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

September 21, 2022

Overview

- Examples 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 Devices

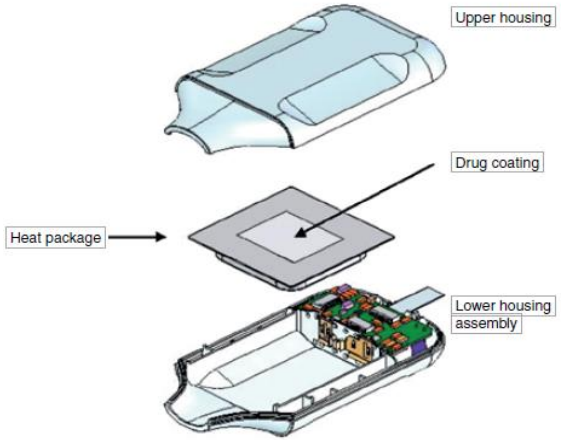
Electronic Devices

Example: ADASUVE

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

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 (~400 °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.

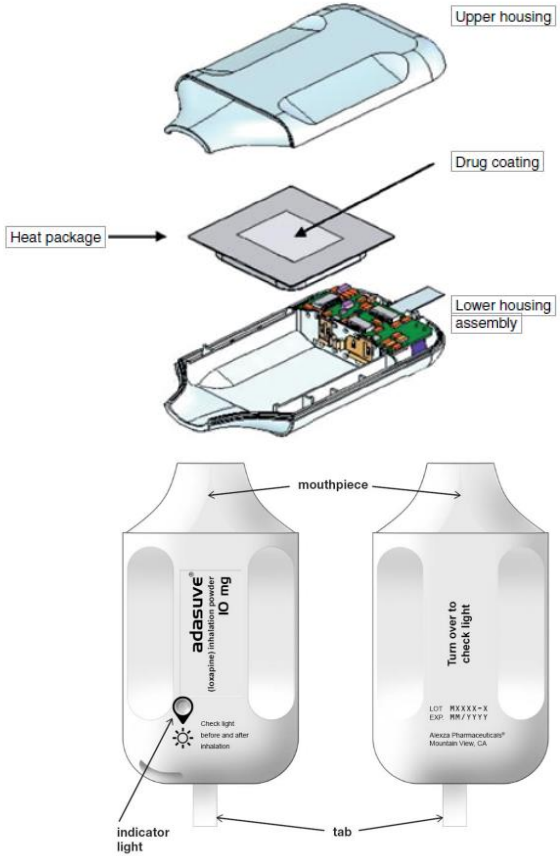


2011 Myers

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.

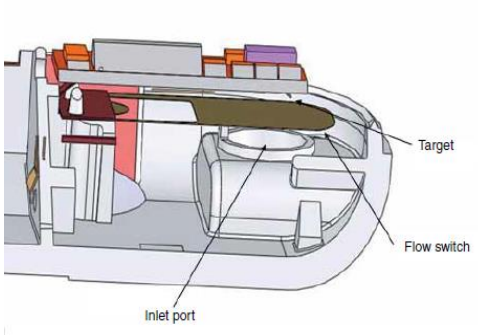
2011 Myers; ADASUVE Drug Label



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.
  - Deflected foil touches and makes electrical contact with the target above.
  - 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 Ca
Professionals: Qualitative
Large Online
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 o a 12-month follow-up controlled trial**. Scand J
Hea 2018 Nov 01;44(6):613-62
Woods L, Cummings E, Duff J, Walker K. **Partnering in Digital Health Design: Engaging the Multidisciplinary Team in a Needs Analysis**
echnol
-181.
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 trials[1]
- 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:

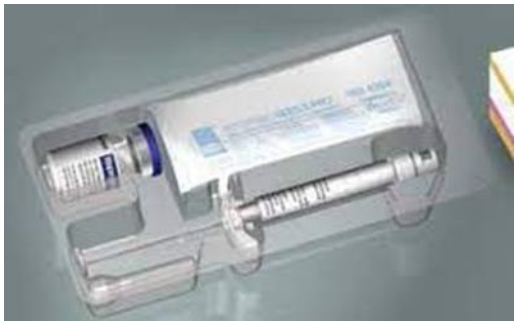
Drug-led Drug-Device Combination Products (DDCPs) with Prescription Drug Use Related Software (PDURS)

What is a DDCP?

Drug-Device Combination Product (DDCP):

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

Single entity



Co-packaged

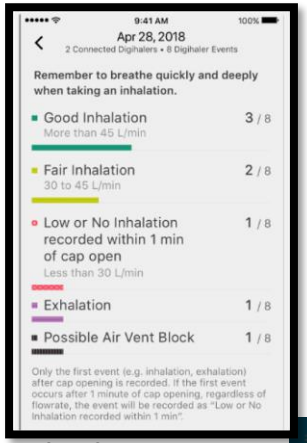
Cross-labeled

Defining PDURS

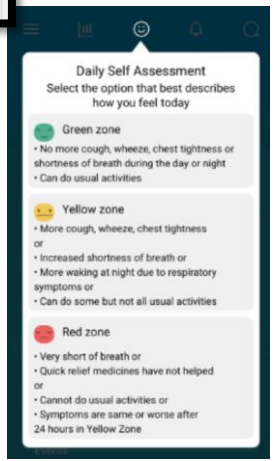
- **Prescription drug-use-related software (PDURS):** software that is
  - disseminated by, or on behalf of, a drug sponsor, and
  - accompanies one or more of the sponsor's drugs or drug-led DDCPs.
- **PDURS Function**: the distinct purpose of the software.
  - Pairing mobile app to the drug-led DDCP.
  - 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 <u>is not</u> 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

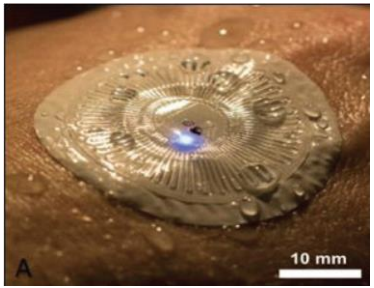
Example of a DDCPs with PDURS

Digihalers [1]: captures inhalation events and shares to a patient via a smartphone app

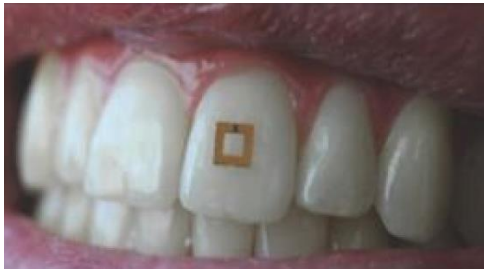
www.fda.gov [1]businesswire.com;

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

i. Controlled correspondences, pre-ANDA development meeting requests

ii. 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!”

Acknowledgements

Yoonjung Lee, PhD PharmD

Elizabeth Bielski, PhD

Katharine Feibus, MD

Markham Luke, MD PhD

Lei Zhang, PhD

Lisa Bercu, JD

Jessica Mavadia-Shukla, PhD, CDRH

MiRa Jacobs, PhD, CDRH

LCDR Abbas Bandukwala

Elektra Papadopoulos, MD

Thank You!


FDA
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