ENVIRONMENTAL MONITORING

Even with the rise of rapid microbiological methods, most environmental monitoring applications are undertaken using culture media, with many alternative methods also being growth-based. This makes the selection, control and release of culture media very important, writes Tim Sandle, Head of Microbiology, Bio Products Laboratory.

How the new draft of Annex 1, Manufacture of Sterile Medicinal Products is impacting environmental monitoring programmes is considered by Daniele Pandolfi, Life Sciences, Aerosol Product Line Manager and Frank Panofen, Life Sciences, Microbials Product Line Manager, Particle Measuring Systems.

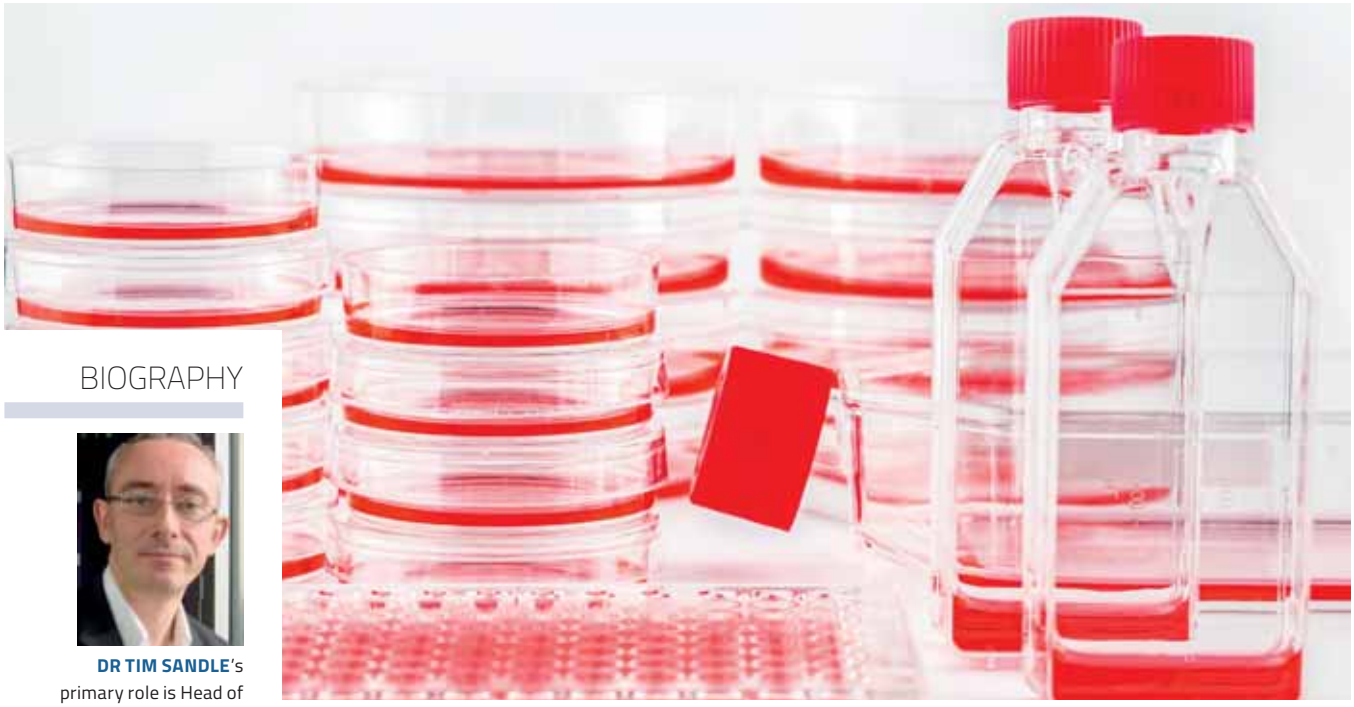
Software tools that enable confident GC-MS analysis of extractables in pharmaceutical products are the subject of this article from Daniela Cavagnino, Gas chromatography, chromatography and mass spectrometry, Thermo Fisher Scientific. Her feature explores the challenges of testing workflows, and how advanced software tools are helping to deliver more precise and confident analysis.

Avoiding environmental monitoring 'false negatives': overcoming disinfectant residues with culture media neutralisers

Tim Sandle

Head of Microbiology, Bio Products Laboratory

Even with the rise of rapid microbiological methods, most environmental monitoring applications are undertaken using culture media, with many alternative methods also being growth-based. This makes the selection, control and release of culture media an area of great importance, given that the quality of the culture media underpins the environmental monitoring programme.[1]



BIOGRAPHY

DR TIM SANDLE's primary role is Head of Microbiology at Bio Products Laboratory, a sterile products manufacturer. In addition, he is a tutor with the School of Pharmacy and Pharmaceutical Sciences, University of Manchester, for the university's pharmaceutical microbiology MSc course, and a longstanding committee member of the pharmaceutical microbiology society Pharmig.

