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Given the above, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA. Instead, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. FDA also regularly posts additional resources for applicants, such as webinars and application tips, on CTP's website and social media.

U.S. FOOD & DRUG ADMINISTRATION

# Memorandum

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**Subject:** Approaches to the Evaluation of Extractables and Leachables in Tobacco Product Application Review

## Background

Extractables and leachables are inorganic or organic compounds that may migrate from container closure systems into products, and extractable and leachable studies[1] may be submitted as a measure of chemical stability for pre-market tobacco product applications (PMTAs) and possibly, other tobacco product applications such as substantial equivalence (SE). Examples of compounds that may be detected or identified in extractable or leachable studies include metals, plasticizers, dyes, polymer species, phthalates, polycyclic aromatic hydrocarbons (PAHs), antioxidants, lubricants, or any other material that may be used during manufacturing of different components of a product or product packaging.[2,3] The main concern with these compounds is user exposure, so it may be important to know if these compounds are, or could be considered, toxic and harmful to the user when inhaled. This memo serves to inform chemistry reviewers about extractable and leachable studies, aid reviewers in how to evaluate submitted extractable and leachable study methods, protocols, and

[1] These may also be called Leachable and Extractable studies, depending on the submission.
[2] Oh J-A, Shin H-S. Identification and Quantification of Several Contaminated Compounds in Replacement Liquids of Electronic Cigarettes by Gas Chromatography-Mass Spectrometry. *J Chromatogr Sci.* 2015;53(6):841-848.
[3] Wei B, Goniewicz M, O'Connor RJ. Concurrent Quantification of Emerging Chemicals of Health Concern in e-Cigarette Liquids by High-Performance Liquid Chromatography-Tandem Mass Spectrometry. *ACS Omega.* 2019;4(13):15364-15372.

data, and help chemistry reviewers understand their role in evaluating extractables and leachables studies in tobacco product submissions.

## Discussion

Overall, extractables and leachables are the inorganic or organic compounds that migrate from container closure systems into products. Container closure systems include any packaging material that are a component or part of the tobacco product or come into contanct with the tobacco product (e.g., atomizer holding pre-filled e-liquid, bottle cap on refill e-liquid bottle, label ink and adhesive on a semipermeable (plastic) bottle). Package or packaging refers to a pack, box, carton, or container of any kind or, if not other container, any wrapping (including cellophane), in which a tobacco product is offered for sale, sold, or otherwise distributed to consumers. In general, extractables are compounds extracted from the container closure systems, or product components, when the components are exposed to extreme conditions, in solvents of varying polarity and solvating power, for varying lengths of time. Extractables generally represent the compounds that migrate under the "worst-case scenario" conditions. In general, leachables are compounds that migrate from the container closure systems, or product components, under normal storage conditions. Since extractables and leachables are compounds that migrate from container closure systems into a product, studies to identify and evaluate these compounds may be submitted as a part of tobacco product submissions to support the expected or intended shelf-life and overall stability of new tobacco products.

Studies have shown commercial products with higher liquid or moisture content have a higher probability of leaching compounds from the packaging.[4,5] Thus, extractable and leachable studies will most likely be submitted with tobacco product submissions for any tobacco product with a higher liquid or moisture content including, but not limited to, refill e-liquids in glass or plastic bottles and closed ENDS with pre-filled e-liquids. Currently, there is limited available literature and guidance specific to investigating and evaluating extractables and leachables in tobacco products and tobacco product container closure systems. Recommended best practices for investigating extractables and leachables in tobacco products is primarily based off published literature[6,7] and guidances developed by the Center for Drug Evaluation and Research (CDER)[8] and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[9], which recommend best practices for investigating extractables and leachables for orally inhaled and nasal drug products (OINDP). Additionally, published and developed United States Pharmacopeia (USP) general chapters provide detailed descriptions of recommended extractable and leachable study conditions and analytical protocols based on the

