Chemical Characterization and Non-targeted Analysis of Medical Device Extracts

FDA Small Business Regulatory Education for Industry (REdI)

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Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Medical Devices









Neurological and Physical Medicine

Reproductive, Gastro-Renal, and Urological

Ophthalmic and Ear, Nose and Throat


Orthopedic

Surgical



Cardiovascular

Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental







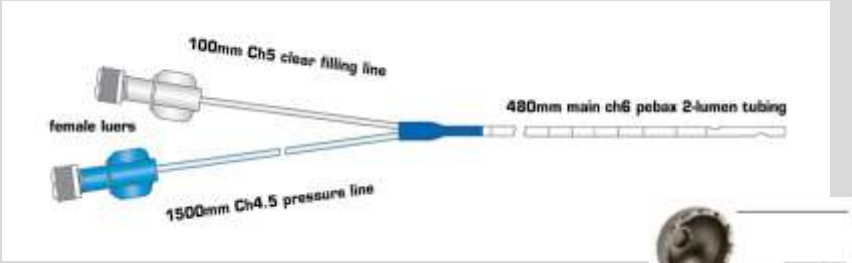
Learning Objectives

- Define purpose of chemical characterization of medical devices
- Identify how chemical analysis of medical devices is performed
- Discuss information obtained by chemical analysis

Purpose of Chemical Characterization of Medical Devices

Materials in Medical Devices

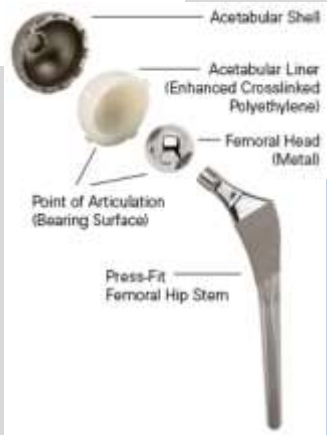
Biomaterial: Material in contact **with living tissues**, organisms, or microorganisms.



Cystometry Catheter

Image credit: Stericom

Pebax® Elastomers: block copolymers made up of rigid polyamide blocks and soft polyether blocks. (trademark of Arkema)



Hip Prosthesis

Image credit: Exactech

UHMWPE
Ultra High MW Polyethylene (Acetabular Cup)
Cobalt, Chrome, Zirconia, Alumina

Vascular Stent

Image credit: Elixir Medical

PLLA bioresorbable Poly(L-lactide) lactic acid (Drug eluting)

Materials in Medical Devices
"Medical Grade"

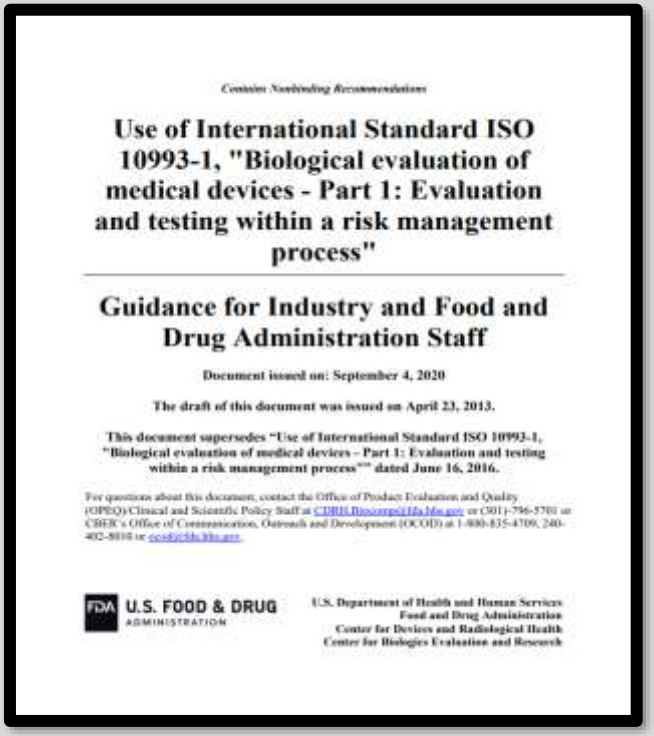
No standard definition for a "medical grade" material:

- Materials designed to make medical product
- Facility has exceeded quality and safety requirements for designing, producing, installing, and serving of medical devices
- Materials tested for biocompatibility and are appropriate to be used for medical applications

❖ Always verify why someone calls a product "medical grade".

