SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Continuous Glucose Monitoring System
Device Trade Name:	Freestyle Libre Pro Flash Glucose Monitoring System
Device Procode:	MDS
Applicant's Name and Address:	Abbott Diabetes Care, Inc. 1360 South Loop Rd. Alameda, CA 94502
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P150021

Date of FDA Notice of Approval:	September 23, 2016
Priority Review:	*Not Applicable*

II. INDICATIONS FOR USE

The device is indicated for the following:

Freestyle Libre Pro Flash Glucose Monitoring System

The FreeStyle Libre Pro Flash Glucose Monitoring System is a professional continuous glucose monitoring device indicated for detecting trends and tracking patterns in persons (age 18 and older) with diabetes. The System is intended for use by health care professionals and requires a prescription.

Readings from the FreeStyle Libre Pro sensor are only made available to patients through consultation with a health care professional. The System does not require user calibration with blood glucose values.

The FreeStyle Libre Pro Flash Glucose Monitoring System (FreeStyle Libre Pro System) aids in the detection of glucose level excursions above or below the desired range, facilitating therapy adjustments. Interpretation of the FreeStyle Libre Pro System readings should be based on the trends and patterns analyzed through time using the reports available.

IMPORTANT: The device may inaccurately indicate hypoglycemia. The results of the clinical study conducted for this device showed that 40% of the time when the device indicated that user sensor glucose values were at or below 60 mg/dL, user glucose values were actually in the range of 81-160 mg/dL. Therefore, interpretation of the FreeStyle Libre Pro Flash Glucose Monitoring System readings should only be based on the trends and patterns analyzed through time using the reports available per the intended use.

III. CONTRAINDICATIONS

The FreeStyle Libre Pro 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 FreeStyle Libre Pro 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 manufacturer has included the prominent statement above following the Indications for Use in the user guide and in all promotional and advertising material (see Section II - Indications for Use above). The statement is being included as a result of the analytical performance of this device that was observed during the clinical study used to support approval of the device. The clinical results, a portion of which are provided below in section X – Summary of Primary Clinical Studies, demonstrate a negative bias (i.e. less accuracy) with respect to a laboratory comparator method, especially in the range of 81-160 mg/dL. This level of bias is worse than similar recently approved continuous glucose monitors (CGMs). However, as discussed in section XII, a benefit-risk assessment of the FreeStyle Libre Pro System has concluded that the potential benefits to patients using this device outweigh the potential risks.

Additional warnings and precautions can be found in the FreeStyle Libre Pro System labeling.

V. DEVICE DESCRIPTION

The FreeStyle Libre Pro System is intended for use by healthcare professionals (HCPs) to aid in the review, analysis, and evaluation of a patient's glucose readings in support of an effective diabetes management program. The FreeStyle Libre Pro System uses a subcutaneously implanted electrochemical sensor, which incorporates the same wired enzyme glucose sensing technology utilized in the FreeStyle Navigator® Continuous Glucose Monitoring System (P050020, approved March 12, 2008) to monitor glucose levels in interstitial fluid (ISF).

The FreeStyle Libre Pro System consists of three primary components:

- A disposable on-body assembly (Sensor) that incorporates a subcutaneously implanted electrochemical glucose sensor and associated electronics,

- A disposable sensor insertion device (Patch Delivery Unit), consisting of two secondary components (Sensor Applicator and Sensor Pack), which is used to assemble and apply the Sensor to the patient's body and insert the sensor tail about 5.5 millimeters below the surface of the skin, and

- A handheld device (Reader) which uses radiofrequency communication to start new Sensors and collect glucose data stored on the Sensor; one Reader can start and read multiple Sensors.

The HCP applies a Sensor to each patient and activates the Sensor using the Reader. Two minutes after activation, the Reader is used to confirm that the Sensor is inserted properly. Once this check is successful, the patient may leave the medical facility. There is no blood glucose calibration needed. The Reader is intended to remain in possession of the HCP. One Reader may be used to activate multiple Sensors by repeating this process for different patients.

The Sensor is disposable and may be worn for up to 14 days before it must be removed. The Sensor is capable of permanently storing glucose data (collected in 15 minutes intervals for up to 14 days), even after the Sensor is removed from the patient. After the wear period, patients have the option to mail the Sensor to the HCP or to physically return with the Sensor, depending on the patient's or HCP office's preference. The HCP can then collect Sensor data for the wear duration by bringing the Reader in close proximity (within 1.5 inches) of the Sensor to scan the Sensor. One Reader can read and collect glucose data from multiple Sensors; however, only the last scanned Sensor data set is stored on the Reader. The HCP can then transfer sensor data from the Reader to a computer for review and analysis using software provided by Abbott.

Description of System Components

- Sensor

  The disposable Sensor can be worn for up to 14 days 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 glucose data.

- Sensor insertion device

  The Sensor insertion device consists of two secondary disposable single use components (Sensor Pack and Sensor Applicator) that require HCP assembly to apply an assembled Sensor on the patient. The Sensor Pack is E-beam 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 safe 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 through wireless radiofrequency communication. The Reader collects the entire set of glucose data available on the Sensor, up to 14 days, with one scan. The Reader employs signal processing algorithms to convert the measurement data into historic 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 Pro data management software. Results can be displayed graphically on the Reader or within the FreeStyle Libre Pro data management software.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Accurate and comprehensive monitoring of patient glucose levels provides a critical input into the clinical interpretation and analysis needed to support an effective patient diabetes management program. These programs may aim to avoid periods of hypoglycemia and improve glycemic control, particularly for patients on intensive insulin regimens and glucose level lowering medications. Patient monitoring options include:

1) Periodic measurement of Hemoglobin Alc (HbA1c), which reflects average blood glucose levels over a two to three month period
2) Standard self-monitoring of blood glucose (SMBG) using glucose meters and test strips to provide quantitative measurements of blood glucose at a single point in time so that patients and their healthcare providers can monitor the effectiveness of glycemic control and make more immediate treatment modifications
3) Home use, real-time continuous glucose monitoring, or retrospective continuous glucose monitoring by healthcare providers.

Each alternative method for monitoring glycemic control has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

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

The FreeStyle Libre Pro System has been marketed in India since March 2015.

