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WHEN DRUG MEETS DEVICE...

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In Brief

When a medicinal product (drug or biologic) meets a medical device, a combined product is created. Incompatibility between the components can present a danger to the patient, but how can one demonstrate the fit between a medicinal product and a device? This paper describes the relevant definitions, the existing regulatory framework for combined products (or better the lack thereof), and focuses on stability testing to assess drug or biological-device compatibility.

What is the legal framework for combined products?

There is no official definition for "combined products." For this paper, **combined product refers to any possible combination of drugs, biologics and devices**. The concept of combined product is broader than a "combination product," a term explicitly defined by US legislation for a drug or biological (or both) combined with a device that are:

- packaged as a single entity, such as a prefilled syringe, drug-eluting stent or transdermal patch,
- co-packaged in a single package or as a unit, such as a surgical kit,
- packaged separately but used solely in one specific combination: a "cross-labeled" combination product, such as a light-emitting device and a light-activated drug (ref. 1).

Given this definition, combination products can be regarded as a subset of combined products. Examples of combined products that are not combination products include, among others, a pump designed and sold by a medical device manufacturer for use with several painkillers in a hospital setting and an infusion set designed to administer various types of drugs or parenteral nutrition to patients. Obviously, such a device will not be used on its own, but only in combination with a medicinal product. It is thus of great commercial interest for the medical device manufacturer to give detailed statements about the possibilities of a medical device as a combined product. The following is an example from the instructions for use of an infusion set: "Chemotherapy, anesthesia, and pain management are the most common treatments where the set can be used for intravenous or epidural infusion both in adult and pediatric patients." **What are the legal requirements for making such a statement and for marketing medical devices as combined products in general?**

The European regulation on medical devices would be a good starting point; it states, *"Devices shall be designed and manufactured in such a way that they can be used safely with the materials and substances, including gases, with which they enter into contact during their intended use; if the devices are intended to administer medicinal products they shall be designed and manufactured in such a way as to be compatible with the medicinal products concerned in accordance with the provisions and restrictions governing those medicinal products and that the performance of both the medicinal products and of the devices is maintained in accordance with their respective indications and intended use"* (ref. 2). **The medicinal products and devices that comprise a combined product need to be compatible with one another while preserving the performance of all components.** The importance of this is emphasized in the recent draft guideline on quality requirements for drug-device combinations published by EMA (ref. 3). Practical instructions on how to do this are lacking in the European regulation on medical devices and the EMA guideline, as well as in the applicable legislation for medicinal products (ref. 2 to 4).

The American legislative counterpart, the US Code of Federal Regulations, establishes requirements for medicinal products, medical devices and combination products (ref. 1, 4 and 5). This regulation does not install new requirements, but clarifies the medicinal products and devices regulations that apply for combination products. FDA issued a guidance document to assist in utilization of this rule (ref. 6). While this document presents a clear overview of the elements required for manufacturing of combination products, detailed practical instructions or guidance for combined products are not provided. With respect to stability testing of combination products, the guideline states, *"Stability testing is performed to determine appropriate storage conditions and expiration dates. Among other considerations, this testing must enable evaluation of any effects on the stability of the drug due to storage in its marketed container closure system, which may be a device constituent part (or component of a device constituent part)" and refers to the stability testing of medicinal products and the associable ICH guideline (ref. 4 and 7). A clear statement on the need for stability testing can be found in the FDA document on infusion pumps, "FDA recommends that the labeling contain the following information (...): For infusion pumps containing a reservoir, container, or other components contacting the drug or biological product being infused,* ***include information regarding the stability and compatibility*** *of those fluids with your device"* (ref. 8). However, no detailed guidance is given.

Even though authorities do consider and question the compatibility of combined products, clear regulation is lacking, leaving the combined product manufacturer confused. This paper intends to help medical device manufacturers overcome what some consider a "guidance vacuum" regarding how to evaluate the stability of combined products. In-use stability testing approaches are described that aid in the assessment of drug or biological-device compatibility. Moreover, the authors ask for more regulatory guidance on this topic, not a rigid list of tests including pass/fail criteria ("checkbox approach"), but rather a risk-assessment based approach comparable to the procedure used for the biological evaluation of medical devices (ISO 10993-1). It is crucial to evaluate existing data regarding the medical device and medicinal product, and to fill gaps in the knowledge of the drug or biological-device compatibility with relevant and fit-for-purpose testing.

How to perform stability testing for combined products?

This section covers two types of combined products: exclusive drug/biological-device combinations (i.e. one device only to be used in combination with one particular drug or biologic), and a device that can be combined with more than one drug or biological.

