Link between PFAS as an emerging E&L Compound and the regulatory framework on the suitability of a polymer in healthcare

Frank De Smedt

DyFrNd



With the support of:

Co n Te nt

1. Setting the stage
2. Pharmacopeia monographs
3. Road to E&L
4. N-Nitrosamines & PFAS
5. Conclusions



Dy.Fr.Nd.

a /dɪf-rənt/ view on chemistry

www.DyFrNd.be

Polymers in Healthcare

Pharmaceutical Packaging

Medical Devices



How do we “know” the starting materials are suited (enough) for a succesful submission ?



Pharmaceutical Grade ?

Medical Grade ?

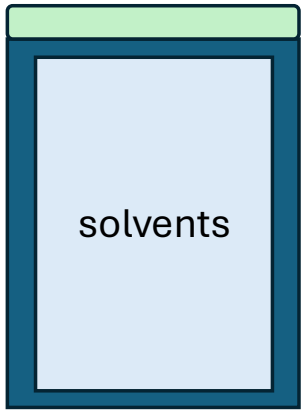
Pharmaceutical packaging / containers : Extractables & Leachables





container









LEACHABLES ← **EXTRACTABLES** ← **Raw materials / containers**

Analytical methods in the drug product

Analytical methods in solvent extracts

Pharmacopeia monographs

USP <1664>

Guideline on plastic immediate packaging materials (EU)

USP <1663>

(USP <665>)

Pharm.Eur. 3.1 / 3.2 /3.3 series

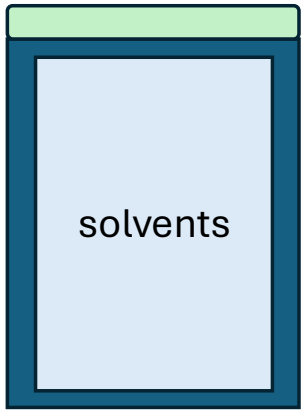
USP <661.1> / <661.2>

Medical Devices : Chemical Characterization





Medical device





Information Gathering

“EXTRACTABLES”

Analytical methods
in solvent extracts

Raw materials

ISO 10993 – 18
Chemical Characterization

(pharmacopeial monographs)



Pharmacopeia monographs

Compendial testing on plastic materials

Dy.66 Fr.87 Nd.60
a /dɪf-rənt/ view on chemistry

The monographs for the european market are divided in 3 series





Ph.Eur. 3.1

Materials used for the manufacture of containers

3.1.3	PolyOlefins (PO)
3.1.4	PolyEthylene (PE) without additives for containers
3.1.5	PolyEthylene (PE) with additives for containers
3.1.6	PolyPropylene (PP) for containers and closures
3.1.7	Poly(Ethylene-Vinyl Acetate) (EVA) for containers and tubing
3.1.9	Silicone elastomer for closures and tubing
3.1.10	Non-Plasticised PVC materials for non-injectable solutions
3.1.11	Non-Plasticised PVC materials for solid dosage forms (oral)
3.1.14	Plasticised PVC materials for intravenous solutions
3.1.15	PolyEthylene terephthalate (PET) for containers
3.1.16	Cyclo-Olefin Polymers (COP)
3.1.17	Cyclo-Olefin Copolymers (COC)
3.1.18	Styrene Block Copolymers (SBC)

Ph.Eur. 3.2

Containers

3.2.2	Plastic containers and closures for pharmaceutical use
3.2.9	Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders

Ph.Eur. 3.3

Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes

3.3.1	Materials for containers for human blood and blood components
3.3.2	Materials based on plasticised poly(vinyl)chloride for containers for human blood and blood components
3.3.3	Materials based on plasticised poly(vinyl)chloride for containers tubing used in sets for transfuson of blood and blood components
3.3.4	Sterile plastic containers for human blood and blood components
3.3.5	Empty sterile containers of plasticised poly(vinylchloride) for human blood and blood components
3.3.6	Sterile containers of plasticised poly(vinylchloride) for human blood containing anticoagulant solution
3.3.7	Sets for the transfusion of blood and blood components
3.3.8	Sterile single-use plastic syringes

New monographs, official 1st jan 2026



European Pharmacopeia (Ph. Eur.)