[4] Westerhoff P, Prapaipong P, Shock E, Hillaireau A. Antimony leaching from polyethylene terephthalate (PET) plastic used for bottled drinking water. Water Res. 2008;42(3):551-556.
[5] Kadam AA, Karbowiak T, Voilley A, Debeaufort F. Techniques to measure sorption and migration between small molecules and packaging. A critical review. Journal of the Science of Food and Agriculture. 2015;95(7):1395-1407.
[6] Ball, D, et al. Development of Safety Qualification Thresholds and Their use in Orally Inhaled and Nasal Drug Evaluation. Toxicol. Sci. 2007;97(2):226-236.
[7] Norwood, DL, et al. Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products: An Overview of the PQRI Recommendations. Pharmaceutical Research. 2008;25(4):727-739.
[8] Food and Drug Administration, Center for Drug Evaluation and Research, Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Control Documentation. 2002. Retrieved September 3, 2020 from https://www.fda.gov/media/70857/download
[9] International Council on Harmonisation, Q3D(R1) Guidelines for Elemental impurities. March 22, 2019. Retrieved September 3, 2020 from https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf

material used for packaging, as well as investigating metals in product samples.[10,11,12,13,14,15,16] Chemistry reviewers may want to familiarize themselves with USP general test chapters <232>,[10] <233>,[11] <661>,[12,13] and general information chapters <1661>,[14] <1663>,[15] and <1664>[16] to evaluate details of submitted extractables and leachables methods, protocols, or data in tobacco product submissions; however, a general overview of the kinds of information used for the evaluation of a tobacco product submission is provided herein.

Recommended best practices to investigate extractables for tobacco products include exposing all relevant components of the tobacco product under review to multiple solvents and heat for a set period of time. For example, in a typical ENDS extractable experiment, components (e.g., gaskets, o-rings, coil, mouthpiece) would be exposed to at least three solvents (e.g., hexanes, isopropyl alcohol, water) under reflux conditions for up to five hours. To analyze for metals, components are generally digested with strong acids (e.g., hydrochloric acid, nitric acid) in water. Several samples of each component are exposed to each experimental condition and then processed and analyzed for metals, volatile organic compounds, or non-volatile compounds. Studies have been conducted to determine the best methods (e.g., high sensitivity) to analyze for various compounds, such as phthalates, plasticizers, and fire-retardant chemicals.[2,3,17] In general, GC-MS-MS analytical methods have the highest sensitivity for detecting extractable compounds.[17] However, the published studies note not all compounds that may migrate from container closure systems are volatile. Therefore, LC-MS-MS methods may be able to isolate and detect more individual compounds, with less specificity.[17] Since extractable studies are non-targeted analyses to identify any compound that may migrate from container closure systems, a variety of analytical methods are generally employed, including several GC and LC methods, and ICP methods for metals analysis. In general, extractables analysis may include at least GC-MS, LC-MS, Headspace GC-MS, and ICP-MS analytical methods.

Leachables experimental conditions should reasonably reflect the conditions the actual product may be exposed to during typical storage. For example, to reflect the conditions for closed ENDS with pre-filled e-liquids with an anticipated shelf-life of one year, the e-liquid would be stored within the closed ENDS at 25°C and 60% relative humidity for up to 1 year before analysis to identify leachable compounds. To reduce the storage time before analysis, alternate conditions that are reasonably expected to represent the actual temperature, humidity, and storage time may also be considered (e.g., 33 days storage at 60°C to represent 12 months storage at 25°C), if the appropriate justification is provided for how the alternate conditions represent actual conditions. Additionally, due to possible interference from product compounds during analysis, simulated leachable experiments may be conducted instead. Simulated leachable experiments are most often conducted when products contain a lot of individual compounds (e.g., flavored e-liquids). Thus, the sample used for the simulated leachable experiment may only contain primary components of the product under review. For example, for a flavored e-liquid, the simulated leachable experiment sample e-liquid may only contain humectants and nicotine in the relevant concentrations and ratios analogous to the product under review. Simulated leachable

[10] United States Pharmacopeia and National Formulary (USP 43-NF 38). Vol 45(5). Rockville, MD: United States Pharmacopeia Convention; 2017:6641. DocID: GUID-D42B645F-6157-4ED7-B0AC-DA2EB52BC7D6_1_en-US.

[11] United States Pharmacopeia and National Formulary (USP 43-NF 38). Vol 46(3). Rockville, MD: United States Pharmacopeia Convention; 2018:6645. DocID: GUID-3B140F3B-B8D0-4E2A-ACB5-C91968146674_2_en-US.

[12] United States Pharmacopeia and National Formulary (USP 43-NF 38). Vol 45(2). Rockville, MD: United States Pharmacopeia Convention; 2017:6887. DocID: GUID-CD2961D5-F0AB-428A-96C1-1E957380C715_2_en-US.

[13] USP Monographs 661.1 and 661.2 are under development to replace USP 661, but are under review until 2025. Therefore, USP 661 is still active, but companies may use recommendations from USP 661.1 and 661.2 as well.

[14] United States Pharmacopeia and National Formulary (USP 43-NF 38). Vol 45(2). Rockville, MD: United States Pharmacopeia Convention; 2018:8434. DocID: GUID-1F18D8EA-7810-4F2B-A703-9CD977E0B2E8_4_en-US.

[15] United States Pharmacopeia and National Formulary (USP 43-NF 38). Vol 39(5). Rockville, MD: United States Pharmacopeia Convention; 2018:8442. DocID: GUID-5B829ECA-165E-46C5-A244-3FF958BBC190_2_en-US.

[16] United States Pharmacopeia and National Formulary (USP 43-NF 38). Vol 39(5). Rockville, MD: United States Pharmacopeia Convention; 2015:8455. DocID: GUID-080B9CD2-A445-44A2-A529-2CC7F86BCC64_1_en-US.

[17] Moldoveanu SC, Yerabolu R. Critical evaluation of several techniques for the analysis of phthalates and terephthalates: Application to liquids used in electronic cigarettes. J Chromatogr A. 2018;1540:77-86

experiments may be considered appropriate with a justification explaining why the simulated experimental sample reasonably represents the product under review. Regardless of the leachable experimental conditions, the techniques and methods used to analyze the samples for leachable compounds will be similar to those used in the extractable portion of the experiment. In an ideal system, leachable compounds would be a subset of the detected and identified extractable compounds. However, in reality, while there may be significant overlap between identified leachable compounds and identified extractable compounds, there will not be complete overlap between the two groups. Thus, leachable compound detection techniques will be a combination of targeted analysis looking for potentially toxic or harmful compounds identified during the extractable experiments, and non-targeted analysis looking for additional compounds that may not have been detected during extractable experiments.

The primary concern with detected extractable or leachable compounds is whether or not they may reach the user, and if the compounds are potentially toxic or otherwise harmful to the user. Examples of compounds that may be detected during these experiments include plasticizers, dyes, phthalates, metals, and PAHs. Inhalation toxicity and permissible daily exposure limits for some of these constituents may be known (e.g., PAHs, metals), but not all detected compounds will have known inhalation toxicity or established permissible daily exposure limits. Therefore, along with providing information on sampling protocols and analytical techniques, as well as appropriate justifications, extractable and leachable experimental data is not complete without a list of the detected compounds and concentrations. If the concentrations of detected compounds are above the threshold limits recommended by ICH or USP, the chemistry reviewer should share these results with the other relevant discipline reviewers (e.g., toxicology) for further evaluation.

In general, chemistry reviewers are only responsible for reviewing the sampling protocols and analytical techniques of the extractable and leachable studies to determine if they are appropriate and sufficient for further review of the provided data by other discipline reviewers (e.g., toxicology). If the sampling protocols or analytical methods are not deemed sufficient for further review of the data, the chemistry reviewer may consider seeking more information from an applicant (e.g., issue a deficiency). Chemistry reviewers may also want to familiarize themselves with the detected compounds and concentrations, and whether the detected compounds may pose a concern to public health to aid in discussions with other discipline reviewers.

## Conclusions

Extractables and leachables are the inorganic or organic compounds that may migrate from container closure systems into products, and studies identifying these compounds may be submitted as a measure of chemical stability in new tobacco product submissions. Current published literature discussing extractables and leachables specific to tobacco products is limited, so our understanding of how to test and analyze for extractables and leachables in tobacco products is based on recommended best practices developed for OINDP by USP, CDER, or ICH. Extractable compounds are generally considered the compounds that may migrate under “worst-case scenario” conditions, whereas leachable compounds may migrate under normal storage conditions. In an ideal system, identified leachables would correspond to a subset of identified extractable compounds; however, because of the difference in conditions for extractable and leachable studies, this rarely occurs. Thus, extractables analysis is generally non-targeted, and leachable analysis is generally a combination of targeted and non-targeted analyses. However, for both extractable and leachable data analysis, similar analytical methods are used to detect, identify, and quantify compounds (e.g., GC-MS, LC-MS, ICP-MS). Chemistry review should focus on reviewing methods and protocols for sampling and analysis (see Appendix for examples of information for chemistry review) to ensure they are appropriate for further review of the data. If the sampling protocol or analytical method information is insufficient or not provided, this may require chemistry to seek more information from an applicant.

## Appendix: Examples of Information for Chemistry Review[18]

| Sample ID | Extraction Technique/Solvent | Number of Components Extracted | Total Surface Area Extracted ($cm^2$) | Solvent Final Volume (mL) |
|---|---|---|---|---|
| COMPONENT NAME SAMPLE ID # | Reflux: Water | 33 | 60.52 | 20 |
| | Reflux: IPA | 33 | 60.52 | 20 |
| | Reflux: Hexanes | 33 | 60.52 | 20 |
| | Digestion: 5% Nitric Acid / 5% Hydrochloric Acid | 33 | 60.52 | 20 |
| | Dry Headspace | 8 | 14.67 | NA |

**Table 1. Summary of Extraction.** This table excerpt is an example of how an applicant may provide the details of the sample protocols for Extractable experiments. It includes the name and sample ID number for the component tested, the extraction solvents used and what conditions the sample is subjected to, the number of components tested, and the final area and volume collected from each sample. This information should be provided for any component tested.

| Parameter | Condition |
|---|---|
| GC/MS Model | Agilent 7890A Gas Chromatograph / Agilent 5977B Mass Spectrometer |
| Column | Restek Rxi-5MS, 20 m x 0.18 mm x 0.18 µm df |
| Oven Temperature Program | 40°C hold 1.0 minutes; 25°C/min to 320°C, hold to 15 minutes (standards) or 30 minutes (samples) |
| Carrier Gas and Flow | Helium at 0.75 mL/min constant flow |
| Inlet | Pulsed Splitless, 2.5 minutes delay, 2.8 minutes for IPA samples |
| Injection Volume | 1 µL |
| Injector Temperature | 250°C |
| Sources Temperature | 230°C |
| Quadrupole Temperature | 150°C |
| Interface Temperature | 300°C |
| Scan Speed | 3125 [N=1] |
| Scan Range | 30 to 550 amu |

**Table 2. Instrument Conditions for the Direct Injection GC/MS Analysis.** This table is an example of one way an applicant may provide the details of a method chosen for sample analysis. In general, applicants may also provide a written summary and provide the full methods and protocols in an attachment.

| Sample ID | Retention Time (Minutes) | Tentative Identification | Est. Conc. (µg/mL) | Est. Conc. ($\mu g/cm^2$) |
|---|---|---|---|---|
| COMPONENT NAME SAMPLE ID # | 4.483 | 5-Ethyl-2-methyloctane | 1.7 | 0.5 |
| | 5.812 | Pentadecane | 1.4 | 0.5 |
| | 6.966 | Octadecane | 1.6 | 0.5 |
| | 7.981 | Unknown alkane | 1.4 | 0.4 |
| | 8.893 | Unknown alkane | 1.2 | 0.4 |
| | 9.715 | Unknown alkane | 0.9 | 0.3 |

**Table 3. Direct Injection GC/MS Results for IPA Extracts.** This table is an example of one way an applicant may provide the identified extractable compounds for one component in one solvent, using one method of sample analysis. Analogous tables should be provided for all components tested in all solvents used, under all methods of sample analysis.

| Sample ID | Retention Time (Minutes) | Tentative Identification | Est. Conc. (µg/mL) |
|---|---|---|---|
| SAMPLE ENDS SAMPLE ID # | 4.167 | 2-Ethyl-1-hexanol | 5.9 |
| | 4.455 | 1-Phenylethanone | 0.7 |
| | 7.59 | Benzophenone | 5.4 |
| | 7.875 | (1-Hydroxycyclohexyl)phenyl-methanone | 5.8 |
| | 9.458 | Drometrizole | 8.5 |

**Table 4. Direct Injection GC/MS Results for E-liquid Zero Nicotine Sample.** This table is an example of one way an applicant may provide the identified leachable compounds from a leachable or simulated leachable experiment under one method of sample analysis. In this case, the e-liquid under review did not contain nicotine, so the simulated leachable sample liquid did not contain nicotine. Analogous tables should be provided for all methods of sample analysis used.

[18] Tables and information provided have been adapted from a prior submission. However, the identity of the product is removed. Bolded caption text represents caption from submission. Not bolded caption text represents explanation for reviewers.