



A Descriptive Study of the Regulations of Leachable and Extractables of US, Europe and Canada

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Article info

Received 24 May 2018

Revised 25 June 2018

Published 29 June 2018

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Abstract

Leachables and extractables are one of the most important reasons for drug product quality deterioration and degradation. These components tend to migrate from the interior regions of the packaging material to the drug product by causing interactions, due to absorption or adsorption of the same on the Drug Product. The USFDA, EU and Health Canada laid down specific non-exhaustive regulation and guidelines that are to be followed in mandatory to attain drug approvals from these regulated regions. The USFDA, in its recent revision of its ANDA (Abbreviated New Drug Application) checklist, has included leachables and extractables as an essential parameter of rejection of the ANDA application. The same agency recommends the applicant to take up leachables and extractables study during the developmental stages, to avoid further repercussions. The EU, on the other hand, suggests the regulations on the same leachables and extractables mainly for the plastic-based packaging containers, while mentioning the testing for glass-based containers. Canada has the least of the three in content regarding the leachables and extractables however, the same country respects a proper protocol in testing, threshold setting and its inclusion in final CTD submission in line with the laid regulations of the USFDA. The complete document describes the regulations of these three regions about leachables and extractables.

Keywords: Leachable; Extractable; FDA; Health Canada; EMEA; Regulatory requirements

Abbreviations

US: United States; USP: United States Pharmacopoeia; USFDA: United States Food and Drug Administration; EU/EMA: European Union/European Medicines Agency; ANDA: Abbreviated New Drug Application; CTD: Common Technical Document; MDI: Metered Dose Inhaler; DPI: Dry Powder Inhaler; CCS: Container Closure System; ROA: Route of Administration; DP: Drug Product; DMF: Drug Master File; GC: Gas Chromatography; MS: Mass Spectroscopy; HPLC: High-Performance Liquid

Chromatography; FTIR: Fourier Transform Infrared Spectroscopy; LCMS: Liquid Chromatography-Mass Spectroscopy; TTC: Threshold of Toxicological Concern; SCT: Safety Concern Threshold; QT: Qualification Threshold; AET: Analytical Evaluation Threshold; PQRI: Product Quality Research Institute; LOD/LOQ: Limit of Detection/Limit of Quantification; TDI: Total Daily Intake.

Introduction

Leachables and extractables are substances that affect broader dimensions of the drug product quality. Leachables are substances that migrate from the container closure to the product by altering its essential integrity, while the extractables are substances extracted from the container system during its contact with a solvent. The Oral liquids, inhalants, parenteral, ophthalmic are some of the essential dosage forms that are profoundly influenced by leachables. The percentage of such contents determined with proper analytical techniques designed in cooperation between the container supplier, applicant, and the agency. The analytical method used will determine the composition of the container and closure material. The composition given by the vendor or manufacturer/vendor of the packaging material and the same can be substantially vitalized to understand a correct analytical sensitive technique to quantify minute substances. The substance constituent and other components vary as per the dosage

form and with more than 800 recalls of products in the US in the year 2014, it is necessary for such dosage forms to have a relevant procedure for identification.

Regulations in US: leachables and extractables

One of the prime reasons for a country like the US and an agency like FDA to concentrate on the part of leachables and extractables was the total number of recalls of products made due to this issue. The agency made a record of 800 plus recalls and most of them had problems with drug product quality during its proposed shelf life [1].

The following table could show the guidelines published by FDA that includes leachables and extractables as a part of regulatory importance [2]:

Table 1: Guidance of FDA and Chapters of USP.

Guidance Published	Year
FDA guidance for industry: container closure systems for packaging human drugs and biologics. Chemistry, manufacturing, and controls documentation	1999
FDA draft guidance for industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) drug Products. chemistry manufacturing and controls documentation	1998
FDA guidance for industry nasal spray and inhalation solution, suspension, and spray drug products chemistry, manufacturing, and controls documentation	2005
FDA reviewer guidance for nebulizers, metered dose inhalers, spacers, and actuators	1998
FDA guidance for industry and FDA staff: technical considerations for pen, jet, and related injectors Intended for use with drugs and biological products	2013
Chapters in USP	Number
Assessment of extractables associated with pharmaceutical packaging/delivery systems	USP 1663
Assessment of drug product leachables associated with Pharmaceutical Packaging/Delivery Systems	USP 1664

The FDA's example chart of the vulnerability of a packaging system to a dosage form [3]

The expectations of the FDA

The of leachable and extractable have thoroughly addressed in many presentations from the FDA officials. The following are the essential requirements to test extractables:

1. By qualifying the container closure system (CCS) components for better acceptability in packaging operations.
2. By applying the same to monitor toxic substances in the CCS.
3. By developing better analytical methods for leachables testing.
4. By using for quality control for acceptance of CCS components.

Table 2: Chart of Vulnerability of a Packaging System to a dosage form.

Degree of concern associated with route of administration	Likelihood of packaging component-dosage form interaction		
	High	Medium	Low
Highest	Inhalations: aerosols, sprays	Injections and injectable suspensions, inhalational solutions	Powders: sterile, injectable inhalation
High	Transdermal ointments and patches	Ophthalmic solutions and suspensions, nasal aerosols and sprays	
Low	Topical: solutions and suspensions, Aerosols oral: solutions and suspension		Oral: tablets, capsules, powders, Topical: powders

Testing extractable substances are crucial to understanding the type of leachables; the drug is about to encounter. It is a process of exposing the solvent based medium such as parenteral or ophthalmics that is solutions or suspensions in contact with the primary packing and secondary packing of the container. The exposure of the packaging components during shelf life or in-stability testing makes it easier to understand the leachable occurrence with passing time. The stability testing is much more appropriate to relate to the leachable than the product, as it faces adverse conditions in the container involving climatic factors or time-based factors.

