed to perform the minimum number of cycles based on Reader's typical use and maintain contact resistance requirements	Pass
Reader and G3cP Strip Claim Support Testing	Verify that laboratory tests – including linearity, dynamic range, within run precision, day-to-day precision, hematocrit, temperature and humidity, interference and altitude studies – support claims of the Reader use Precision Neo strips.	Pass
Work and Trigger Bias Voltage Tests	Verify that the Reader is capable of generating and maintaining poise voltage at the Work and Trigger terminal.	Pass
Work and Trigger Terminal High Impedance (Hi-Z) Test	Verify that the Reader has the ability of setting the Work and Trigger Terminal at the impedance requirement	Pass
Work and Trigger Electrode Accuracy Test	Verify the Work and Trigger electrode current measurement accuracy are at specified requirements	Pass
Work Peak Sampling Frequency Test	Verify that the Reader is able to measure Precision Working Electrode current at specified requirement	Pass
Battery Tests	Verify that the Reader provides circuitry to charge the battery by identified power supply and provides battery monitoring capability. Verify the Reader recharging capability and battery life meets the specified requirements.	Pass
Hardware Tests	Verify the Reader hardware functions including reset, time and date accuracy, audible indicators and volume, display / legibility capability, and USB meet the specification requirement.	Pass

Table 3: Sensor Insertion Device Level Testing

Nonclinical Test	Objective	Results
Physical Design	Verify Sensor insertion device components meet dimensional and mass design requirements.	Pass
Tamper Evidence	Verify packaged Sensor insertion device is tamper evident.	Pass
Mechanical	Verify Sensor Container is operational after	Pass

Stress Tests (Sensor Container)	subjected to drop testing, vibration testing, or shock testing as specified in IEC 60601-1 and IEC 60601-1-11.	
Mechanical Stress Tests (Sensor Applicator)	Verify Sensor Applicator is operational after subjected to drop testing, vibration testing, push testing, or shock testing as specified in IEC 60601-1 and IEC 60601-1-11.	Pass
Functionality over Temperature Range	Verify Sensor Applicator and Sensor Container are operational over temperature range of 10ºC to 45ºC	Pass
Internal Relative Humidity	Verify Primary Sterile Packaged Sensor Container internal cavity maintains a specified internal environment during the shelf life.	Pass
Sensor Container Rigid Finger Test	Verify sharp cannot be contacted by rigid finger when applied to the Primary Sterile Packaged Sensor Container based on the requirement by IEC60601-1.	Pass
Sensor Container Foil Lid Removal Force	Verify force required to remove the Foil Lid from the Sensor Container meets specification.	Pass
Sensor Applicator Cap Removal Torque	Verify torque required to remove the Cap from the Sensor Applicator meet specification.	Pass
Assembly Force	Verify force required to assemble the Sensor Applicator to the Sensor Container meets specification.	Pass
Armed Applicator Component Position	Verify armed Applicator design ensures: • Sharp tip is above the skin interface plane. • Adhesive pad is above the skin interface plane • Sharp tip penetration depth meets specification.	Pass
Applicator Insertion Force	Verify applicator insertion force meets specification.	Pass
Audible and Tactile Feedback	Verify Sensor insertion device provides audible and tactile feedback when: • Preparation of Applicator components for application is complete • Sensor Application is complete	Pass
Applicator Sensor Location	Verify Applicator affixes the Sensor on the user's skin at the intended location.	Pass

Triggered Applicator Visual Indication	Verify Triggered Applicator provides a visual indication that the device has already been triggered.	Pass
Triggered Applicator Rigid Finger Test	Verify sharp cannot be contacted by rigid finger based on the requirement by IEC 60601-1.	Pass
Triggered Applicator Drop Test	Verify Triggered Applicator sharp cannot be contacted by a rigid finger after being dropped as required by IEC 60601-1.	Pass
Applicator Re-Use	Verify Applicator prevents reuse and that sharp is not exposed in the triggered condition.	Pass
IP27 Rating	Verify Sensor (excluding the sensor tail) complies with the waterproof grade (IP 27 rating) per IEC 60529 and remains operational after exposure to 1 meter of water for 30 minutes.	Pass
Mechanical Stress Tests (Sensor)	Verify Sensor (excluding the Sensor tail) is operational after subjected to drop testing, vibration testing, shock testing, or steady force testing as specified in IEC 60601-1 and IEC 60601-1-11.	Pass
Sensor Battery Test	Verify that the Sensor battery has limited battery switch leakage current, provides sufficient energy for beyond the wear duration, and has a means to be turned off.	Pass
Sensor Electrical Tests	Verify that the Sensor electronic clock frequency is accurate over the specified range.	Pass
	Verify glucose sensor current measured by the Sensor meets the resolution and measurement range requirement.	Pass
	Verify operating potential provided by the Sensor electronics meets the poise voltage requirement.	Pass
	Verify Sensor ability to measure temperature accurately at the bottom of the Sensor within the specified temperature range.	Pass

Table 4: Sensor Component Level Testing

Nonclinical Test	Objective	Results
Sensitivity	Verify sensor component has acceptable sensitivity of generating the electrical signal across the range of glucose concentrations.	Pass
Variability	Verify that the sensitivities of the sensor components built within one lot are consistent with low variability.	Pass
Response Time	Verify that the sensor component is able to respond to glucose changes within specification.	Pass

Linearity	Verify that the sensor component output is proportional to glucose across the range of glucose concentrations.	Pass
Temperature Sensitivity	Verify that the sensor functional performance meets the environmental requirements for operation and storage.	Pass
Interference Substances	Verify that potential interferents do not adversely impact sensor performance. Based on testing, the following statements are included in the product labeling: Taking ascorbic acid (vitamin C) while wearing the Sensor may falsely raise Sensor glucose readings. Taking salicylic acid (used in some pain relievers such as aspirin and some skin care products) may slightly lower Sensor glucose readings. The level of inaccuracy depends on the amount of the interfering substance active in the body.	Pass
Dimensions	Verify that the sensor component tail meets the dimensional requirements.	Pass
Maximum Sensor Current Test	Verify that the Sensor current output is less than the specified maximum value over the specified range of skin temperature and glucose concentration	Pass
Sensor Current Measurement Range and Resolution Test	Verify that sensor current measurements performed by the Patch electronics are sufficient to provide the required glucose measurement resolution and range	Pass

Software Verification and Validation

Verification and validation testing was conducted to confirm that the software used in the System performed in accordance with established specifications and FDA Guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," May 11, 2005. This testing confirmed that all requirements were met.

Biocompatibility

Biocompatibility testing was performed on Sensor materials including the outer Sensor casing, adhesive pad, and sensor tail. A summary of the testing performed to support the biocompatibility of the FreeStyle Libre System is provided below in Table 5.

