



**EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
Eversense AP CGM System
DECISION SUMMARY**

I Background Information:

A De Novo Number

DEN230052

B Applicant

Senseonics, Incorporated

C Proprietary and Established Names

Eversense AP CGM System

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
SBA	II	21 CFR 862.1357	Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the Eversense AP CGM System.

B Measurand:

Glucose in interstitial fluid.

C Type of Test:

Quantitative, fluorescent based.

III Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Eversense AP CGM System is indicated for continually measuring glucose levels for up to 6 months in people (18 years and older) with diabetes. The system is indicated for use to replace fingerstick blood glucose measurements for diabetes treatment decisions. The system is intended to:

- Provide real-time glucose readings.
- Provide glucose trend information.
- Provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

Historical data from the system can be interpreted to aid in providing therapy adjustments. These adjustments should be based on patterns and trends seen over time.

The Eversense AP CGM System is also intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Eversense AP CGM System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes.

The system is intended for single patient use and requires a prescription.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The smart transmitter is incompatible with magnetic resonance imaging (MRI) procedures. The smart transmitter is MR Unsafe and **MUST BE REMOVED** before undergoing an MRI (magnetic resonance imaging) procedure. The system is contraindicated in people for whom dexamethasone or dexamethasone acetate may be contraindicated.

Mannitol or sorbitol, when administered intravenously, or as a component of an irrigation solution or peritoneal dialysis solution, may increase blood mannitol or sorbitol concentrations and cause falsely elevated readings of the sensor glucose results. Sorbitol is used in some artificial sweeteners, and concentration levels from typical dietary intake do not impact sensor glucose results.

The Eversense AP CGM System has not been tested in the following populations: women who are pregnant or nursing, people under the age of 18, critically ill or hospitalized patients, people receiving immunosuppressant therapy, chemotherapy or anti-coagulant therapy, those with another active implantable device, e.g., an implantable defibrillator (passive implants are allowed, e.g., cardiac stents), those with known allergies to or using systemic glucocorticoids (excluding topical, optical or nasal, but including inhaled). The system's accuracy hasn't been tested in these populations, and sensor glucose readings may be inaccurate, resulting in missing a severe low or high glucose event.

Antibiotics of the tetracycline class (including tetracycline, doxycycline, minocycline and tigecycline) may falsely lower sensor glucose readings. Users should not rely on sensor glucose readings while taking tetracyclines.

D Special Instrument Requirements:

Not applicable.

IV Device/System Characteristics:

A Device Description:

The Eversense AP CGM System is a continuous glucose monitoring system (CGM) that provides glucose measurements every 5 minutes over a 40-400 mg/dL range. The system calculates glucose, trends and provides alerts for high and low glucose available for display on a mobile platform. It consists of a glucose sensor (the Eversense AP Sensor) that is inserted by a healthcare provider under the skin using Insertion Tools; an externally worn Eversense AP Smart Transmitter (Transmitter); and the Eversense Mobile Medical Application (MMA), which runs on a handheld device, such as a smartphone running on Android or iOS operating systems. The inserted sensor is a radiofrequency (RF)-powered device that collects readings and sends them to the Transmitter. The Transmitter calculates, stores, and transmits the glucose data via Bluetooth Low Energy (BLE) to an MMA on a handheld device (HHD).

The Eversense AP CGM System can communicate glucose readings and other information wirelessly and securely to and from interoperable electronic interfaces; including compatible AID systems. The Eversense AP CGM System is designed to communicate with interoperable devices in several ways, such as described below:

- Wireless communication from the transmitter directly to an interoperable device communicating through the same protocol.
- The app communicates through the cloud to another software device.

B Principle of Operation

The Eversense AP CGM System detects glucose levels in the interstitial fluid just beneath the skin. The Eversense AP Sensor uses a selective, fully reversible binding between glucose and a proprietary fluorescent indicator macromolecule that is grafted on the surface of the Sensor. Glucose binding by the indicator macromolecule results in an increase in fluorescence intensity. Glucose signal transduction is accomplished by measuring the fluorescence intensity modulation using the Sensor's optical system. The transmitter converts the signal using an algorithm to a glucose value read in mg/dL, which is then transmitted to the MMA for the user to see and use accordingly.

V Standards/Guidance Documents Referenced:

IEC 60601-1:2005 + AMD1:2012 + AMD2:2020, Medical electrical equipment – General requirements for basic safety and essential performance

IEC 60601-1-2:2014, Medical electrical equipment – General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic compatibility – Requirements and Tests

IEC 60601-1-11: 2015 + AMD1:2020, Medical electrical equipment – General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

IEC 62133-2 2017/AMD1:2021, Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for portable sealed secondary cells, and batteries made from them, for use in portable applications – Part 2: Lithium systems.

ISO 14708-1, 2014, Active Implantable Medical Devices - Part 1: General Requirements for Safety, Marking, and for Information to be provided by the Manufacturer

IEC 62366, 2015+A1:2020, Medical devices – Application of usability engineering to medical devices

UL 1642, 5th Edition. Standard for Safety – Lithium Batteries

ISO 10993-1:2018, Biological evaluation of medical devices – Part 1: Evaluation and testing

ISO 10993-3:2014, Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity

ISO 10993-5:2009, Biological evaluation of medical devices – Part 5: Tests for cytotoxicity: in vitro methods

ISO 10993-6:2016, Biological evaluation of medical devices – Part 6: Tests for local effects after implantation

ISO 10993-10:2021, Biological evaluation of medical devices – Part 10: Tests for skin sensitization

ISO 10993-11:2017, Biological evaluation of medical devices Part 11: Tests for systemic toxicity.

