BioPhorum

BIOCOMPATABILITY

Biological evaluation of drug delivery devices: unraveling the paradox

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About BioPhorum

We enable the global biopharmaceutical industry to connect, collaborate and accelerate progress for the benefit of all.

Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

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Executive summary

The development of combination products, particularly drug/device integrations such as prefilled syringes, auto-injectors, and inhalers has revolutionized therapeutic delivery by enhancing patient adherence, dosing precision, and self-administration. However, these innovations bring complex regulatory and biological safety challenges that demand harmonized, risk-based approaches to ensure patient safety.

This position paper, developed by the BioPhorum Drug Delivery Workstream, addresses the pressing need for clarity, consistency, and collaboration in the biological safety assessment of combination products. It outlines the foundational role of biological risk assessment (BRA) and the application of ISO 10993 standards, while also exploring the nuanced interplay between International Organization for Standardization (ISO) and USP frameworks. The paper identifies critical gaps in regulatory expectations, supplier data quality, and device categorization, all of which contribute to delays, over-testing, and inefficiencies in product development.

Key themes include:

- Biological risk assessment: emphasizing the importance of structured, risk-based evaluations through biological evaluation plans (BEPs) and reports (BERs), supported by subject matter expertise and cross-functional collaboration
- Supplier data and quality interactions: highlighting the challenges of incomplete or inconsistent supplier data, and proposing best practices for supplier engagement, data standardization, and quality agreements
- Device categorization: addressing inconsistencies in how devices are classified for biological safety testing, particularly in relation to cumulative exposure and contact duration, and advocating for clearer regulatory guidance
- ISO versus USP Expectations: exploring the ambiguity in applying ISO and USP standards to combination products and calling for industry-wide alignment on when and how to leverage each framework.

The paper concludes with a call to action for industry stakeholders to adopt a harmonized, science-driven approach to biological safety. By reducing unnecessary testing, improving regulatory submissions, and accelerating time to market, these efforts ultimately will benefit patients through safer product delivered sooner.

1.0

Introduction

Combination products are transforming therapeutic approaches by offering innovative solutions to meet evolving healthcare needs. Among these, drug delivery devices like insulin pens, prefilled syringes, auto-injectors, and inhalers are pivotal in enhancing patient outcomes by improving medication adherence, optimizing dosing accuracy, and enabling self-administration, particularly for chronic diseases. The development of these devices involves stringent regulatory oversight to ensure compatibility between the drug and device components, as well as usability testing (human factors studies) to meet patient-centric design standards. Biological safety assessment is a crucial step in this development process, ensuring that the finished medical device or combination product can be considered safe from potential biological hazards. The ISO 10993 series is the internationally recognized standard for biological safety assessment, covering a wide range of device types and ensuring comprehensive evaluation. This standard includes various sub-standards, each focusing on different aspects of biological safety, such as cytotoxicity, sensitization, genotoxicity, implantation and irritation testing. Adherence to these standards is a requirement for device manufacturers and demonstrates that their products meet the necessary safety requirements for patients.

Biological safety assessment remains a significant concern, especially since finished device components and packaging typically come into direct contact with the drug formulation and the patient. The primary goal of biological safety assessment is to determine acceptability criteria for biological risks. Given the diversity in device designs, technologies, intended uses, intended populations, etc. a one-size-fits-all approach to biological safety evaluation is not feasible. Each device requires a tailored assessment to ensure its safety and effectiveness. This involves evaluating various device options based on factors such as ease of use, patient safety, and compatibility with drug formulation. By conducting thorough biological safety assessments, manufacturers can ensure that their products meet the necessary safety requirements for patients.

Regulatory challenges arise due to the multidisciplinary nature of combination products. In the US, different FDA centers (e.g. the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH)) may be involved, requiring alignment of regulatory expectations. The involvement of multiple FDA centers necessitates alignment of regulatory expectations to ensure that drug delivery devices meet the necessary safety standards. In other regulatory regions, such as the EU under the Medical Device Regulation (MDR), the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, similar complexities exist. Each region has its own set of stringent requirements and regulatory pathways that must be navigated. Achieving clarity and consensus on regulatory expectations is essential to ensure that drug delivery devices meet the necessary safety and efficacy standards. This involves close collaboration between regulatory bodies, manufacturers, and other stakeholders to align expectations and streamline the approval process.

While ISO 10993 series is the recognized standard for biological safety evaluation, it's important to note that there are additional requirements and considerations for specific registration zones or devices. The United States Pharmacopeia (USP) also provides guidelines for the biological safety assessment of polymeric materials of construction, and polymeric components for pharmaceutical packaging systems and combination products, focusing on aspects such as biocompatibility, sterility, pyrogenicity, and endotoxin testing. By understanding the expectations of both ISO and USP standards, manufacturers can ensure that their products can meet the necessary requirements.

BioPhorum, a collaborative platform for the biopharmaceutical industry, has identified several challenges in the biological safety assessment of drug delivery devices. These include the need for clarity and consensus in regulatory expectations, minimizing unnecessary testing, and improving supplier data quality. The workstream team has outlined problems, impacts, goals, and benefits to address these challenges, aiming to streamline the process, reduce testing burdens, and improve patient safety. The team's efforts focus on creating guidance for executing risk assessments, leveraging supplier data, and clarifying the use of different standards (ISO and USP) for combination products. By improving the selection and appropriate use of reliable supplier data, manufacturers can ensure that their products meet the necessary safety requirements, reducing the risk of adverse effects and improving patient outcomes. Additionally, leveraging supplier data can help manufacturers identify potential issues early in the development process, allowing for timely interventions and reducing the likelihood of costly delays.

This position paper addresses the complexities of biological safety assessment for combination products, particularly focusing on drug delivery devices. It explores the unique challenges faced by the industry, including regulatory alignment across different regions, the integration of diverse standards, and the critical importance of biological safety in ensuring patient safety. The paper provides a comprehensive overview of the current landscape, highlights key problems, and proposes actionable solutions to streamline the development process. The next section will provide a detailed examination of the scope and challenges, setting the stage for a deeper understanding of industry needs and the path forward.

2.0

Establishing the scope and challenges

BioPhorum is a company-to-company collaboration with the mission to create an environment where the global biopharmaceutical industry can collaborate and accelerate its rate of progress for the benefit of all. This is achieved by bringing together organizations and their subject matter experts to define future visions. Expert teams are mobilized to explore opportunities, form strategic partnerships that enable change, and identify the most effective paths to implementation. This collaborative process allows industry to learn, build, and share the best solutions. BioPhorum is a global collaboration network made up of 11 distinct phorums, each dedicated to a specific area of the biopharmaceutical sector.

One of these phorums is BioPhorum Drug Delivery which focuses on global drug delivery and combination products. The phorum provides a channel for companies to network and share real-world challenges in a safe, open and collaborative setting. By working together to develop consensus views and best practice approaches to solve problems, BioPhorum aims to help the industry get these important products to more patients worldwide.

Several member companies emphasized the importance of collaboration on biological safety requirements for combination products, particularly in addressing current and emerging challenges and highlighted the need for clarity and consensus in regulatory approaches. Therefore, an initial team of 14 subject matter experts from 10 companies formed a workstream team to scope the requirements of this topic. The workstream team first focused on the unique challenges and problems in the industry around biological safety assessment for combination products. The team emphasized that these issues adversely affect organizations developing drug delivery products. Unnecessary testing strains resources and compromises animal welfare, while unclear regulatory expectations lead to delayed approval times. Moreover, the burden of resource-intensive testing limits appetite for development of novel products, as the risk–reward balance becomes uncertain. Regulatory bodies have committed as a major goal to reduce animal testing setting the scope for industry. Animal testing should be performed only when adequate alternative methods are unavailable or unsuitable for assessing biological risk, in accordance with ISO 10993-2 guidance. To ensure animal welfare, studies must strictly adhere to the principles of Replacement, Reduction, and Refinement (3Rs), utilizing the minimum number of animals necessary while minimizing pain, suffering, and distress.

Delays in approval market entry for drug delivery products have a direct and significant impact on patients. When the release of crucial therapeutics is postponed, patients who rely on these treatments for their health and wellbeing are left waiting. This can lead to prolonged suffering, worsening of medical conditions, and in some cases, preventable fatalities. The workstream team highlighted that addressing these regulatory challenges and streamlining the approval process is essential not only for the efficiency of organizations but also for the timely delivery of lifesaving therapies to patients in need. Ensuring clarity and consensus in biological safety requirements is a critical step towards minimizing these delays and improving patient outcomes.

This initial output resulted in a top-level team charter organized into the following 'headline statements':

- **Problems**—potential challenges and issues to be discussed and resolved
- **Impacts**—potential risks and negative effects these problems could have on organizations
- **Goals**—the objectives the team aims to achieve and deliver
- **Benefits**—how participation in, and output from, the collaboration will help companies.

These headline statements are expanded below to guide subsequent discussions and shape the detailed goals and benefits. While the team distilled the problems identified into five concise charter headings, additional challenges were identified and grouped into four distinct topic areas, each to be addressed through regular collaborative working sessions. Beyond the immediate benefits of sharing experiences across companies, the team also intends to create a series of outputs that will establish best practices and highlight critical aspects for the drug delivery field, benefiting the whole industry.

3.0

Expanding on the identified challenges

The initial workstream team meetings identified a series of problems, with the objective of exploring options to improve the current situation. Additional input was provided to expand each topic and clarify the impact of the problems, specifically, why they can be challenging to companies, why they can be limiting to progress for important therapies to patient and why industry should be concerned. This was followed by identifying the goals and benefits associated with each topic and how addressing these will benefit the industry as a whole.

The initial discussions, detailed below, were not intended to identify solutions; rather, they were designed to outline what the BioPhorum team will be working toward in future activities. The BioPhorum Drug Delivery—Biocompatibility Team will continue this work exploring each problem in greater depth, sharing industry knowledge and experience, and aiming to reach consensus on best practices and potential solutions to improve the current situation. The next section outlines the proposed actions, summarizing the problems, goals, and benefits for companies, the industry and patients.

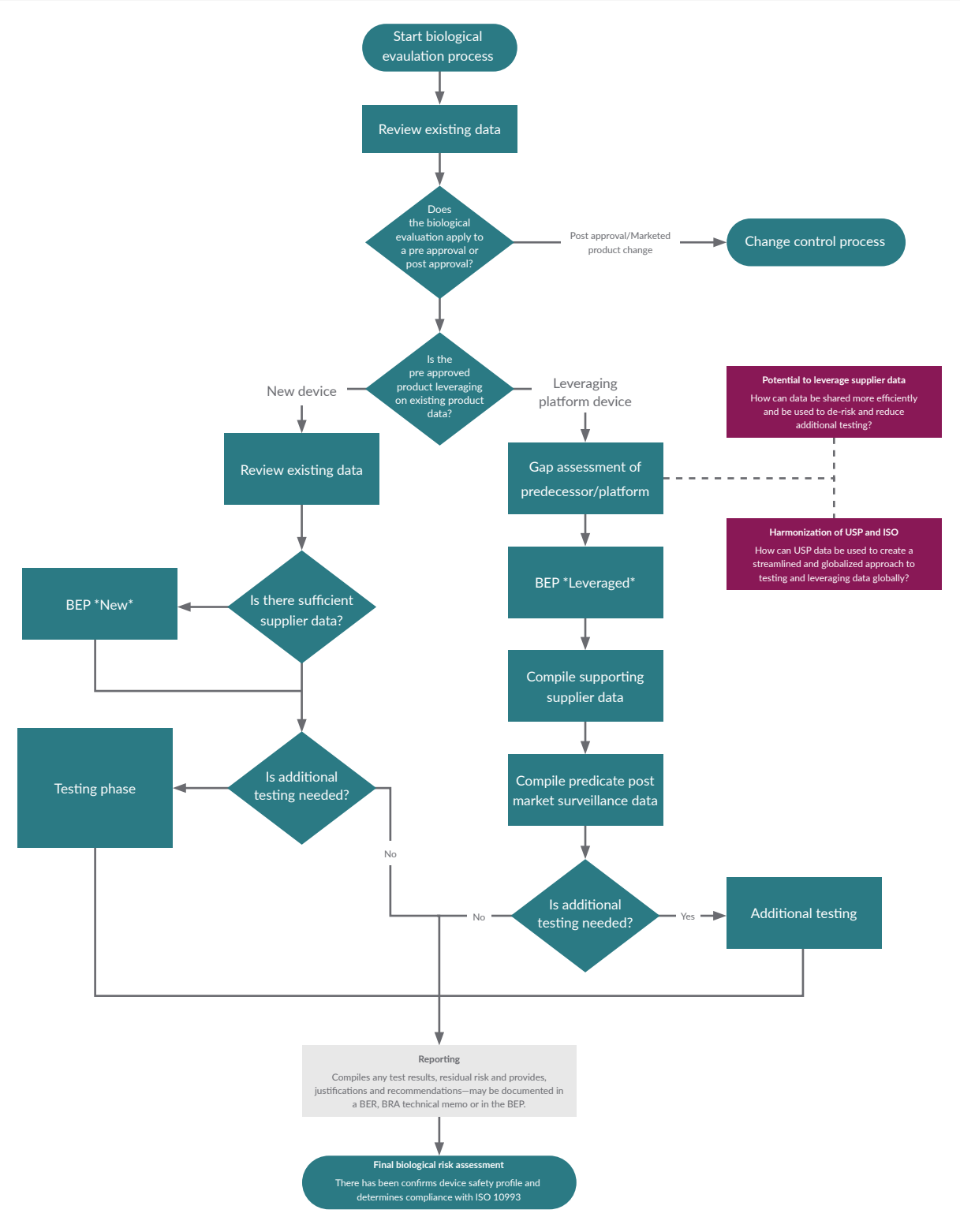
3.1 Biological risk assessment

The initial step in establishing the biocompatibility profile of a device is to conduct a biological risk assessment or biological evaluation. The biological evaluation refers to both the documentation and the process that assess the product or material under consideration. This includes the biocompatibility requirements for the device or component based on the duration and type of contact with the patient, as well as any justifications for not conducting recommended tests required to demonstrate the absence of additional biological hazards or impacts on patient safety. This risk-based process ensures that devices do not pose undue risks to patients, align with regulatory requirements and promote safety.

Before getting into the details of the risk assessment, it is important to define biocompatibility. Biocompatibility is the ability of a device or material/component to perform with an appropriate host response in a specific situation. A biological risk assessment is a risk-based evaluation of a device or material/component based on an analysis and review of available information, comprising a risk analysis and risk evaluation. This assessment is required by ISO 10993. It should not be confused with the previous 'biological safety summary assessment', which was a checklist-based exercise for the tests to be performed based on the standard's end-point designation. A biological safety risk assessment is a risk-based approach to understand potential risks, review current data and identify any residual gaps. This determines if testing may be one of the next steps, if justified. The risk assessment encompasses the biological evaluation plan (BEP) and the biological evaluation report (BER).

The BEP is a critical document that outlines the strategy and methodology for assessing the biological safety of a device. It is developed at the beginning of the risk assessment process and serves as a roadmap for the testing and evaluation to be conducted. The BEP indicates the product category, considering cumulative contact duration, and identifies potential biological hazards, estimates associated risks, and determines necessary tests and evaluations to mitigate these risks. It includes details about the materials of construction, the manufacturing processes, packaging, the intended clinical use of the device as well as any evidence of the product/component in the literature. The BEP sets the foundation for a structured and complete biological evaluation within a risk management framework.

Figure 1: Biological evaluation process



The BER is a comprehensive document that compiles and summarizes the results of biological safety testing and evaluations conducted in accordance with the BEP. It brings together all the elements of the device assessment, following completion of testing. The BER is created after the testing phase and provides a detailed analysis of the data collected, including outcomes of tests and any observed biological effects. The BER assesses whether the device meets the required endpoints based on the type and duration of contact for the intended patient population. It includes a risk assessment of the test results, identifies any residual risks and provides recommendations for further action if necessary. The BER also documents the scientific rationale for any test failures and associated mitigations. The BER serves as the definitive document which establishes the biological safety profile of the device.

In summary, the BEP is a forward-looking plan that outlines the testing strategy, while the BER is a retrospective report that documents and analyzes the results of the testing conducted according to the BEP.

The risk assessment begins by gathering all available information, including details from suppliers, materials of construction, biological endpoint tests conducted by the supplier, and any post-market surveillance data. This information forms the basis for a thorough risk assessment that guides the testing strategy. The device and its components also influence the risk level. For example, risk may be lower if devices or components are used as-is and already have CE marking or FDA approval. Conversely risk may be higher if devices are designed or manufactured in-house or are new to the market.

One of the main barriers to improvement in this area is company management and how much time and resources they are able to allocate to ensuring biological safety of their combination products. This could be a significant issue for some companies as this area is rapidly evolving, both technically and due to the publication of new standards. In larger organizations, with more resources, one solution could involve creating a dedicated biological safety or biocompatibility group. The group could have ad hoc representation, including materials and chemical experts, toxicologists, product development engineers, and manufacturing process subject matter experts (SMEs).

It is imperative to have SMEs in biocompatibility leading and conducting the risk assessment process. These dedicated experts should understand the standards, the product, and any historical testing that can be leveraged. The SMEs could collaborate to complete the risk assessments. This approach may require additional training to bring risk assessment authors up to the same standard and create a consistent process.

Problems

- Drug and device standards are established separately, which creates ambiguity for combination drug delivery products.
- While some harmonization exists (e.g. USP and ISO alignment), gaps remain, leaving limited direction for products that combine drugs and devices.
- Definitions of ‘medical device’ differ across regions (such as the US and EU), leading to inconsistent classifications (e.g. in certain circumstances components could be considered container closure and/or medical device)
- Inconsistent regulatory guidance means that expectations for submissions and testing vary between reviewers; some may approve immediately, while others request additional data.
- The lack of global harmonization causes varying testing requirements in different geographic areas, requiring companies to monitor regulations regionally.
- Interpretation of ISO standards may vary among organizations, resulting in unclear processes for risk assessments applied to combination products.
- There is little guidance on leveraging historical data or determining its appropriateness, especially with evolving standards.
- Uncertainty exists regarding the need for biological evaluation documentation for products already marketed.
- No clear consensus or standardized approach is available for demonstrating equivalency in drug-device interactions.

Impacts

- Lack of clear guidance for combination products leads to submissions that carry risk, due to uncertainty around applicable standards
- Unnecessary animal testing raises ethical concerns, particularly when physical, chemical, *in-silico* and *in vitro* assessments could provide sufficient data
- More resources are required by organizations
- Delays in regulatory submissions results in delays to product launches, often affecting and preventing critical therapies reaching patients
- There is regulatory pushback regarding the extent of testing conducted in the BER

Goals

- Streamline the process for creating a BEP
- Create clear guidance on how to execute the biological safety assessment and optimize process flow for combination products
- Provide industry with clarity on pitfalls when creating a platform approach for biological safety assessment
- Set an industry expectation for levels of acceptable testing, based on scientific rigor and consultation with the standards
- Create a biological safety playbook that includes process flowcharts and case studies to help complete risk assessments.

Benefits

- Reduced time to market
- More efficient use of resources
- Improved patient safety
- Reduced costs for device development
- Reduced testing burden, especially in animals, when unnecessary
- Improved regulatory understanding of device risk
- Accelerated approval process.

3.2 Leveraging supplier data and supplier quality interactions

Biological evaluation is a key design verification activity embedded in a broader risk management framework, as outlined in ISO 10993-1. A critical early step in this process is to gather physical and chemical information of the device or components, where the following steps are typically involved:

- Each material is defined and characterized, including consideration of suitable alternatives
- Hazards are identified in base materials, additives, processing aids, and residuals
- Potential impacts of downstream processes (e.g. sterilization or chemical interactions) on the final product composition are evaluated
- Chemicals that could be released during use, including intermediates and degradation products, are identified
- Exposure levels (total or clinically available amounts) are estimated
- Available toxicological and biological safety data is reviewed

Sources of information may include literature, internal data, supplier-provided or market comparable data where processes and formulations are equivalent. If existing data demonstrate acceptable biological safety, further testing may not be required. However, where data gaps exist, additional chemical characterization or biological testing must be performed to address risks.

Suppliers are often key contributors to biological evaluation by providing biocompatibility data and other safety-related documentation. This information can support material selection and facilitate the regulatory review process. In many cases, however, supplier-provided data is limited.

One common issue is the lack of access to complete supplier declarations or detailed composition information, which hinders accurate toxicological assessments. Safety data sheets (SDS) often lack the level of detail needed for evaluating biological risks. Furthermore, device master files (DMFs), which can be a valuable resource, are not always available or accessible.

Suppliers may have limitations in sharing proprietary formulation details, citing confidentiality concerns. In many cases, testing is conducted to outdated standards or reported without sufficient methodological detail, making it difficult to determine whether the data can be relied upon. Limited internal expertise in biological safety on the manufacturers' side can further hinder effective communication of data expectations to suppliers.

Suppliers may introduce changes without informing the manufacturer, or they may assert equivalence without providing supporting data. Supply chains can be complicated, making challenges for determining accountability, setting expectations and communication for biocompatibility data. Improved communication and data sharing could result in reduction and optimization of resources and time for biocompatibility assessments.

These challenges can have negative impacts. Repeated or unnecessary testing may be required due to insufficient or missing information. Submissions to regulatory authorities can be delayed, increasing time to market and risking product rejections. The resulting misalignment of expectations may strain supplier relationships and introduce inefficiencies that consume additional time and resources.

Sustainability initiatives can introduce further complexity. When materials are substituted for more sustainable alternatives, these changes must still undergo appropriate biological risk assessment. Any proposed material changes should prompt a re-evaluation of available data to determine whether new testing is warranted before the new material can be implemented.

To address these challenges, both internal and supplier-facing strategies should be implemented. Internally, targeted biological safety training should be provided across relevant functions such as R&D, manufacturing, procurement and quality. This helps build the in-house capability necessary to understand supplier data and communicate expectations clearly. Additionally, biological safety experts should be involved in supplier audits and the selection process to ensure key risks are addressed early.

On the supplier engagement side, supplier quality agreements should be carefully drafted and regularly reviewed to clearly define expectations for:

- Material formulation consistency and change notification
- Disclosure of additives, processing aids, residuals and site changes
- Biocompatibility testing responsibilities and access to detailed results
- Use and sharing of DMFs and other regulatory submissions.

In addition to quality agreements, a standardized supplier data request template can be created to define the specific types of information needed, including testing performed, materials of construction, and sterilization compatibility.

Overall, best practice calls for early engagement, detailed agreements, and thorough data review to minimize unnecessary testing and reduce submission risk. Proactive supplier management, including participation in audits, ongoing training, and clear communication of regulatory expectations, can significantly improve outcomes and streamline the biological evaluation process.

Problems

- Supplier-executed studies comply with older standards
- Lack of industry consistency in supplier compliance statements regarding testing conformity
- Supplier test data can be difficult to leverage due to reports lacking information on standard and detailed results of testing
- Misalignment between suppliers and license holders around contact duration and contact type
- Lack of internal training for manufacturers and suppliers
- Lack of in-house expertise and biological safety knowledge

- Inconsistent communication of data requirements to suppliers
- Lack of comprehensive biological safety data from suppliers—not defined in supplier quality agreements
- Critical biological safety data may be shared with reviewers but not manufacturers—who may just get a pass/fail result, which means they go into a submission 'blind'
- Suppliers may not share details of changes to devices/components/raw materials, suggesting that new items are equivalent to previous ones
- Suppliers may add disclaimers that it is the responsibility of the manufacturer to ensure the item supplied is suitable for use in medical devices
- It can be difficult to get information about packaging from suppliers

Impacts

- Repeated testing due to lack of information from suppliers
- Delays in submission and subsequent approval
- Misalignment of expectations can result in strained relationships between suppliers and license holders
- Increased risk when going into submission when relying on supplier data

Goals

- Create a standardized supplier template based on data expectations, which can be used to access the supplier
- Create a best practice template for supplier selection
- Set industry expectation around the data suppliers should provide
- Create guidance/template for biocompatibility training of supplier quality teams on the assessment of supporting data from suppliers

Benefits

- Minimized risk when going into submission
- Reduced patient risk
- Improved time to market
- Reduced resources
- Reduced testing requirements.

3.3 ISO versus USP: what is the expectation?

The link between USP and ISO testing requirements is unclear and inconsistent regarding combination products. There are instances when companies have successfully leveraged USP data to satisfy ISO requirements and others where this has failed. It appears to depend on the reviewer involved and the type of product. For biocompatibility this would include standards such as USP 1663, 1664, 87, 88, 1031 and ISO 10993 series.

Some companies adopt a general approach that materials coming into direct contact with the drug must follow USP guidance, while materials in direct or indirect contact with the patient follow ISO standards. However, there is no formal requirement or enforcement for this approach. Additionally, the decision on how to follow or leverage between the two standards has additional complexities e.g. whether to test as a device or container closure system. Each assessment of how to apply these standards must be conducted on a case-by-case basis, considering factors such as available data, how testing was performed, and whether it covered the entire device or only parts. Effective data collection from suppliers is crucial for increasing the likelihood of selecting the appropriate path forward.

Problems

- Lack of clarity on which guidance to follow with significant differences between ISO and USP extractable testing methods, timeline, and costs
- Reviewers often challenge the extractables testing methods of the contract research organizations (CROs), including solvent selection, instrumentation, dilution, concentration methods, and recovery standards
- Uncertainty regarding which components must comply with specific standards
- Lack of clarity on when USP data should be leveraged to justify not conducting ISO equivalent (or vice versa)
- Testing requirements can vary depending on the reviewer
- Lack of consistency from review process
- Lack of clarity on how to categorize the combination product

Impacts

- Over testing to meet the requirements of all standards without leveraging data
- Delays in submissions and subsequent approvals
- Inconsistent pushback from regulators when data has been leveraged with justification in place
- Inconsistency in regulatory requirements

Goals

- Clear understanding of the overlaps between USP and ISO 10993 standards during biological evaluations, including identifying USP references to ISO 10993 and aligning requirements between drug and device regulations
- Industry clarity around whether it is a component or a part of the device
- Industry clarity on chemical characterization data, including best practices for leveraging existing results to minimize repeat testing
- Clear expectations regarding testing requirements across combination products
- Guidance on when scientific justification is sufficient versus when additional testing is necessary.

Benefits

- Reduced likelihood of pushback from regulators
- Reduced resources
- Reduced burden of testing
- Improved time to market

3.4 Component/device categorization for biological safety risk assessment

Medical device categorization for biocompatibility risk assessment focuses on the nature and duration of body contact, which is critical for determining risk and identifying the required biological endpoint tests to establish the device's biocompatibility. It is important to consider cumulative exposure when calculating the duration of body contact. However, ISO 10993-1 does not provide a detailed guideline on how to determine the duration of contact for repetitive single-use combination devices such as:

- A single-use device
- Patient contact is less than one minute
- Frequency of injections weekly/biweekly/monthly/quarterly basis.

For an adult population, actual patient contact with a device may be less than one day. However, according to ISO/TS 21726:2019, any compound that leaches into the body is considered a daily exposure for toxicological assessment. Under this framework, a delivery device intended for yearly injections would be categorized as long term, as would a device used weekly. This approach may create a disconnect between the actual patient risk and the assigned exposure category.

The updated ISO 10993-1:2025 standard aims to align with the language of toxicological evaluations and has a daily limit of one day for any duration of contact. Therefore, if there is a single five-minute contact in a day, the daily limit has been reached. On the other hand, according to ISO 11608:2022, a needle-based injection system (NIS) with a use frequency of weekly, monthly, or longer is typically considered prolonged or long-term exposure. ISO 11608 does not provide further clarification on what differentiates prolonged versus long-term categorization when considering cumulative exposure.

Given the lack of clarity on device categorization and risk estimation, as well as incorrect category determination, there is a potential risk of under-testing, resulting in the submission of a device that a reviewer does not deem aligned with the testing or category requirements. On the other hand, categorizing all devices as long-term forces the industry to allocate resources and delay the launches of low-risk devices to mitigate program regulatory risk.

The level of scrutiny is often reviewer-dependent, and historically, reviewers have looked at quality papers, regulatory documents, and so on. Increasingly, toxicological experts in biological safety will ask more probing questions about classification and categorization.

Some manufacturers may utilize CROs to assist in defining the testing requirements, but these CROs may not offer guidance on a balanced, risk-assessed approach to the necessary testing. CROs need to be very familiar with the device, and it can be challenging for an external company to provide a comprehensive answer on testing. The conservative approach taken by CROs may categorize devices as higher risk, resulting in testing that is not the least burdensome approach, as advocated by the FDA.

The ISO 10993 standard guides the nature of body contact, although this remains open to interpretation by manufacturers and reviewers. For example, not all components of the device are in the same contact type with the patient. For a prefilled syringe, the device can be categorized into two categories: fluid-path-contacting (higher risk, externally communicating—syringe with needle, needle shield, and stopper) and intact-skin-contacting (low risk, surface medical device—plunger rod and finger flange). The level of scrutiny may vary among different regulatory agencies. ISO 10993-4 emphasizes testing at component level rather than as a system. This is to ensure appropriate testing and risk assessment. For example, testing an entire device for blood-contacting products may dilute the extractables and therefore obscure worst-case scenarios. For combination devices, this may further complicate determining which components are part of the container closer system or primary packaging (and therefore follow the USP standard) and which components are considered medical devices (following the ISO standard).

Problems

- No industry consensus/clear guidance on how to categorize combination products
- Inconsistency in regulatory approval around the chosen category
- Inconsistency in categorization recommendations from CROs
- Categorization of a combination product can be reviewer-dependent
- Lack of clarity resulting in conservative category selection
- No clear guidelines on transitory contact
- Lack of guidance on calculating cumulative exposure
- Changing categories may require new paperwork to be submitted (even within the same specific configuration)
- Using CROs to define testing plans may not be possible as they may not have a comprehensive view of a product
- Categories add extra scrutiny of testing and make the bar harder to reach
- Current heavy use of resources and impact on timeline

Impacts

- Over-testing due to selection of a conservative category
- Additional animal, environmental and ethical concerns around over-testing.
- Additional time and cost associated with over-testing
- Pushback from regulators on the selected device category resulting in delays
- Misalignment between component suppliers and combination product manufacturers regarding device categorization and associated risk

Goals

- Industry consensus/clarity around combination product categorization based on requirements for EU and US
- Industry consensus/clarity around best practices for conducting cumulative calculations
- Clarity around cumulative calculation for combination delivery devices
- Clarity around transitory medical devices
- Clarity on regulatory agency expectations
- Setting industry expectations

Benefits

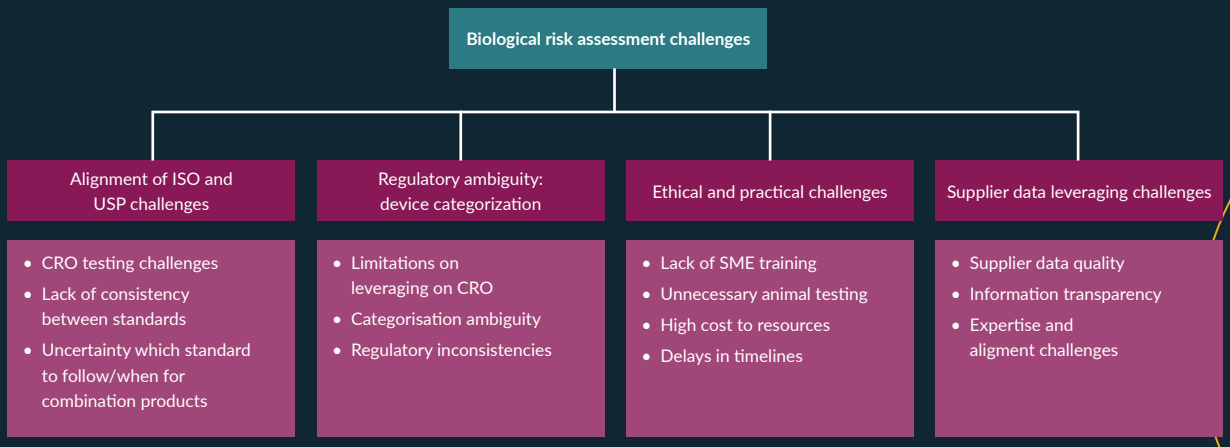
- Reduced uncertainty in device development and program risk
- Reduced approval times
- Reduced testing leading to increased animal welfare and fewer ethical concerns
- Reduced cost of testing

4.0

Conclusion

The development and regulatory approval of combination products, particularly drug-device combinations, present unique challenges, and opportunities for the biopharmaceutical industry. Whilst generally the risk for a delivery device is low—ensuring biological safety through rigorous assessment and adherence to international standards like ISO 10993 is crucial for patient safety. The collaborative efforts of BioPhorum and its member companies highlight the importance of industry-wide consensus and best practices in addressing these challenges. By streamlining processes, leveraging supplier data, and clarifying regulatory expectations, the industry can reduce testing burdens, accelerate time to market and ultimately improve patient outcomes.

To achieve these goals, it is imperative for stakeholders across the biopharmaceutical industry to actively participate in collaborative initiatives. Companies should engage in open dialogue, share real-world challenges, and contribute to the development of consensus views and best practices. By working together, we can create a more efficient and effective regulatory environment, minimize unnecessary testing, and enhance the safety of combination products. Let us commit to continuous improvement and innovation, ensuring that patients worldwide benefit from the advancements in drug delivery and medical device technologies.



Appendix

As updates to ISO 10993 have been recently released, the Biocompatibility team are actively reviewing the changes. The position paper and relevant sections will be revised accordingly to reflect the latest developments. Further updates will be provided as the review progresses.

Glossary

Term	Definition
BEP	Biological evaluation plan
BER	Biological evaluation report
BRA	Biological risk assessment
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CROs	Contract research organizations

Term	Definition
DMF	Device master file
EU	European Union
FDA	Food and Drug Administration
ISO	International Organisation for Standardisation
NIS	Needle-based injection system
SDS	Safety data sheets
SME	Subject matter expert
USP	United States Pharmacopeia

Standards

Standard	Description
ISO 10993 series	Biological evaluation of medical devices
ISO 11608:2022	Needle-based injection systems for medical use—Requirements and test methods
ISO 14971:2019	International standard for the application of risk management to medical devices
ISO/TS 21726:2019	Biological evaluation of medical devices—Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents
USP 1031	The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants
USP 1663	Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
USP 1664	Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/ Delivery Systems
USP 87	Biological Reactivity Tests—In Vitro
USP 88	Biological Reactivity Tests—In Vivo

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