Combination of one drug or biological & one device

Take an infusion set specifically designed for administration of the antibiotic penicillin as an example. The manufacturer wants to know if penicillin will have the same performance before and after contact with the infusion set. Therefore, the characteristics of the drug with and without contact with the device should be compared (i.e. comparative testing of "stability samples" versus "control or reference samples"). Carefully choose a reference sample; ideally, it should be a penicillin solution identical to the stability sample—except for the contact with the infusion set. Select containers that do not interact with the penicillin during the testing itself.

A logical first step when determining the study design is the evaluation of existing information regarding the **medicinal product** alone. For example, if instability for a drug has been demonstrated after 2 weeks at 25°C, stability testing of the device for 3 weeks at 25°C is clearly irrelevant. However, you should consider clinically relevant drug concentrations. A higher testing concentration has possibly more effect on the physical properties of the device (e.g. increased probability of crystallization, degradation of the device by highly active drugs, etc.). Moreover, high concentrations can mask instability; for example, compare the adsorption of 1 ng of a drug substance on a filter in an administration set used with 1 mL of a 10 ng/mL solution (10% loss) versus a 1 µg/mL solution (0.01% loss). Tests at the lower concentration will be a better indicator of this phenomenon. On the other hand, low concentrations can be challenging for the analytical techniques.

Take into account the associated **medical device** as well as the medicinal product itself. For an infusion set, consider reviewing the applied flow rate. Too high of a flow rate can prevent possible adverse interactions between the penicillin and the device. While, a flow rate that is too low does not represent clinical reality. Determine whether only newly manufactured devices should be used, or if it makes sense to include older devices in the study. Degradation of the device material can occur during storage of polymeric devices, with possible negative consequences for the combined product in later stages (e.g. creation of particulates, reactive leachables, etc.).

Prior to setting the actual stability testing conditions (temperature, humidity, time range, etc.); look at the final, real-life application. What are the clinical circumstances when a patient uses the infusion set and penicillin? Based on this information, select worst case simulating contact conditions. For an implantable device, testing at a temperature lower than 37 °C is irrelevant. Determine which time points are relevant for stability testing. Should it be just the starting point ("t0") and the end point? If instability of the penicillin is observed at the end of the stability study, when did this instability happen? Intermediate time point observations can help to answer this question.

Finally, decide which tests to include in the stability study package. Options include, but are not limited to:

- visual evaluation (appearance of solution, color, clarity and absence of visible particulates)
- pH measurement
- HPLC/UV or MS(/MS) assay for determination of the active pharmaceutical ingredient and possibly relevant impurities, degradation products, and excipients
- potency testing to evaluate the activity of biologicals
- determination of the sub-visible particles (according to USP <788>/<787> or EP 2.9.19)

Accounting for analytical and manufacturing variation, consider performing tests in duplicate or preferably in triplicate. Finally, assign the needed quality level (ISO, GMP) and set the acceptance criteria. When selecting these criteria, consider the variation of the tested medicinal product, as well as the variation of the analytical technique, (e.g. for LC-UV, 90-110% makes a scientifically sound acceptance range for the stability of a drug product).

The analytical testing has a targeted approach and a defined measurand. Unexpected or unknown elements can be detected depending on the methodology, (e.g. detection of a leachable or impurity of a drug product by the LC-UV assay targeting the drug itself). This may be interesting and provide additional information, but obviously cannot replace extractables and leachables testing or degradation studies for which clear guidelines do exist.

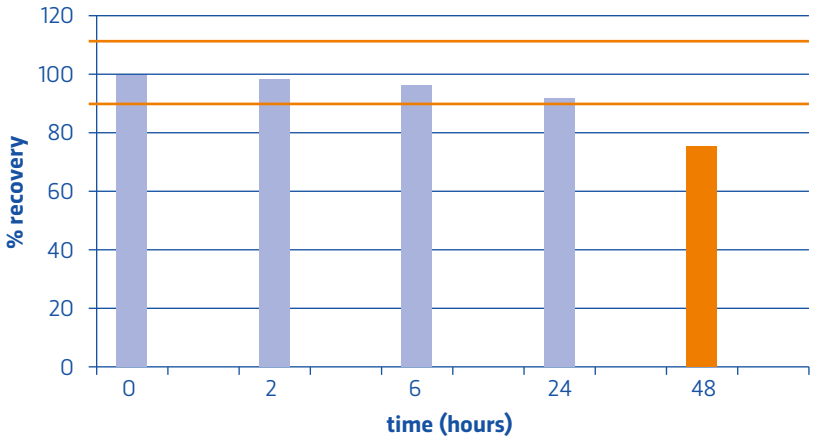
Combination of multiple drugs or biologicals (or both) & one device

Consider an infusion set that can be combined not only with penicillin but with 3, 10 or even 100 antibiotics, the stability testing could be repeated as described in the above section for penicillin another 3, 10 or 100 times. However, a more time and cost-efficient approach is to group the drugs and perform representative testing per group. To define relevant groups, consider the chemical structure and stability data of the drugs and biologicals. A careful selection should be made as it can have a significant impact on the outcome of a stability study. For example, a change in diluent or drug product can alter the leachables profile of a device, possibly resulting in stability issues.