ISO 10993-12:2021, Biological evaluation of medical devices – Part 12: Sample preparation and reference materials

ISO 10993-17:2002, Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances

ISO 10993-18:2020, Biological evaluation of medical devices – Part 18: Chemical characterization of materials

ISO 10993-23: 2021, Biological evaluation of medical devices – Part 23: Tests for Irritation

ISO 10993-7: 2008, Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals

EN ISO 11135: 2014, Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices

EN ISO 11737-1:2018, Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products

ISO 11737-2: 2020, Sterilization of medical devices – Microbiological methods – Part 2: test of sterility performance in the definition, validation and maintenance of a sterilization process

ISO 11607-1:2019, Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems

ISO 11607-2:2019, Packaging for terminally sterilized Medical Devices – Part 2: Validation Requirements for forming, sealing and assembly processes

ASTM F1980-16, Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

ASTM F1886/F1886M-16, Standard Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection

ASTM F2096-11, Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)

ASTM D3078-02, 2013, Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission

ASTM F88-21, Standard Test Method for Seal Strength of Flexible Barrier Materials

ASTM D4169-22, Standard Practice for Performance Testing of Shipping Containers and Systems

CLSI. EP07 3rd Edition Interference Testing in Clinical Chemistry

ISO 14155:2020, Clinical investigation of medical devices for human subjects — Good Clinical Practice

ISO 14971:2019, Medical devices – Application of Risk Management to Medical Devices

ISO 15223-1:2021, Medical devices - Symbols to be used with medical device labels, labelling, and information to be supplied - Part 1: General requirements

ISO 14708-1:2014 Implants for surgery -- Active implantable medical devices -- Part 1: General requirements for safety, marking a Implants for surgery -- Active implantable medical devices - Part 1: General requirements for safety, marking and for information to be provided by the manufacturer

IEC 62304:2015, Medical Device Software – Software life cycle processes

De Novo Classification Process (Evaluation of Automatic Class III Designation) Guidance for Industry and Food and Drug Administration Staff, document issued on October 5, 2021

Guidance for Industry and Food and Drug Administration Staff Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications, document issued on August 2019

Content of Premarket Submissions for Device Software Functions – Guidance for Industry and Food and Drug Administration Staff, document issued on June 14, 2023

Off-The-Shelf Software Use in Medical Devices - Guidance for Industry and Food and Drug Administration Staff, document issued on September 27, 2019

Radio Frequency Wireless Technology in Medical Devices - Guidance for Industry and Food and Drug Administration Staff, document issued on August 14, 2013

Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff, document issued on September 4, 2020

Content of Human Factors Information in Medical Device Marketing Submissions. Draft Guidance. December 9, 2022

VI Performance Characteristics:

A Analytical Performance:

1. Precision/Reproducibility:

iCGM performance was evaluated in clinical studies described in Section C(3) below. A subset of subjects (n=37) wore two Systems concurrently (blinded and unblinded iCGM Systems) at the same sensor insertion site (opposite arms) to evaluate the device precision. A total of 57,519 CGM-CGM matched pairs (matched within the same subject) contributed to the analysis. The precision data are shown in the table below. Precision is described as Standard Deviation (SD), Precision Absolute Difference (PAD), Precision Absolute Relative Difference (PARD) and Coefficient of Variation (CV).

Range of Mean CGM Glucose (mg/dL)	Number (CGM, CGM) Pairs	Number of Subjects	SD (mg/dL)	PAD (mg/dL)	PARD (%)	CV (%)
Overall	57,128	37	18.8	12.7	8.4	5.9
<70	2,538	31	10.1	7.4	12.1	8.6
70-180	37,103	37	14.6	10.4	8.5	6.0
>180	17,487	37	26.1	18.5	7.5	5.3

Mean absolute relative difference (between the 2 concurrently worn Systems) was 8.4% and mean coefficient of variation (CV) was 5.9%.

2. Linearity:

The reportable range for the Eversense AP CGM System is 40 to 400 mg/dL. Data supporting this claimed measurement range were generated in the clinical study described in Section C(3) below.

3. Analytical Specificity/Interference:

Mannitol and sorbitol infusion solutions have previously been shown to present significant interference in earlier generations of similar Eversense CGM Systems that utilized the same glucose-binding indicator. This interference is mitigated by inclusion of a contraindication specifically stating that these are a component of “an irrigation solution or peritoneal dialysis solution” and may “cause falsely elevated readings” of glucose results.

In-vitro interference testing performed in accordance with CLSI EP07 demonstrated that tetracycline class of medications (including tetracycline, doxycycline, minocycline and tigecycline) lowers Sensor readings. A negative bias may create a situation in which a user inappropriately increases their carbohydrate intake or does not dose with insulin during a time in which their blood glucose concentration is euglycemic or hypoglycemic, hazardous situations which do not present imminent risk to the user but which do increase risks associated with hyperglycemia. Risks resulting from tetracycline interference are mitigated through the information provided to users and healthcare providers (HCPs) in the “*Warning*,” “*Medication*,” “*Making Treatment Decisions with Eversense AP*,” and the “*Troubleshooting: Making Treatment Decisions*” sections of the patient User Guide and the “*Warnings*” section of the HCP instructions for use.

4. Assay Reportable Range:

See linearity section above.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

The Eversense AP Sensor has a storage shelf-life of 13 months that was evaluated at 2-8° C (35-46° F).

The Eversense AP Transmitter has sufficient battery life to function for 12 months as intended following its maximum storage time of 12 months. Shelf life was evaluated by functional test after 40 days of accelerated aging at 131°F (equivalent to 1 year real-time).

6. Detection Limit:

If a glucose measurement is less than 40 mg/dL, the result is displayed by the system as ‘LO’. If a glucose measurement exceeds 400 mg/dL, the result is displayed as ‘HI’. Data supporting this claimed measurement range was generated in the clinical study described in Section C(3) below.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison:

Not applicable. Accuracy was determined by comparing iCGM values to an FDA-cleared laboratory glucose analyzer (Yellow Springs Instrument 2300 STAT Plus™ Glucose Analyzer) and referred to as the “comparator method” in Section C(3) below.

2. Matrix Comparison:

Not applicable. Interstitial fluid is the only indicated matrix.

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

One clinical study was conducted to support the accuracy performance of the Eversense AP CGM System.

The ENHANCE study is a prospective, multi-center study enrolling adult subjects (18 years and older) with diabetes mellitus in the United States at 4 sites. The study enrolled a total of 135 subjects of which 111 were inserted with Sensors. Of the 111 subjects with Sensors, 59.5% had Type 1 diabetes mellitus and 40.5% had Type 2 diabetes mellitus. A total of 102 subjects completed 6 months of study.

A summary of demographic characteristics for all Eversense AP CGM system subjects is presented in the table below. Subjects had a mean age of 47 years and a mean body mass index (BMI) of 31 kg/m². Both males and females were represented in the study population.