The FreeStyle Libre Pro System uses the same CGM sensor as the the FreeStyle Navigator® Continuous Glucose Monitoring System, which was approved in 2008 and available until March2013. Neither of these systems has been withdrawn from marketing 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 (e.g., complications) associated with the use of the device.

Potential device-related, non-serious events related to continuous glucose monitor use include:

- Local infection
- Skin irritation or redness
- Skin inflammation
- Pain or discomfort
- Bleeding
- Bruising
- Skin edema
- Skin rash
- Itching
- Scarring or skin discoloration
- Allergic reactions to the sensor needle or adhesives
- Sensor or needle fracture during insertion, wear or removal

Sensor breakage with fragments retained under the skin is a potential procedure-related complication. However, based on post-market experience with this and similar devices, and the results observed in the clinical study, this event is rare and its severity does not raise major concerns.

As described below in Section X - Summary of Primary Clinical Studies, the performance of this device is worse than other recently approved continuous glucose monitoring devices. The device may inaccurately indicate hypoglycemia at a greater rate than other approved CGMs. The results of the clinical study conducted for this device showed that 40 percent of the time when the device indicated that user sensor glucose values were at or below 60 mg/dL, user glucose values were actually in the range of 81-160 mg/dL. If multiple false results are reported that falsely indicate suboptimal blood glucose trends (e.g., high blood glucose when the patient wakes each day), the HCP may

recommend inappropriate changes to a patient's diabetes management plan. Inappropriate treatment changes could increase the risk of acute and long-term complications.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of the non-clinical laboratory studies that were performed in support of the FreeStyle Libre Pro System are summarized below.

A. Laboratory Studies

Bench Performance Testing

Non-clinical testing was conducted at the FreeStyle Libre Pro System level as well as on the reader, sensor insertion device, and sensor, individually.

- 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 FreeStyle Libre Pro System in accordance with EN 62366 demonstrated that the FreeStyle Libre Pro 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 below provides a summary of this testing, along with acceptance criteria for each test. The test protocols and acceptance criteria were reviewed and found to be adequate. Acceptance criteria were met for each test.

Table 1: System Level Testing

Preclinical Test	Objective	Acceptance Criteria
Safety Testing	Verify System compliance with IEC 60601-1.	The test shall 'Pass' if the External Lab certifies that the system complies with IEC 60601-1.

EMC Testing	Verify Reader and Sensor compliance with the Radiated Immunity, Magnetic Immunity, Radiated Emissions, and Electrostatic Discharge requirements of IEC 60601-1-2. Verify Reader compliance with FCC Part 15.209 (General Requirements) and 15.225 (Operation within the band 13.110-14.010 MHz) and with the Conducted Emissions and AC Line requirements of IEC 60601-1-2. Verify System EMC coexistence ability to obtain Sensor glucose measurement in the presence of other RF wireless in-band devices based on FDA guidance.	Meet the requirements in the referenced standards and guidance.
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	• The Reader shall be operational over an ambient temperature range of 10ºC to 45ºC and an ambient humidity range of 10% to 90% RH (non-condensing). • The on-body unit (excluding the sensor) shall be functional over an ambient temperature range of 10ºC to 45ºC and an ambient humidity range of 10% to 90% RH (non-condensing).
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 humidity range of 10%to 90% RH	The Reader shall be operational after exposure to a temperature range of -20ºC to 60 ºC, and humidity range of 10-90% RH (non-condensing) per IEC60601-1-11.

Altitude	Verify System meets the Altitude requirements of IEC 60601-1-11 subclause 4.2.2.	The Reader and the on body unit excluding the sensor shall be Operational under atmospheric pressure range specified in IEC60601-1-11 subclause 4.2.2.
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.	Measurement of the RF Carrier is 13.56 MHz ± 7 KHz inclusive per IEC 15693.
Reader and Sensor Radio Communications Range Test	Verify Reader and Sensor can successfully wirelessly send and receive data within the specified distance.	Reader and Sensor can successfully perform an IEC 15693 Inventory command and Read block commands within the range of 1cm and 4 cm.
System In-Band EMC Rejection Test	Verify System does not produce erroneous glucose data in the presence of RFID systems.	The time required to upload Sensor glucose information to the Reader from the Sensor shall be no more than 20 seconds.
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 25 participants representing the overall characteristics of the intended user populations. Participants were not provided System training, and were given typical use scenarios to complete.	The Sensor can successfully identify in-band RF energy and set the RF data qualification bit of the data packets appropriately for the data packets acquired in its presence.

Table 2: Reader Level Testing

Preclinical	Objective	Acceptance Criteria
Physical Design	Verify Reader meets dimensional and mass design requirements.	The Reader shall not exceed the maximum dimensional requirements below: - Length: 100mm - Width: 65mm - Height: 18mm The Reader shall not exceed 100g in mass.
Mechanical Stress Testing	Verify Reader meets the drop, shock, and vibration test requirements as specified in IEC 60601-1 and IEC 60601-1-11	All units must pass the functional test and have no signs of a hazardous condition.
Button Cycling	Verify Reader button is capable to withstand the specified cycle requirements based on typical use assumptions.	• The button of the tested unit is functional when button is pressed after completion of cycle testing. • No cracks, abrasion, or marring of button. • Button print is legible.
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.	• Test Units must be Operational and Undamaged after testing. • Test Unit labels shall be affixed and label text and symbols shall remain readable.
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.	• When charging from an ADC supplied charger the Reader battery charges from a voltage of 3.700V or less and a capacity of 20% or less to 100% capacity in 3 hours or less. • The Reader battery voltage is 3.700V or less at a remaining capacity of 20% or less. • At 100% remaining capacity the Reader battery voltage is no less than 4.100V.

Hardware Tests	Verify the Reader hardware functions including reset, time and date accuracy, audible indicators and volume, display capability, and USB meet the specification requirement.	• Reader turns on and displays "Connected to Computer" when connected to a powered or to an unpowered PC's USB port. • Reader turns on and shows the home screen with charging battery icon when connected to a USB charger. • The Reader resets in no more than 30 seconds while depressing and holding the On/Off (Home) button. • The measured frequency of CLK_TEST is ≥ 32765.7Hz and ≤ 32770.3Hz. • The measured beeper frequency is > 500Hz and < 5000Hz. • The sound pressure level generated by the Reader will be greater than or equal to 65dBA @ 1 meter.

