MEDICAL ENGINEERING TECHNOLOGIES

Guidebook to Combination Device Validation and Verification

Volume 1

Contents

Foreword

Whilst I am not an expert in this crucial global market, nor do I have a financial interest, I do know just how important quality and service must be. That is why I have agreed to pen a foreword which I hope will complement the greater detail laid out here.

In the ever-growing market of medical combination devices, it is more important than ever to have a clear picture of what is at stake. Not only market statistics matter; it is less important to know how many devices are sold in which continents than it is to know that your delivery systems medical devices are of excellent quality. For this, however, it is not enough that your developments pass inspection; it is equally important to appreciate that the inspection was performed with the kind of diligence that goes beyond mere standards and regulations.

The choice of independent contractors to hire to fulfil the validation and qualification needs of your new products can be difficult to make. Naturally, you want your API and delivery system to pass inspection, but you also want the process to be done conscientiously and with the assurance that if there are challenges or problems, the testing service can offer valuable help.

Independent contractors, such as Medical Engineering Technologies, offer the personalised assistance you are looking for. With their nearly 25 years of experience, their staff of scientists provides the kind of comprehension necessary to help you through every aspect of the process. Headed by CEO and founder, Mark Turner, and supported by his 25 head staff, MET has accumulated varied experience and expertise from serving customers all over the world.

In this guidebook, Turner shares his valuable insight with you, demonstrating the commitment that goes into providing MET's customers with the best service possible, which emphasises continual scientific innovation, friendly customer relations, and of course scrupulous attention to precision and efficiency.

David Blunkett

Member of the British House of Lords
Secretary of State for Work and Pensions 2005
Secretary of State for the Home Department 2001 –2004
Secretary of State for Education and Employment 1997–2001
Member of Parliament 1987 –2015

About MET

Meticulous testing of medical devices requires more than conveyer-belt treatment of parts and particles. In the end, it is the expertise as well as the unique approach to possible challenges that are of real value to manufacturers of medical combination devices.

With current prognoses of the market dynamics of medical devices and especially drug device combination products to grow steadily, the demand for continual device improvement is a natural byproduct. Globally increasing numbers of diseases, such as diabetes, cancer, and respiratory problems, concurrent with increased government spending on health initiatives, give reason to believe that the market will flourish considerably over the next few years.

Nevertheless, the North American market is predicted to dominate, due to increasing numbers of chronic respiratory and cardiovascular diseases, while Asia Pacific is pegged as an emergent market for drug device combination products. And even with the European, Latin American, Middle Eastern and African markets only registering moderate growth, the push to further research and development is inevitable.

In order to keep patients safe, medical combination devices will, therefore, continue to be tested to stringent standards, which will have to adapt to the developing devices accordingly. This continual updating and upgrading of devices and testing standards alike make it necessary for testing technology and contractors performing said tests to stay up-to-date.

In the following articles, written and collected over a period of four years, Mark Turner dives deep into the various standards the industry uses to test and validate medical combination devices. Previously published on ONDrugDelivery.com, Turner takes a critical look at regulations, procedures, and potential challenges, providing the reader with an objective perspective.

The first article, “The Need for a Fully Informed Laboratory in Combination Device Validation Services,” discusses the importance and advantages of partnering with a laboratory whose preclinical device testing and validation procedures are of highest quality when developing a novel combination product. While pharmaceutical companies are more confident about the regulations for active pharmaceutical ingredients (APIs), their understanding of validation procedures for the required delivery systems is often lacking. Therefore, it is important to find a confident and reliable partner to successfully launch a new combination device product that meets, if not exceeds, all the safety regulations.

Next, in his expert view as head of a medical device testing facility, Turner provides a summary of the current requirements of parenteral device manufacturers in the area of design validation testing and its regulations. He discusses various points in “Design Validation Testing – Drug Delivery Devices,” including the importance of design validation testing (DVT) as an integral component of the product master file for all medical devices including delivery systems as well as risk analysis as the starting point of any design validation analysis.

This is followed by “Verification of Injectables in Transport and Storage,” in which Turner discusses the regulations and requirements around testing combination products for their stability in storage over their shelf-life and during transport. If a delivery device is a single integral product including the drug and cannot be reused, it now has to comply with Article 117 of the medical device General and Safety Performance Requirements (GSPRs) of the Medical Device Regulation (MDR) in the EU. This regulation, in effect since May 2021, includes injection devices and prefilled syringes.

Toxicity testing is another important procedure for combination medical devices, and the question of whether testing for extractables and leachables is preferable over ISO 10993 is a valid concern that Turner discusses in “Which Is the Better Toxicity Testing Strategy for Combination Devices?” This article is directed at pharmaceutical manufacturers whose delivery system may be a pre-filled syringe, transdermal patch, inhaler, or an implant and who needs to demonstrate the system’s biological safety.

Turner takes this discussion further in the next article by elaborating on how inadvertent interactions of the delivery device and the active pharmaceutical ingredients (APIs) can alter the effectiveness of the drug to be administered. In “Extractables and Leachables for Injection Devices,” Turner explains the processes that ensure that there is no transfer of toxic substances from the containers that contaminate the APIs.

Finally, “Biocompatibility of Medicinal Product Medical Device Combinations for Airway Delivery,” discusses biocompatibility testing for inhaled medical products with particular reference to ISO 18562. He explains the standards applied to testing prefilled nebulisers, inhalers, and nasal sprays. Further combination devices include breathing tubes, for which Turner discusses risk assessment, particulate emission, and biocompatibility. He draws from three years of testing breathing components for biocompatibility.

The need for a fully informed laboratory in combination device validation services

Abstract

Mark Turner runs through the advantages and processes of working with a high-quality preclinical device testing and validation partner when developing a novel combination product.

Introduction

Typically, pharmaceutical companies are confident that they understand the regulatory pathway for active pharmaceutical ingredients (APIs) and their own formulations. However, sometimes they are less confident about the requirements when these are coupled with a delivery system. A good preclinical partner/test facility, such as Medical Engineering Technologies (MET), can provide regulatory guidance and design validation testing (DVT) to help assist in getting a product to the marketplace.

In some cases, the required testing is well defined (e.g. ISO 11608/ISO 11040 for pen injectors[1] (Figure 1) and prefilled syringes[2]), whilst with others it may not be so clear (e.g. hormone eluting rings and implants[3]). The process of addressing these requirements can be planned to ensure efficient project management and help reduce costs. When you work closely with your chosen preclinical partner/testing facility, they can help provide guidance on the test requirements and the sample requirements using acceptable quality limits (AQL) tables or test standards. Planning, in consultation with your chosen partner, should allow them to deliver testing efficiently and you to meet your deadlines.

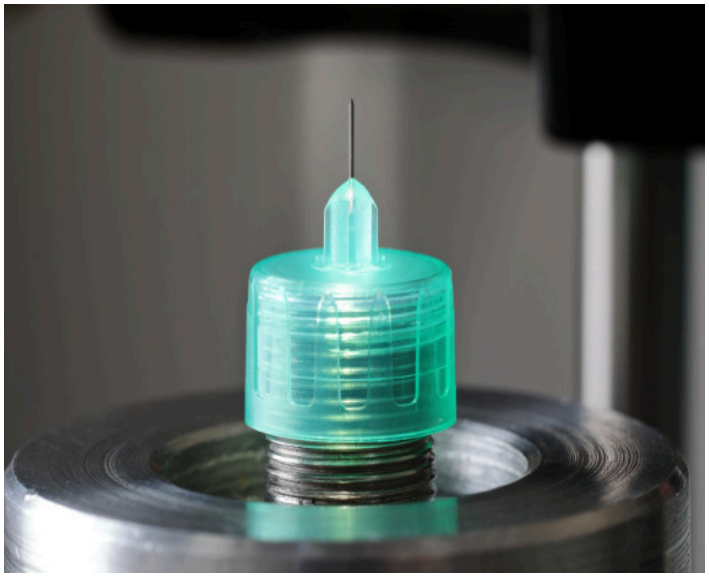

Figure 1: An injector pen needle undergoing testing.

Design Validation Planning

The prerequisites to developing a design validation programme are:

- Competitor submissions review
- Design inputs/targeted product performance
- European and/or US FDA Guidance review
- Risk analysis
- ISO/EN/ASTM/ICH/pharmacopeia standards review
- (If this is a first foray into combination devices) Gap analysis of the quality management system (QMS) and production processes and qualifications in place.

> **"A good preclinical partner/test facility, such as MET, can provide regulatory guidance and design validation testing to help assist in getting a product to the marketplace…"**

These processes can be conducted in-house or with a preclinical partner/test lab. A good knowledge of European and FDA regulations will help to speed up this process. The European Directive, combined with ISO 13485, gives a lot of guidance in the general areas of design control and safety considerations.