"The Agency does not clear or approve individual materials that are used in the fabrication of medical devices."

Guidance and Standards



Contains Nonbinding Recommendations

Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 4, 2020

The draft of this document was issued on April 23, 2013.

This document supersedes "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"" dated June 16, 2016.

For questions about this document, contact the Office of Product Evaluation and Quality (OPEQ)/Clinical and Scientific Policy Staff at CDRH.BiocompQ@fda.hhs.gov or (301)-796-5701 or CBER's Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709, 240-402-8010 or ocod@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

- ISO 10993-1:2018 Biological evaluation of medical devices – Evaluation and testing within a risk management process
- ISO 10993-18:2020 Chemical characterization of medical device materials within a risk management process. (amended in May 2022)
- ISO 10993-12:2021 Sample preparation and reference materials

www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and

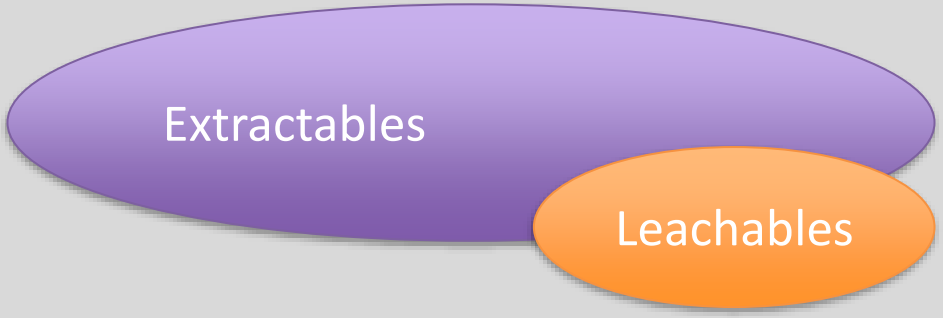
Chemical Analysis and Toxicological Risk Assessment

FDA Biocompatibility Guidance

- "Potential risks from a biocompatibility perspective should be identified."(pg 9)
- "Address the knowledge gaps either by biocompatibility testing or other evaluations that appropriately address the risks." (pg 9)
- "Chemical analyses can be used to assess the toxicological risk of the chemicals that elute from devices. … Extraction solvents should be selected to optimize compatibility with the device materials…" (pg 11)

Extractables and Leachables

- **Extractable:** substance that is released from a medical device or material of construction when the medical device or material is extracted using laboratory extraction conditions and vehicles.
- **Leachable:** substance that is released from a medical device or material during its clinical use.



Definitions from ISO 10993-18:2020

Comparison of Different Industries

	Drug Products	Medical Devices
Contact	Until expiration date	1 minute to lifetime
Dose	Single, multiple or repeated	Single, intermittent or continuous repeat use
Impurities identification	Leachables delivered with the drug product (tablet, liquid/solution)	Extractables released from the device component that contacts the body indirectly or directly

Knowledge Check

True or false: A medical grade biomaterial is an FDA-approved material used in the fabrication of medical devices.

