DE NOVO CLASSIFICATION REQUEST FOR PULSENMORE ES

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Ultrasound imaging system for acquiring images at home by lay users.** An ultrasound imaging system for acquiring images at home by lay users is a prescription home use device that may consist of hardware and/or software intended for acquiring ultrasound images for interpretation by a qualified health care professional (e.g., fetal images for determination of fetal heart rate). The device provides guidance to lay users to aid image acquisition.

NEW REGULATION NUMBER: 21 CFR 892.1590

CLASSIFICATION: Class II

PRODUCT CODE: SGJ

BACKGROUND

DEVICE NAME: Pulsenmore ES

SUBMISSION NUMBER: DEN240074

DATE DE NOVO RECEIVED: December 11, 2024

SPONSOR INFORMATION:
Pulsenmore Ltd.
8 Omarim St.,
Omer, Darom 8496500
Israel

INDICATIONS FOR USE

The Pulsenmore ES is indicated as follows:

> The Pulsenmore ES ultrasound system is intended to enable the acquisition of ultrasound images that allow interpreting healthcare providers to determine fetal heart rate.
>
> The Pulsenmore ES ultrasound system is intended for limited diagnostic ultrasound imaging in B-Mode and M-Mode in Fetal/Obstetric applications, when traditional scanning at a health clinic is impractical or when the use of telehealth (clinician-guided mode) or software-guided self-scanning (app-guided mode) is in the best interests of the patient.

The device is intended to be used by pregnant women with a singleton pregnancy at the gestational age of 14-38 weeks, when clinically indicated to determine the heart rate on the order of a physician in non-clinical environments. When directed by their physician, the patient can either follow the steps specified by the ES software application (app-guided mode) or under the direction of a healthcare professional (clinician-guided mode).

A physician interprets the images acquired with the device in a remote access setup.

Access to the device operation must be granted by healthcare professionals.

LIMITATIONS

- The sale, distribution, and use of the Pulsenmore ES are restricted to prescription use in accordance with 21 CFR 801.109.
- The images and data acquired using the Pulsenmore ES ultrasound device are to be interpreted only by a qualified medical professional.
- Physicians are instructed to review and interpret all images acquired by the Pulsenmore ES system, including practice scans and clinically indicated, prescribed scans, whether app- guided or clinician-guided.
- The Pulsenmore ES is not intended to detect defects, replace a routine scan and/or pregnancy tests of any kind, or replace a medical consultation or a visit to the emergency room/clinic.
- The Pulsenmore ES is designed to be used by patients with Body Mass Index (BMI) under 40.
- To protect patients against unnecessary ultrasound exposure, Pulsenmore ES system includes acquisition limitation features that limit the number and duration of scans that can be performed.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Pulsenmore ES is a compact, handheld diagnostic ultrasound device enabling patients to perform ultrasound image acquisition at home while healthcare professionals review and interpret images remotely. The device does not provide biometric measurements or direct diagnostic information to patients. The device is non-sterile, for use by a single-patient during one pregnancy. The device requires the user to provide a compatible smartphone for image acquisition where the smartphone serves as the primary interface and display mechanism. The system consists of three main components:

- The device **cradle** containing the printed circuit board and transducer,
- The **mobile application** downloaded to the patient's smartphone that provides the user interface (UI) and performs initial image processing, and

- The **cloud-based clinician dashboard** that processes and stores ultrasound clips for healthcare professional review.

The device is comprised of sliding rails that mechanically support the connected smartphone and secure it in-place during device operation. The complete UI is displayed on the user's smartphone screen.

Two device models are available - a Type C model for Android phones and a Type iOS model for iPhones. For Type C, the device houses both the transducer and the electronic board and physically connects to the user's mobile phone via a USB Type C connector (Figure 1) for ultrasound video feeding and control. The device has no buttons or screen and no power source, receiving its power directly from the connected smartphone. The Type C device utilizes cellular data for video feeding and controls.

Type iOS model houses the transducer, internal rechargeable battery, and the electronic board. The device has an on/off button. The Type iOS device utilizes Wi-Fi communication in order to connect the device to the iPhone for ultrasound video feeding and controls. A USB C socket allows charging the rechargeable battery. Table 1 includes specifications of each model.

Figure 1: Illustration of Type C model for Android phones (left), illustration of Type iOS device (right).

Table 1. Device specifications

	Type iOS	Type C
Dimensions	80(W) × 1400(H) × 38mm(D)	
Weight	250 g	200 g
Image display	B-Mode, M-Mode	
Ultrasound frequency	2-5 MHz	
Total scan time	50 minutes with fully charged battery	N/A
Thermal index (TI)	≤ 0.03	

Mechanical index (MI)	≤ 0.4	
Viewing angle	~ 60°	
Depth	Up to 27 cm	
Image resolution	512 × 512 pixels	
Image filtering	Image enhancement, speckle reduction	
Powered by	Internal rechargeable Li- ion Polymer battery	Android smartphone
Battery capacity	1200mAh	N/A
Battery voltage	3.7V	N/A
IP rating	IP22	
Network connectivity (Mobile App to Cloud)	Wi-Fi (Secured WPA2™) or Cellular	
Network connectivity (Device to Mobile App)	Wireless Wi-Fi 4	
Data upload	Secured cloud services	

The workflow begins when a healthcare professional creates a digital scan approval key on the clinician dashboard, which is sent to and accepted by the patient's mobile application.

The system operates in two modes:

- **App-Guided mode:** enables the patient to scan independently, without clinician support, by following video tutorials presented in the Pulsenmore ES mobile application. When the scan is completed, all scan files are uploaded automatically to a secure cloud location, making them available for an asynchronous clinical assessment. The entire scan takes about 5 minutes.
- **Clinician-Guided mode:** starts as a telehealth meeting between a patient and a remote clinician. At the scheduled appointment time, the patient joins the meeting through the Pulsenmore mobile app while the clinician joins the meeting using the Pulsenmore web-based application. During the meeting, the clinician has control over the ultrasound parameters and can instruct the patient on how to perform the scan. The clinician-guided scan duration is at the clinician's discretion and not intended to exceed 30 minutes.