If a good product standard or European/FDA Guidance is in place, a lot of the required validation work may already be defined. Interpreting some standards can, however, be challenging. Even with the defined requirements seen in some standards, carrying out the risk analysis can still be both very important and very helpful. If good guidance is not available, the risk analysis is crucial. This analysis aims not only to identify all the risks, but also to quantify them. It can then be used to ensure that all the necessary testing has been carried out, and also to reduce any superfluous testing. Similarly, if guidance is not available, the key performance requirements must be identified in a product review. This includes design inputs and a literature review, thereby saving time and money. MET has developed standard study plans for a large range of devices.

These reviews and risk analyses can be used to develop the test programme and design test protocols.

Developing a protocol

The testing regimes in a DVT programme could include:

- Assessment of hazards identified in the risk analysis
- Bioavailability studies
- Biocompatibility studies
- Drug/container interaction analysis
- Extractables and leachables studies
- Toxicological risk analysis
- Human factors studies
- Performance and dose accuracy assessments
- Reference listed drug (RLD) comparison
- Standard/FDA Guidance compliance testing

Stability testing, following ICH (Q1A) guidelines, will also be required prior to launch. However, some stability testing will be required that will go beyond a product's launch. This repeat testing is likely to be carried out at intervals up to (and slightly beyond) the claimed acceptable storage period or shelf-life of a product. Evidence for product stability can be gathered using accelerated ageing (AA),[4] where raised temperatures are used to give real-time equivalence (RTE) for storage to the required ageing periods but less time is taken. The data provided by AA testing will require substantiation using data acquired from product that has been held at the normal storage temperature (real-time aged) for the actual ageing period. This can often be done after your product has been agreed for distribution.

> **"If a good product standard or European/FDA Guidance is in place, a lot of the required validation work may already be defined. Interpreting some standards can, however, be challenging…"**

To help a project run smoothly, Gantt charts and a more descriptive plan (provided by your partner laboratory) may be helpful. This plan can include test costing, time requirements, sample numbers, production or sourcing delay and sample description. Notes can then be added, explaining if a test is essential or just helpful. It can be shared between you and your testing facility, in order to ensure efficient communication of your requirements and required timelines.

MET testing plans shown in Tables 1, 2 and 3 use a transdermal patch as an example (though the same principles apply in injectable device testing) and give an idea of the types of testing, sample sizes and time requirements that would need to be considered. These tables are not comprehensive. Your chosen test facility can repeat this process for all the validation requirements identified in your reviews, giving you clear timelines and cost-effective plans.

Other considerations when looking at the timeline for the project, other than the longer-term stability testing, are factors that may not at first be considered to require extended time. For example, if you intend to carry out predicate testing as part of the design process for your device, predicate or RLD

products can be very difficult to obtain (particularly if several batches are required) and, in some cases, they can be very, very costly. Because of this, you need to be clear on what information is required and how many samples are required for statistically significant results.

Design validation testing

The first step when your project is handed to your test facility will be a protocol document, usually developed by the test facility (in conjunction with you). This document will clearly indicate tests, sample allocation, acceptance criteria and reporting requirements. Once the protocol has been agreed and signed by both parties, the project moves to the DVT stage.

The testing stage may be preceded by a gauge repeatability and reliability (GR&R) study to provide evidence that the test protocol is robust and that there can be confidence in the DVT results. Sometimes the tests involved are destructive and cannot be repeated on the same sample by multiple operators. In this case, it is common to use duplicate or triplicate testing on samples from the same batch. For example, during a prefilled syringe project, a technician might test 20 syringes for dose accuracy, and break-loose and glide forces on three different occasions (this could be on consecutive days). For a thorough validation, this would normally involve three technicians with each carrying out the test on three different occasions. Statistically concordant results should be achieved between technicians and instances of testing.

> **"To help a project run smoothly, Gantt charts and a more descriptive plan may be helpful. This plan can include test costing, time requirements, sample numbers, production or sourcing delay and sample description…"**

Although your chosen test facility may have carried out your chosen tests on numerous occasions and have several GR&R studies on file, your device may not be identical to those tested previously. In this case, you will need to consider (in order to keep costs down and timelines tight) if your notified body could accept these previously run GR&R studies.

Once the test procedure is approved, the DVT can proceed. The use of a laboratory with ISO 17025 accreditation will ensure that there is a good, fully-audited quality management system (QMS) and that equipment is qualified and calibrated, whilst processes are subjected to internal audits. It is entirely possible that not all tests will be specifically accredited. However, as long as these are carried out to an agreed protocol under the ISO 17025 QMS, there can be confidence in the results.

Some of the difficult questions relating to testing revolve around whether multiple batch testing is required and what kind of pre-conditioning is required. It may be possible to combine multiple batch testing with pre-conditioning. For instance, the ISO 11608 standard for injector pen testing has pre-conditioning at 70°C and -40°C. If the risk analysis shows that testing at these conditions is indeed necessary, the opportunity to test different batches at the different conditions presents itself. The total amount of testing is then reduced, by examining batch 1 after high temperature conditioning and batch 2 after low temperature conditioning.

Reporting

Test reports can be succinct or extensive. For regulatory submissions, a certificate of analysis will be too brief whereas as a hundred-page report will not be helpful. The report should include at least:

- Competitor submissions review
- Reference to the test protocol (the full protocol can be an appendix)
- Rationale for analyses included and excluded
- Any deviations from protocol
- Details of equipment and technicians
- Details of the product tested (batches, dates, description)
- Test results
- Summary.

> **"Some of the difficult questions relating to testing revolve around whether multiple batch testing is required and what kind of pre-conditioning is required…"**

A report may not finish with a conclusion. If testing has been carried out following a standard with acceptance criteria or if there were definitive acceptance criteria described in the protocol, then it is possible for your laboratory to conclude whether these criteria were met or not. For example, ISO 11608 defines the required dose accuracy for injector devices quite clearly and gives a statistical concordance requirement as well. However, if subtle exceptions are found, such as an oral spray producing an aerosol 10% less dense than the design specification, the clinical knowledge of the pharmaceutical company is needed to assess the importance of this data.

Summary

This article does not end with a conclusion. When developing a combination device, a pharmaceutical company must decide whether to carry out testing in-house or externally.

There is no compulsion for independent testing, as long as a company's own laboratory is fully equipped, has all the control systems in place and will act without bias.

The advantages of using an experienced, well informed external laboratory are:

- Clear independence
- No capital costs
- Efficiency of project management, testing and reporting
- Good advice from a knowledgeable source.

Things to look for when selecting a laboratory are:

- A good QMS and good quality control
- Informed and helpful staff
- Rapid, accurate responses to queries
- Openness of access
- A comprehensive range of services (to reduce multiple sourcing and adding several companies to your supplier list).

MET's staff have developed plans for many projects and a wide variety of devices. These have been successfully implemented within an ISO 10725 QMS, helping clients to achieve a smooth entry into the market.

References

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2. "Prefilled Syringe Testing". Medical Engineering Technologies website.
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4. "Accelerated Ageing Test for Medical Devices". Medical Engineering Technologies website.

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Table 1: Biocompatibility and chemical safety tests.

CE ER Check List	Test	Detail	Sample Requirement	Sample Condition	Time Requirement
ISO 10993	Biocompatibility	Cytotoxicity	30	Final product sterile	8 Weeks
		Sensitisation			
		Irritation			
		Acute			
EMEA Guidance	Chemical Safety	Extractables & Leachables	25	Final product sterile	12 weeks
		Drug compatibility	10	Final product sterile	12 weeks
		Toxicological Risk Analysis	Follows chemical analysis		3 weeks

Table 2: Bench tests.

CE ER Check List	Test	Detail	Sample Requirement	Sample Condition	Time Requirement
1,2 and 3 (4), 9.2USP 5/6EMEA Guidance	Laboratory Performance	Dermal adhesion	5	Final product sterile	4 Weeks
		Conformability	5		
		In vitro dissolution	20		

Table 3: Packaging tests.

CE ER Check List	Test	Detail	Sample Requirement	Sample Condition	Time Requirement
4 ISO 11607	Packaging	Transit simulation followed by pack strength and integrity	40	1 shipper carton	3 Weeks
8.3 ISO 11607	Stability	Accelerated ageing followed by pack strength and integrity	40 per time period, plus 40 reference and 40 real time	Final packs sterile (product not essential)	8 weeks per year

Design validation testing – drug delivery devices

Abstract

From a regulatory perspective, Mark Turner provides a summary of the current requirements of parenteral device manufacturers in the area of design validation testing.

Introduction

Design validation testing (DVT) is an important component of the Product Master File for all medical devices, including those used for delivering drugs and/or biologics to their target in the body.

