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BRIEFING

〈1664.3〉 Assessment of Leachables in Topical Ophthalmic Drug Products. 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 topical ophthalmic drug products (ODPs), including solutions, suspensions, emulsions, and ointments. The chapter examines leachables from two primary sources: process equipment used to produce the dosage form and container closure systems used to package the dosage form over its shelf life. Note that the following discussion is primarily devoted to organic leachables. For consideration of inorganic (i.e., elemental) leachables, see 〈1664〉.

(GCDF: R. Kaja)

Case ID—SUB-2478

Add the following:

▲〈1664.3〉 ASSESSMENT OF LEACHABLES IN TOPICAL OPHTHALMIC DRUG PRODUCTS

1. INTRODUCTION

This section addresses considerations for leachables in topical ophthalmic drug products (ODPs), including solutions, suspensions, emulsions, and ointments. Although other dosage forms (e.g., injectables, implants, inserts) also exist in ophthalmology, the scope of this discussion is limited to topical products. Regulatory guidance and detailed best practice recommendations for treating leachables in ODPs have become available in recent years (*1–2*).

Topical ophthalmic products are dosage forms designed to be administered topically to the eye (principally the conjunctiva or the eyelid) for the treatment of primarily local disorders. Glaucoma, a disease of the interior of the eye, may also be treated using these dosage forms.

Four main types of topical ophthalmic dosage forms are clinically used:

1. Solutions
2. Suspensions (including gels)
3. Emulsions
4. Ointments

Leaching of substances from packaging components will be significantly affected by the ingredients present in the formulation. The first three dosage forms listed above typically have water as the primary phase (continuous phase) in direct contact with the primary packaging. Ointment formulations will have an oil phase (typically mineral oil and petrolatum) in direct contact with the product packaging. The addition of other ingredients to the water or oil phase of the drug product may enhance the solubility of extractable materials and affect the rate of migration.

Most topical ODPs are solutions, suspensions, and emulsions that are often filled into semipermeable plastic container closure systems. These formulations are sterile, isotonic, largely aqueous products that typically include tonicity agents, surfactants, preservatives, and may include some oil phase ingredients (in the case of emulsions). These ingredients have the potential to increase the solubility of extractable substances and affect the rate of leaching into the drug product. Some nonionic tonicity agents may be added to ODPs with the potential to enhance leaching that include propylene glycol, glycerin, and polyethylene glycol. Surfactants (e.g., polysorbate 80, poloxamer, tyloxapol) may be added as suspending agents, solubilizing agents, or wetting agents to help the product spread on the surface of the eye. Regardless of their function in the drug product, these surfactants may affect the solubility of extractable substances and increase observed leachable levels. Oils present in an emulsion may increase the solubility of extractable materials in the drug product, even if they are not in direct contact with the packaging. This may not increase the rate of leaching from a package, but it may increase the maximum amount of material that can be extracted from a packaging system. Some preservatives may also have significant effects—benzalkonium chloride (BAK) is a common preservative with surfactant properties that can solubilize some low-solubility materials, and chlorobutanol is known to migrate into some

plastic packaging materials over time. The presence and concentration of these ingredients in the drug product should be considered when selecting ODP packaging and designing extractables and leachables studies.

Ophthalmic ointments have an oil phase as the continuous phase in direct contact with the primary packaging. The oil phase for an ointment is typically comprised of mineral oil and petrolatum, but may also contain triglyceride oils, lanolin, and lanolin alcohols. Mineral oil and petrolatum are nonpolar oils, and the addition of other polar oils may significantly affect the extraction or leaching from the packaging. Additionally, some ointments may contain surfactants added as emulsifiers to either stabilize the aqueous phase in the ointment or to enhance the ability of water to diffuse into the ointment after application. All of these additional ingredients have the potential to affect the type and concentration of leachables that may migrate into a drug product.