Raw data is temporarily stored on the smartphone before being transmitted to the cloud for reconstruction into ultrasound clips that are made available on the clinician dashboard for physician interpretation and diagnosis.

Modes of operation include B-mode and M-mode. The Pulsenmore M-Mode feature utilizes previously acquired B-mode raw data and does not acquire new ultrasound data to generate the M-mode view.

M- Mode View tool is used to enable fetal heart activity visualization. The Pulsenmore software processes ultrasound scan data by extracting a single beam from the raw data at the specific point

annotated by the clinician to create M-mode images. This M-mode visualization is generated by displaying the single beam data over time, utilizing existing ultrasound data without requiring additional patient scanning after the clinician provides annotations. The system allows users to place 2-3 markers on the image and a number on the screen representing the fetal heart rate.

The Pulsenmore ES system incorporates several hard-coded and prescription limitations that restrict the number scans within specific timeframes and cumulatively during a pregnancy to protect patients against overexposure to ultrasound in accordance with the principle As Low As Reasonably Achievable (ALARA).

Table 2. Device Hard-Coded and Prescription Limitations

	Scans Per Key	Daily Limit	Weekly Limit	Pregnancy Limit
Scan limit	Physician prescription (default quota is 1)	3 scans	10 scans	150 minutes

There are patient facing algorithms for coupling (skin contact indicator) and velocity (speed indicator) guidance during image acquisition. The skin contact and speed indicators inform the patient if they move the ultrasound probe too fast or if the skin contact with the ultrasound probe is not sufficient, two conditions that account for the majority of the cases where the captured ultrasound image is not sufficient for clinical evaluation.

Pre-acquisition Quality Checks

Smartphone Compatibility Testing includes verification against minimum technical specification requirements and operating system stress test simulating repeated connect/disconnect and recovery cycles to validate system resilience under unstable conditions.

The device design includes a pre-scan condition verification process of the smartphone and device before each scan starts to confirm all necessary technical requirements are met to avoid unnecessary ultrasound scans. Pre-conditions are:

- Internet connection
- Smartphone storage
- Battery level (+ device battery for Type iOS)
- Smartphone connects to the device

Before each scan, the system checks if there is an internet connection to ensure the scan can be uploaded to the clinician dashboard for review. It also checks if sufficient free storage space (1 GB) is available on the patient's smartphone to ensure there is sufficient memory to temporarily store the raw data. The system checks the smartphone battery level, and the scan can start only if the battery charge level is above 50%. In addition, the system verifies that the smartphone is not in battery save mode, ensuring sufficient power delivery to the device. These conditions ensure that a continuous scan of at least 30 minutes can be conducted without the smartphone battery

being drained out. Finally, the system checks if the smartphone is connected to the device to ensure that the scan can be performed.

The transducer element check runs automatically every time a Pulsenmore ES device is connected to the patient smartphone to check the integrity of the transducer elements. If an element is found defective, the scan is flagged with caution symbols, and the clinician is notified that the image quality may be degraded. In the event of transducer element check failure, clinicians are instructed to communicate clearly to lay users not to use the device for additional scanning until the issue is resolved by the service provider.

SUMMARY OF NONCLINICAL/BENCH STUDIES

Nonclinical testing includes benchtop performance testing, electromagnetic compatibility (EMC) testing, wireless coexistence testing, electrical safety testing, software and cybersecurity validation, biological safety evaluation, reprocessing validation, and human factors validation testing. The testing was conducted to demonstrate that Pulsenmore ES performs as expected under the anticipated conditions of use.

PERFORMANCE TESTING-BENCH

Preclinical studies were conducted to evaluate the technical performance of the Pulsenmore ES device:

- **Ultrasound Imaging Testing**
  Testing was performed to evaluate the performance of the device using ATS 539 phantom. The evaluation included several measurements of radius of various target points at various depths in the phantom in both vertical and horizontal directions and calculation of Point Spread Function (PSF), Signal-to-Noise Ratio (SNR) of the system at various depths. Additional testing parameters included depth of penetration measurements to determine the maximum depth at which anechoic objects of specific sizes can be distinguished, as well as dynamic range quality assessment through evaluation of decibel-to-grayscale conversion capabilities of the system. The results show that the device meets the acceptance criteria for each test with no deviations.

- **Acoustic Output and Surface Temperature Testing**
  Ultrasound safety testing was performed in accordance with the following standards and FDA guidance document:

  - IEC 60601-2-37 Edition 2.1:2015 Medical Electrical Equipment – Part 2-37: Particular Requirements for the Basic Safety and Essential Performance of Ultrasonic Medical Diagnostic and Monitoring Equipment.
  - IEC 62127-1:2022 Ultrasonics - Hydrophones - Part 1: Measurement and Characterization of Medical Ultrasonic Fields.

- IEC 62359:2010/AMD 2017 Ultrasonics - Field Characterization - Test Methods for the Determination of Thermal and Mechanical Indices Related to Medical Diagnostic Ultrasonic Fields.
- FDA guidance document "Marketing Clearance of Diagnostic Ultrasound Systems and Transducers" (February 2023).

The test report included measurement procedures, equipment used for measurements, raw data and formulas used for calculations and were found to be acceptable. The results showed that the acoustic output of the Pulsenmore ES device does not exceed the levels recommended by FDA and defined in applicable international standards. In terms of transducer surface temperature, the specifications in IEC 60601-2-37 regarding protection against excessive temperatures and other hazards from the transducer assembly at the patient contact surface were met.

