Respiratory Drug Delivery Devices
A CDRH Perspective

Sugato De, M.S.
Biomedical Engineer
Food and Drug Administration
Center for Devices and Radiological Health
Disclosure

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Overview

• CDRH Medical Device Review Program
• Classification Paradigms
  – “General Purpose” vs. “Drug-Specific”
• Respiratory Drug-Device Co-development
• Regulatory Pathways for Drug-Specific Delivery Devices
• Device Review Considerations
promote and protect the health of the public.
- bring safe and effective medical devices to the market as quickly as possible...
- ...while ensuring that devices and radiological products currently on the market remain safe and effective.
Medical Device Classes

• Class I Devices:
  – General controls sufficient to demonstrate safety and effectiveness.
  – Most exempt from premarket submission.
  – Examples: Gloves, scalpels.

• Class II Devices:
  – General controls alone insufficient to demonstrate safety and effectiveness.
  – Special controls are applied.
    • Performance Standards
    • Post-Market Surveillance
  – Require 510(k) Premarket Notification (Substantial Equivalence)
  – Examples: Ventilators, diagnostic ultrasounds, nebulizers.

• Class III Devices: Novel technology, general and special controls insufficient.
  – Require Premarket Approval (PMA) Submission
  – Examples: Drug Eluting Stent
Combination Products

- Nebulizers/MDIs are combination products by nature.

- Combination Product Definition:
  - A product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity.

- Office of Combination Products assigns jurisdiction based on primary mode of action.
Device Categories

- Nebulizers and inhalers are grouped into two categories.
  - General Purpose
  - Drug-Specific
General Purpose Device

- Device intended to aerosolize a range of well-characterized, prescribed drugs for delivery to a patient’s airway.
- Drug components must have prior approval from CDER.
- Examples of drug classes appropriate for general purpose devices:
  - Beta-agonist bronchodilators (albuterol)
  - Anti-cholinergic bronchodilators (ipratropium bromide)
  - Anti-inflammatory drugs (cromolyn sodium).

- Reviewed by CDRH via 510(k) Premarket Notification.
Drug-Specific Device

• Device specifically designed to deliver a single drug to a patient’s airway.
  – All inhaled antimicrobials are delivered by drug-specific devices.
  – Example: Altera Nebulizer System (Cayston)

• Assigned to CDER as the lead review center.
  – Investigational New Drug (IND) and New Drug Application (NDA).
  – CDRH is consulted for review of the device component.
Drug-Specific Device

• For the review of the device component, a manufacturer may:
  – (1) Submit a “device module” as component of the NDA or IND.
    • Include all information pertinent to device.
    • Device review occurs concurrently with NDA.
  – (2) Submit a separate 510(k) for device component.
    • Approval dependent on NDA approval of drug component.

• Device module within context of NDA is preferred.
  – Avoid two separate submissions, conflicting timelines.
Platform Nebulizers

• Base nebulizers that maybe “customized” to deliver multiple drugs.

• All configurations require performance characterization.

• May require both 510(k) and NDA.
Drug-Device Co-development

• Consideration of delivery device should occur early in co-development process.
• Standards for dose uniformity for drug-specific devices are generally higher than for general purpose devices.
• Human factors and usability studies should be conducted on device concurrent to Phase 2.
• Finalized release version of device should be used in Phase 3 clinical trials.
Device Review Considerations

- Indications for Use
- Device Technology
- Labeling
- Sterilization/Shelf Life
- Biocompatibility
- Electrical Safety
- Mechanical Safety
- Electromagnetic Compatibility

- Software Documentation
- Usability & Human Factors
- Performance Tests
  - Particle Characterization
  - Triggering Validation (Breath-Actuated)
Indications for Use

• State intended use of proposed device.

• FDA approves devices for specific patient populations.
  – Population for which there is sufficient data to demonstrate a reasonable assurance of safety and effectiveness.

• Environments for use should be included.
Device Technology

- Describe principle of operation.
- Illustrate and explain breathing gas path.
- Identify patient-interface accessories (e.g. mouthpiece) and device components.
  - Specify single use, single-patient reuse, or multiple-patient reuse for each component.
Performance Tests

- Performance of nebulizers is determined primarily by cumulative particle characterization tests.

- FDA recommends use of a cascade impactor with at least six stages.
  - Multi-stage sampling device.
  - Used to determine the size distribution of an aerosol.
Performance Tests

• Testing should be conducted and minimum, nominal and maximum flow rates allowable by device.
• Conduct testing in accordance with each drug’s labeled concentration, dose volume and nebulization time.
• Continue until device is empty as indicated by sputtering.

❖ Laser diffraction is currently not accepted by CDRH.
Performance Tests

• In vitro testing almost always provides drug mass *emitted* at patient interface.

• Measurement of *delivered* mass to the respiratory tract requires knowledge about its geometry, especially the oropharynx, disease state etc.
Particle Specifications

- **Total Emitted Mass (TEM)**
  - Mass/actuation emitted by device.
  - Not to be confused with clinical dose, where more than one actuation may be specified.

- **Coarse/Fine/Extra-fine Mass (CPM, FPM, EPM)**
  - Mass of sub-fractions representing defined ranges in terms of particle size.

