A Safer, Clearer, and Faster Course to Market

Insights and Guidance for the Medical Technology Industry on the Role of Standards with Biocompatibility, Risk Management, and Sterility

A Report on...

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AAMI

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A Safer, Clearer, and Faster Course to Market

INSIGHTS AND GUIDANCE FOR THE MEDICAL TECHNOLOGY INDUSTRY ON THE ROLE OF STANDARDS WITH BIOCOMPATIBILITY, RISK MANAGEMENT, AND STERILITY

A Report on $S^3$ Challenge 2014

Carol Herman
Senior Vice President,
Standards Policy and Programs
AAMI

Deborah Reuter
Senior Vice President, Education
AAMI

Scott Colburn
Commander, U.S. Public Health Service
Director, CDRH Standards Program
Office of the Center Director
Center for Devices and Radiological Health
U.S. Food and Drug Administration

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Pushing the Envelope

"We’re trying to have standards be different than they were 20 years ago. We’re trying to push the envelope. We have to think about their value.”
—Scott Colburn, Director of Standards, FDA Center for Devices and Radiological Health (CDRH)

Changing the direction of an annual event can be a challenge, both for the organizers and faithful attendees. When creating the S³ Challenge, AAMI and the U.S. Food and Drug Administration (FDA) wanted to take a more global view of the use of standards. By emphasizing key areas of interest—biocompatibility, sterility, and risk management—and how they apply to certain medical devices, focused discussions could take place on the challenges of interpreting standards and regulatory expectations. At the end of the two-day conference, all parties in attendance achieved clarity and alignment on the use of standards and regulatory compliance as they related to the topics discussed, which ultimately will improve patient safety and could help decrease time to market.

A number of other changes also contributed to the valuable discussions. The seating, shorter presentations, expanded time for audience engagement, and polling to gauge the pulse of attendees led to more enriching discussions. In addition, the participation of more than 20 FDA representatives provided industry participants a unique opportunity to ask their questions and share their challenges. These FDA representatives were approachable and open, providing a powerful experience for all in attendance.

For CDRH, the S³ Challenge encouraged active listening and seeking out the ideas of others, and it created an environment in which the agency could explain its decisions and requests for information in a collaborative fashion. The venue allowed the agency to promote the use of existing resources and identify areas in which new ones may be needed. In support of the center’s strategic priority to provide excellent customer service, meetings such as the S³ Challenge enable face-to-face interactions with key stakeholders. The ability to have open discussions with the FDA and stakeholders across the medical device sector is an invaluable asset to achieving the many objectives of the event.

Promoting, protecting, and advancing public health is at the heart of all our work. The ability for all stakeholders to fulfill that vision depends on how we reach decisions, take actions, and collaborate to achieve consensus on critical public health topics such as those discussed at the S³ Challenge 2014.

AAMI and the FDA will soon start planning the S³ Challenge 2015. We conducted a poll during this year’s conference on possible topics of interest, and we extend the invitation for your feedback. Let us know what topics you would like to see covered. And, don’t miss next year’s conference, where you can collaborate on finding solutions to the challenges facing the healthcare technology industry—including the need for greater synthesis in the development, application, and interactions of medical device standards—to improve the safety of medical technology and reduce the time it takes to bring new devices to market!

Finally, we would like to extend our appreciation to Martha Vockley of VockleyLang for authoring this report. Additional thanks to Kristin Blair and Joe Sheffer from AAMI for their work in publishing this report.

Sincerely,

Carol Herman
Senior Vice President,
Standards Policy and Programs
AAMI

Deborah Reuter
Senior Vice President,
Education
AAMI

Scott Colburn
Commander, U.S. Public Health Service
Director, CDRH Standards Program
Office of the Center Director
Center for Devices and Radiological Health
U.S. Food and Drug Administration

“We’re trying to have standards be different than they were 20 years ago. We’re trying to push the envelope. We have to think about their value.”
—Scott Colburn, Director of Standards, FDA Center for Devices and Radiological Health (CDRH)
Getting sophisticated medical technology to market poses ever more challenges to industry and regulators. Those challenges range from developing standards and guidance to the approval or clearance process, from the complex science behind products to the procurement of acceptable materials, and from the rigorous identification of possible hazards to the comprehensive mitigation of risks.

Both industry and the U.S. Food and Drug Administration (FDA) want to navigate a safer, clearer, and faster course to market. Clarifying standards and streamlining the regulatory process is in everyone’s best interest—as long as patient safety is the cornerstone of every action to move medical devices into the field.

To that end, industry and FDA experts came together in March 2014 in Herndon, VA, for the two-day AAMI/FDA S³ Challenge 2014, the first gathering of its kind. More than 100 industry and FDA experts participated in the event, which featured all-hands-on-deck, roll-up-your-sleeves sessions and a spirit of collaboration. The key takeaways from the S³ Challenge are as follows:

Industry has a powerful new forum to shape the regulatory path to market. The AAMI/FDA S³ Challenge gave the medical technology industry the floor for extended dialogue with the FDA. The forum proved to be an engaging opportunity to:

- Understand how the FDA uses standards and to identify gaps in standards covering biocompatibility, risk management, and sterility
- Articulate specific needs for synthesis in the development, application, and interactions of standards and guidance
- Learn about and contribute to solutions to improve the safety of medical technology and reduce the time it takes to bring new devices to market

The FDA wants to engage. The FDA offered unprecedented access and frank discussions with its leaders, scientists, and reviewers of submissions for approval to market medical devices. More than 20 FDA staff members actively participated in this forum—making presentations, answering questions, offering advice, and revealing their thinking about the approval process. (Note: For ease of reading, the term “approval process” is used in this report to refer to all FDA marketing review processes.) The FDA emphasized that it is shifting to “a new paradigm”—collaborating with industry and providing better customer service—to improve patient safety and device effectiveness and expedite the approval process.

To that end, the S³ Challenge brought together industry representatives who are on the front line in the medical device approval process—including executives, scientists, risk managers, and regulatory affairs specialists—and FDA experts who review their submissions for medical device approval. What follows is a
Given the variability and innovations in medical technology, and the lag in standards to address new issues, the FDA is looking to medical device manufacturers to develop and justify their own strategies for managing risk and ensuring safety as well.