IN ADDITION to selecting the right culture media, the use of an appropriate neutraliser is important in relation to surface, and some personnel, monitoring. Neutralisers are required to overcome any residues left by disinfectants, as can be found on cleanroom surfaces or on the gloved hands of personnel.[2] The use of a neutraliser within the culture media formulation is also necessary to overcome residues from antimicrobial compounds so that a false negative is avoided. The use of a neutraliser is recommended in the biocontamination control standard ISO 14698;[3] and, outside of pharmaceuticals, the cosmetics microbiological test standard ISO 21149 contains some useful advice on neutraliser selection.[4]

The selection of an appropriate neutraliser is not straightforward. The neutraliser must be non-toxic to the microorganisms expected to be recovered; be able to stop residual disinfectant activity; and, importantly, be effective against each disinfectant in use. This latter requirement often proves the most challenging.

This article examines the most common neutralisers used; some of the problems associated with their selection; and the complexities around using the most appropriate neutralisers in the culture media most commonly used in the environmental monitoring programme.

Culture media and neutralisers

Culture media is required for the cultivation of microorganisms. Media contains the substances that are needed to support growth. Some media are general; others are designed for specific isolation.[5] There are a myriad of different types, which reflects the diversity of microorganisms and their different metabolic pathways.
With environmental monitoring, there are differences in practice: the use of one universal medium or two (one for the recovery of bacteria and one for the recovery of fungi); differences in incubation temperatures (one or two temperatures, and with the latter the order of incubation); and with incubation time.[6] Whichever strategy is adopted, it should be qualified, and the reliability of the culture media must be assured by assessing the culture media supplier through activities such as audits; defined storage conditions; and on-delivery growth promotion testing.

A neutraliser is needed to overcome the inhibitory effect of any residual antimicrobial substance, as might occur with an established test, such as the sterility test, antimicrobial effectiveness test or disinfectant efficacy tests. In the past the term 'inactivator' was sometimes used, although 'neutraliser' is more common today. Neutralisers are also added to some culture media in case of disinfectant residues when the media is used for the environmental monitoring of surfaces or from the gloved hands of personnel. Neutralisers are also used in pharmaceutical microbiology by being added to rinse solutions, to overcome any residuals that might affix to a membrane filter, and with disinfectant efficacy testing.[7]

Why neutralisers are required

When sampling the gloved hands of personnel and surfaces using contact plates, it is important that the culture medium contains a suitable neutraliser. This is to address residues of disinfectants that are most likely to be present.[8] Most disinfectants will leave some non-volatile residues on a surface after drying. The amount of residue remaining varies depending on the active and product formulation. The type of disinfectant less likely to leave a residue is hydrogen peroxide, which breaks down into water and oxygen relatively rapidly (within 30 minutes on a surface). With other types of disinfectant, residues are likely to remain for prolonged periods. Although some facilities follow disinfectant application with rinsing (either following each application or when changing over between disinfectants), the process is variable and difficult to qualify. It is therefore prudent to consider that any cleanroom surface could contain traces of a disinfectant (***Figure 1***).

FIGURE 1

ABOVE: Taking finger dabs in a laboratory

When contact plates are applied to the surface, or larger plates (typically those of a 9cm diameter size) are used to sample gloved hands, the residues will be transferred to the agar and re-solubilised; hence they may inhibit recovery of organisms.
The use of contact plates or larger plates for finger dab sampling, containing appropriate neutralisers, can prevent this phenomenon.

The presence of a neutraliser is also required for swabbing. Swabs are commonly either plated out or placed into a medium and subjected to a procedure designed to remove bound organisms from the swab. The medium is then filtered.
If swabs are plated the culture medium should contain a neutraliser and if swabs are filtered, the rinse medium should contain a neutraliser. Neutralising additives like polysorbate or lecithin are used to neutralise inhibitory disinfectant residues transferred to the swab during sampling that might inhibit microbial growth.

For the monitoring of process environments where antibiotics are manufactured, the culture medium needs to contain beta-lactamase to neutralise the particular beta-lactam antibiotic being produced, such as penicillins and cephalosporins.[9]

When neutralisers are not required

Neutralisers are not required in all of the culture media article used. Where there is no need to neutralise, the presence of a neutraliser can simply add unnecessary cost to the culture media. For example, if the same size of plate is used for both surface monitoring and active air-sampling, there would be no need for the active air-sample

> *"A plate that 'cracks' is invalid, and this creates a data integrity issue in relation to the reading of environmental monitoring samples"*

RIGHT: Agar plate used as a settle plate showing signs of cracking, post-incubation

FIGURE 2

> *This selection is not always straightforward and must involve a literature review*

media to contain a neutraliser. In other cases, the presence of a neutraliser can lead to poor performance from an article. With settle plate exposure, an important consideration is demonstrating that the plate can be exposed for four hours, under unidirectional airflow, without the loss of moisture that occurs leading to the plate being unable to recover any microorganisms that deposit into the plate through microbial carrying particles landing on the plate through gravity. The exposure time, therefore, requires qualifying.[10] The presence of a neutraliser in the agar can, in this author's experience, lead to the agar matrix breaking and, thus, to the plate cracking during post-exposure incubation. An example is shown in ***Figure 2***.

