Guidebook to the Chemical Characterisation of Medical and Combination Devices

Volume 2

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

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Introduction

Meticulous testing of medical devices requires more than conveyer-belt treatment of samples and results. It is the knowledge and expertise, as well as the care and the personal immersion of our technicians that that are of real value to manufacturers of medical and combination devices.

The diversity of devices and delivery systems is growing, the regulations are growing, the markets are growing. There is an on-going demand for continual device improvement, new formulations, more effective treatments. 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.

All these devices must be safe and effective and it must be recorded that they are safe and effective. We will help you document this by testing to the most stringent standards. Our processes will 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.

The following articles, written by the biocompatibility and chemical analysis teams at MET. The give in depth thought to the various biological safety standards the industry uses to test and validate medical devices. They give an up to date analysis of the current requirements and provide practical guidance on meeting those requirements. The reader is provided with an objective perspective and pathways to success.

An Introduction to ISO 10993-1

Health authorities around the world like to ask one most important questions from every device manufacturer – How much do you know about the safety of your product? It is not about just making a device that luckily passes all biocompatibility endpoints and gets on the market. It is more about showing that the whole development approach considers intrinsically the safest, best known most reliable materials for your product in the first place. This not only saves lots of time and money for the manufacturer, but also allows the new medical device to become safely available to the patient with its potential for improving or saving lives earlier than anticipated if biocompatibility testing is not actually required.

E Couzens
Biocompatibility Assessor

The whole risk assessment concept promotes the use of safer components as well as avoiding further cost and time in preparation to the submission and, of course, sensible, **justifiable only** use of animals for in-vivo tests.

In-vivo tests are still necessary tests on occasions where any toxic effect requires investigation which includes the whole complex biochemical chain of reactions in a mammal species or the local response within certain tissues interacting with the material is still unknown.

In-vivo tests have only 56%1 correlation with human body response. This is where chemical characterisation tests become a vital line of investigation as it provides a more accurate scan of possible leachable and extractable materials that could potentially be released to the patient. The Worldwide chemical and toxicological libraries information have reached such volumes that it is now possible to find toxicity data as well as local response reports relating to many components and materials.

New *in-vitro* tests are slowly but surely replacing in-vivo tests. The increasing popularity of *in-vitro* OECD based methods for irritation and sensitisation tests are tending to become more acceptable for EU submissions. These tests have a much higher correlation of results with the human response (than animal tests) – over 80%. However, there are still many of materials that are not suitable for testing by this method and classic *in-vivo* tests are still recommended by other authorities

It is important to know the end product interaction with the patient before considering the incorporation of a new material into the design of the Medical Device. The deeper (more invasive) and longer the MD goes into the patient tissues – the more intensive the biocompatibility tests become.

Thus, it is best to choose the material that has already been tested against the same biocompatibility endpoints. This is because the Risk Assessment will consider the existing safety data and will allow the avoidance any biocompatibility tests on the final product if good data is already available.

To bear in mind:

Because ISO 10993 is not a tick box exercise, more an information and risk based process, it explicitly explains that review is not limited to ISO 10993 endpoints. Relevant additional standards might need to be considered in the further review the safety of the product.

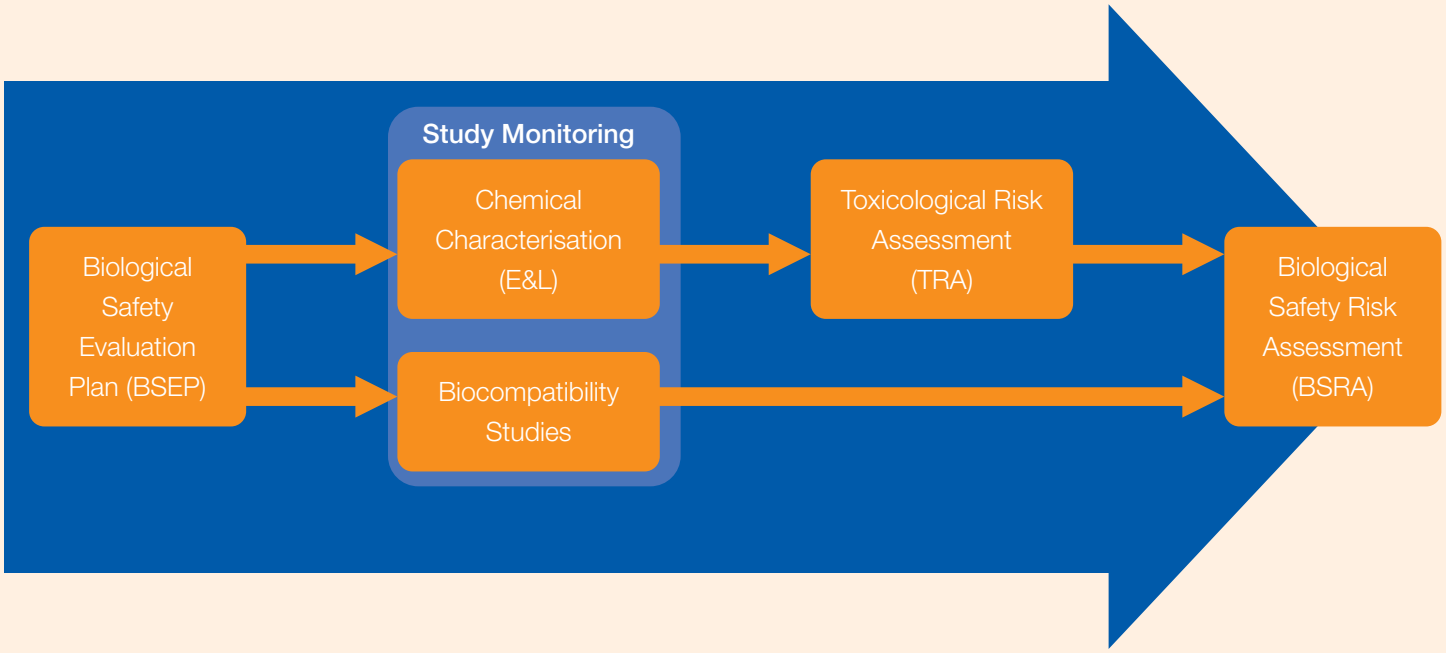
For example:

ISO 18562 – for the Gas Pathway devices

ASTM A555/A555M Specification for General Requirements for Stainless Steel Wire and Wire Rods

Ref 1

https://academic.oup.com/toxsci/article/159/1/3/3869930?guestAccessKey=4dc1e86c-9aed-44e1-8e95-e2a516e91ce7



ISO 10993-1:2018: Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

ISO 10993-1 had a major makeover in 2018. It was always supposed to describe a risk based approach to biocompatibility testing. This had become a tick off exercise in practice. The process was: look up on the matrix which tests are required, perform the tests, submit the application. In 2018 the risk assessment approach was emphasised by making the preparation and completion phases of the project obligatory.

Mark Turner
Managing Director MET

The process steps are:

1. **Develop the Biological Evaluation Plan**
2. **Carry out chemical analysis and biological testing only if necessary**
3. **Complete the Toxicological Risk Assessment (using chemical characterisation data)**
4. **Perform additional testing if requested in the TRA.**
5. **The Biological Evaluation Report.**

The BEP

The Biological Evaluation Plan (BEP) has become an essential precursor to the biological evaluation of medical devices. It has now developed into a risk analysis process which, for non invasive devices, can be combined with the chemical characterisation requirement. Together they can lead directly to a positive Biological Evaluation Report (BER) or to the specification of further testing prior to reporting positively.

The plan looks at each material in a device and its mode of contact with the patient. This definition is compared to the biocompatibility matrix to identify the required end points. Armed with this information the project team can scour their records for documents which demonstrate compliance with the end points.

The information can be tabulated. Here is an example for a mouthpiece which is a component of a larger device. The end points for mucosal membrane , permanent contact, over 30 days are: chemical characterisation, cytotoxicity, sensitisation, irritation, acute systemic toxicity, sub chronic toxicity genotoxicity, implantation, and chronic toxicity.

PVC Mouthpiece Component xxx, Prolonged Oral Contact			
Biological endpoint to be evaluated	**Standard to be applied**	**Available Evidence for Safety**	**Testing rationale**
Chemical characterisation	ISO 10993-18 chemical characterisation of materials	The Material Data Sheets and other referenced reports detail general toxicity concerns without specific reference to human biocompatibility.	Information inadequate when related to the finished device. Carry out leachables analysis and TRA.
Leachates in condensate	ISO 18562-4 leachates in condensate	Material supplier cytotoxicity report number xxx	In accordance with ISO 18562-4, detected leachable components will require further TRA with consideration of the exposure time and dose to the patient
Particulate Matter	ISO 18562-2 Particulate Matter	Component used in another device in the same range with exactly the same format and processing. This device has particulate testing, report number xxx.	No further testing required
Volatile Organic compounds	ISO 18562-3 — Volatile Organic compounds	No evidence found.	In accordance with ISO 18562-3, detected VOC above 2µg/m^3 will require further TRA with consideration of the exposure time and dose to the patient
Cytotoxicity	ISO 10993-5: Tests for *in-vitro* cytotoxicity.	Material supplier cytotoxicity report number xxx	No further testing required
Sensitisation	ISO 10993- Part 10: Tests for skin sensitisation	No evidence found	The available information is inadequate therefore testing is required ISO 10993-5
Irritation	ISO 10993-23: Tests for irritation	Material supplier has USP Class IV report, reference number	The available information is inadequate therefore testing is required ISO 10993-23
Acute Toxicity	ISO 10993-11: Tests for systemic toxicity	Material supplier has USP Class IV report, reference number	The available information is inadequate therefore testing is required ISO 10993-11 acute toxicity end points.
Genotoxicity	ISO 10993-3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	No evidence found	The available information is inadequate therefore testing is required ISO 10993-3
Sub chronic toxicity	ISO 10993-11: Tests for systemic toxicity	No evidence found	The available information is inadequate therefore testing is required ISO 10993-11 sub chronic toxicity end points.
Implantation	ISO 10993-6 Tests for local effects after implantation	Material supplier has USP Class IV report, reference number xxx	The available information is inadequate therefore testing is required ISO 10993-6
Chronic toxicity	ISO 10993-11: Tests for systemic toxicity	No evidence found	The available information is inadequate therefore testing is required ISO 10993-11 chronic toxicity end points.

