

Material Variability-How Much? A Pharmaceutical Sponsor's Perspective

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Introduction

- Review materials typically used in OINDP and an example supply chain
- Considerations for the specification setting process
- How is variability introduced and how much variability is acceptable?
- How is variability addressed?
- Summary

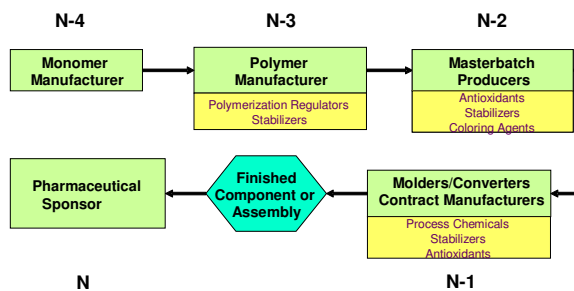


Materials Typically Used in Orally Inhaled and Nasal Drug Products (OINDP)

- **Plastics**
 - Housing/Container
 - Functional/mechanical components
 - Cosmetic components (e.g. color accents)
 - Foil laminates in packaging
 - Bags
- **Metals**
 - Housing/Container
 - Functional/mechanical components (e.g. springs, punches)
 - Foil in packaging
- **Elastomers**
 - Functional/mechanical components (e.g. seals, gaskets, check valves)
 - Ergonomic features (e.g. overmold)

OINDP Manufacturing Scenario

- The Supply Chain varies by:
 - Pharmaceutical Sponsor
 - OINDP



OINDP Examples

- Metered Dose Inhaler (MDI)
 - Description:
 - Coated metal container
 - Plastic/elastomer valve
 - Plastic actuator, mouthpiece, cap
 - Manufacture:
 - Device manufacture and release at Contract Manufacturer (CM)
 - Filling at CM
 - Product assembly and release at Pharmaceutical Sponsor (PS)



OINDP Examples

- Nebulizer
 - Description:
 - Liquid formulation in vial
 - Plastic reservoir with metal aerosol generator
 - Plastic housing, tubing, mouthpiece
 - Electromechanical components and housings
 - Manufacture:
 - Device manufacture and release at original equipment manufacturer (OEM)
 - Liquid fill and release at PS



OINDP Examples

- Dry Powder Inhaler (DPI)
 - Description:
 - Dry powder in capsule
 - Metal punch
 - Plastic device
 - Manufacture:
 - Device release by PS
 - Filling/Packaging of Capsules at CM
 - Assembly and release of product at PS

Material Specification Process

- Pkg/Device design requires specific physical and functional/mechanical attributes
- Pharmaceutical products require use of “safe” materials—OINDP are highest risk
- Specification includes:
 - Attribute
 - Test Method
 - Acceptance criteria

Typical Material Attributes

- Physical
 - Brittleness—Crystalline vs amorphous
 - Swelling—r-value
- Mechanical
 - Impact strength
 - Tear strength
 - Durometer (Test for Hardness)
- Chemical
 - Polymerization—level and type
 - Low level additives
 - Reaction by-products
 - Processing aids

Impact of Change in Material Attributes

- Physical
 - Shelf/use life and breakage rate
 - Device malfunction
 - Product protection
- Mechanical
 - Shelf/use life
 - Device malfunction
 - Dose repeatability
 - Physical harm to patient
- Chemical
 - Toxicity to patient
 - Change in dosage strength
 - Product adulteration

Introduction of Variability

- Material composition—change of ingredient or supplier
- Material processing—change of conditions or aids
- Component processing—change of conditions or finishing steps



Robustness of OINDP to Material Variability

- Physical and mechanical changes—
 - Range of variability tolerated similar to other industries
 - Material mfr published range is typically adopted
- Chemical changes—
 - Range of variability for known chemicals is typically not published
 - Variability associated with non-formulation chemicals is unknown
 - Range of variability tolerated is product dependent and typically assessed by L&E testing



Determination of Acceptable Chemical Variability

- Toxicity is unique to the individual chemical
- Risk-based evaluation of chemicals
 - Does it come in direct contact with the patient?
 - Volatile that may be inhaled
 - Absorbed by mucosa
 - What is the probability that it will leach into the dosage form?
 - Contact type and duration
 - At what level?
 - Controlled extraction studies
 - Simulated leachable studies
 - Product leachable studies



Determination of Acceptable Chemical Variability – Example 1

- Component: Mouthpiece
- Material: Polypropylene
- Chemical assessment:
 - Does it come in direct contact with the patient?
 - Yes, volatiles not likely
 - Saline extraction profile to identify chemical species
 - Toxicological evaluation
 - PP oligomers
 - Fatty acids
 - Antioxidants/additives
- Acceptance criteria based on historical test results



Determination of Acceptable Chemical Variability – Example 2

- Component: Seal
- Material: EPDM
- Chemical assessment:
 - Does it come in direct contact with the patient?
 - No, volatiles may be possible
 - What is the probability that it will leach into the dosage form?
 - Intermittent contact with liquid dosage form
 - Controlled extraction profile to identify chemical species
 - Toxicological evaluation
 - Elastomer oligomers
 - Antioxidants/additives/unintended additives (e.g. DEHP)
- Acceptance criteria based on historical test results

Determination of Acceptable Chemical Variability – Example 3

- Component: Piercing element
- Material: Stainless steel
- Chemical assessment:
 - Does it come in direct contact with the patient?
 - No, volatiles not likely
 - What is the probability that it will leach into the dosage form?
 - Momentary contact with dry powder dosage form
 - Controlled extraction profile to identify chemical species
 - Toxicological evaluation
 - Surface coatings
 - Residual chemicals from washing/passivation
- Acceptance criteria based on materials composition

Determination of Acceptable Chemical Variability



■ Possible Strategies:

- Retrospective—Limits based on clinical results
- Proactive—Historical test results on component incorporating expected material/processing variability over the life of the product
- Preemptive—Toxicologically acceptable levels of known chemical species in material/processing

Summary

- OINDP are categorized as having a high level of concern for patient safety and require high quality materials
- The supply chain is complex and variability can be introduced at several points
- Chemical variability is a primary concern for OINDP
- Allowances for variability typically are established based on historical test results
- A greater knowledge space of material chemical composition may allow greater flexibility in material variability