Table 3: Sensor Insertion Device Level Testing

Nonclinical Test	Objective	Acceptance Criteria
Physical Design	Verify Sensor insertion device components meet dimensional and mass design requirements.	• The Primary Packaged Applicator and Sensor Container combined maximum volume shall be no greater than 325 cm^3. • The Primary Packaged Applicator maximum linear dimension shall be no greater than 100 mm. • The Primary Sterile Packaged Sensor Container maximum linear dimension shall be no greater than 100 mm. • The Packaged PDU mass (exclusive of any secondary packaging or labeling) shall be no greater than 100 g.
Tamper Evidence	Verify packaged Sensor insertion device is tamper evident.	The packaged PDU shall be tamper evident
Mechanical Stress Tests (Sensor Container)	Verify Sensor Container is operational after subjected to drop testing, vibration testing, or shock testing as specified in IEC 60601-1 and IEC 60601-1-11.	All units must pass the functional test and have no signs of a hazardous condition.

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.	All units must pass the functional test and have no signs of a hazardous condition.
Functionality over Temperature Range	Verify Sensor Applicator and Sensor Container are operational over temperature range of 10ºC to 45ºC	All units must pass the functional test and have no signs of a hazardous condition.
Internal Relative Humidity	Verify Primary Sterile Packaged Sensor Container internal cavity maintains a specified internal environment during the shelf life.	When stored at specified storage conditions, the Primary Sterile Packaged Sensor Container internal cavity shall maintain an internal environment below 30% RH for the duration of its shelf life.
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.	The test shall 'pass' if a rigid test finger (see IEC 60601-1, Figure 6) simulator is not able to contact the Sharp when 27 N minimum is applied to any part of a Primary Sterile Packaged Sensor Container.
Sensor Container Foil Lid Removal Force	Verify force required to remove the Foil Lid from the Sensor Container meets specification.	The force required to remove the Foil Lid from the Sensor Container shall not exceed 33N.
Sensor Applicator Cap Removal Torque	Verify torque required to remove the Cap from the Sensor Applicator meet specification.	The torque required to remove the Cap from the Applicator shall not exceed 2.37 N-m.
Assembly Force	Verify force required to assemble the Sensor Applicator to the Sensor Container meets specification.	The force required to assemble the Applicator to the Sensor Container shall not exceed 50 N.
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.	An Armed Applicator shall ensure the location of the sharp tip and adhesive pad. During insertion, an Armed Applicator shall extend the sharp tip no more than 9 mm below the skin interface plane.

Applicator Insertion Force	Verify applicator insertion force meets specification.	The force required to actuate the insertion process with an Armed Applicator shall be at least 5 N and no more than 23 N.
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	• An audible snap (audible feedback) shall be heard when the Platform is collapsed by the Applicator, and • The action of assembling results in a state in which additional force in the direction of collapse shall have no additional effect (tactile effect). • An audible snap (audible feedback) shall be heard when the Sensor is applied to the simulated skin, and • The action of firing results in a state in which additional force in the direction of collapse shall have no additional effect (tactile effect) aside from compressing the simulated skin.
Applicator Sensor Location	Verify Applicator affixes the Sensor on the user's skin at the intended location.	• The Applicator shall affix the Sensor on the user's skin at the intended location. • The Sensor shall be successfully transferred to the simulated Skin.
Triggered Applicator Visual Indication	Verify Triggered Applicator provides a visual indication that the device has already been triggered.	The Sheath shall not be in contact with the skin-mimicking surface after the Applicator has been triggered.
Triggered Applicator Rigid Finger Test	Verify sharp cannot be contacted by rigid finger based on the requirement by IEC 60601-1.	A rigid test finger (see IEC 60601-1, Figure 6) shall not be able to touch the sharp when applied to any part of a Triggered Applicator with a force of 30 N ± 3 N.

Triggered Applicator Drop Test	Verify Triggered Applicator sharp cannot be contacted by a rigid finger after being dropped as required by IEC 60601-1.	The test shall 'pass' if a rigid test finger (see IEC 60601-1, Figure 6) simulator is not able to contact the Sharp when 27 N minimum is applied to any part of a Triggered Applicator.
Applicator Re-Use	Verify Applicator prevents reuse and that sharp is not exposed in the triggered condition.	The test shall 'Pass' if the following is true when the Applicator is in the triggered condition: • The sharp shall not be exposed. • The Puck Carrier is securely attached to the Housing. • The Sheath is locked and non-retractable.
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.	• The analysis concludes the largest opening on the exposed surfaces of the Sensor at worst case tolerances is less than 12.5mm. • The samples remain Undamaged and Operational after exposure to 1 meter of water for 30 minutes.
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.	All units must pass the functional test and have no signs of a hazardous condition.
Sensor Battery Test	Verify that the Sensor battery has limited battery switch leakage current, provides sufficient energy for at least 14 days, and has a means to be turned off and maintain logged data that is accessible to the Reader after the battery has expired.	• Battery specifications and measurements align with Sensor current and voltage operation. • Battery has ≥ 20mAhrs when discharged to 1.45V, and that the self-discharge rate at 18 months is ≤ 5% per year. • Sensor electronics includes writable non-volatile memory.
Sensor Electrical Tests	Verify that the Sensor electronic clock frequency is accurate over the specified range.	Clock frequency is accurate to ± 80ppm in the temperature range 20 - 45°C.

	Verify glucose sensor current measured by the Sensor meets the resolution and measurement range requirement.	• The Glucose Sensor Current measurement range shall cover 0 - 120nA or greater and be tested by determining if the A/D measured result at 120nA is < 16383 Counts. • The resolution shall be ≤ 10pA/Count.
	Verify operating potential provided by the Sensor electronics meets the poise voltage requirement.	Under operating conditions, the measured voltage difference between the WRK connection and the REF connection is between 20mV and 60mV.
	Verify Sensor ability to measure temperature accurately at the bottom of the Sensor within the specified temperature range.	With the unit at a temperature ≥ 20°C and ≤ 40°C the measurement accuracy shall be within +/- 0.5°C of the skin sensor temperature.