Risk Assessment

The mouth-piece component has been made from materials with cytotoxicity testing to ISO 10993 protocols and USP Class testing. This provides insufficient evidence to provide confidence of biocompatibility for permanent mucosal membrane contact. Biological testing for oral irritation, acute toxicity, and local effects due to implantation are required. Chemical characterisation according to ISO 10993-18 combined with a TRA is required for the sensitisation, genotoxicity, sub chronic and chronic end points.

The device is not implanted and degradation is not suspected, therefore degradation testing is not required to ISO 10993-13: Part 13: Identification and quantification of degradation products from polymeric medical devices.

Pyrogenicity testing may be required for certain markets.

The device is employed within the patient airway and therefore is subject to the requirements of ISO 18562. Evidence of safe particle generation is provided but the evidence for VOC release and leachate release is not sufficient. Testing against ISO 18562 parts 3 and 4 is required.

In accordance with ISO 10993-17 the Toxicological Risk Assessment might require additional toxicity endpoints.

Notice that the risk assessment is not restricted to ISO 10993. Other standards or consideration are often relevant to a particular device.

The key question for this risk analysis is, whether the materials going into a device have proven safe use in an application at least as invasive as the application under consideration. If you are developing a novel resorbable suture, it is likely that you are using novel materials and such evidence does not exist. If you are developing a novel hemostatic , you might be applying novel materials or existing materials in a novel way. If you can provide evidence that the materials you are proposing to use are safe for prolonged, breached tissue contact and that your processing does not change the materials in a way which would affect the biocompatibility then no testing is necessary.

The goal here is to ensure that medical devices do not have toxic effects on the end user or at least that the cost benefit analysis of any toxic effects is positive. There is always a risk associated with a medical intervention, but this can and should be minimised. There is a secondary goal, which is to reduce the need for biological testing.

The sort of information that goes into BEP is:

- The application
  - Location and invasiveness of contact
  - Duration and frequency of contact
  - Target population
- The components list
  - The materials list for each component
  - The processing list for each component and the finished device (including any processing aids such as: lubricants, cleaning chemicals, cross contamination, sterilisation media…)
- The existing evidence of biosafety for each material
- ISO 10993 testing data
- MSDS chemical safety data
- Any contra-indications
- Any ecological hazards
- Previous submissions for devices containing the material

If the BEP indicates that all the materials have good evidence of safety, that processing has no possibility of changing this safety, that there is no risk of contamination and that the combination of materials is not toxic, then the Biological Evaluation Report (BER) can conclude that no further testing is required. If the conclusion is that safety has not been proven the BEP should propose a test programmed to satisfy the endpoints found in the ISO 10993-1 biocompatibility matrix.

The TRA

A toxicological risk assessment (of a medical device) is the process of gathering all possible toxicity data about the materials of construction, processing materials and potential contaminants, and using this information to provide a risk profile. For skin contact devices it is commonly the case that sufficient information is available to eliminate the need for any analytical testing. As a device becomes more invasive and the contact more elongated the need for chemical characterisation increases. Also, the intensity of the chemical analysis increases (number of extract solvents, extraction conditions, number of analytical methods applied). This culminates in the need for exhaustive extraction and degradation testing for implants. The TRA considers all sources of information.

The toxicity of many materials has been documented. This information, combined with knowledge of the application of the device, can be used in the safety assessment. The analysis should take into account the maximum available daily dose of all chemicals and the number of days dosing can occur along with a safety factor which often means multiplying the delivered dose by a factor of ten.

The TRA can be complex and time consuming as there are many factors to consider. This is often extended because a large number of chemicals are above the AET (explained elsewhere in this Guidebook). Each one must be individually assessed and also the combination of chemicals.

In the TRA each chemical present is listed along with its toxicity in the application of the device. The conclusion of the TRA can be that no materials of concern have been found at concentrations of concern. Occasionally a material of concern is found, and further biological testing is recommended. Occasionally because designers are aware of the need for biocompatibility and they select materials on that have known safety whenever possible.

The BER

The Biological Evaluation Report should always be a fairly simple exercise. If the BEP concluded that no further testing was required, it is effective also the report. If testing has been carried out the BER confirms that the end points listed in the BEP have been satisfied.

See the following page for how the table now looks:

PVC Mouthpiece Component xxx, Prolonged Oral Contact			
Biological endpoint to be evaluated	**Standard to be applied**	**Available Evidence for Safety**	**Conclusion**
Chemical characterisation	ISO 10993-18 chemical characterisation of materials	The chemical characterisation report referenced herein identify the chemicals which could possibly leach into a patient. The TRA , also referenced, concludes that none of these materials are a cause for concern.	End point satisfied
Leachates in condensate	ISO 18562-4 leachates in condensate	The chemical characterisation and biological testing reports referenced herein along with the TRA , also referenced, conclude that there are no materials that are a cause for concern.	End point satisfied
Particulate Matter	ISO 18562-2 Particulate Matter	Component used in another device in the same range with exactly the same format and processing. This device has particulate testing, report number xxx.	End point satisfied
Volatile Organic compounds	ISO 18562-3 — Volatile Organic compounds	The VOC emission report referenced herein details the chemicals which will be administered into a patient. The TRA , also referenced, concludes that none of these materials are a cause for concern.	End point satisfied
Cytotoxicity	ISO 10993-5: Tests for in-vitro cytotoxicity	Material supplier cytotoxicity report number xxx	End point satisfied
Sensitisation	ISO 10993- Part 10: Tests for skin sensitisation	The biological testing report referenced herein concludes that there are no sensitisation effects	End point satisfied
Irritation	ISO 10993-23: Tests for irritation	The biological testing report referenced herein concludes that there are no local irritation effects	End point satisfied
Acute Toxicity	ISO 10993-11: Tests for systemic toxicity	The biological testing report referenced herein concludes that there are no acute systemic effects	End point satisfied
Genotoxicity	ISO 10993-3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	The chemical characterisation report referenced herein identifies the chemicals which could possibly leach into a patient. The TRA, also referenced, concludes that none of these materials are a cause for concern.	End point satisfied
Sub chronic toxicity	ISO 10993-11: Tests for systemic toxicity	The chemical characterisation report referenced herein identifies the chemicals which could possibly leach into a patient. The TRA , also referenced, concludes that none of these materials are a cause for concern.	End point satisfied
Implantation	ISO 10993-6 Tests for local effects after implantation	The biological testing report referenced herein concludes that there are no acute systemic effects	End point satisfied
Chronic toxicity	ISO 10993-11: Tests for systemic toxicity	The chemical characterisation report referenced herein identifies the chemicals which could possibly leach into a patient. The TRA , also referenced, concludes that none of these materials are a cause for concern.	End point satisfied
Overall Conclusion The reports referenced at the end of this document demonstrate that the finished mouthpiece constructed and processed according to the current specifications and procedures is biologically safe in the application of permanent mucosal membrane contact.			

Conclusion

The BEP, TRA and BER take us through a logical stepwise process of identifying potential hazards, looking for evidence of safety, carrying out any necessary tests, analysing the results and combining this data into a robust safety report. As a result testing requirements are minimised, but care must be taken to include all hazards (these may be highlighted in other Standards or the device risk analysis).

Extractables and Leachables for Injection Devices

Extractions

Mark Turner
Managing Director MET

Pre-filled syringes, injector pens and cartridge pumps are convenient means for self-administration, carers, emergency situations and more general use. The range of treatments to be found is large and growing. Just considering the letter A, we have: antithrombosis (Enoxaparin), arthritis treatment (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 FDA[1]

1. Extracted from: https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM301045.pdf

According to the USA's Food, Drug and Cosmetic Act Section 501(a)(3):

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 Active Pharmaceutical Ingredients (APIs)2 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…

The toxicity concerns are to be expected, but there is also drug interaction to be considered.

Some APIs are complex (proteins such as insulin, and antibodies such as Adalimumab, for example). Yet more complicated are disabled viruses in vaccines. All treatments, particularly those dependant 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 supply the need for these syringes. These materials improvethe situation, but the need for verification of safety and bioavailability (and efficacy) remains.