Although this article uses prefilled syringes as an example, the principles apply to just about any drug presentation that is not a capsule, tablet or pessary (unless it has an applicator). It is a review of the testing required to demonstrate product performance.

> **"…the place to start with design validation is a risk analysis. This is likely to identify drug efficacy and product safety as the key areas to examine, in short: dose accuracy, toxicity, risk of infection and mechanical risk…"**

Standards

The relevant industry standards are:

- ASTM D 4169 Standard Practice for Performance Testing of Shipping Containers and Systems
- ISO 10993 Biological evaluation of medical devices
- ISO 11040 Prefilled syringes
- ISO 11608 Needle-based injection systems for medical use — Requirements and test methods
- ISO 80369 Small-bore connectors for liquids and gases in healthcare applications (replaces ISO 594)
- ISO 11607 Packaging for terminally sterilised medical devices
- ASTM F 1980 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

Dose accuracy

There are many aspects to ensuring dose accuracy. Some of these come from production processes, for example injectable viscosity, fill-volume and active pharmaceutical ingredient (API) concentration. Others come from the delivery system, including syringe dimensions, effectiveness of

actuation and maintenance of formulation (chemical and volume) in storage and transit. The transfer of the drug into the patient must also be effective and without leakage.

Dose accuracy is generally measured gravimetrically. Whilst the balance will be very accurate, attention must be paid to the differences between injecting in air and in flesh. In vitro extrusion of the syringe contents will be subject to evaporation, spraying and the retention of a bead of fluid at the needle tip. All of which could produce inaccuracy relative to an in vivo administered dose.

ISO 11608 and the US FDA Guidance, Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4, provides a number of tests to be considered.

Break-loose force: the force required initially to move the syringe plunger. This can influence the dose accuracy and the speed of injection. Difficulty in operating the syringe due to high break-loose force could cause misplacement, whilst an unrestrained plunger could move in transport.

Glide force: the force required to keep the syringe plunger moving. This can influence the dose accuracy in a similar way to the break-loose force.

Separation force: the force required to remove the needle from the syringe. The FDA recommends the use of a bonded needle to prevent its separation. If the needle is not bonded, the connectivity to any downstream system is important and its integrity and reliability should be demonstrated. Note that due to a high incidence of incorrect connections being made in practice, ISO 594 has been replaced by ISO 80369 which describes specific connector dimensions for different applications.

Unscrewing torque: ISO 11608 gives values for the force required to remove needles which are screwed onto the syringe.

Ease of assembly: another ISO 11608 requirement relating to re-usable pen injectors.

Resistance to overriding: a requirement of screw-on needles and Luer connectors, over-tightening of the needle could damage the thread and reduce the security of the connection.

Stress cracking: this primarily relates to the stress placed upon the male Luer of the syringe by the needle, but other forms of stress cracking should be considered from things such a mechanical or chemical stress, all of which can lead to leakage or particle generation.

Validation of graduation markings: this is a requirement for markings on a syringe barrel or within a dispensing system (e.g. a pen injector). Often the full contents of a syringe will be dispensed and markings are not required. Variable dose dispensers do have markings which can be in the form of a dose selection dial (don't forget to measure the forces required to operate the dial), or on the syringe barrel if there can be a clinical need for a partial injection.

Dead space: air bubbles in the syringes could expand in air transport (causing leakage) or allow oxidation of active ingredients.

Coring needle test: needle blockage will interfere with correct dosage.

Seal integrity testing: this is required to demonstrate that there is no loss of dosage or ingress of liquids and should include verification of any connections, such as Luers or screw-on needles. This can be a difficult test to perform, especially when the syringe is hidden inside an auto-injector. Trace gas leak detection can be applied to good effect as can, in some cases, dye ingress. ISO 80369 gives visual inspection methods using a pressurised system, which should be included in a design validation programme but are not of adequate sensitivity to be used unsupported.

ISO 11608 gives a lot of information about dose accuracy, particularly for products which can be used more than once, such as insulin or growth hormone pens. There is a requirement to maintain the dose accuracy at all cartridge positions, at all dose levels and for the final dose from a cartridge.

Actuation forces are also important for auto-injectors, for example in cases where the force must be such that the device can be operated easily in an emergency situation. In addition, because of the automatic nature of these devices the user cannot verify the insertion of the needle. Therefore, the needle insertion depth and duration of dosing need to be tightly controlled to ensure that the dose is delivered correctly.

Biocompatibility & toxicity

An initial review of biocompatibility might suggest that ISO 10993 provides all the answers, but it does not. ISO 10993 considers how a device contacts a patient and for how long. For a prefilled syringe the pathway is generally clear, blood path indirect, short term contact. However, the modes of testing given in the standard do not consider that the contents of the syringe may have been stored in their container for two years or more, or that some devices are used repeatedly for chronic conditions.

"An initial review of biocompatibility might suggest that ISO 10993 provides all the answers, but it does not…"

The testing chart given in ISO 10993 (with the additions from the associated FDA Guidance) indicates that the required tests for short term contact are: cytotoxicity, irritation, sensitisation, acute toxicity, pyrogenicity and heamocompatibility. In addition, extensive extractables and leachables analysis should be included to account for the risk of the transfer of material into the injected fluid during storage. This need is likely to be highlighted in future versions of ISO 10993, as the emphasis moves from animal testing to chemical analysis. The extractables and leachables study should include consideration of the production processes and materials, the packaging materials and labelling, and, of course, the syringe components and their possible sources of contamination. Particle generation should also be considered in addition to chemical contamination.

For treatments addressing chronic conditions it may be necessary to address genotoxic and chronic toxicity endpoints. In these cases, extremely low levels of migrating material are tolerated. In all cases a toxicological risk analysis should be considered.

sterility & stability in storage & transit

Parenteral products might be rendered sterile by terminal sterilisation (ethylene oxide, radiation or autoclave) or they may be assembled in an aseptic environment. It is not sufficient to demonstrate that the injectable is sterile at the end of this process: it must remain sterile right through to the point of delivery.

Guidance on the maintenance of sterility comes from ISO 11607. Once sterilisation and packaging processes are validated, the shelf-life and transit security can be addressed. The ageing process can be accelerated by the application of methods set out in ASTM 1980 or the ICH Guidelines. Apart from syringe integrity tests, seal strength and integrity tests should be applied to any sterile outer barrier (e.g. blister or pouch).

ASTM D 4169 provides a framework to simulate vibration and handling in transit, whilst the US Federal Aviation Authority tells us what pressure to expect during air transit. We recommend confirmation of sterile barrier performance following transit and an assessment of pressure changes on the volume of the syringe contents. Also particle generation during this phase of the product lifecycle might be considered (due to vibration in transit).

Similarly the sterility of the product should be confirmed at the end of the product storage life. This testing can be combined with an examination of performance aspects such as delivery forces and volumes, which may have been influenced by changes in the fluid, the siliconisation of the syringe or the composition of the stopper.

"Due to a high incidence of incorrect connections being made in practice, ISO 594 has been replaced by ISO 80369 which describes specific connector dimensions for different applications…"

Mechanical safety

Transit testing will have shown that a product remains intact up to the point of use (glass syringe not broken, needle protection in place, etc.). However, it remains necessary to examine any safety mechanism. If the needle is protected by a simple cover, its removal and re-attachment forces should be ascertained. This and any anti-needlestick mechanism should be safe and effective as recommended in the FDA's guidance document, Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features: which cites "connectivity to other devices necessary for use (e.g., needles, adapters, transfer systems, extension tubing, Luer connectors, and sharps prevention features)".

A final consideration is piston seal blowback (the ability of a syringe with a tip cap to hold a certain pressure on the piston)

Method validation

All test results reported in a DVT study should be obtained using validated methods and calibrated equipment. Often the method validation is achieved using trained technicians in a multi-operator study. If risk analysis identifies that a particular product may influence a mode of testing, or behave unusually in any particular test, these tests should be validated for that product.

Conclusion

Validation of drug delivery systems requires the review of a wide range of risks, standards and guides. On the one hand, not all the aspects described here are necessarily applicable to every product, and readers can probably think of many more that are. On the other, this confirms that a thorough risk analysis is required and that time must be made available for method and protocol development, followed by comprehensive testing using well characterised systems.

