Biocompatibility Town Hall #1: Risk Assessment Approaches for Addressing Biocompatibility Endpoints
September 9, 2026

Moderator: CAPT Kim Piermatteo
Presenters: Misti Malone PhD, Shuliang Li PhD, Molly Ghosh PhD and Simona Bancos PhD

Slide 1

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Slide 2

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 first of three town halls that we will be hosting on biocompatibility and medical devices. For today, we will be discussing recent updates to ISO 10993-1:2025 titled "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" and we will also share risk assessment approaches for evaluating biocompatibility endpoints for medical devices, with specific examples for evaluating material-mediated pyrogenicity and systemic endpoints.

We'll begin with a presentation from our presenters and then provide responses to some of your previously submitted questions regarding this topic. We'd like to thank you for the many questions submitted in advance of today's town hall. We have proactively addressed some of those questions in the presentation today and will also respond to more during the previously submitted question segment following the presentation.

Slide 3

CAPT Kim Piermatteo: It is my pleasure to now 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. Shuliang Li, Senior Standards Advisor in the Division of Standards and Conformity Assessment in CDRH's Office of Strategic Partnerships and Technology Innovation; Dr. Molly Ghosh, Biocompatibility Focal Point Co-Advisor in OPEQ's Office of Health Technology number five; and Dr. Simona Bancos, Biocompatibility Focal Point Co-Advisor in OPEQ's Office of Health Technology number one.

Thank you all for joining us. Before I turn it over to Dr. Li, 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 all again for joining us. I'll now turn it over to Dr. Li.

Slide 4

Dr. Shuliang Li: Thank you Kim, I'm Shuliang Li, and again I want to thank everyone for joining us today, so let's get started.

Slide 5

Dr. Shuliang Li: Today we will cover the recent updates for ISO 10993-1: 2025: Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management proce*ss* and explain the risk assessment process and approaches for evaluating biocompatibility endpoints for medical devices, with specific examples for material-mediated pyrogenicity and the systemic endpoints typically acute/subacute/chronic toxicity, genotoxicity, and carcinogenicity.

Slide 6

Dr. Shuliang Li: ISO 10993-1 was updated in 2025, and FDA partially recognized the update in May of 2026. Molly Ghosh and I are the technical contacts on this standard.

Slide 7

Dr. Shuliang Li: The primary change in the sixth edition of ISO 10993-1 standard is a realignment with risk management consistent with ISO 14971:2019, which describes risk management and risk analyses for medical devices. FDA fully recognizes ISO 14971; however, clause 6.9 biological risk estimation of the 2025 version of 10993-1 lacks specificity for implementation purposes and is not fully aligned with ISO 14971:2019. At this time, FDA does not generally request biological risk estimation per clause 6.9 of ISO 10993-1:2025 to be included in a marketing submission.

Additionally, new terminology and the concepts were added to the 2025 ISO 10993-1. For example, intermittent contact, bioaccumulation, reasonably foreseeable misuse, application biological evaluation process over device life cycle. There is ongoing technical work in multiple ad-hoc groups under ISO TC194 working group 1, including defining how to conduct risk estimation; defining bioaccumulation, intermittent contact, reasonably foreseeable misuse, and lifecycle; determination of biological equivalence; how clinical data and literature may be used to support a biological evaluation. FDA received many questions regarding these new terms and concepts. As these are currently being discussed in the working group, we won't discuss these in detail today, but we intend to share updates in the future.

Slide 8

Dr. Shuliang Li: Some of the most noteworthy revisions to the standard are summarized on this and the next slides. Device categorization was refined by adding consideration of exposure durations based on daily or intermittent contact and bioaccumulation. Additionally, the externally communicating device category is removed, and instead, devices are categorized by tissue type (intact skin, intact mucosal, breached or compromised surfaces and internal tissues other than blood, or circulating blood). Please note, the term "externally communicating device" is used in FDA's Biocompatibility guidance, so it is acceptable to continue using the term and category in marketing submissions submitted to FDA.

Slide 9

Dr. Shuliang Li: Material-mediated pyrogenicity was removed from the tables that list biological effects for each categorization, but this biological effect continues to be addressed in the standard under clause 6.5.10 "other biological effects."

Additional requirements for genotoxicity and carcinogenicity were added in the 2025 version compared to the 2018 version. We recommend referring to Attachment A and Sections VI.F and G of FDA's biocompatibility guidance which continues to reflect our current expectations for medical device submissions.

