Technical requirements to Good Manufacturing Practice in metered dose inhalers production and development (2. part) Extractable - Leachable

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Regional Expert Group Meeting
3-5 of October, 2011, Moscow

Definitions

- ***Extractable: Any chemical species that can be removed from a packaging component under stressful laboratory conditions***
- ***Leachable: an extractable that actually migrates into a drug product under normal storage and use conditions***
- **Extractable for non-compendial plastics components**
- **Leachable for all plastic components contact to the formulation**

Extractable-Leachable

- **Best practice: Norwood at all (2006 and 2009)**
- **Consult with the manufacturer at the early development stage**
  - **to identify extractables (if known)**
  - **To get to know the manufacturing process**
    - **Basic materials**
    - **Additives**
    - **Catalyst**
    - **Fabrication process and additives**
    - **Cleaning or washing process of the final part of the device**
  - **www.elsiedata.com : new database on plastics**
- **Selection of the parts and suppliers through risk assessment based on this knowledge**

Ingredients in a sulphur-cured elastomer test article

Ingredient	Registry #(S)	Percent (w/w)
Calcined Clay	308063-94-7	8.96
Blanc Fixe (Barium Sulfate)	7727-43-7	25.80
Crepe	9006-04-6	38.22
Brown Sub MB (Ingredients Below)	NA (not available)	16.84
Brown Sub Loose	NA	33.30
Crepe	9006-04-6	66.70
1722 MB (Ingredients Below)	NA	2.11
SMR (Standard Malaysian Rubber)	NA	60.00
FEF Carbon Black (Low PNA)	1333-86-4	40.00
Zinc Oxide	1314-13-2	4.04
2, 2' Methylene-bis (6-*tert*-butyl-4-ethyl phenol)	88-24-4	0.56
Coumarone-Indene Resin	164325-24-0 140413-58-7 140413-55-4 68956-53-6 68955-30-6	1.12
Paraffin	8002-74-2 308069-08-1	1.12
Tetramethylthiuram Monosulfide	97-74-5	0.11
Zinc 2-Mercaptobenzothiazole	149-30-4 155-04-4	0.29
Sulfur	7704-34-9	0.84

Controlled extraction study

- Janke's directives (2003)
  - Vigorously but not so aggressively to alter the extractable profile
  - The extraction method should be technically justified and optimized to produce a profile correlate to leachable profile
- What to test?
  - Valve components
  - Actuator
  - Mouthpiece
  - Metal components if coated and if not coated (oily processing residues)
- Dichloromethane, Isopropyl alcohol and Hexane
  - Dichloromethane mimics CFC or HFA propellant in MDI
  - Isopropyl alcohol mimics Ethanol as cosolvent
- Reflux, Soxhlet, Sonification

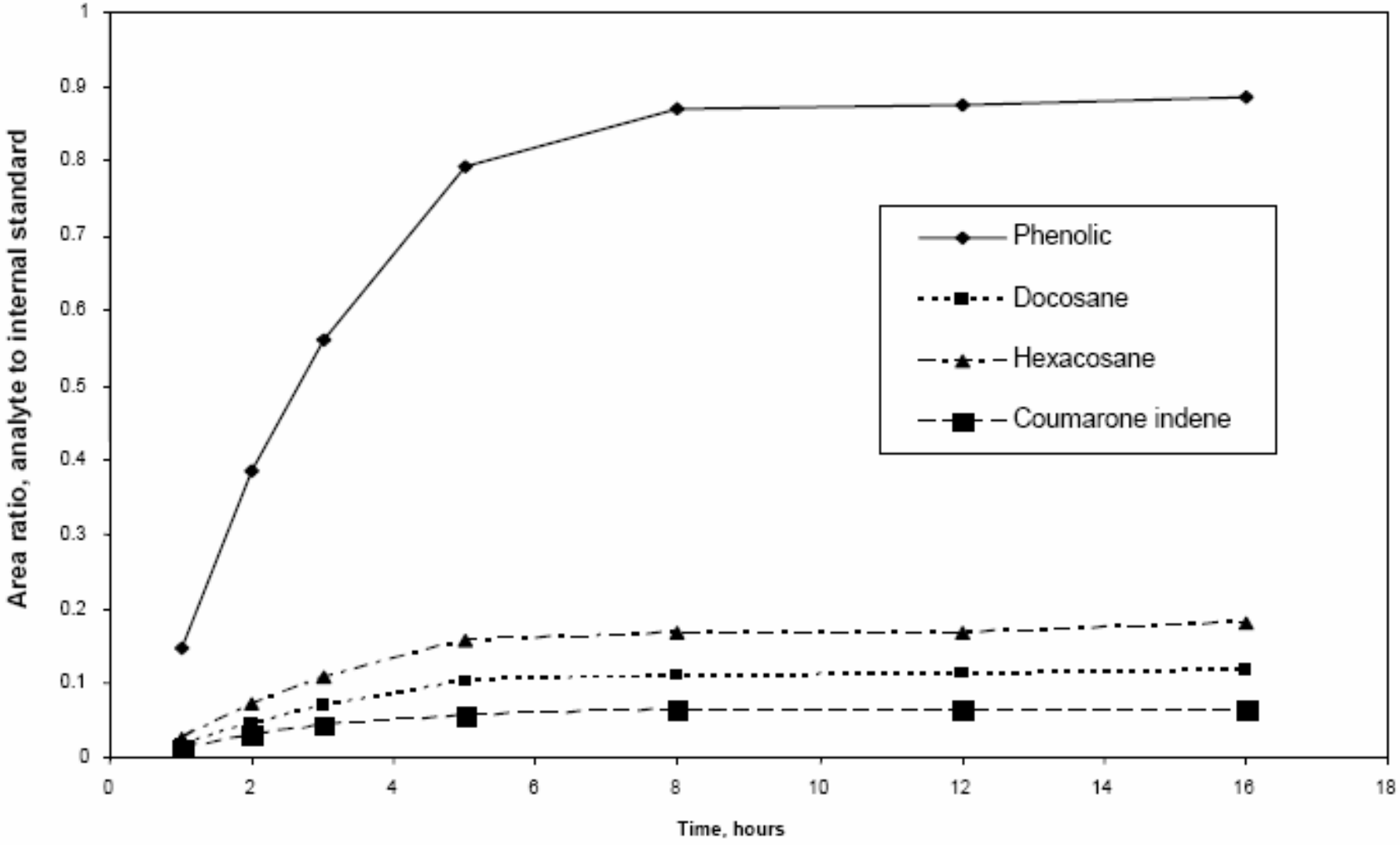
Controlled extraction study cont.

- Gas Chromatography/Mass Spectrometry, Liquid chromatography / MS and LC/ UV Diode array detection
  - Forced temperature program, high elution power!
  - Broad UV range
- Identify Extractable ≥0.15 µg per day (Safety concern threshold)
  - Confirmed, Confident or Tentative identification categories
- Quantitative extraction studies with optimized (near the asymptotic level) methods
  - Uncertainty of each method established
  - Validate the extraction and analytical method, acceptance criteria

Validation of Extractable/Leachable Methods

- **Validated according to ICH Guidelines**
  - **Characteristics of a quantitative impurity test**
    - **Accuracy, Precision, Specificity, LOQ, Linearity and Range**
  - **Validation Parameter Acceptance Criteria**
  - **Characteristics of Limit Tests**
    - **Specificity and LOD**

Soxhlet extraction of the elastomer



Leachable study

- Use the same analytical methods as in the extractable study
- According to the stability study protocol, till the end of shelf-life of the product
- Qualitative and quantitative correlation with extractable exist?
- Assess the risk for leachable ≥ 5 µg per day
- Develop and validate the method for leachable
- Develop and validate the method for routine extractable with acceptance criteria
  - Robustness and ruggedness: detection changed from MS to FID, from DAD to UV
  - Recovery and accuracy should be checked by an extratable spiked with known amount of impurities into the product

Correlation of Extractable and Leachable

- **Comprehensive**
  - **Qualitative**
  - **Quantitative**
  - **Multiple batches of drug product**
  - **Multiple lots of critical container closure components**
  - **All product orientations**
  - **Accelerated storage conditions**
  - **Full shelf-life**
- **End of Shelf-Life Profiles**
  - **Leachable less than or equal to extractable**

How to calculate with threshold values

- **Safety concern threshold: ≥0.15 µg per day**
- **Transform it into Analytical Evaluation Threshold (AET):**
  - **Extractable: µg individual substance per part of the device or g of the construction material of device**
  - **Leachable: µg individual substance per Canister filled with MDI product**

Analytical Evaluation Threshold AET

$$Estimated\ AET = \left(\frac{0.15\ \mu g/\text{day}}{12\ \text{actuations/day}} \times 200\ \textit{labeled}\ \text{actuations/canister} \right)$$

NOT the total number of actuations ≈ 250

$$Estimated\ AET \approx 2.5 \mu g/\text{canister}$$

$$Estimated\ AET \approx \frac{(2.5\ \mu g/\text{canister}) \times (1\ \text{canister/valve})}{0.2\ \text{g elastomer/valve}}$$

$$Estimated\ AET \approx 12.5\ \mu g/g$$

Homogenous and same construction material /valve

MDI product on the market
Analytical Evaluation Thresholds

MDI Drug Product	Estimated Formulation Parameters from Product Labeling			Leachable Concentration Yielding 0.15 µg/day Intake	
	Formulation Net Weight (grams)	Number of Actuations Per Can	Maximum Actuations Per Day	(µg/g)	(µg/can)
Flovent 110	7.9	60	8	0.14	1.1
Alupent	7.0	100	12	0.18	1.3
Beconase *	6.7	80	8	0.22	1.5
QVAR	7.3	100	8	0.26	1.9
Nasacort *	9.3	100	8	0.20	1.9
Tilade	16.2	104	8	0.12	2.0
Azmacort	20.0	240	16	0.11	2.3
Proventil HFA	6.7	200	12	0.37	2.5
Ventolin HFA	18.0	200	12	0.14	2.5
Combivent	14.7	200	12	0.17	2.5
Atrovent	14.0	200	12	0.18	2.5
Serevent †	13.0	120	4	0.35	4.5
Maxair	14.0	400	12	0.36	5.0
median	13.0	120	12	0.18	2.3

Regulatory documents for extractable and leachable

- June 2006 by European Medicines Agency and Health of Canada
  - Guideline on pharmaceutical quality on inhalation and nasal product
- October 1998 by FDA
  - Metered dose inhalers and Dry powder inhalers drug product
- 2005 by European pharmacopoeia
  - Preparations for inhalation No 671
  - Pressurized pharmaceutical preparation No 523
- 2007 by US pharmacopoeia
  - Aerosols, nasal sprays, metered-dose inhalers and dry powder inhalers No 601
  - Uniformity of dosage units No 905
  - Pharmaceutical dosage forms (Aerosols, inhalations) No 1151
- 2009 by International Organization for Standardization
  - Aerosol drug delivery device design verification -- Requirements and test methods No 20072:2009
- September 2006 - 9 by Product Quality Research Institute Leachable and Extractable Working Group, D. Norwood as Chair
  - Safety threshold and best practice for extractable and leachable in orally inhaled and nasal drug products

Regulations for polymers

MATERIAL	USA FOOD CONTACT	EU FOOD CONTACT	EU PHARMACOPEIA
Polypropylene	21CFR177.1520	Food Contact EEC Directives / Framework Regulation 1935/2004/EC 2002/72/EC + amendments 2004/1/EC, 2004/19/EC, 2005/79/EC, 2007/19/EC, 2008/39/EC, REACH	European Pharmacopoeia 6th Edition 2008 + Supplements : Chemical comp. 3.1.3 – 3.1.5
Acetal (Polyoxymethylene)	177.2470 copolymer or 177.2480 homopolymer		N/A
Nylon (Polyamide)	21CFR177.1500		N/A

Drug Master File for any packaging part

- Item numbers
- Source(s) and fabricator(s) for each sub-component
- Composition and quality of materials of each sub-component (including coating, if appropriate)
- Citations of compliance of the materials to defined regulations, pharmacopoeia etc.
- Drawings of each sub-component with precise dimensional measurements
- Description of any treatment processes such as washing, coating, sterilization
- Analysis for residual contaminants and residues of surface treatments, washings
- etc
- - Control extraction studies for elastomeric and plastic components, also for any
- coated surfaces
- - Toxicological evaluation of extractables and residues
- - Performance characteristics of the sub-component and/or assembled finished item
- - Acceptance criteria, test methods, and sampling plans

Summary

- **Leachable evaluations should be based on methods/techniques used in controlled extraction studies**
- **Analytical methods should be guided by the analytical evaluation threshold calculated from Safety concern Threshold ≥0.15 µg per day**
- **Comprehensive correlation may obviate the need for routine implementation of drug product leachable specifications and acceptance criteria**
- **Acceptance criteria for leachables should apply over the proposed shelf life and include quantitative limits for known and new/unspecified leachables**


Thank you for your kind attention!
If you need any documents
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