The purpose of leachable testing as per the FDA is:

1. To monitor container-closure related impurities in drug product in the stability studies or other container qualification studies.
2. To understand the effect of the immediate container fabrication components, migratory label, and secondary packaging-based components and to understand reaction compounds created between the CCS and Drug product.
3. To refer the Compendia involving USP 661, 1151, 601, 1663 and 1664 for testing of leachable and extractable.
4. To account the patient population, ROA (Route of Administration), and potential for interaction between formulation and CCS.

Potential sources of leachable as per the FDA are (non-exhaustive)

1. From the container closure: Plasticizer, lubricant, pigment, stabilizer, antioxidant, binding agent.
2. From the labelling: ink, adhesive, varnish.
3. From the outer carton: sterilization agent, preservatives, sealant, ink.
4. From the parenteral and the ophthalmics, the sources listed from the primary container, the migration of label-based ink through semi-permeable containers or from the resins of the container. As per USP 661, these resins are first developed from the reagents under reaction forming the basic resin, in which specific processing aids or additives are added forming the final resin-based packaging material. It is the process of application of reverse engineering resulting in the detection of the components of the packaging material.
5. From the other sources could be chemicals present in plastic films and tubing, adhesives from labels, elastomeric closures, components of glass, etc.
6. From the small molecules found in some instances crossing the container membranes and entering the drug product. Some of them are Antioxidants, surfactants, plasticizers, acid scavengers, crosslinking agents, residual monomers, polymerization side products, process impurities based on the kind of polymerization process used to make the container's first polymer from monomers and oligomers. These components play a crucial role to understand their possible occurrence in the drug product.

Steps in extractable and leachable study (brief)

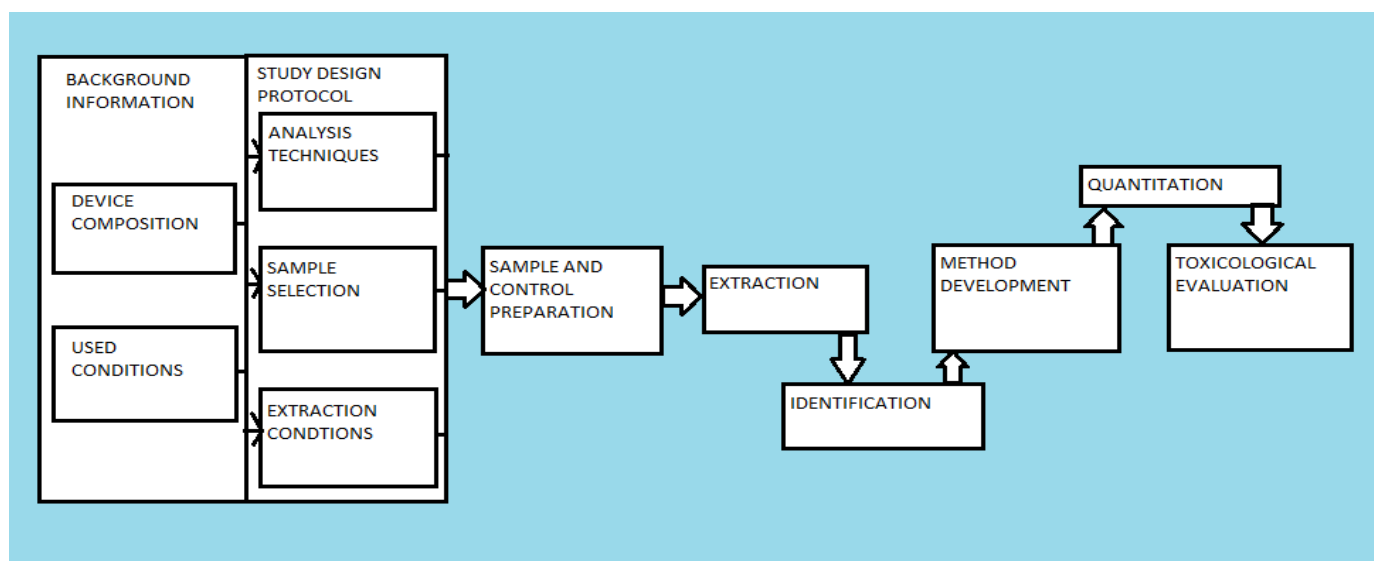


Figure 1: Steps in Extractable and Leachable Study.