Table 5: Biological Evaluation Tests

ISO 10993 Subpart	Test(s) Performed	Test Method	Result
ISO10993-3	Genotoxicity	• In Vivo Mouse Micronucleus • Chromosomal Aberration • Ames Test	Pass
ISO10993-4	Hemocompatibility / Hemolysis	ASTM F756 Extraction Method	Pass

ISO10993-5	Cytotoxicity	MEM Elution	Pass
ISO10993-10	Sensitization	Magnusson-Kligman Method	Pass
	Irritation: Intracutaneous Toxicity	Intracutaneous Reactivity Test	Pass
ISO10993-11	Systemic Toxicity	• Material Mediated Pyrogenicity	Pass
		• Systemic Injection	Pass
ISO10993-6	Implantation	• Systemic Toxicity pathology following 4 Week Implant • Systemic Toxicity pathology following 26 Week Implant	Pass

Sterility

Electron beam sterilization validation of the Sensor Pack, which contains the insertion sharp and sensor tail, was performed per ISO11137-1 and ISO 11137-2. Sterilization validation confirmed that the Sterility Assurance Level (SAL) of 10-6 is achieved with the selected target dose of 25kGy. The sterilization dose was established by the $VD_{max}25$ method described in ISO 11137-2.

An initial bioburden recovery test method was performed on two lots of Sensor Packs to determine the bioburden recovery factor. This value and the average bioburden determined from three lots were used to calculate the $VD_{max}25$ dose. A verification dose experiment conducted using 10 samples from one production equivalent Sensor Pack lot resulted in zero positive tests and substantiated the target 25 kGy dose.

Shelf Life, Packaging, and Shipping of the Sensor Kit

The Sensor Kit device and packaging integrity over the shelf life was demonstrated by subjecting test units to worse case sealing parameters, sterilization parameters, and 24-pack shipping configuration. Units were also conditioned through a worse case sequence of storage, handling and transit challenges prior to testing. Attributes related to seal integrity, user accessibility, and device functionality met acceptance criteria.

B. Animal Studies

No animal studies were conducted in support of the FreeStyle Libre System.

C. Additional Studies

None

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study of one-hundred and twenty-five US subjects under IDE G140124 and two additional clinical studies of one-hundred and twenty-six subjects outside the US (OUS) to assess the clinical accuracy and precision performance of the device. After submission of this PMA, the applicant modified the device to

improve the accuracy of the device over the use life and amended the PMA submission with an updated device design and new clinical data. Fifty additional subjects were subsequently studied in a pivotal clinical study in the US to validate modifications to the device and establish the clinical measurement performance characteristics across the wear period of the sensor (10 days following a 12-hour warm up period). The clinical measurement performance characteristics established in this study included the accuracy across the claimed measuring range (40 to 500 mg/dL glucose), precision, performance of glucose messages (messages are only available for this device when the user initiates a scan), and the number of readings displayed across the wear period. In addition, results from the two-hundred and fifty-one combined subjects in the first US clinical study and two OUS clinical studies were re-analyzed to account for modifications to the final device. These re-analyzed study results were similar to results obtained in the new pivotal US clinical study.

Data from both US clinical studies (the original US clinical study reanalyzed for performance with the modified device design, and the new (pivotal) US clinical study performed using the modified device) were the basis for the approval decision. Results from the pivotal (second, more current) study were the primary source of performance information used to support a decision of safety and effectiveness for the device. An example of the differences in performance observed between in the original US clinical study and the pivotal US clinical study is provided in Section X.D.2 below. Key measures of the accuracy and precision of the device demonstrated in the pivotal US clinical study conducted by the applicant are presented in additional detail in Tables 10-19 in Section X.D.2 below.

The applicant also conducted two additional clinical studies in Europe to asses short and long-term glycemic outcomes in patients with Type 1 and Type 2 diabetes; these studies provided additional information to support a determination of safety and effectiveness of the device and are further discussed in Section XI, below.

A. Study Design

A total of fifty subjects with Type 1 or Type 2 Diabetes and who were at least 18 years of age were recruited to the study. Two subjects were discontinued due to screen failure. Therefore, a total of forty-eight evaluable subjects, defined as subjects that successfully wore at least one Sensor resulting in at least one paired Freestyle Libre System and laboratory reference method result, were included in the analysis. The first subject was enrolled in the study on April 13, 2017; the final visit for the last subject was completed on May 23, 2017 with the last follow up visit on May 30, 2017. The data analyzed for this study reflected all data collected for all forty-eight evaluable patients. There were four investigational sites.

The purpose of the study was to evaluate the clinical accuracy and precision performance of the Freestyle Libre System over the claimed use life (10 days) in adult subjects with diabetes mellitus. This study was a pivotal, non-randomized, single arm, multi-center, prospective study. Subjects wore two Sensors (one on the back of each

upper arm) for up to the full claimed use life (10 days) following Sensor application. The first Sensor that was applied to the subject was considered to be the Primary Sensor, while the other one was considered the Secondary Sensor, provided that both Sensors reported glucose readings for the same duration (i.e. if both survived on-body and collected glucose data for the full evaluation period). If, however, one or both Sensors fell off the body or otherwise failed, the Sensor that reported glucose readings for the longest duration during the evaluation period (i.e. the Sensor that remained on-body and collected glucose data for the longest period of time) was considered to be the Primary Sensor.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the clinical study was limited to patients who met the following inclusion criteria:

   - Be at least 18 years of age.
   - Have a diagnosis of type 1 or type 2 diabetes mellitus.
   - Require insulin therapy through and insulin pump and/or multiple daily insulin injection (at least 3 injections daily).
   - Be willing to perform a minimum of 8 finger sticks per day during the study.
   - Be willing to fast four individual times prior to in-clinic visits, each fast lasting a minimum of eight hours.
   - Be able to read and understand English.
   - Be able to follow the instructions provided to him/her by the study site and perform all study tasks as specified by the protocol.
   - Be available to participate in all study visits.
   - Be willing to provide written signed and dated informed consent.

   Patients were not permitted to enroll in the clinical study if they met any of the following exclusion criteria:

   - Have known allergy to medical grade adhesive or isopropyl alcohol used to disinfect the skin.
   - Be pregnant, attempting to conceive or not willing and able to practice birth control during the study execution (applicable to female subjects only).
   - Have extensive skin changes/diseases at the proposed application sites that could interfere with device placement or the accuracy of interstitial glucose measurements.
   - Be participating in another clinical trial.
   - Have donated blood within 112 days (3.7 months) prior to the beginning of the study activities.
   - Be anemic.
   - Have a concomitant medical condition which could interfere with the study or present a risk to the safety or welfare of the subject or study staff. Such conditions included but were not limited to:
     - History of HIV, Hepatitis B or C

- Have X-ray, MRI or CT appointment scheduled during the period of study participation, and the appointment cannot be rescheduled for a time before study participation starts or after study participation ends.
- Unsuitable for participation due to any other cause as determined by the Investigator.

