AMDM 2019
“Apple Watch: DeNovo Clearance for first Direct-to-Consumer EKG wearable”

Peter J. Yang, Ph.D.
Policy Analyst, De Novo Program
Office of Product Evaluation and Quality (OPEQ)
FDA/CDRH

Outline

- What is a De Novo request?
- De Novo: Electrocardiograph software for over-the-counter use
- De Novo: Photoplethysmograph analysis software for over-the-counter use
- De Novo discussion points

What Is a De Novo Request?

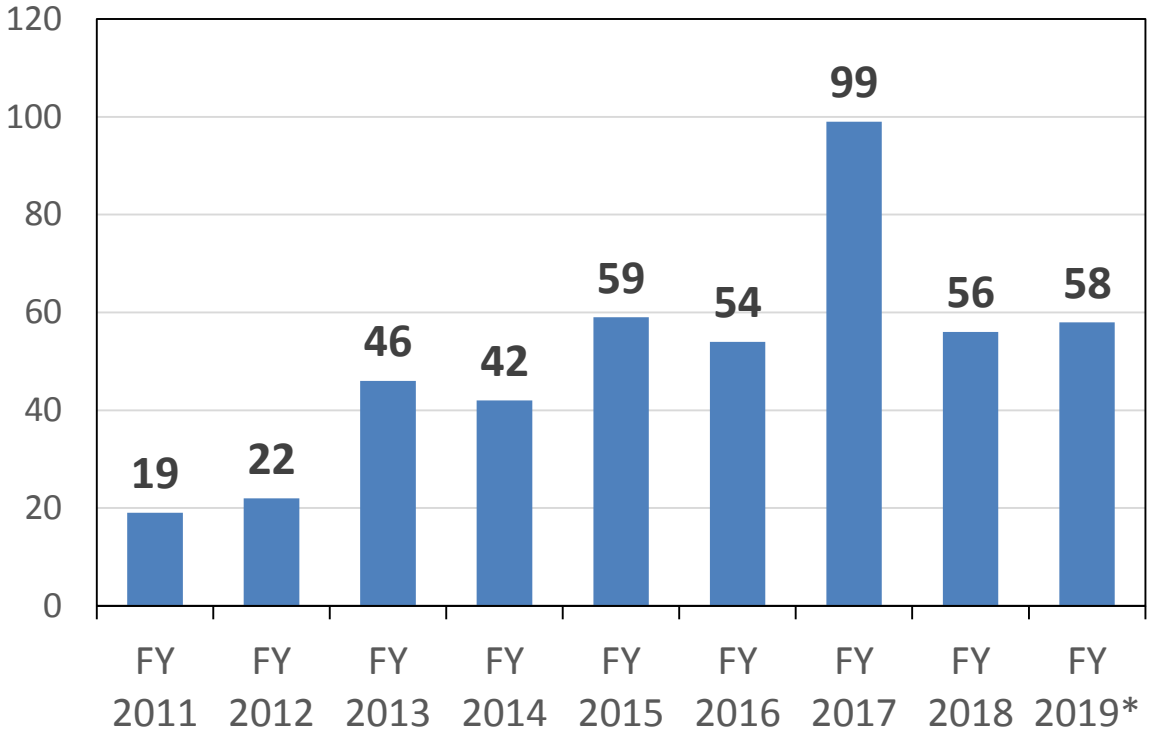
- A type of premarket submission (marketing authorization)
- Intended for devices that would be automatically classified into Class III (new device types)
- A request to classify subject device into Class I or Class II (risk-based classification)
- If granted, creates a new classification regulation for the new device type (regulated through 510(k))

Granting a De Novo Request

1. Identify probable risks to health for the device/product
2. Determine level of control needed:
   - general controls only = *Class I*
   - general controls + special controls = *Class II*
3. Determine if probable benefits outweigh probable risks

These provide reasonable assurance of safety and effectiveness.
This is not a substantial equivalence decision.