2. PACKAGING SYSTEMS FOR ODPS

Multidose solution, suspension, and emulsion ODPs are commonly stored and administered using dropper bottles (also called droptainers), which typically consist of a bottle containing the drug product, a dropper tip, and a screw cap closure to seal the container closure system. Patients squeeze the inverted bottle to administer the ODP directly to the eye, which places mechanical requirements around the physical properties of the bottle material for effective dose administration. In common use for many years, these systems supplanted glass bottles fitted with glass pipettes and elastomeric bulb droppers due to their simplicity, shatter resistance, and ability to serve as effective sterile containers.

Droptainer components are primarily fabricated from polyolefins, for example, low-density polyethylene (LDPE), high-density polyethylene (HDPE), or polypropylene (PP). For dosing, the container must be soft enough to allow facile squeezing by patients. As a result, many ODP bottles are made of LDPE, although exceptions exist. In some cases, more rigid polymers may be used for the bottle, but thinned significantly to facilitate dosing. In either case, dropper bottles are often semipermeable. Lacking a requirement for flexibility, dropper tip and closure components are often molded from harder plastics. Closures for pharmaceutical ODPs are colored to correspond with the class of active ingredient contained within, per American Academy of Ophthalmology (AAO) recommendations (*3*). More recently, specialized closures that prevent microbial ingress during dosing have allowed the distribution of preservative-free formulations in multidose bottles. These closures contain a greater diversity of materials than droptainers, including elastomers.

In some cases, solution, suspension, and emulsion ODPs are filled into single-dose unit vials. This is an alternative means of storing and delivering preservative-free formulations, in which a small volume (i.e., no more than 0.5 mL) is filled into a container closure system that is opened once by the patient, dispensed to the eye, and then discarded. More often than not, these single-dose units are created using a blow-fill-seal process, in which LDPE resin is molded, the product is filled aseptically, and the vial is sealed in a single operation. Water loss from these low-volume, semipermeable vials can limit ODP shelf life, often necessitating the enclosure of the single-dose unit vial in an impermeable foil laminate pouch that serves as functional secondary packaging.

Ointments are typically packaged in flexible plastic or collapsible metal tubes, which include the tube itself, a delivery nozzle, and a screw cap closure. These tubes can be made from metal (such as tin or aluminum) or laminate structures, which typically consist of a polyolefin product contact layer, an aluminum barrier layer, and a printable polyolefin exterior. Metal tubes, especially those made of aluminum, are often coated with lacquer to minimize interactions between the metal substrate and the drug product. Additionally, a crimp sealant may be applied at the distal end of the tube from the nozzle to ensure container closure integrity. Both lacquers and crimp sealants can be sources of extractables from these packaging systems. Screw cap closures are typically molded from polyolefins and are color-coded according to the class of active pharmaceutical ingredient, following AAO recommendations (*3*).

3. PROCESS EQUIPMENT-RELATED LEACHABLES

ODPs are generally manufactured in an aseptic environment using multiple-use, metallic equipment, primarily stainless steel. The manufacturing process, particularly contact between a drug product and plastic components and systems in the ODP manufacturing train, may contribute to the observed drug product leachable profile. It is recommended that an assessment of process equipment-related leachables (PERLs) be performed in accordance with *Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products 〈665〉* and *Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products 〈1665〉* prior to assessing leachables from the packaging system. For ODPs that are sterilized by filtration, this assessment of PERLs should also include an assessment of the extractables from the sterilizing filter.

4. REPORTING PRACTICES AND THRESHOLDS FOR LEACHABLES FROM ODPS

ODPs have long been classified as being in a high-risk category with respect to safety concerns related to leachables, as most recently summarized in *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems 〈1664〉*. Past guidance concerning leachables has grouped ODPs together with parenteral drug products (PDP) (i.e., injectable) because they often share similar product attributes as sterile aqueous solutions, suspensions, or emulsions (*4*). However, beyond these superficial similarities, ODPs and PDPs differ significantly in terms of route of administration (i.e., topical versus systemic delivery, respectively) and dose volume (i.e., tens of microliters versus milliliters to liters, respectively). Thus, the toxicological implications of leachables in these products are also different (e.g., local irritation for ODPs versus systemic exposure for PDPs), suggesting that ODPs require a different assessment approach than PDPs.