Study Demographics (n=111)

Demographic	Value
Gender n (%)	
Male	71 (64.0)
Female	40 (36.0)
Age (years) [mean (SD)]	46.9 (14.5)
Min, Max	18, 77
Ethnicity n (%)	
Non-Hispanic	92 (82.9)
Hispanic	19 (17.1)
Race n(%)	
Caucasian	103 (92.8)
Black or African American	4 (3.6)
Asian	2 (1.8)
American Indian or Alaska Native	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
More than One Race	2 (1.8)
Body Mass Index Class [mean (SD)] kg/m ²	31.4 (7.0)
Min, Max	19, 52
Normal (<25 kg/m ²) n (%)	18 (16.2)
Overweight (>25 and <30) n (%)	25 (22.5)
Obese (>30) n (%)	68 (61.3)

All 111 subjects had two sensors inserted in the upper arms by trained investigators. Subjects were inserted with two Eversense AP Sensors or an Eversense AP Sensor and Sensor with a modified design. Thirty-seven (37) subjects were inserted with two Eversense AP Sensors and 74 were inserted with one Eversense AP Sensor..

Accuracy of the Eversense AP CGM System was evaluated during multiple clinic visits up to 6 months post-sensor insertion. For qualifying subjects, the glucose levels were deliberately manipulated to raise or lower glucose levels to assess system performance over the glucose range (40 – 400 mg/dL) during the clinic visits of 8-to-12-hour durations (day 1 was 12 hours, day 180 was 10 hours and all other sessions were 8 hours). Clinic sessions took place on day 1; and day 7, day 14 or day 22; day 30; day 60; day 90; day 120; day 150; and day 180.

Accuracy was evaluated using paired CGM readings to comparator method values for the Eversense AP CGM System. For values less than 70 mg/dL, the absolute difference in mg/dL between the two glucose results was calculated. For values greater than or equal to 70 mg/dL, the absolute difference (%) relative to Comparator Method values was calculated. The percentages of readings within 15/15% of Comparator Method values or 40/40% of Comparator Method values by CGM glucose ranges are shown in the table below.

Percent and Point Accuracy by iCGM Glucose Range (N=111)

iCGM Glucose Range	Matched Pairs (N)	Percent Within 15 mg/dL (95% LB)	Percent Within 40 mg/dL (95% LB)	Percent Within 15% (95% LB)	Percent Within 40% (95% LB)	Mean Bias (mg/dL) (95% UB)
<70 mg/dL	2,093	89.4 (88.3)	99.6 (99.4)	---	---	-3.9 (-3.6)
70-180 mg/dL	16,027	---	---	83.1 (82.6)	99.2 (99.07)	1.8 (2.0)
>180 mg/dL	10,432	---	---	87.0 (86.5)	99.3 (99.2)	8.1 (8.5)

*95% LB is the lower bound of the confidence interval and 95% UB is the upper bound of the confidence interval

Percentages of readings within 15/15% or 40/40% of comparator method values by Comparator glucose ranges.

Percent and Point Accuracy by Comparator Glucose Range (N=111)

Comparator or Glucose Range	Matched Pairs (N)	Percent Within 15 mg/dL (95% LB)	Percent Within 40 mg/dL (95% LB)	Percent Within 15% (95% LB)	Percent Within 40% (95% LB)	Mean Bias (mg/dL) (95% UB)
<70 mg/dL	2,084	90.9 (89.8)	99.4 (99.1)	---	---	2.1 (2.5)
70-180 mg/dL	16,522	---	---	82.3 (81.8)	99.2 (99.1)	3.4 (3.6)
>180 mg/dL	16,522	---	---	88.8 (88.3)	99.7 (99.6)	4.6 (5)

*95% LB is the lower bound of the confidence interval and 95% UB is the upper bound of the confidence interval

Percentage of readings within 20% of comparator method values, including the 95% lower bound confidence interval, for the overall 40-400 mg/dL iCGM range is shown in the Table below.

iCGM Glucose Range	Matched Pairs (N)	Percent within 20% (95% LB)
Overall (40-400 mg/dL)	28,552	92.1 (91.8)

*95% LB is the lower bound of the confidence interval and 95% UB is the upper bound of the confidence interval

Percent of values within 15/15% mg/dL, 20/20% mg/dL, and 40/40% mg/dL stratified by glucose ranges of <54, 54-69, 70-180, 181-250, and >250 mg/dL for CGM and comparator method were also provided.

Eversense AP CGM System Accuracy to Comparator within iCGM Glucose Ranges (N=111)

iCGM Glucose Range (mg/dL)	Number of paired iCGM-comp	Percent within 15 mg/dL	Percent within 20 mg/dL	Percent within 40 mg/dL	Percent within 15%	Percent within 20%	Percent within 40%	Mean Bias (mg/dL)	MARD (%)
<54	462	80.5	90	99.6	---	---	---	-7.9	15.2
54-69	1,631	91.8	95.3	99.6	---	---	---	-2.8	9.8
70-180	16,027	---	---	---	83.1	91.9	99.2	1.8	9
181-250	5,685	---	---	---	88.2	94.3	99.4	8.1	8
>250	4,747	---	---	---	85.6	93.3	99.2	12	8.4

Eversense AP CGM System Accuracy to Comparator within Comparator Glucose Ranges (N=111)

Comp Glucose Range (mg/dL)	Number of paired iCGM-comp	Percent within 15 mg/dL	Percent within 20 mg/dL	Percent within 40 mg/dL	Percent within 15%	Percent within 20%	Percent within 40%	Mean bias (mg/dL)	MARD (%)
<54	270	88.5	95.2	99.6	---	---	---	5.3	15
54-69	1,814	91.3	95.9	99.4	---	---	---	1.6	11.5
70-180	16,522	---	---	---	82.3	91.2	99.2	3.4	9.2
181-250	5,573	---	---	---	88	94.6	99.6	4.6	7.9
>250	4,373	---	---	---	89.9	96.3	99.9	4	7.3

Concurrence of iCGM values compared to the comparator method across the entire measuring range was also evaluated. iCGM glucose ranges of <40, 40-60, 61-80, 81-120, 121-160, 161-200, 201-250, 251-300, 301-350, 351-400, and >400 mg/dL were evaluated against comparator glucose ranges and percent of iCGM values within those ranges were reported.