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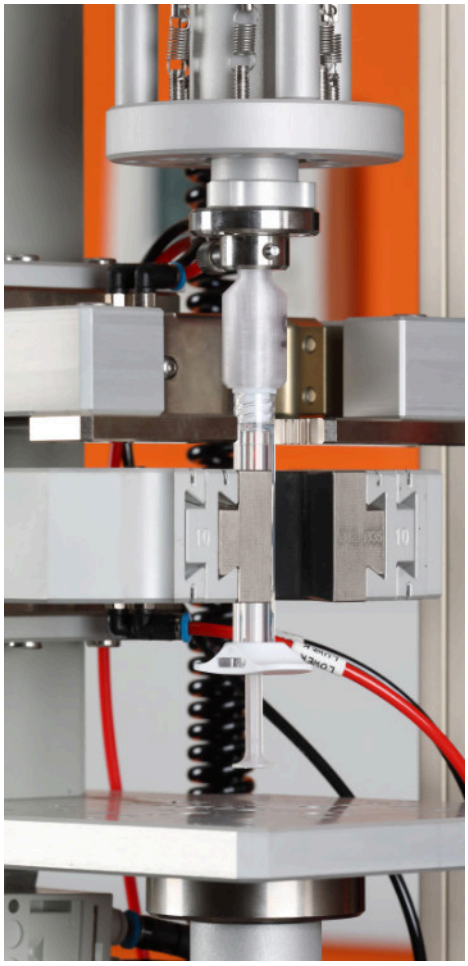

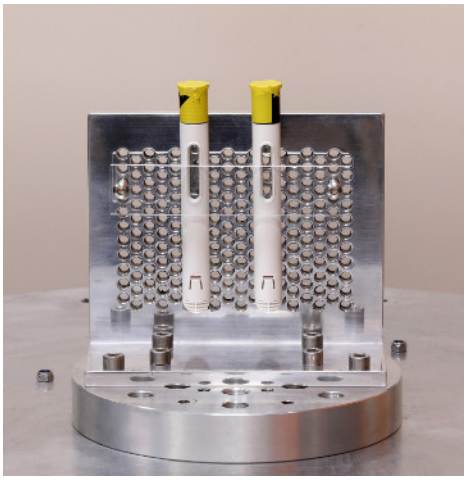

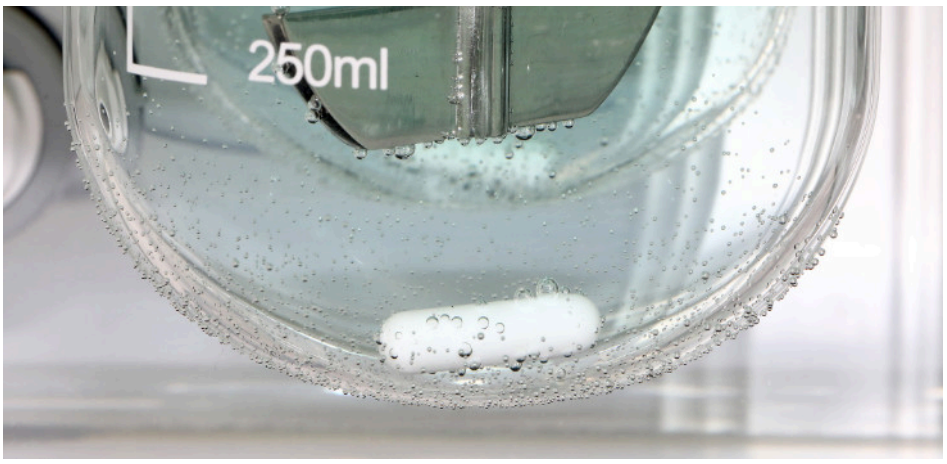
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Verification of injectables in transport and storage

Abstract

Mark Turner discusses the regulations and requirements around testing combination products for their stability in storage over their shelf-life and during transport.

Introduction

From the May 26th, 2021, many combination products will be included in the EU Medical Device Regulation (2017/745), commonly known as the MDR.[1] Specifically this inclusion is by Article 117 of the regulation. If your delivery device is a single integral product, including the drug, that cannot be reused, it must comply with the medical device General and Safety Performance Requirements (GSPRs).[2] These requirements include verification of the device's robustness in storage and transport.

> **"A dose accuracy study for a biosimilar injection will use a product that has been stored at the normal 4–8°C because the product, or other components of the formulation, could denature or degrade at 25°C and thus alter the measured dose dispensed."**

Stability Requirements

Pharmaceutical companies are familiar with the use of ICH guidelines[3] when demonstrating the stability of their formulations. The storage conditions outlined therein can be used for preparing combination products for performance testing at various points throughout their safe storage period, which is often the case in practice. For example, a dose accuracy study for a biosimilar injection will use a product that has been stored at the normal 4–8°C because the product, or other components of the formulation, could denature or degrade at 25°C and thus alter the measured dose dispensed. From the medical device point of view, the syringe is the sterile barrier packaging (GSPR 11.4).

This, for the syringe needle cover and stopper joints, would require a closed container integrity test (CCIT), an example of which can be seen in Figure 1.[4] If the combination product has secondary sterile barrier packaging, there will often be a blister or a pouch pack. Both the syringe seals and any secondary packaging will be subject to ISO 11607 Part 1 as part of the GSPRs.[5] This standard allows the use of accelerated ageing to obtain packaging stability information,

in advance of waiting for natural ageing to produce test material that has completed its recommended storage period. This is acceptable for both the secondary packaging and the CCIT. A temperature of 25°C is acceptable for this accelerated ageing. Typically, the rapid ageing for a medical device is carried out at 55°C (a condition that is not found in the ICH guidelines). At this temperature, for a product that is normally stored at 4–8°C, an equivalent shelf life of three years would be attained in approximately six weeks (ASTM F1980).[6] This allows the stability of the packaging to be validated well in advance of the validation of formulation-related performance aspects.

Transport Requirements

ISO 11607 also requires confirmation of the combination product's robustness in transportation. The specific standard used for this is usually ASTM D41697.[7] This standard gives conditioning (input) recommendations to simulate transit. These include stacking, concentrated impact, vibration and manual handling. There are a variety of pre-conditioning atmospheres that need to be applied, usually for 72 hours, before subjecting a shipping carton to the transit inputs. These would not be relevant for a cold-chain product.

For a device that is shipped without temperature control, consideration must be made of environments into which a carton may be shipped. With regard to the formulation, arctic or desert conditions are likely to be the most severe. When thinking about the carton, tropical (38°C/75% relative humidity) is usually the most severe environment. Other situations should also be considered, the most common one for delivery devices being air transport. For example, it is possible that an air bubble inside a prefilled syringe would expand and contract as an aircraft changes altitude. This can cause movement of the fluid, which in turn might cause a change in the dose available, or lead to evaporation and the deposit of residue which could block the needle aperture. These effects can be simulated in an air transit test chamber (Figure 2).

Conclusion

Drug-device combination products are just that, multi-component systems which straddle the medicinal and medical device regulatory systems. When it comes to stability testing, both pathways must be followed to demonstrate the stability of the formulation and of the packaging components. For the resistance to damage in transit, the two pathways largely overlap with consideration included for any product-specific hazards that have been identified in a risk analysis.

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Which is the better toxicity testing strategy for combination devices?

Abstract

Mark Turner explores the issue of toxicity testing for combination devices and asks which is the better testing strategy – ISO 10993 or extractables and leachables?

Introduction

You have a prefilled drug delivery system and you are wondering how to demonstrate its biological safety. Your product is the pharmaceutical but you are now delivering it in a ready-to-use syringe or transdermal patch, an inhaler or maybe an implant.

A pharmaceutical manufacturer needs to demonstrate that a packaging system is suitable for its intended use and that is does not introduce extraneous materials (of toxicological concern) into the formulation or degrade the formulation's performance. The formulation must also be free from process equipment related leachables at levels of toxicological concern. A medical device manufacturer needs to demonstrate that their device does not cause toxicity in its mode of use.

> **"The pharmaceutical approach still needs the extractables study to examine potential contaminants that could migrate into the formulation over a longer period."**

The US FDA definition serves both camps well: "Drug product containers and closures shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug beyond the official or established requirements."[1]

Significant progress towards the satisfaction of all these requirements can be made in a single extractables and leachables programme. A range of solvents and extraction conditions for the purposes of targeting a variety of potential leachables can be applied for both the device and the formulation packaging.

On Body Devices

Taking an on-body insulin pump as an example, there will be the external components of the cartridge and pump that are in contact with the body. The contact is with skin in this case, whilst only internal components will contact the formulation. A leachables study can be conducted on the fluid path to obtain information on what is likely to leach into the formulation. This same information can form the "simulated use" chemical characterisation of leachates required by ISO 10993.[2]

> **"When considering leachables from a pharmaceutical container, the nature of the formulation should be taken into account."**

The pharmaceutical approach still needs the extractables study to examine potential contaminants that could migrate into the formulation over a longer period. Similarly, the medical device approach will be missing information on cytotoxicity[3] and local irritation.[4] Some extra work is required in each case. Additionally, according to ISO 10993, the biocompatibility of the outside (skin contact) surface should be considered. Therefore, an extractables study should include the entire device – not just the fluid path.