- **Coarse/Fine/Extra-fine Mass Fractions (CPF, FPF, EPF)**
  - Mass of relevant sub-fraction divided by TEM.
Particle Specifications

- **Aerodynamic Particle Size Distribution (APSD)**
  - Particles 2-5 µm have the greatest potential for lung deposition.
    - Likely to be related to clinical response.
  - Extra-fine particles (<1.1 µm) may escape deposition and be exhaled.
  - Course particles (>4.7 µm) deposit in laryngeal and oropharyngeal region
    - No clinical benefit for airway drugs.
Particle Specifications

• **Respirable Mass (RM)**
  
  – Total mass of drug product likely to penetrate and deposit on receptors in the proximal and distal airways.

  – Generally defined as particles recovered between 0.4 - 4.7 µm.
Variability Considerations

- Dose uniformity from a specific device.
- Mass delivered per actuation.
- Inter-sample variability.

Choose adequate sample size to demonstrate...
- Variability in individual device samples do not noticeably affect the particle specifications.
- Develop appropriate level of confidence for particle specifications overall.
Tests For Add-Ons

• Spacers or holding chambers often impact the performance characteristics of the device.

• Compare base device with add-on to base device without add-on.
  – Respirable mass should be comparable.
  – Identify source of variability.
Facemask Tests

• Achieving a seal between facemask and face is critical for effective medication delivery.
  – Measure dead space between mask and face.
  – Inhalation valve movement indicator provides user reassurance of seal.
Test Report Components

- Original nebulizer dose volume.
- Quantity of drug recovered on each plate of the impactor, throat, and outlet filter in addition to the “dead volume.”
- Drug mass recovered in course, fine, extra-fine size ranges.
- Drug mass recovered in the respirable size range.
- Mass median aerodynamic diameter (MMAD) of the particles.
- Geometric standard deviation of the MMAD.
- Graphic depiction of quantity of particles of each size range.
Limitations of In Vitro Testing

• Results with every patient and disease condition cannot be defined.

• Tests can therefore only mimic a limited number of representative (i.e. commonly encountered) conditions.
Need For More Clinically Relevant Tests

- Breathing pattern influences particle motion in the airways, affecting deposition.
- Delay between device actuation and inhalation reduces delivered dose.
- If a facemask is needed, imperfect sealing between facemask and face can prevent effective medication delivery.
Variable Flow Rate Testing

• Problem: Breathing pattern influences particle motion in the airways, affecting deposition.

• Solution: Determine emitted dose of delivery device connected to a breathing simulator.

  – Use representative breathing patterns for patient populations.
    • Tidal Volume, Frequency, I/E Ratio, Minute Volume

  – Determine ED by filter collection at patient interface.
Variable Flow Rate Testing

• 2-Step Procedure
  – Time actuation to onset of inhalation.
  – Time actuation to onset of exhalation.
    • Indicates dose available to patient unable to coordinate actuation and inhalation properly.
    • Indicates how device may perform in clinical use.
Delayed Aerosol Particle Size Distribution (APSD) Measurements

• Problem: Delay between device actuation and inhalation reduces delivered dose.
  – By gravitational sedimentation.
  – Leakage or air ingress into holding chamber.

• Solution: Incorporate brief delay for APSD measurement using a no delay condition as a benchmark.
Simulations: Facemask Testing

- **Problem:** If a facemask is needed, imperfect sealing between facemask and face can prevent effective medication delivery.

- **Solution:**
  - Model realistic facial features including soft tissues where facemask makes contact.
  - Model upper respiratory tract.
Simulations: Facemask Testing

SAINT 9-mo. infant model
Janssens et al. JAM 2001;14:433-441

2-yr. child model
Smaldone et al. JAM 2005;18:354-363

infant face

small child face
Human Factors & Usability

• Step 1: Identify potential device- and user-related risks.
• Step 2: Propose mitigations, safety features and/or labeling warnings.
• Step 3: Test adequacy of proposed mitigations and safety features.

❖ Human factors testing should be complete prior to final pivotal studies.
Additional Considerations

• **Biocompatibility**
  - ISO 10993-1: Biological Evaluation of Medical Devices
  - Level of testing relates to duration and level of patient contact.
  - Example: Mouthpiece is a surface device, skin-contacting.
  - Cytotoxicity, sensitization, irritation tests required for material.

• **Electrical & Mechanical Safety**
  - IEC 60601-1: Medical Electrical Equipment – Part 1: General Requirements for Safety
  - IEC 60601-1-2: Medical Electrical Equipment – Electromagnetic Compatibility: Requirements and Tests

• **Software**
  - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
Key Points

• Drug-specific devices are regulated by CDER via the IND/NDA pathway.

• The particle specifications of the drug should be validated and characterized by cascade impaction tests.

• Final release version of the device should be used in the pivotal study.
Closing Remarks

• The evaluation of nebulization systems is a multifaceted process.
  – Incorporates regulations, standards, risk analysis.
• FDA strives to work cooperatively with manufacturers to ensure safety and efficacy of new devices.
• Guidelines and regulatory practice adapt as necessary to best serve the rapidly-evolving respiratory drug delivery field.
References

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- Guidance for Industry and FDA Staff: How to Write a Request for Designation (RFD)
  http://www.fda.gov/oc/combination/howtowrite.html
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  http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.htm
- Code of Federal Regulations (21 CFR 868.5630)
- Reviewer Guidance For Nebulizers, Metered Dose Inhalers, Spacers and Actuators
  http://www.fda.gov/cdrh/ode/784.html
- FDA General Program Memorandum #G95-1: Required Biocompatibility Training and
  Toxicology Profiles for Evaluation of Medical Devices
  http://www.fda.gov/cdrh/ode/g951.html
- Guidance for the Content of Premarket Submissions for Software Contained in Medical
  Devices
Questions?