Approaches suggested by the FDA

1. It is necessary that information about the Container Closure System and its components are shared between the suppliers, applicants, and FDA. The composition of a container closure system (CCS) and the procedure of fabrication plays a crucial role in understanding the necessary components which can contribute to leaching. Though some of them are already available in public domains, the sharing enables better chances and opportunities to understand potential leachables.
2. For detecting the type and quantity of a leachable in a DP (Drug Product), it is necessary to design an appropriate analytical method. It can play a center specific role in understanding the limits of quantities of leachable and extractable in a Drug product with the potential theories of interaction from the previously published literature of the analytical known leachable components' reaction with the Drug Product. So, there are three kinds of personnel involved in such understanding: the applicant, the supplier, and the agency. The applicant designs the analytical method for detection and determination of the CCS components; the supplier supplies the DMF (Drug Master File) confidentially to the agency which will further review the technique created by the applicant to justify if the technique is capable enough to quantify and qualify such leachable.
3. The study of leachables applies to at least one batch which is under stability studies (accelerated and long-term study through expiry) under six months or more. It is necessary that any study owing to leachables must have appropriate controls and standardized conditions.
4. The detection of leachables performed via HPLC (High-Performance Liquid Chromatography) or GC (Gas Chromatography) with acceptable LOD (Limit of Detection) and LOQ (Limit of Quantification) limits. The generated leachable analytes will be compared with the in-house standards created from extractable study, knowledge of CCS composition and additional information from CCS suppliers. The leachable is reported in units of ppm and identified by CAS (Chemical Abstracts Service) registry number, structure, name and other such identifying characteristics for toxicological assessment.
5. For Parenteral, many applicants do not use a single packaging material as a novel CCS material. In fact, there is no such packaging material called "novel" CCS packaging material. The parenteral is mostly consisting of aqueous solutions at a neutral pH. In certain exceptional cases, where it is a lipid emulsion, it gets destabilized from rubber or plastic components or where it is high-pH formulations that can be vigorous extractors taking out silicone oil. The oil is used to lubricate closures or trace metals from plastic containers contaminating the parenteral or it can be the diluent that makes up the volume of parenteral by enabling it to be incompatible with the packaging components as per FDA. The Total Parenteral Nutrition components in parenterals are tested for Aluminum content, and the same also has a

concern concerning contact with glass containers.

6. Under FDA, there is a three-tiered approach for characterization, involving material of construction characterization, packaging system characterization, and pharmaceutical product characterization.

Regulations and chapters from the FDA on leachables and extractables [2]

1. USP 661 (Plastic Packaging Systems and their materials of construction), USP 1663 (Assessment of extractables associated with pharmaceutical packaging/delivery systems), USP 1664 (Assessment of drug product leachables related to pharmaceutical packaging/delivery systems) mentioned earlier.
2. USP 661.1 Plastic Materials of Construction.
3. USP 661.2 Plastic Packaging systems for pharmaceutical use.
4. USP 1664.1 Orally Inhaled and Nasal Drug Products.
5. USP 1665 Toxicological Assessment.
6. USP 661.3 Plastic Systems used for manufacturing pharmaceutical products.
7. USP 661.4 Plastic Medical Devices used to deliver or administer pharmaceuticals.

The procedure of analysis under FDA regulations (in brief) [2]

1. The sampling mainly involves taking a sample that may be the part of the CCS which is the representative of the packaging container of the actual marketing container.
2. The extraction study can be performed through three types of methods: a) Simulated-use Extraction, which includes an extraction using a method simulating actual and expected conditions. b) Exaggerated Extraction, which provides for extraction involving a technique to extract more in quantity than the simulated process. c) Exhaustive Extraction, which consists of a procedure of extraction repeated until the total amount of extractables is less than 10% of the amount obtained during the initial extraction.
3. The identification is performed via MS (Mass Spectroscopy) or GC or HPLC or NMR (Nuclear Magnetic Reasoning) or FTIR (Fourier Transform Infrared Spectroscopy) or GC-MS or LCMS (Liquid Chromatography-Mass Spectroscopy) or combination of these to find appropriate results.

4. The method to be used must undergo validation too for its check of accuracy.
5. The detectability and approaches for quantification involve Formal Quantification (authentic reference compound) and Relative quantification (surrogate standard).

Three forms of thresholds are required to be identified: Threshold of toxicological concern (TTC), Safety Concern Threshold (SCT), Qualification Threshold (QT) and Analytical Evaluation Threshold (AET). The AET is a threshold at or above which the applicant must identify the leachable or extractable and report the same for toxicological assessment.

$$\text{AET (microgram/container)} = (0.15 \text{ microgram/day/doses/day}) \times (\text{labelled doses/container}).$$

As per the USP 1663, the extractables could be extracted by using suitable solvents of organic origin that doesn't react with the required extractable. There are techniques involved in characterizing the extract. It is essential to understand that though the extract is well taken out from a packaging material, it is necessary to use a proper technique to understand the type of extractable being extracted out. The following are the four processes:

1. **Scouting:** It is a procedure by which an analytical method is used to analyze the type and kind of analyte found as an extractable [9].
2. **Discovery:** It is a procedure where the individual analytical response of a specific analyte in a sample is taken in proportion to the amount of that analyte in the same sample. The response is accepted, when the same is in proportion to the amount. Generally, in such cases, GC or HPLC or combination of various chromatographic techniques could be developed [9].
3. **Identification:** It is done mainly via structural analysis or qualitative analysis. The former includes an analytical process that could give out compound-specific information from which the complete structural data of the unknown analyte with class could be analyzed and understood. The latter one involves matching the unknown analyte with an authentic reference compound and infers the actual characteristics of the same. The HPLC/MS, GC/FTIR, GC/MS and other such combinations of analytical methods are used proficiently [9].
4. **Quantitation:** For this procedure, it is essential to have the instrument detector response of the

extractable as a reference substance recorded separately and compared with the response of the same analyte in the sample under test helping to quantify the extent of the presence of the same substance [9].

