

Routine Control of Extractables

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Definition Review

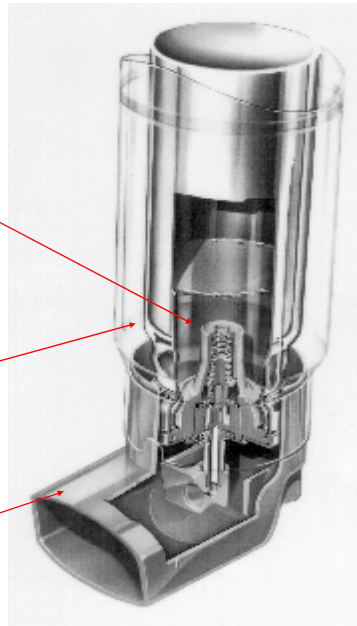
- *Routine Extractables Testing* is the process by which OINDP container closure system critical components are qualitatively and quantitatively profiled for extractables, either for purposes of establishing extractables acceptance criteria, or release according to already established acceptance criteria.

Critical Components

“Critical components” of an OINDP container closure system are defined as those that contact either the patient or the formulation, components that affect the mechanics of the overall performance of the device, or any necessary secondary protective packaging.”

MDI “Critical Components”

- Dose metering valve
 - Metering chamber
 - Stem(s)
 - Seals/gaskets
 - Sealing rings
- Canister
 - Coated?
- Mouthpiece/actuator



MDI Schematic Provided by Bespak Europe

DPI (Dry Powder Inhaler)

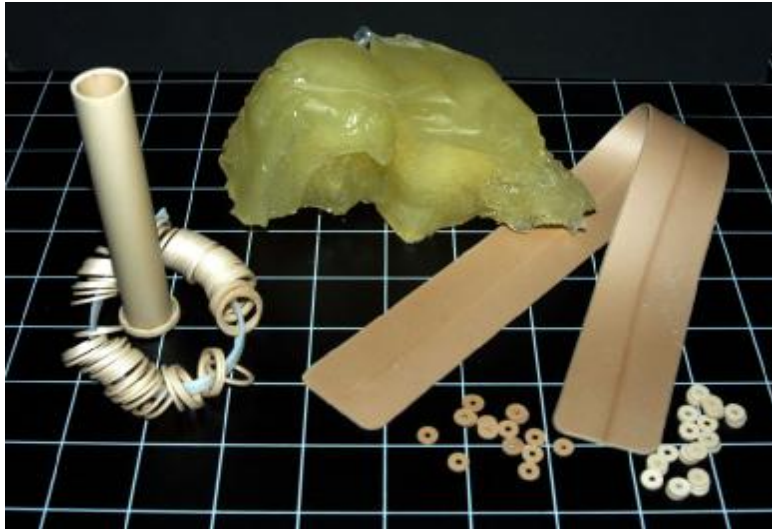


Images provided by Bespak Europe

OINDP Container Closure System Components



Raw Materials – Supply Chain



Raw Materials - Supply Chain



Component Fabrication

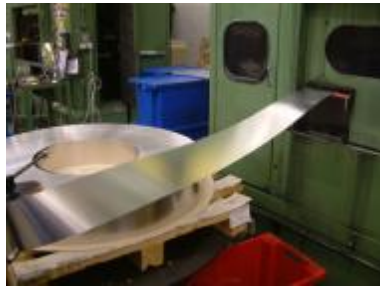
Images provided by Bespak Europe



Moulding machines



Deep Drawing Process



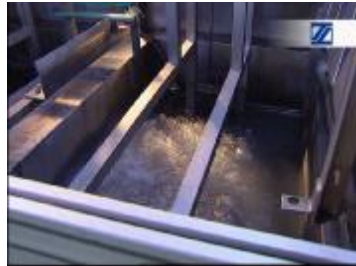
metal rolls

deep-drawing tool



Images provided by Presspart

Deep Drawing Process



Images provided by Presspart

← degreasing process →

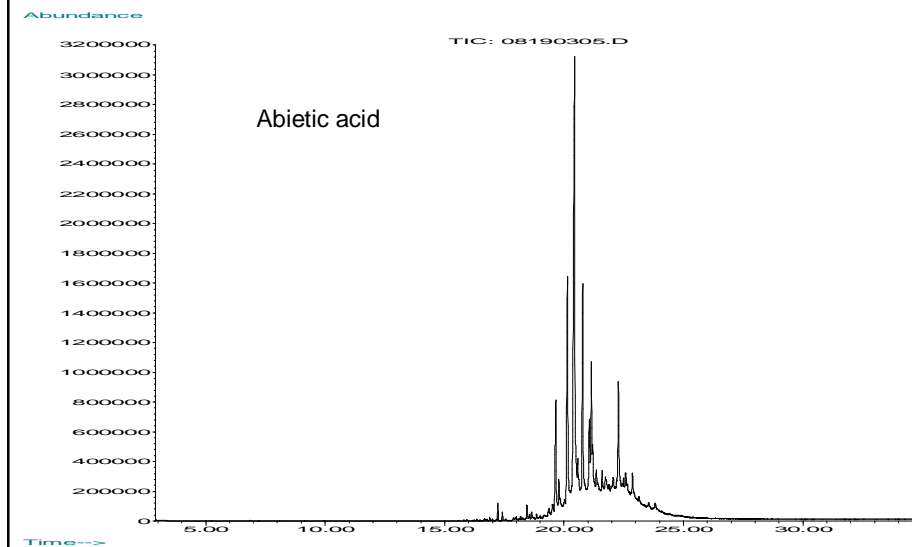
Rubber Formulation A (Sulfur Cured)

Ingredient	%
CALCINED CLAY	8.96
BLANC FIXE (barium sulfate)	25.80
CREPE	38.22
BROWN SUB MB	16.84
1722 MB	2.11
ZINC OXIDE	4.04
2, 2' METHYLENE-BIS (6-TERTIARY BUTYL-4-ETHYL PHENOL)	0.56
COUMARONE-INDENE RESIN	1.12
PARAFFIN	1.12
TETRAMETHYLTHIURAM MONOSULFIDE	0.11
ZINC 2-MERCAPTOBENZOTHAZOLE	0.29
SULFUR	0.84

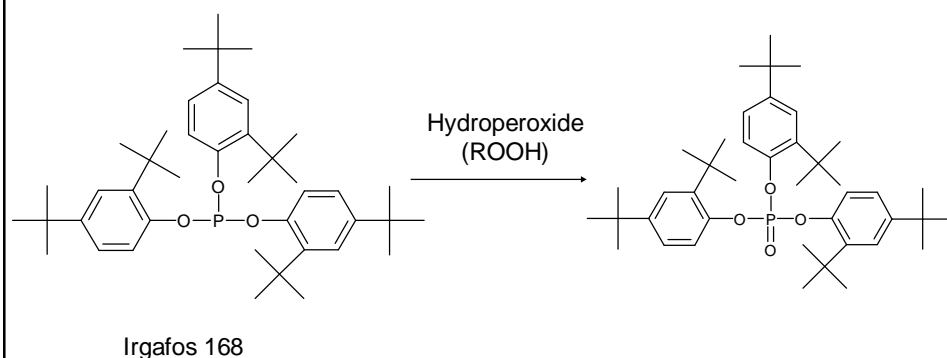
What do we know?

- Carbon black is a known source of PAHs and has also been shown to be involved in N-nitrosamine formation in rubber (“special cases”).
- Thiurams are known precursors of N-nitrosamines.
- 2-Mercaptobenzothiazole is a known “special case”.
- Paraffin and Coumarone-indene resin are natural product materials and are likely complex mixtures of related structures.
- Individual additives are likely GC-able.

What's in a name?



Additive Chemistry



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.

Control of Leachables Through Control of Extractables

- Specifications and acceptance criteria should be established for leachables profiles in OINDP.
- Implementation of routine leachables testing and specifications/acceptance criteria is a policy matter.
- If appropriate extractables/leachables correlations are established, then leachables specifications/acceptance criteria should be noted "*if tested will comply*".
- Therefore, in the ideal world leachables would be controlled through routine testing of extractables.

Routine Extractables Testing

Routine Extractables Testing is performed on all critical components of OINDP container closure systems. Routine Extractables Testing has the following general goals:

- To establish extractables specifications and acceptance criteria for OINDP critical container closure system components.
- To help ensure that the leachables profile in the drug product is maintained within appropriate limits.

Routine Extractables Testing

- To release OINDP container closure system critical components according to established specifications and acceptance criteria, which are designed to:
 - Control the identities and levels of extractables identified during Controlled Extraction Studies;
 - Detect “unspecified” extractables which could be present as the result of component ingredient changes, manufacturing changes, external contamination, or other causes.

Recommendations for Routine Extractables Testing

- A comprehensive “correlation” between extractables and leachables profiles should be established.
 - Qualitative correlation
 - Quantitative correlation
 - Leachables profiles from multiple drug product batches with specific critical component batches should be correlated with extractables profiles from those critical component batches, and across additional critical component batches.

Recommendations for Routine Extractables Testing

- Analytical methods for Routine Extractables Testing should be based on the analytical technique(s)/method(s) used in the Controlled Extraction Studies. Consider the following:
 - Simplicity relative to R&D methods
 - Ruggedness and robustness
 - Transferability
 - Cost effectiveness

Possibilities for Routine Extractables Testing Analytical Methods

- Gravimetric
 - Potentially useful in combination with other more sophisticated methods.
- Bulk spectroscopic (e.g. UV, FTIR)
 - Potentially useful in certain situations (e.g. non-contact critical component)
- Chromatographic (w/o MS or NMR)
 - Gas chromatography (FID, etc)
 - Liquid chromatography (UV detection)

GC/MS and GC/FID

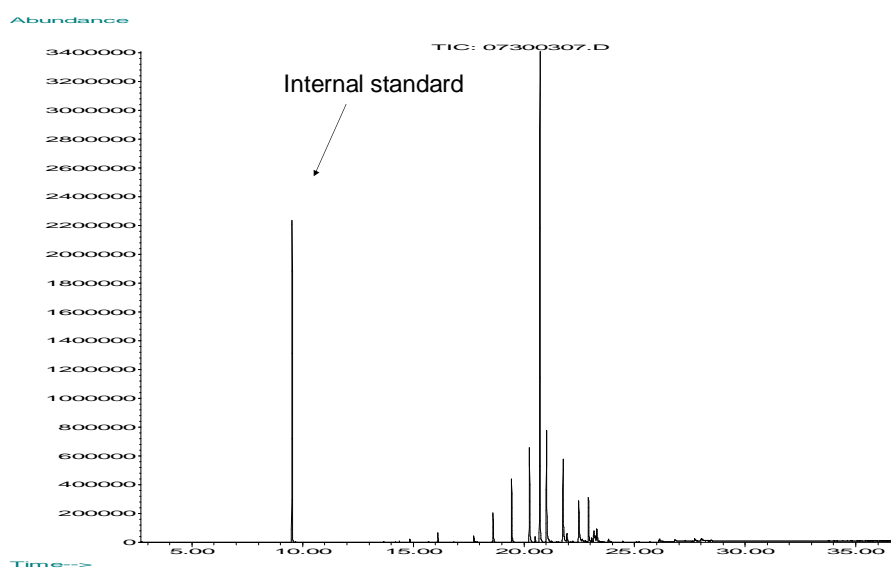


GC/MS
(Controlled Extraction Studies)

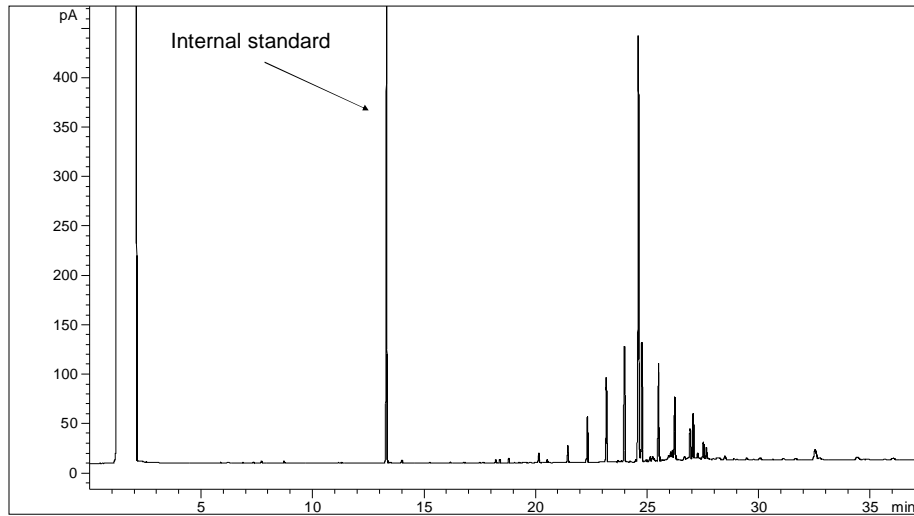


GC/FID
(Routine Extractables Testing)

GC/MS Extractables Profile of an Elastomer



Potential Routine Extractables Control Method – GC/FID



LC/MS and LC/UV

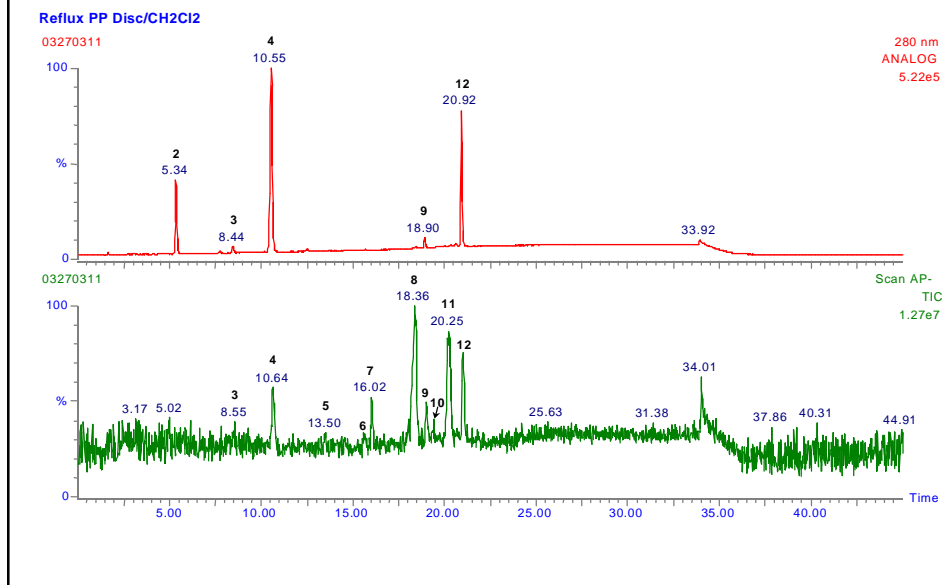


LC/MS
(Controlled Extraction Studies)



LC/UV
(Routine Extractables Control)

Polypropylene – Extractables Profile by LC/UV/MS



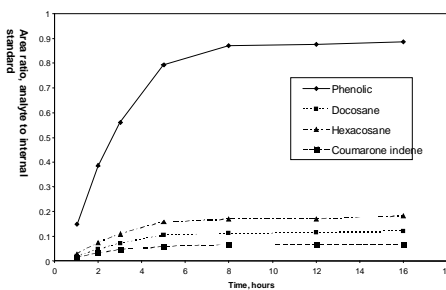
Routine Extractables Testing- Method Development and Validation

- Extraction procedures for critical components should be based on the optimized procedures from the quantitative Controlled Extraction Studies, and should be demonstrated to show asymptotic levels of extractables.
- The linear dynamic range of the analytical method should be established based on levels of extractables anticipated from quantitative Controlled Extraction Studies and of critical components.
- The Limit-of-Quantitation of the method should be established with consideration of the appropriate AET.
- The method should be validated according to the ICH validation characteristics of a quantitative impurity test. These validation characteristics include: Accuracy, Precision (Repeatability, Intermediate Precision), Specificity, Limit-of-Quantitation (LOQ), Linearity, and Range. In addition, System Suitability parameters should be established and a Robustness evaluation should be accomplished.
 - *Note that in certain cases it may be appropriate to validate routine extractables methods as "Limit Tests", in which case only Specificity and Limit-of-Detection (LOD) need be considered.*
- Accuracy can be determined through the analysis of spiked samples. The spiking matrix could be an extract taken through the extraction procedure minus the component sample. Spiking levels should be chosen so as to be representative of anticipated extractables levels based on results from quantitative Controlled Extraction Studies.

Routine Extractables Testing- Method Development and Validation

1. ICH Harmonized Tripartite Guideline, "Text on Validation of Analytical Procedures Q2A", International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. ICH Harmonized Tripartite Guideline, "Validation of Analytical Procedures: Methodology Q2B", International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
3. "Reviewer Guidance – Validation of Chromatographic Methods", Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration, November, 1994.
4. "Guidance for Industry – Analytical Procedures and Methods Validation – Chemistry, Manufacturing, and Controls Documentation", *Draft Guidance*, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration, August, 2000.
5. Michael E. Swartz and Ira S. Krull, Analytical Method Development and Validation, Marcel Dekker, Inc., New York, 1997.

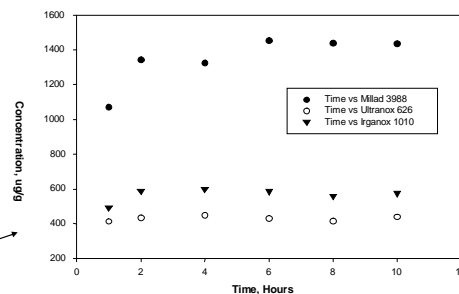
Asymptotic Levels



Methylene Chloride Soxhlet Extraction of Sulfur-Cured Elastomer



2-Propanol Reflux Extraction of Polypropylene



Definition of the AET

“The AET is defined as the threshold at or above which an OINDP pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for potential toxicological assessment.”

Process

1. Convert the SCT (0.15 µg/day for an individual organic leachable) to an Estimated AET (*e.g.* µg/canister for an individual organic leachable in an MDI) by considering the dosing and other parameters of the particular OINDP.
2. Convert the Estimated AET for leachables to an Estimated AET for extractables (*e.g.* µg/g elastomer for an individual organic extractable) by considering the parameters of the particular OINDP container closure system (*e.g.* weight of elastomer per MDI valve).
3. Locate the Estimated AET on a particular leachables or extractables profile (*e.g.* a GC/MS Total Ion Chromatogram).
4. Evaluate the uncertainty of the particular analytical technique/method (*e.g.* GC/MS response factors for various potential extractables/leachables).
5. Convert the Estimated AET to a Final AET by considering this analytical uncertainty.

Recommendation - MDIs

For example, consider an MDI with 200 labeled actuations per canister, a recommended dose of 8 actuations per day, and a critical component elastomer mass per valve of 200 mg. For an individual organic leachable derived from this elastomer, the estimated AET would be:

$$\text{Estimated AET} = \left(\frac{0.15 \text{ mg/day}}{8 \text{ actuations/day}} \times 200 \text{ labeled actuations/canister} \right)$$

$$\text{Estimated AET} \approx 3.75 \text{ mg/canister}$$

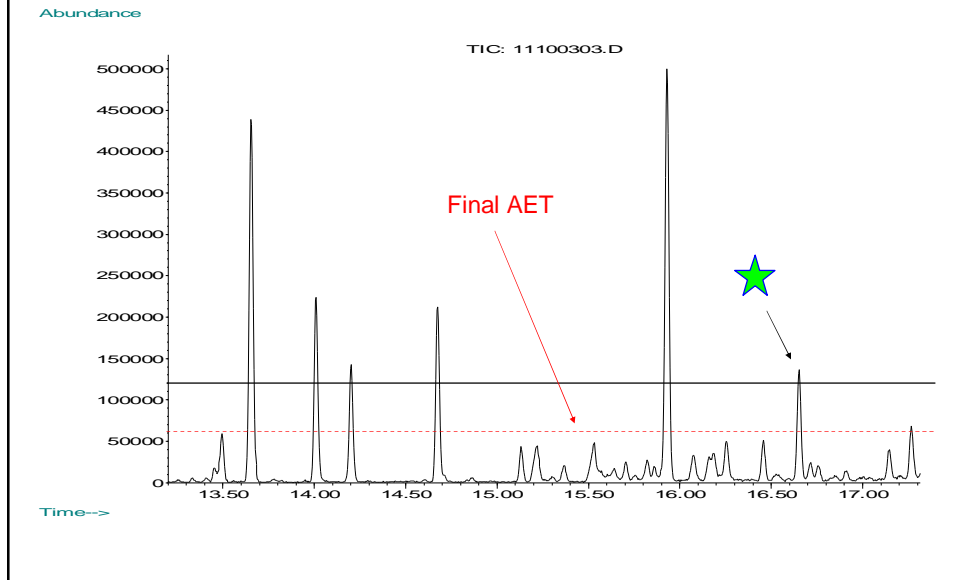
Recommendation - MDIs

Converting to an Estimated AET for individual extractables in an extractables profile of this particular elastomer:

$$\text{Estimated AET} \approx \frac{(3.75 \text{ mg/canister}) \times (1 \text{ canister/valve})}{0.2 \text{ g elastomer/valve}}$$

$$\text{Estimated AET} \approx 18.8 \text{ mg/g}$$

Leachables Profile – 1 Week Timepoint Expanded Section



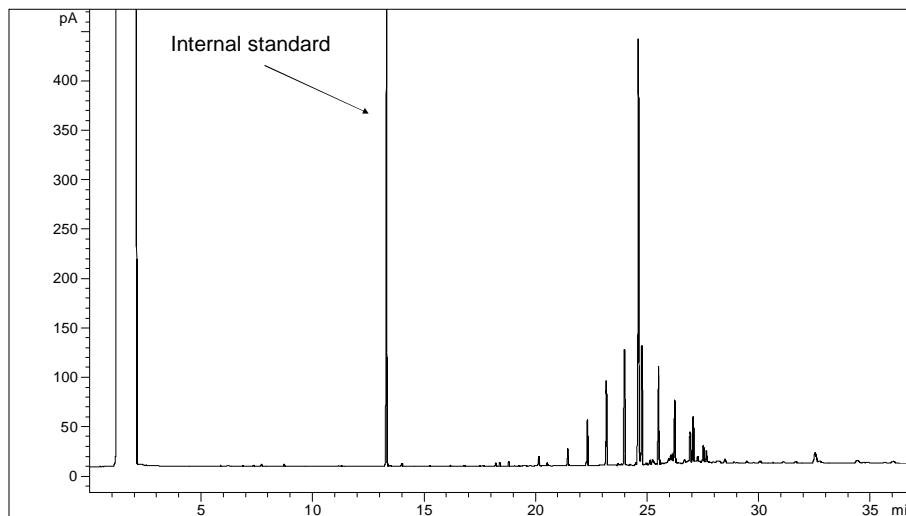
Specifications and Acceptance Criteria for Extractables

- Routine Extractables Testing should be performed on OINDP critical components prior to drug product manufacture. Critical components should be released to drug product manufacture based on carefully defined specifications and acceptance criteria established through:
 - A complete understanding of critical component composition(s), ingredients, and compounding/fabrication processes.
 - Comprehensive Controlled Extraction Studies.
 - A significant database of extractables profiles obtained with fully optimized and validated Routine Extractables Testing analytical methods.
 - A complete leachables/extractables correlation.

Specifications and Acceptance Criteria for Extractables

- Acceptance criteria for OINDP critical component extractables can include the following:
 - *Confirmation of extractables identified in Controlled Extraction Studies.*
 - *Quantitative limits for extractables identified in Controlled Extraction Studies.*
 - *A quantitative limit for "new" or "unspecified" extractables not detected during Controlled Extraction Studies.*

Potential Routine Extractables Control Method – GC/FID

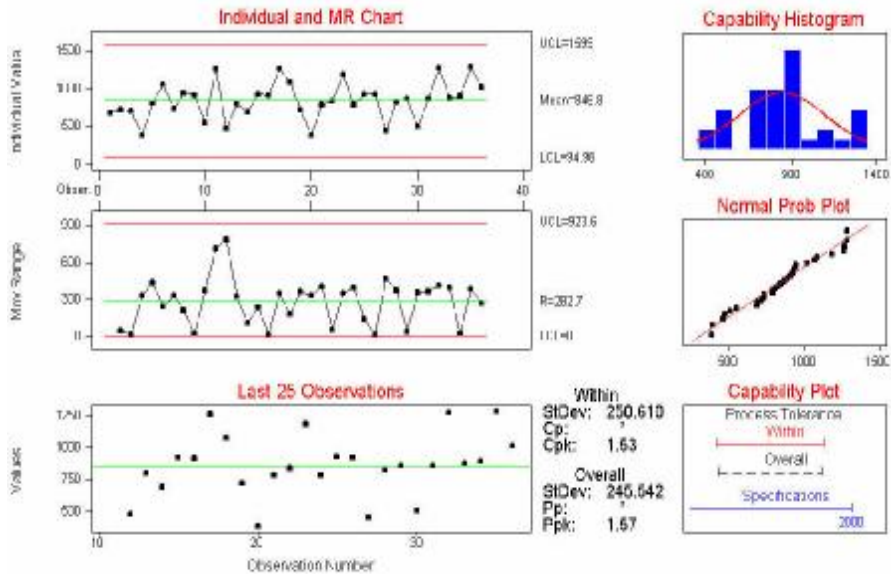


Typical Quantitative Database for a Critical Component Target Extractable

Target Extractable (ppm)

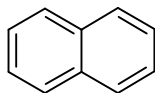
488	460
959	864
899	975
1034	507
1352	1284
1371	1338
841	822
885	879
911	457
492	838
905	968
816	1052
853	866
918	847
477	504
520	1286
838	1297
1324	1275
1016	1326
531	
	Mean 904
	Std Deviation 289

Process Capability Sixpack for Extractable

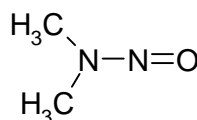


“Special Cases”

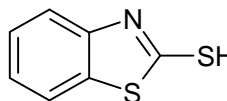
- PAHs - Polyaromatic Hydrocarbons
 - Also referred to as PNAs (Polynuclear Aromatics)



- N-Nitrosamines



- 2-Mercaptobenzothiazole



PAHs/PNAs as Leachables in OINDP

- Historically, the primary source of PNAs is *carbon black* which is used as a filler in certain types of rubber (mostly sulfur cured).
- There is some potential for other PNA sources (e.g. naphthalene contamination).
- Some PNAs are known or suspect cancer causing agents (e.g. benzo(a)pyrene). FDA interest in MDIs traces back to the late 1980s.
- Levels of PNAs in MDIs which employ “black rubber” seals are typically on the order of ng to low µg/canister.
- The FDA historically requires that *all elastomers* in MDIs be evaluated and controlled for PNAs.
- Analytical methods typically involve GC/MS.

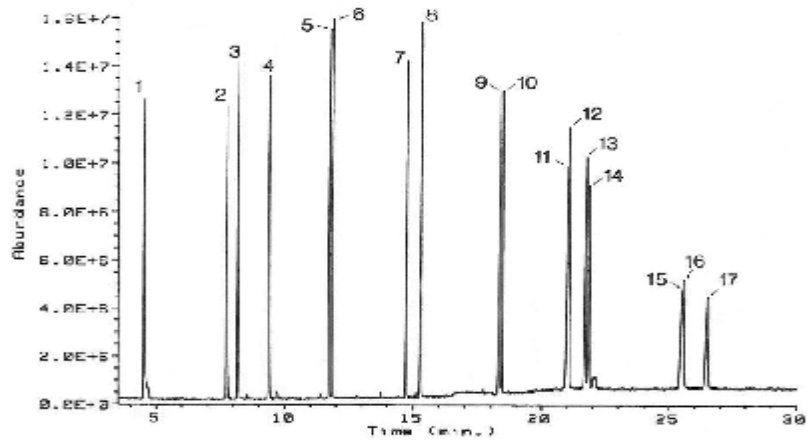
PNA's Typically Analyzed and Controlled (EPA Method 610 list)

- Naphthalene
- Acenaphthylene
- Acenaphthene
- Fluorene
- Phenanthrene
- Anthracene
- Fluoranthene
- Pyrene
- Benzo(a)anthracene
- Chrysene
- Benzo(b)fluoranthene
- Benzo(k)fluoranthene
- **Benzo(e)pyrene**
- Benzo(a)pyrene
- Indeno(123-cd)pyrene
- Dibenzo(ah)anthracene
- Benzo(ghi)perylene

PNA Analysis in Rubber – Possible Method

- Slice (or grind) a measured weight of critical rubber components.
- Add prepared rubber to a boiling flask with a measured volume of organic solvent (e.g. toluene).
- Extract via reflux for a pre-optimized time period (likely 24 hours or greater).
- Remove solvent and reduce in volume.
- Analyze by GC/MS (for example).
 - Note that internal standards can be added at various points in the overall process.

GC/MS Analysis of Target PNAs

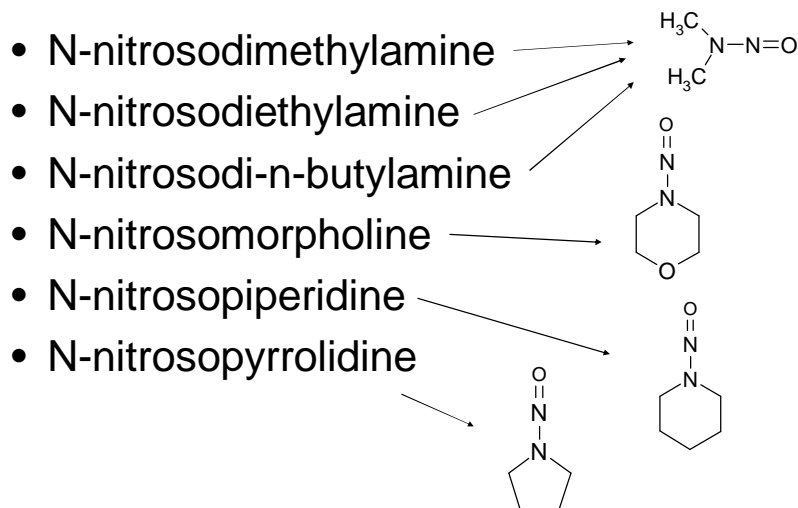


Reconstructed total ion chromatogram demonstrating the separation of target polycyclic aromatic hydrocarbons. This chromatogram was derived from scanning mass spectrometric data. (1) naphthalene; (2) acenaphthylene; (3) acenaphthene; (4) fluorene; (5) phenanthrene; (6) anthracene; (7) fluoranthene; (8) pyrene; (9) benzofluoranthene; (10) chrysene; (11) benzo(b)fluoranthene; (12) benzo(k)fluoranthene; (13) benzo(e)pyrene; (14) benzo(a)pyrene; (15) indeno(1,2,3-cd)pyrene; (16) dibenzo(h,j)anthracene; (17) benzo(ghi)perylene.

N-Nitrosamines as Leachables in OINDP

- Historically, the formation of “nitrosamines” in rubber involves sulfur curing agents (e.g. thiurams).
- The issue of N-nitrosamines in rubber goes back to late 1970s/early 1980s with concern over their presence in baby bottle rubber nipples. FDA became involved in the issue. Official analytical methods for rubber developed and validated.
- FDA interest in MDIs (and other OINDP) traces to the early 1990s.
- Levels of nitrosamines in MDIs which employ “black rubber” seals are typically on the order of ng/canister.
- The FDA historically requires that *all elastomers* in MDIs be evaluated and controlled for nitrosamines.
- Analytical methods typically involve GC with “Thermal Energy Analysis” detection (GC/TEA).

Target N-nitrosamines



N-nitrosamine Analysis in Rubber (AOAC Method 987.05)

- Place 5g cut rubber sample in 250mL flask with 100mL methylene chloride and 100mg propyl gallate, and hold for 17-18h.
- Transfer solvent and rubber sample to a Soxhlet extractor.
- Spike in internal standard.
- Extract for 1 hour.
- Add 100mL 5N NaOH and 2g $\text{Ba}(\text{OH})_2$ to flask and carefully distill methylene chloride (discard). Continue distilling 70mL of aqueous distillate into a separatory funnel.
- Add 300mg anhydrous Na_2CO_3 to funnel, followed by 50mL methylene chloride. Extract (repeat twice more). Combine extracts in separatory funnel.
- Pass through anhydrous Na_2SO_4 (to dry), into a Kuderna_Danish apparatus (with appropriate washes).
- Concentrate to approximately 4mL.
- Remove from KD and further concentrate to 1.0mL with a nitrogen stream.
- Analyze by GC/TEA.

N-nitrosamine Analysis in Rubber (AOAC Method 987.05)



Soxhlet extraction



Steam distillation



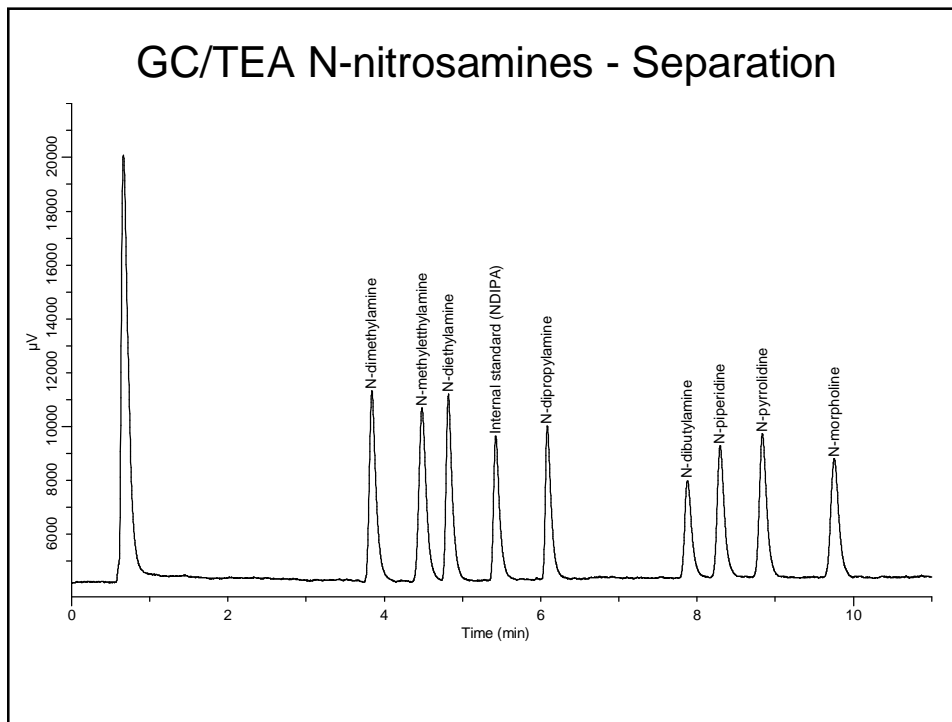
Extract concentration

Image provided by Rubber Consultants

A GC/TEA System

Image provided by Cardinal Health





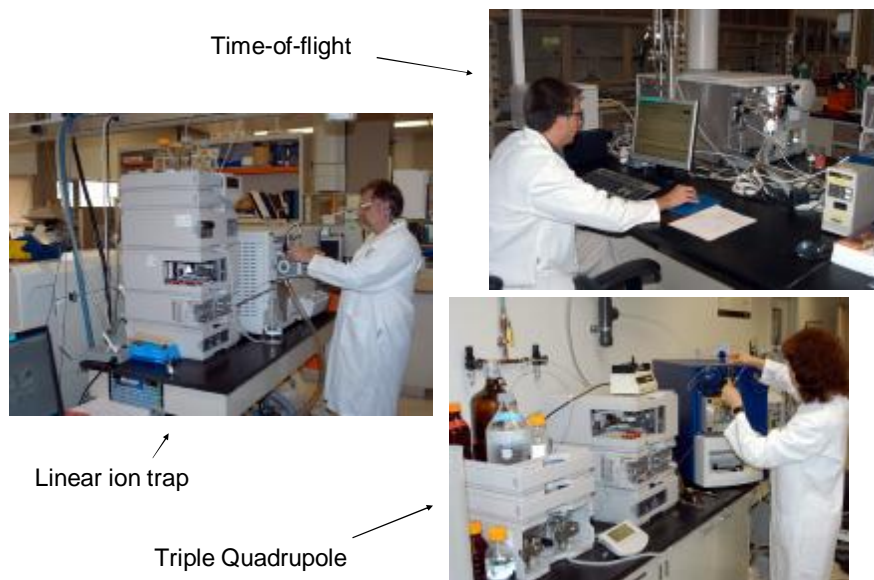
Some Typical Limit of Detection/Quantitation Results for Target N-nitrosamines

- AOAC Method 987.05 LOQs target acceptance criteria of NMT 10ppb (ng/g) for an individual N-nitrosamine.
- Based on the LOQs for rubber, MDI methods should target LOQs around 1 ng/canister.

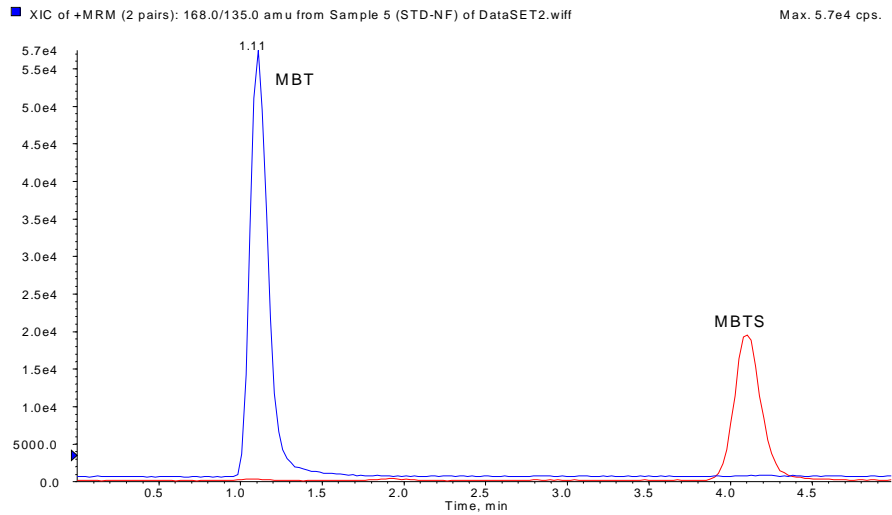
N-nitrosamines in OINDP – Points to Consider

- N-nitrosamines are usually associated with sulfur-cured black rubber.
- Even with the sensitivity and selectivity of the GC/TEA, other peaks are often noted in OINDP leachables profiles.
- N-nitrosamines are very light sensitive, which suggests a possible procedure for identifying “non-nitrosamine” GC/TEA peaks.

“Bench-top” LC/MS Systems



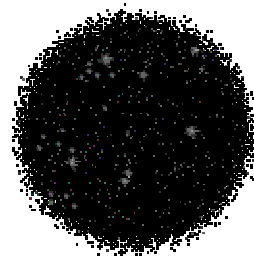
MRM Chromatograms of MBT (blue) and MBTS (red) in the 500 ng/mL standard solution.



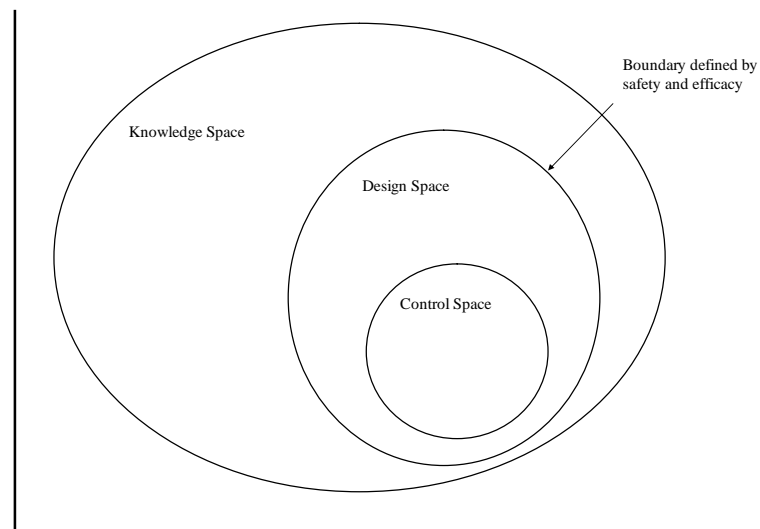
The Future – Quality by Design

- Design Space - “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”

Acknowledgements

- IPAC-RS Elastomer Working Group
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- Boehringer Ingelheim Pharmaceuticals



Thank you for your interest
and attention!!!!