The Process

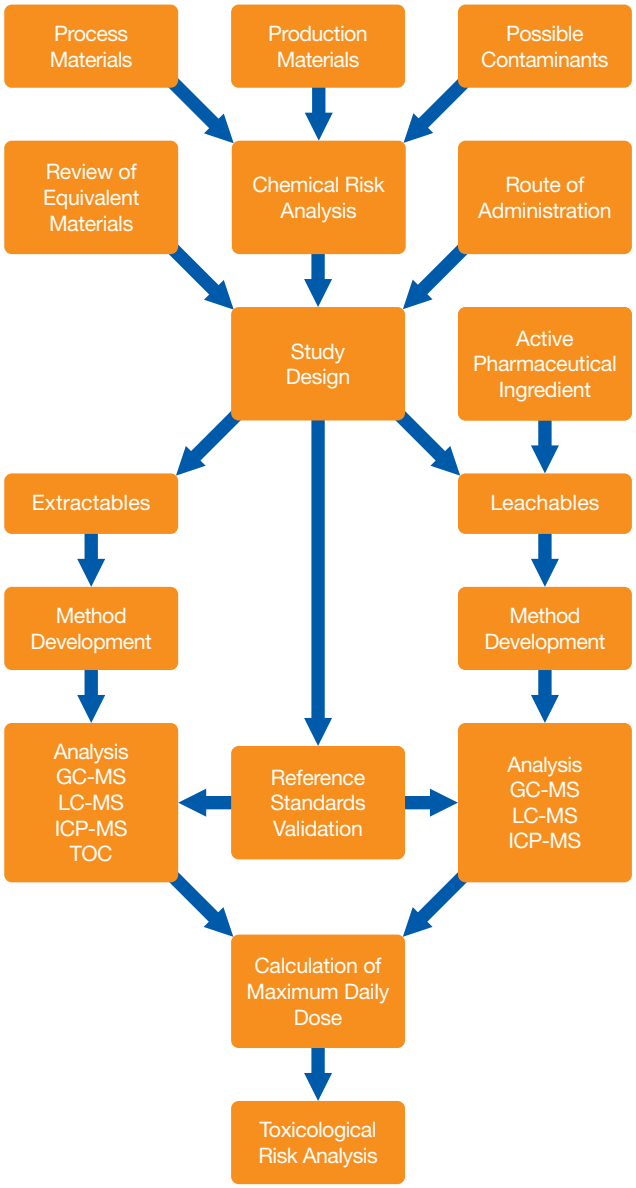
An effective extractables and leachables analysis requires careful consideration to ensure that materials of concern are found and quantified. A thorough risk analysis, to identify potential migrating species (chemicals that can transfer into

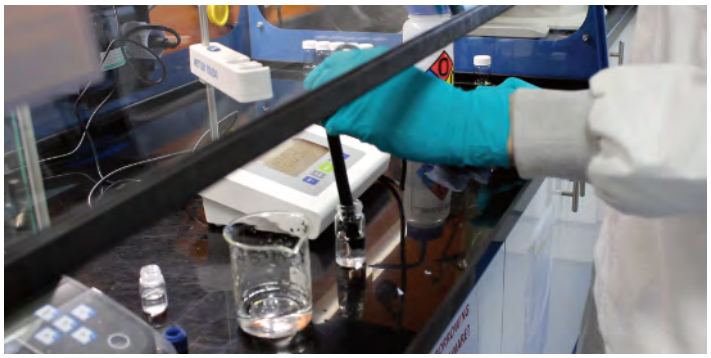
the administered fluid), will lead to a well-designed study. This should consider all of the materials in the product and all of the materials in contact with the product.

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, route of administration, and with consideration to examining 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 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 flow chart on the following page:





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 further complicate matters, 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.

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

A Systematic Approach

According to the flow chart, 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 a company's 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, Toxicological Risk Analysis (TRA).

Analytical Method Development

Once the identity and nature of the possible migrating materials has 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).

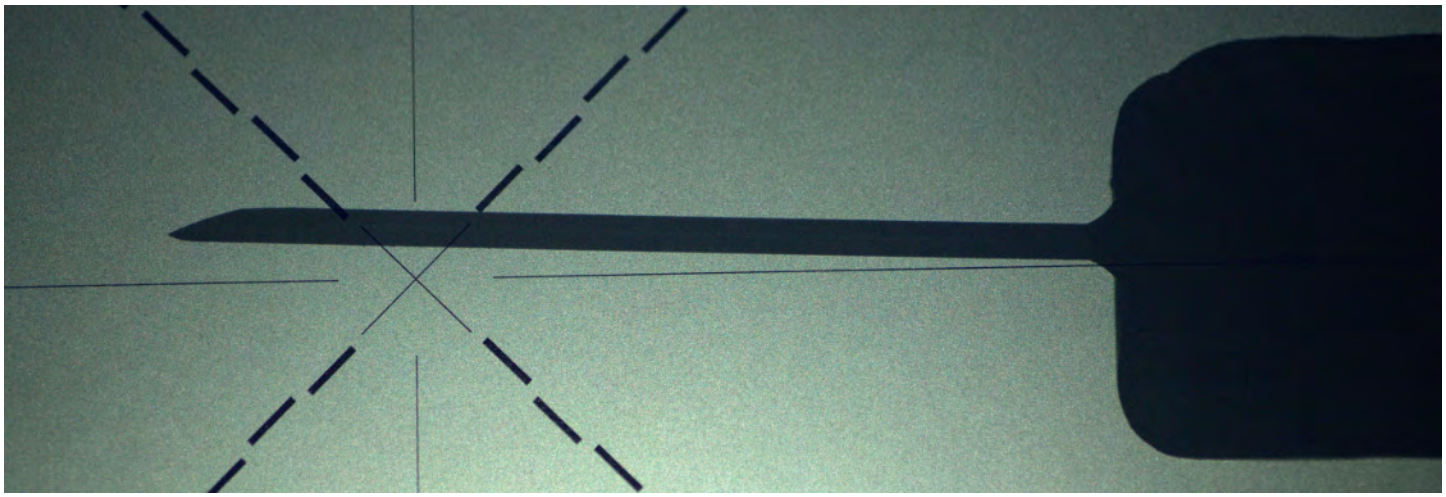
You will have read many times that extractables are forced out of the container system and leachables are materials that are likely to migrate under normal conditions. Normal conditions for a pre-filled syringe are usually two years' contact (often at 4°C).

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. Consider elevated temperatures with agitation for short-term contact containers, but exhaustive extraction for longer-term containers.

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, including (in preference) the drug contacting areas. For extracting, ISO 10993-12[3] gives some guidance.



3. ISO 10993-12 Biological evaluation of medical devices – Part 12: Sample preparation and reference materials.

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.

Note:

ISO 10993-12 also allows an increase 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.

Identification and Quantification

The analytical methods are now validated and may be applied 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 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 PRQI 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 pre-filled 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 PRQI, which uses the Crammer Index to classify risks whilst employing a 10x overdose factor. This classification can be effected by using Toxtree. A 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. Thoroughly examine components and processes 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. Analyse extracts from appropriate solvents, quantifying known substances, and doing the detective work to quantify unknown substances. Finally, know what you can potentially administer and assess its toxicity.

The Influence of Uncertainty on Chemical Characterisation

As with any other measurement or experiment analytical chemistry has uncertainties. When you use the bathroom scale to measure yourself does the screen oscillate between two numbers or the arrow on the dial point between two numbers? So which number is correct, there is an uncertainty between your perfect weight and 5g more. Equally, when we say that there are 10µg of phthalate in your sample, depending on the accuracy of the equipment and all other factors we might actually be saying that it is somewhere between 9.5µg and 10.5µg. ISO 10993-18 compels us to consider this in any analysis.

J Silk
Senior Analytical Chemist

ISO 10993-18, Uncertainty Factor

The quantification of extractables is determined by screening methods, which need to be able to detect a large variety of possible extractables. The accuracy of the estimated concentrations can vary depending on the quantification method used. Quantification methods that use internal standards, assume that all analytes give similar responses to each other, and therefore with respect to the internal standards too. If this assumption is true, the estimated concentrations for all analytes will be very accurate. However, if this assumption is false, i.e. the response factors are not similar for all analytes, the accuracy of the estimate of the concentration will vary depending on the proportional difference in the response factor of the analyte to the response factor of the internal standard.

There are other quantification methods that provide accurate estimates for concentrations. Calibration curves can be generated for expected extractables using the same screening method, by injecting standards over a range of known concentrations. These will give very accurate quantification, if the same compound is found in the extracts. Another quantification method is a hybrid of the previous two described, where relative response factors are obtained for expected extractables. The relative response factors are the ratio of the standards over a range of known concentrations versus an internal standard, which produces another calibration curve. This calibration curve adjusts for the variation in response factors of extractables compared to internal standards.

The variation in response factors of extractables and internal standards is accounted for in the calculation of the analytical evaluation threshold (AET). The AET is the threshold used to determine whether a chemical detected in the test sample is of a high enough concentration to be reported. The AET is only applicable to screening methods such as GC-MS and HPLC-MS. The AET should not be used for methods designed to identify and quantify highly toxic extractables in a cohort of concern. The formula below from ISO 10993-18 Annex E is used to calculate the AET.

$$AET = \frac{DBT \times \frac{A}{BCD}}{UF}$$

A .....is the number of medical devices extracted to generate the extract;

B .....is the volume of the extract in ml;

C .....is the number of devices a patient would be exposed to in a day under normal clinical practice;

D.....is the concentration or dilution factor;

DBT..is the dose-based threshold (e.g. (TTC) or (SCT)) in µg/day;

UF.....is an uncertainty factor that accounts for the analytical uncertainty of the screening methods used to estimate the concentration of extractables in an extract.

Each of the variables that make up the formula for calculating the AET are easily known, when preparing the extraction, apart from the uncertainty factor, which must be calculated or justified beforehand. As shown by the formula for the AET, the uncertainty factor and the AET are inversely proportional to each other i.e. a larger uncertainty factor will give a smaller analytical evaluation threshold and vice versa. A small uncertainty factor is desired, because it shows that the variation in response factors is low and therefore suitable for reporting data, which is the foundation of a toxicological risk assessment.

For analytical methods, where the variation in response factors of expected extractables, applied internal standards and targeted extractables using qualified methods are known to be acceptably low, an uncertainty factor of 1 can be justified. An uncertainty factor of 2 can also be justified for screening methods that use GC-FID or GC-MS, as the response factors of extractables detected by these methods are deemed to be somewhat consistent. For other screening methods, such as HPLC-MS, no guidance is given by ISO 10993 for a specific uncertainty factor. However, rather than assuming and justifying the value of the uncertainty factor to be 1, 2 or another number, the uncertainty factor can be calculated for a specific method, which gives a more accurate value of the AET, and therefore a more reliable threshold to exclude or include peaks when reporting data to be assessed in a toxicological risk assessment for that specific analytical method. ISO 10993-18 has recently had an amendment on how to determine the uncertainty factor. The UF is calculated by using the formula, below, which assumes a Gaussian distribution of response factors, which is not the case for all chromatographic detection methods.

$$UF = \frac{1}{1 - RSD}$$

Where, the RSD is the relative standard deviation of the response factors from the reference database. The reference database is an internal record of response factors specific to the analytical method that the uncertainty factor is being calculated for. These response factors are the peak areas or heights of each compound at a known concentration. One analytical method for an extractables and leachables study should have many response factors in the reference database as they are screening methods. The RSD of a response factor can be obtained from the repeatability section of a method validation. To obtain the combined RSD for all of the compounds in the reference database, the RSDs for all of the compounds should be summed in quadrature.

