

Biocompatibility Town Hall #3: Toxicological Risk Assessment

Approaches for Addressing Biocompatibility Endpoints

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Moderator: Kendra Holter

Presenters: Misti Malone PhD, Alan Hood PhD and Teresa Palacios PhD

Additional Panelist: Qin Zhang PhD

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Kendra Holter: Good afternoon and welcome to today's CDRH Town Hall event. Thank you for joining us. This is Kendra Holter, and I serve as a Consumer Safety Officer in the Office of Industry and Consumer Education or OICE in FDA's Center for Devices and Radiological Health. I'll be the moderator for this town hall.

Today's town hall is the last town hall in our three part series on biocompatibility and medical devices. Today specifically, we will discuss toxicological risk assessments to address biocompatibility endpoints for medical devices.

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

It is now my pleasure 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. Alan Hood, Toxicologist in OPEQ's Office of Health Technology number two; and Dr. Teresa Palacios, Toxicologist in OPEQ's Office of Health Technology number six.

Thank you to all the presenters for joining us today. Before I turn it over to Dr. Malone, I'd like to remind everyone, 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.

Thank you again for joining us today. I'll now turn it over to Dr. Malone.

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Dr. Misti Malone: Good afternoon, my name is Misti Malone and I'm an Associate Director in the Office of Product Evaluation and Quality supporting nonclinical evaluation and policy.

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Dr. Misti Malone: Today we will share a brief introduction of the related consensus standards followed by key considerations in the application of chemical toxicological risk assessments or TRA; common issues that occurred in submitted TRA reports and what to consider that may help address each issue. This presentation builds upon the presentations on September 9th on Biological Risk Assessment and

September 25th on extractables testing for chemical analyses. The information for these town halls was developed following a review of common issues related to extractables testing and TRA with the aim to support transparency and predictability for considerations for evaluating biocompatibility endpoints.

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

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Dr. Misti Malone: Biological risk assessments can incorporate biological testing, chemical testing or information gathering based on the materials, processing, or previous experience; or a combination of testing and information, as presented in more detail in the September 9th town hall. Today, we will focus on toxicological risk assessments.

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Dr. Misti Malone: An extractables study can be broken into several distinct phases, starting with study design and extraction. Those extracts are then processed as necessary and undergo chemical analysis. The data produced by these analyses is evaluated to determine what and how much is present. Finally, those data are compiled in a report that informs a TRA per ISO 10993 Part 17. This diagram is an excerpt from the 2022 publication by CDRH chemists that goes over these steps in greater detail, cited below if you wish to review it.

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Dr. Misti Malone: TRA is a systematic, estimated exposure-based approach to determine whether the chemical constituents identified in, or released from, a medical device pose a negligible or tolerable risk when exposure occurs, and we refer to part 17 of ISO 10993 and ISO Technical Specification 21726. The Supplementary Information Sheets that share additional information regarding the extent of recognition and rationale are linked here.

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Dr. Misti Malone: Extractables testing and TRA are often used to address the biocompatibility endpoints of systemic toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity highlighted here, and may be used in combination with information gathering and/or biological testing. Per our Biocompatibility guidance also linked here and ISO 10993 and its subparts, these endpoints are typically addressed for many prolonged or long-term implants, as denoted by the Xs in this table.

Next, I turn it over to Dr. Teresa Palacios to share common methods and issues for toxicological risk assessments.

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Dr. Teresa Palacios: Thank you, Dr. Malone. Good afternoon everyone. My name is Teresa Palacios Hernandez. I am a board-certified toxicologist with ten years of service in CDRH, and I am currently serving as toxicology reviewer in the Office of Orthopedic Devices, OHT6, Office of Product Evaluation and Quality. Together with my colleague, Dr. Alan Hood, Senior Toxicology Reviewer in the Office of Cardiovascular Devices, or OHT2, we will present updates regarding ISO 10993-17 and ISO/TS

21726:2019 and what stakeholders may wish to consider when conducting a TRA of medical device extractables.

In this brief introduction, we will cover the purpose of Part 17 and TS 21726, what's new in the second edition of Part 17, and what parts of Part 17 are not recognized.

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Dr. Teresa Palacios: The following abbreviations are used in this presentation. Most are sourced from Part 17 or TS 21726. Consult with these ISO documents for definitions, explanations, and information not addressed in this presentation. The remaining abbreviations commonly occur in medical device TRA reports.

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Dr. Teresa Palacios: I would like to start this presentation discussing the purpose of a toxicological risk assessment, or TRA. Estimating toxicological risk of extractables is an important part of the medical device biological evaluation process. The need for conducting TRA is based on an expectation that a medical device that contacts tissue will result in exposure to extractable substances. Toxicity is an inherent property of extractable substances. Biological testing in combination with chemical characterization and TRA is a least burdensome approach to address certain biological endpoints, which may include: subchronic and chronic systemic toxicity, carcinogenicity, reproductive toxicity, and developmental toxicity. Understanding extractable toxicity and estimating toxicological risk can demonstrate that exposure is at tolerable level or can identify a hazardous situation. Following a standard TRA approach facilitates consistent decision making.

