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Expectations for Extractables

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IPAC-RS Supplier QC Guideline Training Session
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According to the GMP Guideline...

◆ Section 7.3.1.1

- “The supplier shall interface with the customer to aid them in determining and demonstrating the fitness for use of the product with respect to performance features...The component(s) should be shown to...maintain stability with respect to...the following relevant properties...as applicable:
 - Chemical characteristics...
 - Extractables...”

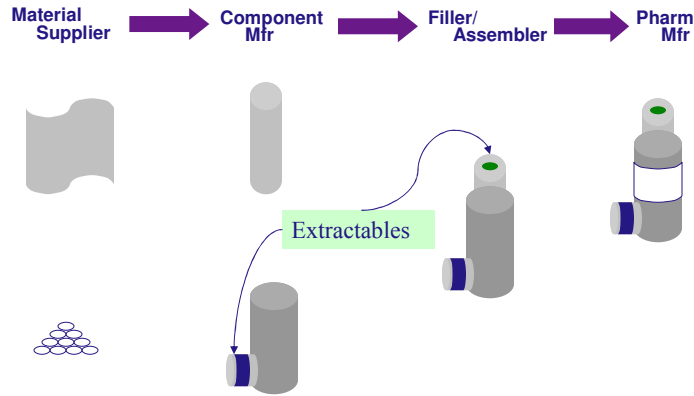
◆ Section 8.2.4.3

- “The purpose of the controlled extraction study is to
 - define an acceptable quantitative extractable profile
 - develop methods for routine control of extractables
 - establish acceptance criteria for a raw material or component”

◆ Section 8.2.4.4

- “The OINDP component supplier and OINDP manufacturer should work together to develop component extractables testing protocols”
- “Extractables testing should be performed...
 - On those components that contact...drug product and/or the patient’s mucosa
 - During design and development and for routine release testing”

The Manufacturing Process & Extractables



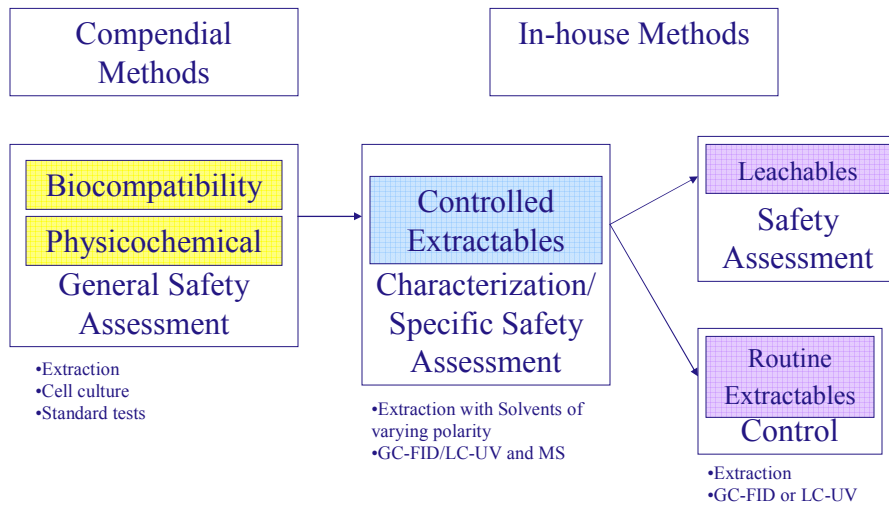
Sources: Polymer, Additives, Ambient Contaminants, Processing Aids

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Extractables Evaluation for OINDP



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The Controlled Extraction Study

◆ To be conducted by:

- OINDP Manufacturer, or
- OINDP Supplier, or
- OINDP Manufacturer with assistance from the Supplier

Manufacturer

- Identify Critical Components
- Obtain Controlled Extraction Info
- Evaluate Extractables
- Correlate Extractables to Leachables

Supplier

- Be Aware of Critical Components
- Provide Process/Composition Info
- Recommend Targets

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Controlled Extraction—Sample Preparation

◆ Solvent Recommendations from PQRI

- Represent drug product
 - MDI—methylene chloride
 - Inhalation Solution—water
- Non-reactive (e.g. not EtOH or MeOH unless justified)
- Range of polarities to maximize profile coverage
 - Methylene chloride
 - IPA
 - Hexane

◆ Extraction Techniques

- Soxhlet or Reflux
- Sonication or Sealed Container
- Instrument based—ASE, SFE, microwave

◆ Conditions

- Maximize extraction and minimize artifacts
 - Temperature
 - Time



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Controlled Extraction—Evaluation

◆ Analytical Techniques

- LC/MS
- GC/MS



◆ Quantitative Analysis

- Optimized extract preparation
- Confirm extractables identification
- Guided by Analytical Evaluation Threshold (AET)—see PQRI recommendations
 - Based on Safety Concern Threshold for OINDP (0.15 µg/day)
 - ~10 µ g/g for components not in continuous contact with the drug

◆ Safety Evaluation

- List of identified compounds
- Toxicological assessment
- AET/SCT does not apply to special class compounds (PNAs, nitrosamines, mercaptobenzothiazoles)

Ref: PQRI Leachables and Extractables Working Group, *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products* (2006). Internet: http://pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

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Controlled Extraction Study Example

- ◆ Material: Polypropylene
- ◆ Solvents: Water, EtOH, IPA, Hexane
- ◆ Extraction Technique: Reflux
- ◆ Analytical Techniques: LC/MS, GC/MS

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Controlled Extraction Study Example

- ◆ Results—List of Identified Compounds (partial list shown for illustration purposes)