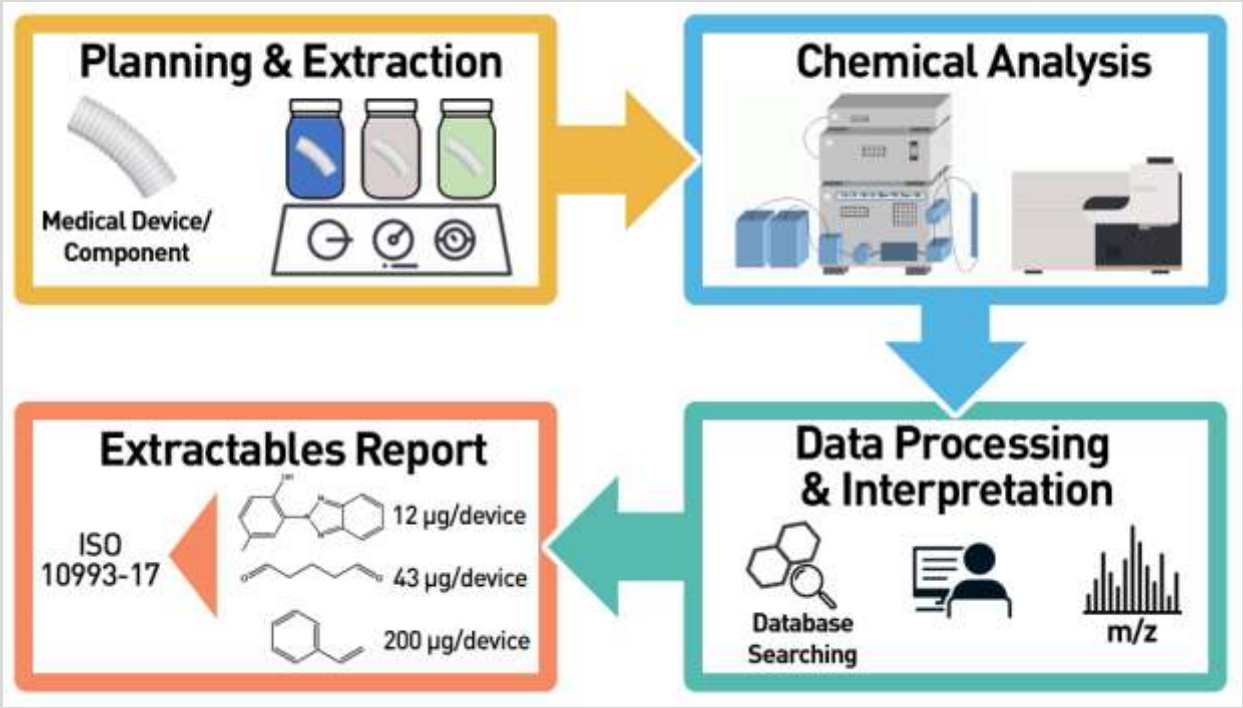
– True

– False

False : "The Agency does not clear or approve individual materials that are used in the fabrication of medical devices." FDA Biocompatibility Guidance 2020; pg 9.

How is Chemical Characterization of Medical Devices Performed?

Overview- Chemical Characterization- Extractables Analysis for Medical Devices



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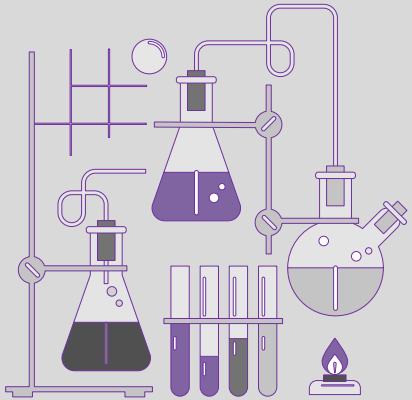
Definitions Extraction

- **Extraction:** "…to produce an extractables profile that equals or exceeds the leachables generated in clinical use.." ISO 10993-18:2020; pg 38.
- **Exaggerated Extraction:** …greater number or amount of extractables as compared to the amount generated under the clinical conditions of use
- **Exhaustive Extraction:** …multi-step extraction until extractables amount in final step is less than 10 % of the initial extraction step