2. Follow-up Schedule
   Subjects were scheduled to make seven visits to the clinical study site; including the Enrollment/Screening visit (Visit 1) and Sensor application visit (Visit 2). Subjects had a total of four in-clinic visits (Visit 3, Visit 4, Visit 5 and Visit 6) across the full claimed Sensor wear period (10 days) for venous plasma sample collection.

3. Clinical Endpoints
   The study characterized the performance of the System in comparison with the laboratory reference venous plasma sample measurements and assessed the system-reference matched pairs obtain in the in-clinic sessions.

   Safety data for the Freestyle Libre System were also collected and characterized by incidence, severity and relatedness. Device incidents and malfunctions were also collected.

B. Accountability of PMA Cohort

Fifty subjects were enrolled in the PMA study; two subjects were discontinued due to screen failure and therefore forty-eight subjects were available for analysis at the completion of the study. A total of one-hundred-and-eleven sensors with attempted insertion were used in the study. Fourteen sensors did not produce real-time glucose readings post insertion because they were erroneously loaded with incorrect software. The remaining ninety-seven sensors were loaded with correct study software. One of these ninety-seven sensors did not produce any glucose readings following the time of sensor activation; the remaining sensors generated real-time glucose readings that were able to be analyzed compared to glucose results from paired samples generated using a laboratory glucose measurement method.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a clinical accuracy and precision study for this type of device performed in the US. See Tables 6 through 9 for a description of the demographics and baseline characteristics of the study population of evaluable subjects.

Table 6: Demographic Information

Demographic		Overall	
		N	%
Sex	Female	25	52.1
	Male	23	47.9
Race	White - Not Hispanic or Latino	42	87.5
	White - Hispanic or Latino	4	8.3
	Native Hawaiian or Pacific Islander	1	2.1
	Other†	1	2.1
Education	College Education and above	21	43.8
	Some College	22	45.8
	Further Education not completed	5	10.4
Type of Diabetes	Type 1	46	95.8
	Type 2	2	4.2
Insulin pump use	Yes	26	54.2
	No	22	45.8

†Race was reported as 'Chilean'.

Table 7: Participant Baseline Characteristics

Characteristic		Mean ± SD	Median	Range
Age (years)		41.1 ± 14.4	41.5	18 to 72
Weight	pounds	180.1 ± 41.0	185.3	110.8 to 328.6
	kilograms	81.7 ± 18.6	84.1	50.3 to 149.1
Height	inches	66.9 ± 4.4	66.0	60.0 to 78.0
	meters	1.70 ± 0.11	1.68	1.52 to 1.98
Body Mass Index		28.1 ± 5.1	28.5	20.2 to 41.1
Duration of Insulin Use (years)		21.3 ± 12.3	18.5	3.0 to 51.0
Total number of injections per day (N subjects=22)		4.3 ± 0.7	4	3 to 6
HbA1c (%)		7.7 ± 1.3	7.4	5.9 to 11.1

Table 8: Participant HbA1c distribution

HbA1c Range	N	%
HbA1c < 7%	14	29.2
7% ≤ HbA1c ≤ 8.5%	21	43.8
HbA1c > 8.5%	13	27.1
Total	48	100.0

Table 9: Participant BMI distribution

Body Type Category (BMI Range)	N	%
Underweight (< 18.50)	0	0.0
Normal (18.50 - 24.99)	17	35.4
Overweight (25.00 - 29.99)	12	25.0
Obese Class I (30.00 - 34.99)	15	31.3
Obese Class II (35.00 - 39.99)	3	6.3
Obese Class III (≥ 40.00)	1	2.1
Total	48	100.0

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on all subjects enrolled. The key safety outcomes for this study are presented below. All fifty enrolled subjects were included in the safety analysis. There were no unanticipated adverse device effects or serious adverse events reported.

Adverse effects that occurred in the PMA clinical study:

There were a total of seventeen adverse events that occurred during the course of the study, as follows:

Six adverse events were reported by five subjects who experienced an adverse reaction at the Sensor application site. There were three reports of mild bruising at the sensor insertion site in three subjects, and three reports of well-defined redness erythema at the sensor insertion site in two subjects.

Eleven adverse events beyond those related to a Sensor application site were reported by eight subjects. Three of these were related to study procedures and included mild bruising at the IV insertion site, one report of IV infiltration reported as moderate in severity, and one report of mild erythema from the left elbow. The eight remaining events were considered to be both unrelated to the study device and unrelated to the study procedures. These consisted of the following: three reports of hypoglycemia, one report of laceration on the right index finger, one report of headache, one report of head cold, one report of coughing, and one report of a lump on the right torso worsening.

2. Effectiveness Results

The pivotal study demonstrated that modifications to the device made by the applicant improved performance relative to the performance observed in the first (original) US study. For example, as one measure of overall performance, the mean absolute relative difference (MARD) relative to a laboratory glucose measurement method determined in the first US study was 12.5%; following the

applicant's modifications to the device the MARD observed in the pivotal US study was 9.7%.

The analysis of effectiveness with regards to device accuracy was based on all paired data points collected during all study visits for primary sensors worn by study subjects during the study that matched readings from the primary sensor worn by each subject for the Freestyle Libre System with reference values ("reference") from a laboratory measurement method (YSI 2300 analyzer) within the Freestyle Libre System measuring range (for Libre readings only) or 40-500 mg/dL. Each study subject had their blood glucose analyzed up to 128 times using the laboratory measurement method over four separate visits to the clinical center. This resulted in a total of 5772 paired data points across all subjects. Additional analysis of effectiveness was based on each pair of glucose readings, obtained within five minutes, of the two Sensors worn simultaneously on each subject with matched wear time for subjects for whom the data were available (7319 paired readings). Analysis of sensor wear duration was based on the use lifetime of ninety-seven primary and secondary sensors applied to subjects in the study. Key effectiveness outcomes are presented below in Tables 10 to 18.

Agreement Relative to Reference

Agreement was characterized using paired Freestyle Libre System values and reference values. These values were compared by pairing the reference blood glucose value to the Libre glucose reading that occurred immediately after the reference glucose value was collected. For values greater than 80 mg/dL, the absolute percent difference (%) from the reference values was calculated and the agreement of the Freestyle Libre System to blood glucose values was assessed by calculating the percentage of Freestyle Libre System readings that were within 15%, 20%, 30%, 40% and more than 40% different from the reference values. For readings less than or equal to 80 mg/dL, the absolute difference in mg/dL between the two glucose results was calculated and the agreement of the Freestyle Libre System to blood glucose values was assessed by calculating the percentage of Freestyle Libre System readings that were within 15 mg/dL, 20 mg/dL, 30mg/dL, 40 mg/dL and greater than 40mg/dL different from the reference values. The results are presented below in Table 10 for all paired data points in the study and broken down by glucose concentration range (as measured by the Freestyle Libre System).