Table 4: Sensor Component Level Testing

Nonclinical Test	Objective	Acceptance Criteria
Sensitivity	Verify sensor component has acceptable sensitivity of generating the electrical signal across the range of glucose concentrations.	Sensor component is factory calibrated
Variability	Verify that the sensitivities of the sensor components built within one lot are consistent with low variability.	Average between-sensor precision %CV must be ≤ 6.1%
Response Time	Verify that the sensor component is able to respond to glucose changes within specification.	Average response time across sensors and glucose levels must be ≤ 300 seconds.
Linearity	Verify that the sensor component output is proportional to glucose across the range of glucose concentrations.	Average bias results from the linear regression line must not exceed ±15mg/dL or ±15% across glucose levels

Temperature Sensitivity	Verify that the sensor functional performance meets the environmental requirements for operation and storage.	Average bias results from the linear regression line must not exceed ±15mg/dL or ±15% across glucose levels at 20°C and 40°C
Interference Substances	Verify that potential interferents do not adversely impact sensor performance. Based on testing, the following statements are included in the product labeling: Ascorbic acid at 1.09 mg/dL or higher may falsely raise Sensor glucose readings. Salicylic acid at 6.94 mg/dL or higher may slightly lower Sensor glucose readings.	Interfering substances tested are: acetaminophen, salicylic acid, Tetracycline, Dopamine, Ephedrine, Ibuprofen, L-dopa, Methyldopa, Tolazamide, Tolbutamide, ascorbic acid, bilirubin (unconjugated), Cholesterol, Creatinine, Triglyceride, uric acid.
Dimensions	Verify that the sensor component tail meets the dimensional requirements.	≤ 0.380 mm wide and ≤ 0.330 mm thick

Software Verification and Validation

Software verification and validation were carried out in accordance with the FDA's "General Principles of Software Validation: Final Guidance for Industry and FDA Staff." Software development activities included establishing detailed software requirements, linking requirements with associate verification tests, software code reviews, unit testing, system level testing and defect tracking and dispositioning to ensure the software conforms to patient needs and intended uses.

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

Sterility Assurance

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} 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} 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 worst case sealing parameters, sterilization parameters, and 24-pack shipping configuration. Units were also conditioned through a worst case sequence of storage, handling and transit challenges prior to testing. Attributes related to seal integrity, user accessibility, and device functionality met acceptance criteria. Sensor shelf life is 9 months from the date of Sensor Pack assembly at storage conditions of 39-77 ºF and 10-90 %RH.

B. Animal Studies

None

C. Additional Studies

None

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the FreeStyle Libre Pro Flash Glucose Monitor System in the US under ClinicalTrials.gov identifier NCT02073058. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

A total of 75 subjects with diabetes were enrolled across 4 clinical sites in the study between February14, 2014 and May 15, 2014. Of the 75 enrolled subjects, three subjects withdrew prior to sensor insertion. All 75 subjects from the study were included in the safety analysis while 72 of the 75 subjects were included in the effectiveness analysis. The 72 subjects had diabetes (81.9% Type 1, 18.1% Type 2) and were aged eighteen or older; all subjects required insulin administration either by an insulin pump or via multiple daily injections to manage their diabetes. Each subject wore two sensors for up to 14 days, one on the back of each upper arm. During the study, subjects tested their blood glucose using fingerstick capillary samples using a FreeStyle Precision blood glucose meter. Additionally, subjects had their venous blood glucose analyzed during three separate visits to the clinical center using the Yellow Spring Instrument Life Sciences 2300 STAT Plus™ Glucose & Lactate Analyzer (comparator method, or CM). Glucose readings obtained from the FreeStyle Libre Pro System were compared to glucose readings obtained from the CM to evaluate the performance of the FreeStyle Libre Pro System. Three lots of sensors were evaluated in the study. CM glucose measurements were performed during three separate visits to the clinic between Days 1 and 3, between Days 4 and 9, and between Days 10 and 14. Each CM glucose measuring session lasted for 8 hours, and CM measurements were taken every 15 minutes, for a total of 32 samples per session. This testing allowed for matched pair comparisons of the FreeStyle Libre Pro System to CM values to characterize the agreement between the FreeStyle Libre Pro System and the CM.

During the home use period, subjects were asked to go about their normal daily activities and maintain their diabetes management plan already established prior to initiation of the study.

The objective of the study was to characterize the FreeStyle Libre Pro System performance with respect to venous sample measurements from the CM. The device performance was evaluated in terms of point and rate accuracy of the FreeStyle Libre Pro

System interstitial glucose results in comparison to plasma equivalent measurements from the CM.

The safety of the device was examined by evaluating the number and percentage of subjects experiencing adverse events, as well as anticipated adverse reactions to the sensor insertion site.

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 type 1 or type 2 diabetes for at least 2 years prior to enrollment; Require insulin therapy administered through an insulin pump and/or multiple daily insulin injections for at least 6 months prior to enrollment; Be able to read and understand English; In the Investigator's opinion, 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 for 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; Has skin lesions, scarring, redness, infection or edema at the application sites that could interfere with device placement or the accuracy of interstitial glucose measurements; Be participating in another clinical trial; Donated blood within 112 days prior to the beginning of the study activities; Have a concomitant medical condition, which, in the opinion of the Investigator, could interfere with the study or present a risk to the safety or welfare of the subject or study staff; Had an increasing risk of bleeding; Subject has X-ray, MRI or CT appointment scheduled during the period of study participation, and the appointment could not be rescheduled for a time before study participation starts or after study participation ends; subject is unsuitable for participation due to any other cause as determined by the Investigator

2. Clinical Endpoints
   With regard to safety, the number and percent of subjects experiencing adverse events during either the glucose monitoring period or the follow-up period was reported. The incidence of adverse events were classified by severity (mild / moderate / severe), and relatedness to device (not related / related). In addition, signs and symptoms related to the Sensor application site were evaluated, including bleeding, bruising, edema, erythema, induration, infection, itching, pain, and rash.