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Dr. Teresa Palacios: As a general overview of consensus standards relevant for this talk, it is important to mention that the applicability of Part 17 and TS 21726 is documented in Clause 1 Scope. For example, the purpose of Part 17 is to establish a common TRA approach, which includes common criteria provisions. Part 17 does not apply to chemicals that are below an appropriate reporting threshold expressed in micrograms per milliliter or micrograms per device or to a medical device shown to be chemically or biologically equivalent to an already biocompatible or U.S. marketed medical device. The purpose of TS 21726 is to establish what threshold of toxicological concern or TTC values can be considered. This technical specification states that TTC is not for constituents with adequate toxicity data, such as a point of departure value, for deriving a medical device constituent specific tolerable intake value, or for toxicological risk estimation from potential exposure to a constituent via a gas pathway medical device or for estimating toxicological risk of a constituent that has high potency, which has a low tolerable intake value for example cohort of concern compounds.

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Dr. Teresa Palacios: Compared to the first edition of Part 17 published in 2002, the second edition published in 2023 contains new methodology information that includes when to conduct a TRA, when to consider screening extractables by applying the specified toxicological screening limits, how to calculate a worst-case estimated per day exposure dose for a medical device constituent, and when to address toxicological risk by other means. For example, refinement of a worst-case estimated per day exposure dose, abbreviated as EEDmax, can be considered when the extractable is poorly identified or the extractable can cause serious harm and the reported quantity is suspected to not be a reasonable estimate of worse-case exposure.

For extractables with well understood toxicity, the estimation of toxicological risk can be further evaluated based on a lowest observable adverse effect level, or LOAEL, from constituent specific and harm-specific dose-response data, if such data is available.

When refinement of the EEDmax is not practical and further assessment of toxicological risk is not feasible, managing the identified risk that results from exposure to a medical device constituent in accordance with ISO 10993-1 and ISO 14971 can be considered in consultation with FDA, such as through the Q-Submission process.

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Dr. Teresa Palacios: FDA does not fully recognize ISO 10993-17:2023. Table E.2 in Clause E.2 is not recognized because the table is not supported by the normative text in Clause E.2 of Annex E of this standard which states "The number of time points within an exposure period shall be sufficient to address late bolus release of the constituents, unless justified with supporting evidence that late bolus release will not occur." In the paragraph before formula E.2 of Clause E.2 and in the paragraph before formula E.4 of Clause E3.1, the phrase "e.g. the largest surface area of device which can be in contact with the body is not the same as the surface area of the device which is in contact with the solution during extraction" is also not recognized because this text conflicts with Section VI.G of FDA's biocompatibility guidance, which states "consider the situation where a patient might receive multiple devices of the largest device size to calculate the estimated worst-case patient exposure."

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Dr. Teresa Palacios: Our next topic for discussion is focused on key considerations in the application of a TRA for medical device constituents. Briefly, we will speak about general aspects of Analytical Evaluation Threshold when analytical chemistry testing is conducted, how elaborating a TRA, how expressing quantity of a constituent, as well as main aspects to consider for total constituent quantity reported in a TRA. We will speak about general considerations when applying a toxicological screening limit, or TSL, how to define a worst-case estimated per day exposure dose, or EEDmax, and finally, main aspects associated with derivation of margin of safety, or MoS, values, per ISO 10993-17.

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Dr. Teresa Palacios: A major component of the design of chemical analysis is Analytical Evaluation Threshold, or AET, as it determines the concentration at which a substance is identified and semi-quantified if present. It is essentially a measure of "How low to go or How sensitive a method needs to be."

The formula you see here is based on the formula in ISO 10993-18:2020 Annex E. For more details on the extent of the partial recognition, please see the Supplementary Information Sheet, or SIS, linked here. Many of these variables pertain to the extraction methodology and instrumentation and won't be discussed today. We will provide more detail on dose-based threshold or DBT.

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Dr. Teresa Palacios: DBT is a potency value and typically equal to Threshold of Toxicological Concern, or TTC, per ISO TS 21726 shown here in this table. Thus, extractables that are less potent than the DBT, which is further reduced by the analytical uncertainty factor, are screened out from further risk evaluation. The selection of the DBT value is based on the device intended use and may be adjusted in special situations with adequate justification.

We recently removed Example C.2 in Annex E from the extent of recognition in the Supplemental Information Sheet for ISO 10993-18:2020. Example C.2 describes using an alternative DBT for a long-

term device to that in ISO TS 21726. While this approach may be acceptable in limited cases, the appropriateness of an alternative DBT is specific to the device under evaluation, the contact categorization by ISO 10993-1, and other considerations. For example, a DBT higher than 1.5 micrograms per day may be used for a long-term implant based on the patient population, for example evidence that patient is not expected to live beyond a specific duration or when shorter constituent exposure duration is reasonably expected. For additional device specific feedback on the proposed approach, please consider engaging with the review office.

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Dr. Teresa Palacios: The elaboration of a TRA begins with a known or estimated quantity in micrograms per device of a constituent or multiple constituents. Per part 17, the total quantity of these constituents is intended to be representative of worst-case release based on duration of contact, for example short-term, limited or prolonged, or long-term. To ensure a conservative assessment of such constituents, the worst-case per day exposure dose is based on clinical use, for example number of devices contacting the body. Finally, the estimated margin of safety, or MoS, is an inherent outcome of the medical device constituent being extracted and the medical device intended use.