- **Skin Contact and Speed Indicator Software Validation**
  - The coupling algorithm analyzes the ultrasound image during the scan and estimates the quality of the probe's contact with the skin in every frame using gray level estimation. About 2,000 frames were captured using a fetus ultrasound phantom that mimics a 15-week pregnant woman's abdomen with an embryo, including adequate and inadequate skin contact conditions to emulate various skin contact conditions, and each frame was evaluated by the coupling algorithm to produce the expected indication. The lab results used the worst result out of four clinicians reviewing the scans as reference standard, indicate accuracy of 98%, sensitivity of 96%, and specificity of 99%.

  - The velocity algorithm analyzes the onboard gyroscope and accelerometer sensors to determine the angular velocity and erratic movement and classifies the speed level and erratic movement level during the scan for every frame. Around 7,500 frames were captured using a fetus ultrasound phantom that mimics a 15-week pregnant woman's abdomen with an embryo, each accompanied with sensor data, including adequate speed, fast speed or erratic movement. The lab results indicate accuracy of 57%, sensitivity of 16%, and specificity of 99%. As the bench test was performed using phantoms where various movement conditions were performed that may not represent how a user would use the device, the field validation results were used to assess the final accuracy of the coupling and velocity algorithms, as described below.

  - To validate user-facing indicators, sensor readings, algorithm classification outputs, and skin contact and speed indicators for every frame were collected, 180,000 frames were randomly selected from the first week of three consecutive months as field validation. The study included 20 patients per week (10 diagnosed as "normal" and 10 with "inadequate scans") to prevent bias based on clinical scan adequacy, totaling about 9,000 seconds of assessed scan footage. The validation data came from one site, collected over 18 months of operation specifically from app-guided mode (self-scan) procedures, which represented a worst-case scenario since patients relied solely on automated indicators without

additional guidance. The indicators were manually evaluated by 4 independent reviewers and looked for wrong indications, taking the worst result of the 4 reviewers for each comparison. For coupling algorithm, the results indicated accuracy of 96%, sensitivity of 90%, and specificity of 99%. For velocity algorithm, results indicate accuracy of 97%, sensitivity of 83%, and specificity of 99%.

ELECTROMAGNETIC COMPATIBILITY, WIRELESS COEXISTENCE, AND ELECTRICAL SAFETY

Electromagnetic Compatibility (EMC), Wireless Coexistence, and Electrical Safety testing has been performed as per the following recognized consensus standards, FDA guidance document, and the results support electromagnetic compatibility, wireless coexistence, and electrical safety:

- ANSI/AAMI/IEC 60601-1-2:2014/A1:2021: Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic disturbances —Requirements and test
- IEEE/ANSI USEMCSC C63.27-2021 American National Standard for Evaluation of Wireless Coexistence
- AAMI TIR69:2017 /(R2020) Technical Information Report Risk management of radio-frequency wireless coexistence for medical devices and systems
- FDA Guidance "Radio Frequency Wireless Technology in Medical Devices" (August 2013)
- IEC 60601-1: 2020 Medical electrical equipment — Part 1: General
- requirements for basic safety and essential performance.
- IEC 60601-1-11:2015: Medical electrical equipment — Part 1-11: 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 60601-2-37:2015 - Medical electrical equipment - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment.

SOFTWARE AND CYBERSECURITY

Software verification and validation testing and documentation was provided according to a Basic Documentation Level per FDA's guidance document, "Content of Premarket Submissions for device software functions" published June 2023, to demonstrate that the device software performs as intended.

The software was developed and tested according to the following FDA guidance documents and recognized consensus standards:

- FDA Guidance document "Off-the-Shelf Software Use in Medical Devices" (August 2023)
- FDA Guidance document "Content of Premarket Submissions for device software functions" (June 2023)

- IEC 62304: 2006 /A1:2016 Medical device software - Software life-cycle processes
- ISO 14971:2019 Medical devices - Application of risk management to medical devices.

Verification and validation testing was conducted for the software mitigations pertaining to acquisition limitation controls, pre-acquisition checks and transducer element check. The verification testing results demonstrated that the implemented software worked as intended. Overall, the software documentation contains sufficient detail to provide reasonable assurance that the software will operate in a manner described in the specifications. All testing and results were considered to be acceptable.

Pulsenmore ES cybersecurity documentation demonstrated that the device meets all the cybersecurity requirements as outlined in Section 524B of Federal Food, Drug, and Cosmetic Act (FD&C Act). This includes a threat model, software bill of materials, cyber risk management, labeling, cyber testing, and post market cyber vulnerabilities and other information for safeguarding the device.

BIOCOMPATIBILITY

The Pulsenmore ES device is a surface device with direct contact with skin for a limited duration (< 24 hours) per Table A.1 of the FDA Biocompatibility guidance entitled, "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" published September 2023. Biocompatibility testing for the endpoints of cytotoxicity, sensitization, and irritation was conducted. The results showed that the device met acceptance criteria according to the ISO 10993 series of standards. The results of these evaluations support the biocompatibility of the device.

REPROCESSING, STERILITY, AND SHELF LIFE

The Pulsenmore ES is provided non-sterile and requires reprocessing after each use. It is intended to be used by a single user, and the device must be disposed of after each patient's pregnancy. It is intended to be used with single gel packets for each use to reduce the risk of infection. Reprocessing methods in the labeling were validated per ANSI/AAMI ST98:2022 and following FDA guidance document: "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling" (March 2015).