The following table shows the application of the above processes with utility [9]

Table 3: The application of scouting, discovery, identification, and quantitation.

Analytical Technique	Analytical Method	Application				Information/Utility
		Scouting	Discovery	Identification	Quantitation	
Spectroscopy	UV	X		X		Bulk property of UV absorbing organic extractables; semi-quantitative with limited identification ability
	FTIR ^a	X		X		Bulk property of IR absorbing organic extractables, moderate identification ability
	NVR ^b , ROI ^c	X				Bulk property reflecting total amount of non-volatile organic and/or inorganic extractables
Wet Chemical	pH	X				Bulk property of acidic or basic extractables
	TOC ^d	X				Quantitative measure of organic extractables
	FID ^e		X	X	X	Discovery and quantitative assessment of individual organic extractables; note that qualitative identification is possible
Gas Chromatography	MS		X	X	X	Discovery, identification, and quantitation of individual organic extractables; note that identification can be either qualitative or structural

	FTIRa		X	X		Discovery and identification of individual organic extractables; note that FTIR has limitations relative to structural analysis (however identification via qualitative analysis is possible)
	UV, CADf, and ELSDg		X		X	Discovery and quantitative assessment of individual organic extractables; note that identification via qualitative analysis is possible and that Diode Array UV detectors can assist with structural analysis
Liquid Chromatography	MS		X	X	X	Discovery, identification, and quantitation of individual organic extractables; note that identification can be by either qualitative or structural and that ionization sources with different selectivities are available
	FTIRa		X	X		Discovery and identification of individual organic extractables; note that FTIR has limitations relative to structural analysis (however identification via qualitative analysis is possible)
	NMRh		X	X		Identification of individual organic extractables;

						note that identification can be by either qualitative or structural
	Conductivity		X		X	Discovery and quantitation typically of individual ionic species
Ion Chromatography	MS		X	X	X	Discovery, identification, and quantitation of individual ionic extractables; note that identification can be by either qualitative or structural and that ionization sources with different selectivity's are available
	MS		X	X		Identification of individual organic extractables
Spectrometry	NMRh		X	X		Identification of individual organic extractables
	IMSi		X	X	X	Discovery and quantitative assessment of individual organic extractables; note that various ionization sources are available and that qualitative identification is possible

a FTIR = Fourier Transform Infrared spectroscopy.

b NVR = Non-volatile Residue.

c ROI = Residue on Ignition.

d TOC = Total Organic Carbon.

e FID = Flame Ionization Detection. Additional GC detectors, such as Thermal Energy Analysis Detector (TEA), may provide greater sensitivity for specific compound classes.

f CAD = Charged Aerosol Detector.

g ELSD = Evaporative Light Scattering Detector.

h NMR = Nuclear Magnetic Resonance spectroscopy.

i IMS = Ion Mobility Spectrometry.

j AAS = Atomic Absorption Spectroscopy.

k ICP-AES = Inductively Coupled Plasma Atomic Emission Spectroscopy.

l ICP/MS = Inductively Coupled Plasma Mass Spectrometry.

USP 1664 explains about the assessment of Drug product leachables that includes the necessary

recommendations from this chapter of the procedure to be followed to place a reasonable explanation

qualitatively and quantitatively for the type of Leachables detected through a formulated procedure. The characterization of leachables using analytical methods or processes avoids scouting as the same process can result in responses that could include interferences from the API-excipient constituents. The primary target of this chapter is to establish a correlation between the extractable and leachable. This correlation is only applicable when the levels of estimated levels of a possible substance as leachable are less than the amount of same substance found as extractable in the extractable profile. The levels of the extractable must be more than the leachable or else the correlation can never take place. In no correlation scenarios, the conclusion made that the procedure of extraction might have been incomplete or inefficient or there has been a change in the unreported manufacturing process of the packaging material or its composition that needs to be rechecked and reanalyzed [9].

There are thresholds under leachables too with TTC, SCT, QT, and AET. The TTC is a threshold below which a leachable of a specific concentration does not cause any possible risk to the human body under-

exposure. The TTC was first used by EMEA (European Medicines Agency) for calculating genotoxic impurities, and the range of 1.5 microgram/ml is acceptable. The SCT is a PQRI initiated interval of a threshold. If the leachable quantity is below the SCT while being low in a dose, then the leachable is not of toxicological concern of testing. The QT is also a PQRI initiated threshold where the level below which the leachable is present, the same is acceptable on safety grounds. The AET is same as extractable, and the levels above the same should be identified and quantified [9].

The GC and HPLC with MS play a crucial role in identifying certain levels of leachable in the DP. The sensitivity of detecting in nanogram/ml or nanolitre/ml or nanogram/gram makes the analytical method more sensitizing and vital. In addition to the procedure to identify, it is also essential to validate the method with parameters like Accuracy, Precision, Range, Ruggedness, Robustness, LOD, LOQ, System suitability and precision tests by place the method so used under better regulatory acceptance of the FDA [9].

Risk assessment for leachables [11]

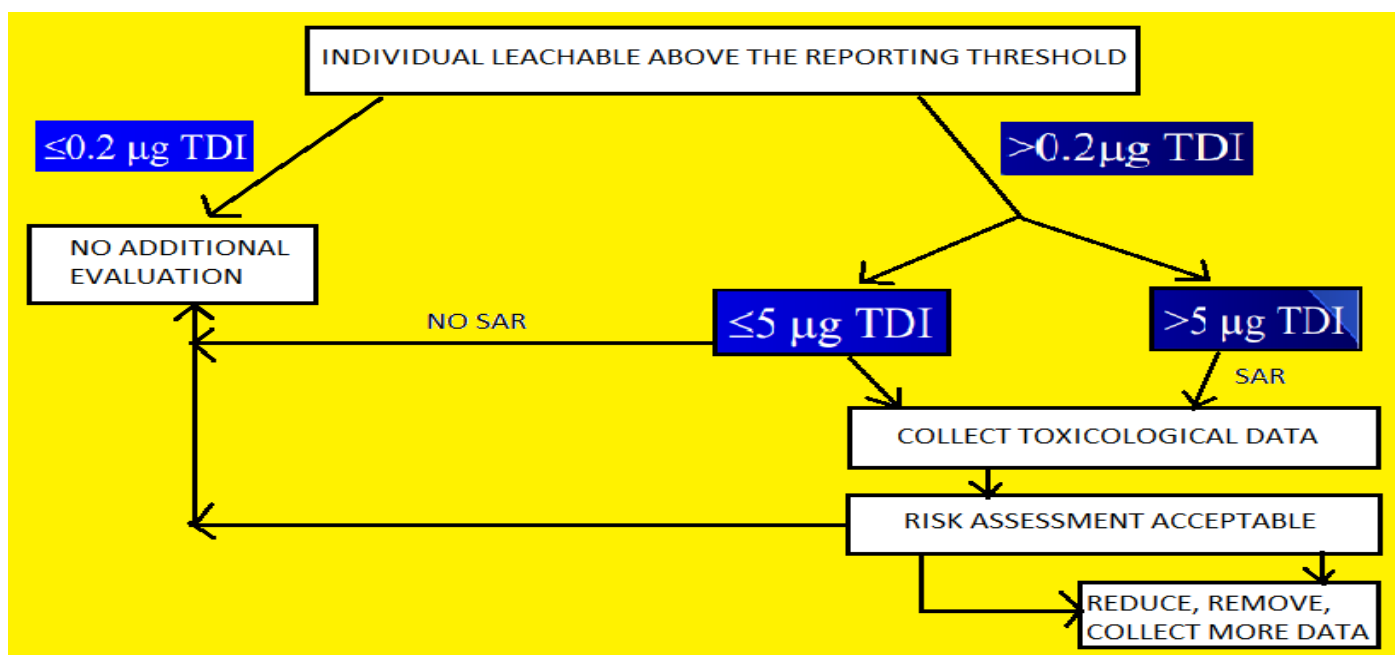


Figure 2: The risk assessment for leachables.

Some of the potential harmful leachables [12]

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds formed during the incomplete combustion of organic materials. During the 1990s, the U.S. Food and Drug Administration (FDA)

became aware of reports concerning PAH contamination within chlorofluorocarbon (CFC)-filled metered-dose inhalers (MDIs), inadvertently introduced by some of the elastomers used as seals in MDI drug products. Although the PAHs were only present in trace amounts, these findings promoted the

first concerted efforts to look for additional leachables in MIDIs.

Vanillin

Vanillin, a phenolic aldehyde used in the food industry has been detected in inhalation solutions within the primary low-density polyethylene (LDPE) containers. It was found to be capable of migrating through the LDPE wall into the product from the outer cardboard packaging. To prevent it, an aluminum foil overwrap was introduced. However, those inhalation solutions that had already been packaged without this new overwrap had to be tested for any foreign contaminants, introducing significant time delays and increasing the costs of manufacturing.

Diethylhexyl phthalate

Diethylhexyl phthalate (DEHP) is used as a plasticizer in various polyvinyl chloride (PVC) products, including several medical devices such as intravenous tubing, bags, and catheters. DEHP has been found in the total parenteral nutrition (TPN) fat emulsions used to help patients gain weight, as it can migrate from the PVC infusion lines into the emulsion and enter the body of the patient.

Other potential sources for leachables [7]

1. **In-process single use systems:** It included Single-Use Bioreactors for product intermediates, IV bags, carboys, filters, tubing, and gaskets, etc.
2. **Primary packaging components:** It included syringes, ampoules, vials, bottles, plastic/metal containers and closures (screw caps, rubber stoppers).
3. **Secondary packaging components:** It included Cardboard containers (cartons), Overwraps and Labels (adhesives and inks).
4. **Tertiary packaging materials:** It included corrugated boxes and pallets.

Regulations in Europe: leachables and extractables

The European guidelines about leachables and extractables are different from the US [5,6].

From the guideline (“Guideline on Plastic Immediate Packaging Materials”)

The EMEA or EU laid out a guideline under CHMP for regulating leachables from plastic-based containers and closures: “Guideline on Plastic Immediate Packaging Materials” effective from December 1, 2005. It concerns the application of-

1. Part 1, Module 3, sections 3.2.1.6, 3.2.2.2 and 3.2.2.7 of Annex I to Directive 2003/63/EC, amending Directive 2001/83/EC for human medicinal products.
2. Part 2, sections A, C and G of Annex 1 to Directive 2001/82/EC for veterinary medicinal products, respectively, to plastic immediate packaging materials.

The guideline omits the elastomers and the natural and synthetic rubber from the guidance.