Table 10: Freestyle Libre System Agreement with Reference Glucose Measurements within Freestyle Libre Glucose ranges

Libre Glucose Range (mg/dL)	Number of Libre-Reference Pairs	Within ±15% / ±15mg/dL	Within ±20% / ±20mg/dL	Within ±30% / ±30mg/dL	Within ±40% / ±40mg/dL	Outside ±40% / ±40mg/dL
Overall	5772	82.1	91.0	97.8	99.3	0.7
40-50	38	44.7	57.9	81.6	94.7	5.3
51-80	461	72.2	81.1	92.0	97.6	2.4
81-180	3236	82.9	91.2	97.9	99.3	0.7
181-300	1799	84.9	93.6	99.2	99.7	0.3
301-400	226	77.0	95.1	99.6	99.6	0.4
401-500	12	58.3	75.0	100.0	100.0	0.0

Agreement When the Freestyle Libre System Reads "LO" or "HIGH"
The System reports glucose readings between 40 and 500 mg/dL. When the System determines the glucose reading is below 40 mg/dL, it displays "LO" on the Reader display. When the System determines that the glucose reading is above 500 mg/dL, it displays "HIGH" on the Reader display. Because the System does not display glucose readings below 40 mg/dL or above 500 mg/dL, the comparisons to the actual blood glucose readings (as determined by a laboratory reference analyzer) when the Freestyle Libre System Reader displays "LO" or are included separately in Table 11. No glucose measurements made by the Freestyle Libre System were above 500 mg/dL in the clinical study. Table 11 include the total number of values and the cumulative percentages when reference values were less than specific glucose readings when "LO" was displayed on the Freestyle Libre System Reader.

When the System displayed "LO" (21 occasions during the clinical study), none of the reference values was less than 40 mg/dL. 100% of the reference values were greater than 40 mg/dL, 95.2% were greater than 50 mg/dL, 80.9% were greater than 60 mg/dL, 42.8% were greater than 70 mg/dL and 19% were greater than 80 mg/dL (all of these values greater than 80mg/dL were between 81 and 120 mg/dL).

Table 11: % Of Reference Readings in Specific Glucose Ranges When the Freestyle Libre Reader Displayed "LO"

Libre Reading	Reference glucose values (mg/dL)						N
	<40	>40	>50	>60	>70	>80	
"LO"	0.0	100.0	95.2	80.9	42.8	19.0	21

Concurrence of System and Laboratory Reference

The percentage of concurring glucose values for each reference glucose range with each Freestyle Libre glucose range is presented in Table 12 below. This table describes the percentage of paired reference values that were in the same glucose range (shaded) or in glucose ranges above and below the paired Libre-reference readings. For example, when readings from the Freestyle Libre System were within 81 to 120 mg/dL, reference measurements of blood glucose in the clinical study were also within 81 to 120 mg/dL 75.9% of time. The table also indicates the total number (N) of paired Libre-reference data points within each Libre glucose range.

Table 12: Concurrence of Freestyle Libre Readings and Reference Values

Libre Glucose Range (mg/dL)	Reference Glucose Range (mg/dL)												
	<40	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**401-500**	**>500**	**N**
<40	0	19	61.9	19	0	0	0	0	0	0	0	0	21
40-60	0.7	25.2	58.7	15.4	0	0	0	0	0	0	0	0	143
61-80	0	7.3	45.8	46.3	0.6	0	0	0	0	0	0	0	356
81-120	0	0.2	5.6	75.9	17.6	0.6	0.1	0	0	0	0	0	1222
121-160	0	0	0.1	13.2	72	14.3	0.4	0	0	0	0	0	1435
161-200	0	0	0	0.3	21.9	67.5	10.2	0.1	0	0	0	0	1087
201-250	0	0	0	0	0.9	28.8	64.5	5.7	0	0	0	0	905
251-300	0	0	0	0	0	0.3	41.2	53.4	5.2	0	0	0	386
301-350	0	0	0	0	0	0	1.2	55.3	40.6	2.9	0	0	170
351-400	0	0	0	0	0	0	0	3.6	66.1	30.4	0	0	56
401-500	0	0	0	0	0	0	0	0	25	33.3	41.7	0	12
>500	0	0	0	0	0	0	0	0	0	0	0	0	0

Difference Relative to Reference

Difference between matched data pairs was calculated as difference between Freestyle Libre System reading and reference glucose value. Freestyle Libre System and reference values were compared by pairing the Freestyle Libre System reading that was obtained closest in time to when the reference sample was collected.

For example, if the reference value was 100 mg/dL and the System reading was 110 mg/dL, there was a +10 mg/dL difference. The *mean difference* expressed in mg/dL is the average of all positive and negative differences across all glucose measurements between the Freestyle Libre System and reference method. Dividing the difference (10mg/dL) by the reference value (100 mg/dL) and converting to a percentage yields a 10% difference between the Freestyle Libre System and the reference measurement. Averaging all of these percent (%) differences across all glucose measurements gives the *mean difference expressed in % units*. Whether the mean difference is positive or negative provides information on whether the System, on average across all glucose measurements in the clinical study, read higher or lower on average than the reference method.

For the Freestyle Libre System, the mean difference is 2.5 mg/dL, or 1%; therefore, on average across all glucose measurements in the clinical study, the Freestyle Libre System read 2.5mg/L or 1% higher than the reference method. The Median Difference (in % units) shows that half of the time the System read 0.9% or higher than the reference blood glucose values.
Another estimate used to show the overall accuracy of the Freestyle Libre System is the absolute difference. The absolute difference reports on the difference or "distance" between the Freestyle Libre System and reference values, but does identify whether the System is reading higher or lower than the reference laboratory method. For example, if the reference value was 100 mg/dL and the System reading was 90 mg/dL, there was a -10 mg/dL difference, but a 10 mg/dL absolute difference. The *mean absolute difference expressed in mg/dL* is the average of all positive and negative absolute differences, or "distances" across all glucose measurements between the Freestyle Libre System and Reference method. Converting each absolute difference measurement to percent absolute difference and averaging these produces the *mean absolute difference expressed in % units*; this value is often also referred to as the mean absolute relative difference or MARD.

For the Freestyle Libre System, the mean absolute difference is 14.7 mg/dL, or 9.7%; therefore, on average across all glucose measurements in the clinical study, the Freestyle Libre System read 14.7mg/dL or 9.7% different than the reference method (i.e., the MARD was 9.7%). The Median Absolute Difference (in % units) shows that half of the time the System read within 7.7% of the reference blood glucose values.