HUMAN FACTORS VALIDATION TESTING

Comprehensive human factors validation testing was conducted for the Pulsenmore ES Ultrasound System across both Android and iOS smartphone interfaces for both app-guided and clinician-guided modes following the FDA guidance: "Applying Human Factors and Usability Engineering to Medical Devices" (February 2016). Testing evaluated whether pregnant patients and healthcare professionals could safely and effectively use the system in real-world home environments. The intended users were qualitatively assessed via observation and cognitive debrief. The participants of this study included 15 healthcare

professionals and 30 pregnant patients (15 app-guided mode, 15 clinician-guided mode). The completed critical tasks included device setup, scan preparation, ultrasound scanning, device maintenance and troubleshooting. Human factors testing demonstrated that both intended user groups successfully completed critical tasks under both operational modes. The human factors assessment supports that the Pulsenmore ES can be appropriately used by the intended use population. It also demonstrated that the intended users adequately comprehended the training and labeling.

SUMMARY OF CLINICAL INFORMATION

Clinical performance data were collected from a pivotal study (Pulsenmore HOLA study) and real-world evidence (RWE) generated from the use of the device in Israel.

Pivotal Clinical Study – HOLA study

A multi-center, prospective study was conducted to demonstrate the safety and effectiveness of Pulsenmore ES. The device was used by pregnant individuals at their home under both app-guided and clinician-guided modes. The scans were evaluated by healthcare professionals (HCPs) for visualization of fetal cardiac activity in comparison to the standard of care in-clinic ultrasound examination.

Clinical sites and patient demographics

A total of 188 pregnant patients were enrolled from four clinical centers in the United States:

- Center for Fetal Medicine and Women's Ultrasound, Los Angeles, California
- University of Florida, Gainesville, Florida
- Mount Sinai Hospital System Faculty Practice: Maternal Fetal Medicine, New York City, New York
- Brigham and Women's Hospital, Boston, Massachusetts

Inclusion Criteria

- Female age ≥18.
- Singleton gestation.
- Gestational age ≥ 14 weeks with a prior scan demonstrating fetal viability and confirming date for established gestational age.
- No known fetal or genetic anomalies, with the exception of subjects with abnormal amniotic fluid volume.
- English or Spanish speaking.
- Ability to understand and sign the informed consent (available in English and Spanish).
- Ability to read and understand instructions that are required for equipment use (instructions available in both languages.

Exclusion Criteria

- Multiple gestation.
- BMI >40.
- Known fetal and genetic anomalies, with the exception of subjects with abnormal amniotic fluid volume.
- Subjects with skin problems in the abdominal area (such as wounds, cuts in the skin and skin rash).

- Subjects allergic to the ultrasound probe materials.
- Non-English/ non-Spanish speaking.
- Unable to provide consent.

The study enrolled a diverse population across multiple demographic categories with respect to age, gestational age, race/ethnicity, education level, BMI distribution, comorbidities and inclusion of high-risk patients.

Study Objectives

The objective of the HOLA US study was to demonstrate the safety and effectiveness of the Pulsenmore ES device.

Study Endpoints and Acceptance Criteria

Primary Endpoints

- Effectiveness
    - The first primary effectiveness endpoint was the proportion of cases in which readers using the clinician-guided mode can correctly visualize the fetal cardiac activity and pass the M-mode line through the fetal heart. The associated null and alternative hypotheses were: H_0: the mean proportion of cases ≤ 90% vs. H_a: the mean proportion of cases > 90%.
    - The second primary effectiveness endpoint was the proportion of cases in which readers using the app-guided mode can correctly visualize the fetal cardiac activity and pass the M-mode line through the fetal heart. The associated null and alternative hypotheses were: H_0: the mean proportion of cases ≤ 80% vs. H_a: the mean proportion of cases > 80%.

The hypotheses were tested through a fixed sequence hierarchical test procedure, and the type I error rate was controlled at 2.5% for one-sided tests.

- Safety
    - Device or procedure-related Serious Adverse Events (SAEs)

Secondary Endpoints:

- Effectiveness
    - The secondary effectiveness endpoint was the image quality based on ACEP image quality scale for fetal cardiac activity. No hypothesis testing was planned.
- Safety
    - All Adverse Events (AEs)

Study Design

The study consisted of up to three ultrasound study sessions over up to three consecutive weeks (one session per week). Each study session consisted of three ultrasound scans performed over the course of a single day: an app-guided scan performed by the subject at home, a clinician-guided scan performed during a telehealth visit at the subject's home, and

an in-clinic (IC) visit using a standard of care ultrasound device. Of the enrolled women, 162 were analyzed in this study, yielding a total of 1370 scans corresponding to 458 app-guided scans, 453 clinician-guided scans, and 459 in-clinic scans. For the final effectiveness analysis, performed retrospectively (following study closure), 10 study readers independently interpreted clinician-guided scans in a blinded fashion, and 10 different study readers independently interpreted app-guided scans in a blinded fashion. Three expert readers interpreted the in-clinic scans, of which majority rule (two of three) was used to determine the results from the in-clinic ultrasound scans as the comparator.

Study Results

Primary Safety Endpoint
None of the SAEs were determined to be device or procedure related.

Primary Effectiveness Endpoints

- Endpoint #1: The mean proportion of cases where readers correctly visualize the fetal cardiac activity and pass the M-mode line through the fetal heart under clinician-guided mode was 99.2% (with the lower bound of the one-sided 97.5% bootstrap CI of 96.7%).

- Endpoint #2: The mean proportion of cases where readers correctly visualize the fetal cardiac activity and pass the M-mode line through the fetal heart under app-guided mode was 97.2% (with the lower bound of the one-sided 97.5% bootstrap CI of 94.3%).

Secondary Safety Endpoint
None of the adverse events were determined to be device or procedure related.15/188 (8%) of women reported 17 adverse events (e.g., hypertension, contractions, infection).

Secondary Effectiveness Endpoint
For fetal cardiac activity visualization, 95.5% of the clinician-guided scans and 95.9% of the app-guided scans had an image quality of ACEP score ≥3.

