M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 6, 2001

To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: Chemistry, Manufacturing and Control Recommendations

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation:	Chemistry, Manufacturing and Control Recommendations
Presented for:	Henry Stuart Conference
Date Presented:	March 30, 2000
Presented by:	Allen Rudman, Ph.D. Deputy Director, DC1
Number of Pages:	10

Melissa Lamb

Attachment

90S-0308

M697

Chemistry,Manufacturing and Control Recommendations

Allen Rudman, Ph.D.
Deputy Director, DC I
Office of Generic Drugs
CDER/FDA

Henry Stuart Conference
March 30, 2000

Components and Composition

- Components: All active and inactive ingredients, including those that are removed in processing
- For MDI's the inactive ingredients are recommended to be qualitatively and quantitatively the same as the RLD.
- Overfill (#doses) is typically allowed only if RLD has the same.

Active Pharmaceutical Ingredient

- Detailed evaluation of the manufacturing procedures as well as the specifications (tests, methods, limits) used to ensure the identity, strength, quality, purity and stability of the drug substance.
- Guidance for Industry, ANDA's: Impurities in Drug Substances.

Components and Composition

- Drug Substance: Description, LOD, ROI, assay, melting range/DSC, optical rotation, identification, water content, solvents/OVI's, heavy metals, particle size, crystal form, impurities
- Propellants: Specifications may be tighter than USP

Manufacturing

- Bio/stability batch needs to be at least 10% of proposed commercial batch and at least 5000 units.
- Copies of the executed batch record and proposed commercial size batch record.

Container/Closure/Metering System

- All components of container/closure/metering system need to be identified by source, composition, and design including schematic drawings with precise measurements.
- Other information needed includes:
  - USP <87> and/or <88> Biological reactivity data
  - Identification and quantitation of extractables
  - Possible pharm/tox consult

Finished Dosage Form

- Appearance
- Identity
- Unit Content Assay - assay of 10 cans
- Net Contents - weight of formulation in cans
- Metering Performance - valve test
- Particle Size - multistage cascade impactor and microscope or twin impinger
- Impurities/Degradation Products
- Moisture Content

Finished Dosage Form

- Spray Pattern
- Leak Test
- Content Uniformity - CU between cans
- Number of Sprays in can - meeting unit spray assay
- Unit spray Assay - CU within can
- Microbial limits test
- Shot weight
- Internal Pressure
- Extractables

Stability

- 0,1,2,3 months data on product stored upright and inverted/horizontal at 40C/75%RH.
- Available long term data.
- Temperature Cycle Study - Product Cycled and tested between freezing and 40C.
- Commitment - First 3 commercial batches and at least 1 additional batch per year thereafter.

Future

- Guidance for Industry, MDI and DPI Drug Products, Chemistry, Manufacturing and Controls
- Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products
- Guidance for Industry, ANDA's: Impurities in Drug Products
- Guidance for Industry, ANDA's: Impurities in Drug Substances