Summary of insights and guidance that will be valuable for the entire medical device industry.

Throughout the forum, interactive polling questions gauged participants’ priorities and reactions in real time, allowing everyone to see at a glance the issues that resonate the most in the field.

The forum offered practical pointers for “telling the story” about managing risk in FDA submissions. As the FDA builds on its operational model of ensuring regulatory compliance by also promoting state-of-the-art practices, the agency made clear that it wants industry to make logical, scientific arguments—with claims, evidence, and reasoning—about patient safety.

Standards, guidance, and other tools and resources, such as safety assurance cases, can support this effort. Given the variability and innovations in medical technology, and the lag in standards to address new issues, the FDA is looking to medical device manufacturers to develop and justify their own strategies for managing risk and ensuring safety as well.

The forum took a deep dive into three of the hottest industry challenges—and explored new ideas for demonstrating patient safety and device effectiveness. Expert presenters and participants zeroed in on three broad industry challenges—biocompatibility, risk management, and sterility. Similar challenges emerged for all three topics, including:

- Understanding how to apply inconsistent standards to meet safety requirements, gaps in standards and guidance, and changing regulatory expectations
- Supply chain management
- Postmarket practices, including increasing use of medical devices in nonclinical settings

Forum participants synthesized these issues as they apply to two widely used devices, endoscopes and catheters. Participants had the chance to “work the challenges” and share new ideas, with key takeaways to consider for ensuring safety from cross-functional, multidisciplinary perspectives.
Biocompatibility

“The Biocompatibility Landscape
The first session of the S3 Challenge opened with brief presentations by an industry expert and an FDA expert to set the stage for discussion about biocompatibility evaluations of medical devices, a format used for all four sessions of the forum.

Edward Reverdy, director of corporate toxicology and biocompatibility services at Boston Scientific Corporation, began with the key question that biocompatibility evaluations must answer: “Are the device materials interacting with a patient going to work safely, as intended and as designed, without causing risk or hazard?” Patient safety must be the overarching consideration that drives biocompatibility evaluations.

In addition to standards and guidance, scientists and risk managers have a portfolio of tools at their disposal for safety assessments of biocompatibility, Reverdy said, including:

- Biological assessment
- Clinical safety assessment
- Toxicological risk assessment
- Risk management tools
  - Risk analysis
  - Failure mode and effects analysis (FMEA)
  - Hazard analysis
  - Use-based risk assessment

The starting point for determining which of these tools to use to demonstrate safety is to map patient exposure to chemical materials

What Is Biocompatibility?
The ability of a material to perform with an appropriate host response in a specific application
ISO/TC 194 N 730

Standards and Guidance

- ISO 10993-1:2009
  - Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
  - Parts 2–18—topic-specific standards for biocompatibility evaluation of hazard types (e.g., cytotoxicity, systemic toxicity)


- FDA G95-1, Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices

- Regions with specific requirements
  - China
  - Japan
  - Korea
in devices—in terms of the type of direct or indirect (fluid path) contact the patient will experience and the duration of that contact—to the potential risk(s) associated with that exposure, Reverdy said. Contact types and durations are classified as follows:

**Contact type**
- Surface (e.g., a wound dressing)
- Externally communicating (e.g., a diagnostic catheter)
- Implant (e.g., a hip implant)

**Duration**
- Limited (less than 24 hours)
- Prolonged (between one and 30 days)
- Permanent (more than 30 days)

In addition, devices may have several classifications, based on intended use, and different components with different classifications, such as a stent delivery system versus a stent implant.

By considering patient exposure first, scientists then can prioritize the tests required for biological evaluation, with more tests for devices with the most patient exposure and, potentially, risk, Reverdy said. Evaluators can leverage knowledge of equivalent devices or materials, using safety data from literature-based evaluations of known materials as part of their chemical characterization of materials. These data can be used to justify whether and why particular tests are performed in the FDA submission.

“You don’t want to analyze the heck out of your materials,” Reverdy said. “You want to have a plan. If you don’t understand the materials in your component, you don’t want to go blindly into an animal study.” He shared

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**Figure 1.** Boston Scientific Decision Tree for ISO 10993-1:2009

a decision tree (Figure 1) that Boston Scientific uses to develop biocompatibility evaluation plans, specifically for ISO 10993-1, which lays out biocompatibility from a risk management perspective.

The FDA’s Ron Brown, a toxicologist in the Division of Biology, Office of Science and Engineering Laboratories at the Center for Devices and Radiological Health (CDRH), echoed Reverdy’s recommendation to leverage existing data, plus standards and guidance, for the biological evaluation of devices.

The FDA paradigm for biological evaluations is changing and evolving rapidly, Brown said. The FDA-recognized ISO 10993-1 standard “is really our roadmap for how to do a biological evaluation of a device,” he said. Invasive devices such as implants are evaluated more carefully than devices that involve less patient exposure.

The FDA’s draft guidance for biocompatibility, released in 2013, interprets and clarifies how the FDA is using the standard and addresses common testing issues, “hopefully to get devices to market more quickly,” Brown said. “We don’t want this to be used as a mindless checklist. We want you to consider it carefully.” By that he means that companies need to explain their rationale for the tests they perform—or don’t. When final, this FDA guidance will supersede Blue Book Memorandum G95-1.

### Biocompatibility Questions, Answers, and Solutions

Following the opening presentations, industry and FDA representatives engaged in an open exchange on specific challenges with biocompatibility standards and the review process. Highlights of the hot topics follow, and they synthesize the discussion among multiple people and representatives of different organizations.

#### Key Points

- Have a plan for testing biocompatibility
- Don’t overanalyze materials—prioritize testing based on patient exposure and risk
- Leverage existing data on equivalent devices and materials, plus standards and guidance—don’t reinvent the wheel
- Tell an evidence-based story about patient safety

### SOURCING AND CHARACTERIZING MATERIALS: A GROWING CONCERN

Several industry participants raised issues around medical device materials and components, which these days are procured all over the world. They want to know whether they need to recharacterize and revalidate materials if they change suppliers, for example.

