Extractables – Characterization and Control

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Quality-by-Testing (QbT) – The Current Paradigm

- Selection of OINDP container closure system components and materials of construction often based on price, availability, and apparent functionality.
- Specifications and acceptance criteria for each component type developed using carefully developed and validated analytical test methods and comprehensive test parameter databases (e.g. extractables levels).
- Individual component batches tested and released for drug product manufacture based on these specifications and acceptance criteria.

Quality-by-Design (QbD) – The New Paradigm

- "QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality."

  Yu (2006)

- "A systematic scientific approach to product and process design and development."

  Nasr (2006)

Quality-by-Design (QbD) Concepts

In a QbD system:

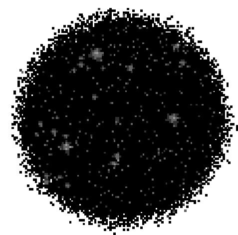
- The product is designed to meet patient requirements.
- The process is designed to consistently meet product critical quality attributes.
- The impact of starting materials and process parameters on product quality is understood.
- Critical sources of process variation are identified and controlled.
- The process is continually monitored and updated to allow for consistent quality over time.

Nasr (2006)

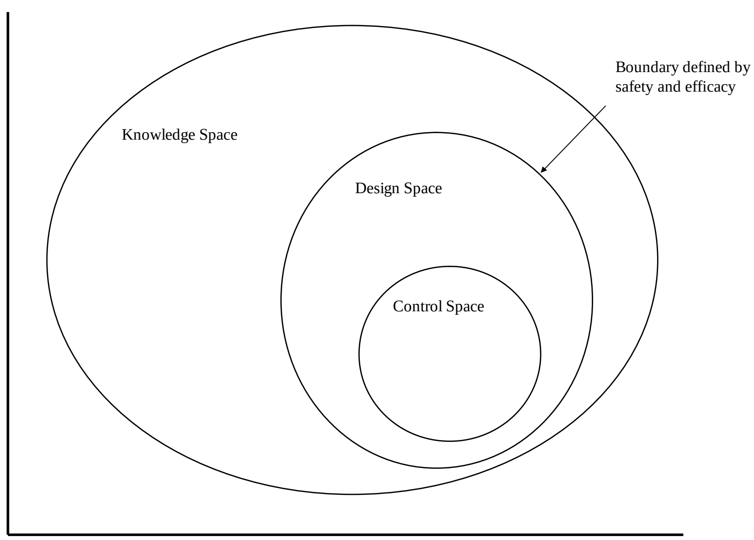
Design Space - Concept

- "The multidimensional combination and interaction of design input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Design space is proposed by the applicant and is subject to regulatory assessment and approval."

ICH Q8 (November 2005); Nasr (2006)



Schematic of the Quality by Design "universe"



Summary Points from Concepts

- Define the “Design Space”
- Control the “Design Space”
- Come to an agreement (i.e. get regulatory approval)

CMC Supplier Quality Control Technical Team

- *Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products* (2006)
  - Quality Management System
  - Management Responsibility
  - Resource Management
  - Product Realisation
  - Measurement Analysis and Improvement
  - Contamination Control

Definition and control of “Design Space”

PQRI - Best Practices Overview

- Application of safety thresholds
  - Ø Safety Concern Threshold (SCT)
  - Ø Qualification Threshold (QT)
- Integration of safety expertise into component selection, controlled extraction studies, leachables studies and routine extractables testing
- Analytical/chemistry
  - Ø Selection of components
  - Ø Controlled Extraction Studies
  - Ø Leachables Studies and Routine Extractables Testing
  - Ø The Analytical Evaluation Threshold (AET)

Definition and control of "Design Space"

Component Selection - Summary of Best Practice Recommendations

- *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," before beginning extractables and leachables studies on a given OINDP and its associated container/closure system components.*
- *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 Selection - Information Required

- The elastomeric/polymeric or other material constituting the principal structure of the component (e.g., High Density Polyethylene, Ethylene-Propylene-Diene rubber, stainless steel, etc.)
- The polymerization/cross-linking/curing process, or processes, for the component base polymer, including any chemical additives employed.
- The compounding/fabrication process, or processes, including any additives designed to assist in compounding/fabrication.
- All individual chemical additives/ingredients in the component, including the composition and chemistry of each individual additive.
- Any cleaning/washing processes for finished components, including knowledge of cleaning, washing, or other agents.
- The storage/shipping environment for both components and drug product, if the potential for environmental leaching exists.

