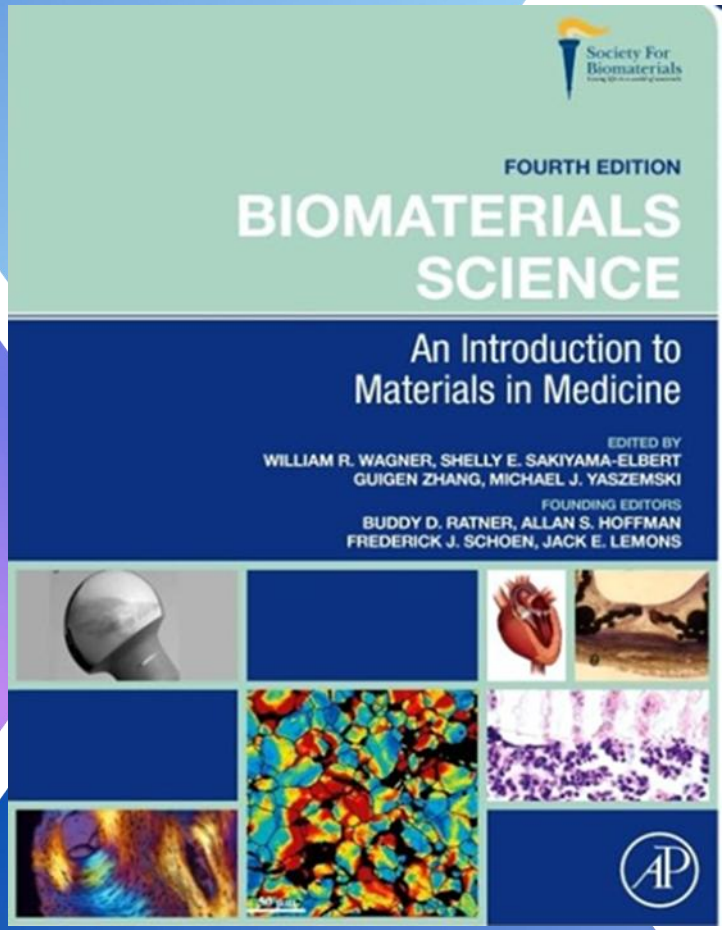


Lifecycle Management and Safety

A Comprehensive Review of Total Product Lifecycle and Risk Considerations for Biomaterials

Based on the work of Elaine Duncan, Paladin Medical, Inc., and the University of Kentucky Department of Biomedical Engineering.

Part 1: Total Product Lifecycle for Biomaterials

Exploring the journey of a medical material from conception to obsolescence and the evolving challenges in managing its safety and performance.

Obsolescence is the fourth phase in a biomaterial’s life cycle, after the phases of launch, growth and maturation comes the phase of decline, exit from market, outdated and no longer used.

Defining the Total Product Lifecycle (TPLC)

Total product lifecycle management refers to the philosophy that **biomaterial has a natural cycle from its initial concept through its eventual obsolescence**.

The management of the product's safety and performance is fundamentally dependent upon its current phase within this cycle.

The TPLC: A Personal Perspective

For a biomaterial, the TPLC means that the ***management of risks and performance controls will vary throughout the product's lifetime***.

Since implanted devices must interface with the patient's own lifecycle processes, the TPLC can become critically important and deeply personal.

The Human Element

When a biomaterial lifecycle interfaces with one's own life or that of a loved one, the concerns are no longer abstract. This personal connection underscores the significance of understanding the total product lifecycle.

Conventional Lifecycle vs. Implant Lifecycle

Conventional Product Lifecycle

This is the period over which a product moves through development, commercialization, and eventual market removal.

Biomaterial Implant Lifecycle

This necessarily includes the in vivo lifecycle: from implantation and integration with the host environment, to eventual disintegration or failure.

The Gap in End-of-Life Design

Quality systems for medical devices account for postmarket surveillance, such as monitoring complaints and reporting adverse events. However, in most circumstances, a product's approval or clearance process does not mandate that design criteria consider the implant's end stage.