Compound	Solvent	Retention Time (min)	Instrument	CAS#	Amount (µg/g)
Palmitic acid	50/50	17.7	LC-MS	57-10-3	0.3
	Water:EtOH				2.2
	Ethanol				2.2
PBHC	Hexane	21.4	LC-MS	6683-19-8	5.7
	Isopropanol				7.6
	Isopropanol				7.6
Stearic acid	50/50	19.0	LC-MS	57-11-4	0.2
	Water:EtOH				201
THBT	Hexane	19.9	LC-MS	27676-62-6	6.4
	Ethanol				6.4
Tris phosphate	50/50	22.8	LC-MS	95906-11-9	0.3
	Water:EtOH				4.9
	Ethanol				4.9
Tris phosphite	Hexane	27.8	GC-MS	31570-04-4	6.3
	Isopropanol				8.8
	Isopropanol				5.0

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Routine Control of Extractables

- ◆ **To be conducted by:**

- OINDP Manufacturer, or
- OINDP Supplier, or
- OINDP Manufacturer with assistance from the Supplier

Manufacturer

- Ensure proper system of controls: In-process, supplier verification, routine extractables
- Identify targets based on safety evaluation
- Ensure methods are appropriate
- Establish acceptance criteria

Supplier

- Implement controls including considerations of processing environment related to extractables
- Identify targets based on composition knowledge
- Support method development
- Support development of acceptance criteria

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Routine Control of Extractables

◆ Method Development

- Quantitative and qualitative
- Based on Composition Information, Controlled Extraction and Leachables Results
- Requirements vary:
 - dependent on clinical phase of product
 - based on product type
 - extractables levels present (content vs. limit test)
 - nature of targets (volatility, chromophore, etc)

◆ Method Validation

- Follow ICH Q2

◆ Lot Testing

- Allow for variability in lot manufacture, different test labs

◆ Acceptance Criteria

- Confirm Critical component consistency is maintained
 - Quantified target compounds appropriate to material of construction
 - Qualitative profile comparability to material used in clinic
- Enable detection of new extractables that result from changes in material/ process

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Routine Control of Extractables-Example #1

◆ Material: EPDM

◆ Method: HPLC-UV

◆ Lot Testing—managed by OINDP Manufacturer

- 15 lots

◆ Acceptance Criteria—set in collaboration with Supplier

- Profile
- Two quantified compounds

◆ Routine Testing—managed by Supplier

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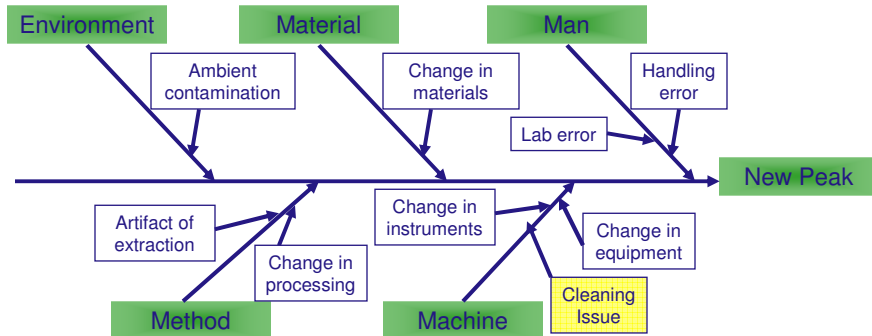
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Routine Control of Extractables-Example #1

◆ **Issue: new peak**

◆ **Sequence of events:**

- Notification from lab to supplier
- Peak identification
- Ishikawa root cause analysis:



◆ **Resolution: Maintenance/cleaning procedure implemented**

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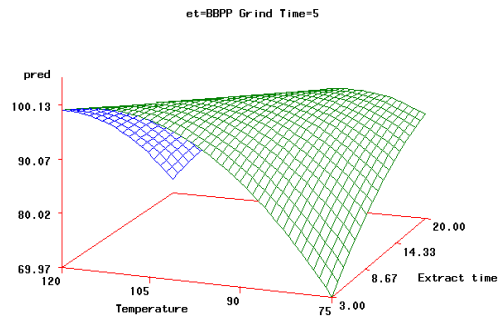
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Routine Control of Extractables-Example #2

◆ **Issue: new polypropylene material**

◆ **Existing Method: HPLC-UV**

- Extract preparation revised using DOE
- Analytical conditions maintained



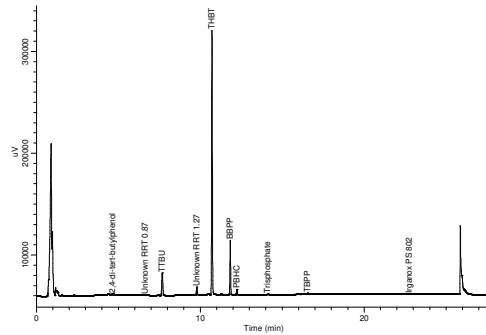
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Routine Control of Extractables-Example #2

- ◆ **Lot Testing—OINDP mfr arranged with Supplier**
 - 10 lots, DOE with supplier
- ◆ **Acceptance Criteria—set in collaboration with Supplier**
 - Profile
 - One quantified compound
- ◆ **Routine Testing—managed by Supplier**
- ◆ **Resolution: new material successfully incorporated**



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Summary

- ◆ Extractables evaluation is expected for drug/mucosal contacting components
- ◆ Controlled extraction studies inform Leachables and Routine Control of Extractables
- ◆ Routine Control of Extractables is only one part of a comprehensive system of manufacturing controls
- ◆ Suppliers and OINDP Manufacturers are expected to collaborate on extractables testing from design through routine control

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