   With regard to effectiveness, various analyses were provided comparing the accuracy of the FreeStyle Libre Pro system to the laboratory based comparator method. The final decision regarding efficacy is based on all clinical data together, and not any one specific type of analysis. See section B below for discussion of effectiveness outcomes.

B. Accountability

At the time of database lock, of 75 subjects enrolled in the clinical study, 72 patients were available for analysis at the completion of the study.

C. Study Population and Demographics

A description of the demographics and baseline characteristics of the study population are provided in Table 6 and Table 7.

Table 9: Subject Demographics (N=72)

Demographic		Overall	
		N	%
Sex	Female	36	50.0
	Male	36	50.0
Race	White	65	90.3
	Asian	2	2.8
	Black or African American	2	2.8
	Other	3	4.2
Education	College Education	66	91.7
	Further Education not completed	6	8.3
Type of Diabetes	Type 1	59	81.9
	Type 2	13	18.1
Insulin Pump Use	Yes	39	54.2
	No	33	45.8

Table 10: Baseline Characteristics (N=72)

Characteristic		Mean ± SD	Median	Range
Age (years)		46.4 ± 15.1	48.5	18 to 71
Weight	Pounds	182.2 ± 42.1	175.8	102.0 to 299.8
	Kilograms	82.6 ± 19.1	79.7	46.3 to 136.0
Height	Inches	67.1 ± 4.3	66.5	59 to 81
	Meters	1.70 ± 0.11	1.69	1.50 to 2.06
Body Mass Index		28.3 ± 5.3	27.4	18.7 to 47.2
Years since diagnosis		23.0 ± 13.1	22.3	2.4 to 50.6
HbA1c (%)		7.8 ± 1.2	7.8	5.5 to 11.5

D. Safety and Effectiveness Results

1. Effectiveness Results

The analysis of effectiveness was based on the 72 evaluable patients at the 2-week time point. Key effectiveness outcomes are presented in Tables 11 to 18.

CGM System Agreement to CM within CGM Glucose Ranges: Table 11 below is categorized with system glucose ranges (in the first column) and outlines how often a reading on the CM matched the FreeStyle Libre Pro System glucose range bin. This table shows the degree of agreement between CM measurements and system values by showing the percentage of CM measurements that agree with CGM measurements within a given level of error.

Table 11: CGM System Agreement to CM within CGM System Glucose Ranges

CGM glucose ranges (mg/dL)	Number of paired CGM-CM data points	Percent of CM within 15/15% of CGM	Percent of CM within 20/20% of CGM	Percent of CM within 30/30% of CGM	Percent of CM within 40/40% of CGM	Percent of CM greater than 40/40% of CGM
Overall	12323	71.7	83.6	94.9	98.2	1.8
40-50	28	17.9	28.6	50.0	71.4	28.6
51-80	586	54.1	70.6	88.2	94.2	5.8
81-180	6685	72.2	83.0	94.2	97.9	2.1
181-300	4449	73.9	86.2	96.9	99.2	0.8
301-400	541	70.1	86.7	97.2	98.9	1.1
401-500	34	55.9	88.2	97.1	100.0	0.0

**For comparator range ≤80 mg/dL, agreement was based on 15/20/30/40 mg/dL*
Note: *System measurement range is 40-500 mg/dL*

CGM System Agreement to CM within CM Glucose Ranges: Table 12 below is categorized with CM glucose ranges (in the first column) and outlines how often a reading on the CGM matched the CM blood glucose range bin. This table shows the degree of agreement between CGM system values and CM by showing the percentage of system data points that agree with CM measurements within a given level of error.

Table 12: CGM System Agreement to CM within CM Glucose Ranges

CM glucose ranges (mg/dL)	Number of paired CGM- CM data points	Percent of CGM within 15/15% of CM	Percent of CGM within 20/20% of CM	Percent of CGM within 30/30% of CM	Percent of CGM within 40/40% of CM	Percent of CGM greater than 40/40% of CM
Overall	12323	71.8	83.8	95.2	98.5	1.5
40-50	30	53.3	83.3	93.3	100.0	0.0
51-80	505	58.4	73.3	89.1	96.0	4.0
81-180	7373	68.3	80.2	93.7	98.0	2.0
181-300	4115	79.0	90.4	98.3	99.5	0.5
301-400	286	84.6	96.5	99.7	100.0	0.0
401-500	14	85.7	100.0	100.0	100.0	0.0

**For comparator range ≤80 mg/dL, agreement was based on 15/20/30/40 mg/dL*
Note: *System measurement range is 40-500 mg/dL*

Agreement of CGM System to CM When CGM System Reads 'LO' or 'HI'

The FreeStyle Libre Pro System reports glucose concentrations between 40 and 500 mg/dL. When the FreeStyle Libre Pro System determines the glucose level is below 40 mg/dL, the value is recorded as 'LO'. When the FreeStyle Libre Pro System determines that the glucose level is above 500 mg/dL the value is recorded as 'HI'. Because the FreeStyle Libre Pro System does not record numerical glucose values below 40 mg/dL or above 500 mg/dL, the comparisons to the actual blood glucose concentrations (as determined by the CM) when sensor measurement is classified as 'LO' or 'HI' are included separately in the following tables. Table 13 includes the results in terms of absolute numbers and cumulative percentages for CM values less than the specified glucose levels (for 'LO').

Table 13 demonstrates that, in the clinical study which included only a few low values, the FreeStyle Libre Pro System correctly identified that glucose values are <40 mg/dL only 16.7% of the time. In addition, two-thirds of the time when the FreeStyle Libre Pro System identified glucose values as 'LO,' the CM glucose value was >80 mg/dL. This low rate of agreement is communicated to the user via the statement required by restriction on all promotional materials, all advertising materials, and following the indications for use in the User Guide regarding inaccurate indication of hypoglycemia.

Table 13. Number and percentage of CM values when CGM system readings are "LO"

		Comparator mg/dL						
CGM readings	**CGM-Comp pairs**	**<40**	**40-50**	**51-60**	**61-70**	**71-80**	**>80**	**Total**
<40 (LO)	Cumulative, n	1	0	0	1	0	4	6
	Cumulative %	16.7%	0%	0%	16.7%	0%	66.7%	100%

Table 14 includes the results in terms of absolute numbers and cumulative percentages for CM values greater than the specified glucose levels (for 'HI').