Difference measurements are based on 5772 paired glucose results; the data are summarized in Table 13 below. Table 13 presents results across all glucose levels combined.

Table 13. Differences between Freestyle Libre System and Reference Glucose Measurements

units	mean difference	median difference	mean absolute difference	median absolute difference	Number of paired data points
mg/dL	2.5 mg/dL	1.5 mg/dL	14.7 mg/dL	11.3 mg/dL	5772
%	1.0%	0.9%	9.7%	7.7%	5772

Detection of Hypoglycemic and Hyperglycemic Events
When a user performs a scan the Freestyle Libre System displays Glucose Messages to inform them that their glucose levels are currently low or high (Low Glucose or High Glucose messages), or that their glucose levels are predicted to be low or high within the next 15 minutes (Glucose Going Low or Glucose Going High messages). As described above, these messages differ from the alerts and alarms in other approved continuous glucose sensors because the user will only be

alerted if a scan is initiated (i.e., no message will be provided when the user is wearing the Sensor but has not actively scanned it using the reader).

In the clinical study, the Low Glucose and High Glucose messages were set to appear when the glucose levels reported by the Freestyle Libre System were less than 70 mg/dL or more than 240 mg/dL, respectively. The same thresholds were used for the Glucose Going Low or Glucose Going High messages, for glucose levels projected 15 minutes into the future. These glucose thresholds levels can be set by users, but performance at other thresholds was not evaluated in the study. The ability of the System to appropriately provide these messages was assessed by comparing a reference blood glucose result with a Glucose Messages displayed within 15 minutes (before or after the reference result) and determining if appropriate Glucose Message was displayed when the Sensor was scanned.

Table 14 displays percentages for three different parameters:

- Detection Rate – the percent of cases where a Glucose Message *was displayed correctly.*
- Missed Detection Rate – the percent of cases where a Glucose Message *was not displayed but should have been.*
- False Notification Rate – the percent of cases where a Glucose Message *was displayed but it should not have been*.

For example, in the clinical study with the low glucose target set at <70 mg/dL, the System correctly displayed a Low Glucose message within 15 minutes (before or after) 85.4% of reference glucose measurements <70 mg/dL (detection rate). However, 14.6% of the time that a reference glucose measurement was <70mg/dL a Low Glucose message was not displayed within 15 minutes before or after this (missed detection rate). Finally, 39.9% of the times that a Low Glucose message was displayed it should not have been (false notification rate) because the reference glucose level was not <70mg/dL within 15 minutes (before or after) of the message being displayed.

Table 14: Detection of Hypoglycemic and Hyperglycemic Events

Type of Notification	Parameter	Rate (%)
Notification of Hypoglycemic Events (Low Glucose message)	Detection Rate	85.4
	Missed Detection Rate	14.6
	False Notification Rate	39.9
Notification of Hyperglycemic Events (High Glucose message)	Detection Rate	95.1
	Missed Detection Rate	4.9
	False Notification Rate	22.1
Impending Notification of Hypoglycemic Events (Glucose Going Low message)	Detection Rate	95.0
	Missed Detection Rate	5.0
	False Notification Rate	46.8
Impending Notification of Hyperglycemic Events (Glucose Going High message)	Detection Rate	97.2
	Missed Detection Rate	2.8
	False Notification Rate	28.4

Accuracy After warm-up period

After a user inserts a Sensor and activates a Sensor session using the Reader, the Freestyle Libre System enters a 12 hour warm-up period during which no readings are provided to a user when the Sensor is scanned. Once the warm-up period is complete the Sensor can be scanned and provides data to the user for up to 10 additional days. The accuracy of the Freestyle Libre System relative to a laboratory reference measurement in the first eight hours of sensor wear following the completion of the warm-up period was assessed by calculating the percentage of System readings that were within 15%, 20%, 30%, 40%, and beyond 40% of reference measurements for glucose values 80 mg/dL and above; and within 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, and beyond 40 mg/dL of reference measurements for glucose values below 80 mg/dL, in intervals of two hours. The results are presented below in Table 15.

Table 15: Number and Percent of Results within YSI Reference

Time Interval (hours)	Number of paired data points	Within ±15% or ±15mg/dL	Within ±20% or ±20mg/dL	Within ±30% or ±30mg/dL	Within ±40% / ±40mg/dL	Outside ±40% / ±40mg/dL
(0-2)	81	69.1	87.7	100.0	100.0	0.0
(2-4)	318	73.9	84.6	97.2	99.7	0.3
(4-6)	374	76.7	88.0	97.3	99.7	0.3
(6-8)	369	79.9	90.8	99.2	100.0	0.0

Sensor Stability Relative to Reference

Sensors can be worn for up to 10 days following the completion of the 12-hour warm-up period. During the clinical study, Libre System performance was evaluated in comparison to a laboratory glucose measurement method at the beginning (Day 1), middle (Day 4 and Day 7) and end (Day 10) of the wear period (Table 16). Additionally, the percentage of System readings were calculated that were within 15%, 20%, 30%, 40%, and beyond 40% of reference measurements for glucose values 80 mg/dL and above; and within 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, and beyond 40 mg/dL of reference measurements for glucose values below 80 mg/dL, at the beginning (Day 1), middle (Day 4 and Day 7) and end (Day 10) of the wear period (Table 17).

Table 16: Differences Measures Between Freestyle Libre System and Reference Readings

Day	Number of Paired Data Points	Median Absolute Relative Difference (%)	Mean Absolute Relative Difference (%)
1	1497	8.7	10.7
4	1470	7.4	9.6
7	1394	7.4	9.1
10	1411	7.5	9.3

Table 17: Number and Percent of Freestyle Libre System Results within Reference Measurements by Day of Wear

Day	Number or Paired Data Points	Within ±15% / ±15mg/dL	Within ±20% / ±20mg/dL	Within ±30% / ±30mg/dL	Within ±40% / ±40mg/dL	Outside ±40% / ±40mg/dL
1	1497	76.2	87.4	97.9	99.5	0.5
4	1470	82.3	91.4	97.6	99.3	0.7
7	1394	85.0	93.5	98.6	99.3	0.7
10	1411	85.3	92.3	97.9	99.4	0.6

Accuracy of Glucose Trends

The Freestyle Libre System displays arrows to indicate the rate and direction of change of glucose levels. Table 18, below, shows the percentage of time in the clinical study that a specific trend arrow displayed by the Freestyle Libre System was observed as it corresponds to the true direction and rate of change in glucose levels as measured using a laboratory glucose measurement method. For example, in the clinical study, when the trend arrow indicated that glucose was changing slowly (-1 to 1 mg/dL/min (→)), actual glucose levels in the body were falling quickly (↓) 0.3% of the time, falling (↘) 3.7% of the time, changing slowly (→) 83.0% of the time, rising (↗) 3.9% of the time, and rising quickly (↑) 0.5% of the time.

