

Biocompatibility Town Hall #2: Extractions for Conducting Chemical Analysis for Biocompatibility Assessment

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Moderator: CAPT Kim Piermatteo

Presenters: Misti Malone PhD, Berk Oktem PhD, Nicholas Keyes and Jinny Liu PhD

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CAPT Kim Piermatteo: Hello and welcome to today's CDRH Town Hall event. Thank you for joining us. This is CAPT Kim Piermatteo of the United States Public Health Service, and I serve as the Education Program Administrator in the Division of Industry and Consumer Education in FDA's Center for Devices and Radiological Health. I'll be the moderator for this town hall.

Today's town hall is the second of three town halls we will be hosting on biocompatibility and medical devices. Today we will discuss chemical characterization testing methodology to address biocompatibility endpoints for medical devices. Specifically, this town hall will focus on approaches for conducting extractions for chemical characterization testing per ISO 10993-18 and share common issues and examples.

We'll begin today with a presentation from our presenters, who I'll introduce shortly, and then provide responses to some of your previously submitted questions regarding this topic. Again, we'd like to thank you for the many questions we received. FDA has proactively addressed some of those questions in this presentation and will respond to more during the previously submitted question segment following the presentation.

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CAPT Kim Piermatteo: I'd now like to introduce today's presenters; Dr. Misti Malone, Associate Director in the Immediate Office of CDRH's Office of Product Evaluation and Quality or OPEQ; Dr. Berk Oktem, Chemist in OPEQ's Office of Health Technology number six; Nicholas Keyes, Chemist in OPEQ's Office of Health Technology number five; and Dr. Jinny Liu, Chemist in OPEQ's Office of Health Technology number one.

Thank you all for joining us. As a reminder, the intended audience for this event is industry. National media and press members are encouraged to submit their questions through the FDA Newsroom at www.fda.gov/news-events/fda-newsroom.

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CAPT Kim Piermatteo: I'll now turn it over to Dr. Malone to start today's presentation.

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Dr. Misti Malone: Thank you, Kim. Good afternoon, my name is Misti Malone and I'm an Associate Director in the OPEQ Immediate Office supporting non-clinical evaluation and policy. We often receive or have questions about chemical characterization extractables testing used to support the safety of a device, so in today's presentation, we will describe common approaches, issues and considerations

focusing on methods and common deviations from relevant recognized consensus standards as well as considerations within FDA's Biocompatibility guidance. As this is a very technical area, we are focusing today's presentation only on extraction conditions. The intended audience for this presentation is device manufacturers and test facilities who conduct extractables testing to support biocompatibility evaluations.

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Dr. Misti Malone: Medical devices may contain or leach a hazardous chemical at levels in which the risk of harm needs to be evaluated and managed. These risks can originate from materials and chemicals that make up the device, including additives, coatings, degradants, or come from processing the device, including cleaning fluids, lubricants, and sterilization residuals. These biocompatibility hazards associated with these materials and chemicals may be addressed through a risk assessment.

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Dr. Misti Malone: Which can incorporate biological testing, chemical testing or information gathering based on the materials, processing, or previous experience; or a combination of testing and information. On September 9th, we shared an overview of the biocompatibility risk assessment and information gathering to address biocompatibility endpoints in lieu of testing.

Today, we will focus on chemical characterization extractables testing and in the town hall on October 7th we will focus on toxicological risk assessments.

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Dr. Misti Malone: As described in the town hall on September 9th, risk-based rationales may be acceptable when there is lower risk and greater understanding or control of the materials and manufacturing process, whereas biological and/or chemical testing are more likely to be needed with high risk and greater uncertainty such as for novel or complex materials or manufacturing. If you are unsure or have questions regarding an approach, you may engage with your review team, such as via the Pre-Submission process.

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Dr. Misti Malone: Chemical characterization is a process that identifies and quantifies the constituent chemicals of a specific device or its components and materials, which may have a direct or indirect human exposure from its clinical use. This presentation focuses on recommendations from FDA's Biocompatibility guidance and ISO 10993-18 version 2020 which is partially recognized and details regarding the extent of recognition are in the Supplementary Information Sheet, linked here.

This presentation does not cover other device-specific standards or device-specific guidance documents that may have additional or different recommendations. For device-specific standards and guidance documents, we recommend referring to those documents. Additionally, CDRH published a draft guidance on chemical analyses for biocompatibility assessment of medical devices in September 2024. As this is a draft guidance, it is not for implementation at this time.

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Dr. Misti Malone: The draft chemical analysis guidance received a large number of comments. The docket containing all comments is linked here. A working group bucketed these comments to drill down to topics of most interest to stakeholders, and over half pertained to extractions and processing, as shown in this chart.

