BRIEFING

〈1664.2〉 Parenteral Drug Products (Intramuscular, Intravenous, and Subcutaneous). It is proposed to add this new chapter as a companion to Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems 〈1664〉. This new chapter addresses specific considerations for leachables in parenteral drug products (PDPs). It focuses on drug products (injections) administered by intramuscular, intravenous, and subcutaneous routes. Note that the following discussion is primarily devoted to organic leachables. For consideration of inorganic (i.e., elemental) leachables, see 〈1664〉.

(GCDF: R. Kaja)

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Add the following:

▲〈1664.2〉 PARENTERAL DRUG PRODUCTS (INTRAMUSCULAR, INTRAVENOUS, AND SUBCUTANEOUS)

1. INTRODUCTION

This chapter addresses specific considerations for leachables in parenteral drug products (PDPs) as defined in *Injections and Implanted Drug Products* 〈1〉 and *Pharmaceutical Dosage Forms* 〈1151〉. It focuses on drug products (injections) administered by intramuscular, intravenous, and subcutaneous routes. Parenteral drug products that use other routes such as intradermal, intra-arterial, intracardiac, intraspinal, intra-articular, epidural, and perineural may have unique leachables concerns specific to their administration route.

Secondly, it is noted that the following discussion is primarily devoted to organic leachables. For consideration of leachables reported as elements, see *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* 〈1664〉.

Lastly, it is noted that in general, 〈1664〉 and its subsections address leachables derived from a drug product's packaging and/or delivery systems. However, drug products can contain leachables derived from their manufacturing equipment. Given the prevalent use of plastic and/or polymeric components in manufacturing equipment used to produce biological parenteral drug products, this chapter discusses leachables derived from manufacturing equipment and its components. A more detailed discussion of extractables and leachables associated with manufacturing components is contained in *Plastic Components and Systems used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products* 〈665〉. For medical devices and combination products regulated as medical devices (e.g., delivery devices), and for packaging that is considered a device-constituent part, users should refer to additional device-specific FDA guidance for industry (*1*).

2. KEY TERMS

In addition to the key terms listed in 〈1664〉, some key terms more specific to PDPs are the following:

- Analytical response factors of organic compounds in chromatographic screening methods applied to leachables study vary, often significantly, from compound to compound, confounding accurate quantitation and application of the analytical evaluation threshold (AET). The uncertainty factor (UF) reflects the variation of response factors.
- Single use and multiple use systems (SUS and MUS) used in the manufacture of primarily biological drug products (bDPs) can be composed of disposable polymer-based components, including connectors, filters, gaskets, process containers (bags), tubing, and valves, etc., see 〈665〉. As many SUS components are polymeric, they are potential sources of primarily organic leachables.

By FDA definition (*2*), a drug product is a "finished dosage form that contains a drug substance, generally, but not necessarily in association with other active or inactive ingredients". Additionally, "a dosage form is the physical form in which a drug is produced and dispensed, such as a tablet, a capsule, or an injectable". Consistent with these definitions, drug products can be classified by their physical form (their dosage form) and/or their route of administration. Of specific interest to this chapter are parenteral drug products, which are injected through the skin to allow the direct administration of the active drug substance(s) into blood vessels, organs, tissues, or lesions. These routes of parenteral administration include, but are not limited to:

- Epidural injections
- Intra-arterial injections
- Intra-articular injections
- Intracardiac injections
- Intracranial applications
- Intradermal injections
- Intramuscular injections
- Intravenous injections and infusions
- Intraspinal injections
- Perineural injections
- Subcutaneous injections

Parenteral dosage forms include emulsions, solutions, suspensions for solutions, and suspensions (including liposomes). These dosage forms can be classified based on the nature of their packaging and the drug product's volume per package unit:

- Type of packaging:
  - Single dose units: ampules, bags, bottles, cartridges, prefilled disposable syringes, and vials
  - Multiple dose units: multiple dose vials, multiple dose cartridges
- Drug product volume per package unit:
  - Small volume parenteral (SVP), volume ≤100 mL
  - Large volume parenteral (LVP), volume >100 mL

Packaging for parenteral dosage forms may be constructed from elastomers, glass, and polymers.

3. LEACHABLES ASSESSMENT RATIONALE FOR INTRAMUSCULAR, INTRAVENOUS, AND SUBCUTANEOUS PARENTERAL DRUG PRODUCTS

PDPs are generally categorized as high-risk dosage forms (as injections) due to the highest risk related to safety considerations related to the route of administration and a moderate probability of packaging component interaction with the formulation (see 〈1664〉, *Table 1*). The packaging systems used in these drug products consist of components of various types, some of which are constructed from polymeric (plastic or elastomeric) materials with complex chemical compositions and therefore a variety of potential leachables. Chemical entities can migrate (i.e., leach) into the drug product when there is direct contact with the primary packaging and indirect contact with secondary packaging.

PDPs typically require:

- Extractables studies for either the commercial packaging system or components thereof, performed as described in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* 〈1663〉.
- Extractables studies for the manufacturing system or its components, as necessary and appropriate, performed as described in 〈665〉.
- A leachables stability study for drug product registration that supports intended storage and use conditions throughout the proposed shelf-life, ideally on drug product stability batches manufactured with the same lots of packaging and manufacturing components used in extraction studies (to facilitate a leachables–extractables correlation). Such studies are described in 〈1664〉.
- Sensitive, selective, and fully qualified leachables analytical methods for both targeted and nontargeted analysis.
- Leachables assessments based on justified toxicological threshold (for the analytical evaluation threshold, AET [e.g., safety concern threshold (SCT)].
- Rigorous leachables–extractables correlations.

Leachables specifications, including acceptance criteria, may be necessary in infrequent circumstances where leachables control cannot be exercised by incoming control of packaging components (e.g., extractables). Note that the development and application of extractables and leachables specifications with appropriate acceptance criteria is a regulatory issue and therefore must be accomplished on a case-by-case basis with input from the regulatory authority.

4. CALCULATION OF THE AET FOR PARENTERAL DRUG PRODUCTS

A critical aspect of a leachables study is establishing the proper value for the AET, the threshold at or above which leachables should be reported for toxicological safety risk assessment. Some parenteral drug products may present a particular challenge with respect to the AET as they are used in chronic therapy (meaning a lower toxicological threshold is applicable) and have relatively large daily dose volumes (e.g., 100 mL or larger). Given the inverse relationship between dose volume and the AET, parenteral drug products with large daily dose volumes may require AETs so low that they cannot be achieved with even state of the art analytical technologies operated by qualified experts.