A plate that 'cracks' is invalid, and this creates a data integrity issue in relation to the reading of environmental monitoring samples. It is better practice to ensure that agar plates used as settle plates do not contain neutralisers.

Types of neutralisers

While the major pharmacopeia provide some guidance as to neutralisers that can inactivate different antimicrobial substances, these tend to be forms of guidance orientated towards preservatives. Care should therefore be taken with the selection. A complexity with neutralisers is that one neutraliser may be effective against a given disinfectant but ineffective against another. This creates a problem where two disinfectants are used in rotation (and rotation of two different disinfectants with different modes of activity is a regulatory requirement). To avoid the need to use two different contact plates, each containing a different neutraliser, effort should be made to find a universal neutraliser.[11] A universal neutraliser is a combination of chemicals, such as lecithin, to neutralise quaternary ammonium compounds, amphoteric surfactants, benzamidines, chlorhexidines and dequadin; and polysorbate 80 to neutralise alcohols and phenolic-based disinfectants.

This selection is not always straightforward and must involve a literature review. The greater challenges arise from disinfectants classed as sporicides. Here, more complex combinations are often required, such as lecithin, polysorbate 80, sodium thiosulphate and L-histidine, which provides the ability to neutralise residues of chlorine-related sporicidal substances in relation to non-sporicidal disinfectants, such as quaternary ammonium compounds, phenolics (of a low pH value), and iodine.[12] The presence of sodium thisulphate inactivates sodium hypochlorite and acidified sodium chlorite. This neutraliser is a variant of D/E Neutralising Agar, which was developed by Dey-Engley.[13] This formulation is capable of neutralising a broad spectrum of antiseptic and disinfectant chemicals, which extends to the alcohol residues that may be present on the gloved hands of operators in relation to finger plate monitoring. However, for hydrogen peroxide, plates containing a separate neutraliser may be required, such as sodium pyruvate, if the breakdown effect cannot be demonstrated.[14] Alternatively, the use of cysteine has been shown to be an effective reducing agent for neutralising oxidising agents such as hydrogen peroxide and iodine.

When the culture media company develops an appropriate neutraliser, the neutralising agent should be added before sterilisation of the media. As part of the development, the neutraliser product should be tested to demonstrate efficacy and absence of toxicity for microorganisms.

Qualifying neutralisers

The culture media supplier should have on file studies that show the suitability of neutralisers in relation to microbial toxicity, using methods such as the quantitative microtitre method or the paper disc assay method. In addition, the facility microbiologist should perform testing to prove that low numbers of organisms can be recovered in the presence of disinfectant residues. Facility isolates should be included in the test panel.

Summary

This article has provided a short overview of neutralisers required for culture media for use with an environmental monitoring programme. The most important points are firstly the need to include a neutraliser and, secondly, selecting the correct type of neutraliser: get this wrong and the validity of tests becomes open to question. Therefore, the experimental design used to establish the efficacy of biocide neutralisation has a major impact on the estimation of antimicrobial efficacy. Microbiologists should work closely with culture media suppliers to ensure that the correct neutralisers are being used.

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How the new draft of Annex 1, Manufacture of Sterile Medicinal Products impacts environmental monitoring programmes

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The new draft[1] of Annex 1, Manufacture of Sterile Medicinal Products, was published on 20th December 2017, setting a milestone for adjustments needed within European agencies overseeing drug product regulatory applications. During the revision process, the US FDA and the Pharmaceutical Inspection Convention and Pharmaceutical Co-Operation Inspection Scheme (PIC / S) worked alongside the EU, demonstrating the critical need for standardised regulations reflecting the current state of sterile pharmaceutical manufacturing on a global scale.

BIOGRAPHY

DANIELE PANDOLFI has worked in particle counter instrumentation and cleanroom contamination control for more than 10 years. While building strong customer relationships, he has helped many people solve their current Good Manufacturing Practice (cGMP) issues. Outside of work, he is a semi-professional photographer, an enthusiast of electronics, a lover of new technology, and a keen traveller.

