Analytical Testing – Extractables and Leachables Testing for Pharmaceutical Products

Xiaochun Yu, PhD
Principal Scientist, Extractables/Leachables and GC/MS Services

Derek Wood
Associate Director, Extractables/Leachables and GC/MS Services

PPD® Laboratories GMP Lab

Introduction

Leachables are compounds (including their degradants and reaction products) or elements that migrate from the container/closure system components, manufacturing process components or drug product delivery system components into the drug product formulations or directly to the patients under normal conditions of storage or use. Leachables are therefore characteristic of the drug products and their delivery to the patients.

Extractables are compounds or elements that can be extracted out with appropriate solvents, such as water, isopropanol, methylene chloride, hexane, etc., under certain extraction conditions or compounds that can be forced out under dry heat, without solvents, from the container/closure components, manufacturing components or drug product delivery system components. Extractables can be considered as potential leachables, although not all extractables leach into drug products or patients. Extractables are characteristic of the materials of the components of container/closure systems, manufacturing systems and drug product delivery systems.

The primary sources of leachables are the components of the container/closure systems, such as rubber stoppers for glass vials, syringe barrels and plungers in pre-filled syringes, valve components for pressurized Meter Dose Inhalers (pMDI) devices, nasal pumps, bottles and caps, etc. Long-term exposure of such components to the drug product formulations make it highly likely that certain compounds and elements in these materials will leach into the drug product formulations.

Leachables also may arise from secondary packaging components, such as foil pouches for low-density polyethylene (LDPE) ampoules. LDPE is a semi-permeable polymer, so it allows compounds in the pouch material to pass through the LDPE ampoule and migrate into the drug product formulation stored in the ampoule. Ink print or labels as part of primary or secondary packaging are also common sources of leachables.

Drug product delivery systems such as IV bags, administration sets, drug delivery pumps and mouthpieces, etc., have short duration exposure to the drug product formulations or the patients, but they are still sources of possible leachables.

Other potential sources of leachables are drug products, active pharmaceutical ingredients (API) and intermediates manufacturing components, including such components as reservoirs, filters and filling tubes.

The type of extractables and potential leachables vary based on the material type. Certain types of these compounds are introduced from the polymer material synthetic process, such as residual monomers, oligomers, polymerization reaction initiators and their degradants, catalysts and polymerization media residuals, curing agents and their degradants for rubber materials, etc. Residual monomers and oligomers are inherent to the polymer materials and are material specific, such as caprolactam monomer for polyamide 6, and cyclic polybutylene terephthalate (PBT) dimer and cyclic PBT trimer for PBT material.

Many extractables and leachables (E&L) are additives to the polymer materials or their degradants. The most common polymer additives are antioxidants such as butylated hydroxytoluene (BHT), Irganox 1010, Irganox 1076 and Irgafos 168. Also, certain polymers include plasticizer additives such as diethylhexyl phthalate (DEHP), epoxidized soybean oil and antistatic agents, colorants and stabilizers, among others.

There are also extractables and leachables that are introduced from the component molding process, and although they are not intentionally added to the material, they can end up being introduced to the product as a leachable. Examples of this are mold release agents and lubricants used in the molding process.

Since leachables may affect drug product safety, efficacy and quality, regulatory guidances have provided recommendations regarding their analysis and toxicological safety assessment, i.e., qualification. Extractables studies are necessary to facilitate the leachables' analysis, providing predictive information of potential leachables and in certain cases controlling leachable amounts in the final drug products through the control of extractable amounts of the container/closure components.

Current Regulatory and Industry Guidance

Many regulatory guidance documents have been established to define the requirements of E&L assessment, including the documents listed below:

- 21 CFR Part 211.94: Drug product containers and closures should not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity beyond the official or established requirements

- Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation (FDA, May 1999)
- Metered Dose Inhaler and Dry Powder Inhaler Drug Products Chemistry, Manufacturing and Controls Documentation (FDA, Oct 1998)
- Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing and Controls Documentation (FDA, July 2002)
- Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (EMEA, June 2006)
- Guideline on Plastic Immediate Packaging Materials (EMEA, May 2005)

These regulatory guidance documents specify expectations but do not include details on how E&L evaluations should be performed, so therefore various industry guidance documents have been established over the years to help complement the regulatory guidances with best practice "how to" approaches for E&L studies.