- Few, if any, biomaterials are specifically designed to incorporate a "fail-safe" mode at the end of life.
- Patients are often not fully informed or prepared for the consequences of biomaterials failure and potential removal.

A Victim of Success: Shifting Expectations

Ironically, the success of biomaterial and medical device technology has allowed the focus to shift from "will it work?" to "how long will it work?"

Implicit design-life expectations for many implants have extended from a nominal 10 years to the entire remaining life of the patient.

Patient Expectations vs. Biological Reality

A patient may accept that their natural hip wears out over time, but they often expect a prosthetic replacement to last forever. This expectation frequently exceeds the performance of the natural organ or structure being replaced.

The Core Question for Biomaterial Design

Can a biomaterial-based device be designed to perform indefinitely within the body? *If not, can its failure mode be designed to limit further damage, allowing for a successful subsequent replacement?*

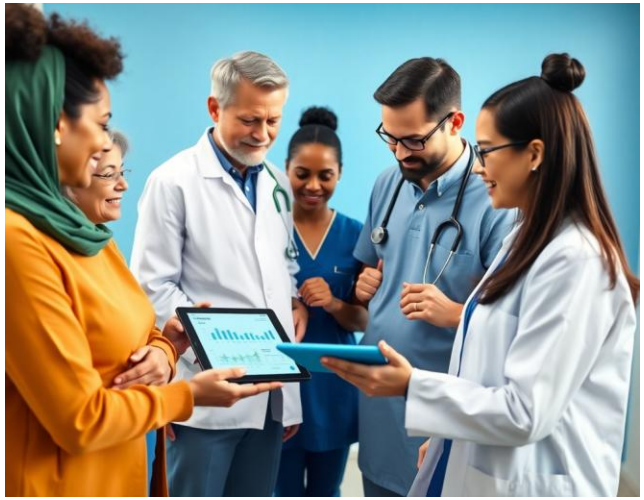
Predicting Performance: Conventional Methods

Conventional bench testing can often predict one or more failure modes and even extrapolate an expected lifetime using standardized test data, such as fatigue cycles and load stresses.

Limitations of Bench Testing

These methods are primarily designed for conventional biomaterials that replace structures. They are ill-equipped to analyze the mechanical performance of a biomaterial intended to integrate in the living tissues with or be absorbed by the body.

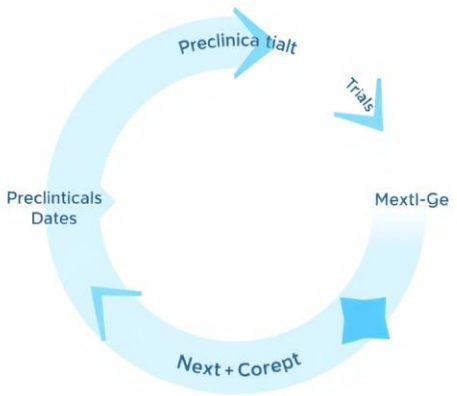
Predicting Performance: Clinical Trials



Clinical device trials are intended to provide the best indicator of device success under controlled circumstances.

Regulators are increasingly insisting upon longer trial follow-ups and the use of device registries to monitor long-term consequences.

The Iterative Nature of Device Development



According to the FDA- US Food and Drug Administration, medical device development is an iterative process.

It is designed to rapidly incorporate preclinical, clinical, and manufacturing experience into the concept and design of the next generation of devices.

Limitations of Predictive Efforts

All attempts to predict and mitigate device failures have serious limitations as predictors of total product lifecycle performance.

- Clinical studies evaluate an idealized device in an idealized patient.
- Market-released devices are placed in patients with pre-existing conditions and confounding health factors.
- A 2- or 5-year follow-up has practical limitations as a long-term predictor.

Practical Challenges of Long-Term Trials

Beyond the high costs of such trials, long-term patient compliance cannot be enforced. Diagnostics for asymptomatic implants have limited value, particularly for biomaterials designed for tissue integration.

The Impossibility of Perpetual Follow-Up

Since most implants are expected to perform indefinitely, managing the TPLC through a controlled trial is problematic.