Subgroup Analyses
Pulsenmore ES performance for fetal cardiac activity visualization was also evaluated in subgroups stratified by clinical site, HCP conducting the scan (for clinician-guided mode only), session number, subject race/ethnicity, subject education level, BMI, gestational age at visit 1, and comorbidities. The subgroup analyses results are presented below in Table 3 and 4.

Clinician-guided scans

As presented in Table 3, there were no observable differences in the mean proportions of cases where readers can correctly visualize the fetal cardiac activity and pass the M-mode line across subgroups under different stratifying factors.

Table 3. Mean proportion of visualization of the fetal cardiac activity (FCA) and pass the M-mode line through the heart for clinician- guided scans, stratified by the subgroups, across readers

(* Results in the "Fetal Cardiac Activity (FCA) Visualization" column reflect evaluation of both fetal cardiac activity visualization and M-mode line placement through the fetal heart assessed together).

Category	Subgroups	N (number of scans)	Fetal Cardiac Activity (FCA) Visualization*	Fetal Cardiac Activity Visualization Mean Proportion % (95% CI)
Clinical Site	*NY*	1590	1571	98.8 (98.2, 99.3)
	FL	1230	1219	99.1 (98.5, 99.6)
	CA	1400	1394	99.6 (99.2, 99.9)
	MA	310	308	99.4 (98.4, 100.0)
HCP conducting Scan	*Sonographer*	3720	3694	99.3 (99.0, 99.6)
	Physician	3630	3596	99.1 (98.7, 99.4)
Visit Number	*1*	1590	1576	99.1 (98.6, 99.6)
	2	1490	1479	99.3 (98.8, 99.7)
	3	1450	1437	99.1 (98.6, 99.5)
Race/ethnicity *Note: Subjects may have multiple racial categories*	*White or Caucasian*	2940	2918	99.3 (98.9, 99.5)
	Hispanic	810	801	98.9 (98.1, 99.5)
	Black or African American	670	665	99.3 (98.5, 99.9)
	Asian	340	337	99.1 (97.9, 100.0)
	American Indian or Alaska Native	60	60	100.0 (100.0, 100.0)
	Native Hawaiian or Other Pacific Islander	30	30	100.0 (100.0, 100.0)
	Unknown	100	99	99.0 (97.0, 100.0)
Educational level	*Less than high school*	140	136	97.1 (94.3, 99.3)
	High school	660	653	98.9 (98.0, 99.7)
	Some college	220	219	99.5 (98.6, 100.0)
	College diploma	1830	1822	99.6 (99.2, 99.8)

	Graduate or Professional degree	1800	1782	99.0 (98.5, 99.4)
BMI	*All*	4530	4492	99.2 (98.9, 99.4)
	< 25	1890	1876	99.3 (98.8, 99.6)
	25 – 29	1540	1532	99.5 (99.1, 99.8)
	≥ 30	1100	11084	98.5 (97.8, 99.2)
Gestational age at V1	*All*	4240	4206	99.2 (98.9, 99.5)
	14 – 21 weeks	1470	1455	99.0 (98.4, 99.5)
	22 – 34 weeks	2770	2751	99.3 (99.0, 99.6)
Comorbidities *Note: Subjects may have multiple comorbidities*	*All*	2280	2250	98.7 (98.2, 99.1)
	Abnormal AF at screening	620	610	98.4 (97.2, 99.3)
	BMI ≥ 30	1100	1084	98.5 (97.8, 99.2)
	Hypertension	120	113	94.2 (90.0, 97.5)
	Diabetes	210	203	96.7 (94.3, 99.0)
	Other	1180	1165	98.7 (98.1, 99.3)

App-guided scans

As presented in Table 4, for fetal cardiac activity visualization in app-guided scans, there were no observable differences in the mean proportions of cases where readers could correctly visualize the fetal cardiac activity and pass the M-mode line across subgroups under different stratifying factors except for education level and comorbidities. For subjects with less than high school education, the mean proportion was 88.6% (95% CI: 82.9%-93.6%); for subjects with hypertension, the mean proportion was 82.5% (95% CI: 75.8%-89.2%.

Table 4. Mean proportion of visualization of the fetal cardiac activity and pass the M-mode line through the heart for app-guided scans, stratified by the subgroups, across readers
(* Results in the "Fetal Cardiac Activity Visualization (FCA)" columns reflect evaluation of both fetal cardiac activity visualization and M-mode line placement through the fetal heart assessed together).

Category	Subgroups	N (number of scans)	Fetal Cardiac Activity (FCA) Visualization*	Fetal Cardiac Activity Visualization Mean Proportion % (95% CI)
Clinical Site	*NY*	1620	1577	97.3 (96.5, 98.1)
	FL	1240	1196	96.5 (95.4, 97.4)
	CA	1400	1364	97.4 (96.6, 98.2)
	MA	320	313	97.8 (96.3, 99.4)