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Dr. Misti Malone: We also reviewed related deficiencies in a batch of deficiency letters from fiscal year 2025 that were previously audited for four part harmony as described in the November 20, 2025 quarterly MDUFA V report, linked here. The majority of these letters requesting Additional Information were 510(k)s. We used the search terms “chemical characterization” or “toxicological”, and in order to focus on issues with completed testing, we excluded deficiencies and additional feedback that suggested conducting chemical characterization or tox risk assessments. We identified 19 letters with 32 deficiencies, most with multiple parts.

Most of the deficiencies requested clarification on the chemistry testing methodology, either due to incomplete information or inadequate methodology details provided in the submission. Similar to comments received for the draft chemical analysis guidance, many of the deficiencies pertained to issues related to extraction methodology, processing such as manipulation of extracts, and lack of clarity with specific values for methods or analyses.

Based on the draft chemical analysis guidance comments and this sampling of deficiencies, we thought focusing on these topics would be helpful to promote further understanding of reasonable approaches for transparency and predictability, which has led to the topics for this presentation.

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Dr. Misti Malone: As such, today’s town hall will focus on important considerations for conducting extractions and common issues for chemical characterization, and the third town hall will share key considerations and common deviations from consensus standards for toxicological risk assessments.

Next, I turn it over to Berk Oktem, who will be followed by Nicholas Keyes and Jinny Liu, to share common methods and issues for chemical characterization extractables testing.

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Dr. Berk Oktem: Thank you, Dr. Malone. I am Berk Oktem, and I’m a chemist in the Office of Orthopedic Devices in the Office of Product Evaluation and Quality.

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Dr. Berk Oktem: Today’s presentation is about the specific components of the design of an extractables study intended for a subsequent toxicological risk assessment. As there is not a single recognized method for how to conduct extractables testing, multiple approaches may be feasible and supportable. Based on comments on the draft guidance and our experience with re-occurring deficiencies and Pre-Submission topics, today’s presentation will discuss some common approaches and commonly identified concerns in each of these topics: Test article selection and preparation; Solvent selection; Extraction time and temperature; Vessel and volume of solvent; Non-Volatile Residue determination or NVR; Particulates; and Replicates.

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Dr. Berk Oktem: We first would like to discuss choosing the test article.

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Dr. Berk Oktem: FDA’s Biocompatibility guidance notes that test article preparation is a critical variable for evaluating biocompatibility, and ISO 10993-12, as well as ISO 10993-1 and ISO 10993-18, describes the importance of characterizing device manufacturing residuals. Clause 8 states “Any residue from the manufacturing processes, intentional or unintentional additives or contaminants, shall be considered

integral to the medical device, medical device portion or component, or representative sample.” I would like to emphasize the term ‘residue’ here as this may include intentionally or unintentionally added constituents of the medical device whether as material of construction or processing additive. The test article can be the final, finished device or a representative test article accounting for all patient-contacting materials, manufacturing and sterilization process, and user manipulation.

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Dr. Berk Oktem: Per FDA’s Biocompatibility guidance, test articles should undergo all manufacturing processes, unless otherwise justified, and if variable processes are used, it’s important to consider how the process impacts the quantity of residuals, again I emphasize the term residuals, such as detergent used to clean the device, or processes that affect the device material in such a way that it releases a greater quantity of extractables for example, such as heating a polymer during molding.

For reprocessed, reused medical devices, consider reviewing FDA’s reprocessing guidance for assessment and justification for residuals and device performance over the intended device life cycle, that is in “Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling.”

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Dr. Berk Oktem: It is also relevant to consider and account for any additional residuals from any steps in the instructions for use performed by a user that may affect the extractables profile of the device. Examples include additional cleaning or rinsing steps prior to first use, instructions for delivery or mixing of components as part of an in-situ polymerizing device.

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Dr. Berk Oktem: There are certain types of medical devices for which evaluating a device at its maximum intended shelf life for testing may be beneficial. Examples include devices like powders, liquids or gels which have a greater potential to leach substances from device packaging. For example, a pre-filled polypropylene syringe containing a liquid embolic.

Similarly, combination products containing or coated with a drug may accumulate leachables of the device within the drug substance or the drug substance itself may produce degradants. When the drug is delivered, it could also contain those leachables and degradants. Depending on the primary concern, this may impact the design of your study. For example, a limited contacting device, such as the catheter portion of a drug coated balloon catheter, may be recommended to undergo exhaustive extraction to capture leachables that may migrate into the drug coating over the product shelf life.

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Dr. Berk Oktem: Cutting is generally discouraged because it can result in extraction from surfaces which are non-contacting. This approach can lead to unnecessary identification of extracted chemicals that are not expected to be in contact with the patient. If cutting is performed, it is important to clearly describe the potential impact on the extractable profile per Annex G.3 of ISO 10993-18.

While using a final, finished device, and largest model of the device, if relevant, is preferred, representative articles may be acceptable with justification. Using the device model or configuration with the largest surface area of each material as the test article produces the worst-case profile of extractables.

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Dr. Berk Oktem: While alternative test articles such as coupons can be challenging to justify, I’m going to walk through several examples where use of representative devices or coupons may be appropriate.