“If your supply chain is international, you have to be very careful,” Reverdy said. “For metals, we generally look at a supplier we’re familiar with that meets a known standard.” He recounted a case of a stainless steel that turned out to be a “mystery metal,” despite procurement specifications. “For polymers,” he said, “the issues are always, what are the additives and what are the processing aids?”

Known suppliers can procure materials from second- and third-tier suppliers, making their origins and specifications harder to trace. Materials certified as “medical grade” are not necessarily different from the same materials without that label. Industry cannot blindly rely on vendors; chemists and toxicologists need to evaluate the risk of new materials.

The FDA advised that quality management systems and supply chain management are critical. The agency has seen changes in materials that affected device performance or sterility processes. That, of course, means that the materials and devices may not be substantially equivalent to predicate materials and devices.
Q. Variation exists between U.S. and international standards, and the FDA has very specific exclusions to international standards. How does the FDA recognize standards?

A. At a high level, the FDA does try to recognize the broadest part of standards. When we have disagreements, we try to make sure those are science based. When we have an opportunity to comment on the standard, we try to very clearly articulate when something is not scientifically defensible.

In the words of one participant, regional standards don’t really exist anymore. It’s a global marketplace. That makes it challenging to develop standards at the global level that meet everybody’s needs. The FDA is trying to figure out what the deviations to international standards need to be.

- **Key Takeaways:** Consider addressing gaps in standards with guidance or technical information reports (TIRs) on specific biocompatibility challenges identified at the forum, including evaluating combination products (e.g., drug/device or biologic/device systems or products packaged together); extractable and leachable studies, toxicity tests, hemocompatibility tests, in vitro and in vivo tests, and stress testing; and testing endpoints. Testing procedures listed in standards could be called out and elaborated as separate standards or annexes to standards.

Q. How does the FDA use recognized standards?

A. Standards are very important, but standards are only one tool. The FDA wrote the draft guidance document for ISO 10993-1. The standard is a starting point. You can do different tests using different techniques. You can use other standards, which are searchable by category in the FDA database. Each standard has a supplemental information sheet with relevant guidance and information on how much of the standard the FDA recognizes.

Just because the FDA does not recognize a standard does not mean it cannot be used. For example, the FDA does not recognize ISO 10993-1 Part 17, which provides one way to handle testing of mixtures (leachables), or Part 18, which covers chemical characterization of materials. But the general approach in Part 17 is acceptable. The FDA is working very hard to get recognition of Parts 17 and 18.

CDRH believes conformance with recognized consensus standards can provide reasonable assurance of safety, effectiveness, or both. Conformance to standards and guidance is voluntary, however. The FDA does not regulate the development or use of standards. It regulates medical devices.

If you are claiming certification of conformance to a standard, however, simply stating this may not be enough. You may have to submit data if specific devices raise safety or effectiveness issues that are not addressed in the standard.

- **Key Takeaways:** Consider developing training to help industry determine whether to claim conformance to a standard or standards—and what to do when no relevant or recognized standards exist. Consider creating an FAQ forum for questions about ISO 10993, which could be used to identify needs for and develop new standards and guidance.

Q. The types of questions we get from FDA reviewers regarding biocompatibility are inconsistent and widely divergent. What is the agency doing to train new staff in the use of standards and articulate consistent policies?

A. The FDA does have a lot of new staff, and with that comes new challenges. New staff members are trained in the standards process, the use of voluntary consensus standards, and device-specific standards. Normally, each new reviewer has a one-on-one mentor. The FDA does have a review checklist, and the FDA goal is for newer reviewers to ask for help internally first before asking questions to submitters. The agency works with AAMI and has staff in the AAMI University program.

Biocompatibility is a challenging area, given the vast diversity of materials and devices.
Because standards don’t necessarily get into granularity, there are gaps. In addition, as science advances and knowledge accumulates, the FDA review practice advances to address new science. By their nature, voluntary consensus standards and guidance documents are developed after the science advances. This contributes to the gaps and perceived inconsistency and variability in how information is reviewed.

- **Key Takeaways:** The FDA encouraged industry to use the presubmission process\(^1\) as an opportunity to ask questions of the FDA about their biocompatibility evaluation plan during product development, preferably before making a submission for marketing a device. FDA technical information experts can help to explain the FDA’s interpretation of relevant standards.

When reviewers have questions about submissions for device approval or clearance, the FDA encouraged industry representatives to pick up the phone and talk to the reviewer directly to clarify points and expedite the review process. Some companies do that already. “We regularly call up and ask questions,” one participant said. “It’s better to ask up front. The reviewers will work with you, help you reduce your risk, and make the process go smoother.”

Other participants expressed reluctance to contact the FDA, stating that they fear retribution or introduction of new issues that could impede the review process. Both the FDA and industry representatives who are comfortable contacting the FDA urged those who hesitate to make that call to put aside their fears. The FDA can offer valuable advice for managing risk and validating device safety—which is everyone’s top concern.

> “You’re putting yourself at an economic risk if you don’t call us,” said the FDA’s Erin Keith, acting director in the Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices, CDRH Office of Evaluation. “Your competitors call us all the time.”

Both the FDA and **industry representatives** who are comfortable contacting the FDA urged those who hesitate to make that call to **put aside their fears.**

The FDA can offer valuable **advice** for managing **risk** and validating **device safety**—which is everyone’s top concern.

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Risk Management

“We’re using safety assurance cases and finding them beneficial. A safety assurance case adds some formality to our thought process: What are the claims we want to make and, if we are going to make claims, what kinds of evidence, testing, or animal studies do we need to support the claims? A safety assurance case lays out the whole story, supports the planning process, and can be used as a communications tool about our goals and what everyone on that product team needs to do support the goals. It convinces regulators that a product deserves to be on the market.”

—Patricia Kranz, Standards Manager, Cardiac Rhythm Disease Management, Medtronic

What Is Risk Management?

When conducting a risk analysis, manufacturers are expected to identify:
• The possible hazards associated with the design in both the normal and fault conditions.
• The risks associated with the hazards, including those resulting from user [use] error, which should then be calculated in both the normal and fault conditions.