Extract Media

A choice of media – such as 50% water / 50% ethanol – will give good information for the pharmaceutical extractable analysis and the device mid-polar leachables. The medical device extraction requires polar and mid-polar extracts to simulate the lipid and aqueous environments within the body (a third more polar extract must be included for invasive devices). Both study sets could use either saline or water as the polar extract medium.

When considering leachables from a pharmaceutical container, the nature of the formulation should be taken into account – is it aqueous and, if so, what is the pH; does it contain compounds that will influence migration of substances; is it non polar? To overcome this, in part of the study the leachables will need to be examined using the actual formulation. This is compatible with ISO 10993, which contains suggestions of which solvents to use but does not dictate them.

Post-extraction concentration and digestion for inorganic testing is also acceptable for both routes. For a pharmaceutical container, there may be more concern about the leachables concentration varying over time and the need for testing multiple batches. This would also be prudent for medical devices but it is not usually applied. Other additional questions for pharmaceuticals relate to bioavailability at the end of the shelf life.

Analytical Methods

The analytical methods are also largely the same. For the extracted materials, inductively coupled plasma mass spectrometry (ICP-MS), gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC MS) are most commonly applied. These methods allow quantification of the majority of the organic materials (across a wide range of volatilities) that might be found and any associated inorganic elements. There can be many variances for other analyses such as infrared absorbance and surface chemistry/morphology on devices and USP monograph and physicochemical analysis for pharmaceuticals.

> **"The quick answer to the question of whether to follow extractables and leachables testing or ISO 10993 for a combination device is that both are required."**

Toxicity Assessment

In both the pharmaceutical case and the medical device case, the chemical information gained goes on to be analysed by a toxicologist. In the toxicity risk assessment (following the analytical study), the same principles apply to both routes. Items such as the application of analytical evaluation thresholds (AET) and safety concern thresholds (SCTs) are common.[5] The Product Quality Research Institute (PQRI, Washington, DC, US)[6] has recommended that the high-risk SCT is set at 0.15 µg/day, whilst the low-risk SCT is set at 1.5 µg/day, both having been justified from toxicological and safety perspectives. Under certain conditions, such as short-term exposure or in the treatment of a life-threatening condition, the SCT can be raised above 1.5 µg/day.[7]

Implant Devices

What if my drug-releasing product is an implant? ISO 10993 includes a biocompatibility matrix[8] which describes the information it is necessary to obtain in order to demonstrate compliance. The matrix cross references body contact with "toxicological end points". These end points are the modes of toxicity that must be considered within a biological risk assessment. For an implant, just about everything is included: implantation, geneotoxicity, mutagenicity and chronic toxicity, to name just a few. Again, this is similar to the requirements for a pharmaceutical agent.

The requirements for an implant are more demanding than those for the surface-contacting insulin pump. Also, the "simulated use" extraction needs to be more aggressive because of the long-term contact at 37°C. There are many parts to ISO 10993. ISO 10993-18,[9] the chemical characterisation part, tells us to use exhaustive or exaggerated extraction for implants. ISO 10993-12,[10] the sample preparation part, is due for an update. It currently defines exaggerated extraction as 24 hours in the solvent at 70°C (however, this process might dissipate volatile contaminants and therefore should be accompanied by lower temperature extractions). The most aggressive possible solvent should be used, as long as it does not degrade the device in a non-representative way.

In situ degradation should also be considered for implanted devices. ISO 10993 has three sections detailing this requirement. One each for metal,[11] ceramic[12] and polymeric[13] devices.

Pharmacopeia Testing

There are a variety of areas in which the USP makes requirements of pharmaceutical manufacturers. Namely, USP chapter <1663>, Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, which is the basis for the chemical safety assessment section of USP <661.2>. This will soon be supported by two documents which are currently in draft form, USP <665> the extractables profile, and the chemical safety qualification draft USP <1665>. The latter applies to manufacturing systems, where a greater range of extraction solvents should be considered.

Study Design

There are well-defined components and structures to be used in analytical and toxicity study design and reporting. The first step is an assessment of the input materials and processes, which is used to define what chemicals might be available from containers, devices and production methods. In pharmaceuticals, this is framed as a justification of methods used. In the device world, it is called a biological risk assessment. This is the information that goes into the study design. It contributes to identifying:

- The extraction media to be used
- The extraction conditions
- The analytical methods to be applied as well as: method development – method quantification standards to be included – method validation – defining the sensitivity needed.

Again, the principles of study design and reporting are largely common between medical devices and pharmaceuticals.

Conclusion

The quick answer to the question of whether to follow extractables and leachables testingor ISO 10993 for a combination device is that both are required. You need to prove the safety of the pharmaceutical agent and the medical device. The practical solution is that a well-designed extractables and leachables study will cover most of the requirements for medical device biocompatibility. In the pharmaceutical case, it is necessary to show that the formulation is still active to the extent expected without the addition of extraneous materials. For the medical device, we don't want to put extraneous materials into the body – whether they come from the formulation or parts of the device not in contact with the formulation.

Some additional work will be required to cover both sets of requirements but there is also a lot of overlap. Both systems have hierarchy of risk related to intimacy of body contact, although low-risk surface or transient contact devices could still be delivering into high-risk environments such as ophthalmics or intravascular.

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Extractables and leachables for injection devices

Abstract

Mark Turner explains the process involved in ensuring that pharmaceutical containers do not inadvertently transmit toxic substances, while maintaining the effectiveness of the active pharmaceutical ingredients (APIs).

Introduction

Prefilled syringes, injector pens and cartridge pumps are convenient ways of self-administrating treatment, as well as being useful for carers, emergency situations and more general use. The range of treatments available in this format is large and growing. Just considering conditions or situations with the letter A, there is: antithrombosis (Enoxaparin), arthritis (Abatacept) and antiseptic (dental hypochlorite).

The containers in these devices may be produced from glass or plastic, and the delivery systems will most likely contain plastics and rubbers. In all cases they form primary pharmaceutical containers, for which it must be demonstrated that toxic substances are not administered to the patient. If they are to be used for intravascular injection, they are classified as "of highest concern" by the US FDA.[1]

> **"Once you know what you are looking for, and that you can find and quantify it, the analysis can begin…"**

According to the US Food, Drug and Cosmetic Act: "The reduction of substances migrating from the hardware into solution (or suspension) during production and what is often a three-year storage life is of primary importance for controlling toxicity and maintaining the effectiveness of APIs," and: "A drug is deemed to be adulterated if its container is composed, in whole or part, of any poisonous or deleterious substance which may render the contents injurious to health…"[2]

The toxicity concerns are to be expected, but there is also drug interaction to be considered particularly where the APIs are complex (for example, proteins such as insulin, and antibodies such as Adalimumab). Yet more complicated are disabled viruses in vaccines. In addition, all treatments, particularly those dependent on protein structure, can be vulnerable to degradation by migrating substances or contact with the container walls.

New materials and processes that minimise migration and maximise stability are being developed and marketed to

address these concerns. These materials improve the situation, but the need for verification of safety and bioavailability (and efficacy) remains.

The verification process

To ensure that materials of concern are found and quantified, an effective extractables and leachables analysis is required. Firstly, a thorough risk analysis to identify potential migrating species (chemicals that can transfer into the administered fluid) needs to be done of all the materials in the product and all the materials in contact with the product.

Once "potential migrants" have been identified, methods can be developed to search for them. These methods need to be validated using reference samples of the materials. Once you know what you are looking for, and that you can find and quantify it, the analysis can begin. Extraction media should be selected according to the potential migrating materials, component materials, drug materials, stability requirements and route of administration, with consideration also given to how to check for unexpected materials.

The resulting solutions – extractables and leachables (migrating materials) – are analysed using a wide variety of validated techniques. Most commonly, gas and liquid chromatography is used followed by mass spectroscopic analysis (for non-metallic materials), and atomic absorption (for metallic materials). Sample concentration may be required to achieve the required sensitivity.

Once the potential problems have been highlighted, a systematic approach to identifying and quantifying what is truly a problem is required. One approach is given in the flowchart in Figure 1.

The materials risk analysis

There can be a large number of potential contaminants (suspected and unsuspected). In many cases, the API in liquid form could influence the amount of material migrating from the delivery system and container components and/or (especially in the case of proteins) the API may be altered by any leachates.

To complicate matters further, the interaction between all these different components can lead to secondary leachables (or reaction products).

The materials to consider in the risk analysis include processing chemicals and contact surfaces, as well as the delivery system components.