For example, if the device material is homogenous such as a dry powder or hydrogel, it can usually be scaled up or down without consequence. Certain devices composed solely of non-permeable, non-degradable metals may also be able to use representative coupons under certain circumstances. Per FDA's Biocompatibility guidance, representative devices should have the same chemical, physical and surface properties as final finished device, which includes equivalent ratio and thickness of component materials and consideration of manufacturing and sterilization processes, unless otherwise justified.

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Dr. Berk Oktem: Next, we would like to discuss solvent selection, which is a very common discussion topic for Pre-Submissions and comment on the draft guidance.

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Dr. Berk Oktem: Per FDA's Biocompatibility guidance, extraction solvents should be selected to optimize compatibility with the device materials and provide information on the types of chemicals that are likely to be extracted in clinical use. As discussed in Annex D of ISO 10993-18, extraction solvents are based in ISO 10993-1 contact categories. Extractables testing is performed with 3 solvents, to capture the potential leachables a device may release during clinical use. Water is typically used as the polar solvent to avoid complications from salts on the analytical equipment. There are many options for semi-polar solvents, but an alcohol such as ethanol or isopropanol are commonly used. These solvents are most similar to the seed oils, for example sesame, cotton, commonly used as solvents in other in-vitro biocompatibility tests, where they are referred to as 'non-polar' solvents. True non-polar solvents such as hexane are commonly used in extractables testing to capture substances that are not soluble or have poor solubility in semi-polar solvents. Typically there is significant overlap between semi-polar and non-polar solvent extractables. Where there is overlap, the primary differences are related to extent of extraction.

Alternative solvent combinations, including the use of two solvents for long term contact, may be considered with appropriately documented solvent incompatibility or well-established simulated use conditions that preclude the relevance of a solvent class. Please note that Table D.3 in Clause D.5 of Annex D listing potential surrogate extraction vehicles for biological testing is not recognized. Please refer to the Supplementary Information Sheet, SIS, for ISO 10993-18 mentioned earlier in the presentation for more detail.

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Dr. Berk Oktem: With that in mind, let's talk about swelling in non-polar solvents and degradation. Swelling most commonly occurs with elastomeric materials for example rubbers.

In the overwhelming number of cases, this swelling is transitory. While swelled, the solvent permeates the material and accelerates extraction of substances that may be slowly released during clinical use. It is not itself a sign of degradation. Similarly, extraction of a large number of material oligomers whether elastomeric or non-elastomeric is not necessarily a sign of degradation. Polymers are not a single, unbroken chain but a distribution of oligomers or polymers of different molecular weight. For the same reason, a large quantity of NVR is also not alone an indication of degradation. Some materials simply release large quantities of extractables, whether they are the aforementioned oligomers or intentional additives such as DEHP in PVC.

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Dr. Berk Oktem: Destructive swelling happens when it results in irreversible damage to the device during extraction. This could be the silicone itself shearing from the device due to the expanded volume, breaking of a hermetic seal, or other similar situations.

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Dr. Berk Oktem: Whether destructive swelling or other visible device degradation, it is important to test at least two alternative solvents of similar polarity to capture the variability of the clinical use environment. As omission of one or more solvent of differing polarity in an extractables testing would insufficiently capture the range of polarities in tissues, it is important to pursue alternatives, if one solvent causes degradation.

Evidence of degradation is helpful, such as photographs clearly showing the degradation that occurs. For a given solvent type causing destructive swelling or other visible device degradation, alternative solvents with different properties, such as the number of carbons or functional groups, is preferable as using solvents that are too similar may not be informative. We acknowledge there may be a very limited set of materials for which it may not be possible to identify a compatible polar, semi-polar, and non-polar solvent.

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Dr. Berk Oktem: In such cases, a Pre-Submission could be helpful to discuss a device specific approach with the relevant review team. Clause 3.7 of ISO 10993-12 states that proposed alternative approaches should be at least as aggressive as the conditions of clinical use. It's also important to consider the impact to TRA for example reporting total quantity.

Finally, consistent with Section III of FDA's Biocompatibility guidance, complete information on the device materials and manufacturing process may be used to assess relevant biocompatibility risks.

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Dr. Berk Oktem: We received multiple questions for this town hall asking about the acceptance of mixtures, such as alcohol-water mixtures. This is also a common topic for Pre-Submissions and accounts for a substantial portion of comments to the draft Chemical Analysis guidance. While mixtures may be referred to as 'simulated use extraction solvent' in literature, neat solvents are preferred to represent "worst case" extraction in extractables studies.

FDA acknowledges the voluminous literature on the use of alcohol and water mixtures for leachable simulation, such as simulation of blood leaching DEHP from PVC commonly used in extracorporeal blood circuits. However, the studies underpinning those suggested extraction conditions have been narrow in scope, often assessing only one material and very specific exposure conditions. This is not particularly applicable to screening studies used in medical devices, where the potential chemical space of extractables is vast, the range of materials are broad with formulation manufacturer specific considerations for example polymer molecular weight distribution, and the exposure conditions may not be representative of the varying tissue environments encountered by medical devices.

Additionally, such solvents would not be analytically expedient that is chemically compatible with subsequent analytical methods, for determining a total quantity for long term contacting devices or in some cases for prolonged contacting devices for determining a total quantity for TRA.

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Dr. Berk Oktem: Solvent mixtures may be useful for performing follow up study to understand the rates of release for a specific constituent if an unacceptable risk is identified. The simulated extraction conditions can be justified based on the best available evidence of what conditions are appropriate to simulate the environment the device would be exposed to clinically. Because the available literature in this space is continuously evolving, the design of these studies will depend on the material and tissue.

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Dr. Berk Oktem: Some common examples of alternative solvents include the following. PBS is often utilized for assessing nickel release from nitinol when corrosion is identified as concern in bench testing, but it is generally not recommended for use in chemical characterization studies due to salt interference with the instrumentation and inability to gravimetrically demonstrate exhaustion. A separate extraction in PBS dedicated to analysis of metals may be advised if you intend to utilize this approach.

Another common alternative is using acidic fluids for extraction of devices intended for contact with gastric fluids may more accurately simulate release of organic and inorganic leachables. Please note that these alternatives are for specific purposes and we welcome Pre-Submission questions, if applicability of these alternative solvents is unclear for your device.

Next, I will turn it over to Nicholas Keyes to share common issues about extraction duration and temperature.

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Dr. Nicholas Keyes: Thank you Dr. Oktem. I am Nicholas Keyes, a chemist in the Office of Neurological and Physical Medicine devices in the Office of Product Evaluation and Quality. And I will be continuing our discussion of extraction.

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Dr. Nicholas Keyes: To begin, let's start with the types of extractions recommended for use in extractables studies. As described in ISO 10993 Part 18, the specific type of extraction is dictated by the device contact category. Limited contacting devices typically undergo exaggerated extraction while long term contacting devices typically undergo exhaustive extraction. Prolonged contacting devices may undergo either of these. Generally, for devices with contact between 24-72 hours, a single exaggerated extraction for 72 hours may suffice. Alternatively, exhaustive extraction would be considered the most conservative approach for this contact category.

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Dr. Nicholas Keyes: When performing exhaustive extraction, each sequential extraction of the same type is performed for the same, fixed duration, consistent with ISO 10993 Part 12. Changing the duration changes the extraction kinetics, preventing an accurate determination of the number of extraction cycles necessary to reach exhaustion, and is therefore not a best practice.

While exhaustive extraction is most commonly performed for sequential 72 hour extractions, alternative, fixed durations such as 24 hours may be acceptable if the device generates sufficient non-volatile residue, or NVR. For example, if you generate 10 mg of NVR in your first extraction cycle, you want to ensure that your balance can accurately measure 10% of that initial value to ensure you can demonstrate the extraction cycle at which exhaustion is achieved. If 10% of the initial amount is not detectable, you may want to consider increasing the extraction duration to 72 hours. We'll discuss NVR in more detail a bit later.

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Dr. Nicholas Keyes: As described in the example conditions of ISO 10993 Part 12, extraction ideally exaggerates both time and temperature. While the human body is approximately 37 Celsius, 50 Celsius is generally used for most extract-based biocompatibility tests, with the notable exception of tests where the extraction solvent itself is not compatible with such temperatures such as cell culture media. For extractables studies, temperatures significantly greater than 50 Celsius may result in excessive

degradation of extracted substances or exacerbate loss of volatile substances. On the other hand, a temperature of 40 Celsius, representing a clinically-significant fever, could be considered minimally exaggerative. Meanwhile, a duration of 24 hours is most frequently used for generation of extracts for limited contacting devices, even when those devices may only have tissue contact for hours or even minutes.

While alternatives may be acceptable with appropriate justification, starting from standardized extraction conditions simplifies study design for test facilities and expectations of regulatory authorities and are a good starting point for most studies.

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Dr. Nicholas Keyes: Next, let's talk a bit about extraction vessels and solvent volume.

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Dr. Nicholas Keyes: ISO 10993 Part 12 makes several recommendations including that extraction be conducted in clean, and chemically inert, closed containers with minimal dead space and to ensure that all contacting portions of the device are covered by the extraction volume.

The Agency recognizes that there are limited sizes of commercially available extraction vessels and that it can be challenging to meet each of these recommendations simultaneously. An iterative approach to optimization of packing efficiency during early study design is often helpful when attempting to meet these recommendations. In some cases, non-standard extraction vessel materials or reassessing the use of modified test articles can provide needed flexibility but should be used with caution.

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Dr. Nicholas Keyes: With that said, ensuring complete, continuous solvent contact throughout the extraction process is critical to obtaining a representative extraction of the device. At the same time, we recognize that it may not be possible to use extraction ratios prescribed in ISO 10993 Part 12 for extractables testing. Using alternative volumes will affect the analytical evaluation threshold or AET and variables, such as the extent of concentration may need to be adjusted to ensure the AET remains greater than or equal to the limit of quantification or LOQ of each of the analytical methods used.

It is also worth noting that using the minimal amount of solvent reduces the extent of concentration needed and the risk of extractable loss. Even if concentration is not required, a lower extraction volume may improve the signal for extractables and improve identification quality. Extraction ratios are also generally not applicable for indirect-contacting fluid pathway devices extracted by filling.

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Dr. Nicholas Keyes: Lastly, consider reducing the headspace or dead space within the extraction vessel whenever possible. As it reduces the loss of volatile extractables. Such losses may also be mitigated by performing solvent-free Headspace Gas Chromatography Mass Spectrometry analysis, however that approach is often limited to small devices or for instruments with dynamic volume capacity.

Using inert filler to reduce extraction volume and overcome poor packing efficiency, while potentially useful, may be more harmful than beneficial for a multitude of reasons. Some key ones to consider are adhesion of extractables to the filler, obstruction of contact with the complete surfaces of the device, and the potential for cross-contamination between uses.

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Dr. Nicholas Keyes: We occasionally receive comments or questions about the use of non-glass extraction vessels, most commonly within the context of elemental analysis. Extraction vessels composed of glass, especially those which are not borosilicate, may leach excessive amounts of certain elements. This is more likely to occur under acidic conditions, therefore if the extraction solvent is acidic you may want to consider alternative extraction vessels.

The same can be said of acidifying extracts as part of preparation for Inductively Coupled Plasma Mass Spectrometry or ICP-MS analysis. And you may want to consider transferring extracts into non-glass extraction vessels.

This can be most impactful for the risk assessment of elements commonly associated with low quality glass, like lead or other heavy metals. Meanwhile there are certain elements commonly associated with glass that may vary between control and test article extracts, such sodium, magnesium, boron, or silicon as silicates. Observation of heavy metals, in particular, at levels of concern, even if they are observed at similar levels in your control, may suggest a test setup including the extraction vessels chosen is not well qualified for detection of those elements.

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Dr. Nicholas Keyes: Now let's transition to discussion of the challenges of using NVR to establish exhaustion as we received several questions related to this topic.

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Dr. Nicholas Keyes: Many comments were received in response to the draft chemical analysis guidance regarding terminology used to describe balance performance. We believe that a majority of the analytical balances in use by test facilities today are adequate, however we don't necessarily believe that the minimum weight tolerances of USP <41> are strictly applicable. For the purposes of establishing exhaustive extraction, we believe a 10-20% error at the lowest end of the balance range is typically acceptable, compared to the tolerance of 0.1% when establishing a USP minimum weight. This is how FDA believes that most test facilities can adequately measure 10-100 µg of NVR.

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Dr. Nicholas Keyes: Previously we mentioned that, if you attempt to perform exhaustive extraction with 24 hour extract iterations and do not obtain a sufficient quantity of NVR, consider returning to the more standard 72 hour iterative extraction approach. However, let's discuss what to consider if even that does not generate sufficient NVR. First, before declaring that to be the case, make sure that you are dedicating an entire extract for demonstrating exhaustion and extracting at least the same number of devices to which someone would be exposed during clinical use. Evaporating an entire extract to dryness maximizes the chance of producing detectable NVR. On the other hand, if you have a device that produces a significant amount of NVR, such as PVC tubing where you may extract 30-50% of the material weight of plasticizer, using an aliquot may be acceptable and could allow for dual use of your extract for both NVR and analytical testing.

If, after all these steps, a sufficient quantity of NVR to demonstrate exhaustion cannot be obtained, it would imply that an individual using your device as clinically intended would be exposed to not more than 100 µg of extractable material and your device is either very small, composed of relatively inert materials, or both. Alternative approaches for demonstrating exhaustion, such as separate analytical testing of each extract iteration to confirm exhaustion has been achieved, may be acceptable under such circumstances. Considering the minimal extractable substances expected to be present, the Agency does not believe this

separate analytical testing to be a burdensome alternative. In such cases, justification of the number of extract iterations would be important.

In these circumstances, also consider whether your device materials pose a risk of degradation that did not occur during your exhaustive extraction. This might occur for some uncommon or novel materials with very slow degradation kinetics. In such cases, your exposure estimate may not be representative of long-term clinical use of your device.

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Dr. Nicholas Keyes: Moving on to mass balance, FDA recognizes that 100% mass balance is not to be expected; however, we have observed significant discrepancies in these values. In some cases the quantity of NVR has been more than an order of magnitude greater than the total quantity of material reported analytically. Because of significant inter-laboratory variability in analytical methods, it is often not clear to the Agency if this discrepancy represents the contribution of large molecular weight oligomers or if the detectability across different test facilities is a primary cause of such significant discrepancies. FDA believes this comparison is still useful, if only to track this discrepancy and investigate it when significant. We believe this will continue to be useful until such time as there is alignment across test facilities on the analytical methods, including performance criteria for those methods, such that we fully understand the gaps that may exist between NVR and analytical testing.

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Dr. Nicholas Keyes: Finally, sometimes we have seen examples where sponsors want to modify the extraction conditions between the extract dedicated for generating NVR and determining exhaustion and that used for analytical testing. Most commonly, there was a request to change the number of devices used. That may be acceptable, provided that the same extraction ratio is maintained, ensuring that the kinetics of extraction are not affected.

And with that, I will hand it off to Jinny Liu to discuss some common issues with observation of particulates in extractables studies and considerations regarding extraction replicates.

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Dr. Jinny Liu: Thank you, Nicholas. Good afternoon, everyone, and thank you for joining today's Town Hall. I am Jinny Liu, a chemistry reviewer in the ophthalmic device team. Next, I will cover some other considerations for device extraction. During device extraction, particulates can be occasionally observed that may impact later instrumental analysis if not addressed. Before taking any action, the first thing to figure out is "what are they?"

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Dr. Jinny Liu: It is important to determine what particulates are because different sources of particulate warrant different considerations. Here are the common sources of particulates. In some cases, the particulate can be particulate matter within the laboratory air during device preparation or cutting debris from the device, or pieces of the device if it is degrading or deforming during the extraction process. Typically, these types of particulates are artifacts which are not related to the test article extractables.

Another common source of particulate is precipitated extractables, which can occur during cooling or concentrating the extract prior to the instrumental analysis. Those particulates are the oversaturated chemicals crashing out of the extract solvent and they are part of the overall extractables.

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Dr. Jinny Liu: So when particulate is observed in the extraction solution, first, investigate the identity and the source of the particulate to determine whether they are extractable relevant. If those deemed not relevant to the extractables, it would be inappropriate to include them in the NVR measurement when determining the exhaustive endpoints. Removal of such particulates to prevent damage to analytical equipment is sometimes necessary. Common removal processes include filtration or centrifugation. When this or other approaches are used, please include a justification describing how the process is not expected to affect dissolved extractables.

If particulate are thought to be precipitated extractables, they are part of the extractables released from the device and it is necessary to include them in the total NVR measurement when determining the exhaustive endpoint. In addition, prior to subsequent instrumental analysis, you may want to bring it back into solution, such as redissolution using a minimal amount of the original extraction solvent or some other suitable solvent, prior to subsequent analysis.

If during the clinical use, the device release particles, you may want to provide additional information to address the clinical safety of those particulates.

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Dr. Jinny Liu: Next, let's talk about one basic issue faced when conducting the study, how many replicates to start? It is important because the replication selection directly impacts the timeline, cost, and validity of the study.

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Dr. Jinny Liu: First, let's briefly differentiate the two commonly used replicates for chemical characterization, analytical replicate vs extraction replicate. For analytical replicate, the goal is to assess the instrumental analysis variability. Here, we show a simplified flowchart. One set of device is used, one set of extract is prepared, and the one extract is injected into the instrument three times, yielding three testing result for one extract.

While for extraction replicates, the goal is to assess the device variability. Typically, at least three sets of devices are used, and each set of devices is extracted to yield three extract solutions. Each extract solution is injected into the instrument once. So, you also get three test results, but they are for three extracts.

Ideally, it is helpful to have both the device and the measurement variations assessed when conducting the chemical analysis for medical devices. However, in practice, with limited resources, we may have to compromise with the test replicates.

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Dr. Jinny Liu: With the advance of the state-of-the-art analytical instrument and methodology, which has reduced measurement variations, and to be least burdensome, the best practice is to perform the extraction in triplicate and only analyze each extract once. This approach can provide more representative information for the device chemical profiles. Please note that in this approach, the three extract solutions are analyzed separately to yield three individual test results, and we recommend against pooling them together prior to the analysis.

Clause 5.6 of ISO 10993-18 emphasizes situations in which multiple extraction replicates are important, when there is information such as engineering data indicating that the device may have variability between individual device batches or lots or in the extraction device preparation process itself. Common

situation arises for devices containing fixed tissues or certain in-situ polymerizing devices, or device extractable variations have been historically known. Those are situations where there is a reasonable expectation that a single extraction replicate may not produce a representative extractable profile.

Sometimes, for well-established materials and manufacturing process, if three or more devices are used to generate a sufficient extract, you may not need to conduct the extraction in triplicate. Occasionally, using a single device in a single extraction can be considered as well, such as a large metal implants which can bring notable challenge with extraction vessels and solvent use if multiple devices are used.

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Dr. Jinny Liu: Finally, I will share two hypothetical examples of those considerations when designing the extraction studies.

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Dr. Jinny Liu: The first example is a blood collection or infusion device. The patient can be on the device for days, so it's considered to have prolonged patient contact. Typically, two solvents, covering both polar and nonpolar are used to extract potential extractables from the device. An exaggerated extraction is typically conducted with exaggeration over duration or the temperature, or both, to maximize the potentially released chemicals. For this extraction, filling the inside of the tube with the solvents to simulate the clinical use is appropriate.

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Dr. Jinny Liu: The second example is a drug eluting degradable scaffold. As a long-term patient contact device, an exhaustive extraction using polar, semi-polar and nonpolar solvents is typically performed. One caveat for this device extraction is that the extraction temperature needs to be carefully selected to avoid resulting in property changes to the polymer or drug which are not expected during the clinical use of the device.

Sometimes when the test article is very small, it can be burdensome to manufacture hundreds of finished devices to conduct the study, so it may be acceptable to use a coupon for the study. However, the coupon is intended to serve as a surrogate of the final finished device, so considerations such as fabricating from same materials, using similar manufacturing procedures, including packaging and sterilization, and a comparable relevant physicochemical characteristics are relevant to demonstrate. In addition, a gap analysis discussing why the manufacturing difference, device vs. coupon, will not introduce different chemicals to the final finished device is helpful.

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Dr. Jinny Liu: In conclusion, remember that there is no single approach to chemical characterization, so consider flexible approaches based on the device contact type/duration and probable hazards of the materials and processes.

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Dr. Jinny Liu: In summary, extraction is the essential and fundamental step for chemical analysis of medical devices. It involves multiple disciplines and considerations of device materials, manufacturing process, clinical use, instrumental compatibility, and more.

As extraction conditions were a common point of feedback received on a draft Chemical Analysis guidance and in current deficiencies, we have shared experimental considerations for extraction studies, which are critical for generating a representative extractable profile for later instrument analyses.

Please note that this doesn't include the totality of considerations for conducting chemical analyses to support biocompatibility endpoints, such as extract manipulation, system suitability, AET determination, and more.

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Dr. Jinny Liu: Here's a list of resources including guidances, standards and the manuscripts on the related topic. Please check this to get a broader view on what to consider for chemical analysis and how it is used in the biocompatibility assessment for medical devices.

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Dr. Jinny Liu: Here's a list of resources mentioned today and the links.

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Dr. Jinny Liu: Here's a list of additional helpful resources not specifically referenced in the presentation, but they can be very helpful.

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Dr. Jinny Liu: As Misti mentioned earlier, today's presentation is part of a series of town halls on biocompatibility and medical device. Please join us on October 7th for the third biocompatibility town hall in this series focused on toxicological risk assessment.

That concludes the presentation piece of today's town hall. I will now turn it back over to Kim. Thank you.

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CAPT Kim Piermatteo: Thank you Dr. Liu, as well as thank you Dr. Malone, Dr. Keyes and Dr. Oktem for your presentations.

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CAPT Kim Piermatteo: Joining our presenters today to assist in addressing your previously submitted questions, is Dr. Joshua Young, Chemist in CDRH's Office of Science and Engineering Laboratories' Division of Biology, Chemistry and Materials Science; Dr. Nahid Ilyas, Chemist in CDRH's Office of Product Evaluation and Quality or OPEQ in the Office of Health Technology number four; and Dr. Jiwen Zheng, Chemist in OPEQ's Office of Health Technology number two. Dr. Young and Dr. Zheng also serve as CDRH's liaisons to ISO 10993-18.

Thank you all for joining us for this segment of today's town hall.

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CAPT Kim Piermatteo: So this segment we will address your previously submitted questions about this topic. I'll read a question aloud and then ask one of our subject matter experts to provide a response.

For our first question, I'll direct that to Nahid. Nahid, the question is, ISO 10993-1 states that exhaustion can be demonstrated through gravimetric or other means. What does the FDA think about the use of using chromatographic techniques to assess exhaustive extraction?

Dr. Nahid Ilyas: Thank you Kim for the question. As discussed during this presentation, direct use of a chromatographic approach is unlikely to be generally acceptable because of significant inter-laboratory

variability in analytical methods. However, there are cases where this approach may be appropriate, such as if the quantity of NVR is so low that it becomes gravimetrically undetectable, as demonstrated experimentally. Additionally, it may be acceptable to use this chromatographic approach if the device manufacturers or test facilities mainly work with limited number of medical device materials. Additional work in this area may be valuable to develop and harmonize methods to allow broader utilization. Back to you Kim.

CAPT Kim Piermatteo: Thanks Nahid. Joshua, I'd like to come to you with the next question, which is, what does the FDA think about the use of alternative extraction durations, such as iterative 24 hours, for exhaustive extraction?

Dr. Joshua Young: Thanks Kim. The starting point for use of 72 hours is based on the extraction conditions described in Clause 10.3.1 of ISO 10993-12. However, as discussed during this presentation and consistent with Annex D of ISO 10993-12, alternative, fixed duration cycles may be acceptable so long as those shorter durations still produce sufficient NVR to demonstrate the exhaustion. Back to you.

CAPT Kim Piermatteo: Thanks Joshua. For our next question I'd like to direct that to Jiwen, Jiwen, the question is, can the Agency provide perspective regarding the validation and acceptance of simulating solvents in the future, such as ethanol: water mixtures?

Jiwen, we can't hear you. I'm wondering if maybe you're double muted.

Dr. Jiwen Zheng: Can you hear me now?

CAPT Kim Piermatteo: Yes, we can.

Dr. Jiwen Zheng: Sorry about that. As we discussed during the presentation, the FDA does not believe there is sufficient information to identify and adequately justify the use of simulating solvents for most medical device material and tissue contact combinations. Further work in this area would be valuable to validate those candidate solvents, including development of experimental models for assessing leachables to compare with alternative approaches, for example post-exposure extraction study; assessing leachables by difference, and use of broader ranges of the materials and generalized applicability to different classes of extractables.

The FDA can envision a future where a well characterized data matrix could be used to identify appropriate extraction solvents that more closely simulate leachables. However, it's important to note that the use of such study data will likely require in re-evaluation of the assumptions within the current framework for toxicological risk assessment. Back to you Kim.

CAPT Kim Piermatteo: Thanks Jiwen. Nahid, I'm going to come back to you with this next question, Nahid, the question is, as ISO 10993-18 and ISO 10993-17 become increasingly central to biological evaluations, how is FDA supporting consistency in expectations for extractables and leachables studies and Toxicological Risk Assessments for medical device evaluations?

Dr. Nahid Ilyas: Thank you Kim for the question. So biocompatibility is one of the topic areas included in the focal point program, with the goal of promoting consistency in review practices and policy applications across device types, Divisions, and Offices within CDRH through engagement and cross-training of resources across the Center. The Biocompatibility focal point program consists of scientists and engineers with expertise in materials, manufacturing, chemistry, and toxicology who conduct reviews, discuss issues, participate in more than 50 consensus standards and active working groups in this space, and develop regulatory science tools. Back to you Kim.

CAPT Kim Piermatteo: Thanks again, Nahid. We have one more question for today's town hall and that question I'll direct to Jiwen. Jiwen, the question is, how does FDA consider extractables testing according to ISO 10993-18 within the framework of an overall biocompatibility risk assessment?

Jiwen, we can't hear you again.

Dr. Jiwen Zheng: Can you hear me now?

CAPT Kim Piermatteo: Yes, we can.

Dr. Jiwen Zheng: Sorry I'm technical challenged.

CAPT Kim Piermatteo: No worries.

Dr. Jiwen Zheng: Extractables testing as part of a chemical characterization is a complex space with significant methodological inconsistency across test facilities. While concerns may be identified in the methodology or results of the extractables study for a particular device, the totality of evidence supporting the overall biocompatibility is always considered in decisions made by the FDA. Back to you Kim.

CAPT Kim Piermatteo: Thank you Jiwen. That will conclude our previously submitted questions segment of today's town hall. Again, thank you to everyone who submitted questions in advance and thank you to our subject matter experts for providing these responses.

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CAPT Kim Piermatteo: Before we wrap up today's town hall, I'd like to turn it back over to Misti for some closing remarks regarding today's topic. Misti...

Dr. Misti Malone: Thank you, Kim. So chemical characterization extractables testing is an important component of biocompatibility evaluation and factors into the totality of evidence to support medical device safety. Based on the many questions and comments we received is clear that this is an area of interest for our stakeholders and I hope you found this town hall helpful.

I would like to thank the presenters today for their and those on the working groups for the development of the materials and for the presentation and the continued engagement on reviews and policy. Thank you and back to you Kim.

CAPT Kim Piermatteo: Thanks Misti and I'd like to reiterate my thank you as well to all the presenters for being a part of today's town hall.

For your information, a recording of today's event, a copy of the slides and a transcript will be posted as soon as possible to the event page, as well as to CDRH Learn under the section titled "Specialty Technical Topics," and the sub-section "Biocompatibility." A screen shot of where you will be able to find these materials on CDRH Learn has been provided on this slide.

If you have additional questions regarding today's biocompatibility topic specifically, feel free to reach out to the email on this slide which is CDRH.Biocomp@fda.hhs.gov.

If you have additional general questions regarding today's town hall, feel free to reach out to DICE at DICE@fda.hhs.gov.

And as Misti mentioned and Jinny, our next and last town hall in this series is scheduled for Wednesday, October 7, 2026. We hope you all are able to join us then as well. Additional information about that

upcoming town hall as well as other CDRH events is listed on our CDRH Events webpage at www.fda.gov/CDRHevents.

Thank you all again for joining. This concludes our CDRH Town Hall.

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