Reporting, identification, and qualification of leachables in other high-risk dosage forms, such as orally inhaled and nasal drug products (OINDPs) (see *Orally Inhaled and Nasal Drug Products 〈1664.1〉*) and PDPs [see *Parenteral Drug Products (Intramuscular, Intravenous, and Subcutaneous) 〈1664.2〉*], are driven by safety concern thresholds (SCTs) on a risk-based, product-specific basis. However, SCTs for those other product types are derived from systemic safety data. In contrast, ODPs lack a sufficient safety database developed on relevant toxicity

endpoints (i.e., local sensitization and ocular irritation) at concentrations relevant to drug product leachables. As a result, no consensus SCT has emerged for ODPs (*1*).

Instead, ODP leachable assessments are driven by their concentrations in the drug product (i.e., the weight of leachable per unit volume or mass of the drug product) rather than daily exposure. Drug product concentration is a more relevant parameter for evaluating the local toxicological effects, which are the primary concern for this product type. As described in *Table 1*, thresholds for drug product leachables are expressed in part-per-million (ppm) quantities as (microgram of leachable per milliliter of product) or (microgram of leachable per gram of product) (*1–2*). Actions would be necessary for any leachable exceeding the limits in *Table 1*.

Table 1. Recommended Leachable Thresholds for ODPs

Action	Threshold (ppm)
Reporting	1
Identification	10
Qualification	20

Thus, unlike OINDPs and PDPs, there is no SCT to convert to an analytical evaluation threshold (AET) for ODPs. Whereas AET calculations are significantly impacted by dose volume and frequency, these factors become irrelevant for ODPs.

In addition to the limits summarized in *Table 1*, other safety endpoints, such as genotoxicity, may also need to be considered. This is primarily a systemic toxicity concern. In such cases, it is sometimes necessary to also assess ODP leachables against the 1.5-µg/day SCT established for PDP (see 〈1664.2〉) or other appropriate SCT value per agreement with regulators. For most eye drop products, the 1 ppm reporting threshold is conservative versus an AET calculated from a 1.5-µg/day SCT. For example, an ODP dosed four times daily in each eye (a total of 8 doses) with a conservative drop size of 40 µL (0.040 mL) would have an estimated AET calculated as:

$$\text{Estimated AET} = 1.5\ \mu\text{g/day} \cdot (1\ \text{day}/8\ \text{doses}) \cdot (1\ \text{dose}/0.040\ \text{mL}) = 4.7\ \mu\text{g/mL or } 4.7\ \text{ppm}$$

While the 1-ppm ODP reporting threshold is generally lower than an AET calculated from an SCT of 1.5 µg/mL, this relationship varies depending on the dosing regimen and volume. A key point of the above example is that ODP leachable studies designed around an SCT of 1.5 µg/mL may lack sufficient sensitivity to meet the 1 ppm reporting threshold outlined in *Table 1*. Regardless, the analytical methods used to detect extractables and leachables in ODPs should be capable of reporting whichever threshold (1 ppm or 1.5 µg/day) is lower.

Sponsors are often required to set specification limits on reportable leachables (e.g., those above 1 ppm) in ODPs. For example, a limit might be set at the 20-ppm leachable qualification threshold. Although identification is not required until estimated leachable levels exceed 10 ppm, identifying all reportable leachables above 1 ppm facilitates accurate quantification and provides better opportunities for the sponsor to manage or even eliminate the leachable from the drug product over time.