Concurrence of Eversense AP CGM System Reading and Comparator Values by iCGM
Glucose Range (N=111)

iCGM Glucose Range (mg/dL)	Comparator Glucose Values (mg/dL)											
	<40	40- 60	61- 80	81- 120	121- 160	161- 200	201- 250	251- 300	301- 350	351- 400	>400	Total
<40	.	100%	.	.	.	.	.	.	.	.	.	1
40- 60	0.6%	54.7%	42.2%	2.6%	.	.	.	.	.	.	.	1,083
61- 80	.	13.7%	68.3%	17.9%	0.1%	0%	.	.	.	.	.	2,266
81- 120	.	0.3%	8%	80.8%	10.6%	0.3%	.	.	.	.	.	6,291
121- 160	.	.	0.1%	17.6%	72.2%	9.7%	0.4%	.	.	.	.	6,120
161- 200	.	.	.	0.5%	24.7%	64.5%	10.2%	0.1%	.	.	.	4,380
201- 250	.	.	.	0%	1%	22.4%	66.2%	9.9%	0.4%	0.1%	.	3,665
251- 300	.	.	.	.	0.2%	1%	25.9%	59.9%	12.6%	0.5%	.	2,611
301- 350	.	.	.	.	.	0.2%	3%	31.8%	60.9%	4.2%	.	1,649
351- 400	.	.	.	.	.	.	0.4%	8%	56.5%	32.2%	2.9%	487
>400	.	.	.	.	.	.	.	1.1%	28.3%	50%	20.7%	92

Concurrence of Eversense AP CGM System Reading and Comparator Values by Comparator
Glucose Range (N=111)

Compar ator Glucose Range (mg/dL)	iCGM Glucose Values (mg/dL)											
	<40	40- 60	61- 80	81- 120	121- 160	161- 200	201- 250	251- 300	301- 350	351- 400	>400	Total
<40	.	100%	.	.	.	.	.	.	.	.	.	6
40- 60	0.1%	64%	33.5%	2.4%	.	.	.	.	.	.	.	925
61- 80	.	18.2%	61.6%	19.9%	0.3%	.	.	.	.	.	.	2,513
81- 120	.	0.4%	6.1%	76.9%	16.3%	0.3%	0%	.	.	.	.	6,613
121- 160	.	.	0%	10.8%	71.1%	17.4%	0.6%	0.1%	.	.	.	6,214
161- 200	.	.	0%	0.4%	13.9%	65.9%	19.1%	0.6%	0.1%	.	.	4,283
201- 250	.	.	.	.	0.7%	12.3%	67%	18.7%	1.4%	0.1%	.	3,626
251- 300	.	.	.	.	.	0.2%	14.6%	62.6%	21%	1.6%	0%	2,498
301- 350	.	.	.	.	.	.	0.8%	19.9%	61%	16.7%	1.6%	1,646
351- 400	.	.	.	.	.	.	1.4%	4.2%	24%	54.5%	16%	288
>400	.	.	.	.	.	.	.	.	.	42.4%	57.6%	33

Trend Accuracy

Trend accuracy describes the accuracy of the sensor during times of rapidly changing glucose and is characterized by slopes, such as from >2 mg/dL to <-2 mg/dL. Trend accuracy was assessed by the concurrence rate of the glucose rate of change (changes in mg/dL of glucose per minute) determined by the comparator values and the corresponding iCGM values for each CGM-comparator measured pairs (typically once every 15 minutes).

Comparator Rate Range (mg/dL/min)	iCGM Rate Range (mg/dL/min)					iCGM-comparator Pairs (n)
	<-2	$[-2,-1]$	$[-1,1]$	$(1,2]$	>2	
<-2	43.5%	27.9%	27.9%	0.6%	0.0%	154
$[-2,-1]$	8.4%	45.7%	45.3%	0.6%	0.1%	1,392
$[-1,1]$	0.7%	5.6%	87.6%	5.3%	0.9%	22,933
$(1,2]$	0.0%	0.5%	46.2%	38.7%	14.6%	1,983
>2	0.0%	0.8%	23.4%	36.2%	39.6%	495

Agreement when iCGM reads “LO” or “HI”

The Eversense AP CGM System reports glucose readings between 40 and 400 mg/dL. When the system determines that the glucose reading is below 40 mg/dL, it displays “LO” in the MMA. When the system determines that the glucose level is >400 mg/dL, it displays “HI” in the MMA. Because the system does not display glucose values below 40 mg/dL or above 400 mg/dL, the comparison to the actual blood glucose levels (using the laboratory comparator method) when the iCGM value is classified as “LO” or “HI” was evaluated separately. The cumulative percentages when the laboratory comparator values were less than certain glucose levels (for “LO”), and greater than certain glucose values (for “HI”) are presented in the table below.

Distribution of Comparator Values when CGM Readings are ‘Lo’ or ‘Hi’

iCGM Readings	iCGM-comparator Pairs	Comparator (mg/dL)					Total
		< 55	< 60	< 70	< 80	≥ 80	
“LO”	n	1	1	1	1	0	1
	Cumulative Percent	100%	100%	100%	100%	0%	
iCGM Readings	iCGM-comparator Pairs	Comparator (mg/dL)					Total
		> 340	> 320	> 280	> 250	≤ 250	
“HI”	n	74	81	91	92	0	92
	Cumulative Percent	80.4%	88%	98.9%	100%	0%	

Alert Performance

The tables in this section show the accuracy of the Eversense AP CGM System’s Low and High Glucose Alarms. The Alarm Rate tells the user how often the alarm is right or wrong. The Detection Rate tells the user how often the Eversense AP CGM System is able to recognize and notify the user about a low or high glucose event (within 15 minutes before or after the event).

Low Glucose Alarm Performance

The hypoglycemic alert rate shows how often the alert is right or wrong. The true alert rate is the % of time the iCGM alarmed when the blood glucose level was at or below the alert setting within 15 minutes before or after the iCGM alarmed (as confirmed by the comparator method). The false alert rate is the % of time the iCGM alarmed when the blood glucose level was above the alert setting within 15 minutes before or after the iCGM alarmed. The confirmed detection rate is the % of time the iCGM alarmed when the blood glucose level was at or below the alert setting within 15 minutes before or after the hypoglycemic event. The missed detection rate is the % of time the iCGM did not alarm when the blood glucose was at or below the alert setting within 15 minutes before and after the hypoglycemic event.