A (non-exhaustive) list might include the following:

From production:

- Cleaning materials
- Mould release or other processing materials and lubricants
- Contamination from nylon or stainless steel transport mechanisms and other processing metals
- Metals from other sources (notably tungsten for glass syringes)
- Residual solvents
- Airborne and environmental contaminants.

From the syringe components:

- Unreacted monomer
- Oligomers
- Solvent
- Initiators
- Accelerators
- Stabilisers
- Side reaction products
- Catalysts
- Vulcanising agents

Within the formulation, some of the materials likely to be present are:

- API
- Excipients
- Buffers
- Lubricant
- Preservatives
- Solvent

Method development

According to the flowchart (Figure 1), once the potential materials of interest are identified, a study is designed. This should take into account what information is already known about these materials (whether potential contaminants or system components). Information on the materials may be available publicly, and also from companies' internal knowledge.

This information is then used to implement the following stages of the study: analytical method development; analytical method validation; extraction, identification and quantification; and toxicological risk analysis (TRA).

Analytical method development

Once the identity and nature of the possible migrating materials have been established, suitable solvents and analytical techniques can be proposed.

The analytical detection techniques will involve chromatography in liquid and gas phases to separate chemicals for individual analysis. The separated chemicals will be examined by UV absorption, mass spectroscopy and a variety of other techniques. Each of these processes will have its own set of conditions and arrangements, which are selected according to the properties of the potential migrating materials to be investigated.

These processes must deliver sufficient sensitivity, and have the resolution (of material identification) required by the TRA.

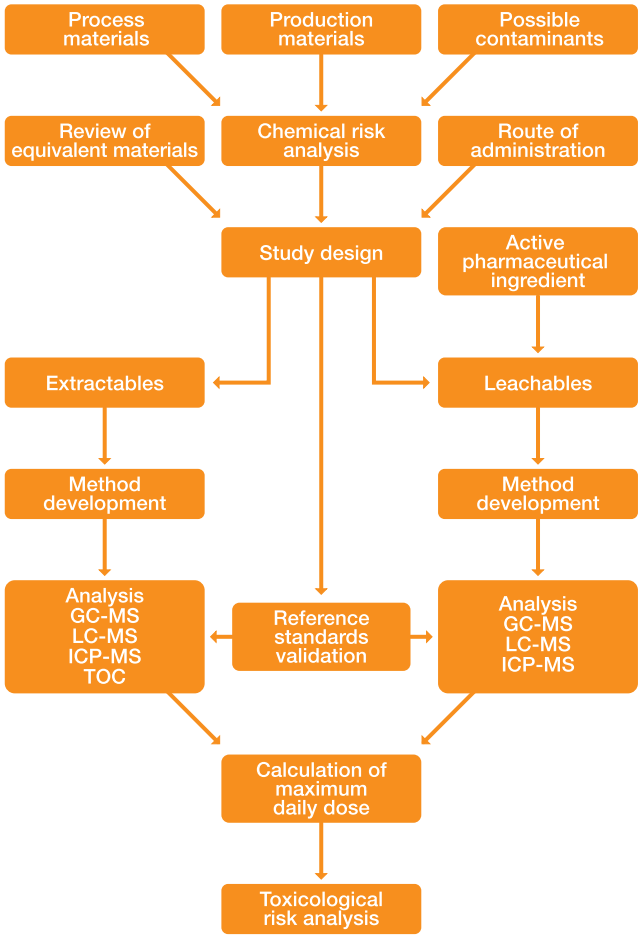

Figure 1: Using a flowchart to identify and quantify potential problems.

Analytical method validation

Validation is achieved by the analysis of reference samples of known concentrations using the same methods and conditions that will be used for identification and quantification of the migrating substances. Once verified in this way, an analytical method can be used to quantify the materials extracted from the test sample.

Extraction

The first phase of the product analysis is the transfer (migration) of materials from the solid phase of the delivery device into a fluid system for analysis (and to simulate use).

Extractables are what is forced out of the container system and leachables are materials that are likely to migrate under normal conditions. Normal conditions for a prefilled syringe are usually two years' contact (often at 4°C).

> **"The materials to consider in the risk analysis include processing chemicals and contact surfaces, as well as the delivery system components…"**

Leaching studies are usually carried out using the API, in its normal presentation, as the leaching medium. The time duration and temperature that can be applied to obtain migrating leachables is limited due to the time available for experimentation and the danger of denaturing components. As a result, stronger solvents and higher temperatures are often used in extraction studies to access materials which migrate slowly. Consideration of the storage period may also necessitate the application of multiple leaching conditions (and periods, according to ICH guidelines – ICH Q1 R2).

Also, because of the different processing parameters and make-up (polarity, pH and viscosity) of different formulations, it is necessary to examine the leachables for each formulation in a delivery system design.

Extractable studies are usually repeated with solvents of several polarities (examples are water, ethanol/water mix, isopropyl alcohol and hexane) in exaggerated conditions. For short-term contact containers, elevated temperatures with agitation would be considered but for longer-term containers exhaustive extraction might be used.

It is not always obvious what surface area to solvent ratio to use for extraction. With leaching it is logical to use the container itself, preferably including the drug-contacting areas. For extracting, ISO 10993-123 gives some guidance.

In this standard, the volume of extraction medium is related to the surface area of the device. A further consideration is the need to obtain a sufficient concentration of any migrating species, in order to allow detection at the sensitivity required by the TRA (see note).

Identification and quantification

The analytical methods are now validated and may be applied to the leachate and extractate solutions.

Unexpected materials will also be found in the analysis. These can sometimes be identified by the absorption spectra and fragmentation patterns (mass spectroscopy), but will need confirmation with reference materials. One of the more effective methods of identifying unknown materials is tandem time-of-flight mass spectrometry (MS/MS-TOF). This analysis is extremely sensitive (both in terms of concentration and in terms of molecular weight), which in turn gives more confidence in library identifications.

Toxicological risk analysis

Once all the data is gathered on what materials could (or would) migrate into the syringe content, the risk to patients can be assessed by calculating the possible quantities of materials reviewed. Typically, this will be the Product Quality Research Institute (PQRI, Washington DC, US) thresholds.

In terms of injection media contact time, injection devices can be broadly split into two categories. In one group the contact time is short, for example the drawing of an antibiotic into a syringe for immediate injection (whilst the syringe contact is short term, the contact time with the ampoule or vial is long term). Others have a long-term contact, such as that for solutions stored in prefilled syringes for several years or products used for chronic conditions. An example of chronic contact is an insulin pump which can be recharged. The contact time for each charge may be short, but the patient chronically receives repeated doses.

> **"It is not always obvious what surface area to solvent ratio to use for extraction. With leaching it is logical to use the container itself, preferably including the drug-contacting areas. For extracting, ISO 10993-12 gives some guidance…"**

The toxicity of each migrating substance found should be assessed with regard to the nature of contact with the patient and the likelihood of migration.

Toxicity is often described as a safety concern threshold (SCT). Information on this can be found (amongst other places) through PQRI, which uses the Crammer Index to classify risks whilst employing a 10x overdose factor. This classification can be effected by using Toxtree software (IDEAconsult, Sofia, Bulgaria). A quantitative structure-activity relationship (QSAR) assessment may also be used to ascertain the risk level posed by a chemical.

There may also be a need for an efficacy risk analysis at this point, because solutes or particles in the dosage form may alter the effectiveness or availability of the treatment.

Conclusion

The key to a successful extractables and leachables study is a systematic approach. It is best to examine components and processes thoroughly and work out what could be present, then develop and qualify processes to detect these materials with the sensitivity that will be required in the TRA. Analysing extracts from appropriate solvents, quantifying known substances, and doing the detective work to quantify unknown substances is also important. Finally, know what you can potentially administer and assess its toxicity.

Note: ISO 10993-12 also allows an increase in temperature to accelerate the migration. Increased temperature will effect heat-labile APIs. This could interfere with bioequivalence studies or change the migration characteristics. This should be considered when analysing the results.

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Biocompatibility of medicinal product medical device combinations for airway delivery

Abstract

Mark Turner discusses biocompatibility testing for inhaled medical products, with particular reference to ISO 18562, and what Medical Engineering Technologies has learned from three years of breathing component biocompatibility testing.

Introduction

Prefilled nebulisers, inhalers and nasal sprays are all drug delivery devices that may need to be assessed for biocompatibility as part of a combination product, under the specific standard developed for demonstrating toxicological safety of airway products – ISO 18562.[1] This ISO standard covers the biocompatibility evaluation of breathing gas pathways in healthcare applications.

The regulatory requirements for combination devices in Europe are given in Article 117[2] of the MDR. Regardless of which jurisdiction and filing approach is used, the US FDA will also be seeking evidence of biological safety.

