Respiratory Drug Delivery Devices

A CDRH Perspective

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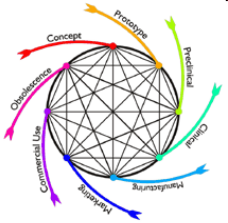
Disclosure

This speaker has had no financial arrangement or affiliation or other beneficial interest with any products or firms relevant to the discussions at this workshop.

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



Ensuring the Health of the Public Throughout the Total Product Life Cycle -- It's Everybody's Business

CDRH Mission

- Promote and protect the health of the public.
  - Bring safe and effective medical devices to the market as quickly as possible…

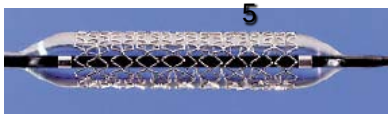
  - …while ensuring that devices and radiological products currently on the market remain safe and effective.

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

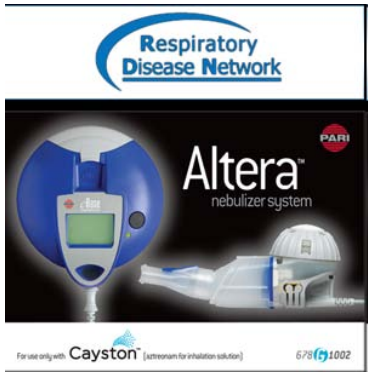
General Purpose Device

- 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.

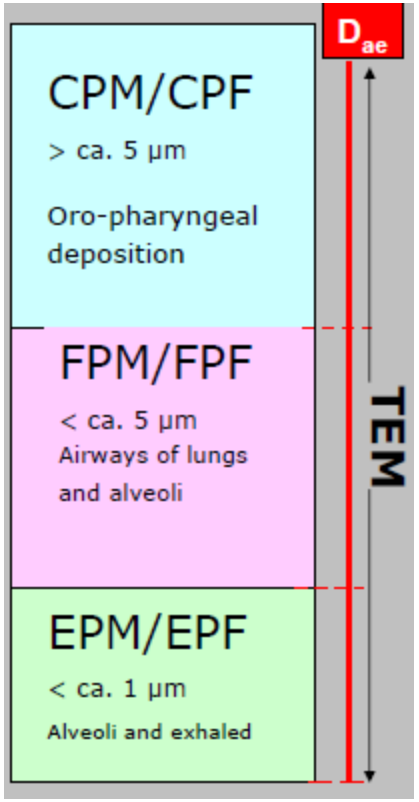
❖ Laser diffraction is currently not accepted by CDRH.

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.

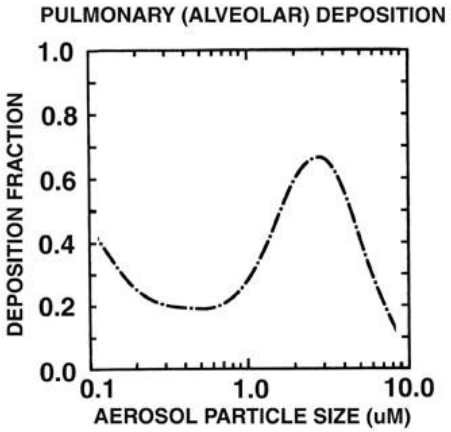
Particle Specifications

- **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.

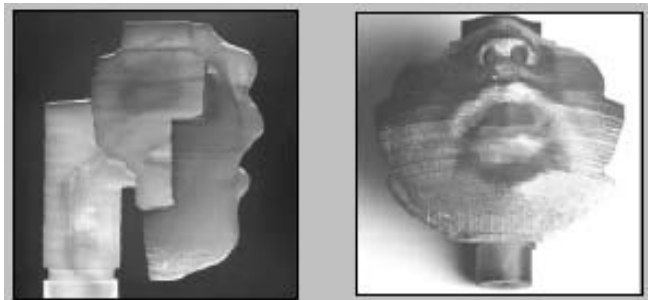
- Solution: Incorporate brief delay for APSD measurement using a no delay condition as a benchmark.

Simulations: Facemask Testing

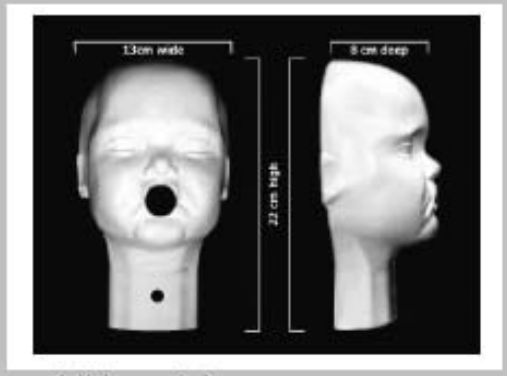
- Problem: If a facemask is needed, imperfect sealing between facemask and face can prevent effective medication delivery.

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

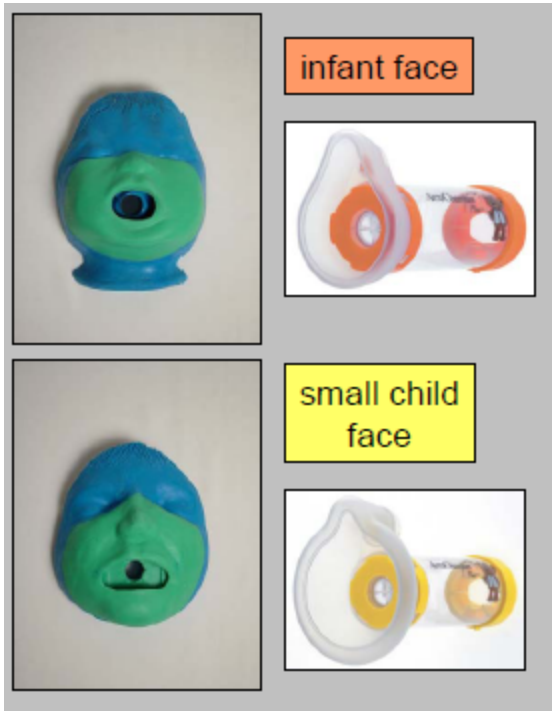
Simulations: Facemask Testing



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



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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  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=868.5630
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- FDA General Program Memorandum #G95-1: Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices
  http://www.fda.gov/cdrh/g951.html
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Questions?