Table 14. Number and percentage of CM values when CGM system readings are "HI"

Comparator mg/dL							
CGM readings	**CGM-Comp pairs**	**<200**	**200-300**	**301-400**	**401-500**	**>500**	**Total**
>500 (HI)	Cumulative, n	0	0	0	2	0	2
	Cumulative %	0%	0%	0%	100%	0%	100%

Concurrence of CGM System and CM Values:
The percentage of concurring CGM readings and CM values are presented in Tables 15 and 16, below.

Table 15 is categorized by CM glucose range (first column) and describes for each range of CM glucose readings the percentage of paired sensor values that fell within the same glucose range (shaded) or in glucose ranges above and below the paired CM readings.

Table 15. Concurrence of CM values and Sensor Readings

Comparator (mg/dL)	**Sensor Glucose Level (mg/dL)**												**N**
	<40	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**401-500**	**>500**	
<40	20.0	80.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5
40-60	0.0	26.4	60.0	11.8	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	110
61-80	0.2	11.1	42.9	43.6	1.7	0.2	0.2	0.0	0.0	0.0	0.0	0.0	422
81-120	0.2	1.8	9.0	61.4	26.7	0.8	0.0	0.0	0.0	0.0	0.0	0.0	2472
121-160	0.0	0.1	0.4	12.4	60.8	25.0	1.2	0.0	0.0	0.0	0.0	0.0	3338
161-200	0.0	0.0	0.1	1.1	16.8	49.8	31.5	0.6	0.1	0.0	0.0	0.0	2853
201-250	0.0	0.0	0.0	0.1	0.8	9.6	62.0	26.6	0.8	0.0	0.0	0.0	1937
251-300	0.0	0.0	0.0	0.0	0.0	0.1	11.3	56.6	29.8	2.1	0.0	0.0	892
301-350	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12.4	53.1	33.2	1.3	0.0	226
351-400	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	35.0	35.0	30.0	0.0	60
401-500	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.3	81.3	12.5	16
>500	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0

**For comparator range ≤80 mg/dL, agreement was based on 15/20/30/40 mg/dL*
***Note:** System measurement range is 40-500 mg/dL*

Table 16 is categorized by CGM sensor glucose range (first column) and describes for each range of CGM sensor glucose readings the percentage of paired CM values that fell within the same glucose range (shaded) or in glucose ranges above and below the paired readings.

Table 16. Concurrence of Sensor Values and Comparator Values

Sensor (mg/dL)	Comparator Glucose Level (mg/dL)												N
	<40	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**401-500**	**>500**	
<40	16.7	0.0	16.7	66.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	16.7
40-60	3.1	22.5	36.4	34.9	3.1	0.0	0.0	0.0	0.0	0.0	0.0	129	3.1
61-80	0.0	13.6	37.3	46.0	2.5	0.6	0.0	0.0	0.0	0.0	0.0	485	0.0
81-120	0.0	0.6	8.5	70.2	19.2	1.4	0.1	0.0	0.0	0.0	0.0	2161	0.0
121-160	0.0	0.1	0.2	20.7	63.5	15.0	0.5	0.0	0.0	0.0	0.0	3197	0.0
161-200	0.0	0.0	0.0	0.8	33.9	57.7	7.5	0.0	0.0	0.0	0.0	2464	0.0
201-250	0.0	0.0	0.0	0.0	1.8	40.1	53.5	4.5	0.0	0.0	0.0	2245	0.0
251-300	0.0	0.0	0.0	0.0	0.1	1.6	48.4	47.3	2.6	0.0	0.0	1067	0.0
301-350	0.0	0.0	0.0	0.0	0.0	0.5	3.8	62.6	28.2	4.9	0.0	425	0.0
351-400	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16.4	64.7	18.1	0.9	116	0.0
401-500	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8.8	52.9	38.2	34	0.0
>500	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100	2	0.0

**For comparator range ≤80 mg/dL, agreement was based on 15/20/30/40 mg/dL*
***Note:** Sensor measurement range is 40-500 mg/dL*

The results presented above, particularly in Table 16, demonstrate that when the FreeStyle Libre Pro System reports glucose values in the hypoglycemic range (<60 mg/dL) a substantial number of the true glucose values in those cases are actually in the euglycemic range (81-160 mg/dL). Based on these results, the manufacturer agreed to include a prominent warning in the FreeStyle Libre Pro System user guide and in all advertising and promotional materials for this device. This warning can be found in Section II – Indications for Use, above.

Additional Evaluation of Agreement:
Agreement between matched pairs of CGM sensor and CM values was estimated by calculating the percent difference between concurrent CGM system readings and CM values.

The absolute relative difference, provided in Table 17 below, provides the percent difference between the FreeStyle Libre Pro System and CM values, but does not demonstrate whether the FreeStyle Libre Pro System is reading, on average, higher or lower than the comparator. The mean absolute relative difference is the average difference (regardless if positive or negative) between System readings and CM values.

Table 17. CGM System differences to CM within CM Glucose Ranges

Comparator glucose ranges (mg/dL)	Number of paired CGM-CM Pairs	Median Absolute Relative Difference (%)	Mean Absolute Relative Difference (%)
Overall	12080	10.0	12.1
40-50*	30	14.2	15.8
51-80*	486	12.4	14.5
81-180	7200	10.7	12.7
181-300	4074	8.7	10.1
301-400	276	7.7	8.6
401-500	14	4.2	7.2

**For CM range ≤80 mg/dL, agreement was based on 15/20/30/40 mg/dL*
***Note:** Sensor measurement range is 40-500 mg/dL*

Table 18 below shows the mean and median absolute relative difference between the FreeStyle Libre Pro System and CM values on different days of wear. This data indicates that the agreement between the FreeStyle Libre Pro System and the CM is, on average, worse during early wear periods and improves over time.

Table 18: CGM System differences to CM by Day

Day	Number of CGM- CM Pairs	Median Absolute Relative Difference (%)	Mean Absolute Relative Difference (%)
1	2050	11.3	13.7
2-5	3973	10.9	13.2
6-9	2865	10.1	12.1
10-13	2175	8.4	10.2
14	1017	7.2	9.0

Precision
Precision of the FreeStyle Libre Pro System was evaluated by comparing the results from two separate sensors worn on the same subject at the same time. Data from two sensors worn at the same time for 72 subjects provided 49,806 pairs of CGM measurements, with a mean Percent Absolute Relative Difference (PARD) during the study was 8.6% with a coefficient of variation (%CV) of 6.1%.

