

# **Chemical Characterization and Non-targeted Analysis of Medical Device Extracts**

**FDA Small Business Regulatory Education for Industry (REdI)**

June 8, 2022

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U.S. Food and Drug Administration

# Medical Devices

Neurological and  
Physical Medicine

Reproductive, Gastro-  
Renal, and Urological

Ophthalmic and  
Ear, Nose and  
Throat

Orthopedic

Cardiovascular

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

Surgical



# Learning Objectives

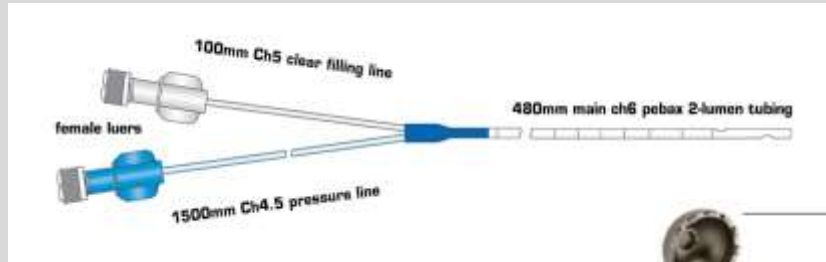
- Define purpose of chemical characterization of medical devices
- Identify how chemical analysis of medical devices is performed
- Discuss information obtained by chemical analysis

# **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: Stericor

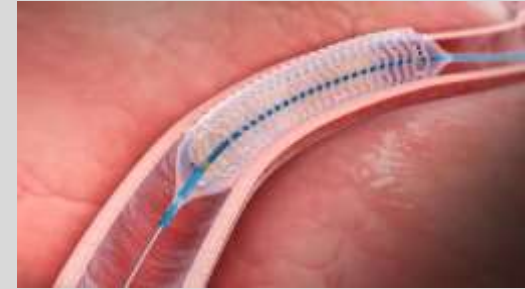
Pebax® Elastomers:  
block copolymers made up  
of rigid polyamide blocks  
and soft polyether blocks.  
(trademark of Arkema)



**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”

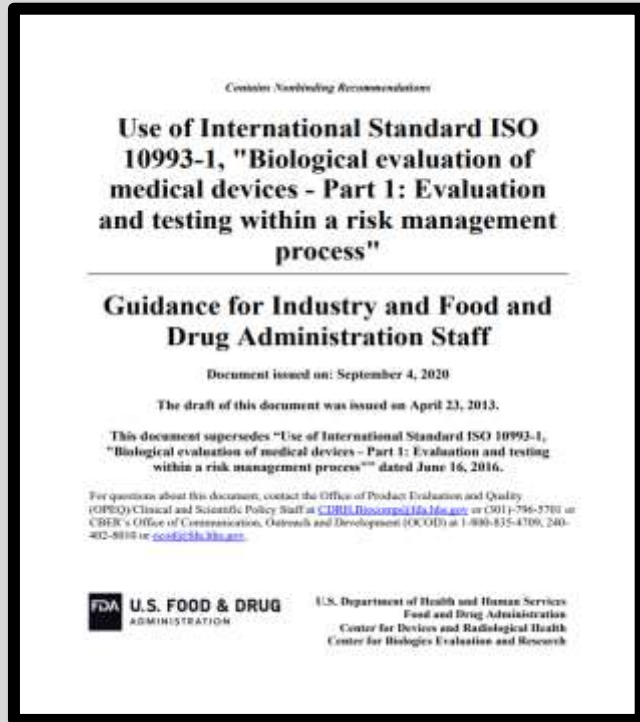
**No standard definition for a "medical grade" material:**

- 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



- 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](https://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
<b>Contact</b>	Until expiration date	1 minute to lifetime
<b>Dose</b>	Single, multiple or repeated	Single, intermittent or continuous repeat use
<b>Impurities identification</b>	Leachables delivered with the drug product (tablet, liquid/solution)	Extractables released from the device component that contacts the body indirectly or directly