Published in 2017, ISO 18562 has become the reference standard for breathing component biocompatibility testing. It precedes the current version of ISO 10993-1[3] the general reference for medical device biocompatibility testing, published in 2018. ISO 10993 includes examples of breathing components and lists them as mucosal membrane contact. ISO 18562 very sensibly adds particulate and gas testing to ISO 10993.

> **"It is relatively simple to test multiple samples of 'mass produced' components for short-term use. This is likely to be the case for combination devices. For long-term use ventilators, the availability of samples can be very limited and the testing procedure protracted, taking up to 30 days."**

ISO 18562 has four components: general principles, evaluation of particle emission, evaluation of volatile gas emission and evaluation of liquid-borne leachables in condensate.

ISO 18562-1 – Evaluation and testing within A risk management process

This section of the standard discusses the applied principles of testing and toxicological risk assessment. In the scope, we are told that it applies to devices that deliver respired air or other materials into the respiratory tract. It also states that if there is contact between the outside of the device and the patient then ISO 10993 should be considered. In keeping with ISO 10993-18,[4] it emphasises that data may already be available and this should be included in the risk analysis. Here we are told that a representative device, which has been manufactured in the same way as the final product, can be tested, as long as there are no subsequent changes. If risk analysis shows that it has the same toxicological hazard, a biological evaluation plan should then be formulated to decide what testing (if any) is required. A re-evaluation is required if processing, materials, handling or purpose change.

Toxicological Risk Assessment

Section six of ISO 18562-1 contains information on calculating the dosage of volatile organic compounds (VOCs) given to a patient during use. It has five categories:

1. Short-term use: use the actual gas flow in calculations
2. Neonate: default inspired volume is 0.23 m3 per day
3. Infant: default inspired volume is 2.0 m3 per day
4. Paediatric: default inspired volume is 5.0 m3 per day
5. Adult: default inspired volume is 20 m3 per day.

These volumes can be used to calculate the inspired dose delivered from the µg of VOC per litre of inspired air figure delivered by the test laboratory.

This section, along with section seven, looks into the toxicological risks posed by any VOCs and leachates found to be entering the patient. It is stated that materials should be assessed according to their individual toxicity data. If no inhalation toxicity data exists there is the possibility to use standard thresholds of toxicological concern[5] according to patient mass and duration of contact. If the volume of condensate entering a patient is unknown, there is an allowance for a volume of 1 mL per day to be used in the calculations.

Sample Numbers

The standard does not specify the number of samples that should be tested. In traditional biocompatibility testing, ISO 10993-12[6] defines a sample requirement by surface area (or mass) and it is not concerned with the number of products used. This applies to section four of ISO 18562, which covers the leachables. However, there is no guidance for particles and gases.

It is relatively simple to test multiple samples of 'mass produced' components for short-term use. This is likely to be the case for combination devices. For long-term use ventilators, the availability of samples can be very limited and the testing procedure protracted, taking up to 30 days. To make matters worse, samples may be bulky, making testing multiple samples for VOCs expensive. For the full duration of sampling, each test unit must be housed in its own temperature-controlled test chamber to avoid cross contamination.

> **"There are several options for collecting the emitted VOCs. Primarily, the standard highlights thermal desorption (TD) systems, but includes alternatives such as activated carbon filters."**

The use of representative samples is allowed. This can mean a pre-production sample for a complicated product, such as a ventilator. Smaller components are generally tested in their final format and from their distribution packaging.

To date, MET has tested single-use components at a sample size of three and a ventilator with a sample size of one. It is expected that there will be pressure for these numbers to rise.

Iso 18562-2 – Evaluation of breathing gas pathways, particulate emission

The standard gives a choice of test methods for capturing particles. The first is gravimetric filtering through a 0.2 µm filter, with all particles that are emitted over 24 hours and caught in the filter being counted. The second method is a particle counter, which siphons off a small part of the airflow.

The test is normally carried out at the maximum recommended flow rate for the product, which is intended to dislodge particles, forming a worst-case test. There is allowance for the use of an expansion chamber to help with the syphoning process. Both methods have their strengths and weaknesses.

> **"Section four of the standard only comes into play if there is a liquid path from the gas pathway to the patient. This can occur if device use involves two-way breathing and condensates from exhaled air can flow into the patient, or if water is introduced into the system through nebulisation or humidification."**

The filtration method lends itself well to longer-term and higher-flow monitoring, as multiple filters can be used in parallel to increase the airflow. The weakness is in obtaining accurate measurements for tiny masses of particles. This method also captures all particles greater than 0.2 µm in size. The standard states that it gives methods for quantifying particles between 0.2 µm and 10 µm, but also implies that other sizes should be included in a risk analysis. So, whilst one 20 µm particle could outweigh many 0.2 µm particles, registering its presence is helpful. Subsequent microscopic inspection can gather information on particle sizes.

Because the particle-counter method siphons off a fraction of the airflow, it cannot be certain that a representative sample has been taken. Additionally, many laboratories previously stocked counters with a minimum particle size of 0.25 µm, which do not conform to the standard. The counters are generally not designed for continuous use, and careful selection is required to ensure that the full reading over 24 hours is obtained. An expansion chamber can be added to the system if very high flow rates over a short time are required. This can be used to simulate a cough or sudden inspiration.

For both methods, measures must be taken to minimise and subtract the background particle count. The test should be conducted with an air supply filtered at 0.1 µm or less and should be very dry.

Iso 18562-3 – Evaluation of breathing gas pathways, particulate emission

VOC emissions testing is normally carried out at the device's minimum flow rate to allow time for diffusion of emitted vapours into the airflow. Additionally, the test is often carried out at an elevated temperature to increase volatility. VOCs are materials that become gases below 260 °C.

For short-term devices, measurements are made after 30 minutes, 60 minutes and 24 hours. The results for 30 and 60 minutes are included to allow an assessment of the rate of decay in emission production.

For long-term devices, measurements are also made after 30 minutes, 60 minutes and 24 hours. Subsequent readings are taken according to the results, usually at 48 hours and then approximately every three days (to a maximum of 30 days) until the emission level falls below 40 µg per day.

There are several options for collecting the emitted VOCs. Primarily, the standard highlights thermal desorption (TD) systems, but includes alternatives such as activated carbon filters. Furthermore, ISO 16000-6[7] is referenced.

Similar to a laser-counting particle test, the thermal desorption system has the disadvantage that it samples only a small portion of the airflow, which decreases sensitivity. Gas mixing is likely to be complete, so a lack of homogeneity should not be a problem in capture. Captured gases are subsequently released for analysis. In this phase of the test, a lack of homogeneity can be a problem and quite complicated release and recapture mechanisms can be required to ensure that low boiling point gases are accurately measured.

Apart from the method of adsorbing the released gas for later analysis, there is very little overlap between ISO 16000-6 and ISO 18562. Gases are sampled externally to the device in the environmental standard and internally in the biocompatibility standard. Additionally, the standard test temperatures are different. For the breathing component, the test device should be chambered at its maximum recommended temperature of use. This ensures that the worst-case VOC release is assessed. The absorbed gas is then desorbed and analysed by gas chromatography mass spectrometry (GC-MS). This technique is ultra-sensitive and can detect parts-per-billion levels or less. Once the chemical analysis data is available, it goes into a toxicological risk assessment.

The test system at MET includes negative and positive controls. The positive control consists of a mixture of 12 possible VOCs at known concentrations. The information from these controls is used to identify the system efficiencies, limit of detection (LOD) and limit of quantification (LOQ).

Inorganic Gases

The environmental standards for respired air contain limits for the abundance of certain very low boiling point inorganic gases. Some of these gases can react with VOCs to produce irritants. Specifically, measurements of carbon dioxide, carbon monoxide and ozone concentrations are required in the US for electrical equipment.

ISO 18562-4 – Biocompatibility evaluation of breathing gas pathway, tests for leachables in condensate

Section four of the standard only comes into play if there is a liquid path from the gas pathway to the patient. This can occur if device use involves two-way breathing and condensates from exhaled air can flow into the patient, or if water is introduced into the system through nebulisation or humidification. In these cases, chemical and biological testing

is required (ISO 18562 does not allow chemical analysis to replace the biological testing, in contrast to ISO 10993-1: 2020). The sample requirement follows ISO 10993-12 with aqueous-only extract for the chemical analysis. It is possible that some nebulised drugs will be aliphatic. This circumstance is covered by the biological testing. Chemical testing includes analysis for metals and organic compounds.

Obtaining samples for test is relatively easy for a nebuliser or vaporiser. However, as with the other tests, VOCs and particles, it can become very complicated for large devices. A sampling strategy is required for many ventilators and diagnostic systems. Because it is the gas pathway that is under test, it is desirable to extract samples from the inner surfaces of the device without cutting or disassembling it. It is stated in the introduction to section four that devices with significant patient contact, such as tracheal tubes, should follow the normal requirements of ISO 10993.

