

Future Challenges: Electronic Devices, Drug Use Related Software, and Impacts on Generic Development and Substitution

SBIA 2022:

Day 1, Session 2: Drug-Device Combination Products with a Focus on Devices

Betsy Ballard, MD

DTP1/ORS/ OGD

CDER | U.S. FDA

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Overview



- Example of challenges with novel electronic devices
- A background for Digital Health Technology
- Examples of challenges for generic drug development in a digital world
- Policy challenges in a Digital world

Challenge # 1

Example of a Unique Electronic Device

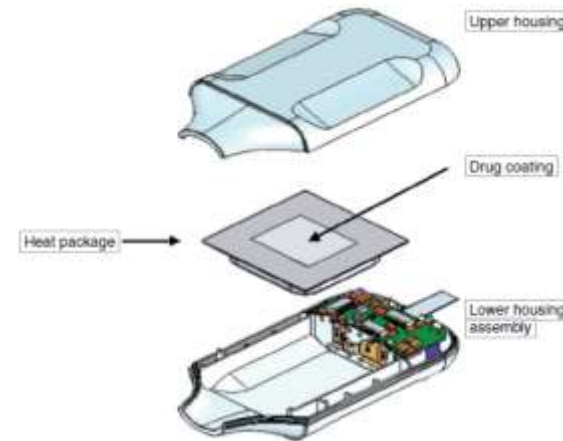
Example: ADASUVE

- Novel drug-delivery platform
 - Pure API Loxapine
 - Breath actuated
 - Thermally generated aerosol

Staccato[®] single-dose device



- **Drug coating:** A thin film of excipient-free drug coated on the exterior stainless-steel surface(s) of the heat package.
- **Heat package:** The sealed assembly composed of a thermite reactant coating on the interior surfaces of stainless-steel substrates that generates heat ($\sim 400\text{ }^{\circ}\text{C}$) to vaporize the drug and produce the drug aerosol.
- **Lower housing assembly:** A plastic housing in combination with electronics that is responsible for the breath-actuation mechanism and initiation of the heat package.
- **Upper housing:** A plastic housing surrounding the heat package; along with the lower housing, it controls and directs the airflow over the vaporizing drug.



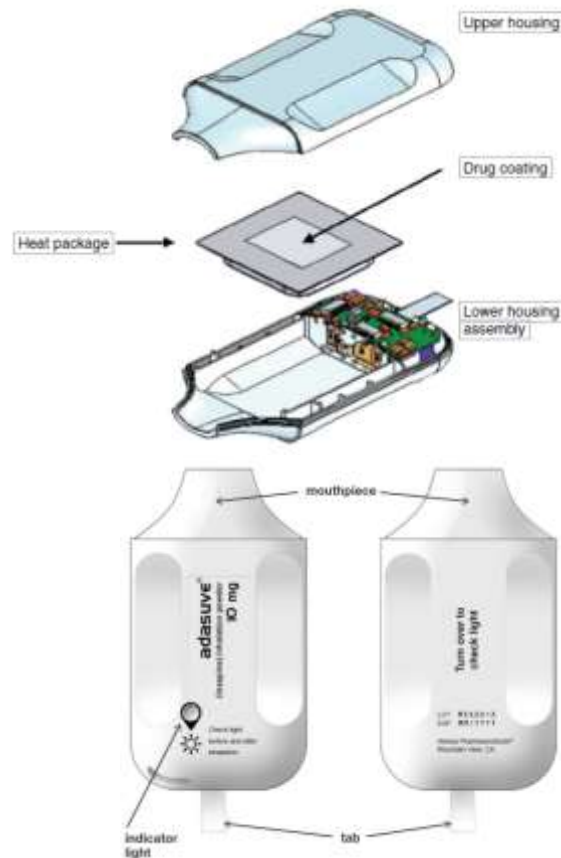
2011 Myers

Staccato® single-dose device Continued



- **Green light-emitting diode indicator light:**
 - **Turns on** when the device is activated (by pulling the plastic tab) and ready-to-use
 - **Turns off** after patient inhales through, actuates the device, and receives the aerosol dose.
 - User tends to sense: Slightly warm air, mildly warm (~ 35 °C) outer surfaces of the airway housing
- **Heating Source: Exothermic chemical reaction** applied to the internal surfaces of the heat package.
 - Upon initiation, the **metal & metal oxide (major component of the chemical mixture)** undergo a thermite-type reaction, releasing approximately **400 J** of energy.
 - **Inorganic binder** (minor component of the chemical mixture): adheres the thermite components to the inner surfaces of the heat package.