It mentions the Sorption and migration studies. It further includes the effect of the packaging material on active substance due to container-API interaction, or on Medicinal Product due to container-MP interaction. It also mentions the packaging material and its monomer if an interaction is seen with degradation of the content in the container-closure system. The additives, plasticizer and other needing ingredients during the manufacture of packaging material must be considered and reported in appropriate sections of the CTD. As per EU, the necessary information about the packaging material needs to be mentioned in 3.2.S.6 (active ingredient container closure system), 3.2.p.2.4 (medicinal product pharmaceutical development) and 3.2.p.7 (medicinal product container closure).

Under 3.2.S.6, it is necessary to include general information on the type and nature of material, specifications, and results of extraction and interaction studies with toxicological documentation wherever necessary. Under 3.2.P.2.4, it is required to show the compatibility between the medicinal product and the plastic material, the photostability of the plastic material and the influence of manufacturing process of the medicinal product on the plastic material. Under 3.2.P.7, the description of the CCS with components of plastic material and its selection for every component and specification for each.

The following data are to be mentioned in an EU submission:

1. It is necessary to specify the chemical name of the material(s) and the monomer.
2. The date is needed to be mentioned wherever the non-solid medicinal products and active substances are in contact with the plastic materials.
3. The qualitative and quantitative composition of the plastic material (active substances).
4. Name of the supplier, if intended for inhalation, ophthalmic or parenteral administration and total qualitative composition of the plastic material (medicinal product).

5. To establish the specifications of the plastic material in contact with the medicinal product or active substance by referring to relevant monographs of European Pharmacopoeia or monograph of the pharmacopoeia of a member state with compliance.
6. If a monograph is not available in the EP or member state pharmacopoeia, an in-house monograph should be established by using general methods given in the pharmacopoeia.
7. The main inclusions and additive inclusions must have a description, identification and characteristic properties of the material with the identification of additives, colorants, and extractables (extractable studies).

Migration studies: It is done during the developmental stage, where the same studies are performed on the active substance and initial formulation to choose suitable packaging material for the active substance and medicinal product respectively. These studies are necessary when several extractables have resulted in the extraction studies. These migratory studies must ensure to show that these extractables will not migrate in toxic quantities to alter efficacy and stability of the active substance/medicinal product. Simulation studies performed with test media cannot preclude the main tests done on active ingredients/medicinal product. The analytical method should be described as per the pharmacopoeia where the non-compendial ones are required to be validated, and leachables must be assigned with appropriate limits.

A migration study may be omitted if the level of specific leachable is non-toxic and when a suitable justification can be given for the same. The same study is only propagated if the amount of extraction shows toxic levels. If the same study was not done during the developmental study, the same should be performed during the stability study batches. It is necessary to conduct migration study on at least one batch of active ingredient.

Sorption studies: These studies are mainly performed when a packaging material is unfit or is under interaction with the active ingredient or an excipient of the drug product via adsorption or absorption, resulting into the overall degradation of drug quality.

Toxicological information /documentation [5,6]

The toxicological information of the plastic packaging material is required when a specific drug product is intended to be marketed in a state of EU (European Union) or overall EU region. There are some packaging materials mentioned in the European Pharmacopoeia or

Pharmacopoeia of any member state of the EU. Such packaging material, if non-compendial is intended to be included as a packaging material to market a Drug Product, and intended to be used in parenteral, ophthalmic or inhalation administration, the same requires toxicological information to be submitted to the agency.

From the guideline (“note for guidance on developmental pharmaceuticals”) [10]

A container-closure system found acceptable for one drug product cannot be assumed to be appropriate for another. The guidance described the necessary steps to consider for selection of the CCS. The following conditions are required to be tested for approving the CCS (irrespective of glass or plastic containers):

1. **Sorption to the container:** There are chances involving sorption of active ingredients or additives into the container from the liquid or semi-solid dosage form in relevant to the safety and stability requirements. This phenomenon is mainly common with the rubber closures and with both the plastic and glass containers and administration sets. In extreme cases, the sorption can permeate through the container walls.
2. **Leaching:** The data is required to ensure that there is no leaching from the pack into the dosage form arising safety concerns irrespective of glass or plastic.
3. **Dose reproducibility:** The data is required to show that the dosing device reproduces the same dose accurately with every use.

The permitted limits of the leachable and extractable substances

As per the Risk Evaluation Matrix, the following is the range and its perception of risk for the extractables:

Risk Index

Table 4: The Risk index is an estimate of the toxic potential of a specific extractables, calculated per ref.

Criterion	Score
RI > 10mg/day	0
<1mg/day RI < 10mg/day	1
0.1mg/day < RI < 1mg/day	2
RI < 0.1mg/day	3

Cramer Classification

Table 5: Established for either the extractable itself or its associate surrogate, per ref.

Criterion	Score
Class I	0
Class II	1
Class III	2

Mutagenicity Alerts

Table 6: Reflects published in vitro mutagenicity alerts as well as calculated in silico alerts per ref.

Criterion	Score	
No alerts	0	Lower
In Vitro alert	1	
In Silico alert	2	
Both in vitro and in silico	3	Higher

Composite safety score ranking

Composite safety score = risk index score + cramer score + mutagenicity score

Table 7: Safety Component of the Risk Evaluation Matrix [13].