Once the extracts are available, chemical analysis is usually conducted for organic and inorganic materials. The inorganic materials (metals) are detected by ionisation followed by spectral or mass measurements in an electric field. The organic materials (most carbon-based materials) are detected by chromatographic separation and mass spectroscopy analysis.

The chemical analysis is controlled and quantified with the use of negative controls, a sample where pure solvent has been through all the same processes with no product present, and positive controls, negative samples spiked with known amounts of suspected contaminants.

The biological testing encompasses cytotoxicity and sensitisation studies. These are carried out according to the standard good laboratory practice protocols.

Conclusion

There is a requirement for the biocompatibility assessment of a huge array of medical and drug delivery devices (both combination products and co-packaged devices) to go beyond ISO 10993 and include consideration of particles and volatile materials delivered to a patient. This assessment can be carried out by examining existing data, but frequently requires testing of each specific product.

Particle testing is relatively straightforward, but the VOC testing can be complicated in both execution and analysis. The devices range in question from inhalers to larger inspiratory systems. Chemical testing is then very likely to identify a number of unexpected materials from these items which need to be analysed by a toxicologist, and there is a variety of ways of expressing the gathered data and toxicity evaluation, which can lead to confusion.

The requirements for leachate testing for fluid that can enter the respiratory system are better established but can still pose challenges. However, there are currently no specific requirements for the interaction between the pharmaceuticals and their delivery device as far as ISO 18562 is concerned.

References

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About Medical Engineering Technologies Ltd

Medical Engineering Technologies Ltd – UK'S Most Valuable Resource for Global Excellence in Device Testing

Medical Engineering Technologies is a world-leading CRO for combination device and pre-filled syringe testing located in the quaint and historic town of Dover in the county of Kent in Southeast England.

Not far from the famous White Cliffs of Dover, right opposite Calais in France and thus closest to the European mainland, MET delivers services to clients all over the world.

MET has successfully delivered testing to medical device and pharmaceutical companies in over 20 countries across every continent except Antarctica.

European, Austral/Asian, African, and US-American customers value our

- knowledge
- precision
- efficiency
- reliability

Delivering these values lies in current CEO and founder of MET Mark Turner's vision of increasing not only expediency but effectiveness and safety when he started the company nearly 25 years ago.

It was in 1997 that Turner's diversified knowledge and experience deriving from working in various industries led him to a desire to improve the field of medical device engineering.

History of MET

With a background in Chemistry, Physics, Cosmology, and Business Administration, Mark Turner became the engineer to revolutionise the industry. Part of his inspiration stems from working as a perfusionist pumping blood during heart operations; the stress of being responsible for somebody's life for up to four hours at a time imprinted on him the importance of reliability in the medical field – not only of people but also of the equipment.

During his rapid career to becoming Principal Engineer at Smiths Industries, Turner took them into unchartered territory with the development of a breathing filter range to which he later added electronic humidifiers.

Within Turner's ten-year tenure at Smiths Industries, he researched the clinical need, the science, and the technology of medical technology – all without the help of the internet – in order to specify and find the right materials and components before setting up manufacturing and contractors.

The reason MET is now at the forefront of medical device testing is that it was Turner who, realising that the progression of start-to-finish projects was slow without all the necessary suppliers for development, engineering, and testing of new devices at hand, created a resource for medical device developers.

In other words, he knows what it takes.

It is Mark Turner's year-long expertise in the field that sets MET apart from other testing facilities.

The Future of MET – The Next Five Years

With a full suite of physical testing for device performance and continual upgrades to our equipment, machinery, and staff, the goal is to become the world's leading independent combination device testing lab within the next five years.

Currently, more than 25 laboratory and administrative staff are dedicated to medical device testing, and the number is ever growing. During the year 2022, the chemistry laboratory will have move to its own building, thereby increasing capacities for the growing demand of analyses we offer. Additionally, stability chambers will be moved to their own building, which makes space for the extension of the physical laboratories, expanding to nearly double its size in the year 2022.

MET – At Your Service

At MET you can choose from a variety of services – all handled with perfectly personable customer service and absolute accuracy within the shortest amount of time. Choose from packaging validation, comprehensive verification support and batch release testing for combination devices, chemical characterisation through extractable and leachables, and human factor services to national as well as international standards.

Further services currently include:

- Biocompatibility and Chemical Characterisation
- Dose Delivery Accuracy
- Formulation Stability
- Mechanical Performance
- Reference Listed Drug Comparisons
- Sterile Barrier Verification
- ISO 17025 Accredited Testing
- GMP for Batch Release Testing

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To stay current on the advancements MET makes and its publication of white papers you can follow relevant journals in the field and subscribe to updates on our website.

You may also request white papers on various topics by contacting us directly.

Contact MET's team here and see what we can do for you:

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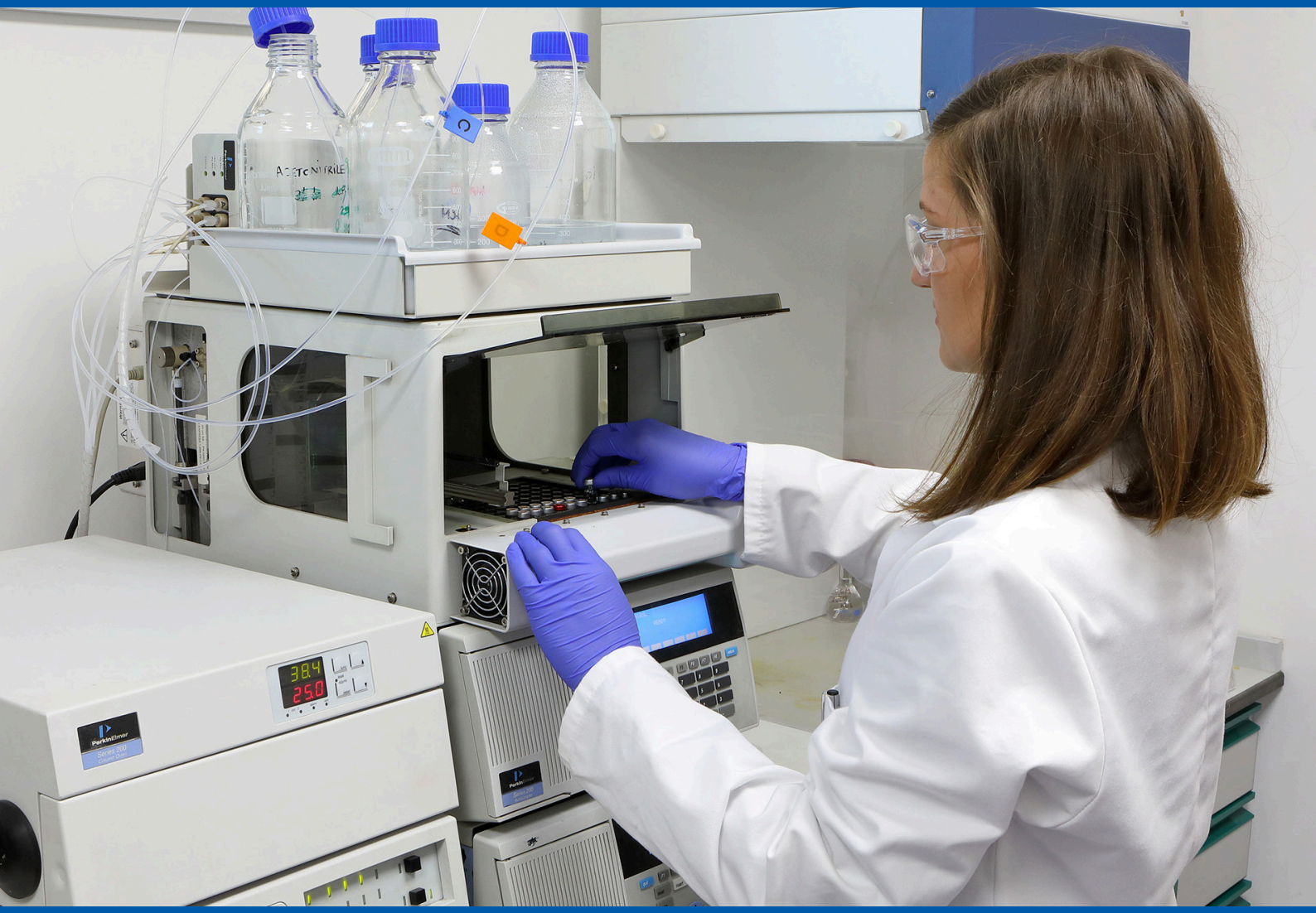

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