Visit Number	*1*	1610	1544	95.9 (94.9, 96.8)
	2	1490	1444	96.9 (96.0, 98.8)
	3	1480	1462	98.8 (98.2, 99.3)
Race/ethnicity *Note: Subjects may have multiple racial categories*	*White or Caucasian*	2950	2858	96.9 (96.2, 97.5)
	Hispanic	810	804	99.3 (98.6, 99.8)
	Black or African American	680	663	97.5 (96.3, 98.7)
	Asian	370	367	99.2 (98.1, 100.0)
	American Indian or Alaska Native	50	50	100.0 (100.0,100.00)
	Native Hawaiian or Other Pacific Islander	30	30	100.0 (100.0,100.00)
	Unknown	100	87	87.0 (80.0, 93.0)
Educational level	*Less than high school*	140	124	88.6 (82.9, 93.6)
	High school	670	661	98.7 (97.8, 99.4)
	Some college	220	218	99.1 (97.7, 100.0)
	College diploma	1830	1770	96.7 (95.8, 97.5)
	Graduate or Professional degree	1840	1795	97.6 (96.8, 98.2)
BMI	*All*	4580	4450	97.2 (96.7, 97.6)
	< 25	1940	1881	97.0 (96.2, 97.7)
	25 – 29	1550	1537	99.2 (98.7, 99.6)
	≥ 30	1090	1032	94.7 (93.3, 96.0)
Gestational age at V1	*All*	4290	4165	97.1 (96.6, 97.6)
	14 – 21 weeks	1520	1447	95.2 (94.1, 96.3)
	22 – 34 weeks	2770	2718	98.1 (97.6, 98.7)
Comorbidities *Note: Subjects may have multiple comorbidities*	*All*	2310	2226	96.4 (95.6, 97.1)
	Abnormal AF at screening	610	595	97.5 (96.2, 98.7)
	BMI ≥ 30	1090	1032	94.7 (93.3, 96.0)
	Hypertension	120	99	82.5 (75.8, 89.2)
	Diabetes	210	201	95.7 (92.9, 98.1)
	Other	1220	1181	96.8 (95.7, 97.8)

As presented in the above table, the device performance among patients with hypertension was significantly lower than among patients without hypertension under the app-guided mode. The low device performance for this subgroup was attributed to two edge cases that contributed disproportionately to the lower overall performance rates. These edge cases involved temporary conditions unrelated to hypertension. When excluding these edge cases, the device performance for this subgroup significantly improved and exceeded the performance goal.

Similarly, the device performance among patients with less than a high school level of education was lower than among patients who had high school, college, or graduate education. The low device performance was attributed to two edge cases involving specific conditions unrelated to educational level that are unlikely to be replicated in other patients within this subgroup. Since the sample size for the subjects with less than a high school level of education is small, even the two problematic cases can dramatically skew the overall success rate. Even though the observed performance for patients with less than a high school level of education was lower, the observed performance still exceeded the 80% performance goal for the app-guided mode. Based on this conclusion, no additional mitigations were needed to caution users on the device performance for this subgroup.

The pivotal study did not include data for patients with gestational age >38 weeks. Therefore, the intended use population is limited to gestational age range of 14 -38 weeks.

The smartphones used in the HOLA study consisted of 181 Android phones and only 7 iOS phones. Additionally, because patients were using clinic-provided phones, the HOLA study was not sufficient to demonstrate compatibility across the range of Android phones that would be seen in real world use. Although, the subject device is meant to be used across iPhones and Android phones, iPhones were minimally represented in the clinical study. To evaluate the use of iPhones with Pulsenmore ES, RWE studies were provided, as described in the next section.

Overall, based on the results presented above, Pulsenmore ES demonstrated acceptable performance for visualization of fetal cardiac activity for most of the indicated population for both app-guided and clinician-guided modes.

Real-world evidence studies

Two RWE studies from healthcare systems in Israel, the Belinson study for the app-guided mode and the Sheba study for the clinician-guided mode, were submitted to address limitations of the pivotal study described above. The RWE encompasses smartphone compatibility data across 920 scans (combined app guided and clinician-guided studies) representing approximately 48 different smartphone models including both Android and iOS phones, intended to provide additional information to interpret clinical study results regarding device performance across diverse smartphone platforms in real-world settings.

The Belinson study analyzed 227 Pulsenmore app-guided scans from 181 pregnant women who used the device at home and then visited the emergency room within 24 hours. Twenty-three scans were obtained using iOS devices and 204 scans were obtained using Android phones. All the phones used were smartphones belonging to patients. The Sheba study analyzed 693 clinician-guided scans from 99 high-risk pregnancy patients who used the device as part of hospital-at-home monitoring program. 281 scans were obtained using iOS devices and 412 scans were obtained using Android devices. The majority of the phones used in the Sheba study were user owned phones with 149/693 (21.5%) of users receiving smartphones provided by the clinic.

The results of the RWE studies are presented in the below tables.

Table 5. Summary of scans conducted by Pulsenmore ES Clinician-Guided modes along with the smartphone type – iOS or Android (*Cardiotocography)

OS: iOS	FCA positive in CTG* or in-clinic scan	FCA negative in CTG or in-clinic scan
FCA positive with Pulsenmore	281	0
FCA negative with Pulsenmore	0	0
Scan quality inadequate for assessment	0	0

OS: Android	FCA positive in CTG or in-clinic scan	FCA negative in CTG or in-clinic scan
FCA positive with Pulsenmore	412	0
FCA negative with Pulsenmore	0	0
Scan quality inadequate for assessment	0	0

Table 6. Summary of scans conducted by Pulsenmore ES app-guided mode along with the smartphone type – iOS or Android.

OS: iOS	FCA positive in-clinic scan	FCA negative in-clinic scan
FCA positive with Pulsenmore	22	0
FCA negative with Pulsenmore	0	0
Scan quality inadequate for assessment	1	0

OS: Android	FCA positive in-clinic scan	FCA negative in-clinic scan
FCA positive with Pulsenmore	201	0
FCA negative with Pulsenmore	1	0
Scan quality inadequate for assessment	2	0

For clinician-guided mode, results demonstrate 100% success for fetal cardiac activity determination compared against non-stress test and subsequent in-clinic ultrasound scan. The study found no instances of failed FCA determination, inadequate scan quality, or false positive/negative results across the diverse range of smartphone models tested, including various iPhone models (11-15) and numerous Android devices from Samsung, Huawei, OnePlus, Pixel, and Xiaomi brands.

The app-guided mode showed successful FCA detection compared to emergency room ultrasound scans within 24 hours, except for four cases. Three cases had inadequate scan quality, while the fourth case where FCA was not detected during the home scan but

confirmed in-clinic may have served as an early warning of fetal compromise, as the patient was hospitalized for reduced fetal movements.