Once calculated, the AET can be expressed in units of:

- µg per product unit (e.g., µg/syringe) to represent the leachables based on the commercial drug product
- µg per container volume (e.g., µg/mL) to represent the leachable's concentration in the PDP
- µg/component in the packaging system (e.g., µg/component) to allow for an assessment of the leachables' source(s)

- µg/day to reflect actual daily patient exposure to the leachables

Examples of how to calculate the AET are provided for the following systems to illustrate the range of AETs that can be encountered:

- Prefilled syringe (PFS) consisting of a 1-mL Luer lock cyclic olefin barrel, 6.4-mm diameter elastomeric plunger stopper and tip cap
- Injection pen consisting of a 2-mL glass cartridge, 6.4-mm diameter elastomeric plunger stopper and seal
- Multidose vial consisting of a 10-mL glass vial and 20-mm diameter elastomeric stopper
- Single dose vial and multiple doses consisting of a 2-mL glass vial and 13-mm diameter elastomeric stopper
- Single dose vial and single dose/day consisting of a 2-mL glass vial and 13-mm diameter elastomeric stopper
- Single dose flexible container (bag) consisting of a 120-mL plastic bag and elastomeric injection site
- Intravanous (IV) bag/single dose/day consisting of a 1000-mL plastic bag and elastomeric injection site
- IV bag and multiple bags/day consisting of a 1000-mL polymer bag and elastomeric injection site

In all cases, the AET is calculated with a toxicological threshold of 1.5 µg/day, the relevant SCT for a chronically administered drug product considering carcinogenic and noncarcinogenic toxic effects. As other quantities can be used as the toxicological threshold in the AET calculation (for example, an acutely administered drug product), it is suggested that the quantity used as the toxicological threshold be discussed and confirmed with the relevant regulatory authority.

4.1 Prefilled Syringes

A PFS is a unit dose packaging and/or delivery system that is prefilled with drug product. Essentially, PFS systems function both as packaging as well as administration devices. The following example is based on a PFS acting as a packaging system. Additional methods for calculating the AET may be applicable when considering the PFS as either a medical device or as the medical device component of a combination product. (e.g., ISO 10993-18 and ISO TS 21726) (*3–4*).

The basic components of a PFS include a barrel, plunger rod, plunger stopper, a conduit for drug product transfer (e.g., needle, Luer), and a needle shield for staked needles or tip cap for Luer lock. An example AET calculation for a PFS considers a PFS containing a 0.8-mL unit dose of drug product. Patient dosing is one PFS per day. The PFS consists of a cyclic olefin copolymer (COC) barrel (1.2 g) with a brominated isobutylene-isoprene elastomer plunger stopper (0.22 g).

Calculated leachables AETs are as follows:

$$\mathrm{AET_{PFS}} = S \div n_d \times N_{\mathrm{PFS}}$$ Equation 1. Estimated leachable AET per packaging system (PFS)

S = safety concern threshold (µg/day)

n_d = number of doses per day

N_{PFS} = number of labeled doses per prefilled syringe

$$\mathrm{AET_{PFS}} = [1.5\ \mu\mathrm{g/day} \div 1\ \mathrm{dose/day}] \times 1\,\mathrm{labeled\ dose/PFS} = 1.5\ \mu\mathrm{g/PFS}$$

Alternatively, the AET for a PFS can be expressed on the basis of leachable concentration in drug product:

$$\mathrm{AET_{dV}} = S \div n_d \div V$$ Equation 2. Estimated leachable AET per dose volume ($\mathrm{AET_{dV}}$)

S = safety concern threshold (µg/day)

n_d = number of doses per day

V = volume of daily dose (mL)

Example calculation with values:

$$\mathrm{AET_{dV}} = [1.5\ \mu\mathrm{g/day} \div 1\ \mathrm{dose/day}] \div 0.8\ \mathrm{mL/dose} = 1.9\ \mu\mathrm{g/mL}$$

An estimated AET for the individual PFS components (barrel and plunger stopper), useful for characterizing both extractables and leachables, is calculated as follows:

$$\mathrm{AET_{component}} = S \div n_d \times N_{\mathrm{PFS}} \div C$$ Equation 3. Estimated extractable AET per component ($\mathrm{AET_{component}}$)

S = safety concern threshold (µg/day)

n_d = number of doses per day

N_{PFS} = number of labeled doses per prefilled syringe

C = number of components per prefilled syringe (e.g., barrel, plunger stopper, tip cap)

Example calculations:

$$\mathrm{AET_{barrell}} = 1.5\,\mu\mathrm{g/day} \div 1\ \mathrm{dose/day} \times 1\ \mathrm{labeled\ dose} \div 1\,\mathrm{barrel} = 1.5\,\mu\mathrm{g/barrel}$$

$$\mathrm{AET_{plunger\ stopper}} = 1.5\,\mu\mathrm{g/day} \div 1\ \mathrm{dose/day} \times 1\ \mathrm{labeled\ dose} \div 1\ \mathrm{stopper} = 1.5\,\mu\mathrm{g/stopper}$$

$$\mathrm{AET_{tip\,cap}} = 1.5\,\mu g/\mathrm{day} \div 1\ \mathrm{dose/day} \times 1\ \mathrm{labeled\ dose} \div 1\ \mathrm{tip\,cap} = 1.5\,\mu g/\mathrm{tip\,cap}$$

4.2 Pen Injectors

An injector pen is a device used for injecting medication subcutaneously. Injector pens are commonly used for medications that are injected repeatedly by a person over a relatively short period of time, for example, insulin and insulin analogs used in the treatment of diabetes (called insulin pens). An injector pen consists of a chamber or cartridge of medication, a tip to attach a needle, and a piston or plunger to inject the dose. In the case of a cartridge, the end of the cartridge opposite to the plunger is sealed by an elastomeric seal. Some pens include dials to adjust the dose of the injection before each administration. Other pens may include a cartridge filled with medication that can be replaced when empty to enable reuse of the pen itself, whereas other pens are designed to be disposed of after their prefilled chamber is depleted.

AETs for a pen injector can be calculated according to *Equation 1*, *Equation 2*, and *Equation 3* and are shown in *Table 1*.

4.3 Small and Large Volume Parenterals

SVPs are defined as solutions or suspensions less than or equal to 100 mL per *Packaging and Storage Requirements 〈659〉*. They may be packaged in bags, vials (often glass or plastic with an elastomeric septum closure), or a PFS. Some SVPs are manufactured and packaged as ready to use solutions and others may be powdered or lyophilized, thus requiring reconstitution in an appropriate solvent before administration. SVPs may be unit dose or intended for multidose use.

LVPs are defined as solution products containing more than 100 mL per *〈659〉*. Typical packaging systems for LVPs are bottles, which commonly include elastomeric closures such as stoppers, and polymeric bags, which commonly include ports that can contain an elastomeric part as an injection site.

AETs for SVPs and LVPs can be calculated according to *Equation 1*, *Equation 2*, and *Equation 3* and are shown in *Table 1*.