When conducting a risk analysis manufacturers are expected to consider:
• If any risk is judged unacceptable, it should be reduced to acceptable levels by the appropriate means, for example, by redesign or warnings.
• An important part of risk analysis is ensuring that changes made to eliminate or minimize hazards do not introduce new hazards.

Source: Code of Federal Regulations (CFR) 21 Part 820 Quality System Regulation, Preamble Comment 83

Standards and Guidance
• ISO 14971:2010, Medical devices – Application of risk management to medical devices
• ISO/TR 24971, Medical devices – Guidance on the application of ISO 14971
• CFR 21 Part 820 Quality System Regulation
The Risk Management Landscape
Keith, of the FDA, led off the session on risk management by summarizing how the agency’s definition of risk management, standards, and guidance are used in the medical device approval process. “Risk management comes together in design controls and the product development process designed to ensure that the device design is consistent and reliable,” she said. “Risk analysis should be completed by the time you complete design validation.” All of the assumptions used to create your risk management processes are indirectly assessed by CDRH when CDRH assesses the relative safety and effectiveness of your device under these programs:

- Premarket approval (PMA) for Class III devices, the most stringent classification, which can require full risk management documentation, including human factors testing (when applicable)
- Premarket notification traditional/abbreviated 510(k) and special 510(k) for devices that are substantially equivalent to predicate devices. The special 510(k) requires an abbreviated analysis of design changes and risk mitigation processes.
- De novo for novel, low- to moderate-risk devices, which establishes an original, valid predicate and includes a risk analysis for the device
 “We look at the output of your risk management system,” Keith said. “If it does not effectively take into consideration the risks, you need to address those risks that were not included. This can come in the form of a request for additional information. Or if it is really incomplete, your device may not be be found substantially equivalent and approved for marketing in a 510(k) submission.”

Infusion pump submissions are getting special attention at the FDA and from industry via an infusion pump pilot program. ISO/IEC 15026-2 specifies minimum requirements for the structure and content of a safety assurance case, which includes:

- A top-level claim (or set of claims) for a property of a system or product.
- Systematic argumentation regarding this claim.
- The evidence and explicit assumptions that underlie this argumentation.

“Safety assurance cases explain why the device is safe and effective,” Keith said. “It’s not just the technical pieces, but a logical argument to identify hazards, the system the device creates, and how those are evaluated.” Safety assurance cases can support safety, reliability, maintainability, human factors, operability, and security, according to the ISO/IEC standard.

In addition, AAMI is developing a TIR that will provide guidance on safety assurance cases for infusion devices, plus standards on general requirements for infusion devices.

Consultant Stan Mastrangelo gauged forum participants’ perspectives on risk management with a series of provocative questions, as shown in the sidebar below. These questions could be useful to companies in scrutinizing and improving their risk management processes and their use of ISO 14971 and other risk management tools.

Notably, a series of interactive polling questions revealed that, while some participants have had training in the use of ISO 14971, many have not had formal training in risk management. Almost none said they had taken an AAMI or AdvaMed (Advanced Medical Technology Association) training course in risk management.

Risk Management Questions, Answers, and Solutions

Q. Would the FDA consider recognizing the 2012 version of ISO 14971 (EN ISO 14971:2012, the European harmonized standard)?
A. It’s not typical for the FDA to recognize an EN standard. The difference in the European standard is the annexes on Medical Device Directives, which are important to exporters to Europe, but not to others. If there is a standard you feel would be appropriate for FDA recognition, there is a process for that.
Guiding Questions for Companies to Consider to Evaluate and Improve Their Risk Management Processes

Stan Mastrangelo
Consultant

Risk Evaluations
• When assigning values to the probability of occurrence of harm during risk estimations, do you use a quantitative or qualitative approach? In either case, how do you support the probability of occurrence values chosen?
• When assigning values to severity of harms during risk estimations, how do you support the severities chosen? Do you use a quantitative or qualitative approach?

Risk Assessment
• How do you use risk management tools to support your position that your device is sufficiently safe and effective to be on the market?
• At what point in the design and development process do you begin implementing risk management processes?
• Do you use system-level and component-level hazards analyses processes?

Human Factors Questions
• How does your risk management program address risks associated with:
  - Systems interfaces in your device?
  - Device/user interfaces?

Risk Acceptability Criteria
• Have you established risk acceptability criteria for products in development? For products on the market? How were the criteria established?
• Do your risk acceptability criteria have two levels—one for acceptable and one for unacceptable? Does your company use three levels? Is the third level called ALARP (“as low as reasonably practicable”)?

Risk Control
• When you determine that a risk control measure is required, how do you justify the risk control measure’s ability to adequately reduce risk? Do you have a formal system for recording such determinations and justifications?
• How do you evaluate risks arising from risk control measures themselves? Are these new risks evaluated within the same documentation as the harms originating from the device prior to the specific risk control?

Risk/Benefit Questions
If you do use the risk/benefit analysis section of ISO 14971:
• Do you perform a comparison of expected medical benefits of the intended use to residual risk for each harm that poses residual risk, or do you perform this analysis with the aggregate residual risk from the total system?
• Do you consider alternative treatments and systems within analysis of risk/benefit to the patient, or is the analysis isolated to benefit of the proposed device?

Production and Postproduction
• What triggers you to reevaluate the risk for a product? Is reevaluation time based, event based, or both? How have you addressed legacy products that are still on the market for ongoing risk?

Miscellaneous Questions
• Do you use a multifunctional team to evaluate risk? Does the team include medical professionals? Engineers? Marketing?
• Implementation of risk control measures and reevaluation of the corresponding risk occurs throughout the design of system. In addition, the adequacy of risk estimations and risk control measures may change after receipt of new information during the course of system development. Is this historical progression captured within risk management documentation and, if so, how is it captured?
• If you use ISO 14971, how do you assess the acceptability of the overall residual risk within the device, as required by Section 7?
• Do you have a formal Organizational Risk Management Process? Do you use ISO 31000? Are you familiar with ISO 31000?

Final Questions
• Is ISO 14971 too strict or too lenient?
• If you are using ISO 14971, do you believe that if you comply with the standard you will also meet the risk analysis expectations of the Quality System Regulation (21 CFR 820)? Why or why not?
Company representatives expressed concern about key differences between the international and European versions of 14971, including:

- ISO 14971 requires risk to be reduced as low as reasonably practicable; the EN version calls for risk to be reduced as far as possible.
- ISO 14971 equates labels with warnings and cautions to the user with risk reduction; the EN version says labels notify the user of risks, but do not mitigate risk.
- ISO 14971 does not require risk-to-benefit analysis for acceptable residual risks; the EN version requires this analysis for all residual risk—but not for each risk individually.
- ISO 14971 requires the benefit from the risk-to-benefit analysis to be greater than the overall risk; the EN version requires the benefit to be greater than the individual and overall risk.

**Key Takeaways:** Consider addressing the Medical Device Directives in the EN standard that are a key topic of interest to companies. Consider the role of risk-to-benefit analysis—some companies find that line-item risk analysis for every risk identified in the FMEA is a robust way of mitigating risks, while others think this requirement would be burdensome. Some companies conduct a risk-to-benefit analysis but never submit this information to the FDA because it is not required.

Consider addressing other identified gaps in ISO 14971, including risk control measures—alarm signals—that specify how long a user has to act to prevent an identified hazard based on the potential of that hazard to cause harm. Related to this issue is specifying the long-term effects in terms of probability and severity of risk to the user.

**Q.** It sounds like safety assurance cases are useful for infusion devices. Does the FDA plan to do more?

A. The FDA is not considering adding a broad requirement for safety assurance cases. The FDA would consider developing more safety assurance cases for other, more complicated medical devices, where it may be able to assist in developing safer devices.

**Q.** It seems like the process of developing a safety assurance case is complicated and produces a lot of paper. We’re hesitant to add another layer that will build complexity. We’re also concerned that risk management and a safety assurance case will overlap.

A. Clearly we have hit a nerve with safety assurance cases. With risk management, you provide a summary of your evaluation activities. A safety assurance case is different philosophically. Think of safety assurance cases as a roadmap on how to assess your device and residual risk. It should be a guide. It should be a level of simplicity, not a level of complexity.

The FDA has received 20 to 30 assurance cases so far for infusion pumps. One FDA reviewer said that if a safety assurance case were available, it would be the first document read. Safety assurance cases are valuable and helpful to reviewers in understanding why a company has determined its device is substantially equivalent in safety and effectiveness and is ready to go to market.

**Key Takeaways:** Consider developing safety assurance cases for more devices and guidance for writing safety assurance cases and for addressing residual risk. Take advantage of AAMI’s new course on developing safety assurance cases for infusion devices.

Think of safety assurance cases as a *roadmap* on how to assess your device and residual risk. It should be a *guide*. It should be a level of *simplicity*, not a level of *complexity*. 
Q. Risk management for devices is a very clear process. We have no real guidance for products that are a combination of devices and drugs.
A. Both the FDA and AAMI have technical working groups developing guidance and TIRs, respectively, for combination products.

Q. In other standards, the definition of harm has been modified to bring in the topics of security and usability. Is that under consideration with the revision of ISO 14971?
A. The revision of ISO 14971 is scheduled for 2015. By the time the standard is revised, we’ll be on the second version of the usability standard. Usability applies to all devices; ISO 14971 could reference usability standards. Usability is part of good risk management. Risk management also could include quality management, security, privacy, and environmental risks.

- **Key Takeaway.** Get involved with standards development organizations in the early stages of standards development or revision—when it is possible to have the most impact in shaping the rationale, topics, direction, and language of standards. Early involvement in standards development also gives companies a heads-up of new standards and changes in the works.

Q. Who should sit at the table to plan and implement risk management activities?
A. The ideal is that it’s everybody you can think of. The reality is that it’s the same three people in a small company—the engineer responsible for design and manufacturing and the quality and regulatory experts. In some companies, it’s standard practice to include writers of technical and user manuals. One company requires an independent expert who has no ties to the product to be at the table as well.

The FDA strongly encouraged companies to bring together a broad group, including clinicians, human factors experts, and end users, and make risk management a collaborative process. The more people at the table, the harder the risk analysis, resulting in a safer device. When companies provide their risk analysis in a submission, it would help the FDA to understand how it was developed if they included a brief description of the risk analysis team used to develop it.

- **Key Takeaways:** Consider broadening the risk management team. Consider documenting the risk management process and the decisions made.

“One lesson learned from other domains, not health domains, is that systems designers would produce the function and performance of a product, and then they would add the security, safety, and usability analysis. Those other analytic steps were separate. What they are doing now is starting to look at all those elements as system attributes that need to have an integrated aspect running through the system, not separate thought processes as entities unto themselves.”

— John Thomas, Past President, International Council on Systems, Engineering (INCOSE)
Sterility

“The bottom line is that when you put a product on the market, it has to be sterile. The patient expects it to be sterile. If it’s not, the consequences are not going to be good.”
—Gerry McDonnell, Vice President, Clinical and Scientific Affairs, STERIS Corporation

What Is Sterility?
Sterility is defined as the state of being free from viable organisms. However, in practice, no such absolute statement regarding the absence of microorganisms can be proven.

What Is Sterilization?
Sterilization is a validated process used to render a product free from viable microorganisms. In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Standards and Guidance
• **Common format**—ISO 14937:2000, Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices (Revised 2009)
• **Consistent definitions**—based on ISO TS 11139:2005 – Terminology
• **Common quality management system elements**—based ISO 13485:2003, Medical Devices – Quality management systems – Requirements for regulatory purposes
• ISO 11135 – Sterilization of health care products – Ethylene oxide
• ISO 11137 – Sterilization of health care products, Radiation
• AAMI/ANSI ST 67, Sterilization of health care products – requirements and guidance for selecting a sterility assurance level (SAL) for products labeled “sterile”
• EN 556, Sterilization of medical devices – Requirements for medical devices to be designated “sterile”
  - Part 1: Requirements for terminally sterilized medical devices
  - Part 2: Requirements for aseptically processed medical devices
• Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA, 2002
The Sterility Landscape

Johnson & Johnson’s Eamonn Hoxey, vice president, market quality, Medical Devices & Diagnostics, grounded the session on sterility in the Spaulding classification of medical devices. These three recognized categories determine the degree of disinfection or sterilization required to mitigate the risks arising from microbiological contamination:

1. **Critical.** A device that normally enters sterile tissue or the vascular system through which blood flows should be sterile. Such devices should be sterilized, which is defined as the destruction of all microbial life.