Controlled Extraction Study

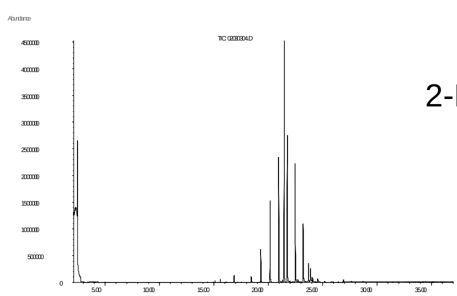
Definition:
A laboratory investigation into the qualitative and quantitative nature of extractables profiles from critical components of an OINDP container/closure system

Purpose:
To systematically and rationally identify and quantify potential leachables, i.e. extractables, to the extent practicable, and within certain defined analytical threshold parameters

Best Practice Recommendations

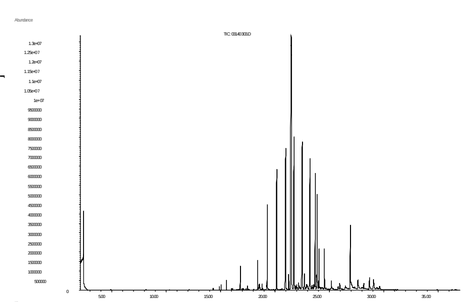
- *Controlled Extraction Studies should employ vigorous extraction with multiple solvents of varying polarity.*
- *Controlled Extraction Studies should incorporate multiple extraction techniques.*
- *Controlled Extraction Studies should include careful sample preparation based on knowledge of analytical techniques to be used.*
- *Controlled Extraction Studies should employ multiple analytical techniques.*
- *Controlled Extraction Studies should include a defined and systematic process for identification of individual extractables.*
- *Controlled Extraction Study "definitive" extraction techniques/methods should be optimized.*
- *During the Controlled Extraction Study process, sponsors should revisit supplier information describing component formulation.*
- *Controlled Extraction Studies should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety evaluation threshold.*
- *Polyaromatic Hydrocarbons (PAH's; or Polynuclear Aromatics, PNA's), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are considered to be "special case" compounds, requiring evaluation by specific analytical techniques and technology defined thresholds.*
- *Qualitative and quantitative extractables profiles should be discussed with and reviewed by pharmaceutical development team toxicologists so that any potential safety concerns regarding individual extractables,* i.e. *potential leachables, are identified early in the pharmaceutical development process.*

Controlled Extraction Study Example – Elastomer GC/MS Analysis

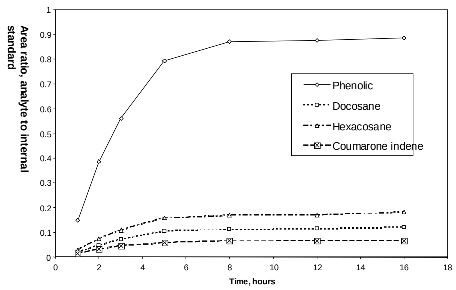


2-Propanol Sonication

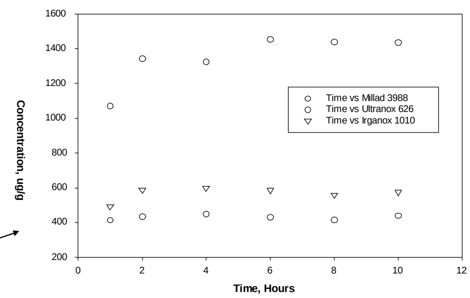
2-Propanol Soxhlet



Asymptotic Levels



Methylene Chloride Soxhlet Extraction of Sulfur-Cured Elastomer



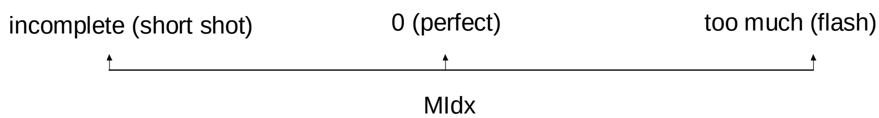
2-Propanol Reflux Extraction of Polypropylene