Table 1 clearly demonstrates the inverse proportionality between dose volume and the calculated AET, with AET values in the product ranging from parts per million to parts per billion. Although AETs in the low parts per billion range or lower are analytically feasible for targeted analysis or analysis of extractables in pure solvents, such low AETs may present a challenge for the nontargeted detection and identification of unspecified leachables in a compositionally complex drug product formulation. This challenge is a hallmark of large volume parenterals, and the reader is referred to *5. Managing Challenging AETs via Extractables Data* for strategies to manage very low AETs (e.g., simulation studies).

Table 1. Calculated AETs for PDPs. Based on a toxicological threshold (SCT) of 1.5 µg/day.

		Usage Information				Calculated AET		
	Type of PDP	Doses per Day	Labeled Doses per Container	Daily Dose Volume (mL)	Component and No. Used	Per Container (µg/container)	Per Dose Volume (µg/mL)	Per Component (µg/component)
SVP	PFS	1	1	0.8	Barrel (1)	1.5	1.9	1.5
					Plunger stopper (1)			1.5
					Tip cap (1)			1.5
	Pen injector	1	10	0.2	Glass cartridge (1)	15	7.5	15
					Plunger stopper (1)			15
					Seal (1)			15
	Multidose vial	1	5	0.8	Glass vial (1)	7.5	1.9	7.5
					Stopper (1)			7.5
	Single dose vial, multiple doses per day	3	1	3	Glass vial (3)	0.5	0.5	0.5
					Stopper (3)			0.5

		Usage Information				Calculated AET		
	Type of PDP	Doses per Day	Labeled Doses per Container	Daily Dose Volume (mL)	Component and No. Used	Per Container (µg/container)	Per Dose Volume (µg/mL)	Per Component (µg/component)
	Single dose vial, single dose per day	1	1	1	Glass vial (1)	1.5	1.5	1.5
					Stopper (1)			1.5
LVP	Single dose flexible container	1	1	120	Bag (1)	1.5	0.0125	1.5
					Injection site (1)			1.5
	Flexible container for IV infusion, multiple doses per day	2	1	1000	Bag (1)	0.75	0.0015	0.75
					Injection site (1)			0.75
	Flexible container for IV infusion, single dose per day	1	1	1000	Bag (1)	1.5	0.0015	1.5
					Injection site (1)			1.5

5. MANAGING CHALLENGING AETS VIA EXTRACTABLES DATA

5.1 Extractables as Worst-Case Leachables

Scenarios in which low AETs exist, such as those presented above for LVPs, serve to emphasize the value of extractable studies for the purpose of detecting, identifying, and quantifying extractables as potential leachables. Generally, extraction solvents present fewer analytical challenges than formulated drug products with respect to interferences, as the drug products likely contain the active ingredient and excipients at high levels compared to levels of leachables. Thus, detection and identification of extractables can be accomplished at lower concentrations than can detection and identification of leachables. Furthermore, simulation studies designed to mimic drug product leaching use solvents (as opposed to placebo formulations) that might highlight those extractables most likely to leach into the drug product (i.e., probable leachables) and simplify the scope of targeted analysis of compounds present in the drug product at low levels.

Extraction profile data can be applied in two ways. First, during component selection, extraction profiles may be used to make suitable design choices to reduce downstream drug product leachable risk. Second, these levels of identified potential leachables can be subject to toxicological assessment and may be useful for justification of reporting thresholds for identified leachable targets, particularly in cases of challenging AETs for LVP.

[Note—Justifications for the AET or alternative reporting thresholds above the AET, extraction conditions, extraction solvents, and analysis should be discussed early in product development with the proper regulatory authority.]

When analytical limitations preclude achieving an AET for a LVP (e.g., the test method's limit of quantification, LOQ, is higher than the AET) and alternative approaches are considered necessary to achieve the AET, data from a properly designed controlled extraction study can be leveraged to inform and/or augment the overall leachables assessment for these products. For a properly designed controlled extraction study, concentrations of extractables would be expected to exceed leachable concentrations present in the formulated drug product. Thus, extractables information can be used to establish target leachables to be monitored in the drug product over shelf life. If an extractable, once identified, could be shown to pose negligible risk to the patient population, this would largely eliminate the need to target that specific compound as a leachable in the formulated drug product, as the level as an extractable is likely higher than the level as a leachable.

Moreover, extractables data can augment inadequate leachables data. That is, although extractables data do not replace leachables data, they can augment leachables data in that:

- Leachables data is used to address those leachables present in the drug product at levels above the LOQ.
- Extractables data is used to address probable leachables that might be present in the drug product at levels between the AET and the LOQ.

However, it is noted that extractables data cannot be used to address two types of impurities that might be present in the packaged drug product:

- Impurities that are degradation products of extractables (that is, the extractable is leached into the drug product where it degrades to produce the detected impurity).
- Impurities that are reaction products between leachables and drug product components, such as the API.

Alternatively, reporting threshold approaches based on a toxicological threshold higher than the SCT might be justifiable, depending on the total body of evidence for safety, intended product use, and benefit-risk to the patient. That is, extraction data could be used to justify setting a compound-specific reporting threshold for a leachable study that is higher than the general SCT-based AET applicable to all compounds. The use of such alternate, compound-specific reporting thresholds, only justified when technical limitations prevent achieving the SCT-based AET, should be discussed with the proper regulatory authority prior to initiating such an approach.

To facilitate toxicological assessment of extractables, the concentration of an observed extractable (taken to be the highest possible concentration for a leachable) can be mathematically converted to an estimated dose. For example, consider a 20-g polyvinyl chloride (PVC) bag intended to contain a single daily dose of 1 L. A 5-g portion of the bag was extracted in 200 mL of solvent, and an extractable was observed at 0.1 µg/mL, which is above the AET of 0.0015 µg/mL. Per *Equation 4*, the estimated daily dose would be 80 µg/day.

$$\text{Estimated daily dose} = C_f \times V_s \times W_b \times n_{\text{bags}}$$ Equation 4. Conversion of found extractable concentration to estimated dose

C_f = concentration of found extractable (µg/mL)

V_S = volume of solvent (mL/bag)

W_b = weight of product (g/bag)

n_{bags} = number of bags (bags/day)

Example calculation:

$$\text{Estimated daily dose} = 0.1\text{µg/mL} \times 200\ \text{mL/bag} \times 5\,\text{g/bag} \times 20\ \text{g/bag} \div 1\,\text{bag/day} = 80\ \text{µg/day}$$

5.2 Considerations for Optimal Extract Concentrations

The ratio of the packaging component mass to extraction solvent volume is a key factor and the first to consider when designing an extractable study plan. The stoichiometric relationship between the AET expressed in µg/mL (*Equation 2*) and the sensitivity of the detection technology can guide the proper ratio of component mass or surface area to achieve optimal concentration for chemical characterization purposes. The concentration of an extracted compound when expressed in µg/g is a measure of the total amount (by weight) that an individual component could contribute as a leachable. To calculate the critical mass required to achieve the AET in µg/mL calculated by *Equation 2*, the dose volume per component can be utilized as shown in *Equation 5*. For example, if the dose volume is 0.8 mL and the desired extraction volume is 100 mL, then a minimum of 125 plunger stoppers would be required.

$$n_{Np} = V_e/V_d$$ Equation 5. Estimated number of components needed to achieve AET

n_{Np} = number of plungers needed

V_e = extract volume (mL)

V_d = dose volume (mL)

Example calculation:

$$n_{Np} = [100\ \text{mL}/(0.8\ \text{mL/plunger})] = 125\ \text{plungers}$$

This information will assist in establishing the proper component to solvent ratio (or concentration of extract as needed) to achieve the estimated AET based on the intended analytical method.