Composite Score	Categorization	Safety Risk
0-1	Negligible Safety Risk	Lower
2-3	Lower Safety Risk	
4-5	Moderate Safety Risk	
6-8	Higher Safety Risk	Higher

Decision tree on the presentation of the document [11]

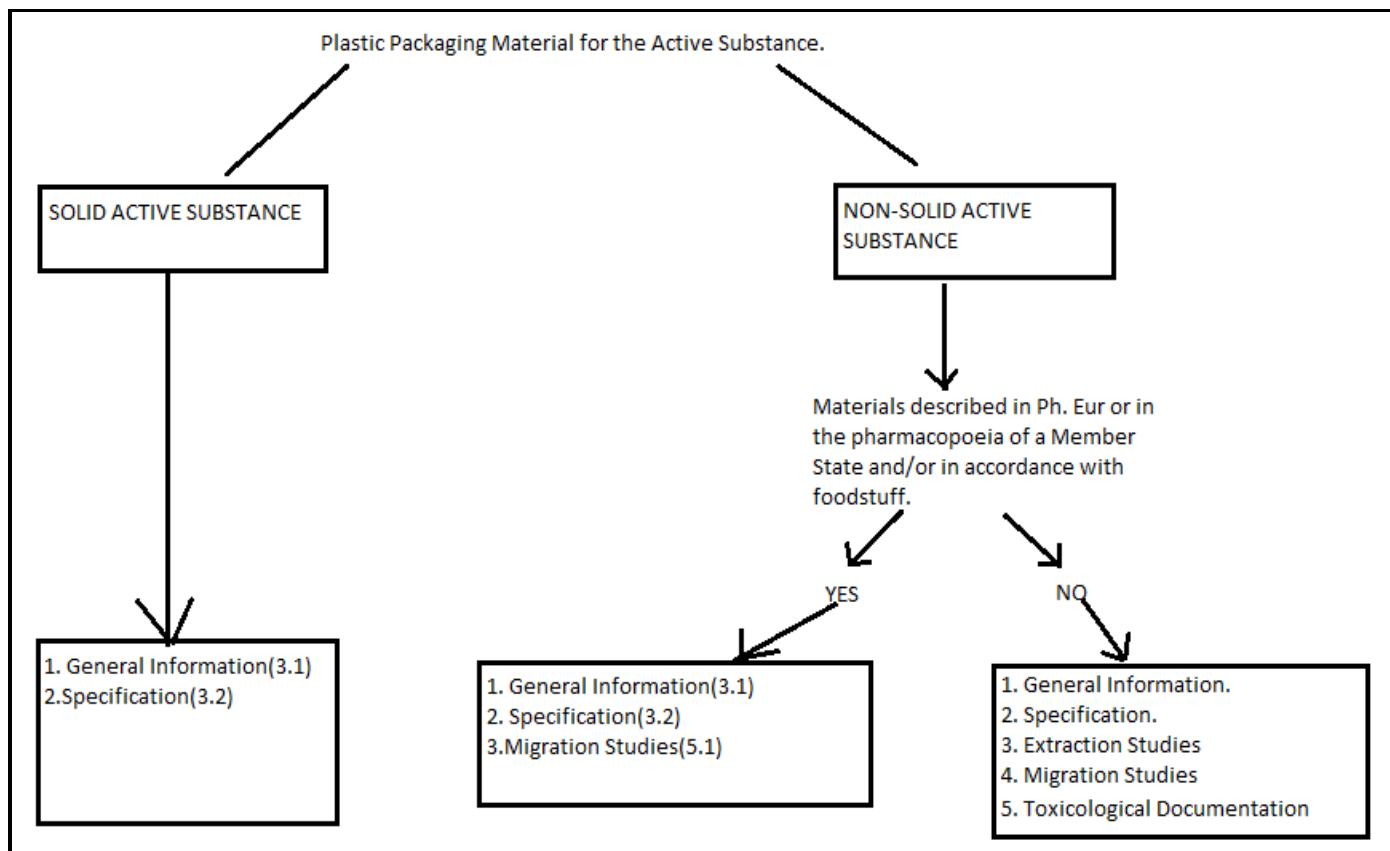


Figure 4: Decision tree on the presentation of the document.

Decision tree on the presentation of the documentation of plastic packaging material [11]