One of the key such industry documents was published by the Product Quality Research Institute (PQRI) Leachables and Extractables Working Group in 2006.[1] This recommendation, "Safety Threshold and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products," known as the PQRI OINDP recommendation, defines how E&L studies should be performed in terms of best practices and how low to go in relation to evaluation thresholds. This PQRI recommendation quickly became the gold standard for the expectation of how E&L studies are to be performed. The scientific principles of the recommendations are widely used in the pharmaceutical industry for E&L studies. United States Pharmacopeia (USP) also has adopted new chapters based upon the recommendations, reflected for example in USP chapters <661>,[2] <661.1>,[3] <661.2>,[4] <1661>,[5] <1663>,[6] <1664>,[7] and <1664.1>.[8] Another PQRI working group currently is working on a similar document to the PQRI OINDP recommendation, but specific to parental and ophthalmic drug products.[9] Also, new USP chapters for E&L are being added.

These documents provide industrial guidelines for evaluating E&L from the drug product container/closure systems.

Another area of more recent focus and discussion within the industry is regarding E&L from the drug product manufacturing process. The BioPhorum Operation Group (BPOG) published a standardized protocol[10] for extractables testing for single-use systems in biomanufacturing, and in a follow-up BPOG document[11] also presented the "Best Practices Guide for Evaluating Leachables Risk from Polymerics Single-Use Systems Used in Biopharmaceutical Manufacturing." USP is working on plastic components and systems used to manufacture pharmaceutical and biopharmaceutical drug products and their characterization under chapters <661.3>,[12] <665>[13] and <1665>.[14] These documents provide industry guidelines for evaluating E&L from manufacturing components.

Specific to medical devices, ISO 10993-12[15] and ISO 10993-17[16] describe in detail the E&L sample extraction procedures and the allowable limit for leachables for the biological evaluation of medical devices.

Other related guidance documents include:

- USP <659>[17] for packaging requirements, USP <660>[18] for glass and USP <381>[19] for elastomeric closures for injections, which describes the general testing requirements for the container/closure components;
- USP <232>[20] and ICH Q3D[21] for elemental impurities; and
- ICH M7 guidance,[22] and FDA guidance for Genotoxic and Carcinogenic Impurities in Drug Substances and Products,[23] which describe the limits of impurities in the drug substance or drug product.

Table 1. Modified FDA/CDER/CBER Risk-based Approach to Consideration of Leachables

Degree of concern associated with the route of administration	Likelihood of packaging component-dosage form interaction		
	High	Medium	Low
Highest	Inhalation aerosol and sprays	Injection and injectable suspension; inhalation solution	Sterile powders and powders for injection; inhalation powders
High	Transdermal ointment and patches	Ophthalmic solutions and suspension; nasal aerosol and sprays	
Low	Topic solutions and suspensions; topical and lingual aerosol; oral solutions and suspensions		Oral tablets and oral (hard and soft gelatin) capsules; topical powders; oral powders

Current Industry Trends for Extractables and Leachables Testing

Nearly all types of drug product submissions require at least some level of consideration regarding E&L evaluation. The extent of the E&L evaluation depends on a risk assessment, partially based upon a consideration of the likelihood of compounds leaching into the drug product formulations and the impact of leachables on the safety of the patient based on the route of administration, as shown in Table 1, which is modified from the FDA guidance on container/closure systems, and which is also included in USP <1664>.[7]

Consistent with industry guidance documents, the greatest need for these types of studies is drug products with a high degree of concern based on the route of administration and the likelihood of interaction between the packaging component and the dosage form. Based upon this, the greatest level of focus and efforts for E&L evaluation was initially centered on inhalation aerosol and sprays.