5. LEACHABLES ENCOUNTERED IN ODPS

5.1 Primary Packaging

Although primary packaging is an obvious source of potential leachables due to direct contact with the dosage form, in practice, the container closure systems used with aqueous ODPs contribute minimal leachables to the drug product. This is partially the result of typical solution, suspension, and emulsion ODPs being primarily aqueous in nature and fundamentally less aggressive than formulations with significant organic content. Although oil-in-water ophthalmic emulsions possess an enhanced ability to leach substances from primary packaging compared to solutions and suspensions, the continuous phase of these emulsions is nonetheless water. Most polyolefin additives are specifically designed for improved solubility in the hydrophobic polymer matrix; however, many of their degradation or transformation products are more polar than the original additives and are therefore more likely to appear as leachables in aqueous products. Additionally, and in many cases, the LDPE from which multidose bottles and unit-dose vials are often molded is a barefoot (additive-free) resin; thus, there are few sources of leachables in the primary packaging. Although the primary packaging components of aqueous ODPs contribute minimally to the drug product's leachable profile, they must nonetheless be assessed as part of a comprehensive extractable and leachable program.

Ophthalmic ointments, on the other hand, are hydrophobic matrices directly contacting the primary packaging. Thus, the dosage form interacts directly with the polyolefin product contact layer of formulations filled into polyfoil tubes or the lacquer and/or sealant materials used in metal tubes. Leachables from polyolefin closures are also possible in cases where the formulation comes into direct long-term contact.

5.2 Secondary Packaging

A key challenge for ODPs arises from the widespread—though not exclusive—use of semipermeable LDPE multidose bottles or unit dose vials as primary packaging. Because many of these solution, suspension, and emulsion primary packaging systems are semipermeable, the packaged ODPs are susceptible to water egress (which can be a shelf-life limiting phenomenon on stability) as well as ingress of chemical entities from outside the primary packaging. Although LDPE is well known to be semipermeable (*4*), containers molded from denser polyolefins such as HDPE and PP may also exhibit semipermeable properties because these containers are often thin-walled to ensure that patients can squeeze them to deliver the ODP. For typical aqueous ODPs in semipermeable packaging systems, substances from chemically diverse secondary packaging materials, such as labels, unit cartons, and patient information inserts, often comprise the majority of migrating substances contained in ODPs. This results from two factors: 1) the semipermeability of the primary packaging system; and 2) the relatively

low propensity of aqueous ODPs to extract the typically hydrophobic additives present in polyolefin primary packaging. In these cases, migrating chemicals are typically relatively low-molecular-weight, volatile, or semi-volatile substances originating from secondary components, such as unit cartons or patient information inserts, that transport to the primary packaging through air. Leachables in ophthalmic ointments, on the other hand, arise exclusively from the primary packaging. Moreover, as most ointments are filled into polyolefin-foil laminate or metal tubes, these container closure systems are fundamentally impermeable and migration from secondary components into the formulation cannot occur. Thus, the remainder of this section focuses on common aqueous ODPs filled into semipermeable containers.

Per _〈1664〉_, "migrants", as opposed to leachables, is the term applied to substances present in the ODP from secondary packaging. This is because migrants accumulate in the packaged drug product after crossing the physical barrier of the primary package. Therefore, they are not leachables per se, as they have not leached from the packaging through the direct action of the drug product, because the barrier prevents such direct interaction. Although the impact of migrants and leachables must be assessed in the same manner, as per *Table 1*, it is nonetheless useful to differentiate between secondary packaging migrants and primary packaging leachables.

The airborne nature of migrants creates further challenges in the study of ODPs in semipermeable packaging systems. Secondary packaging migration is a demonstrably dynamic process in which drug product migration levels vary in response to the driving forces present in the immediate environment around the ODP (*1*). This is in contrast to leachables from primary packaging, which typically represent a binary partitioning system where the substance of interest is either present in the packaging component or in the dosage form, and drug product leachable concentrations increase over time. This is not the case for secondary packaging migrants, because the drug product is only one of several possible sinks for migrants, and its concentration as a function of time is directly impacted by the immediate environment surrounding it. For example:

- Elevated storage temperatures used for accelerated stability studies often underreport migrant levels compared to room temperature studies, because potential migrants tend to distill to cooler temperatures outside the stability chamber. As a result, attempts to accelerate leachable studies for ODPs often produce false negative results for migrants (i.e., migrants that might appear under labeled storage conditions do not appear in the drug product under elevated storage temperatures) or, at best, quantitative data that cannot be readily related to real-time performance.
- Open environments (e.g., an open room) provide infinite sinks for secondary packaging extractables beyond the ODP itself, whereas closed environments (e.g., a stability chamber or ODP enclosed in impermeable pouches) tend to drive migrants to the ODP. Enclosing ODPs in impermeable pouches is often used to prevent water loss. These pouches eliminate migration from secondary components outside the pouch. However, they may drive label migrants into the ODP because those migrants are trapped within the pouch and have nowhere else to go.
- Increasing the number of packaged drug product units in the immediate vicinity of the ODP under study increases the concentration of airborne migrants and thus increases migrant levels in the ODP. Conversely, withdrawal of drug product units from storage near the ODP can result in a reduction in migrant levels. Whereas primary packaging leachables often increase monotonically over time, secondary packaging migrants have been observed to follow parabolic concentration profiles over the course of a stability study, initially increasing, reaching a maximum mid-study, and then beginning to decline as packaged units are withdrawn from the chamber. In these instances, the maximum migrant level reported—and qualified as necessary—will not necessarily be from the end of the leachable study, and the granularity of intermediate time intervals during the study becomes quite important. Note that this scenario is not relevant for foil-pouched ODP.

Each of these factors demonstrably impacts the local environment of the ODP and the ultimate concentration of migrants in that product. Stability chambers set for labeled storage temperatures generally reflect the worst-case storage environment for ODPs with respect to migrants, as they are relatively closed systems filled with multiple migrant sources. The observed dynamic equilibrium of migrants in ODPs therefore results in behavior that is quite different from that of primary packaging leachables.

In order for a compound from a secondary packaging component to become an ODP migrant, it must satisfy three conditions:

1. It must be able to migrate from the original component. Consider a unit carton extractable possessing no significant vapor pressure. Given that unit carton extractables must pass through the air to reach the primary container, an extractable with insufficient vapor pressure to transfer in this fashion will be unlikely to manifest as a migrant.
2. It must be able to permeate the primary container. Despite well-known semipermeable properties, LDPE does not pass all compounds. Rather, the primary container serves as a selectivity element within the packaging system. Thus, compounds that cannot permeate the bottle are not probable migrants.
3. It must dissolve in the formulation. Given that migrants are probed at low parts-per-million or high parts-per-billion levels, this latter point is not a significant condition to be met, as high solubility is not required. Interestingly, this last point is the only one of the three conditions specific to any particular ODP formulation.

For clarity, when this section refers to studies considering both migrants and leachables, leachables will be used as a blanket term. For example, a long-term assessment of migrant and leachable profiles in a drug product will be described as a “leachable study”.

6. CHEMICAL ASSESSMENT REQUIREMENTS FOR ODPS

6.1 Extraction Studies

Leachable targets for primary and secondary packaging components are derived from controlled extraction studies as described in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* _〈1663〉_. Controlled extraction studies are also performed on secondary packaging components (particularly labels with ink and adhesive applied). However, it is noted that direct solvent

extraction may be significantly exaggerated for components that do not come into contact with the drug product. Because direct solvent extraction of secondary components can generate a large number of irrelevant extractable targets if not carefully designed, gentler extraction conditions than those employed for plastic primary packaging components are recommended. Controlled extraction data of secondary packaging can be contextualized by performing simulation studies as described in the following section.

6.2 Simulation Studies—Secondary Packaging Components

Understanding of likely secondary packaging component migrants can benefit from a more nuanced approach. Given that the process responsible for entrainment of migrants into an ODP is fundamentally different from that of leaching from primary packaging, extractable studies meant to address migrants may be designed and implemented differently from those traditionally conducted to forecast primary packaging leachables. To this end, simulation studies offer a valuable understanding of the interactions between secondary packaging and ODP. For ODP, simulation studies can be an extremely useful means to forecast the most probable migrants for a specific combination of packaging system and drug product (*1*,*5*). Details on the conduct of such studies are as follows.

