



Extractables in the Product Development Process

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Extractables in Materials for Inhalation & Nasal Drug Products
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Agenda / Objective

Agenda

▣ Design Controls

- Development Process & Role of Risk Assessment
- Validation & Verification
- Performance Testing/Characterization
- Finalize Specifications
- Customer Communication

▣ Filing DMFs : Whether/Why/How

- ▣ Basic understanding of the roles and documentation for development relevant to OINDP from a supplier standpoint

Quick Review

- ⌞ **These products, while mechanical functional in nature will most likely be filed as drug products**
- ⌞ **Often considered the primary packaging system (container closure), and / or, the delivery system**
- ⌞ **Will be filed with the Center for Drug Evaluation and Research not with the Center for Devices and Radiological Health**
- ⌞ **Will require a higher level of control and greater focus on the chemistry than a standard device**

Design Controls

- ⌞ **The product development process is most adequately described in 21 CFR §820.30 and ISO 13485:2003 Section 7.3**
- ⌞ **Regulations call for manufacturers to “establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met”** ^{21CFR §820.30(a)(1)}
- ⌞ **Provide requirements specifically around:**
 - Design Input & Design Output
 - Verification
 - Validation
 - Transfer
 - Design Review & Changes



Design Controls

↳ **Generally performed in stages:**

- Concept
- Development
- Verification
- Validation
- Transfer
- Commercialization

↳ **These development stages may occur without precise regard to the drug development and phases of clinical investigation**

Role of Risk Assessment

↳ **Risk assessment of some form is required universally by regulatory agencies**

↳ **Reference ISO 14971 Medical Devices – Applications of Risk Management to Medical Devices or GHTF/SG3/N15R8**

↳ **The risk consideration is multi-faceted for the pharmaceutical partner**

Role of Risk Management

▣ **Examples for the pharmaceutical partner based on extractable data:**

- Patient – Product safety in leachables determination and mouthpiece contact
- Product – quality and control of raw materials
- Process – risk of false results on the test method

▣ **Examples for the supplier partner based on extractable data:**

- Process – quality and control of materials
- Product – risk of false results on the test method

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Role of Risk Assessment

▣ **The patient/product risk is mitigated with extraction considerations for**

- Patient interface – oral/nasal pharynx contacting
- Drug Pathway – impact on leachables
- Air Pathway – impact to taste and smell

▣ **Multiple tools available for the assessment**

- FMEA / FMECA / Fault Tree analysis / SHUMA....

▣ **Supplier participation depends on responsibility**

- May require data to support the patient and product
- If assembling may have to produce a process risk analysis
- Consideration of failure identification and mitigations should be a part of all operations – possibly not as formal as in development

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Verification / Validation

- ⌞ **Verification – Does the output equal the input?**
- ⌞ **Validation – Does the product meet the intended use in the user environment?**

- ⌞ **Extractables is on the periphery of this in the product development cycle**
- ⌞ **Controlled extractions typically are used to meet verification or safety design inputs**
- ⌞ **There are validation activities with respect to the method validation and the component formation process validation (gauge r&Rs for instance)**

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Performance Testing / Characterization

- ⌞ **Preclinical → Phase 1 → Phase 2**
 - Documentation Available
 - GRAS certifications
 - DMFs available
 - TSE/BSE free statement
 - Controlled Extraction (Verification of Safety)
 - Routine Extraction Method Development
- ⌞ **Phase 2 → Phase 3**
 - Continue Method Development
 - Begin Method Validation

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Performance Testing / Characterization

└ **Phase 3**

- Finish Method Validation
- Propose Specifications

└ **Submission**

- Routine Control
- Revisit specifications
- Investigation of Out of Trend conditions

Finalize Specifications

└ **Begins with the intended use – the component part**

- Even if this has been completed for the raw material – the submission sponsor will need to consider the component part

└ **Moves into routine control**

└ **Requires a validated method**

└ **Will likely be visited in the submission review**

└ **May require revisiting the specifications as a result of regulatory queries**

└ **Variability is good – multiple lots, multiple runs, multiple raw material lots**

Customer Communication

- ⌞ Channels of communication need to remain open
- ⌞ Levels of communication will depend on who will be submitting and established responsibilities
- ⌞ Remember that everything will apply to the component stage
- ⌞ Regardless of the submission the sponsor will want to know the component specific information
- ⌞ The sponsor may be questioned with respect to the component, the extractables, and the process during the submission review process

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Extractables in the Product Development Process

DMF: Whether/Why/How

What is a DMF

- ⌞ **“A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs”**
- ⌞ **Provided for under 21 CFR § 314.420**
- ⌞ **DMFs are neither approved or disapproved**
- ⌞ **Has limited acceptance outside of the US**
- ⌞ **See Required Specifications for FDA’s IND/NDA/ANDA Drug Master File Binders for assembly information**

Pros & Cons of a DMF

- ⌞ **Pro**
 - Information is confidential
 - Information can be used against multiple filings
- ⌞ **Con**
 - The file must be created
 - The file must be maintained at a minimum annually
 - Changes to the file need to be communicated to all sponsors
 - Deficiencies to DMFs can put the DMF holder on the critical path to approval
- ⌞ **Pro & Con**
 - DMF owner is directly issued deficiencies and will need to correspond with the agency

Information for DMFs

⌋ **There is no specific regulation as to the content of a DMF**

⌋ **Consider following the regulation for the product**

- Contact and Administrative Information
- Development Activities
- Specification Development
- Specifications and Methods
- Process Development
- Manufacturing and Process Controls
- Example Batch/Lot Records
- Facility Information

Information for Extractables

⌋ **Traditional submissions will include the following information:**

- Method
- Method development at least to arrive at specifications
- Acceptance Criteria
- Sampling plan
- Test facility information
- Sample scans
- Any significant safety information

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Extractables in the Product Development Process

Back-up Slides

Abbreviations

- ⌞ **FMEA – Failure Modes and Effects Analysis**
- ⌞ **FMECA – Failure Modes and Effects Criticality Analysis**
- ⌞ **GHTF – Global Harmonization Task Force**
- ⌞ **OINDP – Orally Inhaled and Nasal Drug Product**
- ⌞ **SHUMA – Systems Hazard User-Misuse Analysis**

References

- u **21 CFR § 820 Quality System Regulation**
- u **ISO 13485:2003 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes**
- u **ISO 14971:2000 Medical devices – Application of Risk Management to Medical Devices**
- u **“Guideline for Drug Master Files”, CDER, September 1989**
 - <http://www.fda.gov/cder/guidance/dmf.htm>
- u **“Required Specifications for FDA’s IND, NDA, ANDA, Drug Master File Binders”, CDER**
 - <http://www.fda.gov/cder/ddms/binders.htm>
- u **GHTF/SG3/N15R8 “Implementation of risk management principles and activities within a Quality Management System” May 20, 2005**