Slide 10

Dr. Shuliang Li: FDA partially recognized the 2025 update. The extent of recognition is available in our standards database, and a link is provided. The phrase “consumer product or” in clause 6.5.11.3 is not recognized as part of the 2025 update because it is in conflict with Attachment G of FDA’s biocompatibility guidance. FDA intends to follow Attachment G of the biocompatibility guidance. Clause 6.9 biological risk estimation was explained on slide 7.

The SIS also includes two notes. The first recommends contacting the appropriate CDRH review office for implementing clauses covering topics such as intermittent contact, bioaccumulation, reasonably foreseeable misuse, application throughout the medical device life cycle. The second note highlights differences in genotoxicity evaluation also mentioned on slide 9.

Slide 11

Dr. Shuliang Li: The transition period for the standard is 3 years. FDA will accept declarations of conformity, in support of premarket submissions, to the 2018 version of ISO 10993-1 until July 1, 2029. Manufacturers can make declarations of conformity to either the fifth edition or the sixth edition during the transition period.

How does this impact you? Currently, we do not plan to update the biocompatibility guidance at this time. However, we may update it and/or the SIS when new technical specifications or reports are published. FDA’s expectations for biocompatibility testing are not being increased as could be inferred by the 2025 ISO 10993-1 standard.

Next, Misti Malone will present biological risk and risk assessment.

Slide 12

Dr. Misti Malone: Thank you, Dr. Li. My name is Misti Malone, and I’m an Associate Director in the OPEQ Immediate Office supporting nonclinical evaluation and policy. Our next topic is an overview for biological risk and risk assessment followed by examples for using risk assessment in lieu of biological or chemical testing for material-mediated pyrogenicity and systemic endpoints.

Slide 13

Dr. Misti Malone: As mentioned earlier, the definition of biological risk was simplified in the 2025 version of ISO 10993-1, in which biological risk is defined as the combination of the probability of occurrence of a biological harm and the severity of that biological harm. A biological harm is a harm to health occurring as a result of adverse reactions associated with medical device or material interactions.

Based on FDA’s Biocompatibility guidance, potential biocompatibility risks can stem from material or chemical toxicity; an unacceptable biological response to physical characteristics of the device; or aspects of manufacturing and processing that could alter the physicochemical characteristics of the device that could result in unacceptable risk.

It’s important to remember that the risk of any device is non-zero, and the aim is to reduce or mitigate probable risks. The residual risk remaining after control measures have been implemented may be at acceptable or unacceptable levels, which risk assessments aim to tease out.

Slide 14

Dr. Misti Malone: Device manufacturers manage and mitigate these risks by carefully choosing and assessing the material and chemical components, the manufacturing processes, and the clinical use of the device, including consideration of the intended anatomy, the patient population, such as use in

sensitive patient populations, and the frequency and duration of exposure. The overall evaluation should be conducted in accordance with ISO 10993, ISO 14971, and FDA's Biocompatibility guidance.

Slide 15

Dr. Misti Malone: Sponsors can gather information to determine and evaluate the potential biological risks, and this evaluation may be through nonclinical or clinical testing or Information Gathering based on the device design, materials, manufacturing processes, from similar devices or from published information. Sponsors may use a combination of testing and information gathering to address biocompatibility endpoints. Today, we are focusing on Information Gathering for a risk-based assessment, and future town halls in this series will cover extractables testing and toxicological risk assessments.

Slide 16

Dr. Misti Malone: Material characterization evaluates the body's entire exposure to all chemical entities contained within or eluting from the final finished device. This includes qualitative and quantitative information on the materials and chemicals, including suppliers, additives, coating, degradation products; manufacturing residuals, including processing agents, oils, and cleaning fluids, and manufacturing process, such as, passivation, cleaning and sterilization. For example, sterilization may cause cross-linking or breakage of polymer chains, which can in turn impact the extractables and leachable profile and other engineering attributes. Sponsors may also be able to leverage existing experience, such as applicable master files, conformity to standards, and similar devices with the same or worse-case contact and duration.

Slide 17

Dr. Misti Malone: As part of a sponsor's decision-making, the level of risk and uncertainty is relevant when determining whether a risk-based assessment may be sufficient in lieu of some or all biological or chemical testing. And by risk, I'm not referring to the device risk categorization, class I, II or III devices, but to the potential hazards and risks of the chemicals, materials, and processes and the level of uncertainty around those. When the risk and uncertainty are low, a risk-based assessment may be sufficient in combination with or in lieu of testing.