2. **Semicritical.** A device that comes into contact with intact mucus membranes and does not ordinarily penetrate sterile tissue. These devices should be sterilized. If sterilization is not possible, a secondary option is high-level disinfection, which is defined as the destruction of all vegetative organisms, mycobacterium, small or nonlipid viruses, medium or lipid viruses, fungal spores, and some bacterial spores.

3. **Noncritical.** A device that does not ordinarily touch the patient or touches only intact skin. These devices should be cleaned by low-level disinfection.

Hoxey focused on two key sterility terms that are similar, but slightly different:

1. **Terminal sterilization.** Sterility Assurance Level (SAL) probability of a single viable microorganism present on an item after sterilization, which is determined by extrapolation of microbial inactivation from a measurable range.

2. **Aseptic processing.** Probability that a nonsterile unit has one or more viable microorganisms present, which is determined by process simulation. The goal is to obtain zero contaminated units, with acceptance criteria determined based on limits of detection and sensitivity of test methods.

“With terminal processing, we’re predicting the probability of survival based on a measurable zone,” Hoxey said. “There is no prediction involved in aseptic processing. Some people say the criteria for aseptic processing is less stringent. I don’t believe that. They’re just different. Acceptable criteria for aseptic processing are what we can actually do. We’re measuring things differently and we need to be careful with the terms.

“As always,” he added, “it’s very difficult to prove a negative. We can’t make that absolute statement. There is always a possibility that a microorganism will survive, so the probability can never mathematically be reduced to zero.” He provided the comparison in Table 1 to make that point.

The regulatory landscape is complex, Hoxey said, with a wide range of standards covering many applications and aspects of sterilization, as shown in the bulleted list below and in Table 2.

### Applications of Sterilization Standards

- Defining required assurance of sterility
- Defining sterilization conditions to be applied
- Defining and executing validation
- Defining routine controls
- Maintaining process effectiveness
- Selecting sterilization equipment and accessories
- Operating sterilizing equipment
- Compiling technical dossiers, files, and submissions

Interactive audience polling revealed that forum participants predominantly use ethylene oxide terminal sterilization methods, and most use the mathematical number

<table>
<thead>
<tr>
<th>Frequency of Nonsterile Units</th>
<th>Average Number of Microorganisms Present*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 10</td>
<td>1.04</td>
</tr>
<tr>
<td>1 in 100</td>
<td>1.005</td>
</tr>
<tr>
<td>1 in 1000</td>
<td>1.0007</td>
</tr>
<tr>
<td>1 in 1,000,000</td>
<td>1.0002</td>
</tr>
</tbody>
</table>

*Based on most probable number calculation and assumption of even distribution of microorganisms.

of $10^{-6}$ as their sterility assurance level.

The FDA’s Patrick Weixel, postmarket team leader, CDRH Office of In Vitro Diagnostics and Radiological Health, focused on the FDA’s use of and involvement with sterility and other standards. The FDA finds that its involvement in developing standards is beneficial, because the agency can help shape (minimum) requirements based on industry best practices, understand the rationale behind standards, and help define and harmonize terminology. The majority of device manufacturers state conformance to an FDA-recognized standard, which can limit the data needed in premarket notifications and expedite the review process. The FDA also uses standards in training courses for CDRH premarket reviewers and FDA investigators who conduct field audits to ensure compliance.

Weixel addressed a common question, “What type of information is required for sterilization in a 510(k) and a PMA?,” as shown in Table 3.

For PMAs, the type of data needed in a PMA submission is more robust for devices that are considered critical (i.e., life sustaining or life supporting). The FDA website includes reviewer templates and guidance for 510(k)s as well as PMAs.

Weixel tied the standards discussion to postmarket application as well. When a device manufacturer states conformance to a standard, the FDA will verify the firm is complying with the standard during an FDA audit. “If you state conformance to a stand-

The FDA recently reviewed **134 inspections** from 2012 in which the sterilization processes **ethylene oxide, radiation, and moist heat** were audited. The review found that **process validation deficiencies** were the **most** frequent quality system requirement cited as an inspectional observation.
moist heat were audited. The review found that process validation deficiencies were the most frequent quality system requirement cited as an inspectional observation. If a manufacturer states compliance to a standard for validation, but the validated cycle parameters are not being used in the field, that is a “significant concern,” Weixel said.

**Sterility Questions, Answers, And Solutions**

**Q. For new 510(k) submissions, are we supposed to describe our validation methods, but not the results of validation?**

A. Yes. The FDA guidance document, which in effect updated K-90-1, tells you what data we want and what we don’t want.

**Q. What if an FDA reviewer asks for validation reports, which has happened?**

A. The reviewer should be clear about the reason for that. There might be something the reviewer knows about that product. We do occasionally ask to see data if a red flag is present. Have a discussion with the FDA management chain otherwise.

**Q. Should biocompatibility evaluation be done before or after devices are sterilized?**

A. If the sterilization method can affect the biocompatibility results by leaving residues or making changes to the materials in the device, then biocompatibility evaluation needs to be completed on sterilized devices.

**Q. What is required for labeling devices pyrogen free?**

A. The FDA is working on draft guidance to address this issue.
For the final S3 Challenge session, industry and FDA representatives focused on managing risk with two widely used devices: catheters and endoscopes. At issue: What role can standards play in biocompatibility, risk management, and sterility challenges? What gaps in standards should be addressed? How can the knowledge and best practices from industry and regulators be applied to the medical device approval and clearance processes now?