System Availability
During the clinical study used to support approval of this device, a total of 202 sensors were inserted. 167 sensors produced glucose readings and are included in the above analysis. There were 35 sensors (17%) that failed at insertion (i.e., no glucose reading generated) and were not included in the analysis.

During the clinical study, study participants each had two sensors inserted. One of these sensors was designated as a primary sensor, and the primary sensor values were used for accuracy evaluation for the FreeStyle Libre Pro System. Precision evaluation was accomplished by comparing results from both sensors. There were 62.5% of primary sensors that worked for the full 14 days. The mean sensor duration for all primary sensors was 258 hours (10.75 days), and the median duration was 327 hours (13.63 days).

2. Safety Results

The analysis of safety was based on the severity and frequency of adverse events resulting from the 202 sensor insertions in 72 patients during the clinical study. The key safety outcomes for this study are presented below.

Adverse effects that occurred in the PMA clinical study

During the clinical study that was used to support approval of this device, twelve (12) subjects experienced a total of eighteen (18) adverse events; ten (10) adverse events were related to the device. Twenty-six (26) of the 72 subjects in the clinical study reported experiencing an application site adverse reaction consisting of skin irritation such as bleeding, bruising, edema, erythema, induration, itching, pain, rash and other events (e.g., scaling skin and red dot/raised bump) around the insertion site and adhesive area. Pain was mostly reported as none with a low frequency of mild pain reported and one report of moderate pain.

The following incidence of skin issues were observed in 202 site exams:

- Erythema was reported as ‘well-defined redness’ or ‘intense redness’ 4.0% of the time.
- The rate of moderate incidences for any individual category of skin issues including induration, rash, bleeding, itching and scaling of the skin was no more than 1.0%.
- The rate of mild incidences for any individual category of skin issues above and bruising, edema, pain and red dot/raised bump was less than 9.0%.

During an additional clinical study using this device which included 125 subjects, thirty-three (33) of the subjects who had a FreeStyle Libre Pro Sensor inserted reported experiencing a total of 76 application site adverse reactions consisting of mild skin irritation such as erythema, edema, rash, bleeding, itching and induration around the insertion site and adhesive area. Pain was mostly reported as none with a low frequency of mild pain reported and one report of moderate pain.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Clinical 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the clinical study data used to support this submission establish a reasonable assurance of safety and effectiveness of the FreeStyle Libre Pro Flash Glucose Monitoring System for detecting trends and tracking patterns in glucose values in subjects with diabetes mellitus. The primary effectiveness measurements for this study were based on the performance evaluation of the FreeStyle Libre Pro Flash Glucose Monitoring System compared to the blood glucose values measured by CM during in-clinic sessions spanning the wear period of the sensor.

The performance data presented above (tables 11 to 16) support the effectiveness conclusions and established the clinical performance across the claimed measuring range (40 to 500 mg/dL), including agreement to the CM, precision, and duration of wear period of the sensor. The results presented in these tables show that the system may incorrectly indicate hypoglycemia, and its accuracy in the hyperglycemic range appears to be worse than other recently approved devices. However, the longer sensor life of this device (14 days compared to 6 days for another comparable device), combined with the added convenience that patients do not need to perform fingerstick sensor calibrations, may make this system more desirable to patients. Because sensor data is blinded to patients and must be interpreted by a HCP the risk of inappropriate treatment decisions based on inaccurate sensor glucose values is low (see section XII below for additional discussion of benefits and risks of the system).

The clinical study data demonstrated that the FreeStyle Libre Pro Flash Glucose Monitoring System was effective in the study population.

B. Safety Conclusions

Evaluation of the risks of the device is based on the results of the clinical study described above, post-market data (MDR analysis), and non-clinical data in Section IX above.

While the device does not appear to perform as well as other similar devices in the low glucose range, this device is not used in real time to make acute treatment decisions. Physicians will evaluate the data for trends in the users' daily glucose patterns, and use those trends to make minor adjustments to therapy (e.g., modified

basal rate recommendations, etc.). If the device is reading lower than the user's actual glucose levels, the physician is unlikely to make a change to therapy, unless there is a sustained pattern at the same time every day, in which case they may reduce the amount of insulin the person receives in response to a meal. Therefore, there is not a significant risk to the patient based on the poor performance (see section XII below for additional discussion of benefits and risks of the system).

Potential device-related, non-serious events related to CGM use include:

- Local infection
- Skin irritation or redness
- Skin inflammation
- Pain or discomfort
- Bleeding
- Bruising
- Skin edema
- Skin rash
- Itching
- Scarring or skin discoloration
- Allergic reactions to the sensor needle or adhesives
- Sensor or needle fracture during insertion, wear or removal

Sensor breakage with fragments retained under the skin is a potential procedure-related complication. However, based on post-market experience with this and similar devices, and the results observed in the clinical study, this event is rare and its severity does not raise major concerns.

The indications for use of this device state that sensor glucose readings should only be interpreted based on trends and patterns that appear over time. While this reduces the risk that individual sensor values (which may be inaccurate) will be used to make inappropriate treatment decisions, it is possible that persistent poor sensor performance could appear to be a real trend and result in an inappropriate change to therapy. The risks associated with such a change are deteriorating glycemic control, and increased risk of acute and long-term complications of diabetes.

Although the accuracy of the device especially in the low and high end of the measuring range (40-500mg/dl) is not optimal, diabetes management changes made by a clinician would be accompanied by repeated glycemic trends and/or concurrence with blood glucose measurements or other patient log data (i.e. symptoms, carbohydrate intake, insulin delivery, etc.). Therefore the risks of false positive/negative high or low glucose are somewhat mitigated.