Simulation study designs are quite varied, but generally possess a few common characteristics (*1*,*5*). First, simulation studies tend to use product-like solvents, including placebos, where practicable. By approximating the propensity of migrants to move into the drug product of interest, simulation studies are more likely to return quantitatively relevant data that help researchers focus on the most important extractables. Furthermore, the use of a simple solvent system for simulation in lieu of a drug product holds the potential to facilitate the discovery and identification of probable leachables in a less complex matrix.

An essential characteristic of simulation studies, particularly relevant to ODP, is that they can study packaging systems, or relevant portions of packaging systems, under realistic contact conditions. A fully assembled packaging system filled with simulating solvent will provide more insight into probable migrants than direct solvent extraction of individual secondary packaging components, because it reproduces the path a migrant must follow from the originating secondary packaging component through the primary packaging system and into the drug product (*1*). Simulation studies implemented in this way are particularly useful for ODPs.

For example, consider a label placed on the exterior of an LDPE bottle containing an aqueous ODP. A direct solvent extraction of the label, particularly with a strong solvent such as hexane, which is irrelevant to an aqueous ODP, will likely generate a significant number of extractables (potential migrants), many of which will be false positives. This occurs for two reasons. First, a pool of many extractables exists in labels due to their chemically diverse composition, which includes chemistry associated with the substrate, adhesive, ink, and varnish. Second, direct solvent extraction of a label removes the barrier between solvent and component, thus creating a vector for migration from secondary packaging components that does not exist in the drug product.

If the goal of an extraction study is to develop targets for a follow-up leachable study on the ODP, direct solvent extraction instead leaves the researcher with a multitude of mostly irrelevant targets. Ideally, a label extraction study would generate data that focus on the most relevant extractables (i.e., the most probable migrants). This is something that simulation studies accomplish very well if they are properly designed and implemented.

One simulation technique that is often of value for examining probable volatile migrants from secondary packaging is headspace gas chromatography. The process of measuring analytes in the headspace mimics the mechanism of migration from secondary component to the drug product (e.g., transport through air), although it eliminates any selectivity imparted by the primary packaging barrier. In this regard, headspace makes an interesting screening tool. However, a more refined simulation study design is discussed below that incorporates both the primary packaging barrier properties as well as transport through air.

Based on the above, a simulation study may be conducted to understand key potential migrants. This approach leverages the physicochemical properties of individual extractables and the selectivity of the container closure system itself to identify the most probable migrants. Key design elements of such a study include:

- Filling the primary ODP container closure system with a suitable solvent, sealing the system closure appropriately, and labeling it with a representative label and/or enclosing the ODP in a representative unit carton. Include other relevant secondary packaging components, such as the package insert.
- For ODPs contained in impermeable pouches, including only those secondary components within the pouch (as well as the pouch itself).
- Justifying solvent selection using empirical approaches such as those previously published (*1*,*6*).
- Enclosing the packaged system in an impermeable container, such as a tightly sealed glass jar, to create a driving force for migrants to enter the ODP rather than allowing them to diffuse into the broader environment. Containing the test article in this way allows storage at an elevated temperature without the risk of false negatives, as previously described. Failure to do so will likely produce false-negative results.
- Using elevated temperatures to shorten the study duration, while selecting a temperature that does not cause significant physical changes to the primary container closure system. For example, storage temperatures higher than 60° are likely to soften and cause physical deformation of ODP containers molded from LDPE.
- Conducting the study until the system reaches equilibrium to provide a limiting value for the concentration of each potential migrant. Determine the appropriate study duration for target compounds by testing at multiple time intervals and noting when the target compounds reach asymptotically limiting concentrations. Typical timeframes are 2–6 weeks, but this may vary depending on the study design and the properties of the test articles, such as temperature, simulating solvent, and permeability of the primary packaging container closure system.