A clinical trial patient would need to be perpetually indentured to the manufacturer to serve as a sentinel for lifecycle issues.

The Role and Limits of Registries

Rolling a clinical trial patient into a postoperative database or registry has limited value for ongoing surveillance.

Why Registries Fall Short

- Data are usually "self-reported," leading to potential inaccuracies and biases.
- Lack of active, controlled monitoring means valuable lifecycle data is often missed.

Design Controls: Starting with the User Need

Quality programs for design control and review begin with a deep understanding of the "user need." For biomaterial-based devices, this includes both the physician and the patient.

Learning from the Past

Defining needs in the context of how current devices succeed or fail leads to better designs.

For a TPLC perspective, designers must analyze explanted and failed devices to appreciate requirements for long-term performance.

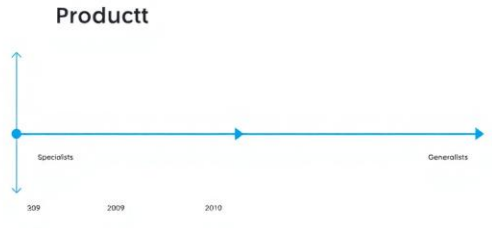
A Critical Design Question

Is it adequate to design a device to have enough strength or flexibility only at the time of implantation, if over time the material weakens or stiffens within the body and thus fails to function?

The Need for Transparency

If such changes in material properties over time cannot be avoided, should the recipient be explicitly warned of a finite life for the device?

The Challenge of Shifting User Profiles



An often-overlooked aspect of TPLC management is the inevitable shift in the skills of the dominant user as a product matures.

From Early Adopters to Mainstream Use

Development Phase

Inputs typically come from highly specialized physicians who are comfortable with new technology and guide the development.

Early Market Phase

Manufacturers naturally sell to these "early adopters," and the product can show immediate success in this controlled environment.

Market Maturity Phase

Success drives demand from more patients and a wider range of physicians, whose skills and patient populations may differ from the initial clinical trial.

The Curse of Success

As a device becomes more successful, the user profile can change dramatically. Instead of a well-trained, dedicated specialist, subsequent users may be physicians who are too busy for extensive training and have a broader patient base with needs unlike those in the focused clinical trial.

A Question for the Design Team

How can the design team anticipate these changing user needs as a product moves from a niche innovation to a mainstream solution?

Benefit-Risk Balance and Market Surveillance

Medical devices can never be totally risk-free. When a device is offered to the market, regulators expect to see evidence that the benefits outweigh the risks. This balance must be maintained throughout the product's lifecycle.

Continuous Monitoring

Continued market surveillance and corrective and preventive action (CAPA) programs are used to constantly attempt to maintain this balance as the device moves from introduction to market maturity.

Global Market Considerations

Another factor in TPLC management is understanding the potential effects as a product moves into different global markets. Factors that can impact product performance include:

- Variations in surgery techniques.
- Challenges of long-range distribution and supply chain integrity.
- Differences in post-implant aftercare protocols and patient access.

Regulatory Expectations: Clinical Evaluation

The expectation, particularly in the European regulatory scheme (e.g., MDR 2017/745), is that the manufacturer will conduct periodic clinical evaluation assessments. These assessments compare the performance of their own device(s) to prevailing market trends.

The Goal

The focus is to ensure the device continues to offer benefits that outweigh the risks, especially in the context of new or alternative therapies.

Challenges in Data Collection and Analysis

This presents a kaleidoscope of changing expectations and assessment methods. Various countries and organizations may collect patient outcome data in registries, but the rules for collecting and retrieving this information vary widely.

- Rules for data collection vary for nearly each registry.
- Methods of data retrieval can differ significantly.
- Access to "private" databases often requires payment.

The Problem of Data Homogenization

Attempting to gather and analyze data from disparate sources to reliably indicate when a device is not keeping up with the "state of the art" has a tendency to homogenize the information to the lowest common denominator.

A Paradoxical Outcome

Although established for noble purposes, can registries truly provide the balanced and qualified data needed for manufacturers to determine if their products remain state of the art?