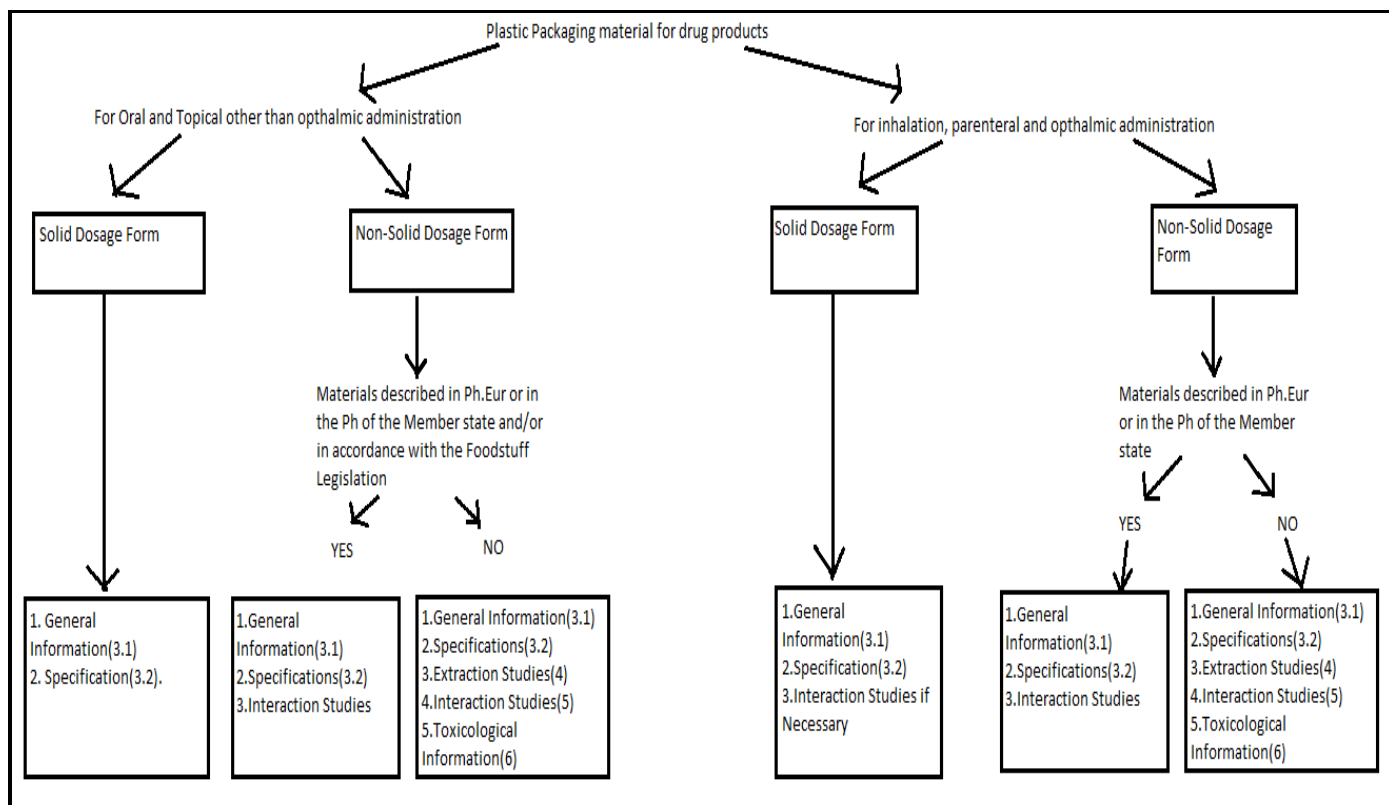


Figure 5: Decision tree on the presentation of the documentation of plastic packaging material.

Regulations in Canada: leachables and extractables [4]

Though very minimal, the regulations or guidelines about leachables and extractables are minimum under Health Canada, the regulatory body overseeing the functioning of drug approval and marketing in Canada. In the specific guidance, “Pharmaceutical Quality of Inhalation and Nasal Products,” the mentioning of leachables and extractables with its required content is highlighted.

Under CTD (Common Technical Document) Module 3, Section 3.2.P.2.4, the agency requires a comprehensive study design of the tests that are performed on the packaging material of non-compensial in nature. The study mainly includes identifying extractables, that can be leachable at the end of the shelf life of the drug product or near to the equilibrium during the test. The tests are done on the plastic and rubber components in contact with the drug product.

For compounds, which are potentially identified as leachables, need to undergo a safety assessment to establish safety thresholds with its inclusion under Module 4 of the CTD.

Establishing a correlation between extractable and Leachables is necessary. The same is required to create results of identification and quantification of leachable when the test will be performed based on its parent extractable. If the results of the same can be derived from raw materials or components, the same should be completed and reported in the CTD. If the levels of leachables are found to be within non-toxic levels, the test for leachables can be omitted from the requirement of its inclusion.

The test for leachables and extractables are also required for Nasal Products and other dosage forms. The same criteria are mostly not done for liquid-based dosage forms under non-parenteral origin.

Conclusion

The regulations of leachables and extractables for the three different regions resemble the necessity to perform studies during the developmental stages of the drug product. An earlier study report can make the applicant informed of the number of leachables and its relative reaction to the cause. The regulations are described briefly in all the three regions discussed in the document. The FDA proposes various guidelines and testing procedures for leachables by establishing an

extractable-leachable correlation. While, the European Regulatory body is concerned with both the plastic-based and glass-based leachables, where the particular focus in on the previous and the Health Canada is mainly concentrating on leachables in line with the US regulations.

It is required for the ICH to include a draft guideline on leachable and extractable with its testing procedures that can help the industrial applicants to penetrate multiple markets with appropriate data on leachables. In addition to the ICH, the individual regulated, and semi-regulated countries should initiate new procedures for detecting leachables to extend the shelf life of their marketed products.

Definitions

1. **SCT:** The safety concern threshold is the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effect.
2. **QT:** A qualification threshold is a threshold below which a given non-carcinogenic leachables is not considered for toxicological assessments unless the leachable present SAR concerns.
3. **AET:** The analytical evaluation threshold is defined as the threshold at or above which one should be identified and quantified for an extractable and/or leachable. It is a source to conclude the necessity of toxicological assessment for a specific leachable.

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Citation: Chakraborty A, Jayashree BS. A Descriptive Study of the Regulations of Leachable and Extractables of US, Europe, and Canada. *Int J Pharm Pharmacol* 2018; 2: 129. doi: [10.31531/2581-3080.1000129](https://doi.org/10.31531/2581-3080.1000129)

This manuscript was peer-reviewed

Mode of Review: Single-blinded

Academic Editor: Dr. Syed Sarim Imam

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