Routine Extractables Testing – Summary of Best Practice Recommendations

- *A comprehensive correlation between extractables and leachables profiles should be established.*
- *Analytical methods for Routine Extractables Testing should be based on the analytical technique)s)/method(s) used in the Controlled Extraction Studies.*
- *Routine Extractables Testing should be performed on critical components using appropriate specifications and acceptance criteria.*
- *Polycyclic Aromatic Hydrocarbons (PAH's; or Polyaromatics, PNA's), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are considered to be "special case" compounds, requiring evaluation by specific analytical techniques and technology defined thresholds for ….Routine Extractables Testing.*

Initial Design Space – inadequate (from Barker, 1990)

FACTOR	SET-POINT (working range)	STD. DEV.
Temperature (°F)	525 (500-550)	25
Pressure (psi)	1100 (1000-1200)	50
Time (sec)	0.85 (0.85-1.2)	0.01
Gate Size (in)	0.25 (0.2-0.3)	0.03
Resin Melt Index	17.5	2.5
Average MIdx	-0.875	0.92



Full Factorial Configuration Experimental Design (from Barker, 1990)

tc	Temp	Press	Time	Gate
(1)	500	1000	0.85	0.2
a	550	1000	0.85	0.2
b	500	1200	0.85	0.2
ab	550	1200	0.85	0.2
c	500	1000	1.2	0.2
ac	550	1000	1.2	0.2
bc	500	1200	1.2	0.2
abc	550	1200	1.2	0.2
d	500	1000	0.85	0.3
ad	550	1000	0.85	0.3
bd	500	1200	0.85	0.3
abd	550	1200	0.85	0.3
cd	500	1000	1.2	0.3
acd	550	1000	1.2	0.3
bcd	500	1200	1.2	0.3
abcd	550	1200	1.2	0.3

First Noise Matrix
(from Barker, 1990)

Run#	Temp	Press	Time	Gate	MI	MIdx
1	475	950	.84	.23	20	-2.7
2	525	950	.84	.17	15	-2.4
3	475	1050	.84	.17	20	-1.7
4	525	1050	.84	.23	15	-1.4
5	475	950	.86	.23	15	-4.1
6	525	950	.86	.17	20	-1.8
7	475	1050	.86	.17	15	-3.1
8	525	1050	.86	.23	20	-0.8

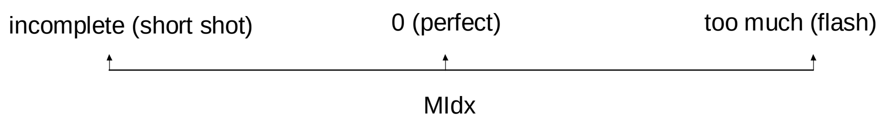
MIdx Average = -2.25
S/N (T) = 11.6

Final Experimental Data
(from Barker, 1990)

tc	Temp	Press	Time	Gate	MIdx	S/N(T)
(1)	500	1000	0.85	0.2	-2.25	11.6
a	550	1000	0.85	0.2	-0.75	18.4
b	500	1200	0.85	0.2	-0.25	18.6
ab	550	1200	0.85	0.2	1.25	15.5
c	500	1000	1.2	0.2	-0.50	18.6
ac	550	1000	1.2	0.2	1.00	17.1
bc	500	1200	1.2	0.2	1.50	14.1
abc	550	1200	1.2	0.2	3.00	9.5
d	500	1000	0.85	0.3	-2.25	11.8
ad	550	1000	0.85	0.3	-0.75	19.3
bd	500	1200	0.85	0.3	-1.75	13.4
abd	550	1200	0.85	0.3	-0.25	20.8
cd	500	1000	1.2	0.3	-0.50	19.6
acd	550	1000	1.2	0.3	1.00	17.8
bcd	500	1200	1.2	0.3	0.00	19.8
abcd	550	1200	1.2	0.3	1.50	14.8

Final Optimized Process (from Barker, 1990)

FACTOR	SET-POINT	STD. DEV.
Temperature	550	5
Pressure	1000	50
Time	1.0	0.01
Gate Size	0.30	0.01
Resin Melt Index	17.5	2.5
Average MIdx	0	0.22



Summary Points from "Design Space" Example

- In theory, 128 separate production runs would be required to optimize this Design Space for 1 quality attribute with 4 defining variables.
- Consider the quality attribute: "<10ppb of any individual target N-nitrosamine in an elastomeric MDI valve component".
  - Define the design space
  - Anyone??????

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Thank you for your interest and attention!!!!!