Examples include when the device is made of well-known and standardized materials, such as metals that conform to an appropriate standard; polymers with an applicable master file; or experience with a very similar device or the same supplier. However, some devices are more complex or have higher uncertainty due to novel or proprietary materials in which the materials or processes may not be fully understood by the submitter or if chemicals have new or increased risk. In these cases, biological and chemical testing may be valuable to qualify or quantify chemicals to determine potential hazards to address biocompatibility endpoints.

Note that this determination may be influenced by consideration of other factors. For example, risk assessments may be adequate to support an early feasibility study for certain endpoints and depending on the potential benefits, unmet need, and the patient's susceptibility or tolerance for the specific risk, and additional information or evaluation may be expected to support expansion to a pivotal study or for a marketing submission.

Now, I'd like to introduce Molly Ghosh to share the considerations for assessing material-mediated pyrogenicity.

Slide 18

Dr. Molly Ghosh: Thank you, Misti. Good afternoon, everyone, and thank you for joining today's Town Hall. As Misti mentioned, Simona and I serve as CDRH Biocompatibility Program Advisors, and we're

glad to be here with you today. The portion of the presentation I'll be walking you through focuses on general recommendations for assessing material-mediated pyrogenicity or MMP.

Slide 19

Dr. Molly Ghosh: Let's start with a foundational question, what is a pyrogen? Simply put, a pyrogen is any substance that can induce fever. As described in FDA's Biocompatibility guidance, the main sources of pyrogens are bacterial endotoxins, and material-mediated pyrogens, chemicals that can leach from a medical device during use.

Today, we're focusing exclusively on MMP. This endpoint is recommended as part of biocompatibility assessment for most medical devices, as it is a critical assessment for patient safety of implantable devices, devices in direct or indirect contact with cardiovascular system, lymphatic system, or cerebrospinal fluid regardless of duration of contact, and devices labeled as "non-pyrogenic".

While FDA's Biocompatibility guidance allows flexibility in how MMP is evaluated, the most common approach seen in regulatory submissions is Rabbit Pyrogen Test, or RPT, conducted in accordance with US Pharmacopeia General Chapter 151. For those who are not familiar with this animal study, the RPT measures the increase in body temperature after test article administration via intravenous injections in rabbits.

Slide 20

Dr. Molly Ghosh: RPT does come with limitations which are not discussed today. However, it is worthwhile mentioning that RPT is one of the biocompatibility studies that generally uses a large number of devices. Beyond that, based on recently published peer-reviewed literature, engagement with external stakeholders, and our review experience, RPT failures are actually quite rare.

The data referenced here is from Table 5 in the Borton and Coleman's 2025 paper. This Table summarizes the low rate of RPT failure. However, I would like to clarify that citation of the table from this paper is not to be interpreted as CDRH agreement of the MMP approach proposed by the authors in this paper.

Slide 21

Dr. Molly Ghosh: As mentioned by Shuliang, ISO 10993 Part 1 2025 version includes recommendations for evaluation of MMP in one of the clauses, as reproduced on this slide. Briefly, it states that MMP should be evaluated in cases where the material is known to induce a pyrogenic response or where the potential of a pyrogenic response is not known.

Slide 22

Dr. Molly Ghosh: One of our key efforts has been to clarify MMP evaluation and to identify device categories where MMP risks are likely to be addressed through a well-supported assessment, rather than nonclinical testing. We believe this approach directly supports FDA's goal of reducing animal testing while maintaining patient safety.

Slide 23

Dr. Molly Ghosh: FDA's Biocompatibility Guidance notes that MMP testing is not needed if previous information indicate that all patient-contacting components have been adequately assessed for pyrogenicity. Based on information covered in previous slides and considering a least-burdensome approach, RPT may be most appropriate in specific circumstances. Those include devices with absorbable or degradable materials with no prior history of safe use in medical devices with similar or worst-case tissue contact, or not well characterized; devices with biologically derived materials with no

prior history of safe use in medical devices with similar or worst-case tissue contact, or not well characterized; devices with any material with no history of safe use in medical devices with similar or worst-case tissue contact; and devices labeled as non-pyrogenic.

For devices that do not fall into those categories, an MMP assessment based on material and manufacturing evaluation is likely acceptable in lieu of RPT.

Slide 24

Dr. Molly Ghosh: When describing this approach, you probably noticed terms like "history of safe use" and "well characterized." These are not new. They appear in FDA's 2023 Biocompatibility guidance**,** though not specifically in the context of MMP. In this context, history of safe use may refer to a material with no history of failed RPT testing or MMP assessment. Regarding similar tissue contact, this language is presented in the 2025 version of ISO 10993-1.