2011 Myers; ADASUVE Drug Label

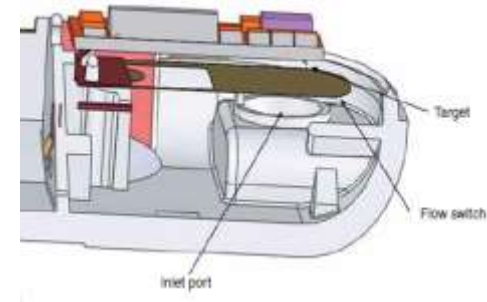


Breath Actuation Mechanism



- **Flow Switch (Heart of the actuation system)**
 - Consists of a 0.025-mm thick foil beam cantilevered (structure fixed or supported at only one end) over the air inlet port of the device.
 - When not in use, the foil remains cantilevered under the electrical contact target to prevent inadvertent activation.
- **During inhalation** (threshold inhalation flow rate: ~ 15 L per min):
 - Air entering the inlet port of the device flows past the flow switch and deflects the foil which completes the electrical circuit.
 - After consistent contact, electronics in the device sense the circuit closure and actuate the heat package by sending current into the initiator of the heat package.
 - Device generates aerosols of consistent emitted dose.

Cross section of the single-dose device



2011 Myers; ADASUVE Drug Label

Device Design Parameters



- Vaporization temperature
 - Previous studies suggest ~400 °C ideal for Loxapine, but may be different for other drugs
- Drug coating thickness
 - Previous studies identified drug coating thickness has minor effect on particle size, but increased drug impurities
- Inhalation flow rates
 - Previous studies identified slight reduction of particle size with increased airflow
- Emitted dose
 - Previous studies identified consistent emitted dose delivery at various testing conditions (Even for flow rate between 15 and 45 L/min, the range was 100-112%)
- Aerosol parameters
 - Particle size, Fine particle fraction (FPF), and Mass Median Aerodynamic Diameter (MMAD) seem to be important parameters to predict % of drug to the target sites
- Aerosol purity
 - For previous studies, aerosol purity measured by using HPLC and comparing absorbances of plain drug powder vs. vaporized aerosols
 - Almost no impurity for Staccato device

Drug Parameters



- Staccato platform allows for active ingredient without any excipients
- Small molecule drugs with low molecular weight
- State of matter (solid vs liquid)
- Melting point
- Crystalline structures
- The coated dose weight and coating area need to be controlled

Challenges with Adasuve



- Selection of appropriate drugs for use with the platform
- Selection for determining bioequivalence
 - Device parameters
 - Drug parameters
 - Heating and delivery of drug with a systemic effect
- Patents

Challenge #2



What is Digital Health?

Acceptability of and Willingness to Take Digital Pills
by Patients, the Public, and Health Care
Professionals: Qualitative Study

Large Online Survey
Chen M, Havermans BM, Boot CR, Brouwers EP, Houtman IL, Heerkens
YF, Zijlstra-Vlasveld MC, Twisk JW, Anema JR, van der Beek AJ.

**Effectiveness of a digital platform-based implementation
strategy to prevent work stress in a healthcare organization:
a 12-month follow-up controlled trial.** Scand J Work Environ Health
2018 Nov 01;44(6):613-622.

Woods L, Cummings E, Duff J,
Walker K. **Partnering in Digital
Health Design: Engaging the
Multidisciplinary Team in a Needs
Analysis.** J Healthc Inform Res. 2018 Jun;2(1-2):1-24.

King CE, Sarrafzadeh M. **A Survey Of Smartwatches
In Remote Health Monitoring.** J Healthc Inform Res. 2018 Jun;2(1-2):1-24.

Effects of a Digital Diabetes Prevention Program: An RCT

Jeffrey A Katula, Emily V Dressler, Carol A Kittel, Lea N Harvin, Fabio
A Almeida, Kathryn E Wilson, Tzeyu L Michaud, Gwenndolyn C
Porter, Fabiana A Brito, Cody L Goessl, Carolyn B Jasik, Cynthia M
Castro Sweet, Robert Schwab, Paul A Estabrooks. Am J Prev Med
. 2022 Apr;62(4):567-577.