De Novos Received In CDRH



* Open cohort (as of 9/13/2019)

Guidance Documents

- De Novo Classification Process (Evaluation of Automatic Class III Designation)
- Acceptance Review for De Novo Classification Requests **NEW**
- FDA and Industry Actions on De Novo Classification Requests: Effect on FDA Review Clock and Goals
- User Fees and Refunds for De Novo Classification Requests

Guidance Documents

- Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
- Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions **NEW**

De Novo RTA Guidance

- **Purpose: Ensure De Novo request is acceptable for substantive review**
- Facilitates efficient and timely review
- Similar to RTA policies for 510(k) and PMA
  - Intend to complete RTA review within 15 calendar days of receiving De Novo
  - De Novo is considered accepted if RTA review is not completed within 15 calendar days
- Final RTA guidance published September 9, 2019 with a **60-day transition period for FDA and industry**
- Fulfills MDUFA IV commitment (“submission checklist”)

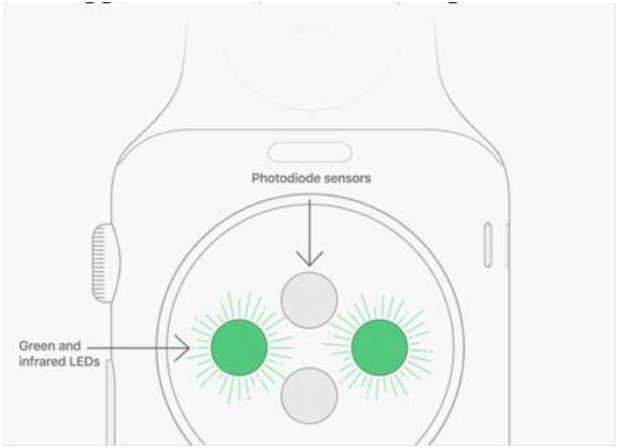
De Novo RTA Guidance

Appendix A	Appendix B
Acceptance Checklist	**Recommended Content Checklist**
Necessary for acceptance	Optional
Examples: Intended use Device description Proposed special controls (if recommending class II)	*Examples:* Prior submissions Classification summary (eligibility) Device labeling

The Recommended Content Checklist will NOT be used to conduct RTA reviews.

DEN180042: Irregular Rhythm Notification Feature

- One minute beat-to-beat sequence (tachogram) every four hours
- 5 of 6 sequential tachograms classified as irregular for notification to be presented to user
- Notification encourages user to seek medical care if they have not been previously diagnosed with AF
- Software only medical device



DEN180042: Irregular Rhythm Notification Feature

- Non-clinical information
  - Software verification and validation, including a discussion of the algorithm
  - Performance testing of the device to analyze effect of signal quality on algorithm performance
  - Labeling to help lay users understand the device and what it is intended for / what it is not intended for, including how to interpret the results

DEN180042: Irregular Rhythm Notification Feature

- Human factors testing in simulated home environment
  - Included “active interest” and “passive interest” individuals; included participants unfamiliar with Apple Watch
  - Participants set up the app, followed by decay period of 1 hour
  - 36/37 participants indicated a lack of notification would not affect their medical decisions
  - 35/35 participants received a notification and indicated they would not reduce care if experiencing acute symptoms

DEN180042: Irregular Rhythm Notification Feature

- Clinical study
  - Sub-study of larger prospective study with Apple Watch, enrolling participants who received a notification from this feature
  - Included 226 patients with tachograms and corresponding patch ECG recordings from 7-day ambulatory patch ECG recorder
  - Patch ECG recording classified by independent cardiologists to compare to the tachogram classification algorithm
  - Probability of diagnosis of AF from 7-day patch recording, given a notification from this feature, is 41.6%

DEN180042: Irregular Rhythm Notification Feature

- Benefit-risk analysis
  - Benefit
    - Use as a screening tool to pre-screen persons for further AF screening and improve diagnostic yield
    - Not intended to definitively diagnose AF
  - Risk
    - False negative: Delay further treatment
    - False positive: Unnecessary medical procedures
    - Misunderstanding and misinterpretation of results in an over-the-counter context

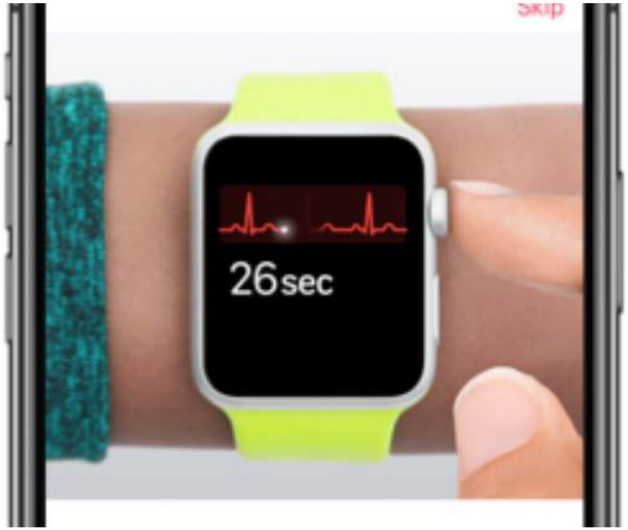
DEN180042: Irregular Rhythm Notification Feature

21 CFR 870.2790. Photoplethysmograph analysis software for over-the-counter use. A photoplethysmograph analysis software device for over-the-counter use analyzes photoplethysmograph data and provides information for identifying irregular heart rhythms. This device is not intended to provide a diagnosis.

1. Clinical performance testing must demonstrate the performance characteristics of the detection algorithm under anticipated conditions of use.
2. Software verification, validation, and hazard analysis must be performed. Documentation must include a characterization of the technical specifications of the software, including the detection algorithm and its inputs and outputs.
3. Non-clinical performance testing must demonstrate the ability of the device to detect adequate PPG signal quality.
4. Human factors and usability testing must demonstrate the following:
   a. The user can correctly use the device based solely on reading the device labeling; and
   b. The user can correctly interpret the device output and understand when to seek medical care.
5. Labeling must include:
   a. Hardware platform and operating system requirements;
   b. Situations in which the device may not operate at an expected performance level;
   c. A summary of the clinical performance testing conducted with the device;
   d. A description of what the device measures and outputs to the user; and
   e. Guidance on interpretation of any results.

DEN180044: ECG App

- ECG is actively initiated by user (as opposed to previous De Novo)
- Software records electrical potential between electrodes and digital crown
- Waveform saved is similar to a Lead I ECG
- Classification: Sinus rhythm (SR), AF, or inconclusive (e.g. abnormal heart rate, other arrhythmias, poor signal quality)
- User can input symptoms saved as part of the result
- Session results stored on iPhone and can be exported to PDF (to email, etc.)



DEN180044: ECG App

- Non-clinical information
  - Software verification and validation, including a discussion of the algorithm
  - Performance testing of the device to obtain quality signal for analysis
  - Labeling to help lay users understand the device and what it is intended for / what it is not intended for, including how to interpret the results
  - Human factors validation study including users diagnosed with AF, users under 65 years of age, users over 65 years of age
  - Performance testing of algorithm against ANSI AAMI EC57:2012, FDA-recognized voluntary consensus standard of databases containing pre-adjudicated rhythms

DEN180044: ECG App

- Clinical study
  - Study enrolled 588 eligible subjects at 5 sites, separated into AF and SR cohorts (301 and 287 subjects, respectively)
  - 30-second ECG App and 12-lead ECG recordings acquired simultaneously
  - Three blinded independent board-certified cardiologists evaluated ECG recordings; PQRST complexes also evaluated by cardiographic technicians for qualitative comparison
  - Probability that a subject with AF would receive an AF diagnosis from the ECG App was 85.2%
  - In qualitative comparison, 97.5% of waveforms considered clinically equivalent to gold standard ECG; 93.2% had good R-wave amplitude agreement

DEN180044: ECG App

21 CFR 870.2345. Electrocardiograph software for over-the-counter use. An electrocardiograph software device for over-the-counter use creates, analyzes, and displays electrocardiograph data, and can provide information for identifying cardiac arrhythmias. This device is not intended to provide a diagnosis.

1. Clinical performance testing under anticipated conditions of use must demonstrate the following:
   a. The ability to obtain an ECG of sufficient quality for display and analysis; and
   b. The performance characteristics of the detection algorithm as reported by sensitivity and either specificity or positive predictive value.
2. Software verification, validation, and hazard analysis must be performed. Documentation must include a characterization of the technical specifications of the software, including the detection algorithm and its inputs and outputs.
3. Non-clinical performance testing must validate detection algorithm performance using a previously adjudicated data set.
4. Human factors and usability testing must demonstrate the following:
   a. The user can correctly use the device based solely on reading the device labeling; and
   b. The user can correctly interpret the device output and understand when to seek medical care.
5. Labeling must include:
   a. Hardware platform and operating system requirements;
   b. Situations in which the device may not operate at an expected performance level;
   c. A summary of the clinical performance testing conducted with the device;
   d. A description of what the device measures and outputs to the user; and
   e. Guidance on interpretation of any results.

De Novo Discussion Points

- De Novo devices are at the center of current issues for novel and innovative medical device technologies
- Regulations created through De Novo classification set the stage for continuing innovation in 510(k) for devices with comparable intended uses, technologies, and risks
- Submit pre-submissions to discuss the regulatory landscape of devices with FDA, understand the risks to health associated with your intended use or technology, and discuss data requirements and study designs for your product


FDA
U.S. FOOD & DRUG
ADMINISTRATION