The Erosion of Adverse Event Reporting Systems

Until recently, manufacturers and regulators could trust professionally managed adverse event reporting systems, like the US FDA's MAUDE database, to signal changes in device risk.

Current Challenges to Data Integrity

The system's utility is compromised when plaintiff attorneys make reports in "batches" without clinically relevant information, or when hospitals withhold critical information due to privacy concerns, making investigation nearly impossible.

Barriers to Failure Analysis

Effective postmarket surveillance is further hindered when failed devices are not returned to the manufacturer.

- Devices are often sequestered for legal reasons instead of being returned for examination.
- Without the physical device, no failure mode analysis can occur.
- Corporate complaint systems are thus limited, as they depend on the voluntary reporting and cooperation of institutions.

The Failure of Idealized Systems

Corporations may attempt to monitor published literature and the internet for signals of dissatisfaction. However, without a direct allegation and the reporter's willingness to provide meaningful information, there is little valuable input.

Conclusion on Surveillance

Therefore, these idealized early warning systems, incorporated into industry regulations, may no longer provide the necessary surveillance to manage TPLC expectations and reliably determine the risk-benefit balance.

Alternative Methods for Lifecycle Assessment

Despite these challenges, manufacturers seek to understand long-term device function.

Methods include standardized chemical characterization (e.g., ISO 10993-18) to identify extractable chemistries under aggressive conditions, modeling material breakdown over time.

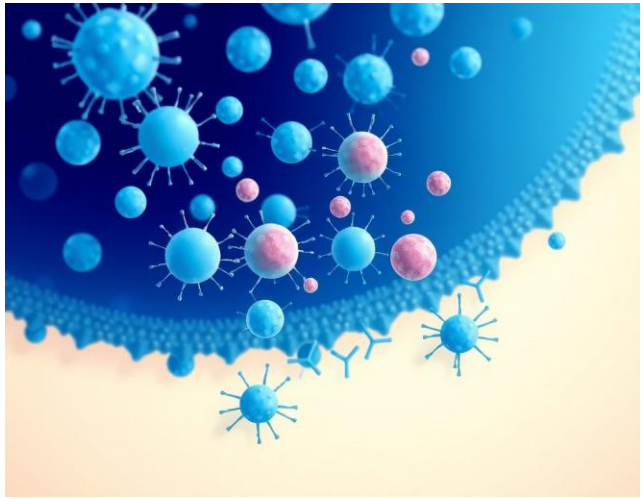
In Vitro Simulators

Various in vitro simulator methods seek to predict failure modes. An example is ASTM F1875-98 for fretting corrosion testing of modular implant interfaces.

Simulator Limitations

- The relationship of simulator data to human performance can only be estimated until real-life human data is available.
- Most simulators evaluate limited stresses (like wear) in simulated biologic environments (like saline), which cannot fully replicate the complex in vivo environment.

Challenges in Simulating the Biological Interface



Trying to estimate the effect of enzymes and cellular attachment can only approximate a finite time window.

As a result, there are few simulators that can reliably predict the mechanisms of late-term biomaterial decline.

Limitations of Animal Models for Long-Term Study

Attempting such studies in live animals is also problematic.

- The animal model may not be an accurate anatomical substitute for the human.
- Maintaining an animal through its natural lifespan to simulate biomaterial decline is prohibitively expensive.
- Animal studies introduce other variables not found in humans.

The Challenge of Regenerative Materials

For conventional biomaterials, a necropsy can yield information via histopathology. But what about materials designed to integrate and be absorbed, leaving behind regenerated tissue?

Unanswered Questions

- How can we assess the long-term health of these regenerated zones in an aging patient?
- Is it a device failure if the newly incorporated tissues suddenly fail to thrive or give way to progressive disease?

The Consequences of Product Obsolescence

A manufacturer's decision to remove a product from the market due to obsolescence can have staggering consequences.

1. **Supply Disruption**

   A sudden disruption of product supply to physicians and patients.

2. **Financial Impact**

   Major expenses for hospitals and distributors holding inventory.