# Knowledge Check

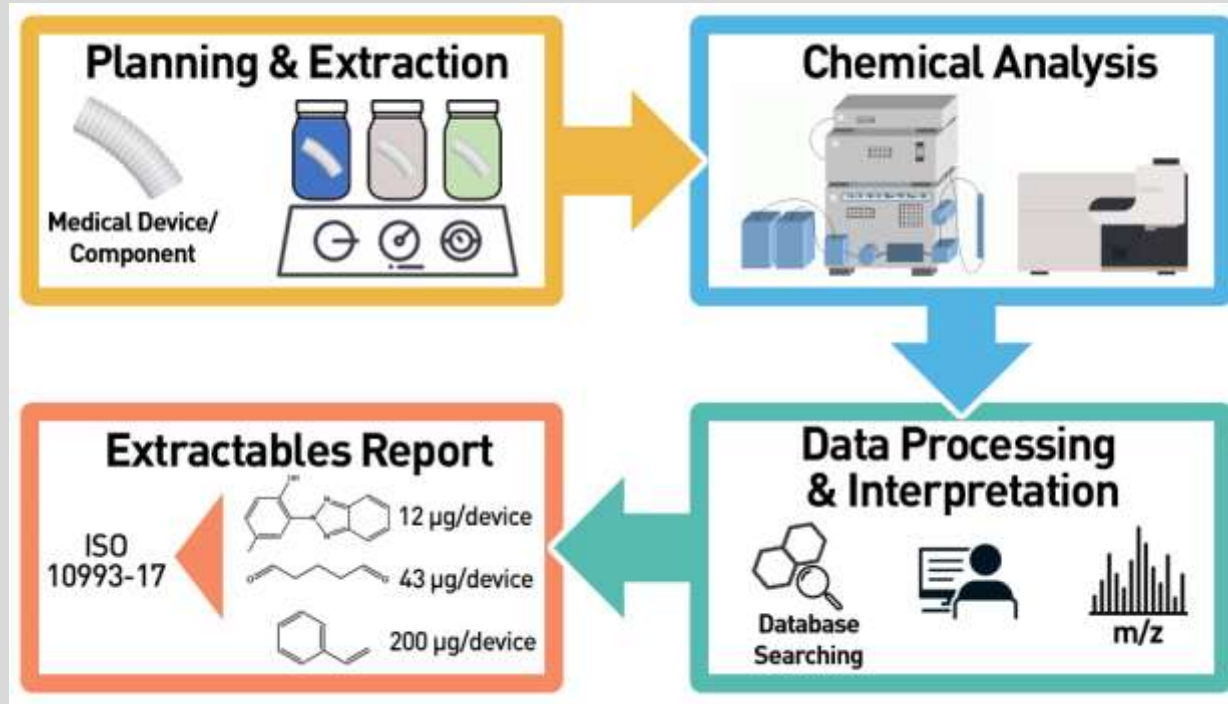
**True or false: A medical grade biomaterial is an FDA-approved material used in the fabrication of medical devices.**

- 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?**

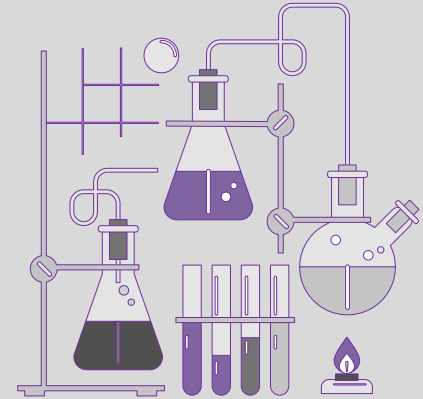
# Overview- Chemical Characterization- Extractables Analysis for Medical Devices



Sussman et al. ACS Biomater. Sci. Eng. 2022, 8, 3, 939–963

# 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)

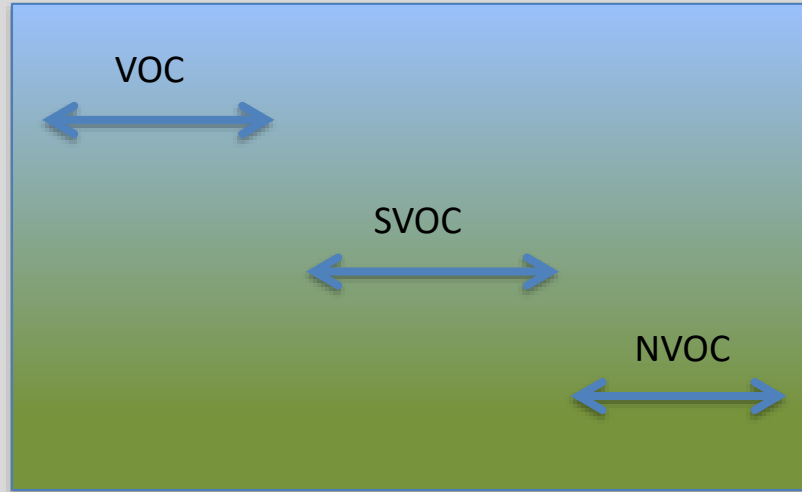
	Solvent	Polarity Index	Boiling Point (°C)
Polar	Water	10.2	100
	Saline (0.9% NaCl)	10.2	100
Semi Polar	Acetonitrile	5.8	82
	Ethanol	4.3	78
	Tetrahydrofuran	4	65
	Isopropanol	3.9	82
	Dichloromethane	3.1	41
Non-Polar	Cyclohexane	0.2	81
	Hexane	0.1	69



# 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:

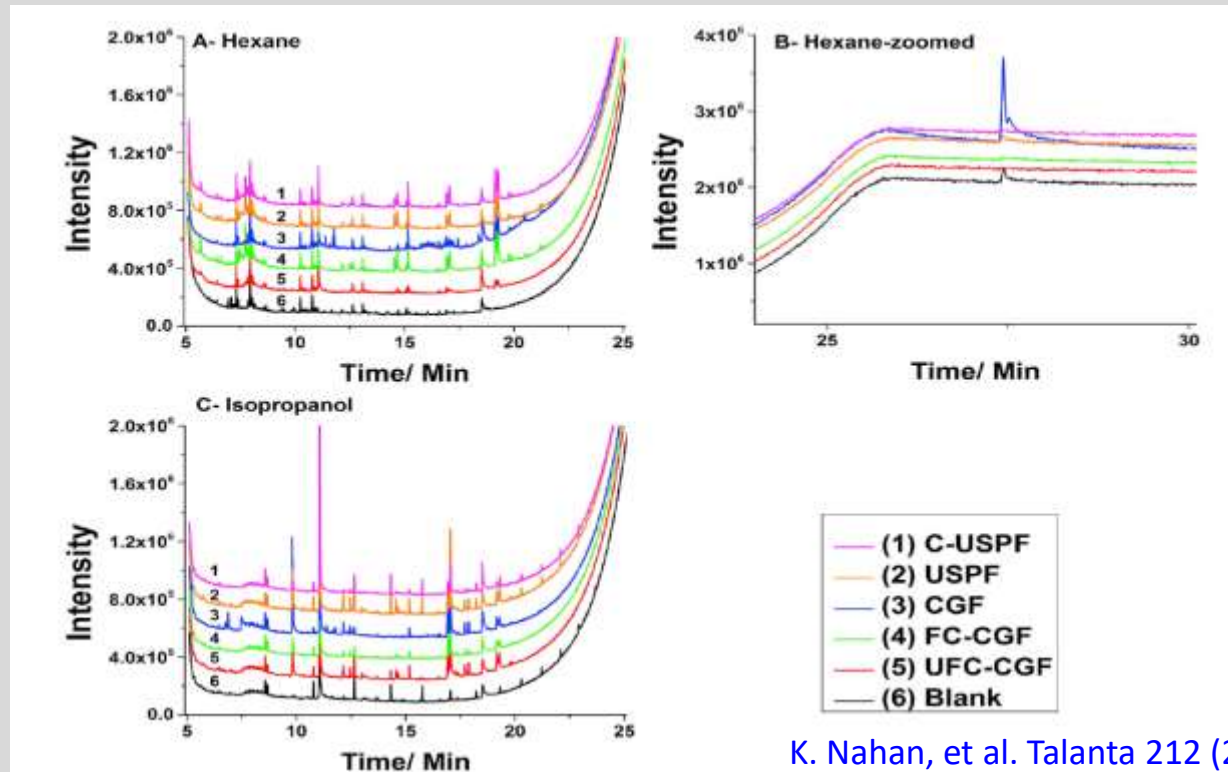
- HS-GC-MS : volatile organic compounds (VOCs)
- GC-MS : semi-volatile organic compounds (SVOCs)
- LC-UV-MS: non-volatile organic compounds (NVOCs)
- LC-ELSD or CAD: non-volatile organic compounds (NVOCs)
- ICP-MS : Elemental analysis, metals
- FTIR, GPC, NMR, Ion Chromatography

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

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

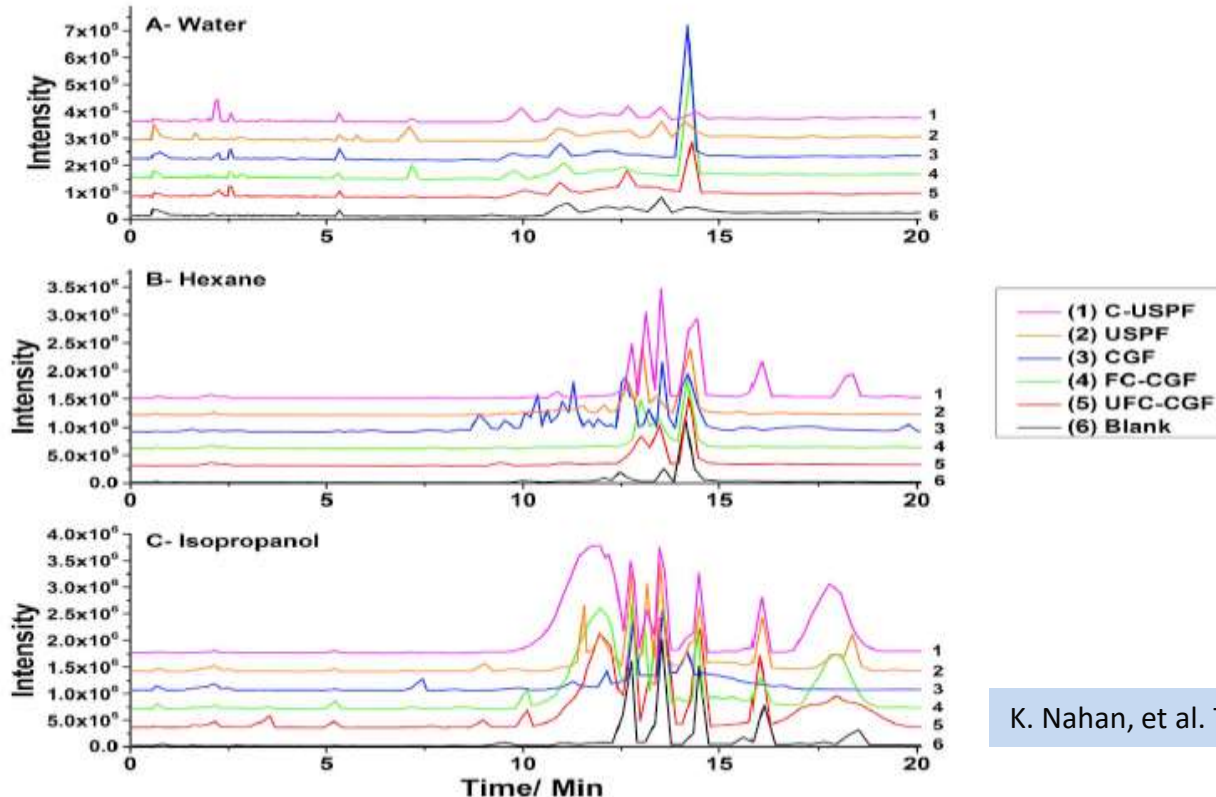
# **Information Obtained by Chemical Analysis**

# Additive-Manufactured Acrylonitrile Butadiene Styrene Orthopedic Cast GC/MS



K. Nahan, et al. Talanta 212 (2020) 120464

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



K. Nahan, et al. Talanta 212 (2020) 120464

# Additive-Manufactured Acrylonitrile Butadiene Styrene Orthopedic Cast –IDs



Compound Name	USPF	C-USPF	CGF	UFC-CGF	FC-CGF
	(µg/g)	(µg/g)	(µg/g)	(µg/g)	(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.

K. Nahan, et al. Talanta 212 (2020) 120464

# E&L - Challenges Ahead: Identification



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

Source	USP <1663> <sup>227</sup>	Schymanski 2014 <sup>225</sup>	Rochat 2017 <sup>230</sup>
Identification Levels and Sublevels	<ul style="list-style-type: none"> <li>Confirmed</li> <li>Confident                             <ul style="list-style-type: none"> <li>Highly Confident</li> <li>Confident</li> </ul> </li> <li>Tentative (Class)</li> <li>Unknown</li> </ul>	<ul style="list-style-type: none"> <li>Confirmed structure                             <ul style="list-style-type: none"> <li>Probable structure (Library Match or Diagnostic Evidence)</li> </ul> </li> <li>Tentative candidate                             <ul style="list-style-type: none"> <li>Structure</li> <li>Substituent</li> <li>Class</li> </ul> </li> <li>Unequivocal molecular formula</li> <li>Exact mass of interest</li> </ul>	<ul style="list-style-type: none"> <li>Confirmed                             <ul style="list-style-type: none"> <li>Utmost Certainty</li> <li>Confirmed</li> </ul> </li> <li>Putative (Compound)                             <ul style="list-style-type: none"> <li>Very Strong</li> <li>Strong</li> <li>Good</li> <li>Fair</li> </ul> </li> <li>Annotated (Compound/Class)                             <ul style="list-style-type: none"> <li>Tentative</li> </ul> </li> </ul>
			<ul style="list-style-type: none"> <li>Suspected</li> <li>Presumptive</li> <li>Unknown (Non-Match)</li> </ul>
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

Sussman et al. ACS Biomater. Sci. Eng. 2022, 8, 3, 939–963

# Considerations for Identification of Non-Targeted Extractables

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

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](https://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](https://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