FDA and Digital Health: Background



- CDRH issued the first Guidance on Device Software Functions and Mobile Medical Applications in 2013 and revised it in 2019.
<https://www.fda.gov/media/80958/download>
 - a “mobile medical app” is a mobile app that incorporates device software functionality that meets the definition of device and used as an accessory to a regulated medical device or to transform a mobile platform into a regulated medical device
- Center for Digital Health Excellence
 - Connect and build partnerships
 - Share knowledge
 - Innovate regulatory approaches
- Fit-for-purpose

What is Digital Health Technology? (DHT)



- Remote sensing and wearables (point of care testing)
- Telemedicine and health information
- Data analytics and intelligence, predictive modeling
- Health and wellness behavior modification tools
- Bioinformatics tools (-omics)
- Digitized health record platforms
- Patient -physician-patient portals
- DIY diagnostics, compliance, and treatments
- Decision support systems
- Imaging

What is DHT?



- A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses.
- Prescription drug-use-related software (PDURS) refers to software disseminated by or on behalf of a drug sponsor that accompanies one or more of the sponsor's prescription drugs (including biological drug products).

Status of Digital Health



- May be used to differentiate between claims of prevention, compliance, improvement in disease status (clinical), and promotional claims (engagement, economic savings)
- Most digital health companies have a low level of clinical robustness and have not been able to make clinical claims in their labeling
- About 20% of firms were able to support their claims through rigorously tested trials¹
- Issues related to confidentiality, security, and data privacy that have not been addressed by industry
- Multiple stakeholders need to see the value of any given product or service.

¹ Day, Sean et al. J Med Internet Res 2022;24(6):e37677)

CDRH References



CDRH Digital Health Center of Excellence: <https://www.fda.gov/medical-devices/digital-health-center-excellence>

CDRH Digital Health Software Pre-certification Program: <https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-program>; <https://www.fda.gov/media/142107/download>

CDRH Guidance updated in 2019: <https://www.fda.gov/media/80958/download>

Digital Health Technologies (DHTs) for Remote Data Acquisition Draft Guidance: <https://www.fda.gov/drugs/news-events-human-drugs/digital-health-technologies-dhts-remote-data-acquisition-draft-guidance-02102022>

Off-the-Shelf Software Use in Medical Devices: Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act: <https://www.fda.gov/media/109622/download>

Software as a Medical Device (SAMD): Clinical Evaluation: <https://www.fda.gov/media/100714/download>

Artificial Intelligence and Machine Learning in Software as a Medical Device: <https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device>

Content of Premarket Submissions for Device Software Functions: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions>

Clinical Decision Support Software: <https://www.fda.gov/media/109618/download>

Medical Device Accessories –Describing Accessories and Classification Pathways: <https://www.fda.gov/media/90647/download>

General Wellness: Policy for Low-Risk Devices: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-wellness-policy-low-risk-devices>

Medical Device Development Tools (MDDT): <https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt>

Challenge #3



Generic development of:

Drug-led Drug-Device Combination Products (DDCPs)
with Prescription Drug Use Related Software (PDURS)

What is a DDCP?

Drug-Device Combination Product (DDCP):

- A combination product containing a drug constituent part and device constituent



Single entity



Co-packaged



Cross-labeled

Defining PDURS

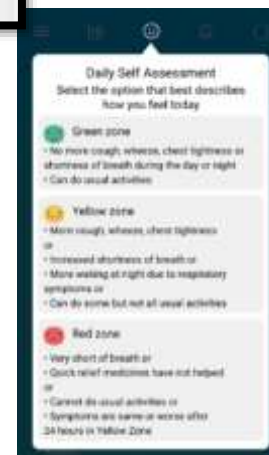
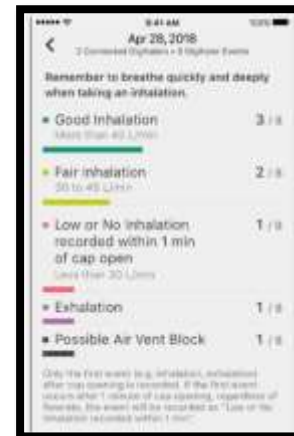