Simulation study designs should skew sufficiently worst-case to credibly avoid false negatives (e.g., failure to observe an important migrant) without being so aggressive that they generate too many false positives (e.g., extractables that will not appear in the ODP as migrants).

Experimental designs must balance the risks appropriately for each system under study. The parameters of a simulation study can be flexible as required to answer specific scientific questions. All experimental designs should be appropriately justified.

In the past, conventional wisdom held that ODPs were sufficiently aqueous that water alone served as a suitable surrogate during extraction studies. However, the presence of various surfactants—including BAK preservative—in modern ODPs makes these formulations more aggressive than saline, and this must be considered in designing simulation studies. This is particularly true for ophthalmic emulsions that contain an oil phase and emulsifying agents that may also significantly modify the polarity of the formulation.

6.3 Leachable Studies for ODP

Leachable studies are intended to assess the real-time passage of both migrants and leachables into an ODP. Their designs do not vary fundamentally from the general principles of 〈1664〉 (e.g., method validation requirements), though a few points critical to ODPs are noted below.

- Leachable studies are conducted in real-time through the end of shelf life, typically in parallel with registration stability studies.
- For semipermeable systems susceptible to migration, maximum migrant concentrations may be observed prior to the end of the study as described previously. Granularity in time intervals for the first year is particularly critical (3, 6, 9, 12 months), with longer intervals between the end of the first year and the end of shelf life being appropriate, in accordance with standard International Council for Harmonisation (ICH) stability intervals.
- As described previously, accelerated stability conditions may generate nonpredictive or false-negative data for secondary packaging migrants. Although accelerated studies are required for general product stability assessment, the use of leachable data from elevated storage temperatures should only be applied with great caution.
- The inclusion of key secondary packaging components (e.g., labels, product information inserts, unit cartons) in the study is critical for ODPs in semipermeable primary container closure systems. Secondary packaging components outside of an impermeable pouch are not required in the study. All container closure systems and secondary components must accurately represent the intended commercial product. Selecting the same packaging component lots for extractable and leachable studies may aid in establishing an extractable-leachable correlation, although it is recognized that this approach is not always practicable. If the same lots cannot be used, justification should be provided to demonstrate that the extractable profiles of the current and previous lots are sufficiently comparable.
- For products offered in multiple fill volumes, those combinations that present the highest ratio of packaging component mass (which generally scales with surface area) to product fill volume tend to generate the worst-case leachable levels over time, barring extenuating variables such as significant changes to container material type or container wall thickness.
- Given the wide variety of potential secondary packaging migrants, it is often useful to run negative controls in parallel with the leachable study. Typically, such controls are implemented by filling bulk drug product that has not been exposed to the final ODP packaging system into clean, impermeable containers. Glass vials with Teflon-faced screw cap closures are often useful for this purpose. A comparative analysis between negative controls and the packaged drug product readily differentiates leachables and migrants from other analytical responses associated with the formulation over time. This approach has been a standard practice in the ophthalmology industry for nontargeted analysis for many years.

6.4 Elemental Impurities Considerations for ODPs

The previous discussion of migrants and leachables primarily focused on organic leachables. For consideration of elemental impurities (migrants and/or leachables), see 〈1664〉 and guidance on drug product elemental impurities per ICH Q3D (7) and *USP Elemental Impurities—Limits* 〈232〉. In addition to the specific elements described by elemental impurity guidelines, ODPs may warrant special attention to elements known to induce allergic contact dermatitis (ACD) of the eyelid skin (8).

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Topic/Question	Contact	Expert Committee
<1664.3> ASSESSMENT OF LEACHABLES IN TOPICAL OPHTHALMIC DRUG PRODUCTS	Ravikiran Kaja Senior Principal Scientist	GCPD2025 Packaging and Distribution
REFERENCE STANDARDS SUPPORT	RS Technical Services RSTECH@usp.org	GCPD2025 Packaging and Distribution

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