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BRIEFING

〈1664.4〉 Assessment of Leachables in Topical and Transdermal Drug Products. This newly proposed chapter serves as a companion to Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems 〈1664〉. Chapter 〈1664.4〉 specifically addresses the unique considerations for leachables in transdermal systems as well as topical and transdermal drug products, encompassing a variety of formulations, including patches, creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. The chapter examines leachables, focusing on those originating from the manufacturing equipment used in the production of the drug product and the container closure systems used to package the drug product throughout its shelf life. Note that the following discussion primarily focuses on organic leachables.

(GCDF: R. Kaja)

Case ID—SUB-2479

Add the following:

▲〈1664.4〉 ASSESSMENT OF LEACHABLES IN TOPICAL AND TRANSDERMAL DRUG PRODUCTS

1. INTRODUCTION

This chapter contains leachables testing guidelines for topical and transdermal drug products and considers leachables from multiple sources, including but not limited to manufacturing processes, packaging, and delivery system components.

Topical and transdermal drug products include pharmaceutical formulations that are applied to the skin with the intention of achieving a local effect (i.e., topical) or a systemic effect (i.e., transdermal). They include but are not limited to soaps, shampoos, creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. These drug products differ in viscosity and consistency, with ointments being the most viscous and solutions being the least viscous, as illustrated here:

Ointments > Cream > Lotion > Gel > Foam > Solution

Topical and transdermal drug products also include topical and transdermal systems (TDSs), which are considered combination products by the US FDA (*1*). Drug products associated with the topical and transdermal routes of administration are defined in *Topical and Transdermal Drug Products—Product Quality Tests 〈3〉*. Definitions and descriptions, as well as brief information on composition and/or manufacturing processes, can be found in *Pharmaceutical Dosage Forms 〈1151〉*.

Practical descriptions of the most common TDSs can be found in the FDA's draft guidance on transdermals (*2*). Microneedle-based TDSs are outside of the scope of the current version of the standard (*3*).

Extractable impurities for a TDS are chemical entities that can be drawn out of the backing membrane, release liner, pouching material, printed ink, internal membranes, or other components (excluding the drug substance and adhesive matrix) by a solvent system under exaggerated laboratory conditions. Additionally, an extraction study can detect compounds introduced into the TDS from the manufacturing process, which can impact the final impurity profile of the TDS product. Extractables impurities for a topical or transdermal product are chemical entities that can be drawn out of the packaging system, as defined in *2. Packaging for Topical and Transdermal Drug Products and Systems*.

Leachables are chemical entities present in a packaged TDS or topical or transdermal drug product because they leach into the adhesive matrix (or, where applicable, the reservoir) or into the product formulation under normal storage conditions or during accelerated stability studies. These compounds may be transferred from the adhesive matrix or product to the patient during use.

2. PACKAGING FOR TOPICAL AND TRANSDERMAL DRUG PRODUCTS AND SYSTEMS

The packaging systems for liquid and semisolid drug forms mainly include:

- *Aerosol metal canisters*—Metal canister (aluminum or stainless steel) fitted with an appropriate actuator and valve system. Metal cans are often coated internally with a polymer to protect the material from corrosion and minimize interaction with the drug product.

- *Dispensers and Applicators*—Used to administer the topical drug product to the patient. These components can be a part of the primary container closure system (e.g., a closure containing a pumping mechanism for liquid topical drug products) or an associated packaging component. These components are packaged separately in the market package and are either attached to the container upon opening or used only when a dose is administered.
- *Jars and bottles*—Rigid containers, typically constructed from glass, polypropylene, or polyethylene. The closure often consists of a plastic (polypropylene or polyethylene) screw cap and may also include an inner liner and/or an induction seal made of multilaminate films constructed from materials such as various plastics, metal foil, paper, and adhesives or heat-sealing polymers.
- *Metal tubes*—Primarily constructed from various grades of aluminum containing trace amounts of copper, iron, magnesium, manganese, silicon, titanium, vanadium, or zinc, depending on the grade. Metal tubes are often coated internally with a polymer to protect the material from corrosion and minimize interaction with the drug product.
- *Plastic-based tubes and pouches*—Often fabricated from multilaminate films bound together by tie layers or adhesives. The films are composed of multiple layers, including a relatively low-interacting product contact layer, a gas or moisture barrier layer, and a protective, printable outer layer that provides puncture and tear resistance to the flexible tubes and pouches. The gas or moisture barrier layer can be either a plastic material or a metal or metallized foil layer. The shoulders of these plastic-based multilaminate tubes are often constructed from a single plastic, such as high-density polyethylene or polypropylene.
- *TDS packaging*—Often consists of a laminated aluminum foil pouch, where the laminated liner material is in direct contact with the TDS. The TDS units can be individually packaged, or multiple units can be packaged in the same laminated pouch. The individual systems are protected with a release liner to prevent adhesive contact prior to use. If the API is moisture-sensitive, a desiccant can be part of the packaging system. Other types of TDS packaging can include various forms of coated or uncoated Kraft paper, such as the wrappers used for adhesive bandages, in which the wound cushion is coated with a drug product, such as an antimicrobial drug.

In general, the following considerations apply as they relate to the evaluation of the packaging material and delivery system components for all topical and transdermal drug products:

- Chemical composition of all plastics, elastomers, adhesives, etc., should be specified for each material of composition, as appropriate.
- For liquid-based products, extractables testing consistent with *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems 〈1663〉* is recommended.
- For TDSs, extractables testing consistent with FDA's draft guidance (2) is recommended, including all the components of the packaging and the TDS.
- *Plastic Materials of Construction 〈661.1〉* and *Plastic Packaging Systems for Pharmaceutical Use 〈661.2〉* testing of plastic packaging for topical and transdermal drug products (including TDSs) is recommended.

3. ELEMENTAL IMPURITY TESTING OF TOPICAL AND TRANSDERMAL DRUG PRODUCTS

See *Table 1* for limits for elemental impurities for topical and transdermal drug products delivered by the cutaneous and transcutaneous route as provided in ICH Q3D (4).

Table 1. Elemental Impurities in Cutaneous and Transcutaneous Drug Products

Element	Class	Permissible Daily Exposure (PDE) (µg/day)	Cutaneous and Transcutaneous Concentration Limit (CTCL) for Sensitizers (µg/g)	Include in Risk Assessment If Not Intentionally Added[a]
Cadmium (Cd)	1	20	—	Yes
Lead (Pb)	1	50	—	Yes
Arsenic (As)	1	30	—	Yes
Mercury (Hg)	1	30	—	Yes
Cobalt (Co)	2A	50	35[b]	Yes
Vanadium (V)	2A	100	—	Yes
Nickel (Ni)	2A	200	35[b]	Yes
Thallium (Tl)	2B	8	—	No
Gold (Au)	2B	3000	—	No
Palladium (Pd)[c]	2B	100	—	No

Element	Class	Permissible Daily Exposure (PDE) (µg/day)	Cutaneous and Transcutaneous Concentration Limit (CTCL) for Sensitizers (µg/g)	Include in Risk Assessment If Not Intentionally Added[a]
Selenium (Se)	2B	800	—	No
Silver (Ag)	2B	150	—	No
Platinum (Pt)	2B	100	—	No
Lithium (Li)	3	2500	—	No
Antimony (Sb)	3	900	—	No
Barium (Ba)	3	7000	—	No
Molybdenum (Mo)	3	15,000	—	No
Copper (Cu)	3	3000	—	No
Tin (Sn)	3	6000	—	No
Chromium (Cr)	3	11,000	—	No

[a] Intentionally added elements should always be included in the risk assessment.

[b] For elements with a cutaneous PDE and a CTCL, both limits need to be met. In the event of conflicting results, the lowest limit is applied. Using cobalt as an example, based on a 10-g maximum daily dose (MDD) of drug product, the calculated cutaneous concentration is 5 µg/g; based on a 1-g MDD of drug product, the calculated cutaneous concentration is 50 µg/g, which exceeds the CTCL of 35 µg/g. In this situation, the CTCL limit should be used.

[c] The palladium PDE will also apply to iridium, osmium, rhodium, and ruthenium.

4. CHEMICAL ASSESSMENT RECOMMENDATIONS FOR TOPICAL AND TRANSDERMAL DRUG PRODUCTS

For extractables and leachables studies of topical and transdermal drug products and TDSs, the analytical evaluation threshold (AET) calculation should be based on the safety concern threshold (SCT) and the maximum daily dose (MDD). For some products, the MDD may require more than one TDS. Typically, an SCT of 1.5 µg/day is used for products intended for chronic conditions and 5 µg/day for other applications as the basis for the AET. Applicants are advised to consult with the regulatory agency before performing leachables or extractables studies to clarify or justify expectations regarding study design topics such as MDD and SCT.

4.1 Extractables for Topical and Transdermal Products (Excluding Recommendations for TDS)

Extractables and leachables must be properly assessed following a robust extractables study that evaluates all packaging components and materials to ensure patient safety. Specifically:

- Extractables testing according to 〈1663〉. Extractables testing can include exaggerated exposure conditions applied to individual components of the container closure system, as well as a simulated-use extraction study on the assembled container closure system. The former will produce an extractables profile representative of tentative leachables, and the latter will produce an extractables profile representative of probable leachables. The media selected for the extraction should mirror the chemistry of the topical or transdermal product matrix. Topical and transdermal products often have matrices that differ in composition and polarity from other drug products.

4.2 Leachables for Topical and Transdermal Products (Excluding Recommendations for TDS)

Leachables testing requires a stability study on drug product registration batches that simulates the end of shelf life for the drug product. This can include batches that are aged under accelerated conditions or have been aged under normal storage conditions. Leachables testing requires:

- Testing at multiple time points throughout normal storage and accelerated temperatures
- Sensitive, selective, accurate, and fully validated leachables analytical methods per *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* 〈1664〉

Regarding the analysis of aged drug product samples for leachables, topical and transdermal drug products present a particular challenge. The complex chemical matrices of certain drug products—such as emulsions, dispersions, foams, gels, and solutions—may contain mixtures of chemicals with varying polarities, pH levels, and extractive power. These matrices cannot always be analyzed directly by the standard chromatography techniques used for leachables studies (see 〈1664〉); therefore, sample processing prior to instrumental analysis is required. Such sample processing methods must be included in method validation.

5. CHEMICAL ASSESSMENT (RECOMMENDATIONS FOR TDS)

5.1 Extractables

Extractable studies are used to confirm and justify the leachable study design. Many TDS formulations include multiple nonmiscible adhesives, solubilizers, permeation enhancers, internal membranes, and other excipients. The physical and chemical properties of these components may induce characteristic microstructures. Extractables and leachables recommendations for TDSs are provided in FDA's draft guidance (2). This guidance notes "All TDS should be evaluated for potential compounds that could be transferred from the product to the patient. This evaluation should include assessments of extractables and leachables, consistent with *USP* _〈1663〉_ and _〈1664〉_".

Specific recommendations for extractables studies:

- The identification of potential leachable compounds can be accomplished through a review of vendor or manufacturer documentation, if available, regarding impurities present in drug product components.
- Extractable studies should be conducted early in the pharmaceutical development process to understand the potential leachables from packaging and components of the proposed commercial TDS.
- Studies should be conducted on components such as backing membranes, release liners, rate-controlling or other internal membranes, identifying label inks, and pouching. The adhesive impurities are not in scope for this chapter; however, they should be tested for impurities separately from the other constituents, as described in FDA's draft guidance (2).
- The tested components should be extracted in a variety of solvents with a range of polarities under vigorous laboratory extraction conditions to maximize the levels of extractables and identify as many potential leachables as possible.
- Extraction solvents employed for the extraction should cover a range of polarities and functional characteristics. One of the solvents is recommended to be identical to the solvent used during the manufacturing process of the finished product or the solvent with which the adhesive is supplied. The choices of solvents used should be justified. The extraction solvent should not compromise the test objects or dissolve the polymeric TDS components. For elemental impurities, an aqueous system with pH adjustment is recommended (e.g., high-purity water with 0.1%–1% nitric acid can be justified) as the extraction solvent.
- The extraction temperature should not be so high as to disintegrate the polymeric parts; however, it should be high enough to provide conditions for effective extraction. Extractions are generally accomplished by immersion. Agitation should be used to accelerate the extraction process.
- The extraction should be performed until the asymptotic level is reached, and data should be included in the extractable report or in a separate development report to support effective regulatory review of the selected extraction conditions.

5.2 Leachables

Leachable testing for TDS requires consideration that the drug products are typically applied to intact skin. As such, leachable studies most commonly consider the following key aspects:

- *Test article*—The release liner must be removed from the product to expose the adhesive system to the extraction medium.
- *Extraction medium*—The conditions of the leachable assessment should attempt to mimic as closely as possible "worst-case" clinical conditions of the skin (e.g., during rigorous exercise, resulting in sweating). Justification for the medium composition (e.g., salt concentrations, organic modifiers, and pH) should be provided (5).
- *Extraction temperature*—Leachable testing should use test conditions that mimic elevated body temperature and/or rigorous exercise.
- *Extraction duration*—The duration of the extraction should be consistent with or exceed the maximum wear period for an individual TDS, as indicated on the product label. For long-term exposure studies, ISO 10993-13 may provide additional guidance (6).
- Applicants should conduct a multi-timepoint leachable analysis (e.g., 0, 6, 9, 12, and 24 months) to provide a comprehensive leachable profile and identify any trends in leachables, as these data may impact the product's shelf life.
- At the time of application submission, data should be submitted from a leachable study performed on samples from multiple batches (i.e., 3 exhibit batches used to support shelf life) that have been stored for a minimum of 6 months under both accelerated and long-term conditions (7).

The recommended practice for performing leachable studies is outlined in *Table 2*; other conditions may be used if justified.

Table 2. Testing Recommendations for Leachables in TDS

Testing Parameter	Suggested Parameters for TDS
Simulation media	Simulated sweat (e.g., 5%–10% of organic modifier) with pH adjustment to 4.5–5.5
Recommended surface-to-volume (S/V) ratio	• For a TDS thickness <0.5 mm, use an S/V ratio of 6 cm^2/mL[a] • For a TDS thickness >0.5 mm, use an S/V ratio of 3 cm^2/mL[a] • For hydrogel-based TDS, use an S/V ratio of 0.5–1 cm^2/mL[a] • The TDS must be covered with the extraction media during the entire test period.

Testing Parameter	Suggested Parameters for TDS
Solvent recovery after extraction	>80%[b] 50%–80%[b]
Extraction temperature	42 ± 2°
Agitation	Yes
Duration of testing	Minimum of the wear period
Analysis	At the end of the extraction
Number of batches and units	Statistically relevant (usually 3 different batches, 3 units from each batch)
Leachable stability period	For the duration of shelf life, test at 3 and 6 months accelerated, then every 3 months during the first year, and every 6 months thereafter, under real-time conditions

[a] According to ISO 10993-12 (*8*), for test objects with a thickness >0.5 mm (measured without the release liner), an S/V ratio of 3 cm²/mL should be used for extractions. The extraction solvent must be in contact with the entire relevant surface area, as required by the standard. For transdermal systems (TDS), this means exposing only the skin-contact surface to the solvent (one-sided testing) or fully immersing the device so that both sides are exposed (two-sided testing). For small-surface-area products (typically <3 cm²), a larger solvent volume may be needed to ensure complete extraction of the product surface

[b] The correction factor should be utilized where recoveries are below 80%. Recoveries below 50% would require redesign of the study.

Appropriate laboratory vessels must be selected for simulated leaching studies of TDS, taking into account whether the testing involves one-sided or two-sided exposure. Vessel selection should ensure complete and uniform contact between the extraction solvent and the active surface of the TDS. A practical guide to vessel types and configurations for different TDS formats is provided in *Table 3*.

Table 3. Overview of Extraction Vessels for the Leaching of TDS

Function or Cell Design	Closed Vessel	Single-Sided Container	Franz-Cell Vertical	ASTM F739 Permeation Cell (*9*)
Volume	Limited to the size of the container	Limited to the size of the system	Minimum volume limited to the cell and the tubing size; maximum volume is not limited	Minimum volume limited to the cell size; maximum volume is not limited
Flow control	NA	NA	Static or dynamic with pump	Static or dynamic with pump
Agitation	With shaker	With shaker	With stir bar	With shaker
Temperature control	If temp-controlled shaker used	If temp-controlled shaker used	Extraction media control	Extraction media with shaker
Test type	Double sided	Single side at a time	Single side at a time	Single or double sided
Media	Single media for both sides	Single media	Single media in a single cell	Different media can be used on different sides
Membrane option[a]	NA	Yes	Yes	Yes
Material of construction	Glass for organics; HDPE of PTFE for elements	Glass for organics; HDPE of PTFE for elements	Glass with elastomer seal	Glass with elastomer seal

[a] This option may be beneficial depending on product geometry. In cases when a membrane is used for testing, it should be extracted to account for the total amount of leachables present.

Recovery of the leaching simulation solvent can be problematic for particular TDSs. For example, hydrogel-based TDS can be problematic as they can absorb a high volume of solvent, which cannot be recovered for testing. An S/V ratio of 0.5–1 cm^2/mL is recommended to recover sufficient liquid for testing.

An assessment of process equipment-related leachables (PERLs) should be conducted in accordance with the principles outlined in *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 evaluating leachables originating from the packaging system.

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Topic/Question	Contact	Expert Committee
<1664.4> ASSESSMENT OF LEACHABLES IN TOPICAL AND TRANSDERMAL DRUG PRODUCTS	Ravikiran Kaja Senior Principal Scientist	GCPD2025 Packaging and Distribution
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