

*Orally Inhaled and Nasal Drug Products (OINDP) Subcommittee
of the Advisory Committee for Pharmaceutical Sciences
Rockville, Maryland
April 26, 2000*

**Dose Content uniformity:
Current Practices for NDAs**

Guirag Poochikian, Ph.D.

Chemistry Team Leader

Division of Pulmonary and Allergy Drug products

Center For Drug Evaluation and Research

Food and Drug Administration

Published Draft Guidances

- **Background**
- **Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug products**
Chemistry, Manufacturing, and Controls Documentation
- **Nasal Spray and Inhalation Solution, Suspension, and Spray Drug products**
Chemistry, Manufacturing, and Controls Documentation

<http://www.fda.gov/cder/guidance/index.htm>

Guidance Philosophy

- Sets forth approaches acceptable to the Agency for submission of CMC information
- Represents Agency's current thinking on CMC documentation for inhalation drug products
- Alternative approaches may be used
- Encourages discussion with Agency division for significant departures
- Does not create or confer any rights for or on any person and does not operate to bind FDA or the public

Activities Since Publication of the Draft Guidances

- Public Comments on MDI and DPI Drug Products Guidance (March 1999)
- AAPS/FDA/USP Workshop (June 3-4, 1999)
- Public Comments on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Guidance (September 1999)
- OINDP Subcommittee (November 1999)

Scope - Drug Products Covered by Guidances

- **Inhalation Aerosols (MDIs)**
- **Nasal Aerosols**
- **Inhalation Powders (DPIs)**
- **Nasal Powder**

- **Inhalation Solutions**
- **Inhalation Suspensions**
- **Inhalation Sprays**
- **Nasal Sprays**

Dose Content Uniformity

- **Unit-to-Unit dose content uniformity within a batch (Inter-unit/Intra-batch)**
- **Dose-to-Dose content uniformity within a unit or container (Intra-unit)**
- **Batch-to-Batch dose content uniformity (Inter-batch)**

FDA DCU for MDIs/DPIs

- **1st Tier (10 MDIs/DPIs, 1 determination each):**
 - NMT 1 determination outside 80-120% target emitted dose
 - None outside 75-125%
 - Mean within 85-115%
- **If 2 or 3 determinations outside 80-120%, none outside 75-125%, and the mean within 85-115%, then,**
- **2nd Tier (20 additional MDIs/DPIs, 1 determination each):**
 - NMT 3 determinations (n = 30) outside 80-120%
 - None outside 75-125%
 - Mean within 85-115%

FDA DCU Through Container Life (MDI/DPI)

- **1st Tier (3 MDIs/DPIs, 1 determination each; B, M, E) :**
 - **NMT 1 determination (n = 9) outside 80-120% target emitted dose**
 - **None outside 75-125%**
 - **Means for each B, M, E within 85-115%**
- **If 2 or 3 determinations outside 80-120%, none outside 75-125%, and each mean within 85-115%, then,**
- **2nd Tier (6 add. MDIs/DPIs, 1 determination each, B, M, E):**
 - **NMT 3 determinations (n = 27) outside 80-120%**
 - **None outside 75-125%**
 - **Means for each B, M, E, within 85-115%**

Dose Content Uniformity Testing - “Ideal Conditions”

- **Specified storage conditions and orientation before testing**
- **Trained personnel (e.g., uniform shaking, duration, cleaning, actuation force)**
- **Units are fully primed**
- **Specified testing conditions (e.g., flow rate and duration)**

Categories of Public Comments for DCU Specifications

- Actual specifications for DCU should not be incorporated into the guidance. “(Note that each drug is unique with respect to the capabilities and reproducibility of the manufacturing process, device components, and analytical methodology and that these parameters should be considered in establishing appropriate specifications)”

Categories of Public Comments for DCU Specifications (Cont'd)

- Establish a process by which DCU specifications may be determined on a case-by-case basis.
- Retain guidance specifications, but widen the individual dose acceptance criteria.
- Retain guidance specifications, but delete mean criterion for the first tier.
- Provide a process for setting DCU specifications using statistical procedures.