Considerations for worst-case tissue contact include whether the type, duration, and surface area of tissue contact are the same or worse than those of the leveraged device or material. Worst-case means the leveraged material was used in a more invasive or high-risk tissue category such as implant or for a longer duration than the device being evaluated**.**

Slide 25

Dr. Molly Ghosh: Over the next few slides, we will list examples of the kind of information companies might provide to demonstrate that their device material as well as manufacturing materials are well characterized.

Please keep in mind this is not a comprehensive list**.** The minimum information and justification for not conducting RPT will depend on the device type and intended use, and therefore, not all examples provided today will be relevant to every MMP assessment. Due to time constraints, we won't be walking through each slide in detail. We recommend that you refer back to these example slides to determine how to best present material characterization information for your specific device and intended use.

Slide 26

Dr. Molly Ghosh: This slide provides examples of material characterization information that may be appropriate for non-absorbable or non-degradable polymers, metals and ceramics. The type of information provided will depend on the specific materials used.

Slide 27

Dr. Molly Ghosh: This slide provides examples of material characterization information that may be appropriate for absorbable degradable materials and biologically derived materials, such as materials derived from human, animal, plant, or bacterial sources. For biologically derived materials, the sponsor may find it helpful to reference applicable recognized clauses from ISO 22442 standard series, these are the standard series on medical devices utilizing animal tissues and their derivatives, or from FDA's 2019 guidance on medical devices containing materials derived from animal sources.

Slide 28

Dr. Molly Ghosh: In addition to device material as well as manufacturing material information, detailed information about manufacturing is also typically critical for MMP assessment. This information may include details regarding the manufacturing steps, conditions, equipment, and manufacturing aids.
In some situations, companies may also be able to provide additional supporting information such as RPT testing on prior versions of the device or device components or marketing experience.

In summary, this approach focuses on material and manufacturing characterization rather than analytical chemistry testing and toxicological risk assessment because ISO 10993 Part 17 that focuses on toxicological risk assessment does not address material mediated pyrogenicity.

Slide 29

Dr. Molly Ghosh: As I mentioned, the type of minimum information provided for MMP assessment will depend on the type and duration of tissue contact, intended use, and clinical risks associated with the specific device. In the next several slides, we'll walk through hypothetical examples where MMP assessment in lieu of RPT could be acceptable. I want to emphasize that the slides include only the summary of information that would be considered for MMP assessment.

Slide 30

Dr. Molly Ghosh: Example 1 includes a device component that is a subcutaneous implant with long-term tissue contact. The component is manufactured of a common polymer, PEEK, which is a commonly used material in long-term implants. Manufacturing processes are standard for this type of device and involve a limited number of manufacturing agents, and previous information is available on one of the manufacturing aids from a repeat-dose animal study evaluating rectal temperature increases. Additionally, a detailed description of the cleaning processes would also be important to support the risk assessment.

Slide 31

Dr. Molly Ghosh: Example 2 is an orthopedic long-term implant manufactured of stainless steel and titanium alloy. The device materials conform to FDA-recognized consensus standard and have documented history of safe use. The device undergoes surface treatment and has validated final cleaning process. While this example is for a metal implant, this approach may be appropriate for other implanted devices manufactured of common materials that conform to consensus standards or have master files which may be relied upon.

Slide 32

Dr. Molly Ghosh: Example 3 is for an ophthalmic implant with prolonged tissue contact. The device is comprised of bacterial-derived sodium hyaluronate. The device is used during ophthalmic surgeries and intended to be removed at the completion of surgery. However, a small amount remains in the eye due to its specific characteristics such as viscosity. Because of the anatomical location of use of the device, it is highly unlikely for the device leachables to reach systemic circulation which is required for a fever response to be triggered.

Due to high viscosity, the test extract for RPT requires further dilution but may still have particulates which once administrated via intravenous injection can lead to embolism in rabbits. Based on all these considerations, MMP assessment in lieu of RPT would be considered appropriate for this ophthalmic device. Information important for the MMP assessment includes material characterization, such as presence of elemental impurities and residues of bacterial origin, and detailed manufacturing information describing the manufacturing steps and relevant equipment.