Key Issues with Catheters
Two speakers decided to forgo their presentations and model the type of dialogue between manufacturers and regulators that the FDA is encouraging. Amy Honey, regulatory affairs specialist at Bard Access Systems, Inc., a manufacturer of vascular access catheters, had a conversation with Mary E. Brooks, Commander, U.S. Public Health Service, and nurse consultant at CDRH. Excerpts from the exchange follow:

Honey: I understand that we need to submit a premarket approval when there’s a platform change—a new intended use or a new intended need. In 1993, Bard started out with power injectable catheters, an innovative device, and made simple changes. Now we’re moving more to combination devices. Where I start is what Mary looks for in a submission.

Brooks: I mainly review drug delivery devices such as intravascular infusion catheters, ports, and injectors. When I receive a submission, I start my analysis by reviewing Form 3514, the CDRH Premarket Review Cover Sheet, Section D1. I ask myself: “Why is the company submitting this submission? What are the changes in the device? Are they expanding their product line? New materials? Correcting a device problem?” The majority of responses from manufacturers check the box stating that it’s a new device, when in fact it’s not; it’s a modified device. A few companies will document exactly why they are submitting the submission, which is extremely helpful because it’s not always obvious in the submission or cover letter. Recently I had a 510(k) for a device modification. The company wanted to explain how it had addressed MDRs (medical device reports), and they wanted their materials and sterilization to be identical. As a reviewer, I will look at predicate submissions for risk assessments, the global product life cycle,
recalls, and MDRs. For biocompatibility, if your claiming it’s identical to your own predicate, we will cross-reference the predicate and subject submission. We also will specifically look to see if the biocompatibility test articles are well defined in the testing protocols of the predicate submission.

**Honey:** The guidance documents on what’s expected in a traditional or special 510(k) very clearly state what is required. Mary is bringing up things what would be helpful in her review. As an industry, we have this information, but we don’t always include it.

**Brooks:** Risk assessment is required for a special 510(k), not a traditional 510(k). If the submission is just six months after the previous one, I’m wondering what went wrong. I’m looking at adverse events. They might not be there yet, but if you add that and explain it, that could expedite the process.

**Honey:** We recently submitted a 510(k) on an existing device. I was asked for new information on the device. Should I always include that?

**Brooks:** We know how to pull up data specific to the manufacturer and specific to the model to see how the device is operating. If you mark the new device with the same specs, I’m going to look into that. It helps to have information about the device.

**Honey:** Specific to catheters, we do need line extensions and iterations of devices. ISO 10555-1:2013 (General requirements – Sterile and single-use catheters) includes power injections, but the ISO standard is different than what we have traditionally used. How is that going to affect our tests?

**Brooks:** The FDA does have a draft guidance document for ISO 10555-1. The FDA is working on recognition of standards for injection tests (ISO 11070:1998, *Sterile and single-use intravascular introducers,* currently being revised, and ISO 23908:2011, *Sharps injury protection – requirements and test methods – sharps protection feature for single-use hypodermic needles, introducers for catheters and needles used for blood sampling*).

Honey also noted that Bard Access Systems is developing a device–drug combination product with antithrombotic or antimicrobial planes. The company’s development team is looking for more guidance and standards on how to apply drug specifications and standards to a combination product. The team also has questions about managing potential biocompatibility risks from leachables and extractables from catheter coatings and about changes in catheter trenches, introducers, guidewires, and needles. “Sometimes the products don’t fit with the standards,” Honey said.

As with many devices, catheter innovations are outpacing adjustments to standards. Brooks advised the company to contact the FDA before submitting its 510(k) for help developing its testing protocol.

**Key Issues with Endoscopes**

James W. Collins, practice manager, Cleveland Clinic Foundation, summarized well-documented issues with endoscopes—workhorses in the healthcare industry. An estimated 35 million diagnostic and therapeutic endoscopies are performed annually, Collins said.

The risk of infection transmission to patients from improperly cleaned, disinfected, or sterilized endoscopes is a top

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**Definitions**

- **Reusable medical device:** A device intended for repeated use either on the same or different patients, with appropriate cleaning and other reprocessing between uses.

- **Reprocessing:** Validated processes used to render a medical device that has been previously used or contaminated fit for subsequent single use on another patient. These processes are designed to remove soil and contaminants by cleaning to inactivate microorganisms by disinfection or sterilization.
concern for regulatory agencies, industry, and professional organizations. The number of reported infections is relatively small, Collins said, and perhaps underreported and unrecognized. The ones that make the headlines are alarming. In 2013, for example, more than 200 patients may have been exposed to a “superbug” that is highly resistant to antibiotics after undergoing medical procedures using duodenoscopes at a hospital outside of Chicago.

Collins located the breakdowns in reprocessing as follows:

- **Cleaning.** Users take numerous shortcuts to save time.
- **Disinfection.** This is the stage of reprocessing where the majority of breaches occur because recommended procedures are not followed or monitored.
- **Rinsing and drying.** Poor ventilation and drying can result in wet instruments, which can harbor organisms.
- **Storage.** Crowded storage facilities can result in cross-contamination if devices or components come into contact, and users do not always wear gloves when they retrieve endoscopes for use.

Industry and healthcare delivery organizations face a “quagmire” in managing risks associated with endoscope reprocessing in the field, Collins said, due to conflicting standards and guidance. The Multi-Society Guideline for Reprocessing Flexible Gastrointestinal Endoscopes, based on 34 evidence-backed procedures, is endorsed by 11 organizations. Not all organizations agree on the guidelines. Other players include:

- Federal regulatory agencies: the FDA, the Centers for Disease Control and Prevention, and the Occupational Safety and Health Administration
- Voluntary regulatory agencies: The Joint Commission and the Accreditation Association for Ambulatory Health Care
- Professional associations, including the Association of periOperative Registered Nurses, Association for Professionals in Infection Control and Epidemiology, and Society of Gastroenterology Nurses and Associates

AAMI’s Endoscope Reprocessing Working Group and other organizations are addressing reprocessing issues by developing standards and TIRs as well.

“Part of the battle we fight is that we need to come together and agree,” Collins said. “We look at the validation that the FDA has awarded to an endoscope reprocessor where we don’t see that a professional organization has endorsed it. Which reprocessor should we choose? Strong consensus would make our accreditation easier.”