Extraction Conditions/E&L Analysis

	Duration of Contact		
	Limited (<24 h)	**Prolonged (1-30 days)**	**Long-Term/ Permanent (>30 days)**
Duration of Extraction/ Number of Cycles	Exaggerated extractions or worst case clinically relevant conditions	Exhaustive extractions or worst case clinically relevant conditions	Exhaustive extractions
Number of solvents	Polar and non-polar solvents (or polar and semi-polar if justified)	Polar and non-polar solvents (or polar and semi-polar if justified)	Polar, semi-polar and non-polar
Non-volatile Residue (NVR) Analysis Performed?	Not applicable	NVR analysis to support if exhaustion is achieved	NVR analysis to support if exhaustion is achieved

Solvent Selection for E&L Analysis

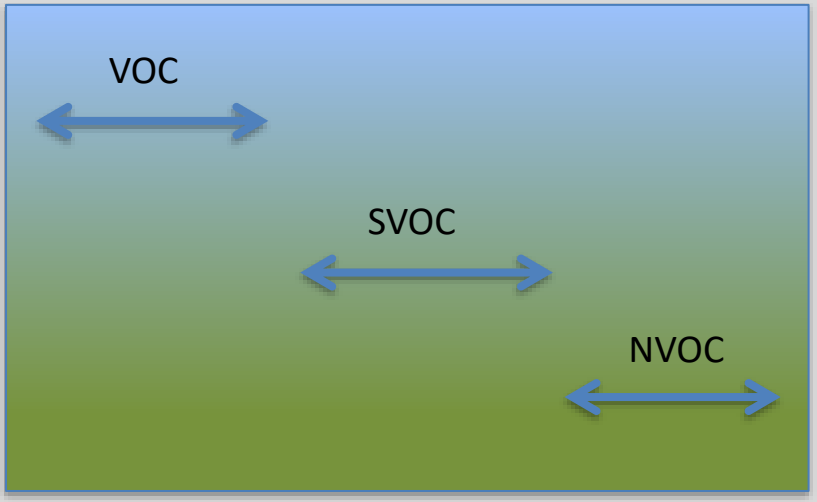
ISO 10993-18:2020, Annex D, Table D.1 (subset)

	Solvent	Polarity Index	Boiling Point (°C)
Polar	Water	10.2	100
	Saline (0.9% NaCl)	10.2	100
Semi Polar	Acetonitrile	5.8	82
	Ethanol	4.3	78
	Tetrahydrofuran	4	65
	Isopropanol	3.9	82
	Dichloromethane	3.1	41
Non-Polar	Cyclohexane	0.2	81
	Hexane	0.1	69

Range of Volatility

Chromatographic Compatibility

HS-GC-FID
HS-GC-MS
GC-FID
GC-MS
LC-MS
LC-UV
LC-ELSD /CAD



Boiling Point of Organic Compounds

HS: Head Space
GC: Gas Chromatography
FID: Flame Ionization Detector
MS: Mass Spectrometry
LC: Liquid Chromatography
ELSD: Evaporative Light Scattering Detector
CAD: Charged Aerosol Detector

VOC = volatile organic compound
SVOC = semi-volatile organic compound
NVOC = non-volatile organic compound

Methods in E&L Analysis

Multiple methods to cover all types of chemicals:

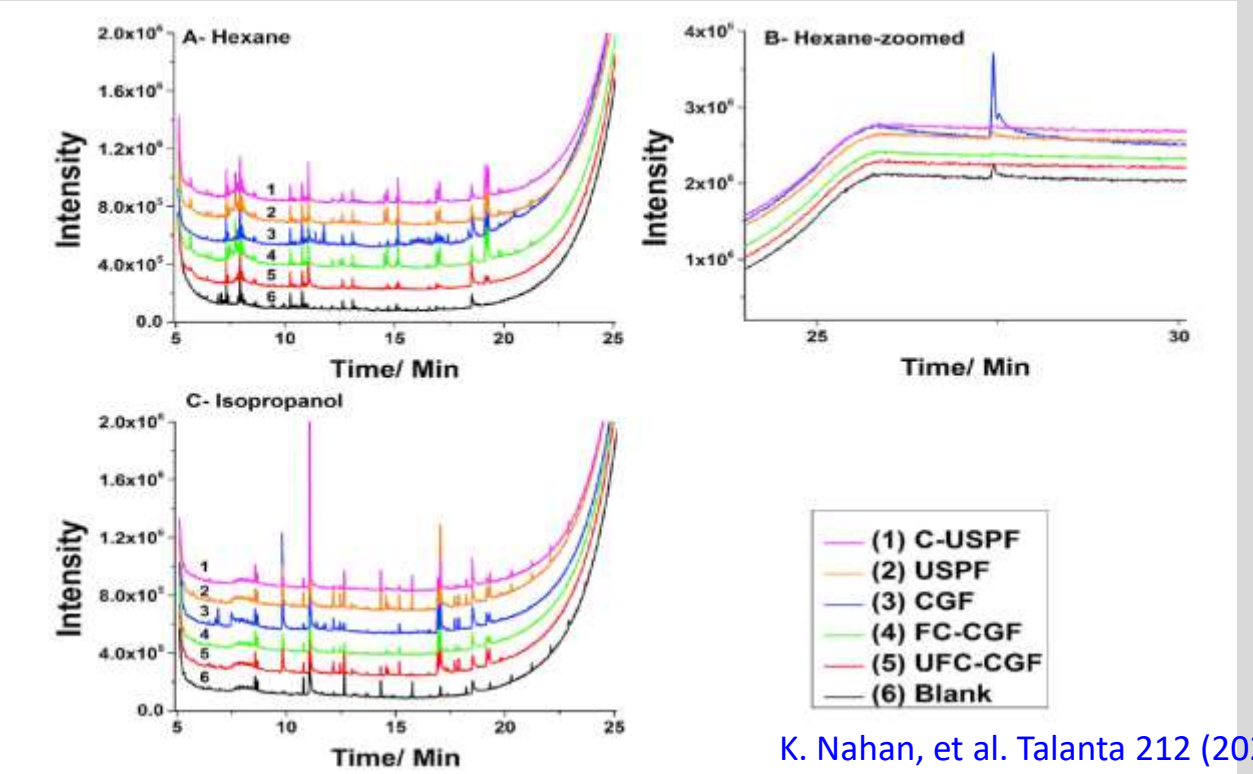
- HS-GC-MS : volatile organic compounds (VOCs)
- GC-MS : semi-volatile organic compounds (SVOCs)
- LC-UV-MS: non-volatile organic compounds (NVOCs)
- LC-ELSD or CAD: non-volatile organic compounds (NVOCs)
- ICP-MS : Elemental analysis, metals
- FTIR, GPC, NMR, Ion Chromatography

ICP: Inductively Coupled Plasma; FTIR: Fourier Transform IR Spectroscopy

GPC: Gel Permeation Chromatography; NMR: Nuclear Magnetic Resonance Spectroscopy

Information Obtained by Chemical Analysis

Additive-Manufactured Acrylonitrile Butadiene Styrene Orthopedic Cast GC/MS



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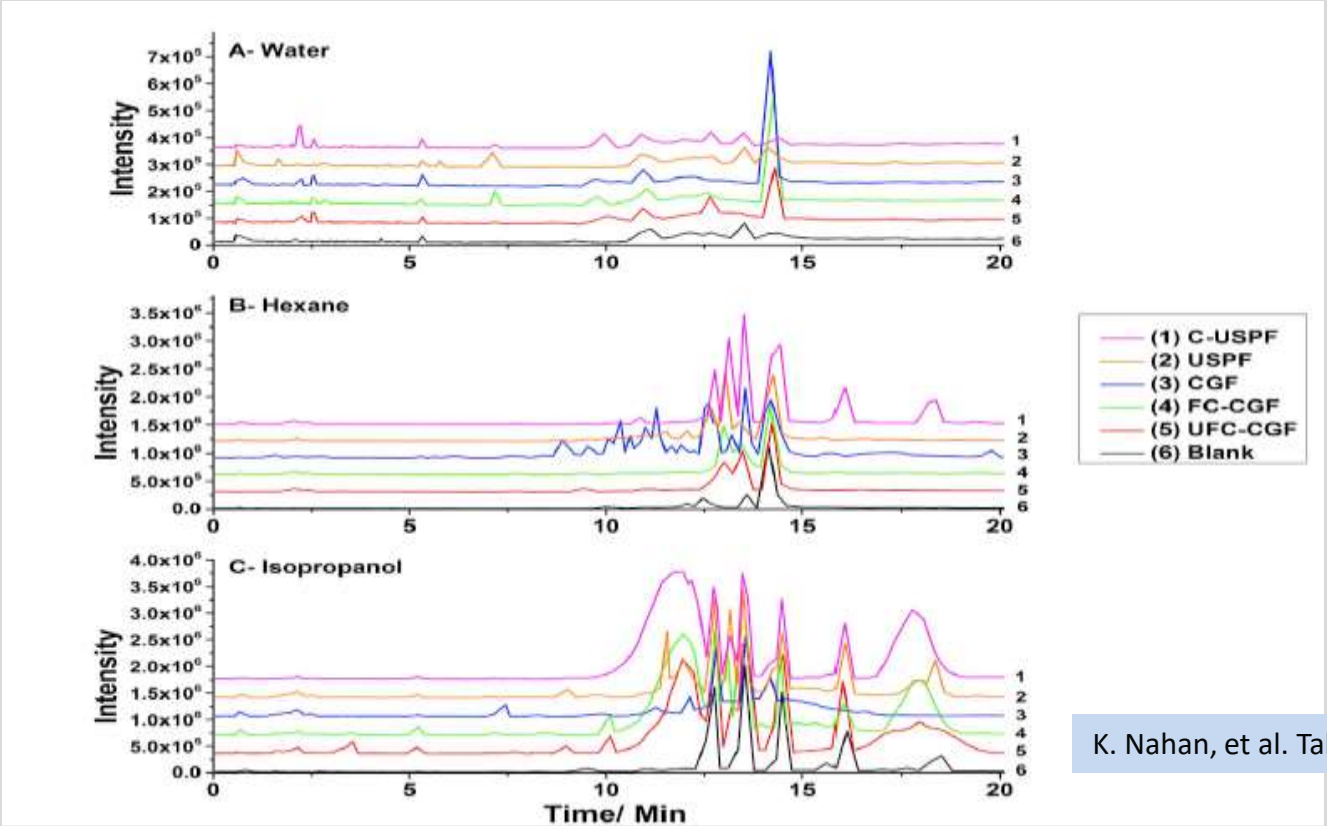
Additive-Manufactured Acrylonitrile Butadiene Styrene Orthopedic Cast–LC/MS



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Additive-Manufactured Acrylonitrile Butadiene Styrene Orthopedic Cast –IDs

Compound Name	USPF (μg/g)	C-USPF (μg/g)	CGF (μg/g)	UFC-CGF (μg/g)	FC-CGF (μg/g)
2-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile Isomer 1	175	N.D.	192	225	153
2-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile Isomer 2	354	N.D.	355	323	250
2-Ethyl-2-hydroxybutyric acid	29	N.D.	N.D.	N.D.	N.D.
2-Phenyl-2-(prop-2-en-1-yl)pent-4-enenitrile	183	N.D.	N.D.	N.D.	N.D.
3-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile Isomer 1	432	N.D.	434	380	353
3-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile Isomer 2	104	N.D.	105	94	84
3-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile Isomer 3	102	N.D.	107	95	N.D.
4-Cyanocyclohexene	N.D.	N.D.	32	N.D.	N.D.
Acetophenone	39	N.D.	41	N.D.	N.D.
Benzene, (1-methylethyl)-	35	31	36	32	31
"Benzene, 1,1'-(1,2-cyclobutanediyl)bis-, cis-" like Compound 1	35	N.D.	N.D.	32	32
"Benzene, 1,1'-(1,2-cyclobutanediyl)bis-, cis-" like Compound 2	33	N.D.	N.D.	31	31
"Benzene, 1,1'-(1,2-cyclobutanediyl)bis-, cis-" like Compound 3	86	N.D.	N.D.	77	81
Benzene, 1,1'-(1,2-cyclobutanediyl)bis-, trans-	169	114	122	140	122
Benzene, 1-ethyl-4-methyl-	N.D.	N.D.	N.D.	32	N.D.
Benzeneacetaldehyde	32	N.D.	N.D.	N.D.	N.D.
Butanedioic acid, phenyl-	N.D.	N.D.	33	N.D.	N.D.
Dodecyl acrylate	89	N.D.	N.D.	75	N.D.
Hexane, 3,3-dimethyl-	29	N.D.	N.D.	N.D.	N.D.
Hydroperoxide, 1-methyl-1-phenylethyl	33	30	37	31	31
Tetramethylbutanedinitrile	N.D.	N.D.	34	N.D.	N.D.