Low Glucose Alert and Detection Rate Evaluations (Threshold only, n=111)

Alert Setting	Hypo Events (n)	Confirmed Event Detection Rate (%)	Missed Event Detection Rate (%)	Hypo Alerts (n)	True Alert Rate (%)	False Alert Rate (%)
55 mg/dL	407	72	28	584	53.3	46.7
60 mg/dL	931	77.9	22.1	1,084	68.2	31.8
70 mg/dL	2,232	88.1	11.9	2,208	86.7	13.3
80 mg/dL	3,444	91.3	8.7	3,350	90.2	9.8
90 mg/dL	4,845	89.7	10.3	4,604	90.8	9.2

Low Glucose Alert and Detection Rate Evaluations (Threshold and Predictive, n=111)

Alert Setting	Hypo Events (n)	Confirmed Event Detection Rate (%)	Missed Event Detection Rate (%)	Hypo Alerts (n)	True Alert Rate (%)	False Alert Rate (%)
55 mg/dL	407	87.5	12.5	855	50.2	49.8
60 mg/dL	931	87.4	12.6	1,399	64.2	35.8
70 mg/dL	2,232	92.7	7.3	2,501	83.0	17.0
80 mg/dL	3,444	94.6	5.4	3,666	86.9	13.1
90 mg/dL	4,845	92.8	7.2	4,947	88.3	11.7

High Glucose Alarm Performance

The hyperglycemic alert rate shows how often the alert is right or wrong. The true alert rate is the % of time the iCGM alarmed when the blood glucose level was at or above the alert setting within 15 minutes before or after the iCGM alarmed (as confirmed by the comparator method). The false alert rate is the % of time the iCGM alarmed when the blood glucose level was below the alert setting within 15 minutes before or after the iCGM alarmed. The confirmed detection rate is the % of time the iCGM alarmed when the blood glucose level was at or above the alert setting within 15 minutes before or after the hypoglycemic event.

The missed detection rate is the % of time the iCGM did not alarm when the blood glucose was at or above the alert setting within 15 minutes before and after the hypoglycemic event.

High Glucose Alert and Detection Rate Evaluations (Threshold only, n=111)

Alert Setting	Hyper Events (n)	Confirmed Event Detection Rate (%)	Missed Event Detection Rate (%)	Hyper Alerts (n)	True Notification Rate (%)	False Notification Rate (%)
120 mg/dL	18,769	98.3	1.7	19,214	95.2	4.8
140 mg/dL	15,435	97.9	2.1	15,883	93.9	6.1
180 mg/dL	10,142	97.3	2.7	10,626	91.8	8.2
200 mg/dL	8,176	97.4	2.6	8,586	91.2	8.8
220 mg/dL	6,521	96.4	3.6	6,842	90.2	9.8
240 mg/dL	5,121	96.2	3.8	5,508	87.9	12.1
300 mg/dL	2,002	88.2	11.8	2,266	76.3	23.7

High Glucose Alert and Detection Rate Evaluations (Threshold and Predictive, n=111)

Alert Setting	Hyper Events (n)	Confirmed Event Detection Rate (%)	Missed Event Detection Rate (%)	Hyper Alerts (n)	True Notification Rate (%)	False Notification Rate (%)
120 mg/dL	18,769	99.0	1.0	19,617	94.5	5.5
140 mg/dL	15,435	98.7	1.3	16,332	92.8	7.2
180 mg/dL	10,142	98.2	1.8	11,013	90.1	9.9
200 mg/dL	8,176	98.3	1.7	8,954	89.3	10.7
220 mg/dL	6,521	97.8	2.2	7,191	87.8	12.2
240 mg/dL	5121	97.3	2.7	5791	85.6	14.4
300 mg/dL	2002	92.0	8.0	2499	72.9	27.1

Sensor Stability

Sensor stability describes the performance over the sensor lifetime. Sensors can be worn for up to 6 months. Performance was estimated by calculating the percentage of Eversense AP CGM System readings within ± 15 mg/dL or 15% (15/15%), ± 20 mg/dL or 20% (20/20%), or ± 40 mg/dL or 40% (40/40%) of laboratory comparator values in 30-day successive intervals.

Sensor Stability Relative to Comparator (Accuracy Over Time)

Wear Period	Number of paired iCGM-comparator	MARD (%)	Percent within 15/15% (%)	Percent within 20/20% (%)	Percent within 40/40% (%)
Day 1-30	10,440	9.6	82.4	91.2	99.1
Day 31-60	2,953	8.3	87	94.2	99.7
Day 61-90	3,825	9.1	85.8	92.4	99.4
Day 91-120	3,787	8	88.5	96.2	99.9
Day 121-150	3,108	8.7	86.6	94	99.5
Day 151-180	4,439	7.9	89.7	95.9	99.9

Sensor Life

A total of 111 sensors were evaluated to determine the percentage of sensors that lasted through the 180-day sensor life. A total of 96.9% of the sensors lasted through the end of the entire wear period. Among the 111 sensors evaluated, 3 had “early Sensor retirement” where the Sensor algorithm would have detected Sensors that did not function as intended and retired them.

Sensor Survival Rate by Wear Day (n=111)

Days Since Insertion	Subjects in Study	Number of Sensors	Survival Rate (%)
1	111	111	100
30	108	107	99.1
60	106	104	98.1
90	103	101	98.1
120	101	99	98.0
150	99	95	96.0
180	98	94	95.9

The capture rate characterizes the reliability of the communication between components of the system. The Eversense AP CGM System provides a glucose reading every 5 minutes, or up to 288 readings per day. The percentage of readings expected to be received for the system over the sensor life was evaluated from 111 Sensors and is 99.9%. The table below describes the percent of readings received throughout the life span of the sensor (Capture rate).

Reading Capture Rate by Wear Day

Wear Day	Number of Sensors	Capture Rate (%)
1-30	111	99.8
31-60	107	100
61-90	103	100
91-120	101	99.9
121-150	98	99.9
151-180	94	99.9

Calibration Stability

A calibration study was performed during day 1 after sensor insertion in which the iCGM was evaluated against the comparator.

Time from Calibration	Number of Paired iCGM-comp data points	Percent 15/15% of Comparator	Percent 20/20% of Comparator	Percent 40/40% of Comparator	Percent Greater than 40/40% of Comparator
0-2 hours	5,732	88	93.9	99.4	0.6
2-4 hours	3,942	85.8	93.7	99.4	0.6
4-6 hours	3,178	84	91.8	99.5	0.5
6-8 hours	2,444	85.1	91.5	99.6	0.4
8-10 hours	1,893	82.4	89.5	99.4	0.6
10-12 hours	1,949	83.3	92.1	99.3	0.7
12-14 hours	1,460	86.2	95.1	99.3	0.7
14-16 hours	1,527	87.4	95.4	100	0
16-18 hours	1,508	86.2	94.1	99.5	0.5
18-20 hours	1,510	88.5	95.5	99.9	0.1
20-22 hours	1,544	84.3	94.8	99.6	0.4
22-24 hours	1,593	85.6	94.9	99	1
24-26 hours	256	85.2	94.1	99.2	0.8
26-28 hours	16	81.3	93.8	100	0

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

Not applicable.

F Other Supportive Performance Characteristics Data:

Software

Software regression testing was conducted in accordance with established specifications and documentation was provided as recommended by FDA Guidance "Content of Premarket Submissions for Device Software Functions," published June 14, 2023. The test results met acceptance criteria and support that the subject product is acceptable for its intended use.

Cybersecurity

Cybersecurity verification and validation processes were conducted, and documentation was provided as recommended by FDA Guidance "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions," published September 26, 2023. The cybersecurity processes and software testing establish a strategy for ensuring secure and reliable data transmission. The test results met acceptance criteria and support that the subject cybersecurity is acceptable.

Sterility and Package Integrity/Shipping Integrity

Final, finished product was evaluated for sterility and package integrity/shipping integrity with compliance to ISO 11135-1:2014, ISO 10993-7:2008, ISO 10993-7 and found to be acceptable.

Biocompatibility

Based on the ISO 10993-1 standard Biological Evaluation of Medical Devices - Part 1: Evaluation and testing within a risk management process, an appropriate biocompatibility program was selected for the Eversense AP CGM System. Testing and the Biological Risk Assessment concluded that the Eversense AP CGM System meets the requirements of ISO 10993-1:2018, EN ISO 14971:2019, and the 2020 FDA guidance on use of international standard ISO 10993-1.

In Vitro Elution of Dexamethasone Acetate

All lots of Eversense AP Sensors have been tested for in vitro elution kinetics with specifications established in P160048. Results conformed to the same endpoints established in P160048.

In vivo Dexamethasone exposure

Based on the same dexamethasone acetate drug load in the subject product and results from the in vitro elution testing the in vivo dexamethasone exposure results from P160048 was leveraged.

The following supportive performance characteristics are not affected by the modifications in this De Novo, and are therefore leveraged from the review of prior versions of the Eversense CGM systems in P160048 and its supplements:

- Human Factors
- Mechanical Engineering
- Electromagnetic Compatibility
- Electrical Safety
- Environmental Testing
- Wireless
- Chemistry, manufacturing and control of the dexamethasone acetate active ingredient
- Manufacturing of dexamethasone acetate eluting collar in the CGM sensor

The information provided in this de novo, as well as data incorporated by reference to P160048 (and supplements) and the relevant drug master file for dexamethasone acetate constituent, supports the decision to grant the De Novo request.

VII Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this product.

VIII Identified Risks and Mitigations:

Identified Risks to Health	Mitigation Measures
Clinical action based on falsely high or falsely low inaccurate glucose values or inaccurate alerts may lead to inappropriate treatment decisions.	Certain design verification and validation activities, including documentation of certain studies and other information. Certain labeling information, including certain limiting statements and performance characteristics.
The inability to make appropriate treatment decisions when glucose values are unavailable due to sensor signal drop-out or loss of communication with digitally connected devices.	Certain design verification and validation activities, including documentation of certain studies and other information. Certain labeling information, including certain limiting statements and performance characteristics.
Patient harm due to insecure transmission of data.	Certain design verification and validation activities, including documentation of certain information.
Use of an iCGM as part of another digitally connected medical device system, such as an AID system, when the iCGM has inadequate analytical or clinical performance to support the intended use of the digitally connected device.	Certain design verification and validation activities and documentation. Certain labeling information, including certain limiting statements and performance characteristics.

Identified Risks to Health	Mitigation Measures
Adverse reactions to the drug constituent	Documentation of certain studies and other information including: • Product characterization, including drug substance • Drug quality attribute performance testing, including elution • Stability and shelf-life testing • Pharmaceutical manufacturing information Certain labeling information, including identification of the net content of dexamethasone (or one of its ester forms) for the product and description of safety events attributable to the dexamethasone constituent.
Adverse events related to the insertion and removal of the device	Certain design verification and validation activities, including documentation of certain studies. Certain labeling information, including certain limiting statements and performance characteristics.

IX Benefit/Risk Assessment:

A Summary of the Assessment of Benefit:

There is significant patient burden in terms of glucose monitoring, for diabetes management, including psychosocial aspects which include burnout and stigma. Although self-monitoring blood glucose (SMBG) remains commonly used for diabetes glucose monitoring, adherence to SMBG is known to be suboptimal. Benefits of non-adjunctive use of integrated continuous glucose monitoring (iCGM) in general include real-time knowledge of glucose values and trends, 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 may allow patients to make more informed diabetes treatment decisions rather than relying solely on intermittent glucose point data as provided by SMBG devices. In particular, the Eversense AP CGM System has advantages associated with a significantly longer wear period (up to 180 days) compared to currently marketed transdermal CGM systems (up to 15 days). The longer-term sensor eliminates the need for users to insert a new sensor every 7-15 days. The transmitter which is placed over the sensor and secured in place with adhesive can be removed and replaced without ending sensor life. The longer-term sensor, in conjunction with a removable transmitter and a mobile display device, could result in increased utilization of CGM technology by patients. The discreet design and long wear period of the Eversense AP CGM System may also benefit patients with diabetes by alleviating current stigma.

Compared to previously approved Eversense CGM systems, the Eversense AP CGM System is able to be integrated with compatible digitally connected devices, such as Automated Insulin Delivery (AID) systems, offering users more flexibility and convenience in managing their diabetes.

The silicone collar provides the corticosteroid dexamethasone acetate for elution to the local area in a controlled release manner for the reduction of tissue inflammation around the sensor to maintain its in vivo use life. The clinical benefits are sustained performance of the sensor over 6 months, reducing the need for more frequent removal and insertion, in addition to reducing local discomfort due to inflammation.

B Summary of the Assessment of Risk:

There are risks relating to the clinical performance of the product and the continuous availability and cybersecurity of the data. Clinical action based on falsely high or falsely low iCGM glucose values, inaccurate glucose trend information, or inaccurate alerts may lead to inappropriate treatment decisions, which may increase risk of severe dysglycemia due to undetected or mistreated low or high blood sugar especially when used with other digitally connected devices designed to automatically administer insulin. There are also risks of delayed therapeutic intervention when glucose values are unavailable due to sensor signal drop-out or loss of communication with digitally connected devices.

Additionally, risks relating to insertion and removal procedures include pain, inflammation, infection, and sensor breakage leaving a sensor fragment under the skin in the subcutaneous tissue. There are also risks relating to difficulty with sensor removal, and risks associated with subsequent procedures (i.e., anesthesia, pain, infection) to attempt sensor removal. In addition, there may be risks relating to repeated insertion and removal procedures including scar tissue buildup, as the outside side of the upper arms is the only sensor insertion site. These risks are mitigated by the required training for the insertion and removal procedures for qualified healthcare providers performing these procedures as well as product labeling.

The risks of dexamethasone acetate may involve adverse effects in multiple systems when used in high doses or over prolonged periods, with adverse reactions affecting skin, eyes, growth, and in the musculoskeletal, immunologic, metabolic, neuropsychiatric and endocrine systems, especially hypothalamic-pituitary-adrenal axis suppression.

Based on in vitro and in vivo drug elution data, the estimated bioavailability for dexamethasone acetate for systemic exposure to cause glucocorticoid adverse effects is expected to be very low, especially when compared to the dose recommended for approved dexamethasone products (up to 8 mg/d for injection or orally administration).

C Patient Perspectives:

Patient perspectives considered during the review included patients' preference for CGMs that can be used non-adjunctively, longer CGM sensor wear times, elimination of frequent self-insertion, and a discreet and fully implantable sensor. The comparatively short sensor life of 7-15 days for other non-adjunctive CGM systems, the need to self-insert the sensor, the need for the

transmitter to remain adhered to the skin for the sensor duration, and the inconveniences of wearing a percutaneous sensor that can be dislodged during normal activities have been noted as sources of patient dissatisfaction with other non-adjunctive CGM systems. The benefits of the Eversense AP CGM System may result in increased utilization of CGM technology.

D Summary of the Assessment of Benefit-Risk:

The benefits of the product are described above. The risks associated with the product described above are mitigated by certain design verification and validation, including analytical and clinical studies and risk mitigation strategies to reduce the likelihood of user and system errors. In addition, risks associated with the product are mitigated by certain labeling information, which will assist the users in correctly using the product and will assist healthcare providers in understanding the intended use and performance characteristics, including contraindications, warnings, limitations and precautions of the product.

In addition, the special controls are intended to provide reasonable assurance of the safety and effectiveness of the combination product in the hands of the intended users, adequate controls for secure and reliable inter-device communication, manufacturing controls to assure all released products (including drug component) maintain adequate performance to mitigate the risks identified above, and adequate transparency to allow users and healthcare providers to understand expected sensor performance. The risks for dexamethasone acetate adverse effects are also mitigated by the small dexamethasone quantity in the sensor and its controlled release elution.

While general controls alone are insufficient to mitigate the risks associated with the device, the benefits outweigh the risks given the special controls.

X Conclusion:

The De Novo request is granted and the product is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code(s): SBA

Device Type: Integrated continuous glucose monitoring system with sensor containing dexamethasone (or one of its ester forms)

Class: II (special controls)

Regulation: 21 CFR 862.1357

(a) *Identification.* An integrated continuous glucose monitoring system (iCGM) with sensor containing dexamethasone (or one of its ester forms) is intended to automatically measure glucose in bodily fluids continuously or frequently for a specified period of time. iCGM systems are designed to reliably and securely transmit glucose measurement data to digitally connected devices, including automated insulin dosing systems, and are intended to be used alone or in conjunction with these digitally connected medical devices for the purpose of managing a disease or condition related to glycemic control. The dexamethasone constituent is intended to reduce inflammation at the sensor insertion site.

(b) *Classification*. Class II (special controls). This product is subject to the following special controls:

(1) Design verification and validation must include the following:

- (i) Robust clinical data demonstrating the accuracy of the product in the intended use population.
- (ii) The clinical data must include a comparison between iCGM values and blood glucose values in specimens collected in parallel that are measured on an FDA-accepted laboratory-based glucose measurement method that is precise and accurate, and that is traceable to a higher order (e.g., an internationally recognized reference material and/or method).
- (iii) The clinical data must be obtained from a clinical study designed to fully represent the performance of the product throughout the intended use population and throughout the measuring range of the product.
- (iv) Clinical study results must demonstrate consistent analytical and clinical performance throughout the sensor wear period.
- (v) Clinical study results in the adult population must meet the following performance requirements:
 - (A) For all iCGM measurements less than 70 milligrams/deciliter (mg/dL), the percentage of iCGM measurements within ± 15 mg/dL of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 85 percent.
 - (B) For all iCGM measurements from 70 mg/dL to 180 mg/dL, the percentage of iCGM measurements within ± 15 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 70 percent.
 - (C) For all iCGM measurements greater than 180 mg/dL, the percentage of iCGM measurements within ± 15 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 80 percent.
 - (D) For all iCGM measurements less than 70 mg/dL, the percentage of iCGM measurements within ± 40 mg/dL of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 98 percent.
 - (E) For all iCGM measurements from 70 mg/dL to 180 mg/dL, the percentage of iCGM measurements within ± 40 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 99 percent.
 - (F) For all iCGM measurements greater than 180 mg/dL, the percentage of iCGM measurements within ± 40 percent of the corresponding blood glucose value must be calculated, and the lower one-sided 95 percent confidence bound must exceed 99 percent.
 - (G) Throughout the product measuring range, the percentage of iCGM measurements within ± 20 percent of the corresponding blood glucose value

must be calculated, and the lower one-sided 95 percent confidence bound must exceed 87 percent.

