MEDICAL ENGINEERING TECHNOLOGIES

GLOBAL EXCELLENCE IN DEVICE TESTING

THE NEED FOR A FULLY INFORMED LABORATORY IN COMBINATION DEVICE VALIDATION SERVICES

In this article, Mark Turner, President, Medical Engineering Technologies, 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.

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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.

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.

These processes can be conducted in-house or with a preclinical partner/test lab. A good knowledge of European and

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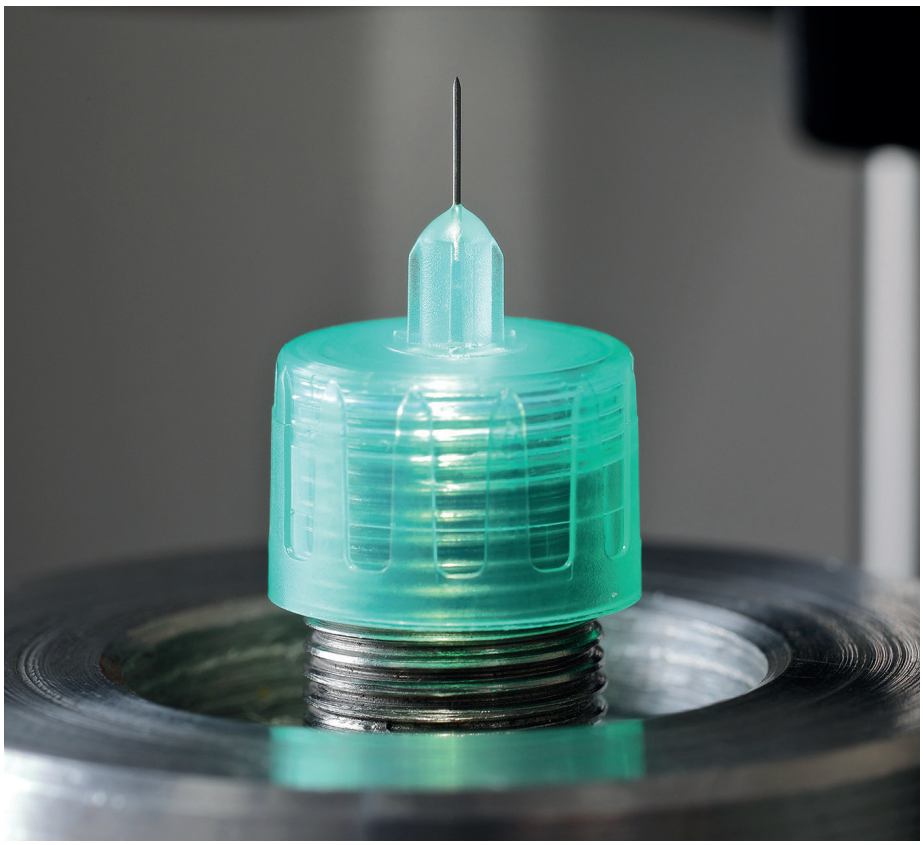

Figure 1: An injector pen needle undergoing testing.

"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."

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.

"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."

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.

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

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 and Leachables	25	Final product Sterile	12 weeks
		Drug compatibility	10		
		Toxicological Risk Analysis	Follows chemical analysis		3 weeks

Table 1: Biocompatibility and chemical safety tests.

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

Table 2: Bench 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

Table 3: Packaging tests.

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.

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

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.

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:

- 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, etc)
- Test results
- Summary.

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.

ABOUT THE COMPANY

Medical Engineering Technologies has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and the US. MET knowledgeably, reliably and effectively delivers medical device and packaging testing. Services include protocol development, laboratory testing, and data analysis. The laboratory is equipped for performance testing, chemical analyses and sterile barrier verification, and with accreditation to ISO 17025, customers can have complete confidence in the quality and accuracy of the results.

REFERENCES

1. *"Auto Injector Validation". Medical Engineering Technologies website.*
2. *"Prefilled Syringe Testing". Medical Engineering Technologies website.*
3. *"Performance and Delivery Testing of Sustained Release Devices". Medical Engineering Technologies website.*
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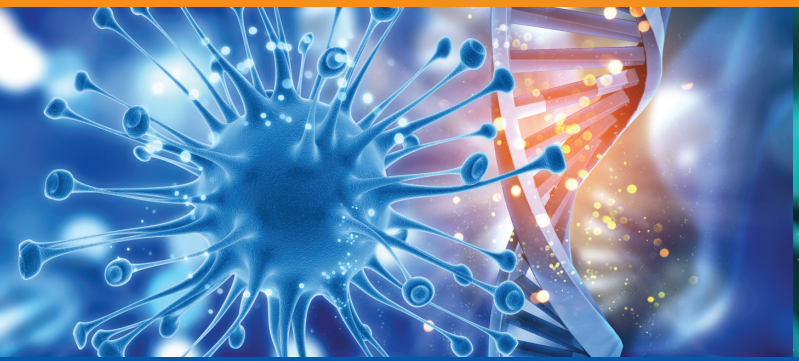
ABOUT THE AUTHOR

Mark Turner is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a Perfusionist in the cardiac unit of Kings College Hospital, London, UK, providing experience of the application of medical devices first hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales (UK) in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

- CCIT
- ISO 8009
- ISO 11040
- ISO 11608
- Glide Force
- Connectivity
- Trigger Force
- Needle Testing
- Dose Accuracy
- Human Factors
- Break Loose Force
- Performance Testing
- Transit /Altitude Testing
- Design Validation Testing
- On Body Delivery Systems
- Extractables and Leachables



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