Overall, both the RWE studies demonstrated consistent performance for fetal cardiac activity detection across multiple smartphone models and manufacturers for both app-guided and clinician-guided modes. No statistically significant differences were observed between iOS and Android devices. No device or procedure related adverse events were noted in the RWE studies, further supporting the safety profile across different smartphone models.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

TRAINING

Pulsenmore ES provides the following training to the users (pregnant women and healthcare professionals). The training program encompasses both Type-C and iOS platforms. The patient training plan focuses on comprehensive mobile app instruction, beginning with a description of the main features displayed on the welcome screen. Trainees receive education on both app-guided and clinician-guided workflows along with their corresponding interface screens. App-guided training encompasses scan duration expectations, pre-step video explanations, proper preparation techniques and ultrasound gel application, detailed descriptions of interface icons such as contact and speed indicators, image upload procedures, and a brief demonstration video showcasing the self-scan process. Clinician-guided training covers workflow information, preparation steps and ultrasound gel application, video conference setup requirements, icon descriptions including contact and speed indicators, call termination procedures, upload screen navigation, and a short demonstration video illustrating the clinician-guided scanning process.

The clinician training plan introduces healthcare professionals to the clinician dashboard functionality for prescribing scans, reviewing scan results, and performing measurements, and clinician-guided instruction that details the process of guiding patients through the clinician guide interface, including recommended verbatim communication protocols.

Pulsenmore ES requires patients to complete the training and pass a short assessment with 100% score before the first use of the device. This training program ensures that users upon completion of the training can operate the device in the intended use environment.

LABELING

The labeling meets the requirements of 21 CFR 801.109 for prescription devices. The Pulsenmore ES labeling includes separate labeling for patients and clinicians. The patient labeling included hardware platform requirements, scan limitation instructions, reprocessing procedures for reusable components, instructions for access to training, and device handling and disposal methods after end of use by patients. The clinician labeling incorporates specific instructions for configuring acquisition limitation controls to ensure appropriate clinical use. Both patient and clinician labeling materials indicate that the device is designed for single

patient use and contain a summary of clinical performance testing data, along with warning statements emphasizing that images and data must be interpreted by qualified healthcare professionals, that the device should not replace or delay necessary in-office clinical assessments, that users must complete device-specific training before performing the first scan, and that adherence to ALARA principles is important during acquisition with clear guidance on available device controls to minimize ultrasound bioeffects.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of ultrasound imaging system for acquiring images at home by lay users and the measures necessary to mitigate these risks.

Risks to Health	**Mitigation Measures**
Device malfunction/failure leading to injury to user (e.g., shock, burn)	Non-clinical performance testing Electrical, mechanical and thermal safety testing Electromagnetic compatibility (EMC) testing Technological characteristics Software verification, validation and hazard analysis Labeling
Poor image quality or failure to obtain adequate scan by lay user, leading to incorrect interpretation or misinterpretation of device output and inappropriate patient management or delayed care	Clinical performance testing Non-clinical performance testing Technological characteristics Software verification, validation and hazard analysis Human factors assessment Training Labeling
Unnecessary ultrasound exposure leading to patient injury	Non-clinical performance testing Technological characteristics Training Labeling
Adverse tissue reaction	Biocompatibility evaluation
Infection	Reprocessing validation Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, ultrasound imaging system for acquiring images at home by lay users is subject to the following special controls:

(1) Clinical performance testing of software with representative compatible hardware must demonstrate that the device system performs as intended under anticipated conditions of use in the intended patient population. Testing must include the following:

(i) An evaluation of device performance in a representative user and patient population;
(ii) An evaluation of the diagnostic utility and quality of images/data acquired using the device;
(iii) Results comparing device performance to a clinically justified clinical comparator with established clinical performance; and
(iv) An evaluation of all adverse events.

(2) Non-clinical performance testing must demonstrate that the device system and its components perform as intended under anticipated conditions of use. Testing must include the following:
(i) Validation of pre-acquisition quality control checks by software;
(ii) Evaluation of the function of device software and hardware control safety features;
(iii) Validation of device system guidance functionality in a simulated use environment;
(iv) For ultrasound hardware, testing including:
(A) Acoustic output measurement;
(B) Image quality evaluation; and
(C) Clinical measurement accuracy.

(3) Performance testing must demonstrate the electromagnetic compatibility (EMC), electrical safety, thermal safety, mechanical safety, and wireless coexistence of the device system hardware in the intended use environment.

(4) Performance testing must validate the reprocessing instructions for reusable components of the device system hardware.

(5) Performance testing must demonstrate that all patient-contacting components of the device system hardware are biocompatible.

(6) Software verification, validation and hazard analysis must be performed.

(7) Device technological characteristics must incorporate design features to limit the number of scans and duration of device system use by the lay user to mitigate unnecessary ultrasound exposure.

(8) A training program must be included with sufficient educational elements so that upon completion of the training program, the user can operate the device system in the intended use environment.

(9) Human factors assessment must demonstrate the following:
(i) The user can correctly use the device system in the intended use environment with the provided instructions and training materials; and
(ii) The user understands situations in which the device system should not be used.

(10) Labeling must be included for the patient and healthcare professional that includes the following:

(i) A summary of clinical performance testing written for the intended reader;
(ii) For software labeling, hardware compatibility information;
(iii) The following statements:
    (A) A statement that the images and data acquired using the software are to be interpreted by qualified healthcare professionals;
    (B) A statement that the device system should not be used to replace or delay in-office/in-clinic assessment when needed;
    (C) A statement that users of the device system must complete the device-specific user training program prior to performing their first scan; and
    (D) A statement on adherence to the As Low As Reasonably Achievable (ALARA) principle and the device controls available to minimize ultrasound bioeffects.
(iv) For healthcare professional labeling, instructions for configuring the limits on device system use; and
(v) For patient labeling:
    (A) Hardware platform requirements;
    (B) A warning that the device system is not intended to be used outside of what has been prescribed, and to be aware of limits placed upon device system use by their healthcare professional;
    (C) Instructions for reprocessing of any reusable components; and
    (D) Instructions for proper handling of the device hardware when it is no longer needed, including disposal methods, and/or return requirements.