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Dr. Teresa Palacios: Now, let's talk about reporting a constituent quantity from a medical device. Medical device extraction studies often report the quantity of a constituent in micrograms per device. However, reporting quantity of an extractable in these units may not represent a maximum total quantity of the extractable that could be released from the medical device and exposed to the user. The micrograms per device unit alone may be inadequate for communicating a maximum total quantity because this unit does not inform whether the intended use of the medical device involves a single or multiple medical devices.

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Dr. Teresa Palacios: Reporting a total quantity of an extractable in micrograms per device is not considered by default to represent a maximum total quantity, abbreviated as TQmax, that could be released and expose the user of the medical device. The reported TQmax can be considered adequate for TRA when it is calculated in accordance with Formula B.2 and Formula B.3 in Part 17. The examples in this table illustrate that the same total quantity of an extractable can represent different TQmax values. For this reason, it is critical that a reported quantity of an extractable not be used to infer toxicological risk without first considering the TQmax calculation that is described in Part 17.

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Dr. Teresa Palacios: When evaluating the total constituent quantity, or TQ, expressed in micrograms per device, it is important to emphasize that such quantity is relative to the duration and frequency of exposure of a medical device, the size of such device, and the number or quantity of devices that contact tissue on the same day. Evaluating the TQ value is based on the method used to extract constituents from the medical device, the impact of post-extraction processing steps, and the analytical chemistry test applied. Obtaining a TQ that considers these aspects is useful for the subsequent application of the toxicological screening limit, or TSL, and the calculation of the estimated worst-case per day exposure dose, or EEDmax, based on maximum release, as described in section E.3.1 of Part 17.

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Dr. Teresa Palacios: Now, when speaking about the maximum total constituent quantity of an extractable, expressed in micrograms, it is important to consider that, when constituent quantity may not be a reasonable estimate of a total for a specified time-period, a TRA is conducted per Part 17. Examples may include the following: the constituent is present at a very low level, or the source of such constituent is unrelated to the medical device material of construction.

A constituent is deemed as low based on the patient exposure duration and risk level of the medical device intended use. In chemical screening studies low quantity may be defined by one, analytical evaluation threshold, or AET, or the lowest reportable quantity, or LRQ, and two, sensitivity of mass balance used for NVR. Please note that, for TRA perspective, a constituent quantity is deemed as low when it is at or below the 120 microgram TSL value, or worst-case estimated per day exposure dose for such constituent is below the applicable TTC value, or below the tolerable intake, or TI.

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Dr. Teresa Palacios: The source of an identified constituent influences whether its reported quantity is known or estimated value. The reported constituent quantity can be considered known when its source is a material of construction and quantification method is a calculation based on material use and composition information. Alternatively, the reported constituent quantity is estimated when its source is a material of construction or manufacturing material, and the quantification method is by chemical analysis. In general, expressing the maximum total quantity of a constituent in micrograms per device or on a per quantity basis, such as micrograms per square centimeter, per gram or per milliliters is necessary for estimating a worst-case per day exposure dose that is used for assessing constituent toxicological risk.

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Dr. Teresa Palacios: Now, let's talk about the toxicological screening, or TSL. TSL is applied based on the following considerations: the TSL applies to identified constituents, see clause 6.2.2 of Part 17, and the TSL determines whether a constituent TQmax with low toxicity is too low to pose a short-term or long-term risk for genotoxicity, cancer, systemic toxicity, or reproductive harm and the applicable subpopulation does not include very young infants or neonates, including preterm, per Annex B in Part 17.

The applicable TSL value, for example short-term value of 120 micrograms, long-term value of 600 micrograms, is compared against the TQmax of a constituent for which toxicity has been deemed as low, see Annex B in Part 17.

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Dr. Teresa Palacios: Regarding TSL application, per Section B.3 of Part 17, the process begins when three conditions are met as identified on the left box of the slide: an adequate chemical screening study method for medical device extractables has been conducted, constituents that exceed the reporting threshold have been identified, and toxicological information for those constituents is understood. The first decision diamond asks whether the TQmax of the constituent is at or below 120 micrograms. If the response is No, proceed directly to calculate and evaluate the MoS per Part 17, Clause 10. This is the path used when the constituent quantity is present at a sufficiently high quantity that a moderate to low potent constituent could present a toxicological risk. However, if the response is Yes, move to the conditional check and verify whether any of the specific risk scenarios listed apply.

If the scenarios listed on the checkbox are not applicable, then no further assessment is needed; document the decision. This is the outcome where the constituent poses negligible risk because the constituent is not adequately potent relative to the low quantity reported. However, if one of the specific risk scenarios listed does apply, the MoS is calculated and evaluated per Part 17, Clause 10, because a possible risk cannot be ruled out without a full margin of safety assessment.