Although OINDP products still require extensive E&L evaluation, the explosive growth in E&L testing has been with the follow-on emphasis in parenterally administered drugs, which includes the predominance of biologic products. The growth in this area is not only due to the number of drug products requiring E&L testing, but also the extent of E&L testing for drug product. There are many reasons for the rapid growth of E&L testing for parental products. We will discuss three of them.

Significant growth in parenteral product development

Many new, innovative therapies are being accomplished with biologic drug products, and a vast majority of these products are administered parenterally. A result of this is an overall increase in the number of drug products that are parenterally administered. When coupled with the large number of parenterally administered small molecule drugs, the result is that this route of administration outnumbers all others. Biologics and other parental drug products are typically stored in pre-filled syringes or in a glass vial with a rubber stopper, in the form of liquid or lyophilized cake. E&L testing is required for container/closure components for such products, including syringe barrels, plungers, tip caps, glass vials and stoppers, as well as the final drug products. Parenteral products often are delivered to the patient with IV bag/administration sets, which also require E&L evaluation.

High risk of safety concern associated with the route of administration

It is well known that the parental administration route presents one of the highest safety risks in terms of leachables, but what is less well understood

is that this concern applies as much or even more in certain cases for lyophilized/powder products compared to liquid formulations. Although sterile powders and powders for injections, along with inhalation powers, are categorized as "low" risk for the likelihood of leachables in Table 1, PPD Laboratories' experience from many years of performing E&L testing is that this categorization probably underestimates the risk of leachables for powders, especially regarding volatile and semi-volatile leachables. Powders exhibit a unique mechanism of taking on leachables compared to solvent-based products. Powders absorb leachables based on the large surface area presented by a fine particle size and the chemical/physical characteristic of the surface, thereby circumventing reliance on the solubility of leachables in a liquid solvent. The result is that certain low polarity compounds - such as BHT, butyl rubber oligomers and brominated/chlorinated butyl rubber oligomers from the rubber stoppers - that may not leach into an aqueous product because of low solubility, may leach out and be absorbed by a powder formulation. Also, many biological products contain polysorbate as a surfactant, which enhances the capability of the formulation to extract compounds from the container/closure components.

Potential leachables impact on the drug product itself

Another risk of leachables for biological products is that leachables may affect the conformational structure of the large molecule drug substance, thus affecting drug product efficacy.

E&L testing also is expanding more and more into testing for other types of dosage forms other than parenteral and inhaled/nasal products, such as ophthalmic products, transdermal products and oral liquids. This growth in testing is being experienced both in the amount of testing and the extent of testing. Oral liquid product testing frequently is requested for products that contain organic solvent and ingredients that increase the likelihood of leachables. E&L studies are even performed in certain cases for solid oral product containers, as many migration type label studies have been performed for plastic containers with labels affixed, to evaluate the likelihood of leachable migration to tablets, as leachables may cause issues with solid oral product appearance, stability or shelf-life integrity.

Also notable is the expansion of E&L testing for drug product delivery components, including IV bags, administration sets, mouthpieces, drug delivery pumps, syringes and needles, etc. These components have short exposure duration to the drug product or patient, so the approach for the E&L testing is different and the extent of testing also usually is not as extensive as for the final container/closure systems.

Another rapidly growing area is E&L testing for components used in the manufacturing process, including the traditional design of multiple-use systems (MUS) and especially for single-use systems (SUS).

SUS have been widely used for biopharmaceutical manufacturing suites. The components for SUS manufacturing mostly are made of plastic and rubber materials that exhibit a higher risk of introducing leachables into the final drug products compared to the traditional stainless steel components. Also, large-molecule/biologic products can be more susceptible to leachables, as discussed earlier in this article. BPOG published a standardized protocol for the extractables testing of the SUS components for component suppliers to follow. This protocol calls for extensive extractables testing based on six solvent extraction systems and multiple time points up to 70-day extraction time, to cover a majority of the potential manufacturing processes used. The scope of this testing is so large and the testing takes so long that many of the suppliers are opting to perform modified or abbreviated testing in-house and outsource the comprehensive testing to contract laboratories that have more expertise and experience in this area.

