

Container Closure System Components

Composition and Selection

PQRI L & E Recommendations

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Introduction

Critical First Step

- Careful component selection
- Attention to formulation information

Allows the Pharma Development Team to:

- Obtain early information on types of potential extractables and leachables
- Develop a base of knowledge about the components which will help define selection of extraction technique(s)/method(s)
- Begin risk assessment on potential extractables/leachables
- Compare results of extraction studies with the component formulation as a check on the extraction technique(s)/method(s)

Second Critical Step

- Pharmaceutical Development Team must:
 - Determine the “critical components” of their product

Critical Components for OINDP

- Those that contact the patient (i.e., the mouth piece)
- Those that contact the drug formulation directly
- Those that effect the mechanics of the performance of the device
- Any necessary secondary protection packaging

Recommendations for Container Closure System Components

- The pharmaceutical development team should obtain all available information on the composition and manufacturing/fabrication processes for each component type to the extent possible, and determine which components are “critical.”
- Component formulation should inform component selection.
- Risk Assessment should be performed during the selection of components and materials.
- Extractables testing, including Controlled Extraction Studies and the development and validation of Routine Extractables Testing methods, should be accomplished for all critical OINDP components.

Component Information

- The Pharma Development Team should obtain all available information:
 - Composition
 - Manufacturing/fabrication processes for each component

Examples of This Type of Information

- The base elastomeric/polymeric material (e.g., high density polyethylene, butyl rubber, stainless steel)
- The additive composition of the component
 - Reaction/degradation chemistry
- Polymerization process plus associated polymerization/curing agents
- Fabrication process, including additives designed to assist in fabrication
- Cleaning/washing processes for finished components
- Storage/shipping environment for components and drug product

Ancillary Components

- Ancillary components required by the OINDP label and which are deemed critical:
 - Nebulizers
 - Spacers

Example of Critical Components for a MDI

- Canister
- Elastomeric seals
- Plastic valve components
- Metal valve components
- Mouth piece

Considerations in Component Selection

- Materials, when possible, should comply with accepted standards for food contact and/or generally recognized as safe (GRAS) materials
- Materials should meet the indirect food additive regulations in Title 21 of the Code of Federal Regulations (CFR), when possible

Considerations in Component Selection

- Components containing sources of known potent carcinogens or mutagens should be avoided/minimized, e.g.:
 - Polynuclear Aromatic Hydrocarbons (PNAs)
 - N-nitrosamines
 - Mercaptobenzothiozole (MBT)

Risk Assessment Should be Performed During the Selection of Components/Materials

- Sponsor should conduct risk assessment on the component based on supplier provided information
- Sponsor toxicologist should estimate worst-case Total Daily Intake (TDI) for ingredients
- Toxicologist can provide an estimate of risk were the components to appear in a leachables profile

Extractable Testing for Critical OINDP Components

- Extractables testing should be accomplished for critical OINDP components
 - Controlled extraction studies
 - Development and validation of routine quality control methods
 - Appropriate characterization and control of extractables profile in new patient-contact critical components should be completed

Examples Illustrating Recommendations

- Knowledge derived from component composition and risk assessment

Overview of Test Articles

- Working group started with test articles of known composition:
 - Polypropylene
 - Sulfur-cured elastomer
 - Peroxide-cured elastomer

Example Composition of Sulfur-cured Elastomer Test Article

Ingredient	Percent (W/W)
Calcined clay	8.96
Blane fix (barium sulfate)	25.80
Crepe	38.22
Brown sub MB	16.84
Carbon black MB	2.11
ZnO	4.04
2,2 Methylene-bis (6-tert-butyl-4-ethyl phenol)	0.56
Coumarone-indene resin	1.12
Paraffin	1.12
Tetramethyl thiuram monosulfide	0.11
Zinc 2 – mercaptobenzothiazole	0.29
Sulfur	0.84

Ingredients in Polypropylene Test Article

Chemical Name	Percent (W/W)
Tetrakis (methylene (3,5-di-t-butyl-4-hydroxy hydrocinnamate)) methane	0.08
Bis (2,4-di-t-butyl (phenyl) pentaerythritol diphosphite	0.05
Calcium stearate	0.03 – 0.4
Vegetable oil derived 90% alpha monoglycerides	0.3
3,4-dimethyldibenzylilene sorbitol	0.2

Considerations in Testing Sulfur-cured Elastomers

- Presence of carbon black – polynuclear aromatics (PNAs)
- Tetramethyl thiuram monosulfide and other curing agents – N-nitrosamines
- 2-mercaptobenzothiazole – special case compound needing special analytical investigation
- Paraffin and coumarone-indene resin – natural products likely to produce complex extractables/ leachables

Considerations in Testing Polypropylene

- High density polypropylene – high levels of soluble oligomers
- Chemical properties of additives such as Irganox 1010 – HPLC methods are indicated
- Complex chemical additives (e.g., Ultrinox 626) – desirable to obtain additives to facilitate identification
- No reason to suspect special case compounds so special analytical studies to characterize these types of entities are not needed

Summary

- No matter how detailed supplier information is, this does not preclude the need for comprehensive controlled extraction and leachable studies and appropriate risk assessment for safety