BENEFIT-RISK DETERMINATION

The probable risks of the device are based on nonclinical study information as well as data collected in clinical studies described above. The probable risks of the device include:

- Need for repetitive and additional ultrasound imaging if inadequate views or images of insufficient quality are obtained using the Pulsenmore ES system;
- Tissue heating from repeated imaging due to misuse or overuse of the device that could negatively impact fetal growth and/or development; and
- Poor image quality leading to incorrect interpretation or misinterpretation contributing to misdiagnosis.

These risks have been mitigated through device design/configuration (e.g., lock out time in the app-guided mode and maximum total time of use per device), patient instructions, usability testing, and mandatory training required for lay users before the first use of the device. The Pulsenmore ES system can perform a scan only with a valid scan key that can only be generated by the prescribing physician. The prescribing physician decides on the number of scans permitted by the key, the time window for performing the scans, and the conditions under which the scan should be performed. The device blocks the user from acquiring scans if the required number of scans under the unique scan key is performed and if the scan duration for app-guided mode goes beyond 3 minutes. Additionally, the device has other controls to block the user from scanning past a defined number of scans per day, per week, and over the use life of the device.

Clear information on these controls have been provided in the labeling. The risks of overuse and misuse of the device are further mitigated by warnings and cautions in the labeling.

The device has software controls in place to block the user from using the device before completing the training and scoring 100% on the competency test. Additionally, the clinician also confirms the completion of the training by the lay users before providing them access to the scan key. Human factors and usability testing shows that the training and labeling enable users to acquire images that a clinician can use to determine fetal heart rate. Clinical study results demonstrated that lay users successfully acquired adequate ultrasound images under both clinician-guided and app-guided modes, enabling physicians to determine fetal heart rate. Image quality assessment by two independent panels of 10 readers each confirmed that most images met minimum diagnostic criteria for visualizing fetal cardiac activity. The combination of comprehensive training, human factors testing, clinical performance evaluation, and appropriate labeling effectively mitigates the risk of poor image quality acquisition by lay users. Clear information on these controls have been provided in the labeling. The risks of overuse and misuse of the device are further mitigated by warnings and cautions in the labeling.

Some sources of uncertainty in risk are related to study design and its limitation to fully capture the risk during the duration of participation of each subject and lack of follow up through the end of the pregnancy, delivery and neonatal period. The study design and practicality of performing the scans, in addition to a mobile fetus, did not allow for all the studies per subject to be done at the same time or even the same day which limits ability to adequately compare when evaluating the primary endpoint. Additionally, the user population and study practices (repeated practice scans before the images are acquired and sent to the interpreting physician) in the clinical study may not be representative of the intended use population and real world use conditions.

The probable benefits of the device are based on the nonclinical testing as well as data collected in the clinical studies as described above. The probable benefits of the device include improved healthcare access by providing valuable access for patients in remote areas or those with limited healthcare access where ultrasound is clinically indicated episodically for visualization of fetal heart when obtaining fetal heart rate. Additionally, the Pulsenmore ES system has added benefit over existing home-use handheld doppler devices, which only provide episodic fetal heart rate display without visualization of fetal heart and fetal heart rate activity. The additional visualization component and inclusion of M-mode on the clinician platform allowing the clinician to draw a line through the fetal heart, precludes the possibility of detecting the maternal heart rate with the fetal heart rate. The results from the clinical study demonstrated meaningful benefits for fetal cardiac activity visualization through both clinician-guided and app-guided ultrasound image acquisition modes for the intended use population. The observed results in the real-world evidence studies for both app-guided and clinician-guided modes were consistent with the results from the pivotal study, demonstrating the effectiveness of Pulsenmore ES System in a real-world population.

Some of the sources of uncertainty in the benefits include the methodological clinical study limitations from protocol deviations, temporal gaps of days to weeks between study scans, and reference standard of care comparisons, unlimited practice sessions that introduce bias and may not reflect the real-world usage. Given the fact that this device is a prescription use device and

can be used in the home environment under the guidance of a healthcare provider, which may mitigate some of the concerns regarding the identified sources of uncertainty.

Based on the above information, the probable benefits of the Pulsenmore ES system outweigh the probable risks considering the listed special controls and the general controls.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The Pulsenmore ES ultrasound system is intended to enable the acquisition of ultrasound images that allow interpreting healthcare providers to determine fetal heart rate.
>
> The Pulsenmore ES Ultrasound System is intended for limited diagnostic ultrasound imaging in B- Mode and M-Mode in Fetal/Obstetric applications, when traditional scanning at a health clinic is impractical or when the use of telehealth (clinician-guided mode) or software-guided self-scanning (App-guided mode) is in the best interests of the patient.
>
> The device is intended to be used by pregnant women with a singleton pregnancy at the gestational age of 14-38 weeks, when clinically indicated to determine the heart rate on the order of a physician in non-clinical environments. When directed by their physician, the patient can either follow the steps specified by the ES software application (app-guided mode) or under the direction of a healthcare professional (clinician-guided mode).
>
> A physician interprets the images acquired with the device in a remote access setup. Access to the device operation must be granted by healthcare professionals.

The probable benefits outweigh the probable risks for the Pulsenmore ES system. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Pulsenmore ES is granted and the device is classified as follows:

> Product Code: SGJ
> Device Type: Ultrasound imaging system for acquiring images at home by lay users
> Regulation Number: 21 CFR 892.1590
> Class: II