Pharmaceutical companies that are responsible for their drug product manufacturing must still assess if the BPOG extraction study (if performed) will represent the real or worst-case scenario for their specific manufacturing process. Leachable studies normally will still be required for evaluating leachables in the drug product, which is not covered by BPOG extractable studies. Pharmaceutical companies also usually perform the E&L testing of the manufacturing components with a testing scope appropriate to their specific manufacturing process if no BPOG E&L study is performed.

MUS components also include many plastic and rubber components and they, too, require E&L evaluation, and E&L testing frequently is requested for stainless steel components.

E&L testing of manufacturing components includes all the processes from the manufacturing of the API, process buffers and intermediates to the final drug product. The test requirements and extent of testing are based on risk assessment, which includes an evaluation of the degree of concern associated with the route of administration of the drug product manufactured and the likelihood of the manufacturing components leaching compounds that may end up in the final drug product. Downstream processes closer to the final drug product formulation may have higher risk than upstream processes, and processes that involve high organic solvent content, high surfactant contents or extreme pH, etc., may have higher risk than neutral aqueous solutions with few or no surfactants. Also, the extent of E&L testing for various components in the process may range from simple USP <661.1> testing to comprehensive chemical safety assessment based on USP <1663> and <1664>.

Current Best Practices for E&L Testing

Designing and conducting a complete E&L program can be challenging because of the complex nature of such studies, particularly with all the required considerations and variables. Pharmaceutical products may incorporate the use of or interaction with a wide variety of polymer materials, numerous sources for possible E&L compounds and a diversity of different dosage forms, manufacturing processes and drug product delivery mechanisms. It is not possible, therefore, to present a universal test condition that applies to all E&L testing. However, the study design should harmonize with regulatory expectations and be based on sound scientific principles that are appropriate for the type of dosage form(s) and route of administration.

The safety concern threshold (SCT) approach proposed in the PQRI recommendation for OINDP for the evaluation of E&L is widely applied in industry, not only to OINDP, but also to other dosage forms, although different thresholds may be used for different dosage forms. A total daily intake (TDI) of 0.15 µg/day is used as the SCT for OINDP dosage forms, consistent with the PQRI recommendation, while a TDI of 1.5 µg/day is often used for parental, ophthalmic[9] and other dosage forms. Higher thresholds may be justified if the drug products are not for chronic use based on the ICH M7 guidance.[22]

With the exception of the special case compounds for OINDP products, if an extractable or leachable amount is below the SCT, it generally is considered that its safety concern is negligible, whereas E&L compounds at amounts at or above the SCT should be evaluated further for safety impact.

The SCT is converted to an analytically meaningful value, which is termed the Analytical Evaluation Threshold (AET), reported in µg/mL, µg/g or µg/component units and used as a guide throughout the whole

Table 2. Acceptable Daily Intake for Individual Impurity per ICH M7

Duration of treatment	< 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

E&L study program. The overall E&L study program usually includes all or some of the following parts.

Controlled extraction study

The primary purpose of the controlled extraction study is to generate a complete profile of the extractables of the components evaluated, which may be potential leachables in the drug product. The controlled extraction study typically is guided by the AET for selecting the appropriate sample preparation procedures and analytical methods. The following are key considerations for the design of the controlled extraction study.