C. Benefit-Risk Conclusions

Summary of Benefits:

This device is intended for retrospective monitoring of interstitial glucose levels as a supplement to self-monitoring of blood glucose. Continuous glucose monitor measurements are performed every 15 minutes for 14 days via an indwelling sensor. These functions are not feasible using traditional blood glucose monitoring as blood glucose meters only provide information about discrete, intermittent blood glucose levels and therefore are unable to provide information regarding patterns of glycemic excursions throughout the day and night when patients may be unable to test their blood glucose.

This continuous glucose monitor can provide an unbiased (blinded to the patient) representation of a patient's blood glucose patterns in response to lifestyle factors such as diet, exercise, or medications throughout the sensor's 14 day wear period. The clinician can then obtain reports of the continuous glucose values during this time period and, in conjunction with the subject's log of diet and activities, the clinician can recommend therapy changes to improve glycemic control. For patients who do not already use CGM to monitor their glucose levels throughout the day, the FreeStyle Libre Pro System is helpful for identifying patterns of poor glycemic control that may indicate the need for adjustments to therapy or behavior.

The device may be helpful to help HCPs identify individuals who frequently become hypoglycemic overnight. Preventing hypoglycemia can prevent (or possibly reverse) the development of hypoglycemia unawareness (these individuals may develop severe hypoglycemia with loss of consciousness, seizures, or rarely death without the normal warning symptoms).

This system may be desirable to patients relative to similar previously approved devices because of the convenience associated with wearing the glucose sensor for a longer period of time (14 days, compared with 3-7 days for previous continuous glucose monitors), and the corresponding reduced burden of glucose sensor changes.

Previously approved CGM systems require frequent calibration using a blood glucose monitor, and CGM performance can be degraded by inaccurate calibration measurements. The FreeStyle Libre Pro System does not require calibration by the user, so the risk of degraded accuracy due to improperly calibrating the device is eliminated.

Summary of Risks:

Adverse events observed during the clinical study were similar to those observed for other approved CGMs and were associated with local skin reaction to the sensor insertion or to the adhesive used to secure the sensor recording device.

The clinical study did not directly assess risks associated with HCPs making therapy adjustments based on values reported by the FreeStyle Libre Pro System. However, the low rate of agreement between the FreeStyle Libre Pro System sensor values and the comparator glucose values seen during the clinical study raises the risk that sensor inaccuracy could lead to inappropriate therapy changes by HCPs. There is a possibility of deterioration in glycemic control or hypoglycemic or hyperglycemic events with use of this device if repeated trends of erroneous glucose are used to make inappropriate treatment adjustments. Repeated trends of falsely high or falsely normal continuous glucose readings when the patient's glucose is low may prompt clinicians to prescribe more glucose lowering medications and increase the risk of severe hypoglycemia. Repeated trends of falsely low or falsely normal continuous glucose readings when the patient's glucose is high may prompt clinicians to decrease glucose lowering medications (or perform no adjustments in treatment) which can increase the risk of glycemic deterioration or hyperglycemia. However, these risks are low since consistently erroneous repeated trends would likely not occur in conjunction with symptoms, and a patient log of events (e.g. blood glucose measurements, exercise, etc.) may be considered before making therapy changes based on CGM values.

Summary of other factors:

The average overall rate of agreement between the FreeStyle Libre Pro System and the CM in the clinical study was slightly better than what has been observed for another similar device in a similar study when the entire measurement range is considered. However, the accuracy in the hypoglycemic range appears worse for the FreeStyle Libre Pro Flash System compared to previously approved CGMs. For example, during the clinical study, when the FreeStyle Libre Pro Flash sensor reported glucose values in the range of 40-60 mg/dl, the true blood glucose value was in the same range only approximately 23% of the time, compared to 37% of the time for a similar approved device. Additionally, when the Freestyle Libre Pro reported glucose values in the hypoglycemic range of 40-60 mg/dl, the corresponding true blood glucose values were in the euglycemic range of 80-160 mg/dl 38% of the time.

In the high end of the measuring range, the accuracy of the FreeStyle Libre Pro Flash continuous glucose monitor appears worse compared to other similar approved devices. For example, according to the studies performed, when the FreeStyle Libre Pro Flash CGM value was in the range of 300-350mg/dl, the true blood glucose was 300-350 mg/dl only approximately 28% of the time, compared to 49% of the time for a similar approved device. However, head-to-head studies were not performed and therefore a direct comparison is not possible.

The accuracy results presented by Abbott in support of this approval appear worse than results from other similar devices observed in similar clinical studies, particularly in the hypoglycemic range. As a result, Abbott must include a prominent warning in their user guide and in all advertising and promotional materials for the

FreeStyle Libre Pro System. See Section II – Indications for Use, above, for the text of this warning.

While the device does not appear to perform as well as other similar devices in the low glucose range, the potential benefits of this device outweigh the potential risks and the device is still adequately safe and effective for this intended use. This device is not used in real time to make acute treatment decisions. Physicians will evaluate the data for trends in the users' daily glucose patterns, and use those trends to make minor adjustments to therapy (e.g., modified basal rate recommendations, etc.). If the device is reading lower than the user's actual glucose levels, the physician is unlikely to make a change to therapy, unless there is a sustained pattern at the same time every day, in which case they may reduce the amount of insulin the person receives in response to a meal. Therefore, there is not a significant risk to the patient based on the poor performance, and the benefits of not having to calibrate the device and being able to wear the device for 14 days outweigh the potential risk from the poor performance in the low glucose range.

This system may be desirable to patients relative to similar previously approved devices because of the convenience associated with wearing the glucose sensor for a longer period of time (14 days, compared with 3-7 days for previous continuous glucose monitors), and the corresponding reduced burden of glucose sensor changes.

Additionally, since calibrations are not required, the risk of reduced accuracy due to improperly calibrating the device is mitigated.

Patient Perspectives

Patient perspectives considered during the review included patients' preferences for longer CGM sensor wear times and no need to calibrate the CGM sensor. The comparatively short sensor life of 3-6 days for other similar CGMs, and the need to perform additional finger stick blood glucose measurements, have been sources of dissatisfaction from patients. These benefits may result in increased utilization of CGM technology.

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 using the FreeStyle Libre Pro Flash continuous glucose monitoring system, as discussed above, outweigh the risks.

XIII. CDRH DECISION

CDRH issued an approval order on September 23, 2016.

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

XIV. **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.