The size of the uncertainty factor must not be too large or too small, as this indicates that the method being used is not suitable. A large uncertainty factor e.g. greater than 10, shows that the method is inaccurate and therefore, should not be used as the basis for a toxicological risk assessment. In addition, a large uncertainty factor could give an AET that is so small, that it would not be detected by the analytical method, because it is smaller than the method's limit of detection (LOD). If this occurs, the method should be improved before it is used as the foundation of a toxicological risk assessment. When the RSD is greater than or equal to 1 (this occurs when the standard deviation is greater than or equal to the mean), the uncertainty factor will equal infinity or a negative number. An analytical method with this much variation of response factors is obviously not suitable to be used as the foundation of a toxicological risk assessment, and the method should be improved.

Screening for extractables and leachables is usually done using orthogonal and complementary analytical methods, for example, GC-MS and HPLC-MS. This use of multiple techniques can be used to decrease the response factor variation and can be considered in the determination of the uncertainty factor that is then applied to all of the complementary methods. Alternatively, a separate uncertainty factor can be calculated for each method and applied to each individual method, which gives a more accurate and specific AET than combining all of the techniques for each analytical method. Whichever is chosen, the use, value and the means of calculation of the uncertainty factor used should always be justified for each analytical method used.

Conclusion

The purpose of chemical characterisation is to ascertain if a device is likely to be toxic or have negative effects when applied to a patient, and ideally obviate the need for biological testing. The data from an analysis is frequently used by a toxicologist to ascertain this. They will need to know how accurate the data is in relation to the AET in order to form conclusions. Here we show how to quantify this as required by ISO 10993-18.

Chemical Characterisation and the Non-Targeted Analysis of Medical Devices

L Moraru MSC, MRSC
Analytical Chemistry Manager

At Medical Engineering Technologies Ltd. (MET), we are conducting a variety of Medical Devices Testing.

Chemical Characterisation is vital for new medical devices released on the market.

When a new medical device (MD) is developed, it is mandatory to know the potential effects that this can have on the patient.

Besides the materials that the medical devices are manufactured from, there are other materials that can be used during cleaning, processing and sterilisation of the products. These materials can be easily missed from further investigations; the focus is mainly on the materials of construction. Any contaminants or impurities are referred to as 'Non-Target Materials' (NTM). When chemical analysis is performed, is important that screening methods are developed to detect all potential extractables and leachables, rather than only target materials.

The scope of the medical devices is to monitor, diagnose or treat an injury or medical condition, or to prevent and monitor a disease.

There are many medical devices being designed every day, such as insulin pumps, syringes, oxygenators, diabetic pens, heart valves, brain implants, dental implants, etc.

At MET, we are specialised in developing bespoke ISO 10993-18 and extractables and leachables studies for a whole range of these devices.

Medical Devices can be categorised by the duration of body contact (e.g., =1day, >1 to 30 days, or >30 days), frequency

of body contact (e.g., continuously versus intermittently), and type of body contact (e.g., surface contact with intact skin, mucosal contact, implantation in tissue, or intravascular implantation) according to ISO 10993.

The investigation of the potential risks is developed based on the information provided by the manufacturer, of the device, components and materials.

Information Gathering

Information Gathering by the Biological Evaluation Plan (BEP), which is a risk assessment and gap analysis (as per *ISO 10993-1 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*), detailing all the materials that the medical device is composed of and the potential risks that the patient could be exposed to. The BEP includes a review of existing scientific information and it can lead to new testing to determine if the device is safe for the intended use. Based on the information provided in the BEP, the testing study is designed.

Depending on the contact route of the MD, further tests covered by ISO 10993: Biological Evaluation of Medical Devices for direct contact devices or ISO 18562: Biocompatibility evaluation of breathing gas pathways in healthcare applications are recommended.

Chemical Analysis

Chemical Analysis performed in accordance to ISO 10993 series and it involves a broad range of studies, designed specifically for each product.

Extractable and leachable studies are mostly used to assess direct-contact medical devices. For example, implant devices, due to their permanent duration of contact in the tissue, must be evaluated for any potential degradation and the degradation products must be analysed.

Extractable and Leachable studies are designed according to ISO 10993 parts 12 & 18, whilst degradation studies follow parts 13, 14 and 15, depending of the materials of construction.

- **Extractables** are materials that can be extracted from the medical device during exaggerated and accelerated conditions. The accelerated conditions are simulated by increasing the temperature of the extractions, e.g. for a medical device with an intended use at body temperature, the exaggerated extraction will be performed at a higher temperature, such as 50°C.

  Extractable compounds can be forced out from the medical device using aggressive solvents. The extraction vehicles are chosen considering the intended use, exaggerating the polarity of the solvent, temperature and extraction time, without dissolving the product.

  When choosing the extraction vehicles, ISO 10993 suggests that the scope is not to dissolve or compromise the device, so the selection of the extraction conditions must be well-evaluated prior to testing and the selection justified.

- **Leachables** are materials that can be extracted from the medical device during exaggerated and accelerated conditions. The accelerated conditions are simulated by increasing the temperature of the extractions, e.g. for a medical device with an intended use at body temperature, the exaggerated extraction will be performed at a higher temperature, such as 50°C.

  For an insulin pump, a leachable assessment will involve keeping the pump in contact with the insulin at body temperature for a long duration of time, considering the repeated use over the time.

  It is mandatory to assess the medical devices for leachable compounds, as these possess a high risk to the patient. Leachable compounds are transferred in the body by the drug and could lead to reactions that can harm the patient.

In addition to extractable and leachable testing, implant devices, where there is a potential for degradation, must be assessed for any degradation products.

The degradation studies are intended to simulate the complex environment in the body; they are performed using hydrolytic and oxidative solutions.

It is important to know that the accelerated degradation uses high temperatures and the extraction solutions must be analysed over specific periods of time (given in the standard or justified in the testing protocol). If there is no degradation observed in the accelerated solutions, any real time degradation may be interrupted.

However, it can be challenging to use this approach to identify all the hazards present and released by the devices, due to the complexity of the materials and different manufacturing processes. For example, complex devices can introduce chemicals that are not accounted for by formulation information solely.

To cover the gaps, MET is conducting targeted and non-targeted screening analysis using a variety of analytical techniques, in order to investigate any residual impurities that could be volatile, semi-volatile, non-volatile, organic or

inorganic that are present at concentrations above the AET (Analytical Evaluation Threshold).

The studies are developed bespoke for each product. They consider worst case scenarios of release of materials by the device. The selection of extraction media and conditions and the instrumentation used is based on sample proprieties, the chemical makeup and the application of the device.

At MET, we have a broad range of analytical techniques available:

- **Head Space-Chromatography coupled with Mass Spectrometry (HS-GC-MSD)** is used to screen and identify any potential volatile organic impurities or residual solvents released by the MD or from the manufacturing process that could harm the consumer. HS-GC-MS may be performed on an aqueous extract or directly on a solid test article.
- **Gas chromatography coupled with Mass Spectrometry Detection (GC-MSD)** methods are developed to search for a multitude of potential semi-volatile impurities that could be released by the device. These may derive from the manufacture and storage of polymers and precursors or be added (purposely or inadvertently) during the manufacturing, sterilisation or any other treatments of the raw materials, components or device. The extract media is normally introduced into the analytical equipment by direct injection. The goal of chromatography is to elute analytes in patterns of sharp elution “peaks” that are subsequently subjected to ionization and detection. Analytes elute from the GC-MS column primarily based on their properties (volatility and interaction with the column stationary phase) in relation to the stationary phase chemistry, oven temperature, and flow rate.
- **High Performance Liquid Chromatography methods with Photodiode Array Detection coupled with Mass Spectrometry (HPLC PDA-MSD) detection** are developed based on the material of construction of the medical device and the potential non-volatile residuals that could harm the user. The dual detection method PDA and MS is designed to have a higher sensitivity, as it has the capability to detect organic compounds that do not ionise and contain chromophore groups (such as colorants or monomers added to the devices) and molecules that can ionise. LC-MS is a technique used for separation, detection, and quantification of semi- and non-volatile extractables. The consideration of mass resolution, mass accuracy, and chromatographic separation requirements is integral to LC method selection and development. LC is predominantly performed using reversed phase chromatography (C18 or C8 stationary phases) to separate analytes by increasing hydrophobicity.
- **Inductively Coupled Plasma Optical Emission Spectroscopy** (ICP-OES) is used to search for any potential non-organic (metallic) residuals left behind from manufacturing machinery or from any metals or pigments associated with the MD.

The selection of the analytical methods is made based on the material information provided by the manufacturer, the materials of construction of the medical device and the cleaning and sterilisation processes involved.

The analysis involves screening for Target materials chosen and screening methods designed to search for any Non-Target impurities (that are not already known to be present or possibly present).

Materials can be quantified by using either targeted (fully-quantitative) or non-targeted (semi-quantitative methods. Targeted quantification refers to the analysis of a specific analyte or a group of analytes of interest using pure reference standards within a defined concentration range. To evaluate analytical suitability for use in quantification, a calibration curve is produced with 5 to 6 non-zero calibration points.