The FDA’s Shani Haugen, a microbiologist with the CDRH Office of Device Evaluation Division of Reproductive, Gastro-Renal, and Urologic Devices, focused on the regulatory expectations for reprocessing in device approval submissions. Manufacturers are responsible for:

- Labeling devices with reprocessing instructions for use.
- Validation testing of cleaning and high-level disinfection and/or sterilization validation.

In 2011, the FDA issued Processing/ Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling. When final, this document will supersede Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities—a 1996 guidance document.

The FDA has no recognized standards specific to flexible endoscope reprocessing and testing. “This is an area where standards development is really needed,” Haugen said. However, standards providing relevant guidance are available:

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**Do-It-Yourself Disinfection**

Hospitals seem to be getting the message about the danger of infection from improperly cleaned or reprocessed devices. Their efforts to prevent infection are creating new worries, however. Manufacturers and regulators are seeing overprocessing and overcleaning of devices—to a point that hazards, such as fires, can result. Users are wiping or spraying devices with chemicals that can harm the electronics or mechanics of devices. Essentially, they are using disinfectants that are not labeled for use on medical devices. Manufacturers need to validate disinfectants to ensure that they are safe and effective if they are packaged with the devices.
Labeling
- AAMI / ANSI ST81:2004/(R)2010, Sterilization of medical devices – information to be provided by the manufacturer for the processing of resterilizable medical devices
- AAMI TIR 12:2010, Designing, testing and labeling reusable medical devices for reprocessing in health care facilities: A guide for device manufacturers

Testing
- AAMI TIR 30:2011, A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices

Reprocessing Validation Testing
- AAMI TIR30 provides a review of published literature on cleaning tests. It does not specify methods or acceptance criteria. A statement that “reprocessing validation was conducted in conformance to AAMI TIR30” does not provide a meaningful description of the reprocessing validation, Haugen said.

She offered these challenges and questions to consider when developing a needed standard for endoscope reprocessing and cleaning validation testing:

Endoscope Reprocessing
- Although endoscopes are ubiquitous, there are relatively few flexible endoscope manufacturers. Does sufficient interest exist to develop standards specific to flexible endoscope reprocessing labeling and testing?
- Endoscope reprocessing instructions are complicated. How do you write instructions that minimize user error?
- Reprocessing instructions vary among manufacturers. How do you standardize testing and still account for that variability in the instructions?
- Views differ on how to conduct cleaning validation tests. How do you reach consensus on the many variables in a cleaning validation test (e.g., test soil, inoculation method, analyses)? How can reprocessing validation testing better simulate clinical use?

Endoscope Cleaning Validation Testing
- What acceptance criteria should be used? If using 6.4 μg/cm² protein, what does that mean? What surface area should you use?
- What acceptance criterion is relevant from the patient perspective?
- What amount of soil prevents high-level disinfection/sterilization?

Synthesizing Standards, Regulations, And Practices for Managing Risk
Forum presenters and participants offered these suggestions to overcome the challenges of an inconsistent standards and regulatory landscape. Many of these ideas apply horizontally to biocompatibility, risk management, and sterility, and vertically to catheters, endoscopes, and other devices:
- Get involved with standards-setting organizations and create a process for following standards development
- Harmonize regulatory, accreditation, and international expectations
- Consider developing standards and guidance that address safety testing, usability, and human factors challenges and expectations for devices intended for use with subpopulations, such as pediatric patients, and for devices used in homes and other nonclinical settings
- Consider updating the Spaulding classification of medical devices to make it clearer and more relevant to today’s medical technology
- Develop usable instructions for use (IFUs) and educate users on the importance of following IFUs
- Establish an industry consortium to address common challenges with standards and the regulatory process and to promote best practices
- Develop innovative validation processes for biocompatibility, risk management, and sterility, which could become best practices and inform standards
- Create a new business line of simulated environments, such as operating rooms or sterile processing facilities, where users could be trained in proper practices

Reprocessing Summit Report
Medical device reprocessing was the topic of an AAMI/FDA Summit in 2011. The summit publication is available at www.aami.org/meetings/summits/reprocessing/Materials/2011_Reprocessing_Summit_publication.pdf.
Conclusion

The aim of the inaugural S³ Challenge was to foster more open and collaborative working relationships between the medical device industry and the FDA and create a safer, clearer, and faster course to market.

Participants overwhelmingly agreed that the focused sessions on biocompatibility, risk management, and sterility—and the synthesis and pointed discussions on key challenges—would be beneficial to them and to their companies:
- 85% agreed that they would be able to use what they learned to improve policies, processes, and procedures in their own workplace
- 81% agreed that the level of their experience was a good match with the level of discussion
- 72% agreed that they had obtained answers to the questions that they brought to the event

Company representatives had unprecedented access to FDA leaders, scientists, and reviewers—and ample time for thoughtful conversations on uncertainties and thorny issues they’re encountering right now. The FDA had the chance to hear about and offer advice on complex difficulties that are bubbling up in the field.

Being there in person delivered another benefit: the chance to weigh in on the agenda for next year’s S³ Challenge. After the final interactive poll, the topics of greatest interest are as follows:
1. Medical device directives
2. Human factors and usability
3. The revision of ISO 13485:2003, Medical Devices – Quality management systems – Requirements for regulatory purposes
4. Amendments and collaterals to IEC 60601-1, Medical electrical equipment – Part 1: General requirements for basic safety and essential performance

Other potential topics suggested:
- Small-bore connectors
- The FDA Case for Quality, an initiative to foster medical device quality
- Testing methodologies for extractables, leachables, and combination products
- Changes to ISO 10993-4:2002, Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood
- Packaging

The forum brought to light emerging issues that need greater clarity in guidance, standards, and evaluation tools. The FDA is eager to continue to engage and help improve the path to market. AAMI was attuned to the needs expressed by attendees, as described in the key takeaways of the report, and is committed to keeping key issues in the spotlight and on the table of standards-setting organizations and professional associations. The inaugural S³ Challenge was a potent forum for generating ideas and stimulating collaboration. Next year, in addition to lively sessions on hot topics, expect to hear updates and see progress on this year’s to-do list.

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