Cleanroom classification and qualification

Most of the relevant principles of the ISO 14644-1:2015 standard[2] are included in the new Annex 1's Chapter 5.26. The minimum requirements needed to classify a cleanroom, including the initial number of sampling sites and the required sample volume in critical zones (Grade A and B) are now present in Annex 1. All further decisions must be based on process knowledge and risk assessment. Consequently, it will become difficult to justify why lesser parameters for the qualification are chosen, especially for inspection of manufacturing environment sampling. This ties in deeply with the statement in Chapter 5.28, where "Clean room qualification (including classification) should be clearly differentiated from operational process environmental monitoring". A clear distinction needs to be made between each phase of a clean environment's lifetime.

This concept is represented in the equation shown in ***Figure 1***.

The classification of a cleanroom is based on particle load. There are no microbial limits given for this part of the process, but the revision contains a major change from the 2008 version.[3]

In chapter 5.25, particles of the size equal to or bigger than 5µm have been removed from the classification and qualification limit table for Grade A, but kept in the recommended limits for monitoring of the process environment.

The reasons for de-emphasising the 5µm limit in Grade A include:

- Harmonisation of the European Requirements with the recent release of ISO 14644-1, where the 5µm limit in ISO Class 5 has already been removed
- Sampling and statistical limitations for particles in low concentrations make it inappropriate
- Sample collection limitations for particles in low concentrations and sizes greater than 1µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

De-emphasis of the 5µm limit refers only to the cleanroom classification process. The 5µm particles still represent an important indicator of possible contamination during the manufacturing process and, therefore, must be kept under control continuously during filling and manufacturing. Discrepancy in the treatment of 5µm particles between classification and monitoring are a foremost concern and may necessitate discussion on the possible risks of leaving out certain particle sizes during initial qualification. These sizes will still need to be within certain limits during monitoring.

The language pertaining to the responsibility of defining alert and action levels and limits has been made stronger and clearly refers to the cleanroom user, who must define the appropriate values based on a formal risk assessment and data trending analysis. This change emphasises regulators' expectations that manufacturers set their action and alert limits based on historical data, process knowledge and a risk-based approach. In addition, it is important not only to define particle limits, but also an appropriate alarm strategy, which encourages the evaluation of ISO 14644-2[4] and its recommended practices.

The strategies set out in ***Figure 2*** consider the importance of evaluating an alert or alarm situation using a series of events rather than a single spot value.

Requalification frequency

Paragraph 5.29 presents manufacturers with a challenge: bi-annual requalification of critical zones (Grades A and B) are becoming a standard of the industry. It is already a widespread practice, but many pharmaceutical companies have differing strategies that will need to be thoroughly explained in upcoming inspections. Modern technologies – including real-time methods for viable counts that minimise downtimes caused by the requalification process and therefore increase productivity – will become more crucial to the success of pharmaceutical companies.

It is interesting to note that throughout the new draft, Grade A and B environments are considered almost equal in the way they are treated for cleanliness.

FIGURE 1

INITIAL CLASSIFICATION ≠ RE-QUALIFICATION ≠ PROCESS MONITORING

Annex 1 and microbial impurities

Microbial impurities can be divided into "viable" and "non-viable" particles. "Non-viable" particles are inert and act as vehicles for viable particles, meaning they do not contain any microorganisms themselves. Laser-based

> *"Sampling and statistical limitations for particles in low concentrations make it inappropriate"*