- **Prescription drug-use-related software (PDURS):** software that is
 - disseminated by, or on behalf of, a drug sponsor, and
 - accompanies one or more of the sponsor's drugs or drug-led DDCPs.
- **PDURS Function:** the distinct purpose of the software.
 - Pairing mobile app to the drug-led DDCP.
 - Communicating information to the end user (e.g., patient, care giver, healthcare provider).
 - Tracking and displaying drug administration (e.g., ingestion, injection, inhalation event).
 - PDURS can have more than one function

Independent vs. Integrated PDURS



- Software that is a device constituent part or element of a drug-led DDCP.
 - Software capturing data on ingestion from an embedded sensor in an oral tablet.
 - Software capturing injection data from an autoinjector to display in an app.
 - Software capturing inhalation data from an inhaler to display in an app.
- Software is not a device constituent part or element of a drug-led DDCP.
 - Patient/user inputs health information related to the condition (incidence or severity of symptoms) for which they were prescribed the drug (e-diary).
 - Information regarding pollen content from a weather website.
 - Copy of Prescribing Information or Instructions for Use.
- PDURS provided in a drug-led DDCP can have **both types of software**



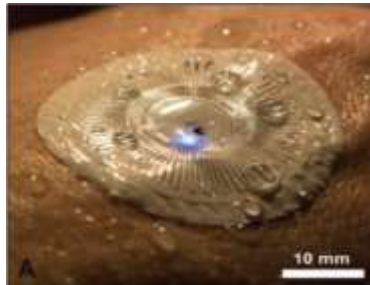
Example of a DDCPs with PDURS



Digihalers¹: captures inhalation events and shares to a patient via a smartphone app

Examples of Sensors

Digital biomarkers collect body fluids for analysis using a smartphone



Sweat Sensor

Reeder et al.
Sci Adv 201.Jan;5(1):eaau6356



Saliva sensor

Tseng et al
Adv Mater 201May;30(18):e1703257



Exhaled breath analysis

Aeonose -The eNose Company

<https://www.enose.nl/products/aeonose>

Challenge #4



Developing CDER Policies and Guidances for Digital Health

CDER Actions and Initiatives



- PDUFA Commitment Letter agreement to establish a CDER/CBER committee on digital health
- OND/Division of Clinical Outcome Assessment
 - Use of technology to collect clinical outcomes
 - Measure traditional efficacy endpoints more accurately or reliably
 - Measure endpoints that were not previously possible
- CDER FDA Guidance for PDURS under development

Generic Products with PDURS

- If you are developing a generic with software that the RLD does not have or proposing not to include software the RLD has, early engagement with FDA will allow for a case-by-case evaluation
- Intellectual property concerns
- Comparative Analyses
 - Performing a use related risk analysis (URRA) may be helpful during design development

CDER Resources

Patient reported outcome measures: <https://www.fda.gov/media/77832/download>

Drug development tools: <https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs>

Biomarker Qualification program: <https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program>

BEST (Biomarkers, Endpoints, and Other Tools) Resource:
<https://www.ncbi.nlm.nih.gov/books/NBK338448/>

Clinical Outcome Assessment (COA) Qualification Program: <https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessment-coa-qualification-program>

Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program:
www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

Challenge Questions?



How is CDER responding to the Digital World?

- a) Making PDUFA commitments
- b) Developing a Guidance
- c) A and B
- d) None of the above

Challenge Question 2



What is the best way to engage with FDA for generic product that has a PDURS?

- i. Develop a generic without PDURS for an RLD that has software
 - ii. Controlled correspondences, pre-ANDA development meeting requests
 - iii. Seek input and advice early in drug development process
-
- A. i and ii
 - B. ii only
 - C. ii and iii
 - D. All of the above

Summary



- DHT is a rapidly developing field with many new challenges:
 - Opportunities for use of novel endpoints
 - Requires a multi-disciplinary and collaborative approach
 - Patient centered
- Generic Drug Program/CDER recommends
 - Watch for publication of the CDER PDURS guidance
 - Seek input and advice early in drug development process
 - “Come early, Come often!”

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Thank You!