- (H) When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.
 - (I) When iCGM values are greater than 180 mg/dL, no corresponding blood glucose value shall read less than 70 mg/dL.
 - (J) There shall be no more than 1 percent of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL per minute (/min) when the corresponding true negative glucose rate of change is less than - 2 mg/dL/min as determined by the corresponding blood glucose measurements.
 - (K) There shall be no more than 1 percent of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements.
- (vi) Data demonstrating similar accuracy and rate of change performance of the iCGM in the pediatric population as compared to that in the adult population, or alternatively a clinical and/or technical justification for why pediatric data are not needed, must be provided and determined by FDA to be acceptable and appropriate.
- (vii) Data must demonstrate that throughout the claimed sensor life, the product does not allow clinically significant gaps in sensor data availability that would prevent any digitally connected devices from achieving their intended use.
- (2) Design verification and validation must include a detailed strategy to ensure secure and reliable means of iCGM data transmission to provide real-time glucose readings at clinically meaningful time intervals to devices intended to receive the iCGM glucose data.
- (3) Design verification and validation must include adequate controls established during manufacturing and at product release to ensure the released product meets the performance specifications as defined in paragraphs (1) and (2).
- (4) The product must demonstrate clinically acceptable performance in the presence of clinically relevant levels of potential interfering substances that are reasonably present in the intended use population, including but not limited to endogenous substances and metabolites, foods, dietary supplements, and medications.
- (5) The product must include appropriate measures to ensure that disposable sensors cannot be used beyond its claimed sensor wear period.
- (6) Design verification and validation must include results obtained through a usability study that demonstrates that the intended user can use the product safely and obtain the expected glucose measurement accuracy.
- (7) The labeling required under 21 CFR 809.10(b) must include:
- (i) Identification of the net content of dexamethasone (or one of its ester forms) for the product (i.e., net content per sensor) in the product labeling.

- (ii) A separate description of the following sensor performance data observed in the clinical study performed in conformance with paragraph (1) for each intended use population, in addition to separate sensor performance data for each different iCGM insertion or use sites (e.g., abdomen, arm, buttock):
 - (A) A description of the accuracy in the following blood glucose concentration ranges: less than 54 mg/dL, 54 mg/dL to less than 70 mg/dL, 70 to 180 mg/dL, greater than 180 to 250 mg/dL, and greater than 250 mg/dL.
 - (B) A description of the accuracy of positive and negative rate of change data.
 - (C) A description of the frequency and duration of gaps in sensor data.
 - (D) A description of the true, false, missed, and correct alert rates and a description of the available glucose concentration alert settings, if applicable.
 - (E) A description of the observed duration of iCGM life for the product.
 - (F) A description of safety events (if any) that may be attributable to the dexamethasone constituent of the product.
- (8) The label required under 21 CFR 809.10(a) must include identification of the net content of dexamethasone (or one of its ester forms) for the product (i.e., net content per sensor).
- (9) Elution kinetics studies must be conducted to determine the *in vitro* drug release profile from the product lot(s) used for the clinical performance testing studies.
- (10) Characterization of the finished product (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must demonstrate that critical quality attributes and specifications, including compendial requirements, are met and must include:
 - (i) Identification of, and justification for, the drug constituent specification(s), including the specification for dexamethasone (or one of its ester forms).
 - (ii) Confirmation that the specifications for dexamethasone (or one of its ester forms) and inactive ingredients or material components conform to any corresponding United States Pharmacopeia (USP) monographs. In addition, the specification for dexamethasone (or one of its ester forms) must also include other tests that ensure the quality of the product, such as appearance, identification, assay, drug content uniformity, related substances, and impurities. Such tests must be conducted using appropriate analytical techniques, such as high performance liquid chromatography (HPLC).
 - (iii) Identification of, and justification for, the finished product specification(s) to be met on release of each batch and on stability, including description, identification, dexamethasone acetate assay, in vitro elution/drug release, degradation products, impurities, content uniformity, residual solvents, sterility, and endotoxin.
 - (iv) For the specifications noted in paragraphs (i)-(iii) above, a description of the analytical procedures and a summary of the analytical procedures development and validation must be provided. For in vitro elution/drug release specifications, data must be provided to demonstrate method adequacy (e.g., in terms of discriminating power for changes/differences in critical quality attributes that could impact product performance, stability-indicating potential, and/or *in vitro-in vivo* correlation).

- (11) Performance data from testing at release and on stability batches of the finished product (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must characterize the drug quality attributes of the finished product (see paragraph (10), demonstrate product specifications are consistently met, and support the claimed expiration date/shelf-life. This information must include the following:
- (i) Finished Product Batch Release Testing: Batch release data on multiple lots of the finished product manufactured using the proposed commercial process (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must demonstrate that specifications are met.
 - (ii) Stability Testing: The finished product manufactured using the proposed commercial process and in the proposed commercial packaging (or alternatively, a justification determined to be appropriate by FDA for why the product tested is representative of the finished product) must be stored under tightly controlled conditions and periodically tested to demonstrate the stability of the finished product. Testing must include three batches placed under long-term storage and accelerated stability conditions and then one batch placed on long-term stability each year. Testing must verify that the acceptance criteria for each specification are met at each stability time point. Parameters that are not expected to change on stability (e.g., elemental impurities, only need to be tested at batch release, and a justification must be provided).
- (12) Pharmaceutical manufacturing information must be provided, and appropriate documentation be available on inspection or if requested by FDA, for the drug constituent part and the finished product to demonstrate that the production processes are properly developed, conducted, controlled, and monitored. This information must include the following:
- (i) A description of the manufacturing process and controls, including in-process controls, to ensure consistent quality. Such information may be provided by reference to a drug master file (DMF).
 - (ii) A description of the commercial batch formula, including the quality standard (e.g., USP/National Formulary) to be met for each inactive ingredient or material component, and representative Certificates of Analysis (COAs) to confirm quality.
 - (iii) Information or reference to one or more DMFs regarding the drug substance to understand the impurity profile, and representative COAs for the drug substance to confirm quality.
 - (iv) Identification and qualification of in-process hold times for the drug constituent part, where applicable.
 - (v) A description of how compliance with the current good manufacturing practice (CGMP) requirements is achieved at the facilities manufacturing the drug constituent

part and finished product. This includes identification of the activities that occur at each site, and for any facilities for which 21 CFR 211 is not the established CGMP operating system, a description of how the facilities perform the responsibilities related to the subset of 21 CFR 211 requirements established in 21 CFR 4 subpart A.

- (13) Performance data must support the claimed expiration date/shelf life by demonstrating continued sterility, stability (see paragraph (11)(ii)), package integrity, and product functionality over the identified expiration/shelf life. Data to demonstrate continued sterility, stability, packaging integrity, and product functionality must be collected for the finished product (or alternatively, a justification, determined to be appropriate by FDA, must be provided for why the product tested is representative of the finished product). Extension of the expiration date/shelf life must be submitted in a premarket notification and be supported by either:
 - (i) Real-time data as specified in this special control; or
 - (ii) A combination of real-time data and a scientifically justified statistical modeling approach to extrapolate expiration/shelf life.
- (14) Performance data must confirm that sterilization has no significant adverse impact (e.g., the generation of new degradants) on the drug quality attributes (e.g., assay, elution) of the finished product.