3. **Patient Anxiety**

   Serious anxiety for patients who have an implanted device now deemed obsolescent.

Regulatory and Logistical Hurdles to Market Removal

Some regulatory jurisdictions have no category for "recovery" or "removal," only for "recall," which typically implies a failure to meet specifications.

There are no obvious reasons for a product to stop being marketed beyond a lack of demand.

Furthermore, who determines when a product no longer offers a benefit above risk in the absence of a standardized, objective measure?

The Logistical Challenge of Product Recovery

Removing a device from the market is not as simple as stopping production. Long-term purchase agreements, consignments, and international distribution pipelines mean a device can be legitimately on a shelf for 5 years after manufacture.

Recovering these devices is a massive undertaking with severe financial and logistical consequences.

Summary: TPLC Management Systems

Conventional wisdom relies on a suite of integrated quality systems for TPLC management:

- Design controls and risk analysis
- Control of raw materials and equipment
- Verification and validation of performance
- Postmarket surveillance and adverse event reporting

The Current State

While applicable, these systems are inchoate (imperfectly formed) for the foreseeable future of biomaterial-based implants. There are ample opportunities for innovation in lifecycle management strategies to keep pace with biomaterial innovation.

Safety and Risk Considerations in Biomaterials

An examination of the systematic assessments required to ensure a medical device is safe and effective for its intended use.

Introduction: The Mandate for Systematic Assessment

Medical device development requires a systematic assessment to assure the device will meet its intended use.

Even a device designed to be "like" another product on the market (a "me-too" device) must demonstrate equivalence on two distinct levels.

The Two Levels of Equivalence

1. Performance Equivalence

Does this device meet the same performance requirements of the predicate device? It must perform in essentially the same way to do essentially the same function.

2. Safety Equivalence

Is this device as safe as the predicate device? The device must not introduce new risks. This is the threshold for a premarket notification [510(k)].

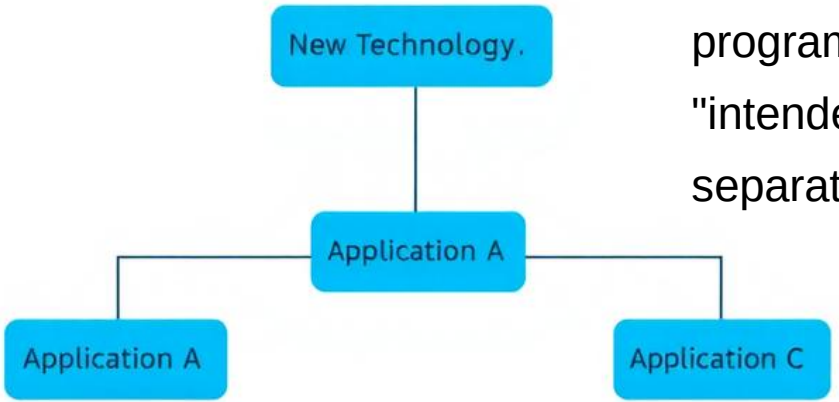
The Pathway for Truly New Devices

A new device with new performance claims and unproven safety (e.g., due to new technology) must undergo a more rigorous process. This requires a Premarket Approval (PMA) application.

PMA Requirements

- Must prove not only safety but also efficacy.
- Must demonstrate that the intent to treat is medically justifiable.
- Must show a reasonable benefit over existing risks.

Focusing Development: Intended Use



A new device may have multiple potential applications. To create a realistic development program, a company must select a single target "intended use" to focus its efforts, or maintain separate development tracks for each use.

Intended Use vs. Indication for Use

Recognizing the difference between "indication for use" and "intended use" is extremely important.

Example: Wound Dressings

A wound dressing may have the same indication (wound protection), but the requirements are vastly different if it's intended for a surgical wound (used by a surgeon) versus a skin scrape (applied by a lay user). The intended user and environment define the requirements.