Case studies of stability testing for combined products

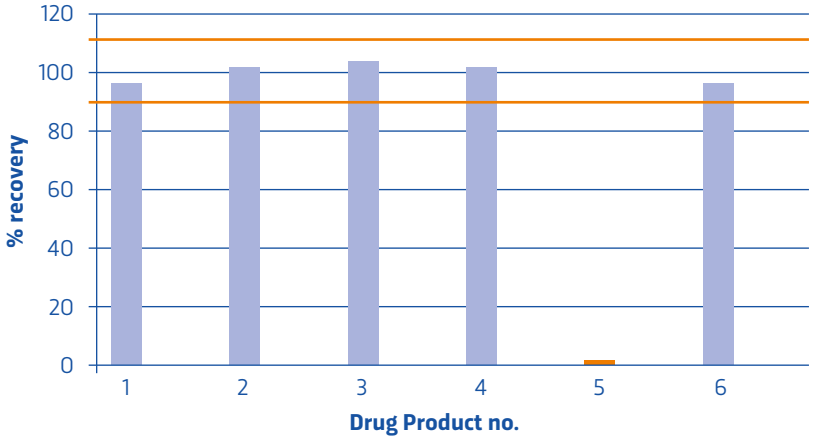
The following represents a real-life case study. A medical device manufacturer wants to evaluate the compatibility of a pump with a certain painkiller. The combined product is designed for drug administration for a maximum of two days. For in-use stability testing, three samples of the pump were filled with a clinically relevant concentration of the painkiller and stored at room temperature for up to 48 hours. Reference samples of the drug product were also stored in three separate, inert containers. At predetermined time points, a sample of drug product was collected from the devices and reference containers and the level of painkiller in the collected fluid was measured by a validated LC-UV method. The concentration ratio of the painkiller detected in the device samples versus the concentration detected in the corresponding reference sample was compared to the concentration ratio measured at 0 hours (i.e. immediate collection from the device), which provides the recovery percentage. A recovery of the painkiller between 90%-110% was used as acceptance criterion for stability. The graph below summarizes the test results of the in-use stability testing of the painkiller in the pump. From zero to 24 hours, the concentration measured by LC-UV decreases, but was within the acceptance criteria for recovery of 90%-110%. The measurement at 48 hours confirms the observed trend as actual instability. Since there is no concentration loss in the reference samples (considered in the calculation of the recovery percentage), possible explanations of the loss include degradation of the painkiller caused by the contact with the pump, absorption or adsorption of the painkiller by the device, or interaction with possible leachables released by the device.

Figure 1. Stability of painkiller in a pump



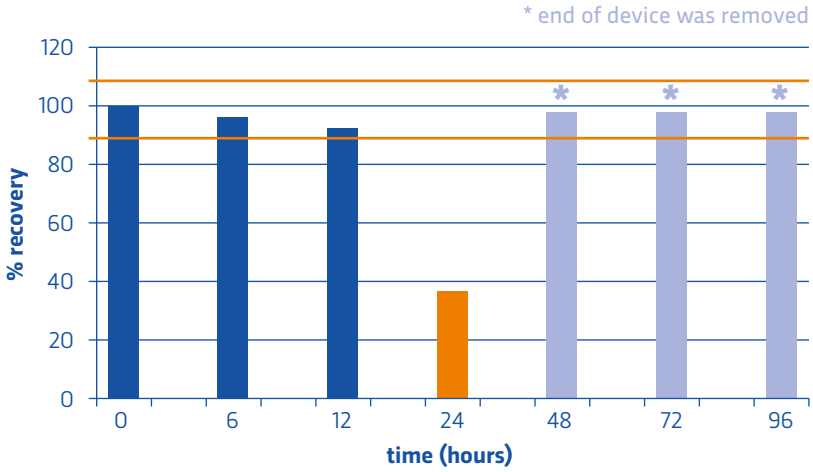
In a second case study, a medical device manufacturer would like to test their infusion set with six different antibiotics. In-use stability testing, as described above, was performed for each of the six antibiotics. Using LC-UV, the concentration was measured in the liquid collected after storage of the antibiotics in the infusion set as well as the reference samples after a predetermined time. All recoveries were higher than 90%, except for antibiotic no. 5. The hypothesis was that this drug was unable to pass a certain membrane in the device. The manufacturer did not conduct further investigations of the combined infusion set and antibiotic number 5. The manufacturer, to ensure that no weaknesses developed during handling and storage, conducted physical examination of the infusion device after contact with drugs 1, 2, 3, 4, and 6. This testing demonstrated device integrity for combined products numbers 1, 2, 3, and 4; but not for number 6. From this data, the end users of the combined product should be warned not to use drugs 5 and 6 with the infusion set.