FIGURE 2

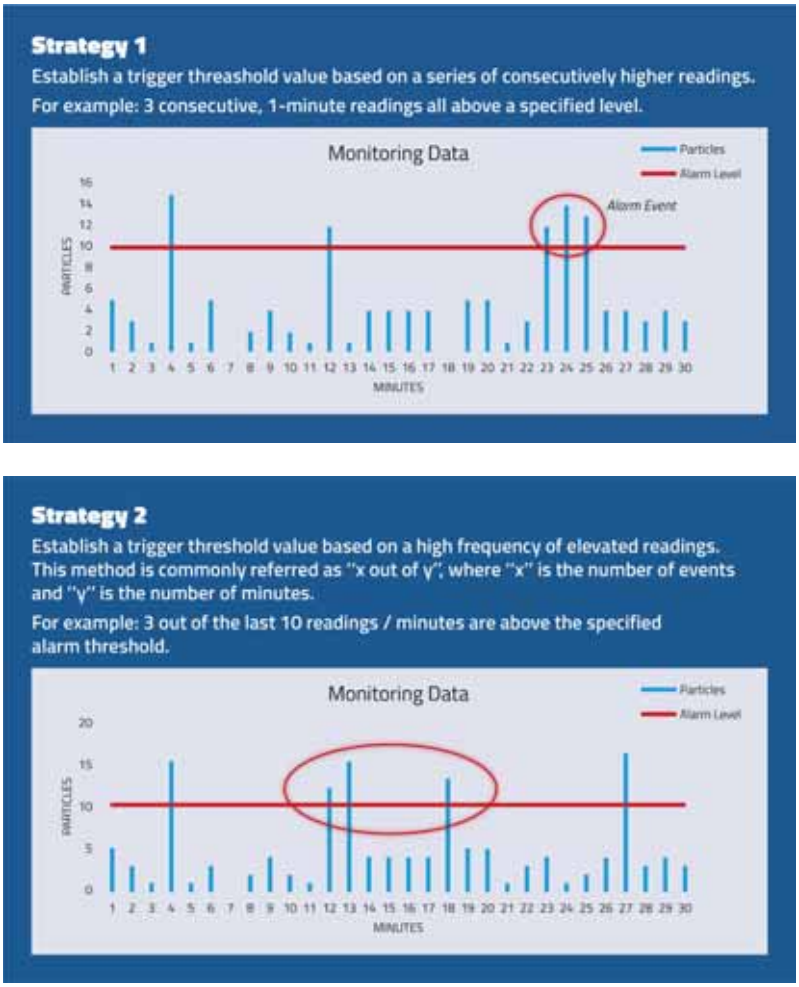

FIGURE 3

NON-VIABLE = INERT
+ VIABLE AND CULTURABLE
+ VIABLE BUT NOT CULTURABLE

particle counting, typically used for determining "non-viable" levels in a critical pharmaceutical environment, displays both "non-viable" and "viable" particles, which is comprised of "viable and culturable" and "viable but not culturable" (VBNC) impurities. The equation shown in ***Figure 3*** represents what is seen by laser-based particle counting.

The components of this equation have widespread, and often incorrect, usage. Pharmaceutical cleanrooms are not classified using microbiological parameters, but by using non-viable / inert counts. Therefore, microbiological considerations start when the rooms are qualified for their intended use. As in the 2008 version, this is called the "in operation" stage and proposed action limits can be found in Table 2 of the draft. Although the values in the table look familiar, some major changes have been made:

- The values for Grade A zones are now set to 1 (was previously <1)
- No averaging of results is allowed.

Consequently, manufacturers are no longer allowed to 'average out' non-welcome results by looking at a scale of multiple measurements.

Each single result should be considered and cause a deviation resulting in a full investigation. However, this is true only for the qualification of the "in operation" stage and does not apply for the monitoring of the process. True routine "in operation" monitoring limits can be based only on historical data and locations, frequency, volume and duration of monitoring on a risk-based approach and data generated during the qualification, as stated in Chapter 9.5. This may create some confusion between the qualification stage's "in operation" and the routine monitoring programme's "in operation".

Chapters 9.7 and 9.27 follow previously-established standards in terms of viable sampling, which can be found in other regulatory documents. In essence, sampling should be carried out as close as possible to the critical area in Grade A environments, but without posing any risk to the process and sampling itself. To do both has been a long-standing dilemma, and often requires a specialised approach using technologies such as single use.

The frequency of viable sampling has received an almost revolutionary renewal in the Annex 1 draft. Chapter 9.25 indicates that sampling must be frequent, and the combination of methods gives manufacturers ample control regarding which methodology and resulting data should be considered relevant for the sampling point. As always, the reasoning for all decisions must be documented and based on risk assessment and historical / scientific data. Interestingly, these strategies also apply to personnel monitoring (Chapter 9.26). Currently, manufacturers tend to avoid multiple samplings of operators in order to prevent contamination build-up and subsequent risk to the process and products. A possible solution could be the implementation of alternate sampling techniques, such as the use of swabs instead of contact plates.

One significant change is the recommendation for viable sampling to be performed continuously during routine process monitoring, as stated in Chapter 9.27. It will no longer be acceptable to have only small, snapshot sampling that does not characterise the entire manufacturing process. This concept was applied in the 2008 version for "non-viable" counts and has now been expanded into "viable" counts. Currently, continuous data generation can only be achieved by either real-time methods or long-term, traditional viable sampling that is quasi-continuous. The right combination of methods will become critical in the decision-making process.

Grade A and B zones are now considered almost equivalent in how they are treated from a monitoring perspective, and Chapter 9.33 imposes on manufacturers the need to identify all microorganisms found in these environments down to the species level. This new requirement emphasises:

- The importance of Grade B in final product quality
- The need for investigations in both cleanrooms
- The need for understanding the instruments used in these zones and their capability to contribute to contamination.

Conclusion

The consultation document for the new Annex 1 revision provides insight into upcoming regulatory trends. Significant emphasis is placed on manufacturers basing their decisions on an applied, risk-based approach. Monitoring plans should be proactively revised using growing knowledge of the process and risk assessment tools. The overall quality of products is sure to increase as a result of the released draft, with a stronger and deeper understanding of cleanroom performance.