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E&L - Challenges Ahead: Identification

Table 3. Summary of Approaches for Categorizing the Confidence of Identification

Source	USP <1663>[227]	Schymanski 2014[225]	Rochat 2017[230]

Identification Levels and Sublevels	• Confirmed
	• Confident
	  ○ Highly Confident
	  ○ Confident
	• Tentative (Class)
	• Unknown
		• Confirmed structure
		  ○ Probable structure (Library Match or Diagnostic Evidence)
		• Tentative candidate
		  ○ Structure
		  ○ Substituent
		  ○ Class
		• Unequivocal molecular formula
		• Exact mass of interest
			• Confirmed
			  ○ Utmost Certainty
			  ○ Confirmed
			• Putative (Compound)
			  ○ Very Strong
			  ○ Strong
			  ○ Good
			  ○ Fair
			• Annotated (Compound/Class)
			  ○ Tentative

			○ Suspected ○ Presumptive • Unknown (Non-Match)
Approach to assigning identification level based on supporting data	Qualitative	Qualitative	Qualitative and Quantitative
Minimum Level for Complete Molecular Structure	Confident	Tentative Candidate	Annotated
Requirement(s) for Confirmed Level	Authentic Reference Compound	Authentic Reference Standard	Authentic Reference Standard or NMR data
Application Emphasized	Pharmaceutical packaging and delivery systems	Environmental samples	Metabolomics samples

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Considerations for Identification of Non-Targeted Extractables

- Purpose
- Identification Levels: confident or confirmed per USP <1663>
- Identification Data: spectral library, supporting chemistry

Name of Compound	CAS #	Extraction Vehicle	Analytical Instrument	Major Ions Observed (m/z)	RT (min)	Identification Level	Identification Data	Quantity (µg/device)	Quantification Method and Reference Standard
Diethyl phthalate	84-66-2	Hexane	GC/MS	279,167, 149	6.2	Confirmed	Confirming Spectral library and RT match	10	Full Quantification-authentic reference std
Irgafos 168	31570-04-4	Ethanol	LC/MS	647.4608	7.25	Confident	Library match plus Supporting data	2	Semi-quantitative; Tinuvin P

Supporting data can include, but is not limited to, generation of a single molecular formula, matching retention time (RT), functional group data (e.g., UV), absence of possible alternative isomers, etc.

Knowledge Check

Which analysis method is suitable for non targeted chemical analysis of medical device materials?

a) GC/MS only

b) LC/MS only

c) NMR only

d) Multiple analytical methods are used to generate data

Resources and Further Information

- **Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process**
  www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and

- Review Paper: Sussman et al. *ACS Biomater. Sci. Eng.* 2022, 8, 3, 939–963

  pubs.acs.org/doi/10.1021/acsbiomaterials.1c01119

Summary

- Chemical characterization of medical devices include information gathering, extractables analysis and data processing-interpretation
- Multiple analytical methods are used to generate data
- Chemical analysis is used to detect, identify and quantify extractables in order to provide data to support toxicological risk assessment

Questions