Slide 33

Dr. Molly Ghosh: Our final example regarding MMP assessment is for a gas pathway device that has long-term indirect tissue contact. The materials are well-characterized polymers such as polypropylene, polycarbonate, acrylonitrile-butadiene-styrene plastic, or polyethylene, and manufacturing aids made of common metals such as aluminum or stainless steel.

MMP assessment in lieu of RPT is an approach that aligns with the device-specific ISO 18562 consensus standard. In addition, based on the device's intended use, it is very unlikely that condensate that can form during the use of the device would reach systemic circulation, which as I mentioned, is a necessary condition for a fever response to occur.

Now, I would like to invite Simona to discuss the risk assessment for systemic endpoints.

Slide 34

Dr. Simona Bancos: Thank you, Molly. I am a biologist in OHT1 and also serve as the Biocompatibility Co-Advisor with Molly. I will provide an overview and examples where risk-based assessment was appropriate in lieu of biological or chemical testing to address specific biocompatibility endpoints.

Slide 35

Dr. Simona Bancos: For purposes of today's presentation, evaluation of systemic endpoints includes acute systemic toxicity, subacute/subchronic/chronic toxicity, genotoxicity, carcinogenicity, and reproductive or developmental toxicity. These endpoints may often be addressed through information gathering, biological testing such as animal study or biological assay for genotoxicity or chemical characterization and toxicological risk assessment or a combination of these approaches.

I would like to note that our discussion refers to the ISO 10993 standard series recommendations. For device-specific evaluation, we recommend that you also refer to device-specific consensus standards and applicable device-specific FDA guidance documents.

Slide 36

Dr. Simona Bancos: As mentioned earlier by Misti, the determination of whether risk-based assessment via information gathering in lieu of testing may be appropriate will depend on the probable risks and how much is known regarding the materials, chemicals, and processes. The considerations for this approach are similar to those Molly shared for MMP.

Slide 37

Dr. Simona Bancos: Listed here are a few examples where risk-based assessments may be sufficient and those where testing may be appropriate. Note that these are general examples, and additional specific considerations may apply to the device under review. Testing is typically more appropriate when there are novel, complex, or unknown chemicals and processes. For example, some additives and impurities may cause harm and may be more appropriately evaluated via chemistry testing and toxicological risk assessment.

Slide 38

Dr. Simona Bancos: To exemplify the risk-based assessment approach, I will share a few hypothetical examples for new devices and manufacturing changes in which a risk assessment may be acceptable in lieu of testing.

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Dr. Simona Bancos: The first example is for a bare metal stent and it is similar to the example Molly shared for a metallic orthopedic implant. The systemic endpoints can often be assessed via a risk assessment in lieu of biological or chemistry testing if the materials are well-characterized, for example, with conformity to consensus standards for metals such as stainless steel, cobalt chrome, nitinol and if supplementary information, as identified on the slide, is provided. For these devices, there are often

downstream manufacturing processes that reduce the risk of manufacturing residuals, such as passivation, electropolishing, and cleaning. We also consider additional testing regarding the corrosion potential or nickel leaching.

Based on the available information in this example, there are no expected toxicity, genotoxins, or carcinogens, so a risk-based assessment is likely acceptable. It's important to note that if a stent includes a coating, drug, polymeric graft material, or is made of a novel alloy or polymer, chemistry testing would likely be needed to evaluate the extractable/leachable profile which is a source of greater uncertainty.

Slide 40

Dr. Simona Bancos: A second example where risk assessment may be considered is for a PEEK orthopedic polymer implant. As noted previously, PEEK is a well-characterized material, and in this case, an applicable Master File includes information for both raw material biocompatibility assessment and manufacturing recommendations. In this example, the sponsor has access and follows the master file manufacturing recommendations. In addition, the sponsor confirms that no manufacturing chemicals are used for their device. Therefore, the biocompatibility endpoints recommended for this type of device could be addressed with no additional testing.

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Dr. Simona Bancos: For a third example, we turn to manufacturing change for an acrylic intraocular lens, which is a long-term implant. In this example, a new surfactant in the water solution and related changes to the cooling and milling temperatures are proposed. Relevant information includes the safety data sheet for the new surfactant and a detailed manufacturing description. In this case, the process includes a validated cleaning process downstream of the change. Given the available information, the biocompatibility risk of this change is low, and no new biological or chemistry testing would be requested. Note that the considerations for this change could also apply to other manufacturing aids, such as processing or cleaning aids for which sufficient information is available.

Slide 42

Dr. Simona Bancos: The last example is for a manufacturing change for a new injection molding machine and molding parameters used for manufacturing of a critical device component for an externally-contacting circulatory support device with prolonged tissue contact. In this example, the device materials and downstream processes, including a pre-drying process, are not changing. Due to differences in the injection molding machine parameters, it is important to include a detailed comparison of the parameters and a discussion on whether the change impacts the polymer. For example, information demonstrating that the polymer in its molten state is thermally stable at both the current and proposed processing temperatures. Based on the similarity in parameters and performance of the device components manufactured using the new injection molding machine the changes are unlikely to impact the biocompatibility of the marketed device, so the risk assessment is acceptable in lieu of new biocompatibility testing.

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Dr. Simona Bancos: And now I would like to provide the concluding remarks.

Slide 44

Dr. Simona Bancos: Biological risk assessment using material and manufacturing information may be used for addressing MMP and systemic endpoints. CDRH continues to engage on standards, working groups, and with stakeholders on risk-based approaches to support biocompatibility evaluation of medical devices. Focal Point Program includes representatives from each office and is dedicated to supporting

review consistency. For device-specific recommendations please refer to applicable device-specific consensus standard or guidance document. For specific proposed approaches please consider using the Q-Submission program.

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Dr. Simona Bancos: This concludes the presentation section of the Town Hall meeting today. We hope you are able to join us on September 23 and October 7 when we will discuss chemical characterization-extraction recommendations and toxicological risk assessment, respectively.

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Dr. Simona Bancos: Here are the resources mentioned in the presentation, along with the full URLs that you can access after the presentation.

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CAPT Kim Piermatteo: Thank you Dr. Bancos, as well as thank you Dr. Li, Dr. Malone, and Dr. Ghosh for your presentations on medical devices and biocompatibility.

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CAPT Kim Piermatteo: We'll now transition to the segment of today's town hall where we address your previously submitted questions about this topic. I'll read a question aloud and then ask one of our presenters to provide a response.

For our first question, I'll direct that to Shuliang, Shuliang the question is, ISO 10993-1:2025 requires genotoxicity as a biological effect to be evaluated for all prolonged or long-term contact devices with all tissues except intact skin, while Attachment A in the FDA Biocompatibility guidance does not list genotoxicity as a biological effect for devices having prolonged contact with intact mucosal membrane, breached or compromised surfaces, or for external communicating devices with prolonged indirect blood path contact.

The question is, will FDA require genotoxicity testing for all prolonged contact device categories, except intact skin, per ISO 10993-1:2025?

Dr. Shuliang Li: Thank you for highlighting the differences in the genotoxicity evaluation recommendations between the 2025 version of ISO 10993-1 and Attachment A of FDA's Biocompatibility guidance. FDA will continue to follow our existing Biocompatibility guidance, and for device-specific input, you may contact the respective office for clarification whether the additional genotoxicity testing would be relevant for consideration. Consistent with our biocompatibility guidance, FDA would generally not recommend genotoxicity evaluation for devices having prolonged contact with intact mucosal membranes, breached or compromised surfaces, or for externally communicating devices with prolonged indirect blood path contact.

However, genotoxicity evaluation may be recommended for these types of devices if the devices are made of materials that have not been previously used in a U.S. legally marketed device with same or worst case type and the duration of contact.

CAPT Kim Piermatteo: Thank you Shuliang. Molly, I'll direct the next question to you, that question is, tables 1–4 of ISO 10993-1:2025 do not include material-mediated pyrogenicity, whereas Table A.1 of the FDA guidance titled, Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing within a Risk Management Process does. For FDA submissions,

can submitters follow ISO 10993-1:2025 when it differs from the FDA guidance, such as for material-mediated pyrogenicity?

Dr. Molly Ghosh: Thank you for your question. It should be noted that while material-mediated pyrogenicity or MMP evaluation was removed from Tables 1 through 4 of ISO 10993-1:2025 version, the evaluation of this biological effect is addressed under “Other biological effects” in clause 6.5.10.5 of ISO 10993-1:2025 version. For evaluation of MMP, we recommend sponsors follow ISO 10993-1:2025 version and FDA’s Biocompatibility guidance along with the information provided in today’s presentation on a risk-based approach for MMP assessment.

CAPT Kim Piermatteo: Thank you Molly. For our next question I’ll direct that to Simona. Simona the question is, is FDA planning to apply the new concepts of intermittent contact as described in ISO 10993-1:2025 sub-clause 6.4.3.2 and bioaccumulation as described in ISO 10993-1:2025 sub-clause 6.4.3.3 to breathing gas pathway devices whose development is guided via ISO 18562:2024 but refer to ISO 10993 for biocompatibility?