BIOGRAPHY

FRANK PANOFEN has a Diploma in Chemistry from the University of Bielefeld and a PhD in molecular and cell biology from the University of Osnabrück. He has expansive experience in the field of applied pharmaceutical microbiology and serves as the Sterility Assurance / Microbiology Product Line Manager at Particle Measuring Systems. Frank has been an invited speaker at international conferences including ECA and PDA, with a strong regulatory background in pharmaceuticals. He is a certified Microbiological Laboratory Manager from ECA.

> *"The components of this equation have widespread, and often incorrect, usage"*

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Software tools that enable confident GC-MS analysis of extractables in pharmaceutical products

Daniela Cavagnino

Gas chromatography, chromatography and mass spectrometry, Thermo Fisher Scientific

Pharmaceutical products come into contact with a wide range of polymeric materials on their journey from the production line to patients. Plastic and rubber contact surfaces are present at almost every stage of a product's lifecycle: they're present in single-use systems, such as filters and tubing employed in manufacturing processes; the packaging components that protect medicines during transport; and the delivery devices, such as syringes, pens and inhalers used to administer treatments to patients.

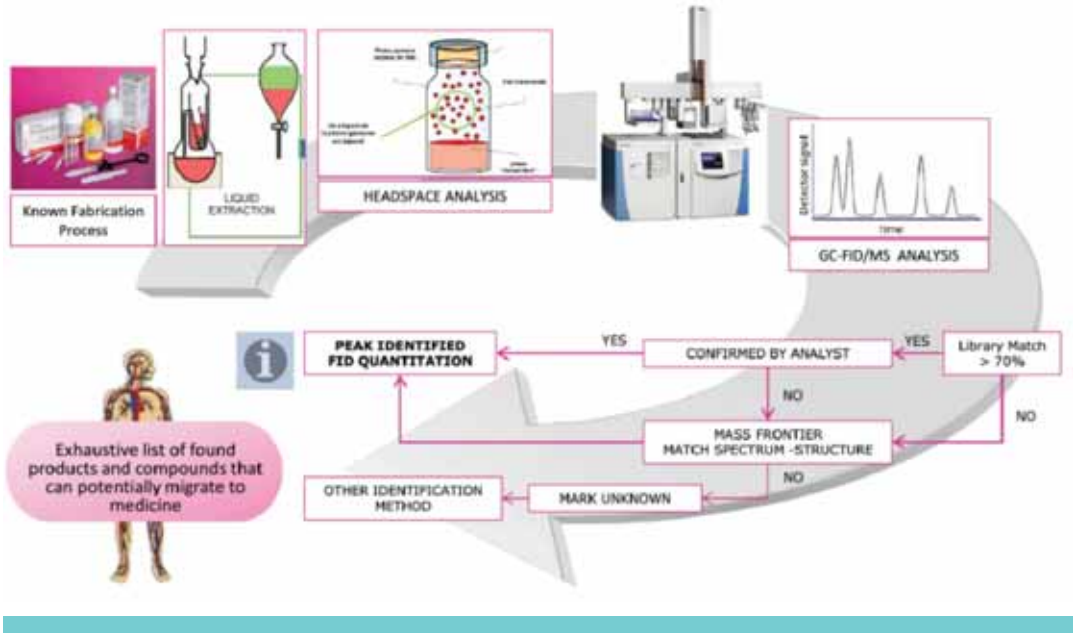
BIOGRAPHY

DR DANIELA CAVAGNINO received a Master's Degree in Chemistry from the University of Milan, Italy. She started her career in gas chromatography at Thermo Fisher Scientific, spending several years in the R&D laboratories working on GC technology innovation. She then conveyed her technical background into product management and marketing management roles, and she now has more than 10 years of experience promoting GC / GC–MS technology and applications in several different market segments. During her career, she has participated as an author and co-author in technical publications and as a lecturer at international conferences.

LEFT: For volatile components, gas chromatography mass spectrometry, using either direct headspace analysis or liquid injection following solvent extraction, is typically employed

WHILE these materials are essential to ensure the sterility and quality of medicines during their manufacture and storage, they can also pose a serious risk to human health. Certain pharmaceutical products and packaging materials are incompatible and, if paired, can result in the leaching of potentially dangerous substances into products, possibly compromising the stability or, even worse, the pharmacological activity. These components, known as extractables and leachables, are the focus of rigorous testing workflows to ensure therapeutics are safe for use and meet regulatory requirements.

FIGURE 1



LEFT: Typical workflow for extractables analysis

Extractables are chemicals that can be extracted by the pharmaceutical products from contact materials under accelerated laboratory conditions, such as elevated temperatures or aggressive solvents. Leachables are typically a subset of extractables that can migrate from packaging into a drug product under normal usage or standard storage conditions. Both extractables and leachables have the potential to react with an active ingredient or formulation excipients, potentially compromising the efficacy of the product and the dosage consistency, with serious implications for human health.