Material preparation: Controlled extraction studies are performed on individual components whenever possible to trace back the source of leachables, if leachables are detected in the drug product samples. However, components made of the same material type may be combined for the extraction study since this will not affect the leachables' traceability. Sometimes components of different materials are combined in the controlled extraction study and the reason components of different material would be combined is typically a decision by the pharmaceutical company to save cost and time compared to evaluating each individual component separately. The potential draw-back of combining components is that it removes the possibility of tracking back the extractables from specific components. Components may be extracted whole or reduced to a smaller, possibly more appropriate size for extraction. The industry trend is to extract components whole and cut to smaller size only as needed or required, such as to fit the components to the size of the extraction vessel. Alternatively, cutting into smaller pieces or powdering of the material using techniques such as cryo-grinding may be used. Arguably there are certain advantages with cryo-grinding the components to powders for extraction, such as ease in achieving extraction amount plateau while using milder extraction conditions and shorter extraction times. The drawback is that the number of extractables with amounts at or above AET may be much greater than when extracting whole components, and many of these extractables observed will likely not be observed as leachables. Therefore, more time and effort is required to go through such data to identify and report peaks, which in the end may likely not be present as true leachables.

Extraction solvent: Extraction solvents should be appropriate for the dosage forms and materials being evaluated, and should provide the worst case possible leachables profile for the drug product formulation without degrading the material. Typically, multiple solvents are used with one solvent being the same or similar to the drug product formulation. Considerations for selecting the appropriate extraction solvent include both solvent extraction capability (while avoiding material degradation) and the feasibility of detecting extractables from the extraction solvents. Extraction solvents with complex composition may interfere with the chromatographic detection of extractables, so, in this regard, simple and high purity solvents are preferred. In addition, solvent selection should consider possible side reactions between the extraction solvents and possible extractables in the materials. Justification of the selection of extraction solvents should be provided.

Extraction ratio: The ratio of material amount to the extraction solvent volume and the follow-up preparation of testing solutions should be guided by the AET. The ratio must be high enough to achieve the AET level with the applicable analytical methods. If not achievable directly, the extraction solutions can be further concentrated to help achieve the AET sensitivity limit. Justifications are required if the AET cannot be achieved. For medical devices, the ratio of the sample amount and extraction solvent volume is defined in ISO 10993-12.

Extraction techniques, extraction temperature and extraction time: The most common extraction techniques are still reflux, Soxhlet extraction, sealed vessel extraction and solvent soaking, but other techniques are used, including sonication, microwave extraction, pressurized solvent extraction with Accelerated Solvent Extractor (ASE) and supercritical fluid solvent extraction, among others.

For volatile extractables analysis, a sealed vessel extraction is preferred to prevent the loss of volatile extractables during the extraction process.

Extraction temperature and extraction time selection ideally should be based on achieving an extraction amount plateau. In reality, extraction plateaus may not be feasible for multiple reasons. For instance, there are usually many extractables from the same extraction, and some compounds may degrade before other compounds achieve the extraction plateau. In addition, some compounds may take so long to achieve an extraction plateau the lab testing becomes impractical. Finally, some compounds may never achieve extraction plateau before the materials are degraded. A balanced consideration and approach should be applied, with the goal to achieve optimal extractables amount under practical lab conditions without causing degradation of the material.

For medical devices, the extraction temperature and extraction time are defined in ISO 10993-12.

Analytical methodology: Based on knowledge of the materials of the components many of the main extractables may be known and expected, but there is almost always the possibility of unknown and unexpected extractables to be observed from the materials, so the methodologies should be able to detect and identify not only the known and expected extractables, but also the unknown and unexpected extractables. The diversity of materials and possible compounds and elements present in the materials require a methodology that is able to detect, identify and quantify a wide range of possible extractables. An array of methods including headspace GC/MS, direct injection GC/MS, LC/MS (complemented with UV or CAD detection), and ICP/MS is used to screen all known and unknown, expected and unexpected extractables, targeting but not limited to, volatile, semi-volatile, non-volatile extractables and extractable inorganic elements, respectively. These MS methods are run in scan mode across a wide mass range, with appropriate gradients, column and mobile phases to elute, separate and detect any known, expected or unknown, unexpected extractables.

The method sensitivity should be guided by the AET. The screening methods, with combination of the sample extraction and preparation, should be able to achieve a sensitivity that is equal to or below the AET level.

There are also other methodologies with targeted extractables analysis for special case compounds, or compounds that may not be detected with the methodology discussed above, such as:

- Nitrosamines analysis with GC/TEA, LC/MS/MS, GC/NCD
- PAH analysis with GC/MS/MS or GC/MS in SIM mode
- Silicone oil analysis with AA, ICP/OES, ICP/MS, HPLC (including GPC) with RI, CAD or ELSD detectors
- Ionic extractables analysis with IC

Forced Migration Study or Leachables Screening Analysis of Aged Drug Product Samples

Increasingly, forced migration study or aged drug product leachables screening studies are performed in addition to the controlled extraction study and stability leachables testing. The purpose of the forced migration studies or leachables screening of aged drug product samples,

if available, is to obtain an initial qualitative and semi-quantitative leachables profile to provide an initial reading of potential safety concerns from leachables and to facilitate the selection of targeted leachable compounds for development and validation of leachable methods. Note that the leachables profile from the forced migration study or screening study may not represent the worst case amount of leachables over the product shelf life and may not account for all leachables; because: 1) the samples may not be representative of the full shelf life storage duration; or 2) screening methods are not validated for the detection and accurate quantitation of specific leachables, and therefore formulation excipients may interfere with the detection and quantitation of some leachables in the drug product matrix.

Forced migration normally is performed with the drug product contained in the whole container/closure system, so the exposure to the container/closure components is the same as for the actual intended drug product storage. The solvents utilized include the drug product formulation or drug product placebo. The temperature and duration of the forced migration study may vary from product to product. ASTM F1980-07 (2011)[24] is a useful guide for establishing forced migration study conditions.

The forced migration samples or aged drug product samples along with appropriate control samples which are not exposed to the container/closure system, are screened for leachables with headspace GC/MS, GC/MS, LC/MS in combination with UV, CAD, or other suitable detectors, and ICP/MS, and preferably the forced migration samples or aged drug product samples are screened together with the controlled extraction study samples, so a direct qualitative correlation of leachables to extractables may be established. This also helps to evaluate if any extractables of interest from the controlled extraction study may be interfered with by the drug product active or formulation excipients.

Extractables and Leachables Profile Assessment and Selection of Target Leachable Compounds

The extractables profile of the container/closure components from the controlled extraction study and leachables profile from the forced migration study or aged drug product screening analysis should go through a careful toxicological and physical/chemical assessment. The toxicological assessment includes an evaluation if any of the extractables and leachables present a structure activity alert, which may indicate a safety concern for the drug product and the physical/chemical assessment includes an evaluation of how likely the extractables from the container/closure components are to leach into the drug product formulation (including an evaluation of the leachables detected in the aged product screening analysis or forced migration study). Some of the factors that should be considered in this assessment include: extractable compound solubility; direct/indirect contact with the drug product; duration of contact; and any physical barrier for the migration of the compounds to the drug product.

The results of E&L profile assessment will provide an initial reading of the risk of leachables from the container/closure system to drug product safety. The assessment results also will provide a list of likely leachable compounds that may require further evaluation, including their possible inclusion as targeted compounds for leachables method development and validation, which are utilized for monitoring leachables during stability programs over the shelf life of the drug products. The targeted compounds list may include some peaks that are only observed in the controlled extraction studies, but not in the forced migration study or leachables screening study of aged drug product based on a: 1) toxicity assessment indicating that such compounds may present a safety concern; or 2) chemical assessment indicating that the compounds are likely to leach into the product and that in the leachables screening study screening method conditions may not have detected them for various reasons, such as interference from the drug product matrix, or low response or low recovery of the compound from the drug product matrix.

The target compounds list also may include peaks that could not be positively identified in the controlled extraction study, forced migration or leachables screening study, for example compounds detected as leachables in the aged drug product samples but which are not fully identified. These compounds then require further monitoring during the stability program of their amounts over the product shelf life. If present in stability studies above the threshold, then further efforts to identify the leachables are required.

Leachables Method Development and Validation

Leachable methods are for the detection and accurate quantitation of leachables in the drug product. Leachable methods development and validation should be guided by the AET, although the AET may be justified higher for drug products not intended for chronic use, and for leachables compounds that are not carcinogenic or genotoxic. The method sensitivity should be able to achieve the AET level or lower and the method range should cover from the AET level to the expected worst case leachable amount that will be observed over the shelf life of the drug product.

Increasingly in industry, certain leachables methods are developed and validated as limit test methods. In this case, the method limit usually is set at the AET level or otherwise justified at a higher level. This approach is more suitable for drug products with container/closure systems for which the leachables amounts are not expected to exceed the AET levels based on the assessment of the drug product composition and extractables profile of the container/closure components.

Historically, non-mass spectrometry (HPLC/UV or GC/FID) methods have been used for routine leachables testing because of greater availability of such instrumentation versus mass spectrometry detection instrumentation, and method accuracy/precision and robustness may benefit from the non-mass spectrometry instrumentation. GC/MS and LC/MS methods are now becoming more and more common for leachables testing because of convenience for determining and identifying unknown and unspecified leachables.

Target leachables compounds, including targeted unknown leachable compounds from the extractables and leachables profile assessment, should be chromatographically separated from the drug product formulation excipients and their degradants.

It is preferred that at least certain of the leachable methods are able to detect unspecified unknown leachable compounds so unspecified unknown leachables can be monitored during the leachable stability program.

Stability Sample Testing for Leachables

Stability sample leachables testing should cover the drug product shelf life with multiple time points, preferably consistent with the ICH guideline for drug product stability analysis. Early time points are monitored to allow for leachable profile trending.

Stability sample leachable testing typically is performed with validated leachable methods. Increasingly, control samples are included in the stability program, so unspecified unknown leachables peaks can be distinguished from matrix-related chromatographic peaks and monitored. Control samples are stored in containers with known knowledge of little or no leaching propensity, such as Teflon bottles with Teflon caps, etc.

Notably, PPD Laboratories has observed an increase in stability leachable testing performed with non-validated leachable screening methods. This approach is more suitable for situations such as when: 1) drug product composition is simple and is not expected to interfere with the detection of potential leachables; or 2) the extractable profiles do not indicate any major extractables of safety concern. With that approach, control samples must be included; an evaluation of feasibility of the screening methods for the specific drug products is normally performed as well. If leachables are observed during stability testing with amounts at or above the AET level, further work may be required to qualify the methods for accurate amount quantitation of the leachables.

The leachable testing results are assessed for any situations where the leachable levels are above the AET and pose any safety concern for the drug products and also for correlation with the extractables profile. If there are leachables of potential safety concern, then their amounts may need to be controlled for lot-to-lot variation. In that case, the two most common ways to address this are to:

a. Establish a correlation of leachables amounts in the drug product vs. the extractables amounts of the source components of the container/closure system and perform batch extractables testing of the source components, thus controlling potential leachable variability by performing routine, extractable testing; or

b. Perform leachables testing of different lots of drug products. However, since leachables amounts need to be monitored over the drug product shelf life with multiple time points, that approach is costly and inconvenient.

Batch Extractables Testing for the Container/Closure Components

As noted earlier, for leachable compounds that are present at a concentration that may represent a potential safety concern, the amounts must be controlled. A convenient way to control leachables amounts widely used in industry is to control the amount of extractables in the source components (since extractables and leachables are correlated). This is accomplished by performing batch extractables testing of the source components used for the drug product.

Batch extractables testing of container/closure components also is used to control extractables profile variations of the critical packaging components as a quality control test; it commonly has been used for the testing of critical components of dry powder inhalers.

