EXTRACTABLES AND LEACHABLES FOR INJECTION DEVICES

Mark Turner, Managing Director, Medical Engineering Technologies, 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).

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]

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.

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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.

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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.

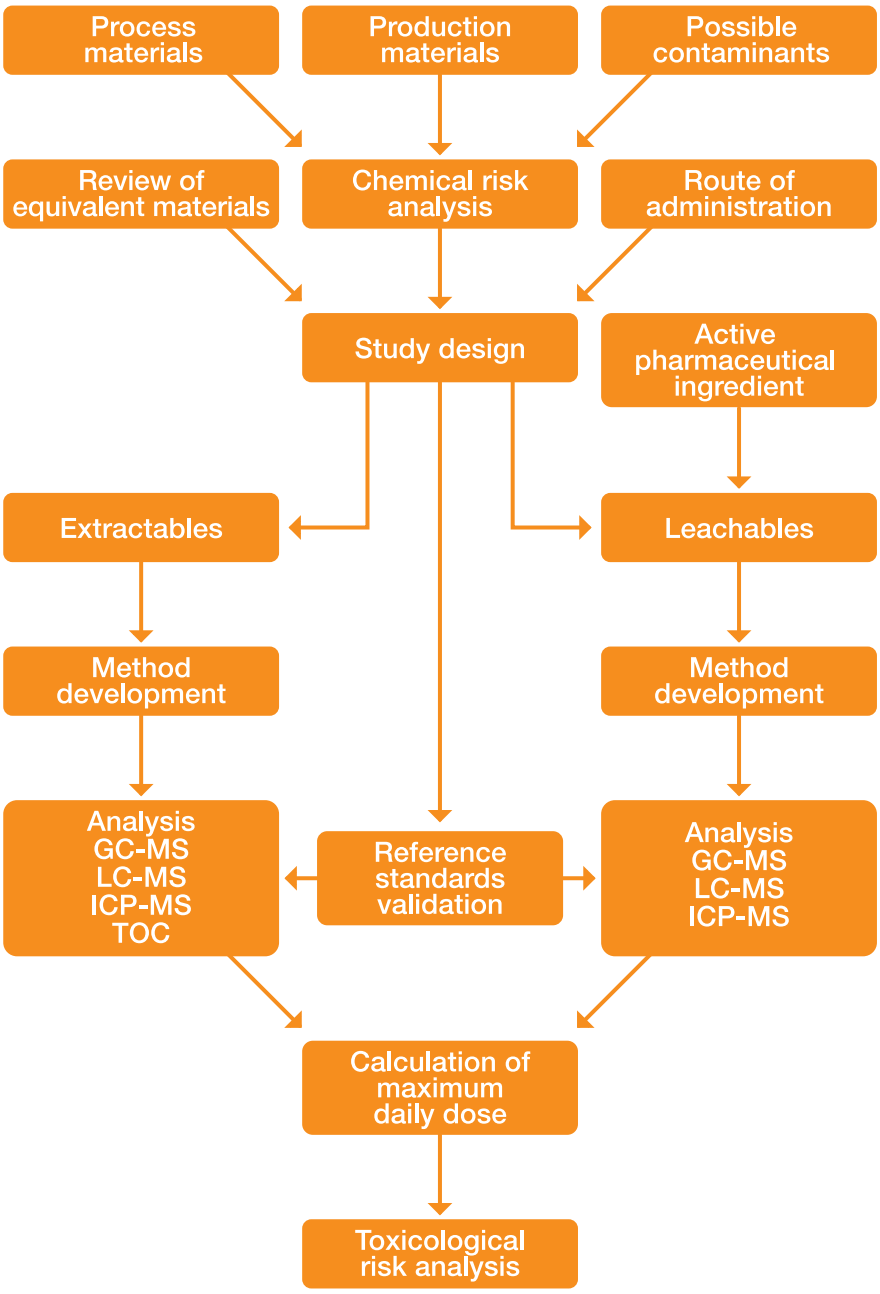

Figure 1: Using a flowchart to identify and quantify potential problems.

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).

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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.

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).

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.

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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[3] 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.

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.

REFERENCES

1. *Lewis D (US FDA), "Current FDA Perspective on Leachable Impurities in Parenteral and Ophthalmic Drug products." AAPS Workshop on Pharmaceutical Stability – Scientific and Regulatory Considerations for Global Drug Development and Commercialization, Washington, DC, US, October 22-23, 2011 (https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM301045.pdf, Accessed April 2018)*
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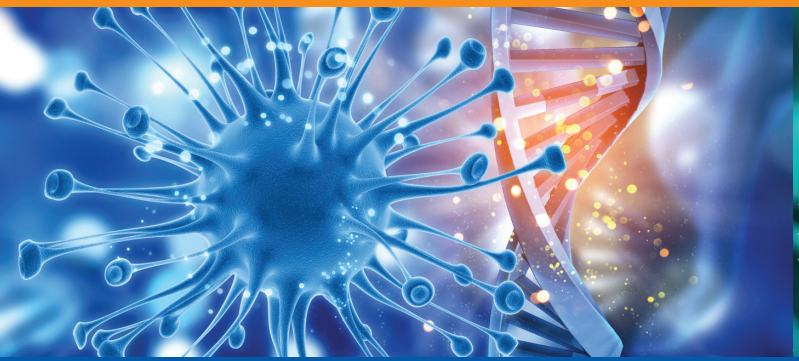
ABOUT THE COMPANY

Medical Engineering Technologies (MET) has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and the Americas. 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 confidence in the quality and accuracy of the results.

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. Mr 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 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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