This article addresses the challenges facing these testing workflows, and how advanced software tools are helping to deliver more precise, confident analyses.

Extractables and leachables testing

Given the broad range of materials that may be present in a single device, packaging unit or storage container, identification of the contact component from which an extractable or leachable originates is essential. Plastics can contain a wide range of extractables and leachables derived from additives and storage aids such as antioxidants, plasticisers, emulsifiers and colourants. While information can be obtained from component manufacturers, given the complex supply chains involved in pharmaceutical manufacturing, robust testing workflows are required.

The identification of potential extractables typically involves a preliminary extractable study (***Figure 1***). This can be performed using a range of analytical methods, depending on the nature of the component under investigation. For the analysis of elemental composition, inductively coupled plasma analysis is typically used, while liquid chromatography mass spectrometry (LC-MS) is generally employed for the identification and quantitation of non-volatiles. For volatile components, gas chromatography mass spectrometry (GC-MS) using either direct headspace analysis or liquid injection following solvent extraction is typically employed.

A growing analytical challenge

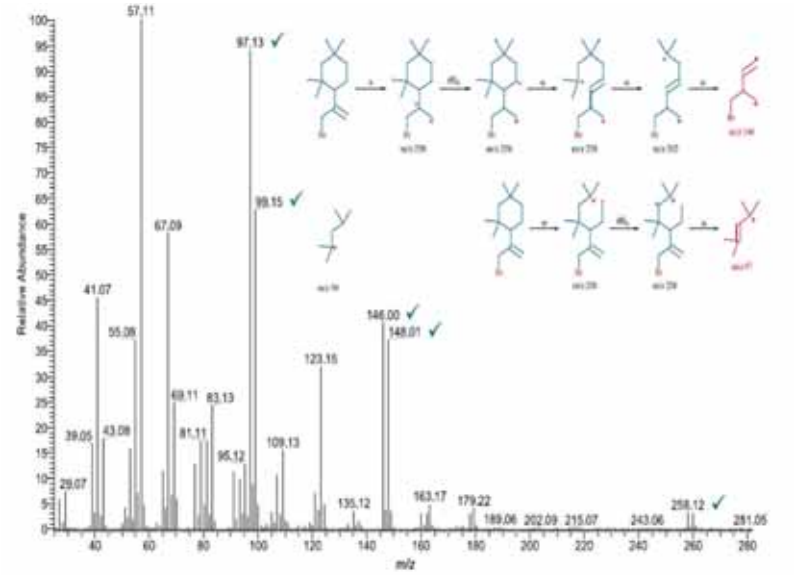
The risk of polymer-derived extractables entering pharmaceutical products has increased in recent years due to the growing adoption of single-use technologies, novel packaging solutions and drug delivery systems. To protect patients and consumers from exposure to these components, regulatory bodies are demanding more information about drug contact materials and their potential to interact with pharmaceutical products, putting additional pressure on testing laboratories.

One of the biggest challenges associated with extractables testing workflows is identifying and quantifying compounds at very low limits of detection. A particular challenge relates to the large variation in potential dose between ›

> *"One of the biggest challenges associated with extractables testing workflows is identifying and quantifying compounds at very low limits of detection"*

> *"Plastics can contain a wide range of extractables and leachables derived from additives and storage aids such as antioxidants, plasticisers, emulsifiers and colourants"*

FIGURE 2



ABOVE: MS fragmentation pathway of an unknown compound in the isopropyl alcohol (IPA) extract of a plastic syringe

pharmaceutical products. An asthma inhaler, for example, may administer three or four doses of just 50 microlitres, while a dialysis bag may deliver a volume of several dozen litres. The ability to quantify potentially dangerous extractables at the trace level is therefore essential.

Fortunately, advances in instrument design and increasingly powerful data analysis packages are driving remarkable improvements in quantitative analysis. Using the latest spectral deconvolution software, analysts are able to overcome the challenges associated with background noise and possible analytical interferences, to produce very clean spectra from which to draw confident conclusions. Deconvolution programmes can be used to extract 'clean' single compound mass spectra from a complex Total Ion Chromatogram (TIC) and match them with available mass spectral libraries for reliable identification.

> *"Deconvolution in this way enables the precise isolation of mass spectra even from co-eluting compounds"*

Such software operates in a three-step process. Firstly, the software counts the number of eluted compounds based on a minimum number of ions present at a common retention time. The corresponding mass spectrum is then extracted, and its contribution to the baseline and co-eluting mass intensities is eliminated. The software then checks against a user library to determine whether the target compounds are present, by simultaneously matching the retention time or retention index and mass spectrum. Finally, all the detected compound spectra are compared against the reference spectra of linked libraries. Various criteria can be used to filter the results; for example, isolating only the most abundant compounds in terms of peak area, or those with a minimum percentage area over a given value.

Deconvolution in this way enables the precise isolation of mass spectra even from co-eluting compounds. The ability to use an individual library of target compounds and combine retention time with mass spectral data makes it a powerful tool for analysis.

Detect the unexpected

With the increasing use of novel single-use components and innovative packaging, the potential for unknown extractables entering testing workflows is also set to rise. Determining the identity of compounds not present in commercial libraries was once a complex challenge, requiring a significant amount of time and a good deal of analytical detective work. However, advanced software solutions are helping testing laboratories identify unexpected compounds more quickly and confidently than ever before.

While acquired spectra may not fully match commercial library references, some matches may show structural similarities. These subtle clues as to the unknown compound's identity can be used to piece together the full structure. Tools can generate plausible proposals to explain the mass spectrum pattern for such an unknown compound by associating fragmentation pathways and ion structures with the unknown spectral pattern calculated using known fragmentation rules.

Figure 2 highlights how this approach can be used to provide a likely identification for an unknown compound extracted from a plastic syringe component using isopropyl alcohol. The proposed structures can explain the mass spectrum pattern and fragmentation pathway, providing a valuable tool for unknowns elucidation.

Parallel detection using full-scan mass spectrum and Gas Chromatography-Flame Ionisation Detector (GC-FID) showed well correlated chromatographic patterns. In this way, after identification of compounds, routine analysis can be performed reliably using the GC-FID, as an easy-to-use screening solution.

Conclusion

Extractables and leachables found in polymer-based single-use technologies, packaging components and drug delivery systems present a serious health hazard that demands robust safety testing protocols. The ability to accurately identify and quantify known and unknown extractables in these materials is therefore essential to safeguard human health. Thanks to powerful GC-MS instrumentation and the software solutions used to investigate this data, analysts can cut through the complexity of extractables testing workflows and ensure pharmaceutical products are safe for the patients who need them.

Environmental monitoring programmes: key tools for risk management

Dr Lynne Murdoch, Business Manager – Microbiology, Wickham Laboratories Limited

Environmental monitoring programmes are all about risk management. The use of risk management techniques and a thorough understanding of laboratory processes can assist in identifying problematic areas.

WHEN considering environmental monitoring for viable organisms, fully cataloguing the flora and its precise location in the site is vital. This means regularly identifying microorganisms; not only to genus level but also species level. This can be very useful in investigations where product contamination has occurred. Problem-solving techniques can assist in identifying the source of the contaminant using historical and current data trending on the catalogued microbial flora.

In addition, understanding the microorganisms enables the facility to determine the best course of action for remedying the contamination; such as which disinfectant should be used and whether cleaning should be conducted more regularly. If there is a fungal or spore contaminant, more radical action may be required for decontaminating the site or resolving the root cause of the contamination problem.

There are many inherent challenges with microbial environmental monitoring programmes and companies often struggle with understanding where to start in this process. This is particularly true in instances where no microbiologist works in the laboratory or manufacturing site in question. The optimal solution for these companies is to seek help in navigating the regulatory guidance – with assistance specific to their site, processes and products. There can also be difficulty in determining suitable action to take and what alert limits should be based on. This is usually identified from initial monitoring and identification of the flora in the manufacturing facility and surrounding areas; however, it is a time-consuming process and, for this reason, many manufacturers choose to outsource the task.

There have always been alternating trends of outsourcing and conducting microbial methods in-house. However, with increasing regulatory burdens on staff in Good Manufacturing Practice (GMP) settings, it is highly likely that the outsourcing of environmental monitoring – either in whole or in part – will continue, as it is not seen as 'value-adding'. It is, however, extremely important and regulators do tend to focus on this during audits.

Given the time-consuming nature of setting up and maintaining a robust environmental monitoring programme, there has been a drive to look at changes to processes that would save time and money. Unfortunately, despite some innovations in rapid microbiology, in general terms of quantitation and identification these have not fully translated to use in environmental monitoring programmes. The reasons are several-fold.

Rapid systems for use in environmental monitoring are not always quantitative and can be difficult to interpret or correlate to traditional methods of microbial sampling. Although they can potentially offer time savings, this may be at the cost of precision. There is also a perception that regulators will expect the traditional settle plate, contact plate and active air sampling over newer methods, of which regulators may have little or no experience. However, automation of some of the elements surrounding environmental monitoring – such as tracking settle plates (barcoding), locations of monitoring, and scheduling – can enable the process to be more efficient, less time-consuming and error prone.

Given the slow uptake of these new methods, industry standard guidance still tends toward somewhat complicated and often onerous processes. Despite this, those involved in the set up and monitoring of these environmental programmes must continue to prioritise this activity, given its importance to regulatory authorities and its role in identifying contamination issues at an early stage in the product life cycle. ■