Dy.66 Fr.87 Nd.60
a /dif-rənt/ view on chemistry

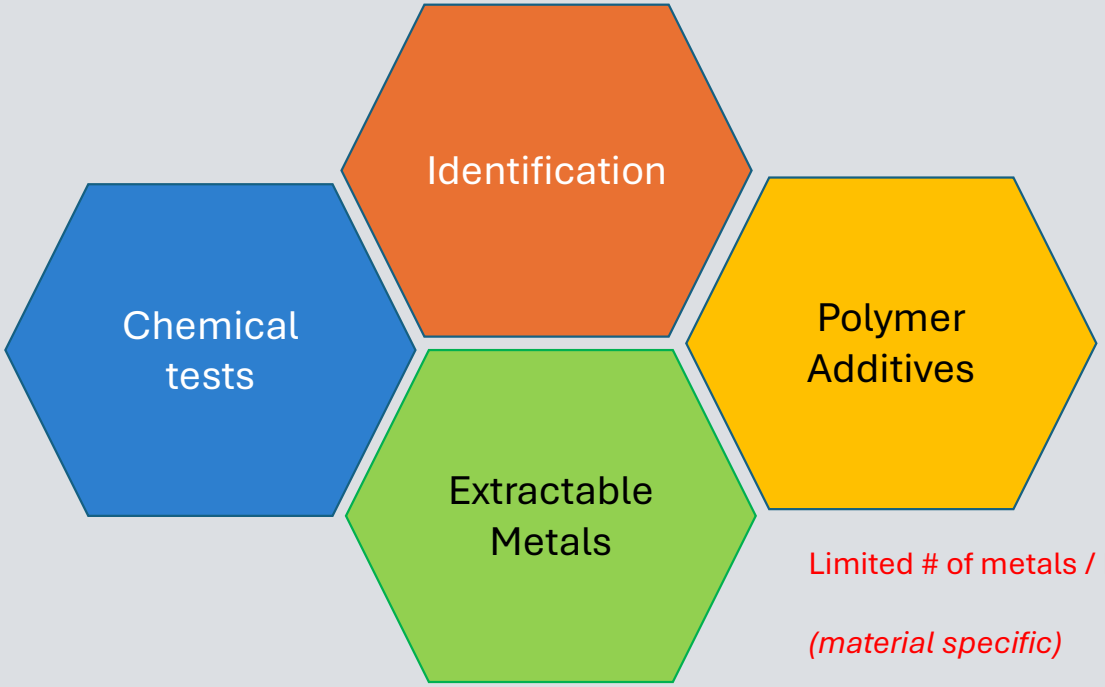
In general, the compendial testing for packaging & packaging materials

can be divided into:





- **Identity**
- **Physicochemical tests**
- **Extractable polymer additives**
- **Extractable elements**



Note:
not all tests are mandatory nor described for each material,
see the specific monograph for details

Ph.Eur. 3.1 series (materials)



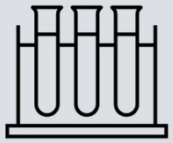
Structure of a Ph.Eur. monograph:

- Definition
- Production
- Characters

- **Identification**
- **Tests**
- **Supplementary Tests**

Sample Prep	Analysis	Evaluation
Amount solvent	“techniques”	limits









European Pharmacopeia (Ph. Eur.)

Polymer Additives

QUID ?

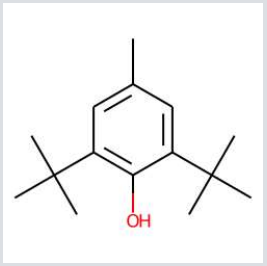
PA 07	=	BHT
PA 09	=	Irganox 1010
PA 13	=	Irganox 3114
PA 11	=	Irganox 1076
PA 08	=	Hostanox 03
PA 10	=	Irganox 1330
PA 14	=	Weston 618
PA 16	=	Irganox PS 800
PA 17	=	Irganox PS 802
PA 12	=	Irgafos 168

Commercial names

Chemical (IUPAC) names

PA07:
Butyl Hydroxy Toluene

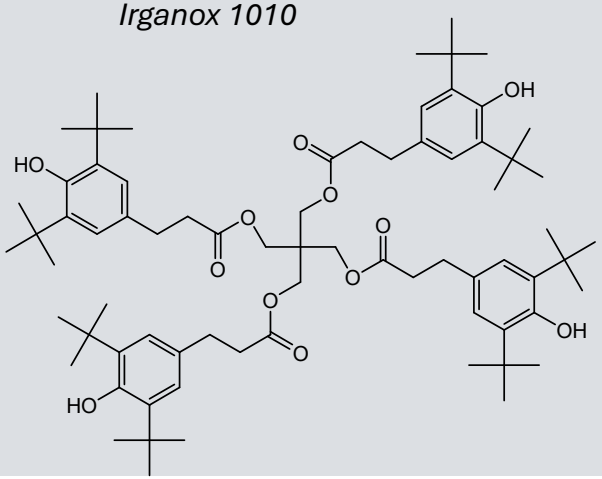
BHT



chemeo

PA 09 :
Pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate]

Irganox 1010





European Pharmacopeia (Ph. Eur.)