5.3 Simulation Studies

Delineating a drug product's leachable profile is the most definitive means of providing the information that is necessary to assess the potential patient exposure to, and product impact of, leachables. Generation of the leachables profile is a multifaceted undertaking, and often difficult to accomplish because this requires that all leachables present in a drug product at a level above a well defined, justified, and often analytically challenging threshold (e.g., AET) be detected, identified, and quantified.

In situations of analytically challenging AETs for certain PDP (e.g., LVPs), a simulation study can supplement and guide subsequent drug product leachables studies. These studies can establish an extractables profile to represent the probable leachables profile of the packaged drug product that the study simulates. Use of a simulation study would need to be appropriately justified.

It is not uncommon that PDPs have daily doses of one or more liters (i.e., LVP), which leads to challenges in utilizing the AET. As shown in *Figure 1*, the daily dose volume can vary from less than 1 mL to greater than 2000 mL; as the daily dose volume increases, the AET decreases significantly. At some daily dose volume, the magnitude of which varies based on the therapeutic intent, the AET may become so low that it cannot analytically be achieved. In such a circumstance, potentially impactful leachables may go either undetected or uncharacterized and an impact assessment based on the analytically generated leachables profile will be incomplete. An approach to the issue described above is to simplify the chemical nature of the sample that is being tested. This can be achieved by using a solvent to simulate the product formulation. This approach has three primary benefits. First, analysis of the extract obtained with a simulation solvent will produce a background response

that is lower or less variable than that background response generated by analysis of the more complicated drug product. Thus, responses produced by the compounds of interest (extractables as potential leachables) will be more prominent versus the lower and less variable background. Second, the simulation extract will be more amenable to sample preparation for analytical testing. Last, analytical interferences caused by drug product formulation will be reduced when the simulation solvent is used.

The purpose of using a simulation solvent in place of the more chemically complex and more analytically challenging drug product is to mimic the “leaching power” of the drug product. In this respect, a study in which the simulation solvent serves as a surrogate for the drug product is termed a “simulation study.” Since by classical definition a leachable profile is a profile obtained by testing the drug product, the profile generated in a simulation study cannot be a leachables profile and thus is a specific type of extractables profile.

By definition, a simulation study is a controlled extraction study, the purpose of which is to produce an extractables profile for a packaging system that represents the leachables profile that a drug product stored in the packaging system may have. The value in performing the simulation study is that the simulating solvents are more analytically expedient than the drug product. This facilitates the process of detecting, identifying, and quantitating the packaging system extractables and informing potential drug product leachables.

The success of the simulation study depends on the degree to which the “extracting power” of the simulation solvent is consistent with the “leaching power” of the drug product. Thus, this design parameter must be justified and is essential for establishing the validity and applicability of a simulation study.

The simulation study provides significant value by providing focus to the subsequent leachables study. For example, the extractables profile of the simulation study would reveal probable leachables and as probable leachables these substances would be targeted during the leachables study. Such a strategy facilitates the leachables study as it is generally more feasible to measure targeted analytes in drug products at their expected accumulation levels.

Furthermore, a simulation study may provide data that a leachables study cannot. For example, it is required that all leachables above the AET be reported for toxicological safety risk assessment. However, in the case of a challenging AET, the test method might not be sensitive enough to achieve the AET (e.g., LOQ > AET), even after due diligence has been used in optimizing the sensitivity of the test method. In this case, leachables can only be reported down to the method’s LOQ and leachables between the LOQ and the AET cannot be reported. To address these leachables between the LOQ and AET, extractables data from a simulation study can be used.

It is important to recognize that, regardless of how well the simulation study is designed and executed, its outcome will likely only approximate the results of a drug product leachable study and cannot fully replicate a true leachable profile of the drug product. As the intent of the simulation study is to augment or replace a leachables study, the simulation study must meet all the quality requirements for a leachables study, including test method qualification.

Use of a simulation study is an alternative to the recommended necessary practice of performing leachables studies. Thus, the intended application, justification, and qualification of a simulated leaching study for a particular drug product should be based on a scientifically sound rationale with demonstration of due diligence supported by appropriate testing and experimentation. When considering the use of a simulation study, consultation with the relevant regulatory agency or health authority prior to implementation may be warranted.

[Note—Justifications for the AET, or alternative reporting thresholds above AET, for leachables analysis should be discussed early in product development with the relevant regulatory agency division.]

The value of the AET is inversely proportional to the daily dose volume. Thus, drug products with a high daily dose volume will have low AETs.

Figure 1. Consideration of the analytical challenge associated with the daily dose volume.

6. LEACHABLES FROM SECONDARY PACKAGING

Where appropriate, extractables assessments, extraction studies, and leachables assessments for parenteral drug products and their packaging systems should consider the possibility of migration of leachables from secondary or tertiary packaging (i.e., drug product labels, adhesives, inks, etc.) across packaging barriers (e.g., primary packaging).

For those dosage forms packaged in semipermeable containers, chemical entities could migrate into drug products from nonproduct contact (secondary) packaging components. For example, pressure-sensitive labels affixed directly to the exterior of a semipermeable primary container are common sources for such migrating substances, though other source components such as overwraps, product information inserts, and unit cartons are known as potential migrant sources. A typical example of this migration is the appearance of a photo initiator in the drug product that is a component of a UV-cured ink applied to a product label. Migrating substances are evaluated in the same manner as are leachables arising from primary components. For example, consider a single label applied to a 120-mL, multiple dose, low density polyethylene bottle designed to hold 90 mL of a formulated parenteral drug product intended for 1.5 mL daily dosing (60 labeled doses per container).

$$\mathrm{AET_{CL}} = [(1.5\ \mu\mathrm{g/day} \div\ 1\ \mathrm{dose/day})]\ \times\ (60\ \mathrm{doses}/1\ \mathrm{bottle})\ \times\ (1\ \mathrm{bottle}/1\ \mathrm{label}) = 90\ \mu\mathrm{g/label}$$

Equation 6. Estimated leachables AET per container label

Alternatively, expressed on the basis of leachable concentration in drug product:

$$\mathrm{AET_{dV}} = [(1.5\ \mu\mathrm{g/day})/(1\ \mathrm{dose/day})]\ \times\ (1\ \mathrm{dose}/1.5\ \mathrm{mL}) = 1\ \mu\mathrm{g/mL}$$

Equation 7. Estimated AET Leachables per dose volume

An example of a detailed simulation study that included an investigation of migration behavior of chemical entities in a paper label can be found in reference 5.

7. ANALYTICAL UNCERTAINTY

An AET is the concentration at or above which unknown leachables should be characterized and reported for toxicological assessment. Targeted leachables (previously characterized as potential or probable leachables from extractables or simulation studies) will have known safety profiles and previously established limits. Authentic reference compounds, if available, for previously characterized potential leachables will allow for accurate and precise quantitation of those target leachables as actual drug product leachables.

Characterization of unknown leachables requires consideration of analytical uncertainty as the use of an AET by a specified analytical method [e.g., gas chromatography and mass spectrometry (GCMS)] must be accomplished relative to an internal standard that may possess a different analytical response from the unknown leachable. Uncertainty may typically include:

- Uncertainty in the proposed structure and elemental composition of the unknown leachable (e.g., positional isomerism, geometric isomerism, stereoisomerism, functional groups, heteroatoms, isobaric compounds)
- Uncertainty in response of a unique, unknown leachable with regard to detection and quantitation with a particular analytical technique
- Sample matrix effects and interference
- Quantification approach employed (e.g., internal or external standard)

Thus, it is recommended that the estimated AET values calculated as per the prior examples and equations be adjusted for analytical uncertainty when applied to unknown leachables; adjustment of the AET for uncertainty should be achieved through a rational, scientifically justified approach.

By way of example, analytical uncertainty for a particular analytical technique or method can be estimated based on the analysis of a series of representative reference compounds to create a response factor database. The reference compounds included in this database should represent known potential leachables (i.e., as determined from extractables assessments). A recommended practice for orally inhaled and nasal drug products (OINDP) is that the estimated AET be lowered by analytical uncertainty defined as “one (1) % relative standard deviation in an appropriately constituted and acquired Response Factor database OR a factor of 50% of the Estimated AET, whichever is greater” (see *Equation 8*). Examples of the OINDP recommended approach may be found in *Orally Inhaled and Nasal Drug Products 〈1664.1〉* and other relevant publications (*3,6–7*).

$$\mathrm{UF} = 1/(1 - \mathrm{RSD})$$ Equation 8. Calculation of the uncertainty factor (UF)

RSD = the relative standard deviation of the response factors in a response factor database

At the current time, there is no consensus on proper values for the UF for the various chromatographic screening methods applied to organic leachables. However, discussions of the issues associated with establishing and justifying the values for the UF have been published (*8–9*).

Given the reduced risk profile of parenteral drug products versus OINDP (*10*), other methods of managing analytical uncertainty might be applied provided that a rational, scientific justification of that approach is given.

Use of the UF to adjust the AET is illustrated in *Equation 9*:

$$\mathrm{AET}_A = \mathrm{AET}_I/\mathrm{UF}$$ Equation 9. Adjustment of the AET with the UF

AET_A = adjusted AET

AET_I = initial AET

8. LEACHABLES CONSIDERATIONS FOR INJECTABLE BIOLOGICAL DRUG PRODUCTS

8.1 Biological Drug Products

A biological product is officially defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings” (*11*).

A protein is any α-amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer will be based on the total number of amino acids in those chains, and not limited to the number of amino acids in a contiguous sequence (*12*). Through a greater understanding of critical disease relevant targets, new biological products continue to emerge, e.g., RNA therapeutics, macrocycles and cyclopeptides for protein–protein interactions, antibody drug conjugates, and gene (and cell) therapies (*13*).

Biological products may be comprised of more than one molecular entity produced by biotechnology or isolated from biological specimens. Many biological products involve one or more therapeutic proteins in a complex matrix. Advances in protein engineering have resulted in several forms of complex therapeutic proteins that include protein conjugates (e.g., Fc fusion, antibody-drug), derivatives (PEGylated), and genetic alterations [e.g., chimeric or humanized monoclonal antibodies (mAbs)].

8.2 Leachables Effects on Biological Drug Products

For many dosage forms, the adverse effect of leachables is limited to their direct effect on patient safety and dosage form stability. However, leachables-mediated interactions between bDPs and packaging, manufacturing, and delivery systems can indirectly and negatively affect product quality, stability, purity, and patient safety. Considering the biological drug substance itself, reactions between leached substances and the biological drug substance affect the physical and chemical characteristics of the biological drug substance and the bDP

(e.g., aggregation, deamidation, oxidation, formation of clipped variants), potentially leading to issues related to aspects of product quality or patient safety, either directly via the leachable' s own toxicity or indirectly via induced immunogenic effects.

Considering indirect patient safety effects, leachables can compromise patient safety by interacting with the protein, thereby indirectly modifying product quality (14). The abundance of both hydrophilic and hydrophobic sites and extensive surface area of a protein can serve as potential interaction sites.

Therapeutic protein products can generate immune responses to themselves and to related proteins or induce immunologically related adverse clinical events. Physical degradation and/or chemical decomposition of the proteins may enhance the immune response (15). The consequences of immune responses to therapeutic protein products can range from no apparent effect to serious adverse events, including life-threatening complications. Interactions between therapeutic protein products and packaging systems may negatively affect product quality, and in some cases provoke or increase immunogenicity. Examples of protein product–packaging systems interaction include the release of organic compounds with immunomodulatory activity based on polysorbate-containing formulations and oxidized metals causing aggregates or activation of metalloproteinases. Interactions would be specific to each therapeutic protein product and thus leachables must be studied for each bDP under real-time storage conditions (16).

Leachables may include aldehydes, ketones, free radicals, peroxides, residual solvents, moisture, oxygen, and metal ions or salts. Well known risks to the quality of biological products associated with packaging systems include silicone lubricants from packaging systems, polytungstate from the syringe manufacturing process, and glass lamella caused by surface corrosion (17-19). Leachables that can potentially bind covalently to protein include Michael acceptors, Schiff base formers, acylating agents, aliphatic nucleophilic substitutions, aromatic nucleophilic substitutions, and transition metals (20). Often, highly reactive organic and inorganic compounds can cause irreversible, covalent binding with therapeutic proteins (i.e., adducts, aggregates) or modification of residues (e.g., oxidation, deamidation), which may indirectly or directly compromise product safety.

Examples of leachables affecting the quality of a bDP include:

- A change in formulation from a lyophilized to a liquid formulation resulted in product degradation at the N-terminal site due to a divalent cation that leached from a rubber stopper causing activation of metalloprotease (21).
- A change in formulation excipients from human serum albumin to a polysorbate caused pure red cell aplasia (PRCA) in chronic kidney disease patients treated with epoetin. The source was suspected to be a vulcanizing agent that leached from the plunger. PCRA was mitigated by modifying the plunger with a barrier film (22).
- A prefilled syringe system for subcutaneous delivery-induced protein denaturation and aggregation and elicited immunogenicity. This was correlated to the presence of covalent dimers. The cause was traced to tungsten oxide and salts that leached from the fluid channel of the tip of a glass prefillable syringe due to residual tungsten sputtered off the tungsten pin used to maintain the fluid channel during formation of the cone (23).
- A change in the forming of glass vials from molding to tubing glass caused formation of visible particulates after 12 months storage. Aluminum leached from the glass and reacted with the sodium phosphate buffer, creating aluminum phosphate crystals (24).
- Particulates can arise from interactions with leachables or environmental changes that lead to aggregation due to surface chemistry, morphology, and system interfaces. Particulates are also inherent to protein products and critical to the control of biological product quality having potential to cause immunogenicity (25).

8.3 Quality Considerations for Biological Products

The quality of the final biological product is established by defining critical attributes and then determining the extent to which they can vary without affecting the safety or efficacy. Biological molecules have numerous quality attributes and are very sensitive to physical and chemical stressors, including freeze-thaw cycles, agitation, light, pH, and other environmental effects. The impurities or contaminants can be of a known structure, partially characterized, or unidentified. Process-related impurities encompass those that are derived from starting materials and equipment used in the manufacturing process or downstream processing. Product-related impurities are molecular variants that arise during manufacture and/or storage and that do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety. If process or product-related impurities are known to be introduced or formed during the production and/or storage of the biological product, the levels of the impurities should be determined, and acceptance criteria should be established, and the impurities should be controlled (26).

8.3.1 Packaging Systems and Components in Contact with Biological Drug Products

A packaging system and its individual components must be chemically and physically compatible with a bDP to ensure patient safety and product quality. Information that is needed to qualify a packaging system as being compatible with a bDP is described in the FDA container closure and packaging guidance for drugs and biologics (27). The guidance recommends that one choose materials and components that will be safe, perform appropriately, be compatible with the product formulation, and will protect the product from moisture, gases, microbial ingress, and light. Suitability encompasses risk associated with:

- Chemical substances that have potential to leach harmful substances
- Safety of materials and components
- Potential adsorption of the product onto container–closure surfaces
- Functionality of the system for intended use
- In-use performance of the final system

Essential compatibility information for investigational new drug applications (INDs) also includes comparability studies, acceptable limits, and assurance of product stability and in-device stability associated with clinical treatments.

The US FDA recommends that every proposed packaging system be shown to be suitable for its intended use, meaning that the packaging system:

- Protects the drug product
- Is compatible with the drug product
- Is constructed from use safe materials
- Meets material performance and system functional requirements (27)

Examples of representative suitability factors are listed in Table 2 (28).

Table 2. Suitability Factors, Interactions between a Drug Product and Its Packaging System.

Protection	Compatibility	Safety	Performance
Agitation			
Contamination			
Degradation	Aggregation	Adduct formation	Accurate delivery
Deep cold storage	Impurities	Aggregates	Component particles
Foreign particles	Loss of potency	Altered conjugated forms	Freeze-thaw cycles
Gas permeation	pH shift	Immunogenicity	Hydrophobic surfaces
Leakage	Precipitation	Isomerization	Mechanical attributes
Microbial	Product adsorption	Leachable-induced toxicity	Physical attributes
Permeation	Reducing agents	Structural stability	Shear force impact
Product loss	Surface interfaces	Toxic impurities	System fit
Water vapor	Surface morphology	Unfolding	System shelf life

The packaging system must protect product safety, identity, strength, quality, and purity to ensure safe delivery of finished pharmaceuticals (29). Quality assessments for biological products should include identifying and mitigating risks related to the following:

- Changes in the purity, safety, and stability of the dosage form
- Alterations in product appearance, molecular structure, and physical or chemical characteristics
- Loss of potency due to absorption or adsorption of the active biological substance
- Degradation of the active biological substance induced by leachables
- Reduced concentration of the active biological substance due to physical or chemical changes
- Leachable-induced changes in formulation pH, leading to product degradation, precipitation, and aggregation
- Modifications in the packaging and delivery device components or system, including discoloration, surface integrity, functionality, and brittleness

Critical packaging components should not cause unacceptable changes in product quality, safety, or delivery to patients. The suitability of a final packaging system covers a wide range of interrelated factors that may not always be evident during the initial component qualification studies. Incompatibilities between the packaging system and biological product often occur over time and can result in serious consequences if risks are not identified and mitigated in advance.

The compatibility of the biological product with the packaging system should be investigated commensurate with the bDP's stage of development. An iterative process that is initiated early in development will allow for progressive understanding to establish packaging system critical quality attributes over the product life cycle. A high-level diagram for such a process is shown in Figure 2.

Figure 2. Process Flow Diagram for the Evaluation of a Packaging System over the Shelf-Life of a Biological Product. CCS, container closure system; CQAs, critical quality attributes; PK/PD, pharmacokinetics/pharmacodynamics.

Qualifying a packaging system as being compatible with a bDP is a dynamic process that involves understanding changes in quality attributes with respect to packaging system component extractability, physicochemical compatibility, and safety. Possible interactions between the packaging system and the bDP should be considered from early development stages through commercialization to avoid unexpected packaging-related product quality issues. Packaging systems components must be qualified for specific use with consideration of changes that may occur at any time over the product life cycle.

Qualification of the packaging system with respect to leachables is an iterative process starting with securing prior knowledge about the packaging system (e.g., materials of construction), continuing with obtaining chemical characterization information for individual packaging system components (e.g., extractables studies), and concluding with simulation and/or leachables studies of the packaged product. The packaging systems should also be evaluated as part of biological product stability studies (accelerated and real time) and during clinical phases to understand if any critical product attributes have been impacted (16). The packaging system will be qualified in the context of the biological product and any changes (e.g., product formulation, manufacturing process, or packaging components) that occur throughout the life cycle of the product should be assessed based on risk to product quality and safety (12,30).

The process for gene therapy product development advocates a quality by design approach that will establish critical quality attributes based on product and process knowledge to ensure the desired quality. It is recommended to carefully control and assess product

compatibility and the final steps of product preparation and administration (*8*,*31*). One aspect that can be a particular challenge for gene therapies is final product release due to small lot sizes. Availability of multiple products for stability assessments may not be feasible for final storage and transport steps. Due to the diversity of biological products and end use, a strategy for extractables and leachables should be justified case by case to demonstrate suitability of materials and components used in the manufacture, storage, and final delivery to patients.

[NOTE—Due to the increasing complexity and diversity of bDPs and the increased risk of adverse effects due to leachables-bDP interactions, bDP sponsors should discuss qualification strategies of packaging systems, including leachables testing, with the proper regulatory authority.]

8.3.2 MANUFACTURING COMPONENTS IN CONTACT WITH BIOLOGICAL DRUG PRODUCTS

The quality and safety of biological products can be affected by the numerous components of the manufacturing system of the product. These components must meet certain physical, mechanical, and chemical performance requirements that are impacted by the chemical makeup of each material, the conditions of contact between the materials and the process stream, and the configuration of the final manufacturing system.

Manufacturing components consist of various materials of construction, including different grades of stainless steel, aluminum, glass, plastics, and thermoset or thermoplastic elastomers. In many cases, fixed stainless steel bioreactors are being replaced by single-use systems (SUS) to overcome cleaning and maintenance issues. The materials of construction used in a single use bioreactor can be comprised of multiple layers of polymer films to achieve strength, ductility, mechanical stability, and gas barrier as needed. These films will have specific properties for use relative to various polymer families (e.g., polyethylene, polypropylene, polyvinyl alcohol, polyesters, and polyamides). Other related manufacturing components such as connectors, tubing, and filters could include other materials (e.g., polyvinyl chloride, polycarbonate, polysulfone, silicone, fluoropolymers, and polystyrene).

Extractables studies performed on manufacturing components can provide composition information to establish a material's compatibility with product and process, to exercise change management, and to identify potential risks associated with product quality or cell culture operations. As an example, a cytotoxic breakdown product from a common phosphite antioxidant used in polyethylene was found to have leached into culture media resulting in detrimental cell growth (*32*). Downstream processing may include similar materials in addition to anionic and cationic exchange or bind elute resins and cellulose. Chemical or physical incompatibilities can result in failures due to harsh environments, extreme temperatures, strain, wear and tear. The user and manufacturer requirements will need to define the chemical and physical performance criteria for a given application. The physical structure of materials and associated chemistries are key for determining suitability and control of manufacturing components.

Risk for leachables should be considered for components used during preformulation, final formulation, and final filling considering both clinical and commercial use. Not all manufacturing components will require the same type or degree of assessments for qualification. Studies should be designed based on the knowledge of individual components, intended conditions of use, and application relative to the level of risk. Biological products are often stored frozen with more than twelve months shelf life. Cold storage may minimize leachables but not necessarily overcome all compatibility issues associated with freeze thaw cycles or handling.

The extent of leaching and the patient impact of leachables from manufacturing components will depend on numerous factors including the specific use of the component, the characteristics of the component, and the chemical nature of the process solutions contacted by the component. *Table 3* shows typical applications of manufacturing and packaging components and considers the types of components used in certain unit operations and the type of solutions that are contacted by the components.

Ultimately, data generated to understand the extraction propensity (e.g., "extracting power) of process solutions or the biological product itself under conditions of use will be critical for qualifying manufacturing and packaging systems.

Table 3. Leachables Risk Factors for Packaging System and Manufacturing Components.

Process	Application	Risk Factors	
		Components in Contact	Contact Solutions
Upstream			
Expression and harvest	Bioreactor transfer Cell bank Cell cultivation Centrifugation Concentration Fermentation	Bioreactors Caps/gaskets Connectors Harvest tanks, tank liners Mixing vessels and/or bags Single use systems Tubing assemblies Vial/flasks/bottles	Culture and/or fermentation media **Excipients:** Buffer, salts, sugars, additives **Nutrients:** Sugars, fats, water, amino acids, electrolytes, vitamins, serum, minerals
Downstream			
Isolation and purification	Final concentration and/or polish Formulate/Transport	Biocontainers and/or carboys Chromatography resins Connectors and/or O-rings	Chemical denaturants Cross-link agents Cryo- and/or lyoprotectants

Process	Application	Risk Factors	
		Components in Contact	Contact Solutions
Upstream			
	Purification Separations Sterile filtration UF and/or DF filtration Viral inactivation Viral clearance	Filtration systems Hoses and/or tubing systems Modular process skids Needles and/or valves and/or sensors Septa/diaphragm	Fermentation broth Ion exchange, affinity resins, Preservatives
Preformulation, formulation, and filling (packaging)	Biological substance, thawing and pooling Filling Final formulation Preformulation Sterilization	Connectors and/or gaskets Filter and/or tubing assemblies Peristaltic pumps/needless platform technologies	Absorption enhancers Biological substance, thawing and pooling Complexing agents **Excipients:** Water/buffers, complexing agents, polyhydric alcohols, surfactants, polyhydric alcohols, sugars, stabilizers, absorption enhancers, preservatives, stabilizers, protectants Lubricating agents Polyhydric alcohols Preservatives Protectants Stabilizers Sterilization agent Surfactants Water and/or buffers
Storage of packaged drug product over shelf life	Storage over shelf life Product use in the clinical setting	Packaging system including primary (bag, stopper, syringe, tip cap, and vial, etc.), secondary (label, pouch, tray), and tertiary packaging (carton) as appropriate	Drug product formulation
Life cycle and change management	Postapproval marketing of approved product	All of the above	Any of the above as appropriate

8.3.3 CONSIDERATIONS FOR QUALIFICATION OF PACKAGING AND MANUFACTURING COMPONENTS

As noted previously, the packaging system of a drug product must be physically and chemically compatible with the drug product over its shelf life while the manufacturing systems of the drug products must be physically and chemically compatible with the process solution(s) they contact during manufacturing operations. Furthermore, substances cannot leach from the packaging and manufacturing systems and accumulate in the drug product in reactive and unsafe quantities. Thus, packaging and manufacturing systems and components must be qualified as being appropriate for their intended use. Because user needs can be wide ranging, the use of certain materials in certain applications will be precluded based on performance requirements. Additionally, verification that materials are suitable for every application is not practical because of the great diversity in performance requirements and wide differences in materials' performance capabilities. Identification of risks followed by scientifically justified studies and clinically relevant data will lead to proper component selection and qualification.

Considering compatibility, the following incompatibilities are noted: changes in product concentration can occur due to material adsorption of product or absorption of formulation. Aggregation at product interfaces can include formation of visible particles, subvisible particles, soluble aggregates resulting from conformational changes due to interfacial stresses such as hydrophobicity, charge, and mechanical stress (*33*).

Thus, compatibility studies should be performed to establish the risk that incompatibilities could destabilize or alter the final product. For example, stability studies should be conducted on the biological substances and product under accelerated and stress conditions and should take into consideration potential leachables that could interact with and degrade therapeutic proteins (*8*,*26*,*34*). Furthermore, all packaging-manufacturing system combinations that produce marketed product should be assessed for potential interactions with biological products

as they may affect the purity or quality of the final product. Compatibility studies should provide evidence that demonstrates the following (35):

- Component materials will not hasten the deterioration of the product or otherwise render it less suitable for the intended use.
- Final container closures and delivery system component surfaces will be free of surface solids, harmful levels of leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use.
- Filling, sealing, and sterilization processes will be performed in a manner that will maintain the integrity of the product during the labeled shelf life.

Ultimately, compatibility between a bDP and its packaging and manufacturing systems is dictated by the physical and chemical properties of the components that constitute these systems. The material's physical and chemical properties establish the system's propensity to interact with the bDP and to protect the bDP. Dimensional stability of components, proper fit of multiple parts, seal integrity, and performance of the final system is necessary to ensure safe and accurate dosing over time. Risks to performance of packaging systems include gas permeation, component fracture and breakage, surface interaction, and material swell or outgassing. Moreover, the packaging system's processing and use environments will impact the material's compatibility. Physical and chemical properties of the packaging can be affected by multiple stressors such as exposure to sterilization and decontamination processes, fill-finish, vacuum, agitation, freeze–thaw cycles, and shear forces.

Considering leaching and leachables, the correlation of extractables and leachables with product quality is a process that involves understanding how product quality attributes and patient safety are affected by leachables throughout the biological product's life cycle.

It is noted that the control of leachables begins with materials selection. Guided by prior knowledge, potentially suitable components and materials of construction are selected based on an expectation that they are likely to be compatible with the drug product and/or the process stream, where chemical compatibility includes a consideration of leachables and their potential adverse effects. The selection process, and ultimately the qualification process, correlates leachables to product quality attributes, the potential for immunogenicity and to potential safety impact, recognizing that the presence of a leachable could exceed a safe limit or induce conformational changes or modifications that could result in harm to a patient.

After selection, manufacturing and packaging components and systems are tested for extractables and manufactured and packaged drug products are tested for leachables. Comprehensive extractable studies should be designed to develop material characterization profiles for packaging system, delivery device, and manufacturing systems as appropriate. These should employ robust methodology and consider use of simulated potential leachable profiles to support detection and identification of probable leachables. Materials composition, prior knowledge and extractables information can guide investigation and assessment of leachables and augment understanding of potential risk to the quality of biological products.

Such studies have two aspects, generating the test sample and analyzing the test sample. In the case of extractables studies, the test sample is generated by extracting the test article under specified laboratory conditions. In the case of leachables studies, the test sample is generated by storing the manufactured and packaged drug product under actual and accelerated conditions of use.

The occurrence of leachables in the packaged drug product (and extractables in an extract) will be influenced by several factors including:

- Extraction or leaching propensity of the drug product (established by the drug product's chemical composition)
- The chemical composition of the manufacturing or packaging components (chemicals present in the components are logically potential leachables)
- Proximity of the component to the biological substance and product (e.g., direct or indirect contact)
- Sterilization and handling of component prior to use
- Conditions of contact (temperature and duration)
- Stoichiometric factors (e.g., contact surface area to solution volume ratio)
- Dynamics of contact (e.g., static or dynamic)

For example, the occurrence of leachables will be influenced by the nature of the contact between the bDP and the component. Packaging system components that have direct contact with biological products would be considered primary packaging systems, while those with indirect contact would be secondary or tertiary systems (e.g., labels, inks, adhesives, cartons, inserts, overwraps, etc.). The probability that leachables would originate from the primary packaging system is greater due to immediate contact and longer duration compared to manufacturing systems that have a shorter, transient contact duration followed by comprehensive filtration steps.

Additionally, when a biologic liquid formulation contains cosolvents or surfactants, there is greater potential for organic leachables from contacted components; for example, uncoated stoppers (22). Biological formulations containing ethylenediaminetetraacetic acid complexing agents and phosphate buffers can facilitate the migration of metal ions into solution. Alkali and alkaline earth metals will bind proteins predominantly through electrostatic interactions, and transition metals will covalently bind to proteins depending on the pH and ionization state of amino acid residues (36). Thus, these factors must be taken into account in designing an extraction process.

Considering the analytical aspects of extractables and leachables profiling, detection and identification of leachables in biological products may be difficult as the formulations are often complex and may contain nonionic surfactant mixtures (e.g., poloxamers or polysorbates) or other excipients that can obscure known or unknown chemical entities, labile compounds or degrade (autoxidize), interact with other excipients, other leachables or the active molecular entities. Thus, both extractables and leachables studies should be performed to evaluate the capacity of packaging components to interact with and modify the biological product (16). Studies for targeted (known) and nontargeted (unanticipated) leachables should be designed and performed using knowledge acquired through the initial establishment of a comprehensive extractable profile and thorough understanding of the biological product.

Moreover, initial chemical characterization studies can utilize the PDP SCT of 1.5-µg total daily intake to derive the AET and identify compounds to be assessed for toxicity (37). The methodology to screen for leachables should consider compounds of toxicological concern as well as impact to biological product quality attributes. The risk to quality attributes can be assessed on the basis of knowledge of primary, secondary and tertiary structure of the biological molecule(s) along with extractable profiles from chemical characterization studies using exaggerated or aggressive extractions. Simulation studies can reduce interferences and inform the propensity of chemicals to migrate and identify targets for leachable studies. Placebo studies (e.g., formulation without biologic product), when guided by chemical characterization studies, can assist with development and optimization of leachable methods involving complex formulations, while conserving use of expensive biologics. Leachable methods should include comprehensive screening for targeted, nontargeted, and unexpected compounds by leveraging extractable or screening methods, whereas analyte-specific methods may be needed to target special case compounds at the appropriate sensitivity. Extractable knowledge, together with biological product characterization data from clinical studies, is an important aspect to understand potential risk to product quality and provide evidence of the safety and compatibility for manufacturing and packaging systems.

In the final analysis, a properly conducted chemical characterization study should provide a complete and comprehensive profile of organic and inorganic extractables in a test sample without physically compromising the test sample (e.g., altering its surface, shape, of physical form). Use of simulation studies with the final packaging and delivery system can facilitate identification and quantification of probable leachables to be toxicologically assessed. Chemical composition information and toxicological assessment of chemical profiles can indicate compounds of concern representing leachables for which to develop, optimize, and qualify targeted analyte methods. Nontargeted leachable screening methods may be useful for detection of unanticipated leachables but may not have the proper sensitivity or specificity for critical targets, which should be monitored by optimized and fully validated methods.

Nevertheless, the degree and type of manufacturing and packaging component assessment should be holistic with consideration of relevance to intended use, and qualification will depend upon the potential risk to biological product quality and safety.

8.3.4 INJECTABLE DELIVERY SYSTEMS

Many biological products are sterile injectables that may be administered frequently, at relatively high volumes, or in concentrated doses. These products are often marketed in single or multidose vials; however, delivery devices such as a prefilled syringe or auto-injector are becoming more prevalent as they provide a more simplified procedure for patient administration. When injectors are combined, copackaged, or labeled for use with a specific biological product, they are designated as a combination product (12,38). A biologic device combination product can be categorized as either a drug, biologic, or device based on the biological primary mode of action, technological characteristics, proposed labeling, and packaging. This categorization could lead to different legal, regulatory, and scientific approaches for packaging system qualification.

Combination product packaging systems should be qualified within the context of use and by accounting for the combined requirements for drugs, biologics, and devices.

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