System suitability is an assessment that used to determine the performance range or window of the analytical instrumentation prior to testing. The system suitability assessment determines whether the method has been implemented properly, maintains its performance at the same level as during qualification, and performs acceptably throughout its use. System suitability for NTM work has been proposed to include the use of blanks, pooled samples such as matrix controls, and multi-analyte-spiked (with reference/control materials added) samples. The selection of the reference or target materials is based on prior information and is used to perform calibration and system suitability analysis.

Analytical Evaluation Threshold

Analytical Evaluation Threshold is defined as the level below which quantification of a material is not required; the analyst doesn't need to identify, quantify or report peaks for toxicological risk assessment. The AET was adapted for medical devices in the 2020 edition of ISO 10993-18. The calculation of the AET considers the dose-base threshold (DBT), which depends of the frequency and duration of a patient’s exposure to a device, as described in ISO/TS 21726:2019. It should be noted that, according to ISO 10993-18:2020, AET is not applicable to substances named

as 'cohorts of concern'. These materials are considered highly toxic at very low concentrations, such as volatile organic compounds and Non-organic compounds. Therefore, AET is only valid for semi-volatile and non-volatile organic compounds and it is calculated as shown below:

$$AET = (DBT \times (A/(B \times C)))/UF$$

A is the number of devices extracted, B is the extract volume, C is the number of devices that contact the body divided by 1 day, D is the dilution factor, and UF is the uncertainty factor of the analytical method. The value of the UF depends on the analytical method and accounts for variation in the response factors (RFs) of individual analytes.

As most of the time the test extract fluid sample goes through multi step preparation, including concentration and dilutions, a D factor must be considered (D<1 where the sample is concentrated and D>1 for diluted samples).

Once extracts of the devices are obtained, the solutions prepared (diluted, concentrated, etc.) are injected into the systems; analysis involves separation of the molecules extracted using the methods explained above. The results are presented as peaks for each molecule detected in the extracts. The identification of these responses is performed using the National Institute of Standards and Technology Libraries (NIST), where present, as well as internal libraries. Where the libraries do not have enough information for identification, the identification relies on the information available and the experience and expertise of the analysts.

Quantification of the target materials confirmed is performed using the pure standard responses, for which calibration curves will have been obtained.

For Non-Target materials, the concentration is only estimated or semi-quantified, using surrogate standards, internal standard response factors and, in some cases, external standard responses.

Analytical Evaluation Threshold

The extraction process is intended to transfer mobile chemical constituents from the medical device into a liquid phase/ solvent. The extractions can simulate the real-life or worst-case scenarios, with respect to clinical use.

The selection of the solvents is made from a broad range of candidate organic solvents. The goal is to cover all the polarities that are clinically-relevant. The extractions are conducted on patient-contacting devices/components to result in a worst-case scenario, with respect to the clinical use.

Solid-liquid extraction is not the only possibility; r liquid-liquid extraction applies when the device is in a liquid form and gas to solid phase extraction (followed by return release to gas for analysis) applies for breathing components.

The extraction process is controlled by the interaction of the device or material with the extraction vehicle (solvent) and is governed by the solubility, diffusion of the chemical into the solvent and partitioning of the chemical between the solvent and the material, extraction temperature, extraction duration and surface area. The goal of the extraction is to facilitate migration of chemical constituents that could potentially leach out of the device during clinical use without changing their chemical identities or physically destroying the device.

In some cases, exhaustive extraction is required (for example: in the case of implanted devices). This is defined as repetitive extraction, repeated until the amount of material extracted in

a subsequent extraction step is less than 10% (by gravimetric analysis of that determined in the first extraction step). The most common method for checking is to assess the Non-Volatile Residue (NVR) analysis.

This method is relatively simple, however the approach is limited by the sensitivity of gravimetric analysis and is insensitive to volatile and some semi-volatile compounds.

When a device is invasive but not permanent, exaggerated extraction may be appropriate. This is performed by the use of solvents and temperatures which represents a worse case than the conditions of the clinical use (temperatures chosen above 37°C and extraction duration longer than the duration of the device use).

Because clinical use of a device can extend over a considerable time period, accelerated extraction is used to allow analysis to be performed in a reasonable timescale. This is defined as an extraction with a duration shorter than the duration of the clinical use, whilst not causing degradation, chemical, or physical changes to the substances being extracted. The accelerated extraction is usually achieved by increasing the temperature used.

When selecting materials and components for use in a medical device, designers will pay attention to the biocompatibility of these items. However, final proof of biocompatibility must be given for the device presented to the patient. Therefore, the selection of the test article for the study is very important. The study aims to replicate the real use of the product and it must, therefore, be representative of the final product (as opposed to a raw material, resin or unfinished medical device).

There are a multitude of factors that need to be considered prior to the extractions, such as the selection of the extraction containers (to ensure that they do not introduce contaminants), temperature, (the efficiency of the extraction is influenced by the temperature; higher temperature extractions generally increase the amount of extractables), time, extraction rate, different polarities solvents, solvent volume-to-sample size ratio, and agitation of the solution.

In targeted analysis, the chemistry of the extractable of interest is known, allowing extraction optimisation. In NTA, however, the chemistry of each potential extractable is typically unknown and varies. Therefore, to maximise the extraction of chemicals having a broad range of chemistries, non-targeted extraction conditions usually include the use of polar, semi-polar, and non-polar solvents, elevated temperature, and longer extraction times.

The polarity selection of the solvent is performed as per FDA guidance, as well as Table D.1 of ISO 10993-18:2020. The selection of polar, semi-polar and non-polar solvents is recommended for devices intended for long-term use (>30days). The selection of the solvent must also consider the tissue that the device will contact, in order to simulate the worst-case scenario.

One example would be alcohol-water mixtures that can have polarities in the semi-polar to non-polar range. Extractions using alcohol-water mixtures can result in lower concentrations of extractables and can underestimate their presence in comparison to extractions purely using alcohol.

Another important parameter in extraction study design is the solvent volume-to-sample size ratio. In general, the higher the solvent volume-to-sample size ratio, the greater the extraction yield, since the concentration gradient is the driving force for mass transfer of extractables into the solvent. The use of larger solvent volumes can also allow for complete immersion of the test article in the solvent and helps ensure that an adequate solvent volume remains at the end of the extraction if there is solvent uptake by the test article. Concentration or dilution of the extract is performed with consideration of the reporting limit and the sensitivity requirements of the analytical techniques used for extractable profiling .ISO 10993-12:2021 contains recommendations for various ratios of the device surface area or mass-to-solvent volume, depending on the device characteristics, and ISO 10993-18:2020 contains recommendations to use these ratios as potential starting points in planning an extractables study. However, the final solvent volume determination is based on factors that include the properties of a device/material and the extraction

techniques used. For example, absorbent materials will require additional extraction fluid.

Extraction techniques include Soxhlet extraction, reflux extraction, microwave extraction, accelerated solvent extraction (ASE) and closed-vial incubation. Compared with the other extraction methods listed above, vial incubation can overcome many of the challenges and be used to apply various temperatures, agitations, and solvent conditions simultaneously for a substantial number of samples, while retaining volatile analytes.

It is important that extracts, once generated, are compatible with the analytical methods. The analytical methods must be adequately sensitive and achieve the necessary reporting limit can support a biocompatibility evaluation. In many cases, extracts can be directly analysed using GC and liquid chromatography (LC) techniques without further sample processing. However, further processing of the samples is often required for analytical instrument compatibility and reliable analytical outcomes. For example, sample dilution, sample concentration, liquid-liquid extraction (solvent exchange), solid phase exaction (SPE) are some of the techniques used to process the sample extracts prior to injection in the analytical systems.

Highly concentrated samples are diluted using suitable solvents in order to prevent column damage, prolong column life, and avoid exceeding upper detection limits. Similarly, high sample viscosity may not be compatible with the HPLC mobile phase or with the GC stationary phase. However, without careful consideration, samples can be diluted to the extent that the resulting analysis lacks sufficient sensitivity to meet the AET.

The need of chemical characterisation and toxicological risk assessment for evaluating and support the biocompatibility of medical devices is constantly increasing. This article is presenting different approaches for NTM analysis starting with information gathering, extraction, sample processing, system selection, quantification, and identification.

The design and performance of the suitable chemical analysis depends on the collaboration of the team of experts in areas including medical device manufacturing, analytical chemistry and toxicology.

Medical Devices industry is in continuous growth and the development of new reliable and accurate approaches in order to assess the safety of the products is constantly reviewed.

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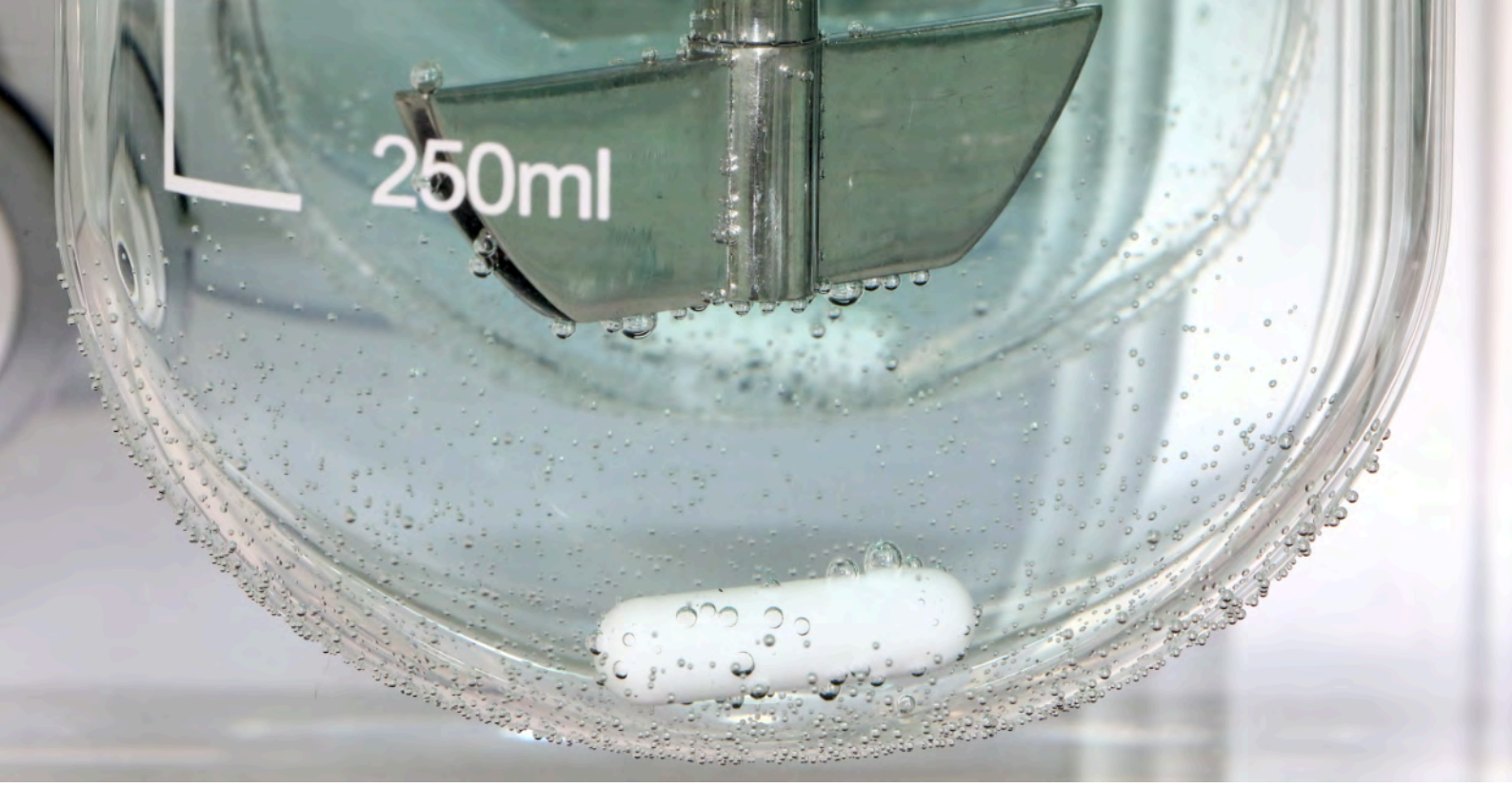
ISO 10993-1 ISO 10993-1:2018: Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

ISO 10993-18:2020: Biological evaluation of medical devices — Part 18: Chemical characterisation of medical device materials within a risk management process

ISO 10993-12: Biological evaluation of medical devices: Part 12: Sample preparation and reference materials

ISO 10993-17:2002: Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances

ISO 10993-13:2010: Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices



Medical Devices, the interplay between ISO 10993 and ISO 18562

The medical devices industry is continuously growing and every day engineers, together with scientists, combine their work to design and develop new products, in order to save lives or to provide care and treatment to patients all over the world.

Before being used on patients, the safety and effectiveness of the medical device (MD) must be proven, otherwise changes are mandatory.

Medical Engineering Technologies Ltd. (MET) are conducting medical device testing and offer consultancy to manufacturers, to assist with the submission of the devices on the EU and US markets.

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Analytical Chemistry Manager

There are a variety of medical devices on the market and many more to be designed; the categorisation of them considers the contact time, intended clinical use, patient group and contact type.

One of the most important details to consider is the contact of the medical device (whether the medical device is contacting the patient directly or indirectly).

Direct contact medical devices come into physical contact with a body tissue; this may be skin, mucosal membranes, blood path, tissue, bone or dentin communicating. These are assessed for toxicological safety according to ISO 10993-1: Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process. A few examples are insulin pumps, syringes, urinary catheters, dressings or healing devices, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haem adsorbents and immunosorbents.

Indirect contact medical devices are products through which a fluid or gas passes prior to the gas coming into physical contact with the body tissue (the MD itself or component does not physically contact the body). These devices may be Breathing Gas Pathway Devices; in which case they are risk assessed using ISO 18562-1: Biocompatibility evaluation of breathing gas pathway in healthcare applications - Part 1: Evaluation and testing within a risk management process.

Prior to final testing, it is very important for the manufacturers to consider complete information about the device for a Biological Evaluation Plan as, at this stage, the decisions about what route of contact the device has with the patient and what the potential risks with the device must be made. This reveals which testing is required in order to assess the effects.

For both direct and indirect contact medical devices, the manufacturers have to prove the safety of the product using a range of tests, alldepending on the nature of the device and the conditions of use.

The safety of the medical devices is evaluated with both in *vivo* and in *vitro* testing. In current times, in vitro testing cannot completely replace the in vivo results, but the approach is definitely trying to reduce animal testing by attempting to develop and validate laboratory methods.

However, there are frequently end points that cannot be satisfied without studies on animals (commonly, those end points relating to local toxicity effects). These studies are usually required as part of the Toxicological Risk Assessment, in order to address any concerns raised by the Chemical Analysis.

Your team at MET have the capabilities to cover all ISO 10993 and ISO 18562 in vitro testing requirements.

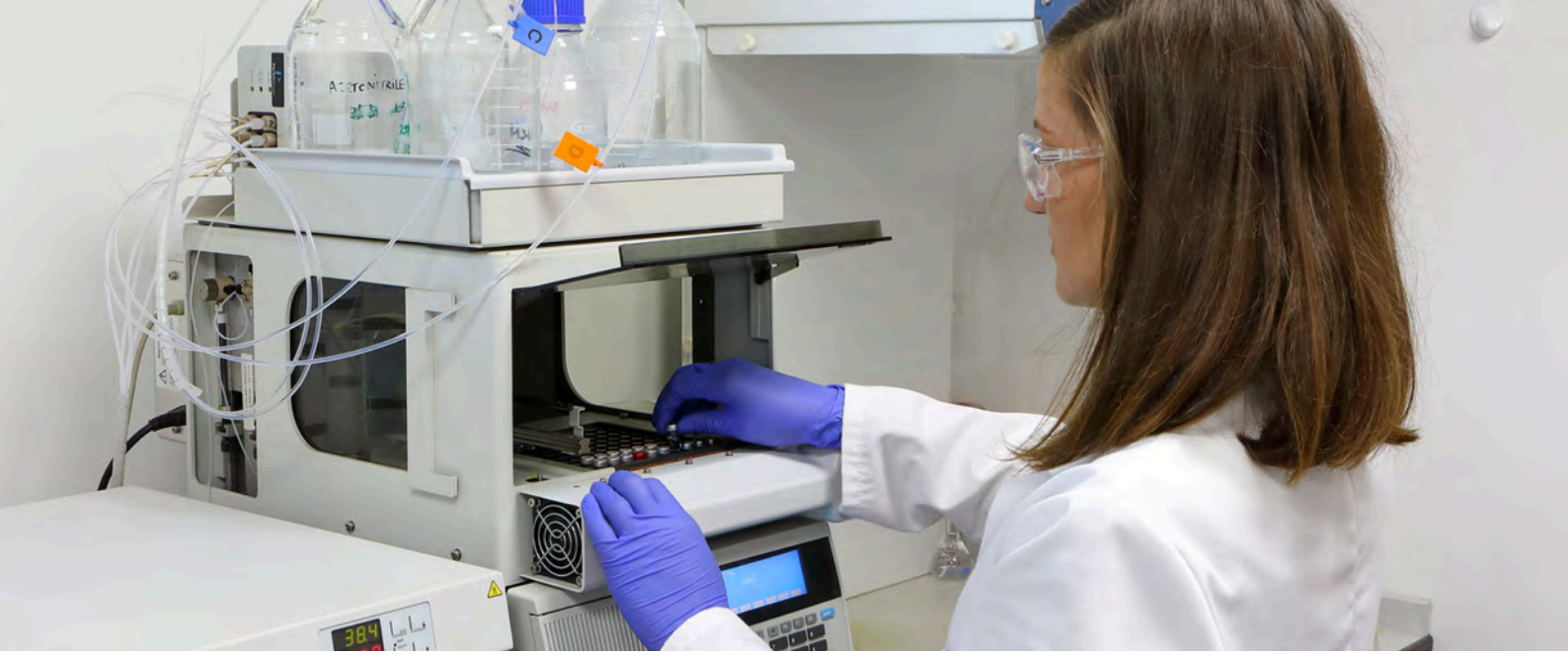
For direct contacting devices, the authorities are expecting to see Chemical Analysis. Chemical Analysis is designed to simulate potential extractable and leachable (E&L) conditions found in both the body and in more extreme environments, to show which materials can be released by the devices. The E&L studies are designed bespoke for teach device, in order to detect all residuals left behind from manufacturing, cleaning and sterilisation, as well as other unexpected impurities that could harm the patient.

The main difference between the ISO 10993 and ISO 18562 standards is that direct contact medical devices must be scanned for any expected and unexpected volatile, semi-volatile, non-volatile and non-organic materials while, for breathing devices, the ISO 18562 standards are focusing mostly on the volatile compounds released from the gas pathway and the particulates that are being released at the beginning of the medical device use. Only in situations where there is a risk of condensation occurring from gas pathway devices, ISO 18562-4 applies (this describes the methodologies of assessing semi-volatiles and metals from the components exposed to the condensation, as well as cytotoxic effects and sensitisers).

Extractable and leachable studies simulate the real life and worst-case scenarios of clinical use by using a range of organic solvents of different polarities and temperatures to achieve simulated, exaggerated and aggressive extractions. Simulated extractions are mainly used to release the leachable substances from the product under real clinical use conditions, while extractable studies use aggressive and exaggerated extractions.

For implants (medical devices that are introduced into the human body and are intended to remain in place after a procedure), degradation studies are also performed in addition to the extractable and leachable studies. The degradation studies are also designed based on the material of construction of the devices (e.g. polymeric, ceramic, metallic. etc.). Degradation studies are performed under real life conditions and this type of degradation is designed to prove what reactions and processes the device will undergo in real life. This ‘real life’ degradation is performed in parallel with accelerated degradation, which has the goal of highlighting the worst-case scenario of the degradation products. The first analysis in the accelerated degradation should be gravimetric, in order to evaluate the mass of the degradation product. The gravimetric analysis must be performed at defined periods of time, in order to see if the product is degrading further or if it has reached an equilibrium.

Once the product mass is not changing under the accelerated degradation conditions, the real life degradation



extractions may be stopped (as no further changes are expected). The degradation studies for polymeric implants must be performed in oxidative and hydrolytic extraction solutions at body temperature (37°C), as well as at a higher temperature (70°C) as per ISO 10993-13: Biological Evaluation of medical devices - Part 13: Identification and quantification of degradation products from polymeric medical devices.

Categorising medical devices by the contact duration with the patient is another critical matter. Both standards series 10993 and 18562 agree on the anticipated duration of contact, as follows:

a) Short-term exposure or limited exposure: Medical devices whose sum of single, multiple or repeated duration of use does not exceed 24 hours.

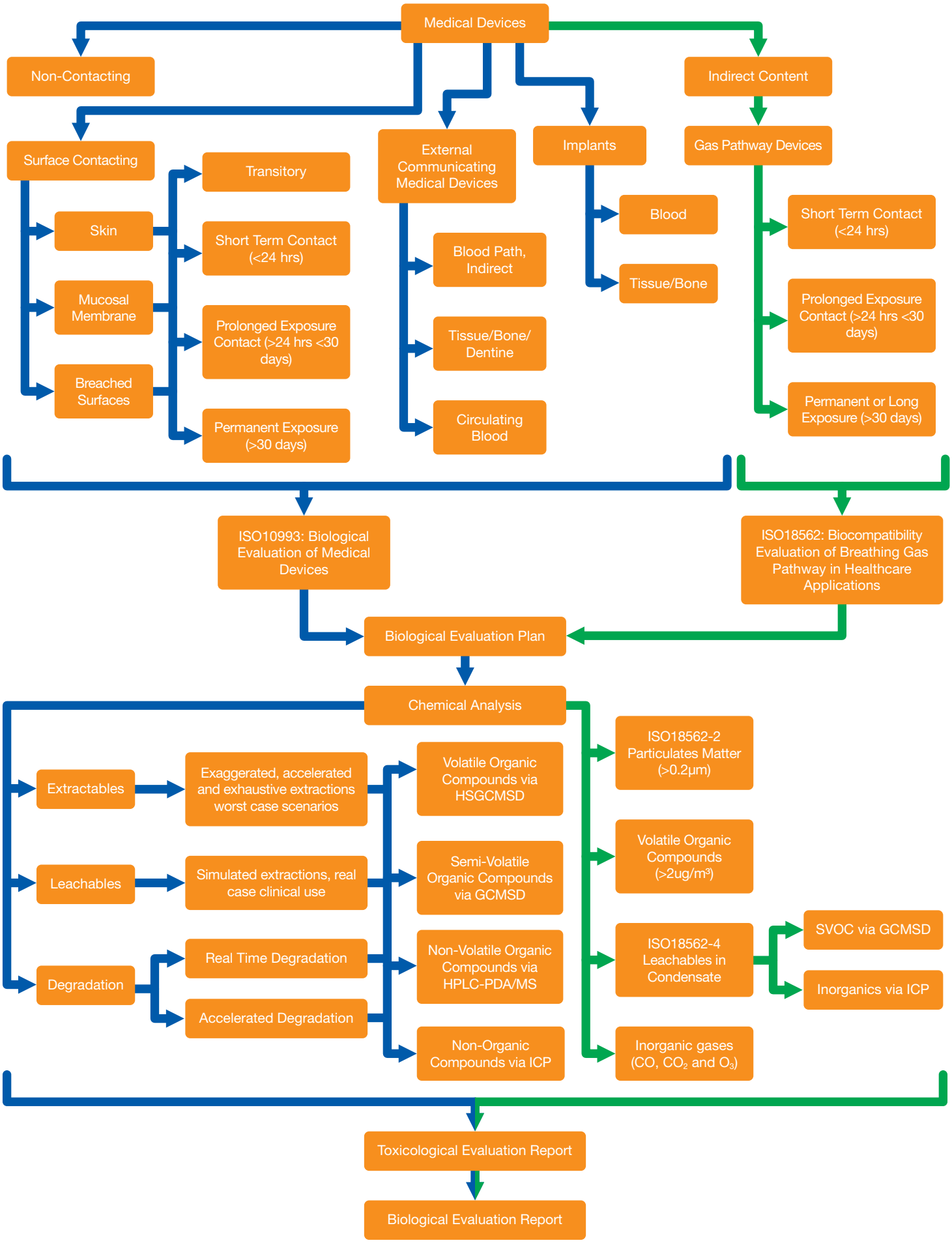
b) Prolonged exposure: Products whose cumulative sum of single, multiple or repeated contact time is likely to exceed 24 hours but not likely to exceed 30 days.

c) Long-term exposure devices or permanent contact: Cumulative sum of single, multiple or repeated contact time exceeds 30 days.

All studies, following either ISO 10993 or the ISO 18562 series, must assess the results in a Toxicological Risk report. In the Toxicological Risk Assessment, the risk of using the medical device is reviewed, considering the intended use, patient group, duration of use, contact of the device and materials released in the Chemical Analysis studies; either volatiles, semi-volatiles, non-volatiles, particulates or inorganics.

One discrepancy in the two governing standards is the body weight of a neonatal patient. *While ISO 10933-17: Establishment of allowable limits for leachable substances* suggests using 3.5kg as the standard body mass for neonatal patients, ISO 18562-1 suggests using only 0.5kg.

The exposure assumption is achieved by calculating a daily patient dose, based on the anticipated duration and frequency of the device usage and the daily dose of the material that the patient is exposed to. The derived risk is then estimated as highly conservative and is, most of the time, likely to overestimate the actual potential for adverse effects in patients (in this way, worst case scenarios are covered). Once the end points of the Toxicological Risk assessments are addressed and the device is deemed as having an acceptable toxicological risk from the clinical use, the Biological Evaluation Report can be put in place, reviewing that all the recommendations made in the Biological Evaluation Plan have been addressed and the device is safe to be used.


Medical Devices
Non-Contacting
Surface Contacting
Skin
Mucosal Membrane
Breached Surfaces
Transitory
Short Term Contact (<24 hrs)
Prolonged Exposure Contact (>24 hrs <30 days)
Permanent Exposure (>30 days)
External Communicating Medical Devices
Blood Path, Indirect
Tissue/Bone/ Dentine
Circulating Blood
Implants
Blood
Tissue/Bone
Indirect Content
Gas Pathway Devices
Short Term Contact (<24 hrs)
Prolonged Exposure Contact (>24 hrs <30 days)
Permanent or Long Exposure (>30 days)
ISO10993: Biological Evaluation of Medical Devices
ISO18562: Biocompatibility Evaluation of Breathing Gas Pathway in Healthcare Applications
Biological Evaluation Plan
Chemical Analysis
Extractables
Exaggerated, accelerated and exhaustive extractions worst case scenarios
Leachables
Simulated extractions, real case clinical use
Degradation
Real Time Degradation
Accelerated Degradation
Volatile Organic Compounds via HSGCMSD
Semi-Volatile Organic Compounds via GCMSD
Non-Volatile Organic Compounds via HPLC-PDA/MS
Non-Organic Compounds via ICP
ISO18562-2 Particulates Matter (>0.2µm)
Volatile Organic Compounds (>2ug/m³)
ISO18562-4 Leachables in Condensate
SVOC via GCMSD
Inorganics via ICP
Inorganic gases (CO, CO2 and O3)
Toxicological Evaluation Report
Biological Evaluation Report

The Practical Application of ISO 18562

Medical Devices Industry has grown and is expanding daily. With this in mind, manufacturers must prove the safety and effectiveness of the products before being used in humans. All over the world, US, EU, Asia, authorities are reviewing the data considering similar bullet points.

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Analytical Chemistry Manager

The world has faced COVID19 crisis and during these times, many medical device manufacturers have designed breathing devices to save lives. The safety of these ventilators had to be proven and the risk versus benefit measured.

The respiratory devices are classified as indirect contact medical devices as per ISO *ISO10993: Biological Evaluation of Medical Devices* and are being assessed following *ISO18562: Biocompatibility evaluation of breathing gas pathway in healthcare applications standards*.

Even if breathing medical devices are assessed by a different standard, the process to submission is similar to direct medical devices. The first step is assessing the risk and for this information gathering is mandatory for the Biological Evaluation Plan (BEP). At this stage, the next steps are defined. If the information is incomplete or the risk is not minimised, further testing is required.

While for contact medical devices, extractables and leachable studies, degradation studies (when the potential for degradation exists), chemical characterisation and often animal testing, are required as per ISO10993: Biological Evaluation of Medical Devices.

For indirect contact medical devices, specifically Breathing devices, a similar approach is required. The main difference is that the assessment of the potential extractables and leachables is performed using gas, to simulate real life scenarios. The main focus is to gather data about any materials that could be released in the gas pathway and inhaled by the user. While in direct contact medical devices, the chemical data is generated using extraction solvents, temperature and different time conditions, breathing medical devices are tested by simulating the worst case scenarios and instead of using extraction solvents, the 'extractables and leachables' released into the gas pathway are analysed, the extraction vehicle in this studies is the air.