Figure 2. Stability of 6 antibiotics in an infusion set



As a last case study, another medical device manufacturer wants to combine their infusion set with penicillin. This combination is intended for use up to four days. The following graph summarizes the observed in-use stability testing of the combined product. After 24 hours of storage, the tests showed a significant increase in backpressure when emptying the devices, indicating physical blockage of the infusion set. After 48 hours, emptying the infusion sets in the same manner as at previous time points was not practically feasible, and a part of the device had to be removed to collect the drug. The results obtained for 48, 72, and 96 hours came from samples that were not emptied via the end of the device. These data confirmed there was a physical problem with the infusion set first observed at 24 hours, while the penicillin itself remained stable up to 96 hours. Though the stability of the penicillin was not affected, the device in its current form is not compatible with penicillin for the intended application.

Figure 3. Stability of penicillin in an infusion set



Conclusion

When a medicinal product meets a medical device, a combined product is created. Incompatibility between the components can present a danger to the patient. Despite the indisputable need to demonstrate the fit between drugs, biologicals and devices and to ensure that the performance of all components is preserved, there is a vacuum of guidelines regarding how this should be done. In this paper, we presented stability-testing methodologies for the assessment of drug, biological-device compatibility in an attempt to provide a reference for medical device manufacturers involved in the marketing of combined products. Moreover, the authors plead for more regulatory guidance that assists in safeguarding the health of combined product users.

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About the Authors

Ruth Verplaetse, PhD

Ruth Verplaetse received her PhD from the Faculty of Pharmaceutical Sciences at the University of Leuven (Belgium) in 2011. Afterwards, Ruth was active in the field of development and validation of bioanalytical methods with LC-MS/MS. She started at Nelson Labs Europe (formerly Toxikon Europe) in 2016 as study director at the Extractables & Leachables department. In 2017, she became part of the Pharma Services Department where she is involved in identifying organic impurities in drug products, stability testing of drug-device combinations as well as development and validation of analytical methods.

Lise Vanderkelen, PhD

Lise Vanderkelen received her Ph.D. from the Faculty of Bioscience Engineering at the University of Leuven (Belgium) in 2012. She started at Nelson Labs Europe in 2013 as Study Director Extractables & Leachables, focusing on parenteral applications, and in 2014, she became responsible for the chemical characterization testing of medical devices (ISO 10993-18). In 2016, she became Department Head Pharma Services at Nelson Labs Europe. The main focus of this team is identifying organic impurities in drug products as well as in-use stability for drug-device combinations. In 2017, the scope expanded and now she is also responsible for all microbiological as well as in vitro toxicological testing and cleaning validations at Nelson Labs Europe. Lise actively speaks about extractables and leachables, material characterization of medical devices, impurities, and drug-device interactions at conferences and workshops. She is also one of the key lecturers at the Impurities Forum organized by ECA.

About Nelson Labs

Nelson Labs, A Sotera Health company, is the leading, global provider of lab testing and expert advisory services. We perform microbiological and analytical laboratory tests across the medical device, pharmaceutical, and tissue industries. The company is regarded as a best-in-class partner with a strong track record of collaborating with customers to solve complex problems. We have over 700 scientists, technicians, and service specialists who diligently perform more than 700 rigorous tests in 13 global laboratory locations.

Based in Belgium, Nelson Labs Europe specializes in providing premium Extractables & Leachables testing services to the pharmaceutical and medical device industries. We also support pharmaceutical companies across the globe in developing worldwide compliance testing strategies to qualify container/closure applications and pharmaceutical production equipment from an Extractables & Leachables perspective.

With decades of expertise, we stand behind the quality of our results and the strength or our customer partnerships. Along with sister companies Sterigenics and Nordion, we are part of Sotera Health, the world's leading, fully-integrated protector of global health.