Dy.Fr.Nd.
a /dɪf-rənt/ view on chemistry

Polymer Additives

QUID ?

– hydrotalcite: maximum 0.5 per cent;
– alkanamides: maximum 0.5 per cent;
– alkenamides: maximum 0.5 per cent;
– sodium silico-aluminate: maximum 0.5 per cent;
– silica: maximum 0.5 per cent;
– sodium benzoate: maximum 0.5 per cent;
– fatty acid esters or salts: maximum 0.5 per cent;
– trisodium phosphate: maximum 0.5 per cent;
– liquid paraffin: maximum 0.5 per cent;
– zinc oxide: maximum 0.5 per cent;
– magnesium oxide: maximum 0.2 per cent;
– calcium stearate or zinc stearate or a mixture of both: maximum 0.5 per cent;
– titanium dioxide only for materials for containers for ophthalmic use: maximum 4 per cent.

The supplier of the material must be able to demonstrate that the qualitative and quantitative composition of the type sample is satisfactory for each production batch.

Screenshot from Ph.Eur. monograph



!

Commonly found Extractables *(Polymer additives)*:

- Irgafos 168
- Irganox 1076
- Irgafos 168 oxidized
- Irganox 1010
- Palmitic acid
- Stearic acid

Not in the monograph list
or a reaction product (non-intentionally added; NIAS)

Very limited example of E&L species



European Pharmacopeia (Ph. Eur.)

Dy.Fr.Nd.
a /dɪf-rənt/ view on chemistry

Ph.Eur. 3.1.3 PolyOlefines

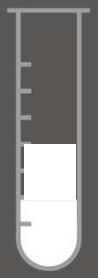


Identification	Identification	FTIR, TiO_2, *sulphated Ash*
Water extraction (UPW; S1)	Chemical tests	→ Absorbance; Acidity / alkalinity; Appearance; Reducing Substances
Acidic water extraction (HCl; S3)	Extractable Metals	Extractable Al, Ti, Zn, heavy metals
Toluene extraction (S2)	Polymer Additives	Phenolic and non-Phenolic Antioxidants, amides & stearates



European Pharmacopeia (Ph. Eur.)

Dy.Fr.Nd.
a /dif-ront/ view on chemistry

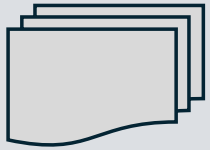


Compendial testing - US market

United States Pharmacopeia

Dy.Fr.Nd.
a /dɪf-rənt/ view on chemistry

Packaging Materials for Pharmaceutical Use







<1661>

Evaluation of Plastic Packaging Systems and their Materials of Construction with respect to their User Safety Impact

<1663>

Assessment of Extractables associated with Pharmaceutical Packaging/ Delivery Systems

<1664>

Assessment of Drug Product Leachables associated with Pharmaceutical Packaging/ Delivery Systems

<1665>

Characterization and Qualification of Plastic Components and Systems to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products

<661>
Plastic Packaging Systems and their Materials of Construction

No longer valid after 1st dec 2025

<661.1>

Plastic Materials of Construction

<661.2>

Plastic Packaging Systems for Pharmaceutical use

<665>

Plastic Components and Systems to Manufacture ....

<381>

<382>

<383>

Note: <1662> & <662> (drafts) for metals in packaging

United States Pharmacopeia (USP)

Dy.Fr.Nd.
a /dif-rənt/ view on chemistry

Packaging Materials for Pharmaceutical Use





<661.1>

For

CO	Cyclic Olefins
PA	PolyAmide 6
PC	PolyCarbonate
PE	PolyEthylene
PET / PETG	PolyEthylene Terephthalate
EVA	Poly(Ethylene-Vinyl Acetate)
PP	PolyPropylene
PVC	PolyVinyl Chloride

Sample Prep	Analysis	Evaluation
Amount solvent	“techniques”	Limits or specifications







USP did a “copy-paste” of *Ph.Eur.* Monographs in 2016, so **a lot is common** (approach, testing, evaluation),

But also differences and more updates / changes in USP !!

e.g. Specifications versus limits, e.g. TOC and Absorbance



United States Pharmacopeia (USP)

Dy.Fr.Nd.
a /dif-rənt/ view on chemistry

What's new ?