Dr. Simona Bancos: Thank you for your question. The exposure categorization framework of ISO 10993-Part 1:2025 version also applies to gas pathway devices, and the worst-case clinically relevant use scenario should govern the categorization decision. The total exposure period is calculated by summing up all contact days from first to last use on a single patient, regardless of daily use duration. Where a device type can reasonably be used across a range of clinical scenarios, sponsors should apply the worst-case use when categorizing the device. This concept is consistent with FDA's Biocompatibility guidance for determining device contact categories that is limited, prolonged, or long-term.

For bioaccumulation, the potential for constituent accumulation should be affirmatively addressed for all exposure duration categories. While gas pathway materials commonly used in manufacturing do not typically present bioaccumulation concerns, the biological evaluation plan should document this determination explicitly.

CAPT Kim Piermatteo: Thank you Simona. Shuliang, I’d like to come back to you for this next question, which is, for ISO 10993-1:2025 version clause 3.34 defines reasonably foreseeable misuse as "use of a medical device in a way not intended by the manufacturer, but which can result from readily predictable human behavior." Given that the relevant technical specifications are not yet available, can FDA provide examples of reasonably foreseeable misuse scenarios and describe how they were, or should be, addressed in the context of biocompatibility evaluation?

Dr. Shuliang Li: Thank you for the question. We would like to clarify that application of this definition of “reasonably foreseeable misuse” does not automatically lead to more biocompatibility testing and foreseeable misuse may be addressed by approaches such as updating labeling or communications within a risk management approach. For example, a few years ago FDA became aware of pharmacies using insulin syringes for certain intraocular drugs which, in some cases, lead to transfer of silicone oil from syringe coatings to the patient’s eye. The manufacturer of the syringes sent a letter to their customers informing them of this risk and modified their labeling to include a Caution in their Instructions for Use regarding such use. Since the risk was mitigated via labeling and public communication, FDA did not ask for additional testing to mitigate the identified risk.

Another example comes from FDA’s evaluation of neurological devices. While not intended, some neurological devices may have high potential for contacting CSF/brain tissue raising neurotoxicity risks due to surgical procedure and/or anatomical location of implantation. In such cases, FDA’s approach has been to request additional information regarding neurotoxicity risks associated with potential CSF/brain tissue contact, rather than necessarily requiring additional testing.

CAPT Kim Piermatteo: Thank you Shuliang. Alright Misti, I'd like to ask you this next question. The question is, FDA's partial recognition of ISO 10993-1:2025 version, indicates that FDA will accept declarations of conformity to ISO 10993-1:2018 version through July 1, 2029. Given the differences between the two versions and the ambiguity in some terms, like intermittent contact, bioaccumulation, and reasonable foreseeable misuse, does FDA plan to update the 2023 Biocompatibility guidance and is there planned approach to help ensure consistency and predictability regarding this issue and the framework for risk assessment shared today?

Dr. Misti Malone: Thank you Kim for the question. So FDA's 2023 Biocompatibility Guidance remains existing policy and appropriate for implementation. We've also provided training to CDRH staff on the 2025 version of ISO 10993 Part 1 and the biocompatibility approach is discussed in today's presentation. Additionally, we utilized the biocompatibility focal point program, which includes representatives across CDRH that will continue to support review consistency, align technical approaches, and share scientific expertise across these various areas. FDA will also consider whether additional internal training and external resources, such as CDRH Learn modules would further support transparency and consistent biocompatibility evaluation approaches.

CAPT Kim Piermatteo: Thanks Misti. We have a few more questions I'd like for us to cover today, so the next question I'll direct to Molly. Molly, the question is, many devices undergo large animal GLP testing. Which biocompatibility endpoints can be leveraged from a large animal study? A follow-up question to that is, would FDA accept GLP large animal studies to address other biocompatibility endpoints such as local tissue effects, hemocompatibility, irritation, genotoxicity, or systemic toxicity?

Dr. Molly Ghosh: Thank you for the question. As discussed in FDA's 2023 Biocompatibility guidance, in Section III, C.3., we support the principles of 3R, which are replace, reduce and/or refine animal use in testing when feasible, and we support proposals where biocompatibility assessments are considered in the same animal study.