There are 4 parts of the standard:

- **ISO18562-1: Biocompatibility evaluation of breathing gas pathways in healthcare Applications-Evaluation and testing within a risk management process:** This document presents the key steps that need consideration when assessing the breathing devices. The most important is information gathering process and the Biological Evaluation Plan before any testing is performed. The standard guides on the different types of patient groups, breathing volumes, body weight and Threshold of Toxicological Concerns.
- **ISO18562-2: Biocompatibility evaluation of breathing gas pathways in healthcare applications: Tests for emissions of particulate matter:** The standard is presenting different ways of simulating the worst case scenario for any particulate matter to be released from the medical device and that can land on the patient's lungs. For this test, the highest flow rate is considered as the worst case scenario as more particulates can be released when the device is working harder to provide more air. Only particulates with a diameter above 0.2µm are of interest for this study. There is a maximum allowable mass limit of 12µg/m3 of accumulated particulate mass, without differentiating the size.

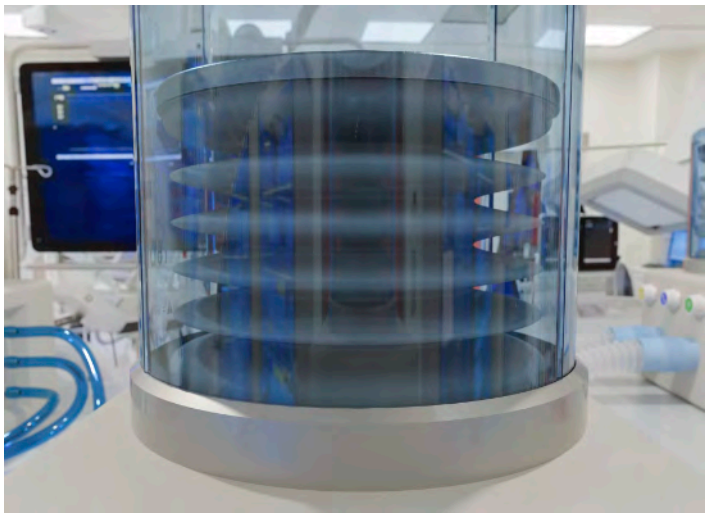
  When the size of the particulates is differentiated the limit for the particulates with a size between 0.2 µm to 2.5 µm has a maximum limit of 12µg/m3, while the mass of particulates with a size between 2.5 µm and 10 µm cannot exceed 150 µg/m3. The evaluation must consider the expected service life, any expected or processing or reprocessing and the patient contact.
- **ISO18562: Biocompatibility evaluation of breathing gas pathways in healthcare applications: Tests for emissions of volatile organic compounds (VOCs):** In this part of the standard the focus is on any volatile organic compounds that can be released by the breathing device during the use. As some volatile organic compounds can become gas at room temperature, and to simulate the worst case scenario, the testing must be performed at the highest clinically relevant temperature. This accelerates the volatilisation of any potential harmful materials. The flow of

Exposure Category	Length of Patient Exposure	Patient	Bodyweight (kg)	TTC (ug/day)	Breathing Volume (m3/day)
Limited Exposure	< 24 Hours but	Adult	70	360.00	20.00
		Paediatric	10	51.43	5.00
		Infant	3.5	18.00	2.00
		Neonate	0.5	2.57	0.21
Prolonged Exposure	> 24 Hours but < 30 Days	Adult	70	120.00	20.00
		Paediatric	10	17.14	5.00
		Infant	3.5	6.00	2.00
		Neonate	0.5	0.86	0.21
Permanent Contact	> 30 Days	Neonate	70	40.00	20.00
		Paediatric	10	5.71	5.00
		Infant	3.5	2.00	2.00
		Neonate	0.5	0.29	0.21

the testing is also one crucial parameter to consider and the lowest clinically relevant flow is considered as the most appropriate as it slowly allows the volatiles to be released and be absorbed.

As per ISO18562-1 different patient groups breath different volumes of air per day and have different body weights. The permitted concentration of the volatiles is adjusted considering these details. The standard states that any materials bellow 2µg/m3 are not to be reported.

- **ISO18562-4: Biocompatibility evaluation of breathing gas pathways in healthcare applications: Tests for leachable in condensate:** This part of the standard only applies when is a potential for condensation to form during the clinical use of the medical device. The rationale is that the condensation could lead to materials leaching from the device's pathway and contacting the patient. The standard presents the testing requirements and the testing involves a polar (water) extraction performed at body temperature (37oC) of the gas pathway components. If possible, the device should be run as in real-life and the condensate to be collected and tested. When this is not possible, an extraction of the relevant parts is performed. The extract is followed by a screening for semi-volatile organic compounds and metals. As part of the study, cytotoxicity and sensitisation must be assessed as there are not know in-vitro adequate methods.



Same as ISO10993, ISO18562 classifies medical devices based on their duration of use in direct or indirect contact with the user:

a) Short-term exposure or limited exposure: Medical devices whose sum of single, multiple or repeated duration of use does not exceed 24 hours.

b) Prolonged exposure: Products whose cumulative sum of single, multiple or repeated contact time is likely to exceed 24 hours but not likely to exceed 30 days.

c) Long-term exposure devices or permanent contact: Cumulative sum of single, multiple or repeated contact time exceeds 30 day.

Knowing the duration of use of the medical device is very important as this dictates the testing periods, mainly for Volatile Organic Compounds, where ISO18562-3 splits the duration of the testing based on the duration of use.

At the end of the testing period, all the data is captured and must be assessed in the Toxicological Risk Assessment, where all materials are evaluated for any toxic effects. If toxicity data is not available TTCs presented in ISO18562-1 are used.

Biological Evaluation Report (BER) is the last step in the process and all the data is reviewed and concluded if the results are satisfactory.

In conclusion, even if Breathing Medical devices are not captured by ISO10993 standards, the approach of proving the safety is identical.

Biological Evaluation Plan ➞ Testing ➞ Toxicological Risk Assessment ➞ Biological Evaluation Report

The Importance of Quality in Medical Device Testing

At MET, we are a Quality Assurance focused and dedicated team and we understand that quality is of the utmost importance. We perform testing to the highest standard and we believe that quality must always be of the highest standard to ensure patient safety.

At MET we pride ourselves that our highly trained personnel deliver concise and accurate reports just what you would expect from a World Leading Testing Laboratory, please visit the home page for more information on the tests we provide here at MET.

As a Testing Laboratory, UKAS our accreditation body annually audit us, being reaccredited every third year to the ISO 17025 and any required UKAS accredited tests, the quality and attention we give to our scheduled tests is also consistent with all other testing conducted at MET.

N Allkins
Quality Assurance Manager

We have a comprehensive Quality management system (QMS) in line with ISO 17025 requirements and we also work to the principles of the GMP guidance, with the aim of supporting all our Clients' needs.

We want to collaborate with you to ensure we fully understand your product and any associated risks to assist you in ensuring that your product works as you intended and allows its safe use by the patient or clinician providing excellent patient care.

We welcome our Clients to conduct audits against the testing processes they require, where after we will work with you to ensure any special requirements you may have, are met, not conflicting with those of international standards or regulatory requirements.

The reports and results you receive from MET will allow you to make the right decisions to ensure patient safety for your product to be used, we are dedicated to demonstrating that this is what your product does by actively doing the best for the patient. Underpinning, our service to you is our excellent client-driven service.

Our FEI number is 3011572006

Mission Statement

"Meeting highest expectations, Excellence in medical device testing and Total commitment to Quality"

You can access our ISO 17025 accreditation here:

You can access our schedule of accreditation here:

Use our contact page to request an audit or to have your supplier information questionnaire completed.

Mark Turner

Managing Director MET

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 in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

L Moraru MSC, MRSC

Analytical Chemistry Manager

Luminita Moraru is the Analytical Chemistry Manager at Medical Engineering Technologies Ltd, has more than 6

years of experience in Medical Devices Testing. She is a committee member of ISO10993: CH/194 Biological evaluation of medical devices and ISO18562: CH/121/09 Lung Ventilators & Related Equipment having insight knowledge for in the applications of those on medical devices to meet the requirements, ensuring the data is generated in appropriate form to be risk assessed in Toxicological Risk Assessments. She earned her Masters in Chemistry at the University of Bucharest.

J Silk

Senior Analytical Chemist

James Silk, Senior Analytical Chemist at Medical Engineering Technologies. James is SME in Extractables and Leachables based on ISO10993 standards, designing studies on a broad range of Medical devices. James is also passionate about statistics and has become the SME in Uncertainties, calculating uncertainties for analytical methods used for the identification and quantification of materials released by the Medical Devices. James has 2 years' experience at MET in performing Volatile Organic Compounds released by medical devices following ISO18562-3, therefore a good understanding of the standards.

James obtained his Chemistry Degree at Cardiff University.

N Allkins

Quality Assurance Manager

Naomi Allkins, Quality Assurance Manager at Medical Engineering Technologies Ltd since Jan 2022. Naomi has over 20 years' experience in the medical devices industry from decontamination of medical devices to testing of medical devices. Naomi is a qualified Lead Auditor, with a range of knowledge in standard and regulatory requirements in line with BS EN ISO 13485, MDD 9342EEC (annex 5 article 12) and most recently ISO 17025.

E Couzens

Biocompatibility Assessor

Elena Couzens is the Biocompatibility Assessor with 7 years of Biocompatibility management experience at Medical Engineering Technologies Ltd. She is a member of British Toxicological Society having a most up to date knowledge in the new discoveries of toxic effects to the human body and to the future generations. She has been certified for Biological Evaluation of Medical Devices and leading numeral ISO 10993 Biocompatibility projects, Biocompatibility Evaluation Plans and Reports, ensuring efficient high-quality testing prior to the product submission for FDA or EU approval. She achieved her top grades BSc in Biology at the Donetsk National University in Ukraine.

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

Stay Up-To-Date with the Leader in Its Field – MET in the Press

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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Package Validation

Stability Testing

Accelerated Ageing

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