⇨ **Evolving regulatory landscape !**



Ph.Eur.	**3.1.16**	**COP**	*01/jan/2026*
	3.1.17	**COC**	*01/jan/2026*
	3.1.18	**SBC**	*01/jan/2026*
USP	**<382>**	**Elastomeric Closure Functionality …**	*01/dec/2025*
	<661.1> & <661.2>		*01/dec/2025*
	<665>	*Plastic systems …..*	*01/may/2026*
	<383>	*Cured Silicone Elastomers*	*01/dec/2027*
ISO	**10993-1 … 10993-18 : Medical devices**		*active*

A lot is being drafted, reviewed, planned …

- ▶ In Extractables & Leachables Pharma *(USP chapters)*
- ▶ Medical Devices - chemical characterization *(TS)*



Compendial on the Road to E&L

Dy.66 Fr.87 Nd.60

a /dif-rənt/ view on chemistry



Pharmacopeia Testing provides





- Identity confirmation
- Physical characteristics (general and not highly specific)
- Tests on some additives and/or elements (limited scope)

No specific, detailed information on individual compounds except the ones on the limited list !

- Monographs (or parts) can be used in Batch-to-Batch control of polymers, or a supplier selection criterion.
- NOT all materials have a monograph ("unadressed materials") !!
- Ph.Eur. has alternatives for DEHP (banned polymer additive). *(PA 24 / 25 / 26 / 27)*



Pharmacopeia testing doesn't provide a full E&L profile !





→ focused on general characteristics, not identification of extractables above AET

→ it's not detecting degradation or reaction products of polymer additives, e,g, Irganox 1010

→ it can not provide enough data for a Toxicological assessment !

- Compendial testing on raw materials has to include the possible (effect of) sterilisation.

- Define a strategy for the assessment and the testing for elemental impurities !

Compendial	= limited set of extractable metals
ICH Q3D	= Scientific Guideline on Elemental Impurities in Finished Drug Products
USP <232> & <233>	= monographs on Elemental Impurities (limits & procedures)

Extractables study



Chemical Characterization study



PHARMACEUTICAL CONTAINER / DELIVERY SYSTEM

MEDICAL DEVICE



e.g. <1663>, PQRI

ISO 10993 – 18

Appropriate solvents for extraction



knowledge on the composition

FOCUS = **IDENTIFICATION**





Nitrosamines
PFAS
Phthalates
PCA, PCB
.....

Dy.Fr.Nd.
a /dɪf-rənt/ view on chemistry

COMPOUNDS IN THE PICTURE

EXAMPLES

TiO_2
DEHP
BPA
n-Nitrosamines
Pthalates
PCA, PCB
PFAS
……

Most of these compounds are not standard-wise "detected" / assessed during compendial testing or E&L (NTA screening)

In general:

Need for specific techniques / methods due to sensitivity needs

Targeted more then NTA

More dedicated (and complex) sample preparation

Nitrosamines

= **group**-name for molecules which exhibit the same functional group ….

- ► Generated in the course of a chemical reaction: prerequisites
- ► Toxicological concerns (Cohort of Concern – ICH M7)



2018 : DP Valsartan & NDMA (n-Nitrosodimethylamine)

Since 2018:
- → more and more n-Nitrosamines in scope (“list” with maximum intake – “ng/day range”)
- → not only drug products (API) under scope

! N-Nitrosamines are only formed in a chemical reaction that requires : “amine-structures” and an oxidizing species / context (nitrosating agent – nitrite)

PFAS

Per- and polyfluoroalkyl substances

= a group of synthetic organo-fluorine chemical compounds

(multiple fluorine atoms attached to an alkyl chain)

PFOS & PFOA

Perfluoroctanesulfonates

Perfluorooctanoic acid (perfluorinated carboxylic acid)

Concerning PFAS due to health and environmental concerns:
they're persistent and non-biodegradable

PFAS

Per- and polyfluoroalkyl substances

= a **group** of synthetic chemical compounds



Fsawwa.org

They're everywhere !

"Excellent" properties in many applications
water / oil / grease repellent

→ **analytical challenges !**

- ▶ **sample preparation**
- ▶ **background presence**
- ▶ **sensitivity** — *state of the art MS-based methods*
- ▶ **NTA or targeted ?** — *How can you screen for thousands ?*



Conclusions

Polymers used in pharmaceutical packaging or medical devics

- → basic quality can be assessed by compendial monographs
  = compliance
- → not a garantuee for a succesful E&L study or Chemical Characterization
- → “medical or pharma” grade is not a compliance

Evolving landscape of regulations

Emerging chemical species bring challenges and the need to focus / add scope to existing analytical assessments



Screen or target group of chemical species ?

Dy.66 Fr.87 Nd.60
a /dɪf-rənt/ view on chemistry