Separate assessment for local tissue effects or implantation, in vivo thrombogenicity, and systemic toxicity may not be needed if these endpoints were incorporated in the in vivo animal study. However, the acceptability of this approach is predicated upon the acceptability of the study design including but not limited to animal model, controls, sample size, duration of the study, and study endpoints. For example, if the large animal study also proposes to evaluate chronic toxicity, then in addition to the large animal study observations, the study would include additional assessments including, but may not be limited, to hematology and clinical chemistry measurements and histopathology of relevant tissues and organs.

Regarding genotoxicity, we do not believe that this assessment can be conducted in a large animal study. As discussed in our FDA's 2023 Biocompatibility guidance, Section VI, F, genotoxicity testing may not be needed if chemical characterization of device extracts and literature references indicate that all components have been adequately evaluated for genotoxicity. Genotoxicity testing is generally requested when genotoxicity is not addressed in a toxicological risk assessment and/or when genotoxicity profile has not been established such as when the materials have not been previously used in a U.S. marketed medical device. As described in our guidance, when genotoxicity testing is requested, we typically recommend two in vitro tests. An optional third in vivo test should be considered for devices that contain novel materials and the quantities of the materials in a test extract following exhaustive extraction of the device are above the threshold of detection of the in vivo assay.

Now regarding irritation, leveraging information from a large animal study in lieu of irritation, may be acceptable in some cases. We recommend that you consult with the respective office in cases where you intended to follow this approach.

CAPT Kim Piermatteo: Thanks Molly, I have another follow-up to that question on animal studies, the question is, can chemical characterization and TRA be accepted in lieu of genotoxicity testing and systemic toxicity animal studies?

Dr. Molly Ghosh: Thanks for the follow-up question. In some cases, in lieu of biological testing, an analytical chemical characterization on the final, finished, sterilized device per ISO 10993 Part 18 and a toxicological risk assessment per ISO 10993 Part 17 and ISO/TS 21726 can be used for systemic toxicity and genotoxicity. However, FDA may request additional assessments, including biocompatibility testing, or toxicity testing of a chemical of concern for devices made from novel materials never used before in a legally marketed medical device with similar intended use, devices with known toxicities, devices made of degradable or absorbable materials, or when unexpected findings in biocompatibility testing were reported. Similar to our prior response regarding genotoxicity assessment, genotoxicity testing is generally requested when the genotoxic profile has not been established such as when the materials have not been previously used in a U.S. marketed medical device with the same type and duration of tissue contact.

CAPT Kim Piermatteo: Thanks Molly, that is great information for our audience. For our last question today, I'd like to direct that to Simona. Simona, the question is, is a risk-based approach acceptable for addressing changes to device materials due to supply-chain constraints? For example, in cases where a replacement material has the same intended function and chemical identity as the currently approved material, and meets the current specification, but may differ in aspects not fully captured by the material specification such as the manufacturing process, impurity profile, or trace constituents.

Dr. Simona Bancos: Thank you Kim for the question. As discussed today, a risk-based approach is acceptable for addressing specific biocompatibility endpoints. We also provided examples of information that may be used for material characterization. Also as highlighted today, the type of information provided will depend on several considerations such as the type of material, intended use, type and duration of contact. This topic was also discussed during the CDRH webinar held last year on December 10 regarding material changes in 510(k) submissions. Presentation materials from the December 10 webinar are available on the FDA public website under Medical Devices News and Events. In addition, for material changes that are due to supply chain shortages we also recommend that you refer to the FDA guidance titled, Notifying FDA of a Premarket Discontinuance or Interruption in Manufacturing of a Device under Section 506J of the Food, Drug & Cosmetic Act.

CAPT Kim Piermatteo: Thank you Simona. That will conclude our previously submitted questions segment of today's town hall. Thank you all again 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 to provide some closing remarks. Misti…

Dr. Misti Malone: Thank you, Kim. I'd first like to express my appreciation for CDRH's biocompatibility focal points and the working groups that developed this material engaged on the standards update. The goal of this effort has been to clarify regulatory expectations for biocompatibility evaluations in consideration of benefit-risk principles and least burdensome approaches. And lastly, I'd like to thank all of our attendees for the interest in this topic and the questions we received and we hope you will join us in the next town hall in the series. Thank you.

CAPT Kim Piermatteo: Thanks Misti and thanks again to all our presenters for being a part of today's town hall.

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 email CDRH.Biocomp@fda.hhs.gov.

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

And just as a reminder, our next town hall in this series is scheduled for Wednesday, September 23rd, 2026. We hope you all are able to join us again. And 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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