E&L testing for components with short-term exposure to the drug product formulation or the patient, for example, components used for drug delivery, such as IV bags, IV administration sets, mouthpiece and components used in the manufacturing process, is somewhat different from the final container/closure components discussed earlier. Typically, in the case of short-term contact components, an in-use simulation leachables study is performed, in which, the components are exposed to the drug product solution, or a product simulation solution, such as saline, or manufacturing process solutions, the same way as in actual use, or representing the worst-case scenario of exposure. The solutions from before and after the exposure are then analyzed to screen for leachables with the methodology discussed in this article. In addition, an extraction of the short-term contact components with simple and clean solvents representing the worst-case extraction capability comparing to the actual drug product or process solutions, also usually are performed. The solvent extraction facilitates the correlation of extractables and leachables, and facilitates the evaluation of whether any leachables present in the exposure study are being missed, for example because of interference of the drug product matrix. The same sound scientific principles discussed in previous sections should be followed.

Conclusion

Overall, E&L testing is greatly expanding from the historical emphasis on ONIDP to parental products and nearly all other dosage forms. At the same time, the focus of the testing is expanding from just evaluating the final container/closure system components to now needing to consider the drug product manufacturing components and drug product delivery system components as well.

E&L testing also is expanding in the extent and complexity of testing, which requires comprehensive design of the E&L program based on sound scientific principles. Trending from just detecting and quantifying the known and expected leachables has transitioned to now addressing the issues of unknown and unexpected leachables. The complexity of the E&L study program poses significant challenges for pharmaceutical product development, and requires significant expertise for the successful design and execution of an E&L program.

References

1. Product Quality Research Institute, Safety Thresholds and Best Practices for Orally Inhaled and Nasal Drug Products, September 8, 2006
2. USP <661>, Plastic Packaging and Their Materials of Construction, USP 40
3. USP 40 <661.1>, Plastic Materials of Construction, USP 40
4. USP <661.2>, Plastic Packaging systems for Pharmaceutical Use, USP 40
5. USP <1661>, Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact, USP 40
6. USP <1663>, Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, USP 40
7. USP <1664>, Assessment of Drug Product Leachables Associated With Pharmaceutical Packaging/Delivery Systems, USP 40
8. USP <1664.1>, Orally Inhaled and Nasal Drug Products, USP 40
9. Paskiet, D. The Threshold and Best Practice for Leachables and Extractables in Parenteral and Opthalmic Drug Products (PODP), Smithers-RAPRA Extractables and Leachables Conference, USA 2016, Bethesda, MD.
10. BioPhorum Operations Group (BPOG), Standardized Testing Protocol for Single-use Systems in Biomanufacturing, Pharmaceutical Engineering 34 (6), 2014, 1 – 11.
11. BioPhorum Operations Group (BPOG), Best Practice Guide for evaluating Leachables Risk in Biopharmaceutical Single-Use System, BPOG Leachables White Paper, March 22, 2017
12. USP <661.3>, Plastic Components and Systems Used in Pharmaceutical Manufacturing, Pharmacopeial Forum 42 (3), May 1, 2016
13. USP <665>, Polymeric Components and Systems Used to Manufacture Pharmaceutical and Biopharmaceutical Drug Products, Pharmacopeial Forum 43 (3), May 1, 2017
14. USP <1665>, Characterization of Polymeric Components and Systems Used to Manufacture Pharmaceutical and Biopharmaceutical Drug Products, Pharmacopeial Forum 43 (3), May 1, 2017
15. ISO 10993-12, Biological Evaluation of Medical Devices, Part 12: Sample Preparation and Reference Materials, ISO 10993-12:2012
16. ISO 10993-17, Biological Evaluation of Medical Devices — Part 17: Establishment of Allowable Limits for Leachable Substances, ISO 10993-17:2009
17. USP <659>, Packaging and Storage Requirements, USP 40
18. USP <660>, Containers — Glass, USP 40
19. USP <381>, Elastomeric Closures For Injections, USP 40
20. USP <232>, Elemental Impurities — Limits, USP 40
21. ICH Q3D, Guideline for Elemental Impurities, Q3D, International Conference on Harmonization, December 16, 2014
22. ICH M7 guidance: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, International Conference on Harmonization, June 23, 2014
23. FDA, Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, Draft Guidance, 2008
24. ASTM F1980-07 (2011): Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices