

# The Complexities of Biocompatibility Testing for Combination Products

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Biocompatibility testing for combination products is complex and challenging, and, if not performed correctly, can have serious and costly consequences. Choosing the wrong regulatory path, test program or study design could, at a minimum, require retesting or even possibly delay or derail a promising product in the regulatory cycle.

Designing a successful testing program requires dealing with complexities that arise from working with a combination product. While each combination product has its own particular set of challenges, outlined below are five major areas of consideration for any manufacturer about to embark on a program of biocompatibility testing.

## Regulatory Guidance

Setting up safety assessment programs for combination devices presents unique challenges because not only do the constituent parts require safety and biocompatibility data, but so does the final product. Each subset of testing can require adherence to vastly different regulatory guidances. In the example of a combination product consisting of a device and a drug, each constituent will require safety data individually as will the final product. The device should be assessed using biocompatibility guidelines such as ISO 10993, Biological Evaluation of Medical Devices, whereas the pharmaceutical component would be assessed by ICH Guideline M3 (R2) Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Subsequent testing on the final device should then incorporate a blending of the two guidances to produce a program of testing that accurately assesses safety in light of clinical relevance and use. Adding an additional level of complexity is the need to address requirements set forward in vertical guidances. Without adequate understanding of the entire safety assessment scope, the risk is that a particular product's testing program design may miss important biocompatibility and safety questions.

## Components

Defining the appropriate testing strategy can also be impacted by the choice of constituent components. Because safety data is required on the constituents as well as the final product, as many as three separate programs may be required to meet the regulatory expectation with significant expenditure of time and money. Use of previously approved constituent components may reduce the scope of the assessment, but not fully eliminate the need; and it is important to consider that if the components were previously approved for specific indications other than that intended for the combination product, then the prior data sets may be of limited usefulness. In addition, because incorporation of different components can lead to unexpected changes in properties – such as mechanics, stability, efficacy, and physical properties – the possible interactions of the constituents in the final product must be assessed.

## Testing Approaches and Protocols

Many currently available biocompatibility test protocols and testing approaches were designed for traditional medical devices made of simple polymers, metals or ceramics. Traditional biocompatibility assays were designed to test single dose levels and limited dosing regimens, typically single applications. Device design today includes a diverse array of materials from biodegradable or bioresorbable materials to new polymer and metal formulations. And with combination products, the design may incorporate not only these newer, complex materials but also a second or third constituent component that is classified as a drug or biologic. These evolutions require protocol modifications that can include dose range studies, multiple doses in definitive studies, multiple test article applications and multiple sample collection points. Traditional pharmaceutical protocols often frequently incorporate these concepts, but may not address the correct route of administration. For example, many devices are implanted, which can dramatically impact the efficacy and distribution of pharmaceutical components, so protocols need to be designed to incorporate a clinically relevant implant site.

### **Sample Preparation**

Sample preparation for the testing of a single component is usually straightforward and can be accomplished in accordance with recommendations put forth in the respective guidance documents. However, for a combination product, specific device-based or pharmaceutical-based instruction for sample preparation may be inappropriate and clinically irrelevant. By way of illustration, in the ICH M3(R2) document, the pharmaceutical sample can be prepared and tested at concentrations fifty times that of the anticipated clinical dose and applied directly to the test system. In typical combination products, the amount of the drug component is much lower. Furthermore, the drug component is typically incorporated within the device material or as a coating, and direct application of the recommended exaggerated doses to the test system may be physically impossible. In contrast, certain device guidances suggest the use of extracts of the device as the substance to be applied to the test system. In this case, it would not be a direct application of the pharmaceutical test substance and possibly a dose substantially lower than recommended in ICH documents. Conversely, an extract of a combination product may result in a drug dosing artificially higher than is relevant.

### **Test-System Delivery**

Likewise, selecting the best manner by which to deliver a combination product to the test system can be a challenge as device- and pharmaceutical-based guidances take dramatically different approaches. Many of the device-based assessments of biocompatibility are performed using extracts of the device. Extracts can be performed in several ways, but generally involve immersing a device in a solvent and incubating at elevated temperatures for various periods of time. The subsequent supernatant is then used for testing. Use of an extract is frequently necessary because the physical size of a device precludes direct contact with the test system or because it is necessary for a relevant route of administration. In contrast, pharmaceuticals are typically prepared in a similar fashion to their clinical use and applied directly to test systems. How then should a combination product – with both a device and drug component – be introduced to the test system? In some cases, a blending of approaches can present the most clinically relevant method. This may include performing multiple iterations of tests to achieve dose routes applicable to both the device and the pharmaceutical.

### **A Final Consideration**

Biocompatibility programs for combination products can be complex and daunting, particularly because – as discussed above – planning must take into account the impact of both device and drug. With so much at stake, a final consideration for manufacturers is a thorough evaluation of advisors, laboratories, and any outsourced services to ensure the highest level of expertise and experience. Selecting the best team to implement your plans will increase the likelihood of submission success.

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