Table 18: Freestyle Libre System Trend Arrow Concurrence

Libre trend arrow	YSI Reference Rate of Change (mg/dL/min)							N
(mg/dL/min)	**<-2**	**[-2, -1)**	**[-1, 0)**	**[0, 1]**	**(1, 2]**	**>2**	**NA***	
<-2 (↓)	26.3	45.5	10.3	1.3	0	0	16.7	156
-2 to -1 (↘)	4.3	27	54.6	3.8	0.6	0	9.7	652
-1 to 1 (→)	0.3	3.7	49.4	33.6	3.9	0.5	8.6	4175
1 to 2 (↗)	0	0.6	8.8	38.6	33.3	9.2	9.4	477
>2 (↑)	0	0	2.8	14.6	34.9	40.6	7.1	212
NA†	2.5	9.1	33.1	20.7	14	9.1	11.6	121

*Glucose rate of change not available due to the time difference between laboratory reference measurement of glucose readings exceeding 30 minutes.
†Glucose Trend Arrow not available.

Precision of System Readings
In the clinical study all subjects wore two Sensors, each paired with a separate Reader. The purpose of this was to determine the similarly with which two Sensors functioned on the same subject (sensor precision). Precision was evaluated by comparing the glucose readings from the two Systems worn on the same subject at the same time. Results based on 7319 paired readings between two sensors worn on the same subject showed that System readings from the two sensors agreed with each other with a 6% coefficient of variation.

Sensor Life
After the 12 hour warm-up period, the Sensor can be worn for up to 10 days. To estimate how long a Sensor will work over the wear duration, 97 Sensors were evaluated in the clinical study to determine how many days of readings each Sensor provided.

Of these 97 sensors, 75 (77.3%) lasted until the final day of use. 84 sensors (86.6%) lasted more than 5 days. There were 22 (22.7%) sensors that failed early, of which 11 (11.3%) failed on or before the fifth day of wear.

System Glucose Availability
The System is designed to produce a glucose reading after each user initiated scan that is performed after the warm-up time throughout the entire wear period. To assess the availability of glucose readings, all scans were analyzed for all Sensors which produced at least one reading during the clinical study over the total wear period. The percentage of available Freestyle Libre System readings was calculated in comparison to the number of scans attempted. Overall, 99.5% of Freestyle Libre Scans produced a reading (9,228 readings from 9,272 scans).

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population. The applicant provided information to support their claim that the device could be used in people with diabetes aged 18 and up.

The Freestyle Libre System is not approved for use in people less than 18 years of age. The labeling states that Sensor readings in this population may be inaccurate and that in general, continuous glucose monitoring systems are recognized to be less accurate in children than in adults and therefore existing clinical data generated with this device in adults could not be leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information

concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The applicant conducted two additional clinical studies, described in additional detail below. These studies were conducted in Europe and enrolled patients with Type 1 or Type 2 diabetes representing subsets of the broader Type 1 and Type 2 diabetes populations in the US. The design and conduct of these studies allowed results to be used to inform an understanding, but not to establish, the potential safety and effectiveness of the device in US patients.

- The REPLACE study, conducted in the European Union, evaluated use of the FreeStyle Libre for diabetes treatment decisions in subjects with Type 2 diabetes on intensive insulin therapy with suboptimal glucose control. This was a 6-month, prospective, open-label, multicenter, randomized controlled trial (RCT), with additional 6-month observational open-access phase, enrolling adults with type 2 diabetes for ≥6 months and an HbA1c between 7.5-12.0% (inclusive). The first six months of the study evaluated the use of the device by patients with Type 2 diabetes. An additional 6-month observational Open Access phase (Days 208-388) was also included for all Intervention group subjects who had completed the first 6 months of the study. The primary purpose of this clinical investigation was to evaluate the effectiveness of the device in improving glycemic control in the self-management of type 2 diabetes as compared to Self-Monitoring Blood Glucose (SMBG) testing. The safety of the device was assessed by recording and analyzing all adverse events (AEs) and insertion site symptoms. Additional safety endpoints around subject-reported or device-derived hypoglycemia were reported. As this study involved subjects with type 2 diabetes, cardiac events were also monitored and reported. A total of 302 subjects were enrolled in the study, 224 of which were randomized in a 2:1 ratio to the Intervention (n=149) or Control group (n=75). Adverse event rates were similar between intervention and control arms. Adverse events such as pain, rash, bleeding, edema, induration, bruising, sensor site infection, allergy, insertion site reaction, erythema, itching, necrosis at insertion site, stress, hypoglycemia, and hyperglycemia. There were three deaths during the study; none were related to the device or study procedure.

- The IMPACT study**,** conducted in the European Union, evaluated use of the FreeStyle Libre for diabetes treatment decisions in patients with well-controlled Type 1 diabetes. This was a 6-month, prospective, open-label, parallel group, randomized controlled trial (RCT), multicenter study, which was conducted to assess safety and outcomes of the device in adult patients with Type 1 diabetes. Male and female subjects aged 18 years and older, diagnosed with Type 1 diabetes for at least 5 years

and with an HbA1c ≤7.5% at the time of screening were enrolled from 23 study centers across the European Union, including Austria (6 centers), The Netherlands (6 centers), Germany (5 centers), Spain (3 centers), and Sweden (3 centers). The primary purpose of this clinical study was to assess the impact of the device on time in hypoglycemia (hours per day with Sensor glucose <70 mg/dL) as measured by the device itself between subject using the device (Intervention group) compared to self-monitoring of blood glucose (SMBG) (Control group). The safety of the device was assessed by recording and analyzing all adverse events (AEs) and insertion site symptoms. Additional safety endpoints around symptomatic (subject reported) or asymptomatic (device derived) hypoglycemia as well as severe hypoglycemic episodes were reported. A total of 328 subjects were enrolled in the study, 241 of which were randomized in a 1:1 ratio to the Intervention (n=120) or the Control group (n=121). Adverse event rates were similar between intervention and control arms. Adverse events such as pain, rash, bleeding, edema, induration, bruising, sensor site infection, allergy, insertion site reaction, erythema and itching, necrosis at insertion site, stress, hypoglycemia, and hyperglycemia. There were no deaths during the study.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Toxicology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the pivotal clinical study performed by the applicant establish a reasonable assurance of safety and effectiveness of the Freestyle Libre System to be used as intended in the intended use population. The primary effectiveness measurements for this study were based on the performance evaluation of the Freestyle Libre System compared to the blood glucose values measured by a laboratory glucose analyzer during in-clinic sessions that spanned the wear period of the device (days 1, 4, 7 and 10).

The performance data presented above (Tables 10-18) are comparable to the performance of current generation CGM systems accepted in the field of diabetes management to provide information that can be used for diabetes treatment decision-making; and therefore support the effectiveness conclusions. These data establish the accuracy across the claimed measuring range (40 to 500 mg/dL glucose), precision, the 10 day wear period (following the warm-up period) for the sensor, the notifications (Glucose Messages), and the number of readings displayed during the wear period.

The clinical study data demonstrate that the Freestyle Libre System was effective in the study population designed to be reflective of the intended use population.

B. Safety Conclusions

The risks of the device are based on the adverse events observed in the clinical study which are described in Section X.D.1 above and the potential adverse effects of the device on health described below:

The following are possible adverse effects of inserting a sensor and wearing the adhesive patch: local erythema (redness), local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, and adhesive irritation. There is a remote risk of sensor or needle fracture during insertion, wear or removal, with fragments retained under the skin.

There are potential adverse effects associated with making diabetes treatment decisions when glucose values and rates of change provided by the device are inaccurate, as follows:

The risks of making treatment decisions based on falsely high readings include inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong existing hypoglycemia which can result in seizures, loss of consciousness, and rarely, death.

The risks of making treatment decisions based on falsely low readings include inappropriate administration of carbohydrates. These inappropriate treatments could increase the risk of hyperglycemia or prolong existing hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and acute diabetic ketoacidosis (DKA) which can result in weakness, seizures, and death.

Inaccurate calculation of the rate of change of glucose by the device could increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. Inaccurate calculation of the rate of change of glucose by the device could also prevent a patient from taking measures to prevent a sustained increase or decrease in glucose levels, which could lead to serious hypoglycemia or hyperglycemia.

There are potential adverse effects associated with making acute and long-term therapy adjustments when glucose values and rates of change provided by the device are inaccurate. The risks of making therapy adjustments based on inaccurate device information include inappropriate adjustment of diabetes medication regimens. This could increase the risk of hypoglycemia and corresponding risk of seizures, loss of consciousness, and rarely, death; it may also increase the risk of hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye,

kidney, nerve and heart disease) and risk of acute diabetic ketoacidosis (DKA) which can cause weakness, seizures, and death.

The device also provides glucose threshold and predictive messages (alerts) when the Sensor is scanned; these alerts may cause a user to take action to prevent future potential future glycemic events (e.g., set reminders for future glucose checks or future action, or take immediate treatment-based action). Potential adverse events may therefore also result from inaccuracies that cause a failure to trigger alerts, or cause false alerts. This may cause users to take an inappropriate action, or incorrectly take no action, and result in increased risk or prolongation of hyperglycemia or hypoglycemia. In the absence of a user-initiated action (scan) the system cannot provide glucose-related alerts, which could serve to notify users of an actual or impending glucose value above or below glucose thresholds. The lack of alerts in the absence of user-imitated action (scan) could increase the risk of severe hypoglycemia or diabetic ketoacidosis through decreased opportunities for detection of hypoglycemia or hyperglycemia relative to other similar currently marketed continuous glucose sensors.

Users may experience different levels of performance from each sensor inserted (e.g., based on the specific insertion site and individual physiology), at different times of use (e.g., days of wear) or under different conditions (e.g., before or after meals or exercise). User understanding that each sensor may perform differently and that for any given sensor the performance may be affected by multiple factors and may vary throughout a wear session, depends on a user checking glucose information provided by the Freestyle Libre System against blood glucose values obtained using a glucose meter. Because the Freestyle Libre System is factory calibrated, there is not a minimum number of daily glucose meter checks that a user should make (i.e., to calibrate the system, as for other currently marketed similar systems). Factory calibration may therefore reduce the opportunity of some patients using the device to become familiar with the performance of any given sensor or the performance of the system at specific times during a sensor session by checking readings from the device using a self-monitoring blood glucose device (glucose meter).

These risks are mitigated by warnings in the labeling and through required patient training. In the labeling, users are advised that if their symptoms do not match readings from the Freestyle Libre System, they should perform blood glucose testing and make treatment decisions based on the blood glucose reading, not the Freestyle Libre System reading. The frequency with which user symptoms did not match Freestyle Libre System readings, as assessed in clinical studies, is sufficiently low to be adequately mitigated through labeling warnings.

There is a potential for overtreatment, especially with insulin, for Freestyle Libre System users because glucose values are less burdensome to obtain than by performing a typical glucose meter test. The ready availability of glucose information at all times could prompt some users to incorrectly react to a post-meal increase in glucose levels by taking an insulin dose without accounting for a previously delivered

meal insulin does (this is known as insulin stacking). This could result in subsequent hypoglycemia. Users are therefore advised in the labeling to avoid stacking insulin (re-administration of insulin within a 2 hour timeframe).

Users are also advised in the labeling to use their Freestyle Libre System concurrently with a blood glucose meter for a period of time until they are comfortable with how the device is best used. The Reader incorporates a built-in blood glucose meter that can be used with compatible test strips to conduct blood glucose tests.The Reader also displays a non-actionable icon under conditions when the device should not be used for treatment decisions to inform patients that blood glucose testing with a glucose meter should be performed prior to making a diabetes treatment decision. The icon is displayed under the following conditions:

- The glucose as reported by the Sensor is below 70 mg/dL (when the "low glucose" message is displayed);
- The glucose will be below 70 mg/dL within 15 minutes (when the "glucose is going low" message is displayed);
- The glucose is rapidly changing (when the glucose trend arrow as reported by the Reader is rising quickly or falling quickly);
- The glucose trend arrow is not displayed; and
- The glucose as reported by the Sensor is above 500 mg/dL (when the HI message is displayed).

C. Benefit-Risk Determination

The probable benefits of the device were assessed using data collected in clinical studies conducted to support PMA approval as described above in Sections X and XI. Risks of the device were assessed using data collected in clinical studies conducted to support PMA approval as described above in Sections X and XI and potential adverse effects of the device on health as described above in Section VIII. A summary of the Benefits and Risks of the device is presented below:

The FreeStyle Libre Flash Glucose Monitoring System is a continuous glucose monitoring system which is intended to replace blood glucose testing for diabetes treatment decisions. The system does not require user calibration with blood glucose values.

The Freestyle Libre System is intended to detect trends and track patterns aiding in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. Interpretation of Freestyle Libre System readings should be based on the glucose trends and several sequential readings over time.

The system is intended for single patient use and requires a prescription. The user begins scanning with the FreeStyle Libre System after a 12 hour warm-up period and uses the Sensor for up to 10 days.

Benefits of FreeStyle Libre System use, when used as intended, include real-time knowledge of glucose levels, whether glucose levels are increasing or decreasing, and the identification and/or confirmation of patterns of glycemic excursions throughout the day and night, when patients may be unable to test their blood glucose. Access to retrospective glucose trend information for diabetes treatment decisions with this device may allow patients to make more informed diabetes treatment decisions than relying solely on glucose point information as provided by self-monitoring of blood glucose (SMBG) devices.

Non-adjunctive use of the Freestyle Libre System can be expected to provide the benefit of decreased pain relative to fingerstick measurements. Factory calibration of the FreeStyle Libre System provides the additional benefit that the system does not require calibration with fingersticks, further decreasing the burden, pain, and discomfort associated with blood glucose meter use. Factory calibration also provides the benefit of avoiding potential errors or delays that could arise during user calibration and which can negatively influence performance of CGM systems that require calibration. Non-adjunctive use of the FreeStyle Libre device is expected to be associated with increased access to glucose information and decreased burden of SMBG-based diabetes treatment decisions. The decreased daily burden of use of the Freestyle Libre System to replace fingerstick glucose measurements can additionally have psychosocial benefit (e.g. reduced burnout and perceived stigma). SMBG adherence is known to be suboptimal, and non-adjunctive use of the FreeStyle Libre System could increase adoption of continuous glucose monitor use and provide opportunities for easier and more convenient glucose monitoring to patients with diabetes, while providing the added benefits of this device.

The IMPACT and REPLACE studies conducted in support of this application demonstrated that the average number of daily glucose checks using the FreeStyle Libre System was greater than with SMBG, supporting the potential benefit of greater awareness of information related to glucose trends and more frequent glucose values to users of the FreeStyle Libre System compared to SMBG alone.

The longer intended duration of use of this device (10 days) is beneficial to patients, in that less frequent sensor insertions are required relative to similar systems with a shorter use life, and patients may endure pain and other symptoms associated with sensor insertion less frequently.

The clinical performance study demonstrated that the performance of the FreeStyle Libre is comparable to the performance of current generation CGM systems accepted in the field of diabetes management to provide information that can be used to make diabetes treatment decisions.

Risks of treatment decisions made from falsely high CGM readings include inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong hypoglycemia which can result in seizures, loss of consciousness, or rarely, death. Risks of treatment decisions made from falsely low CGM readings include inappropriate administration of carbohydrate.

These inappropriate treatments could increase the risk of hyperglycemia or prolong hyperglycemia.

Inaccurate calculation of the rate of change of glucose by the device could prevent a patient from taking measures to stop a trend of increasing or decreasing glucose levels which could lead to serious hypoglycemia or hyperglycemia. This could also lead patients to make inappropriate adjustments to their treatment, resulting in serious hypoglycemia or hyperglycemia. Inaccurate calculation of the rate of change of glucose by the device could also increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. However, labeling specifically advises not to make changes in dosing based solely on the arrows indicating rate of change.

The risks of these uses above are mitigated by strong warnings in the label and training. In the labeling, users are advised that if their symptoms do not match their CGM reading, they should perform blood glucose testing and make treatment decisions based on the blood glucose reading, not the CGM reading. Users are also advised to avoid stacking insulin (avoid re-administration of within a 2 hour timeframe). Users are also advised to use their CGM concurrently with SMBG for a period of time until they are comfortable with how the device is best used. In addition, at specific glucose levels and rates of change, the Reader displays a non-actionable icon, which informs patients that SMBG should be performed prior to making a diabetes treatment decision.

As a condition of approval, labeling must specify the specific training or experience users need in order to use the device. Patient training will be helpful to provide additional risk mitigations and optimize safety and usability of the device, including use of the non-actionable icon described above.

Further, the factory calibration could potentially reduce the opportunity of some patients using the device to become familiar with the performance of any given sensor or the performance of the system at specific times during a sensor session by checking readings from the device using a self-monitoring blood glucose device (blood glucose meter).

There are warnings and precautions in the labeling relating to use of the device in populations in which the device has not been studied (i.e., pregnant patients, critically ill patients, dialysis patients, and hypoglycemia unaware patients) and in populations in which device performance is not established but generally accepted to be less accurate (i.e., pediatric population).

The lack of passive alerts in the absence of a user initiated action (as compared to other marketed systems with the same intended use) notifying patients of a glucose value above or below (or predicted to reach above or below) user-specified thresholds could increase the risk of severe hypoglycemia and DKA through decreased opportunities for detection of hypoglycemia or hyperglycemia. The lack of passive alerts is conveyed to users and healthcare providers through a warning in the labeling. There are also risks associated with inaccuracies in the performance of glucose

messages, including false messages that cause users to take an inappropriate action, or missed messages that cause users to incorrectly take no action, resulting in increased risk or prolongation of hyperglycemia or hypoglycemia. Labeling includes a warning about the lack of passive alerts in the absence of user-initiated action for patients using the device and for healthcare providers potentially prescribing the device.

There is a minor risk of local skin erythema (redness), local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, and adhesive irritation. There is also a remote risk of sensor or needle fracture during insertion, wear or removal, with fragments retained under the skin. This event was not observed during the clinical studies reviewed for this submission.

Despite the differences in accuracy of this device relative to blood glucose meters, it provides benefits not available from blood glucose meters. If the expected performance of the device is understood, the benefits of additional information gained from this device outweigh the risk of inaccurate results, rates of change, and false negative and positive messages.

Patient Perspectives

Patient perspectives considered during the review included information provided directly to the Agency by patients in written statements and also obtained through discussion with patients at public forums regarding their experience with continuous glucose monitoring system devices in general.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefits of this System, as discussed above, outweigh the risks.

XIV. CDRH DECISION

CDRH issued an approval order on September 27, 2017. The final conditions of approval cited in the approval order are described below.

The applicant is required to conduct a Post Approval Study (PAS) meeting the following criteria: the study will provide a confirmatory evaluation of the safety and effectiveness of the device in the intended use population. The study will be a prospective, multi-center, single-arm study of continuous glucose monitor (CGM) naïve subjects with diabetes utilizing the FreeStyle Libre Flash Glucose Monitoring System. Subjects will utilize capillary self-monitoring of blood glucose SMBG for their diabetes management for the first 6 months (control phase) of the study, and then will utilize the FreeStyle Libre System for the following 6 months (intervention phase) of the study. At least 900 patients will be enrolled. The occurrence of severe hypoglycemic and diabetic ketoacidosis events, device related severe adverse events, and unanticipated adverse

device events will be captured. Additionally, device utilization metrics will be captured including FreeStyle Libre System scan frequency and frequency of self-monitoring of blood glucose. Subjects will complete Quality of Life questionnaires at the end of the control phase and at the end of the intervention phase of the study. Results will be stratified by the following: age (<65 years or ≥65 years), and diabetes type (Type I or Type II). Subjects will be followed for a total of 12 months. PAS reporting will occur biannually for the first two years of the study and then annually thereafter. A description of the study protocol, interim, and final results will be published on the Post Approval Study Webpage http://www.fda.gov/devicepostapproval.

The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience users need in order to use the device.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

None.