Design Controls: Voice of the Customer

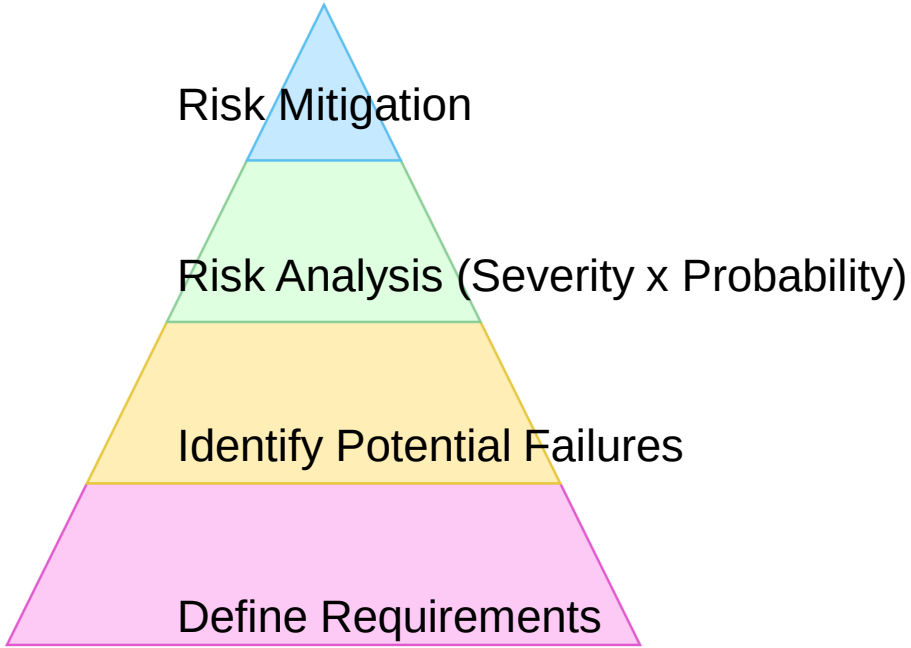
The proper design and development of a medical device (known as design control or stage-gating) must recognize these "inputs" from the "voice of the customer" and convert them into technical specifications. This process establishes a set of performance expectations that fulfill a specific function.

Translating Inputs into Specifications

Typically, the translation of user needs into technical specifications will consider prevailing expectations and standards within the industry to help set boundaries on the requirements. Even a totally novel device may be subject to standardized evaluation methods or constraints from industry best practices.

Risk Analysis: The Next Step

Once input requirements are described, the process moves to determining the potential risks associated with the failure of the device to meet each requirement. This analysis is ideally done on a detailed, requirement-by-requirement level.



Elements of Detailed Risk Analysis

A comprehensive risk analysis assesses each potential failure mode for its probability of occurrence and its associated risk (severity) if it does occur.

- Appreciating the "detectability" of a failure mode helps predict probability.
- Parsing risks (hazard severity × probability) allows the team to focus mitigation efforts effectively.
- Resources for analysis include historical designs, publications, and testing of comparable devices.

Core Principle: Absence of Toxicity is Not Evidence of Safety

For decades, the industry has tried to qualify biomaterial biocompatibility through a series of tests (e.g., the ISO 10993 series). However, this testing scheme has not been proven to assure biomaterial safety.

The Reality of Testing

This scheme is a means to rule out the likelihood of risk (e.g., toxicity), not a method to prove safety. The logic has been that higher risk requires more testing, even if it's not proven that more results offer better risk mitigation.

Shifting from Checklists to Risk Assessment

One attempt to rectify the "checkbox-testing" mentality is to encourage a systematic assessment of biological risks associated with the device and its materials. This approach considers factors like prior clinical use of the material in the same intended use.

Resistance to Change

This more comprehensive safety assessment has met resistance from development planners seeking simple instructions, test labs with no incentive to minimize testing, and regulators who prefer checklists over subjective risk analyses.

The Challenge of Material Databases

Efforts to create a database of materials used in specific applications were rejected years ago. The logical basis was that materials and processing methods are often proprietary, so an inventory of uses does not provide transferable "evidence" of safety.

Final Manufacturing is Key

Even if a material supplier provides baseline biocompatibility data, the final manufacturing methods (machining, cleaning, sterilization) must be considered in the final safety assessment.

The True Role of Standardized Tests

Despite the ideal of a logical risk analysis, safety assessment invariably comes back to a table of standardized tests. It must be understood that these tests cannot and do not prove the safety of the biomaterial in its intended use.

What They Provide

The role of standardized tests is to provide comparative data derived within the confines of a specific protocol. These data may indicate a relative level of hazard compared to a control material, but not absolute safety.

FDA Guidance on ISO 10993-1

The FDA's 2016 guidance on the use of ISO 10993-1 emphasizes that the biological evaluation plan must be made "within a risk management process in accordance with ISO 14971."

Key Principles

- The standard urges a move away from repetitive live animal testing toward validated in vitro models.
- It gives preference to identifying chemical constituents where such methods yield relevant information.
- Chemical concentrations are then compared to established toxicity safety thresholds.

Chemical Toxicity vs. Biocompatibility

While chemical toxicity assessment may help identify the risk of a biological reaction, such tests are "not evidence of biocompatibility."

Definition of Biocompatibility

"The ability of a material to perform with an appropriate host response in a specific application." (Williams, D.F., 1987)

Beyond the ISO 10993 Annex A Table

The table of "endpoints" in Annex A of ISO 10993 considers tissue contact and duration of use, but a true biocompatibility evaluation needs a far more detailed risk analysis. This is why the FDA guidance and Annex B stress the need to characterize materials and processes in the context of the device's intended use.

The First Step: Material Characterization

Characterization of the materials and processes in a medical device is the first step of any biological risk assessment.

Qualify Sources

The source of each material should be carefully qualified.

Verify Materials

The actual material received should be scientifically verified, not just identified by what was sold.

Establish Specifications

Critical materials should have verifiable specifications to permit future qualification of alternative sources.

Process Mapping and Control

All manufacturing processes should be "mapped" to demonstrate the points where energy and other chemicals (including water) are introduced. This helps identify if a process alters the known safety of the starting materials.

Key Controls

- Quality of water and other cleaning agents is essential.
- Controlled, validated processing (especially for polymers) is necessary to ensure safe and uniform batches.

The Continuum of Biological Risk

ISO 10993, Annex B, lists "physical and chemical material properties." More accurately, this list represents energy or force vectors that might act on a biomaterial, and it reminds us to consider the contribution of the material's physical form (e.g., porosity, roughness) to the body's response.

Biomaterial Alteration Over Time

A biomaterial could pass all standardized tests, yet be altered by biologic processes over time. These converted forms of the biomaterial could drastically change its biocompatibility.

Potential Altering Factors

- Static compression
- Wear fatigue
- Crumpling due to scar contraction

Modeling Performance with Simulators

Modeling device performance using an in vitro simulator, such as a fatigue tester, can provide insight into the failure modes of materials. Such systems can test for wear debris and its nature (size, morphology, toxicity) or identify internal weaknesses through fracture failures.

The Limits of Toxicity Testing

When assessing biological risk, "toxicity" tests are only one of a large number of mitigations.

Tests alone cannot prevent toxicity and can only provide an oblique assessment of risk.

They may even introduce a "false positive" due to errors in sample preparation (e.g., wrong pH in an extraction solution).

The Need for In Vivo Assays

For certain applications and functional claims, common wisdom holds that only an in vivo assay can be trusted to characterize biocompatibility.

Example: Bone Growth

To support the claim that a biomaterial enhances bone formation, toxicity assays are insufficient. Only a postmortem evaluation showing the presence of new bone in association with the biomaterial provides sufficient evidence for osteointegration.

The Complexity of Animal Performance Studies

Studies for biomaterial performance in a functional device require careful protocol design and can be as complex and expensive as a human clinical study.

They must begin with an understanding of comparative anatomy and physiology to ensure the animal is the correct model.