Please note that this flowchart is essentially a tiered risk screening tool based on the constituent specific quantity extracted and a chemical specific TI value. This approach allows screening exceptionally high, very high and highly potent constituents, if present at low quantities where a MoS less than one is not a reasonable expectation, while ensuring that borderline and less potent constituents extracted at a

relatively low quantity are appropriately screened from further toxicological risk assessment, and constituents of any potency value that may be extracted at a quantity exceeding the TSL receive a rigorous quantitative toxicological risk assessment.

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Dr. Teresa Palacios: Per section 3.3.2 of Part 17, the EEDmax, or worst-case estimated per day exposure dose, is the exposure dose that is a maximum value for a specified intended clinical-use scenario. This calculation applies to three key considerations: constituent quantity, the amount of a specific chemical extractable or leachable from the device; specific time periods, the calculation is tied to defined exposure windows, ≤ 1 day, 2–30 days, 31–365 days, ≥ 366 days, and a conservative estimate, the calculation defaults to the most clinically relevant medical device intended use scenario where the highest possible exposure dose is estimated rather than an average estimated exposure dose. Please note that the term conservative does not apply to the toxicological threshold, TI, or TTC, because the threshold values is not derived based on medical device clinical use factors.

The EEDmax is informed by patient-specific and use-specific clinical factors, including: sensitivity of the patient which accounts for vulnerable populations and is generally based on biological parameters such as patient age, body weight, in addition to clinical considerations inherent to the intended population treated with the proposed medical device for example, immunocompromised patients, pregnant women, etcetera; duration and frequency of use relevant to the EEDmax, how long and how often the device contacts tissue directly affects the exposure dose, and number or quantity of medical device(s) that contact tissue, if multiple devices or units are used simultaneously or sequentially, the combined exposure is considered.

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Dr. Teresa Palacios: As final part of the second section of this talk, I will speak about margin of safety. For Part 17, Margin of Safety, or MoS, represents the ratio of the constituent's tolerable intake and its worst-case estimated per day exposure dose.

There are two scenarios under which a constituent can be considered acceptable; MoS larger than one, the estimated exposure is below the tolerable level, meaning there is an adequate safety buffer. This is the straightforward, favorable outcome resulting in no further action. MoS less than one, the estimated exposure exceeds the tolerable level. This does not automatically mean the device is unsafe, but it involves two additional steps; a root cause analysis and adequate risk management.

When MoS is less than one, the first consideration is to understand why by identifying the source of the constituent and the feasibility of exposure at EEDmax for the entire duration of use, including confirming if the worst-case exposure scenario is actually realistic and plausible, based on a reasonably estimated total constituent quantity present in or on the device. In other words, does the source support that the patient to be exposed at that level for the entire duration of use? When the decision is that the patient could be exposed at the EED_{max} level for the entire duration of use, then further risk assessment as described in Part 17, Section 10.2, ISO 10993-1, and ISO 14971 may address the risk. When the source of the constituent is undeterminable, then worst-case assumptions apply. The decision that the source of the constituent does not support that patient will be exposed at the EED_{max} level for the entire duration of use would be documented and justified.

Alongside the root cause analysis, adequate risk management is typically applied through one of two approaches; risk estimation and risk mitigation, if practical, by quantifying the risk and, where feasible, implementing measures to reduce or control it for example, design changes, material substitutions, use limitations, excreta. ISO 10993-1:2025 and ISO 14971:2019 addresses when to consider benefit-risk, such as when risk mitigation approaches may not be practical. Alternative application of benefit-risk

factors from ISO 10993-1, ISO 14971, or FDA guidance documents focused on benefit-risk factors may be relevant for consideration.

Please note that the use of a TTC in the calculation of a MoS is not required per ISO 10993-17; however, FDA/CDRH will accept MoS values that are calculated based on a TTC value provided that when to use, and what specific TTC value is used, are in accordance with the standard.

Now I will turn it over to my colleague, Dr. Alan Hood. Dr. Hood, the floor is yours. Thank you.

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Dr. Alan Hood: Thank you, Dr. Palacios. My name is Dr. Alan Hood, I am a Senior Toxicologist in OHT2, Office of Cardiovascular Devices.

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Dr. Alan Hood: In the third part of this presentation, common TRA issues will be discussed, which include general observations, challenges when applying the current second edition of ISO 10993-17 related to constituent specific tolerable intake values or worst-case estimated per day exposure dose, challenges with the application of threshold of toxicological concern as described in ISO/TS 21726, and margin of safety reporting.

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Dr. Alan Hood: A well conducted chemical screening study will generally generate constituent data that is adequate for TRA. It is common to find that an explanation for why the chemical screening study method can be considered adequate is absent from the report when submitted to FDA. This issue can be addressed by including a statement that explains the basis for the adequacy of the chemical screening study in the FDA submitted report.

For example, for a release kinetics study where constituent release is quantified by targeted analysis, an adequacy statement would address the representativeness of the quantity based on clinically relevant extraction conditions that can generate a worst-case amount that could be released in a single day. For a chemical screening study where quantification is by non-targeted analysis, the adequacy statement would address representativeness of the quantity based on the extraction method intended to generate a total amount that could be released for the longest time-period that applies to the medical device intended use.

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Dr. Alan Hood: When deriving the TI value for constituents with toxicological data that is available, the uncertainty factors are often not appropriately selected, as some of them are assigned with values lower than expected or are absent. Please select the uncertainty factors in accordance with Annex C.2.2 to properly address variation among humans, species extrapolations and other uncertainties in the data for assessing toxicological risk of a constituent released of a medical device during its intended use.

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Dr. Alan Hood: When applying the read-across approach to derive the TI value for identified constituents with incomplete toxicity data, the detailed criteria used to select the analogue are often not provided. Consider Clause 6.2.4 in Part 17 when selecting an analogue for toxicological risk assessment.

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Dr. Alan Hood: Numerous chemical specific threshold values are publicly available for uses other than medical devices. These non-medical device threshold values were not derived in a way that considers the

specific tissue contacted, frequency of medical device use, or patient susceptibility. The non-medical device thresholds can be a useful resource to quickly identify a PoD value and its source. Understanding the source of the PoD that a non-medical device threshold uses is critical information to determine whether the PoD is relevant for a medical device intended use and whether medical device specific uncertainty factors specified in Part 17, Annex C are applicable.

Use of an LD50 value from an acute systemic toxicity study to derive a TI value that addresses short-term and long-term exposure durations is another challenge when applying Part 17. This issue may be addressed by identifying a relevant PoD from an acute or a subacute study to derive a short-term TI value. For a device that contacts tissue long-term, a relevant PoD from a subchronic or chronic study is selected and used to derive a long-term TI value. When a PoD from an acute or subacute study is not available and the device tissue contact is long-term, the long-term TI value can be used to demonstrate that short-term exposure will be at a tolerable level. When a relevant PoD value is not available to derive a constituent specific TI value, the margin of safety can be calculated based on the applicable threshold of toxicological concern value.

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Dr. Alan Hood: The constituent that is a human carcinogen or suspected human carcinogen, not reporting cancer risk is another challenge. Estimating cancer risk is necessary because it is often the lowest threshold compared to other harms associated with exposure to the constituent. If the estimated exposure dose for the carcinogen is sufficiently high or it can also cause serious systemic toxicity, then reporting an MoS for systemic toxicity in addition to carcinogenicity can be helpful to demonstrate exposure to the constituent will be at a tolerable level. Consider conducting the cancer risk assessment using the slope factor or TD50 approach as described in Clause C.3 of the Part 17 standard.

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Dr. Alan Hood: Another challenge is when the calculation of EEDmax does not represent the worst-case exposure of a constituent to patients. For example, in some devices with intermittent use, the daily exposure dose from a 24 hour extraction study is adjusted by applying a proportional factor such as three days divided by seven days, based on the clinical treatment frequency.

Another example is calculation of the daily exposure dose over the entire lifetime, which results in a less conservative long-term daily exposure dose. Consider calculating the EEDmax in accordance with Clause 8 and Annex E in the Part 17 standard.

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Dr. Alan Hood: When calculating the worst case estimated exposure dose, the reported total quantity does not always represent a cumulative exposure dose for all constituents based on the extraction method or a small quantity is reported. For these constituents, the quantity is not sufficient to calculate a worst-case estimated exposure dose in accordance with Annex E.3.1.

For example, a medical device that contacts tissue long-term, the TQ obtained from an exaggerated extraction at 50 degrees Celsius for 72 hours and used to calculate the EEDmax by dividing the TQ by 366 days is not in accordance with the standard since it is not obtained from an exhaustive extraction study and not representative of a long-term cumulative exposure dose to patients.

When the extraction study is exhaustive and the reported quantity is small, and the source of the constituent is unknown, then the EEDmax can be calculated in accordance with E.3.2.

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Dr. Alan Hood: When prolonged contact applies to the medical device cumulative exposure duration, a release kinetics study conducted in accordance with Part 17, Annex E.2 where constituents are quantified by targeted analysis can be used to obtain a worst-case estimated exposure dose. However, a study duration that is too short or if targeted analysis is not used for quantification can prevent reporting the highest measured representative quantity that is needed to calculate the worst-case estimated exposure dose.

Prior to conducting a release kinetics study, sponsors can consider consulting with FDA via the Q-Submission process to confirm that the release kinetics study design and quantification method will be acceptable. The design of a release kinetic study is highly customized because the extraction method for example, clinically relevant worst-case temperature, clinically relevant test article, and the number of data points, is unique to the specific medical device prolonged contact duration. When non-targeted analysis is used for quantification, conducting a traditional exaggerated or exhaustive chemical screening study that generates a total quantity representative of the medical device cumulative prolonged or long-term exposure duration is typically sufficient to address constituent toxicological risk.

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Dr. Alan Hood: When the tissue contact duration for a single medical device use is limited, less than or equal to 24 hours, use of Formulas E.3 and E.4 do not result in a worst-case estimated exposure dose as explained in Clauses E.2 and E.3 of the Part 17 standard. For these medical devices, the worst-case estimated exposure dose is calculated from Formulas E.1 and E.2.

When toxic constituents are not reported and the extraction method equals or exceeds the worst-case medical device intended use, Formulas E.1 and E.2 are typically adequate for calculating the worst case estimated exposure dose without repeating the extraction study. When one or more toxic constituents are reported and the extraction method exceeds the worst-case medical device intended use, repeating the extraction study using clinically relevant worst-case conditions, targeted analysis, and calculating the worst-case estimated exposure dose using Formulas E.1 and E.2 may be needed to prevent a false positive TRA outcome.

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Dr. Alan Hood: Some other challenges when applying the Part 17 standard include use of TSL to excluded constituents. For example, unknowns, or constituents with incomplete identity, or highly potent constituents, for example cohort of concern substances. Additionally, TRA that addresses all biocompatibility end points is another challenge. These issues are addressed when the TSL limit is applied in accordance with Part 17 and those biocompatibility end points that TRA cannot address are addressed as described in Part 1 and FDA CDRH's biocompatibility guidance.

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Dr. Alan Hood: These are some examples when the TTC is not appropriately applied, such as when TTC is applied to all constituents without considering the constituent toxicity, which includes its TI value, if available, or applying non-cancer TTC value to unknowns, or the TTC value is applied in a novel way without sufficient toxicological evidence.

The Part 17 standard and ISO/TS 21726 includes when not to apply TTC and describes approaches that addresses these challenges, such as derivation of a TI value when a relevant PoD is available per Annex C or obtaining constituent identity information when identity is inadequate for toxicological risk assessment per Figure 1. Applying TTC in accordance with the standard is preferred rather than applying

a novel approach unless the TTC approach described in the standard will result in a false negative TRA outcome or the novel approach improves the quality of the toxicological risk assessment.

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Dr. Alan Hood: When a margin of safety value below one occurs, further risk analysis or risk evaluation or risk mitigation can generally address the concern. In these cases, the lowest observable adverse effect level, abbreviated as LOAEL, which is the lowest toxic dose for a specified harm, could be included in the TRA report, when the LOAEL is available. Reporting the LOAEL value in addition to a NOAEL is helpful for understanding the dose-response relationship and determining whether the EEDmax value is sufficiently high to indicate that toxicological risk could be at a higher level. Then, risk mitigation can be considered, for example, after the probability of occurrence and severity levels are established and used to estimate and evaluate the identified risk. When risk mitigation does not adequately address the risk, then assessing whether the benefits of the device use outweigh the identified risks as described in FDA Benefit-Risk guidance documents can be considered to complete the risk management process.

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Dr. Alan Hood: A common challenge is when reporting the toxicological risk assessment results, where the MoS value reported does not include the time period. Reporting the calculated MoS values with the applicable time period is helpful when more than one time-period specific MoS value is calculated and reported, for example a medical device that is implanted in the body. The exposure assessment principles described in ISO 10993-18, Clauses 5.4 through 5.8 and ISO 10993-17, Clause E.3.1 are helpful.

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Dr. Alan Hood: In summary, the first edition of ISO/TS 21726 was published in 2019 and the second edition of Part 17 was published in 2023, which have been widely adopted. The extent that Part 17 or ISO/TS 21726 provisions and approaches are applied necessitates verification of submitted chemical data and TRA outcomes. Compliance to the standard provisions and approaches facilitate consistent TRA outcomes. The Agency is committed to implementing a least burdensome approach and requesting the minimum additional TRA information needed to determine whether possible exposure to a constituent will be at a tolerable level.

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Dr. Alan Hood: The current second edition of Part 17 addresses the gaps of the first edition and describes for medical device stakeholders a complete TRA process that begins with reporting constituent toxicity followed by estimating a worst-case per day exposure dose for a constituent, estimating and evaluating risk by calculating and reporting a margin of safety value, and finally describes ways to resolve a margin of safety value below one.

When considering risk management principles to address a margin of safety value below one, the outcome of a root cause analysis that addresses the sources of the constituent is helpful to include in the TRA report, as well as the applicable specific risk mitigation measure, which can include risk notification for a non-serious harm or risk reduction for a serious harm, or if risk mitigation is not practical, then the benefit-risk factors described in the FDA Benefit-Risk guidance documents can be considered. When deviating from the standard or FDA guidance, consultation with the Agency via the Q-Submission process may prevent deficiencies during a submission.

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Dr. Alan Hood: Here are the resources that were mentioned earlier in the presentation, along with the full URLs that you can access after the presentation.

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Dr. Alan Hood: Continuation of resources. And this concludes our presentation. Thank you very much for your attention. I turn over this presentation to our moderator, Kendra.

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Kendra Holter: Thank you so much to Dr. Hood, Dr. Malone and Dr. Palacios for your presentations. It's greatly appreciated. I would now like to introduce an additional panelist that's going to join our presenters today to assist in addressing your previously submitted questions.

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Kendra Holter: Dr. Qin Zhang, Toxicologist in CDRH's Office of Product Evaluation and Quality or OPEQ in the Office of Health Technology number three. Thank you so much for joining us today, Dr. Zhang.

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Kendra Holter: We'll now transition to the segment of today's town hall where 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 Teresa. Teresa, the question is, does FDA believe the toxicological screening limit or TSL is suitable for constituents with sufficient chemical identification?

Dr. Teresa Palacios: Thank you very much Kendra. I would like to start by mentioning that per section 6.2.2 of Part 17, the TSL is applicable for identified constituents, by comparing the maximum total quantity of such constituent to the applicable values that represent short term for example less than or equal to 30 days or long term, for example, more than or equal to 30 day exposure. Please note that, per Section B.1 of Part 17, TSL is not applicable to harms that the TTC values are not protective in accordance with ISO/TS 21726, Clause 1.

Kendra Holter: Thank you for that Teresa. For our next question I'll direct to Alan, Alan the question is, as demonstrated in the article authored by Street et. al. 2025, tentative identifications are common and expected but do not necessarily impact the toxicological risk assessment. Can FDA describe their view on confidence levels and how the chemical characterization report should approach these identification levels for downstream toxicologist usage?

Dr. Alan Hood: That is a really good question. Tentative identity can be acceptable when the information provided is sufficient to adequately address its toxicological risk that takes into consideration the sources of the constituent, the reported quantity, how the extraction study was conducted, the reference standard used for quantification, and the applicable medical device intended use.

Kendra Holter: Thank you for that Alan. Qin, I'll come to you with our next question, the next question is, there have been previous conversations pertaining to confidence levels and the need for confidence to be either confident or confirmed, however, confidence levels do not affect the toxicological risk assessment. If conclusions can be made based on tentative confidence levels for the toxicological risk assessment, what benefit do confident or confirmed IDs provide?

Dr. Qin Zhang: Thanks for the question. In general, confident identity reduces uncertainty in the overall toxicological risk assessment. Confident identity is useful when the reported quantity of the extractable is not small and the source of the constituent is not understood. Confident identity is recommended when the constituent is suspected to be toxic. Back to you Kendra.

Kendra Holter: Thank you Qin. For our next question, I'll come back to Teresa, Teresa the question is, when applying the exceptionally potent, very high potent, and highly potent values prior to applying the toxicological screening limit or TSL, is it necessary to derive a tolerable intake, also known as the TI value, for all extractables?

Dr. Teresa Palacios: Thank you for raising this question. Briefly, deriving a TI for all extractables prior to applying the applicable TSL is not expected because not all extractables will have TI values at these low exposure levels. Subject matter experts have the knowledge to recognize constituents with TI values greater than and less than these low exposure levels.

Some examples of chemicals with TI values below these low exposure levels are included in some of the Cohort of Concern chemical categories; however, the Agency understands that not all chemicals in those categories have potency at these low exposure levels. Additionally, the Cohort of Concern chemical categories is not a definitive list of exceptionally potent, very highly potent, and highly potent chemical substances. Chemical specific points of departure values are readily available for many chemical substances, including analogues, that aid in rapid determination of a constituent's potency. Back to you Kendra.

Kendra Holter: Thank you so much. And if its ok Teresa, I'd like to ask you the next question as well, that question is, Figures 1 and 2 in ISO 10993-17:2023 version, Clause 5.1.3 indicate that a constituent specific TI is derived after a toxicological screening limit or TSL is applied; however, in Annex B.1 it indicates that TSL does not apply to cohort of concern or excluded compounds. Does the derivation of constituent specific TI in Figures 1 and 2 apply to extractables that are highly potent or otherwise excluded from use of the TSL?

Dr. Teresa Palacios: Thanks again Kendra. To respond to this question I would like to briefly explain that the two TSL values of 120 micrograms and 600 micrograms in Annex B of Part 17, are based on the short-term and long-term TTC values, which are 2.0 and 0.33 micrograms per kilogram per day, respectively. Then it is not necessary to derive a constituent specific TI before applying the TSL when high potency does not apply to such compound. For the remaining constituents, deriving the constituent specific TI before applying TSL will apply when high potency is suspected. Although high potency may be reasonably expected for many carcinogens, high potency also applies to non-cancer effects. Back to you Kendra.

Kendra Holter: Thank you again Teresa for answering both of those questions. For the next question, I'll direct that to Qin, Qin the question is, can you clarify how FDA defines highly potent toxicants for each time period shown in ISO 10993 Part 17?

Qin, I'm not able to hear you. Are you perhaps doubled muted?

Dr. Teresa Palacios: I think I will respond to that question. For this particular concern, the term highly potent is not used in ISO 10993-17. This term is explained in ISO/TS 21726, 5.1 Applicability of TTC to medical device constituents and 5.3.1 Cohort of Concern constituents. A highly potent constituent usually has a TI value below the time-period specific mutagenic TTC value. For example, in accordance with Table 1 in ISO/TS 21726, a highly potent constituent has a TI value below two micrograms per kilogram per day, which corresponds to the short-term exposure time-period for equal or less than 30 days. Back to you Kendra.

Kendra Holter: Thank you Teresa. I was going to give Qin this next question as well. We'll see if she is able to come on. So that question is, does the Agency still have concerns about compounds that have margin of safety, or MoS, values less than 10 but greater than 1.0? If so, what information is the Agency looking for in a Toxicological Risk Assessment regarding these MoS?

Dr. Qin Zhang: Yea, I hope you can hear me. Can you hear me now?

Kendra Holter: Yes, yes we can. Thank you so much.

Dr. Qin Zhang: Okay, sorry about the technical issue. Yeah, so I can answer this question. When a MoS value is greater than one and the worst-case estimated exposure dose is adequately conservative and toxicological threshold is protective, then additional information is not typically expected. When a MoS value is greater than one, FDA may request additional information if the worst-case estimated exposure dose is not adequately conservative or chemical toxicological threshold like TI or TTC is not protective and the actual MoS may be less than one, please see Part 17 for additional information. When the toxicological threshold is based on less than confirmed identity, additional chemical analysis that confirms the identity can be considered, if practical. Consultation with FDA is recommended if you are uncertain whether additional identity information could address a MoS value for a specific extractables. Back to you Kendra.

Kendra Holter: Thank you so much. We have about three more questions we'd like to get to, so we appreciate everyone staying with us as they can. Alan, I'll going to direct the next question to you, and that question is, can the Agency provide any information on tools they have made or are working on to aid in toxicological risk assessments?

Dr. Alan Hood: Thank you Kendra. The Office of Science and Engineering Laboratories in CDRH has developed a Regulatory Science Tool called TSL/EEDmax/MoS Calculator or TEEM Calculator. This is a web-based tool aligned with Part 17 that standardizes toxicological risk assessments for medical device extractables by applying TSL and EEDmax formulas from Part 17 to derive MoS values for medical device extractables.

Users of the TEEM Calculator provide the minimum information needed to calculate an MoS for medical device extractables, such as intended use, identity and quantity, and chemical toxicity information. Based on the inputs provided, the TEEM Calculator applies TSL, if instructed, the applicable TTC, and reports the time-period specific EEDmax and MoS values that apply to the medical device and its intended use. The TEEM Calculator streamlines consistent application of updated risk assessment approaches introduced in the ISO 10993-17 Second Edition Standard. Because the TEEM Calculator does not verify that the inputs into the toxicological risk assessment are valid; subject matter experts ensure that the inputs are adequate. The source of the TEEM Calculator is at cdrh-rst.fda.gov/tsleedmos-teem-calculator. Back to you Kendra.

Kendra Holter: Thank you Alan. Qin, I'm going to come back to you with this next question, the next question is, when Cramer classification is used to support a Threshold of Toxicological Concern or TTC-based toxicological risk assessment, what principles are applicable when different accepted Cramer decision tree methodologies produce different classifications for the same chemical?

Dr. Qin Zhang: Thanks Kendra. So FDA is aware of different Cramer Class decision tree tools that can result in different outcomes. This issue is addressed when expert judgement is applied, which is manually answer Cramer Class decision-tree questions. When expert judgement is not applied, the lowest non-cancer TTC value can be considered as described in TS 21726, Clause 5.2. Back to you Kendra.

Kendra Holter: Thank you again Qin. We have one final question for today and I'll direct it to you Alan. Alan, the question is, what approaches are applicable for addressing unidentified compounds or extractables that exceed analytical evaluation thresholds when compound-specific toxicological information is limited or unavailable? And if the intended user group such as infant, youth, or adults vary, are there different approaches to consider?

Dr. Alan Hood: Thank you Kendra. When unidentified extractables exceed an appropriately derived analytical reporting threshold, the minimum identity information for constituent toxicological risk assessment is chemical class information. ISO 10993-17, Figure 1, first diamond and footnote a includes how to address adequacy of the reported identity.

For an identified constituent that exceeds the analytical evaluation threshold, and a relevant compound-specific point-of-departure is unavailable, then applicable TTC can be considered based on experimental or in silico analysis information for the constituent. Clause 5.2 in ISO TS 21726 includes what to consider when selecting the TTC that applies to the constituent.

For differences in subpopulations, in general, application of the appropriate TI or TTC in micrograms per kilogram body weight per day combined with a conservatively established constituent specific worst-case estimated exposure dose and the risk estimation, risk evaluation, and risk management approaches described in the Part 17 standard can be considered adequate to address the differences in subpopulation sensitivity to chemical induced systemic toxicity, carcinogenicity, reproductive toxicity, or developmental toxicity. Back to you Kendra.

Kendra Holter: Thank you Alan. And that will conclude our previously submitted questions segment for today's town hall. 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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Kendra Holter: 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, Kendra. And thank you all for those that called into this fall's biocompatibility town hall series and today's presentation. Chemical analyses and toxicological risk assessments are important components of biocompatibility evaluations and they factor into the totality of evidence to support medical device safety. Based on the very many questions and comments we received, it is clear that these are areas of interest for our stakeholders and I hope you have found the information helpful. I'd like to again thank our presenters for today for their development of the materials for this presentation and their continued engagement on these topics. Thank you, and back you to, Kendra to close it out.

Kendra Holter: Thank you so much Misti and yes, thank you again to all our panelists for being a part of today's town hall. It's greatly appreciated.

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 the slide showing.

If you have additional questions regarding today's biocompatibility topic specifically, please feel free to email CDRH.Biocomp@fda.hhs.gov.

If you have general questions regarding today's town hall, please feel free to reach out to the Office of Industry and Consumer Education also known as OICE at AskOICE@fda.hhs.gov.

We hope you are able to join us for a future event, and you can see these 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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