Postmortem Assessment in Animal Studies

While in-life monitoring is important, postmortem assessment can be the most revealing. A study with serial sacrifice of animals over sequential time periods can provide insight into:

- Progression of tissue integration
- Device wear over time
- Any potential for material migration

Secondary Processes and Biological Risk

A comprehensive biological risk assessment must analyze potential risks contributed by all manufacturing and secondary processes. It is prudent to assume that every process could impact biomaterial properties until evidence confirms otherwise.

Case Study 1: Coating Adhesion Failure

A manufacturer perfected an anticoagulant coating for a hemodialysis catheter. When moved to the factory, "overspray" from a silicone release agent on an adjacent line contaminated the catheters.

This contamination prevented the critical coating from adhering properly. The issue was caught only because a quality control check was in place based on a prior risk analysis.

Case Study 2: Embedded Contaminants

A company brought a manufacturing step in-house to save money but failed to understand the need for serial cleaning steps. Oils became embedded in the porous surface of a prosthesis. A superficial final cleaning was inadequate, and the contaminants interfered with bone growth after implantation, leading to device failure and patient harm.

Biological Risks from Sterilization

Sterilization methods introduce their own biological risks. These include not only the potential for an inadequate cycle but also risks from process residuals or changes to the biomaterial itself.

1

Ethylene Oxide (EtO)

Standards exist to evaluate residuals and by-products.

2

Gamma Radiation

Can alter biomaterials, requiring protection or avoidance of this method.

3

Steam/Dry Heat

Can also alter biomaterial properties.

4

New Methods

Require careful analysis as they may interact with polymers and alter chemistry.

The Risk of Pyrogenicity

Even a sterilized device can introduce pyrogens, which invoke a febrile reaction. Reducing this risk is critical for intravascular devices and implants.

Material-Mediated Pyrogens

Chemicals that might leach from the device material itself (e.g., from a mined mineral).

Bacterial Endotoxins

Remains of the outer membrane of Gram-negative bacteria left on a device after sterilization.

Shelf-Life and Storage Considerations

Transportation, storage, and shelf-life aging for most conventional biomaterials can be characterized by standardized testing. Evaluation of in-package, shelf-life aging is standard practice to ensure the device performs as intended up to its expiration date.

Unique Challenges

Combination products (drug/device) and tissue-engineered materials have unique requirements, sometimes requiring immediate use and manufacturing at the point of care.

Risk of Aging Biomaterials in the Aging Patient

Device development focuses on performance at the time of delivery, but performance requirements do not stop there. All clinical trials have an endpoint, and trials beyond 2-5 years are problematic due to patient mobility and reluctance of healthy patients to return for follow-up.

Challenges of Long-Term Data Collection

Post-market programs like registries attempt to follow patients, but data often becomes less reliable over time. True understanding of long-term performance might require tens of thousands of patients over many years.

Limitations of Monitoring

Device tracking is for recalls, not data collection. In-situ imaging can only detect gross failures like fractures. There are few assays to show with certainty that a biomaterial is performing safely as it ages.

Implant Retrieval and Forensic Analysis

The only method that could provide long-term data for biomaterial performance is systematic implant retrieval from patients with both normal and abnormal outcomes. Interpreting findings from retrieved biomaterials should be incorporated into any new product biological risk assessment.

A Key Limitation

Currently, research groups mostly collect "failed" implants. This can skew understanding, as retrieving only failed implants fails to teach what went right.

Summary and Conclusion

Medical devices using biomaterials in medium- to high-risk applications are subject to risk-based technical evaluations. Standardized biological test schemes help reduce risk but do not prove safety.

The Path Forward

Well-designed, risk-based technical assessments that consider the entire device lifecycle, including manufacturing processes and long-term patient factors, are necessary to bring the safest possible medical devices to market. Success is achieved when benefits are commensurate with the risks over the full lifecycle of the product.

FDA Overview

The FDA is:

- The U.S. Food an Drug Administration, an agency within the U.S. Department of Health and Human Services.
  - Tasked with enforcing laws set be congress, primarily the ***Federal Food, Drug, and Cosmetic Act (1938).***
    (and it's amendments).

- Actual regulations, within the Code of Federal Regulations Part 21 (CFR21) are under the discretion of the agency, with oversight from congress, and the general public.
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm