

EPR

EUROPEAN PHARMACEUTICAL REVIEW

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Brexit: a US perspective on how pharma companies are planning to cope with the uncertainties

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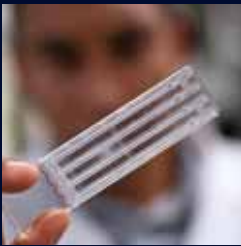
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Brexit 'no deal fears' begin to bite... and the pharma industry is no exception

As alarm continues to grow about the prospect of the UK crashing out of the EU on 29 March 2019 without any exit agreement in place, we explore the implications for the pharmaceutical industry.



MIKE STONES
EDITOR

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WHETHER you like your Brexit hard, soft – or even lightly poached, there is no doubt big questions remain about how Britain's historic decision to quit the EU next year will impact businesses. The pharmaceutical sector finds itself centre stage in this debate, with concerns raised about UK access to key drugs and medical devices.

About 37 million packs of medicines are imported into the UK every month from the EU and European Economic Area (EEA) countries, according to the BBC. Exports to the EU and EEA totalled 45 million packs of medicines. To mitigate the risks of severe disruption to supply chains, should no deal be reached, Big Pharma is reportedly stockpiling supplies of medicines across Europe.

The Government claims to remain confident an exit deal will be agreed before 29 March but is publishing a series of technical notices exploring the sector-specific implications of failing to reach an agreement.

In this edition of *European Pharmaceutical Review*, we report in our News Roundup, on page 10, a Viewpoint published in *The Lancet* that warns a post-Brexit trade deal between the UK and USA could risk increasing drug prices in the UK, which could diminish the affordability and accessibility for the NHS.

A U.S. perspective on how Brexit is likely to impact the global pharmaceutical industry is delivered by law firm Arnold & Porter. Read how its experts believe pharma executives should prepare for any possible disruption to business, in general, and supply chains, in particular, in our Regulatory Insight feature, starting on page 12.

Moving on from Brexit, this edition offers a detailed insight into three key topics, with an In-Depth Focus devoted to each. Our Environmental Monitoring In-Depth Focus begins on page 17, followed by QA / QC on page 37 and Biopharma Processing & Development on page 61.

This edition also contains a preview of CPhI Worldwide plus a host of other information devoted to the fast-moving world of global pharmaceuticals. We hope you enjoy this edition and, as always, would welcome your comments on Brexit or any of the other topics under discussion. 📧

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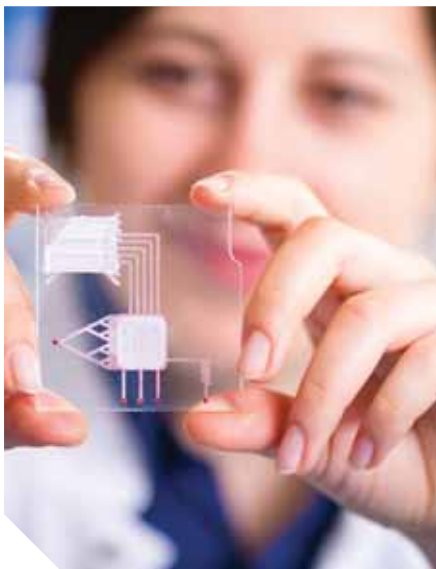
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Understanding the importance of analytical Target Profile: the key questions to ask

Dave P Elder

JPAG Member and David P Elder Consultancy



Methods, like other pharmaceutical processes, have operational lifecycles.¹ These can be summarised as (i) defining the requirement, ie, analytical target profile (ATP), (ii) developing the method, (iii) risk assessment, (iv) validation, and (v) continuous re-appraisal of the method's performance.²

AS PART of the ATP, it is important to consider several fundamental aspects. Those include: the purpose of the method; how the output of the method compares to pre-defined criteria, ie, specifications; how to assure ourselves that we are confident in these outputs and how to increase our confidence in these outcomes.³ Thus, the ATP describes the performance characteristics of the method, ensuring that the method will be fit for purpose. Importantly, the ATP does not cite a specific analytical technique or an operating mode, eg, High-Performance Liquid Chromatography with ultraviolet detection (HPLC-UV). Instead, it establishes the requirements of that technique – particularly the necessary sensitivity requirements.^{4,5}


Analytical procedure

Therefore, a typical Phase I ATP for a mutagenic impurity⁶ could be described as follows: the analytical procedure must be able to accurately quantify mutagenic impurity RS123 in API RS23456, at levels of not greater than 5ppm (detection limit (DL)) for clinical dosing periods of not greater than 30 days, equivalent to a staged Threshold of Toxicological Concern (TTC) of not greater than 120µg/day. In its first incarnation, this sensitive method – eg, HPLC-MS (mass spectroscopy) – could be a simple limit test, which has been developed to facilitate a binary outcome. That is a pass / fail of the measured analyte and requires limited validation, ie, specificity and DL.⁷ This approach utilises an Option 1 control strategy,⁶ where the mutagenic impurity is defined on the drug substance specification. Post proof of concept (PoC), the method is likely to require full validation⁷ to ensure some guarantee of the method's performance.

The ATP will therefore evolve to reflect these new challenges, which could be defined as follows: The analytical procedure must be able to accurately quantify mutagenic impurity RS123 in API RS23456 at levels of not greater than 1ppm (ie, quantitation limit (QL)) for clinical dosing periods of not greater than 12 months, equivalent to a staged TTC of not greater than 20µg/day, with appropriate accuracy and precision such that the measured values are $\pm 20.0\%$ of the true value, with at least 95% probability. This may now need to be an HPLC-MS-MS method to reflect the need for greater sensitivity for the analyte. However, this is still an Option 1 control strategy;⁶ but the specification limit, as defined by the appropriate staged TTC, has been reduced to reflect the longer duration of the clinical studies.

Mutagenic impurity

Finally, with the extensive knowledge of the purging capability of the mutagenic impurity RS123 in the synthetic process, which can only be derived during late development,⁸ it may no longer be necessary, or required, to test for absence of RS123 in the final API at a pre-defined and very sensitive limit, ie, staged TTC. Instead, this greater knowledge allows us to monitor and control mutagenic impurity RS123 as an in-process test at a higher level than the TTC and at some earlier stage of the synthetic process. That is an Option 3 control strategy⁶ for the mutagenic impurity on the specification of a designated intermediate, or raw material or starting material.

Thus, the design intent of the ATP has not changed and remains an effective control strategy for mutagenic impurity RS123. However, during development phases it may have evolved from an HPLC-MS, to an HPLC-MS-MS and finally an HPLC-UV method, whereas the control strategy has evolved from Option 1 to Option 3 approaches. 

BIOGRAPHY

DAVE ELDER has nearly 40 years of service within the pharmaceutical industry at Sterling, Syntex and GlaxoSmithKline. He is now an independent GMC consultant. Dr Elder is a visiting professor at King's College, London, and is a member of the British Pharmacopoeia. He is a member of the Joint Pharmaceutical Analysis Group (JPAG) and a member of the Analytical Division Council of the Royal Society of Chemistry.

REFERENCES

To view references, please visit:
europeanpharmaceuticalreview.com/4-18-Elder

ROUND UP

The editor's pick of the most interesting developments within the pharmaceutical industry



Epigenetic qPCR tool detects disease in newborns

INHERITED DISEASES

A NEW study has identified a novel diagnostic approach to screen newborns for inherited diseases that are not presently screened for.

Currently, newborns undergo a 'heel-prick' test, and the dried blood spots are analysed for Severe Combined Immunodeficiencies (SCID). Despite more than 300 Primary Immune Deficiencies (PIDs) are known, in the UK, the test checks for signs of only 9 diseases including sickle cell disease, cystic fibrosis, congenital hypothyroidism and other inherited metabolic disorders.

The alternative method uses epigenetic quantitative real-time PCR (qPCR) assays and successfully detects a larger number of PIDs, including SCIDs and immune dysregulation, X-linked agammaglobulinemia (XLA) and other severe diseases that usually become apparent within a few months of birth.

"While further research is needed, these initial results are very encouraging as they provide early evidence that this epigenetic technology could eventually be a newborn screening method that would identify primary immune diseases that are currently very difficult to detect," said Dr Rosa Bacchetta, one of the study investigators and an Associate Professor in the Department of Paediatrics, Stanford School of Medicine.

The new method could allow treatment to begin soon after birth, with improved disease outcomes and better survival.

UK-US post-Brexit trade deal risks increased drug prices

BREXIT

A TRADE deal between the UK and USA could risk increasing drug prices in the UK, which could diminish the affordability and accessibility of the NHS, according to a Viewpoint published in The Lancet.

The opinion piece outlines how the USA's targeting of so-called 'foreign free-riding' in trade deals could lead to a poor deal on pharmaceuticals for the UK post-Brexit. The authors raise concerns that the USA could pressure the UK to change the way it regulates pharmaceuticals in trade deals.

Currently, all the UK's international trade deals are negotiated through the European Union, but, the UK Government will need to negotiate new deals to replace existing agreements post-Brexit. The USA is one of the UK's most important trading partners after the rest of the European Union, and a US-UK bilateral trade deal is a key post-Brexit priority, with conversations already taking place to achieve this.



Metabocin shows promise as a potent anti-obesity treatment

OBESITY

A NOVEL drug based on capsaicin, the compound that gives chilli peppers their spicy burn, caused long-term weight loss and improved metabolic health in mice eating a high-fat diet, in new studies from the University of Wyoming School of Pharmacy. The drug, Metabocin, was designed to slowly release capsaicin throughout the day so it can exert its anti-obesity effect without producing inflammation or adverse side effects.

"We observed marked improvements in blood sugar and cholesterol levels, insulin response, and symptoms of fatty liver disease," reported Dr Baskaran Thyagarajan, the lead investigator, describing how Metabocin reversed many damaging effects of the high-fat diet.

The research team developed Metabocin, which can be taken orally, to target receptors called TRPV1 (transient receptor potential vanilloid subfamily 1) that are found in high numbers in fat cells. Stimulating the TRPV1 receptors causes white fat cells to start burning energy instead of storing it, which, in theory, should cause weight loss.

"It proved safe and was well tolerated by the mice," Dr Thyagarajan concluded.

"Developing Metabocin as a potent anti-obesity treatment shows promise as part of a robust strategy for helping people struggling with obesity."

The results of this study were presented at the annual meeting of the Society for the Study of Ingestive Behavior.



Impurity in valsartan leads to voluntary recall

DRUG RECALL

HEALTHCARE professionals and patients have been alerted by the US Food and Drug Administration (FDA) of a voluntary recall of drugs containing the active ingredient valsartan. This active ingredient is used in drugs to treat high blood pressure and heart failure.

The impurity, N-nitrosodimethylamine (NMDA) was found in the recalled products. NMDA is known to be a probable human carcinogen, based on laboratory results. The presence of NMDA was unexpected and may be related to changes in the method the active substance was manufactured.

The FDA's review is ongoing and has included examining the possible effect on patients who have consumed the drugs, measure to reduce or eliminate the impurity from future batches and the levels of NMDA in the recalled products.

FDA commissioner Dr Scott Gottlieb said, "The FDA is committed to maintaining our gold standard for safety and efficacy. That includes our efforts to ensure the quality of drugs and the safe manner in which they're manufactured.

"We have carefully assessed the valsartan-containing medications sold in the United States, and we've found that the valsartan sold by these specific companies does not meet our safety standards. This is why we've asked these companies to take immediate action to protect patients," said Dr Janet Woodcock director of the FDA's Centre for Drug Evaluation and Research.

The FDA continues to investigate this issue and will provide additional information when it becomes available. Any adverse reactions should be reported to the FDA's MedWatch programme.



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METTLER TOLEDO

U.S. perspective on the impact of Brexit on the pharmaceutical sector

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Partner and co-chair of Arnold & Porter's Life Sciences and Healthcare Regulatory practice

Jacqueline Mulryne

Counsel in Arnold & Porter's London Office

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Associate in Arnold & Porter's London Office

The UK's official withdrawal from the European Union, commonly known as Brexit, will occur on 29 March 2019 at 23:00. In anticipation, the UK and EU are currently negotiating what this means, for both sides, and the relationship between the two entities going forward.



BIOGRAPHY



JACKIE MULRYNE, Counsel in Arnold & Porter's London Office, advises clients in the life sciences, medical devices, cosmetics and foods sectors, and has a broad practice providing regulatory compliance and public policy advice. She advises on UK and EU law, and has experience with a range of regulatory issues that arise throughout the product lifecycle, including borderline classification, clinical research, authorisation, advertising and labelling, and pricing and reimbursement.

She has assisted life science and medical device companies in developing and implementing cross-border regulatory action and compliance programmes.

WHAT the final relationship will be is currently unknown, and as the rhetoric within the UK political spectrum increases, it is difficult for U.S. companies to fully understand the risks and implications of Brexit. This article provides an overview of the impact of Brexit on life sciences companies in the U.S., and outlines potential steps that such companies should be considering.

What could Brexit mean for the industry?

The UK medicines regime is governed by EU legislation and many of the procedures, institutions

and personnel are currently common between the UK and EU. As such, every aspect of the lifecycle of medicinal products may be affected by Brexit as will the associated legislation and oversight. In summary these include:

- Authorisation holders: there are more than 1,200 centrally authorised products, 36% of which are held by UK entities. EU law requires certain roles and activities relating to centrally authorised products to be performed in the European Economic Area (EEA); for example, the marketing



LEFT: It remains difficult for U.S. companies to fully understand the risks and implications of Brexit

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BIOGRAPHY



LIBBY AMOS, an Associate in Arnold & Porter's London Office, focuses on advising pharmaceutical and medical device clients on UK and EU regulatory matters. She assists companies on strategic issues arising during the lifecycle management of pharmaceutical products and maximisation of IP regulatory rights including regulatory data protection, supplementary protection certificates, paediatric rewards, and orphan market exclusivity. In addition, Ms. Amos advises companies on the boundaries of the ABPI and EFPIA codes of practice and UK and EU legislations regarding the advertising and promotion of medicinal products and medical devices, including use of social media, packaging and labelling, presence at conferences, use of consultants, and marketing materials.

authorisation (MA) holder, the qualified person for pharmacovigilance (QPPV), and the pharmacovigilance system master file (PSMF) must be in the EEA. As such, each of these products will require separate UK MAs to be placed on the UK market, and centralised MAs held by UK entities will need to transfer the authorisation to an entity within the EU to remain on the market.

- Authorisation procedure: the UK will no longer participate in the centralised authorisation procedure. Companies obtaining a centralised MA would have to submit a separate application to the UK regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA), and undergo a separate assessment procedure. Furthermore, the MHRA currently undertakes an estimated 30% of the European Medicines Agency's (EMA) casework. Although the EMA has sought to re-distribute this work to other countries, without the capacity and expertise of the MHRA, the EU regulatory system may experience disruption and delays.
- Integrated supply chain: more than 2,600 finished products have some stage of manufacture in the UK.¹ In addition, 1,300 medicinal products in the EU are tested and released from the UK: the UK supplies 45 million patient packs to the EU each month. Currently, these products travel freely between the EU and UK, but post-Brexit border controls may well be set up between the two bodies.
- Clinical trials: 1,500 clinical trials are being conducted in the EU with a UK sponsor, 50% of which are set to continue past

March 2019. Further, the recently agreed Clinical Trials Regulation, aimed to ensure a greater level of harmonisation of the rules for conducting clinical trials, is unlikely to come into effect until after Brexit, and therefore will not automatically become part of UK law.

While there is much uncertainty, if the UK adopts significantly different legislation to the EU, this is likely to increase costs and complexities for U.S. companies wanting to place products on the market in the EU and UK. However, some level of harmonisation with regard to testing and release of products is likely to remain. Brexit may also afford the UK a chance to move away from some of the more controversial aspects of EU legislation, making the UK a more inviting place in which to do business. However, this is likely to take some time and may not be at the immediate forefront of the UK government's mind during the ongoing negotiations.

What is the current position?

On Brexit Day, all EU legislation will cease to be applicable in the UK. However, to ensure legal continuity, the UK has enacted the European Union (Withdrawal) Act 2018, which will implement all current EU legislation into UK law on Brexit-day. Further, as part of their negotiations with the EU, a transition period has been agreed to 31 December 2020, during which time, if a Withdrawal Agreement can be reached, EU rules will continue to apply.

Negotiations between the EU and the UK regarding the terms of the Withdrawal Agreement are ongoing. Phase 1 of the negotiations focused on how the UK would leave the EU. A Joint Report published in December 2017² explains that "goods placed on the market under Union law before withdrawal may freely circulate on the markets of the UK and the Union with no need for product modifications or relabelling". Phase 2 of the negotiations is ongoing and focusing on the future relationship between the EU and UK, and on the role and obligations of the UK during the transition period. If no agreement can be reached, there will be no transition period and EU law will cease to apply to the UK; the "no deal" scenario.

In preparation for the negotiations, on 12 July 2018, the UK published a White Paper setting out its position on the UK's continued relationship with the EU post-Brexit.³ The paper proposes that there will be a "common rulebook" for medicinal products enabling "frictionless trade" across the EU-UK border, to which no tariffs will apply. Further, only one set of approvals will be necessary to place medicinal products on the UK and EU market. The paper proposes that the UK will continue to participate in the activities of the EMA, ▶



BELOW: EU-based companies are reported to be stockpiling drug products in the UK in the anticipation of supply disruption

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BIOGRAPHY



DANIEL KRACOV, based in Washington, D.C., is a partner and co-chair of Arnold & Porter's Life Sciences and Healthcare Regulatory practice. For decades he has been one of the foremost life sciences regulatory lawyers in the U.S., and his expertise in critical regulatory matters has been widely recognised by Chambers, the Legal Times, Best Lawyers in America, and other publications. A particular focus of his practice is assisting pharmaceutical, biotechnology, medical device and diagnostic companies – including start-up companies, trade associations, and large manufacturers – negotiate challenges relating to the development, approval and marketing of FDA-regulated products. He also has extensive experience in civil and criminal enforcement matters, global compliance programme development, and regulatory diligence in transactions.

accepting its rules but with no voting rights, and that the MHRA can continue to serve as rapporteur or reference member state in the assessment of individual products, and participate in other activities such as pharmacovigilance and clinical trials. Such close ties to the EU pharmaceutical regime would be welcomed by the industry. However, the arrangement sought by the UK is ambitious, as Prime Minister Theresa May has frequently stated,⁴ and goes beyond the scope of what the EU has previously agreed with third countries, such as Norway. From initial reactions, it seems unlikely the EU will agree to the proposals.

How should U.S.-based pharmaceutical companies prepare?

Given the tempestuous negotiating environment, the European Commission is working on the basis that no agreement will be reached. As such, in joint advice with the EMA, it advises centralised MA holders that certain roles and procedures established in the UK should be transferred to an EEA entity, and that active substances and finished medicinal products manufactured in the UK will be considered as "imported" into the EU post Brexit. Similarly, the EMA has announced that "the UK will no longer be able to engage as (co)-rapporteur for new marketing authorisation applications for which the centralised procedure would finish after 30th March 2019", and has redistributed the UK's portfolio of centrally authorised products to rapporteurs and co-rapporteurs from the remaining Member States.⁵ The MHRA is taking a more positive approach, and has stated that in the event of "no deal", it will "be pragmatic in establishing UK regulatory requirement" to "ensure the minimum disruption and burden on companies" and, where possible, make "use of the information [it] already [has] to complete administrative tasks for continuity of work and licences".⁶

What is the current status of preparations?

In January 2018, the EMA launched a survey to gather information from companies on their Brexit preparedness. The results⁷ revealed that the 58%

of products are on track to make the necessary changes to ensure their MAs remain valid after Brexit. However, there are 108 medicines for which all, or a major part, of the batch release sites, quality control sites and / or importation sites are in the UK, and changes to amend these sites may not be submitted before Brexit. This raises major concerns that if plans are not adapted, these products may no longer be available on the EU market. The survey identified that the majority of the necessary submissions are scheduled for the first quarter of 2019, which is the same time as the EMA will be relocating from London to the Netherlands. Pharmaceutical companies are, therefore, advised to submit their change requests as early as possible, and before the end of the fourth quarter of 2018.

What does this mean for the pharmaceutical sector in the U.S.?

While statements by regulators indicate that ongoing efforts to minimise complexities associated with Brexit will be minimised, the actual terms for the transition remain nebulous. In addition to making decisions regarding the placement of facilities and personnel, reviewing banking relationships and other areas potentially impacted by Brexit, U.S. companies should have monitoring mechanisms and contingency plans in place to ensure that planned and pending applications and other matters before the MHRA and EMA are not unduly delayed or adversely impacted as the transition occurs. This is particularly important with respect to requirements and associated filings for manufacturing sites and pending applications for new products and uses. Moreover, U.S. companies should consider plans for continuity of supply to patients in the UK and EU in the event of UK-EU trade disruption associated with Brexit. EU-based companies are reported to be stockpiling drug products in the UK in anticipation of supply disruption, and U.S. companies should consider similar measures, particularly if product is supplied to the UK from EU-based facilities.⁸ 

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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.



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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

FIGURE 1



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**).


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

 **ABOVE:** Taking finger dabs in a laboratory

“ 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



“ 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 thiosulphate 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

Daniele Pandolfi

Life Sciences, Aerosol Product Line Manager,
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The new draft¹ 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 standard² 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 14644-2⁴ 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 –

FIGURE 1

INITIAL CLASSIFICATION ≠ RE-QUALIFICATION ≠ PROCESS MONITORING

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.

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

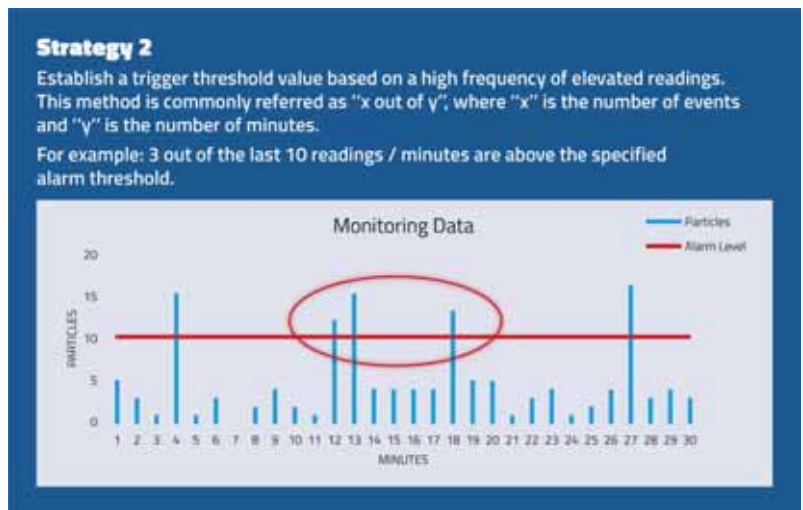
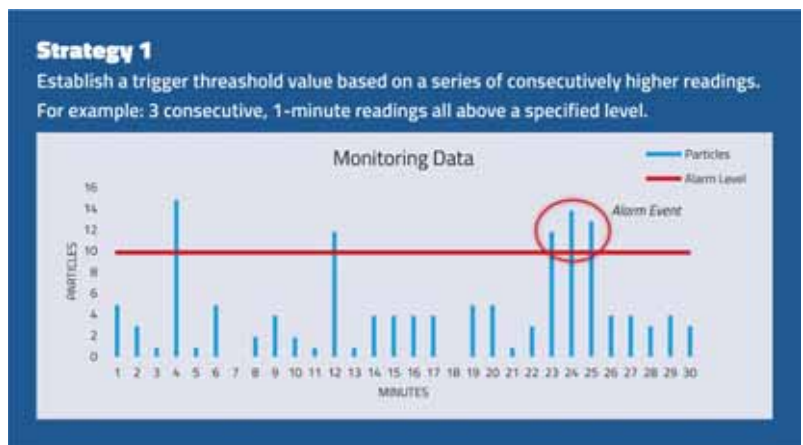


FIGURE 3

$$\text{NON-VIABLE} = \text{INERT} + \text{VIABLE AND CULTURABLE} + \text{VIABLE BUT NOT CULTURABLE}$$

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.

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.

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.

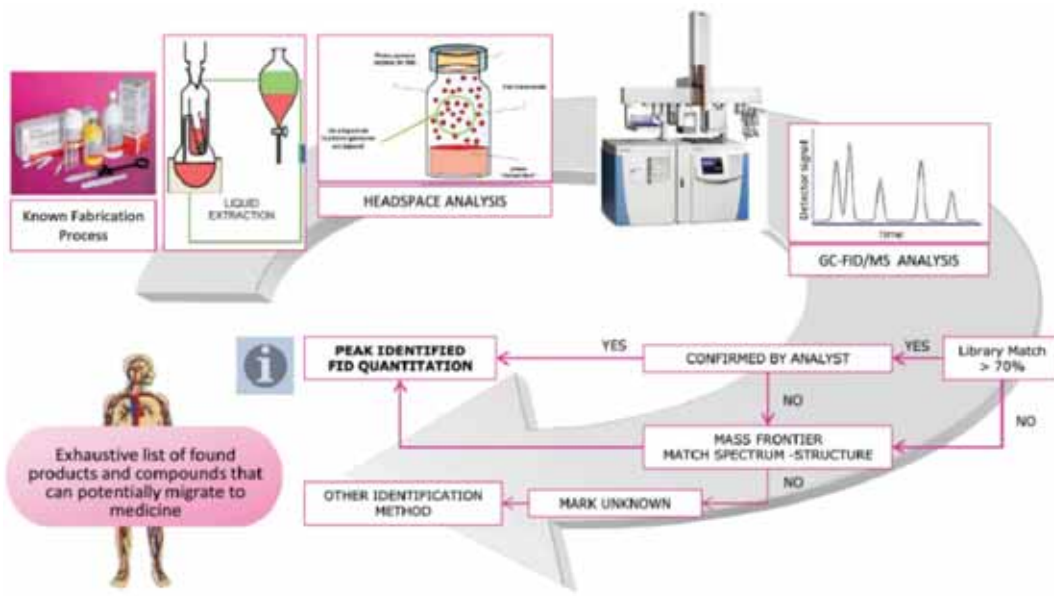


LEFT: For volatile components, gas chromatography mass spectrometry, using either direct headspace analysis or liquid injection following solvent extraction, is typically employed

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

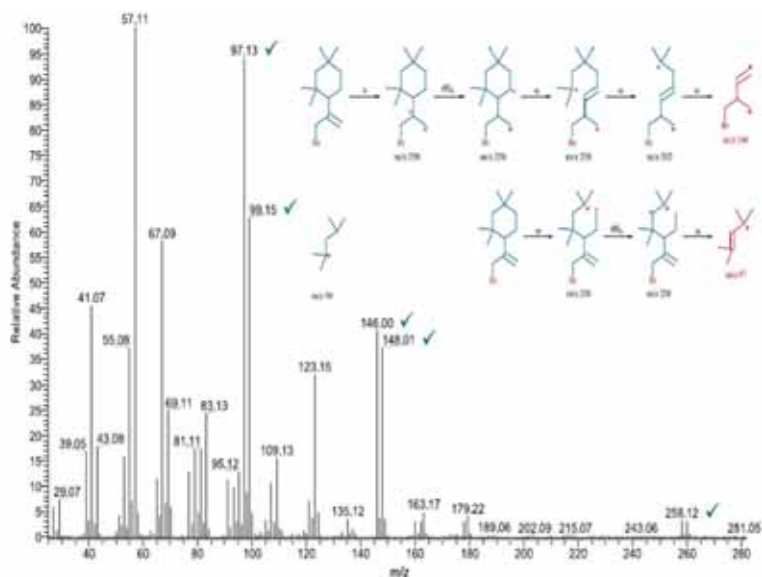
The risk of polymer-derived extractables entering pharmaceutical products has increased in recent years due to the growing adoption of single-use technologies, novel packaging solutions and drug delivery systems. To protect patients and consumers from exposure to these components, regulatory bodies are 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.

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. 

“Deconvolution in this way enables the precise isolation of mass spectra even from co-eluting compounds”

Environmental monitoring programmes: key tools for risk management

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.



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

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. ■



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Why should you care about *Burkholderia cepacia*?

The *Burkholderia cepacia* complex (BCC) species are a group of gram-negative, rod-shaped bacteria that have been shown in recent years to be of concern for patients, and thus for manufacturers of drugs and products that contribute to patient health. Species belonging to the BCC are opportunistic pathogens that have been involved in negative patient outcomes, especially for particularly vulnerable patient populations. As such, regulatory bodies tasked with protecting public health, such as the US FDA, have taken notice and issued numerous recalls for products that contain species from the BCC complex. In turn, manufacturers have begun to revisit microbiological controls and their efficacy in preventing BCC-contaminated products. Aside from the need to detect the presence of *B. cepacia* complex species in tested samples, another important tool in the repertoire of microbiological controls is the ability to accurately identify microorganisms to the species level. *B. cepacia* species have proven problematic in this regard, challenging traditional methods and necessitating advances in microbial identification strategies.

IT IS CRITICAL that our academic knowledge about this complex of microorganisms continues to evolve as we also strive to expand our understanding of the clinical impact of BCC and the importance of microbiological controls against it in the manufacturing process. Clinically, BCC has been implicated for decades in outbreaks and cases of illness and even death.^{1,2}

Members of the *B. cepacia* complex are often opportunistic pathogens among mechanically ventilated patients, the immunosuppressed, and those with serious underlying disease. Of particular note is the threat that BCC infections pose to patients with cystic fibrosis (CF). In a recent review, Sousa notes that BCC may cause serious infections in individuals with CF, and while all BCC species may give rise to infection, the large majority of such infections are caused by two species in particular: *Burkholderia cenocepacia* and *Burkholderia multivorans*.³ Further, Sousa notes that BCC infections are especially frightening for CF patients because of the antimicrobial resistance demonstrated by members of the *B. cepacia* complex, the highly contagious nature of BCC species, and the possibility that such an infection might give rise to additional complications like cepacia syndrome, which develops in 20% of cases and is characterised by a swift, and



often deadly, necrotising pneumonia along with septicemia, sometimes progressing to the point of death in a matter of days.

Though *B. cepacia* is certainly of great concern for those who are immunocompromised or living with cystic fibrosis or chronic granulomatous disease, there are occasional cases in which *B. cepacia* has caused serious illness in non-immunocompromised, previously healthy, patients.⁴ BCC is highly contagious and especially virulent. With this risk to patients in mind, in recent years regulatory bodies like the FDA have taken a close look at products that contain BCC, issuing recall after recall and even an advisory statement to drug manufacturers in May of 2017,⁵ warning

of the particular risk posed by BCC in non-sterile water-based products.

Non-sterile water-based products have featured prominently in BCC-related recalls, including products such as sanitisers, oral pharmaceuticals, gas relief drops, eyewashes, nasal sprays, mouthwashes, anti-cavity rinses, skin creams, baby and adult washcloths, surgical prep cloths, electrolyte solutions, and radiopaque preparations. In products such as these, BCC is especially troublesome because of its ability to resist preservatives and antimicrobial agents, growing even in unfavourable environments. One species in particular, *B. multivorans*, has been noted to grow well in low-nutrient environments such as distilled water, and is a good biofilm former. A recent case study shared by the FDA examined a situation in which *B. multivorans* was detected in a product (albeit prior to release of the product by the manufacturer). As it happened, two batches of a nasal spray containing an antimicrobial preservative were discovered during microbial testing to contain *Burkholderia cepacia* complex. Retesting other batches revealed that five additional lots contained BCC as well, though they previously had tested negative. The firm established that bacterial growth was initially inhibited by preservative in the

product, but later overcame the preservative system and flourished. Detailed testing to elucidate the exact BCC species responsible for the contamination revealed *Burkholderia multivorans* as the culprit. Identification of the microorganism not just as a member of the *B. cepacia* complex, but specifically as *B. multivorans* allowed the firm to link the batch contaminations to each other and perform a high-quality internal investigation to find the source of the contamination. Ultimately, the organism was traced back to a *B. multivorans* biofilm that had formed in the purified water system, and, having established root cause, the firm was able to correct the plumbing and continue with additional corrective and preventative actions (CAPAs).

Some might suppose that defining the precise BCC species in such a situation should not matter, but in fact, it is important to know which particular species is implicated. It is not enough to assume that any one measure (CAPA) is sufficient to eradicate all different species, as they have distinctive characteristics and may respond differently to attempts to decontaminate. Additionally, as mentioned earlier, some species like *B. multivorans* demonstrate exceptional virulence, and may merit extra concern, action, or a broadened scope of investigation should they be discovered in products, especially those that might be encountered by susceptible populations. Important though it is for the industry to be able to define the different species that make up the *B. cepacia* complex, it's a difficult prospect to do so. At present, speciation of BCC is problematic, with many available methods yielding incorrect results or being incapable of distinguishing one species from another within the complex altogether.⁶

With respect to more advanced methods such as genetic sequencing, reliance on typical 16S sequence data is not a fully viable option either, as the species of BCC are so closely related that they are not distinguishable from each other in these genetic regions. Historically, the first 500 base pairs of the 16S rRNA gene have been used for sequence-based identifications of microbial samples sourced from manufacturing facilities' environmental monitoring programmes and root-cause investigations. This approach has shown to be very successful in providing identification results to the species level. However, even 16S rRNA gene sequence analysis has limitations with differentiating some groups

of closely related organisms that share a high percentage of 16S rRNA gene sequence similarity, *B. cepacia* complex included.

As such, the pharmaceutical industry has taken a recent interest in the possible use of the entire 1500 base pairs of the 16S rRNA gene versus just the first 500 base pairs as is current common practice in bacterial identification. To evaluate whether this full-length gene sequencing might be a more appropriate approach, especially in situations wherein species cannot be differentiated with only 500 base pairs of sequence, a study was carried out by Hong and Farrance.⁷ Findings showed that the overall performance of the first 500 base pairs of sequence of the 16S rRNA gene was quite high. When compared to the full-length 1500 base pair sequence for identification, 93.7% of the samples showed no differences between the two approaches. Considering the comparable performance of both 500 base pair and 1500 base pair sequencing identifications, as well as logistical limitations of generating the full-length sequence data for the 16S rRNA gene, it was concluded that in cases in which additional resolution is needed for confident speciation, it would make more sense scientifically and operationally to target alternate regions of the genome.

One proposed alternate gene target for providing the genetic discrimination needed to reliably differentiate closely-related species, including BCC species, is a protein-coding gene called *recA*. *recA* codes for a protein essential for repair and recombination of DNA,⁸ and its sequence data have proven very valuable for the identification of *B. cepacia* complex species⁹ as well as other closely-related bacteria.¹⁰ *recA* is uniquely suited to discernment of related BCC species as it exhibits higher sequence heterogeneity than 16S rRNA, yet is still highly conserved. Typically, members of the same BCC complex species demonstrate 98-99% sequence similarity at the *recA* target, whereas sequence similarity between different species drops to 94-95%.¹¹

Recognising the advantages presented by the *recA* sequencing approach when attempting to speciate members of the *B. cepacia* complex, service laboratories such as Charles River have developed the capability of distinguishing BCC species from one another with services like Charles River's ProSeq offering. Because of the novel and complex approach in targeting *recA*, it is imperative that service providers use high quality sequence data, curated

reference databases, and updated bacterial nomenclature and taxonomy for phylogenetic analyses in order for an identification to be accurate and reliable. Charles River Labs puts all these safeguards in place as they recognise that accurate and reliable microbial identification data is critical not only for certain organisms such as the *Burkholderia cepacia* complex, but for all microbial isolates that are part of quality control practices. ■

Author

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Therapeutics trends and pharma technologies – in a state of flux

The global pharmaceutical industry has been expanding steadily at varying rates of regional growth; the pace of growth being relatively slow in the developed, matured markets but rapid in developing nations. This has been fuelled by the demand for medicines – due to government policies and their increased affordability and improved access. This, in turn, will influence the actions taken by equipment suppliers and other business partners of the pharma industry.

THE INDUSTRY is currently witnessing increasing interest in Continuous Manufacturing. Some pharmaceutical equipment manufacturers have deployed resources to develop such technologies and it is just a matter of time before those companies succeed in achieving results. This will usher in a transformation from current batch processing to a continuous one.

It is well known that the number of formulations going off patent has been dwindling for some time, with very few New Chemical Entities (NCEs) having been patented and introduced as new drugs in the past decade. Hence, there has been some focus on developing super generics to extend the product lifecycle of existing generics.

Due to the reducing numbers of new, off-patent molecules for generics, considerable focus has shifted to developing platforms for personalised medicine, digitalised medicines, nanotechnology and bio-nanomedicine. Technologies such as 3D printing, cognitive computing, and Artificial Intelligence (AI) have found new grounds in pharmaceutical applications.

Turning to containment technologies, there is a focus on the development of highly potent molecules; mainly in the oncology segment. It is evident from various

market research papers that the percentage of oncology products being developed – or in the various stages of clinical trials – is between 30 and 40%, which is considerably higher than previously. This will certainly expand the need for containment technologies.

Closed loop systems are being increasingly used, even for current generics, to improve safety for products and the environment, and to facilitate efficient material transfer but with less stringent requirements than those for potent molecules. Robotics are being inducted wherever possible for high-volume generics, as well as for processing in containment zones for potent molecules.

It has been widely stated that this century belongs to the biologics. The share of biological products and biosimilars in the development pipeline is believed to be 40% or more. Exciting breakthroughs in biomedical sciences are producing truly novel therapeutics for unmet patient needs. Many newly-developed molecules are highly potent, which has also added to the demand for containment solutions for biologics along with those for chemical entities.

The methodology of research and development of new drugs and drug delivery platforms has transformed over the past decade; it is no longer confined to just one



Ajit Kanetkar, Head of Process Technology & Training, ACG

or two disciplines, as with pharma and general engineering. Drug research has now become multi-disciplinary, requiring the involvement of pharmacists; mechanical, electronic, chemical, and instrumentation engineers; biologists and molecular biologists. Medical professionals too are involved – not only during clinical research but also during the development of new delivery platforms, especially in biologics.

In conclusion, generic markets demand large-scale and continuous manufacturing solutions with high levels of automation and new potent molecules need containment technologies. Concurrently, we will also see the development of new platform technologies in mature markets that will lead to the need for technologies for commercial manufacturing.

For the equipment and technology providers, one can confidently say that the path to the future is both exciting, in terms of innovative technologies being developed, and challenging, in terms of uncertainty for developers of equipment and technologies. ■

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Packaging solutions for clients' changing market needs

In this Spotlight on Manufacturing, ACG explains how it meets clients' changing needs and identifies emerging market trends

What are the main manufacturing products and services your company provides?

ACG's diverse product range includes a complete range of pharmaceutical and nutraceutical solutions, including: empty hard capsules, granulation machines, capsule-filling machines, tablet press and tablet coating machines, packaging films, blister packing and carton packing machines, vision inspection systems, and track & trace solutions.

What differentiates your products and services from your competitors?

ACG is the only supplier worldwide that offers integrated manufacturing solutions for the pharmaceutical and nutraceutical industry. Our unmatched, extensive expertise in the pharmaceutical industry leads us to develop a range of tailored, in-house value-added services to provide the best user experience. Our value-added services are designed to answer industry needs and enhance our solutions.

What value-added service does your company offer?

We have dedicated teams ready to optimise process times and consumption of utilities and reduce material losses. We also provide regulatory support to facilitate compliance with relevant regulations. Our value-added services include: sharing process knowledge through onsite training and working with our customers to improve overall equipment efficiency (OEE).

What are the additional benefits of working with you?

We have an extensive international network of more than 10 offices and 15 manufacturing facilities, offering the full range of pharma manufacturing solutions. Our products and facilities comply with all relevant global regulations.

We have also been certified by all relevant certification bodies.

In an increasingly global market, how can your company address clients' manufacturing needs?

Its extensive global network allows ACG to work closely with its customers to understand and cater to all their manufacturing needs. Further, an extensive global network of warehousing facilities ensures quick deliveries to local markets. Our solutions can be easily adapted to conform to local regulatory and quality requirements. The company's vision is to further strengthen our position in the global market through extensive R&D investment and strategic alliances.

What emerging trends are you noticing in your area of the manufacturing sector?

Digitisation has been used to enhance manufacturing efficiencies and productivity gains by streamlining processes, allowing a smooth production flow. Pharmaceutical companies are exploiting technologies like the Internet of things (IoT), advanced robotics, and augmented reality (AR), which can revolutionise human-machine interaction and automation. IoT aids in consolidating real-time, actionable data, while AR can overlay system-generated data from a variety of sources onto physical surroundings. They offer benefits such as the ability to identify problems in processing equipment and components that will soon require replenishment, even including a tool that indicates when preventative maintenance is required.

Another emerging trend is the development of sophisticated anti-counterfeiting technologies to tackle the growing problem of counterfeit medicines. Apart from adopting relevant serialisation and traceability techniques,

pharma companies are using anticounterfeit measures at both the primary packaging and dosage-form levels.

How are customers' requirements for powder, tablet and capsule making technology changing and what factors are driving those changes?

In solid dosage forms, we see new developments to meet two requirements: development of super generics to extend product life cycles and continual upgrading of manufacturing technologies, writes Ajit Kanetkar, Head of Process Technology & Training, ACG.

Development of super generics is gaining ground, considering the shrinking pipeline of off-patent products. We have also seen growth in the use of HPMC capsules.

The industry has experienced an increase in the level of machine sophistication, especially with respect to operation, data storage, and real-time trend analysis. For manufacturing high volumes, there is a growing demand for automation and closed systems to reduce human intervention and errors. In addition, a wide range of containment systems are available for processing potent molecules, including options to use robotic systems. ■

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Overcoming challenges in the characterisation of monoclonal antibodies by LC-MS from early to late stage of development

This webinar, staged on 25 July 2018, focused on dealing with challenges in the characterisation of monoclonal antibodies by LC-MS, spanning the period from early to late stage of development.



DIFFERENT modalities of monoclonal antibodies are pushing the limits of characterisation by MS. So, new critical quality attributes need to be carefully monitored from developability in early phases, as well as during process development and clinical phases.

This webinar featured several case studies, all addressed using X500B QTOF System from SCIEX. It illustrated the first stages of antibody development, as well as the support it provided to process and product understanding, with the characterisation of unusual modifications – such as sulfation, additional glycosylation – and of structural heterogeneity with

both traditional methods as well as native SEC-MS method.

Here, the keynote speakers – Séverine Clavier, Deputy Head of Structural Analysis Lab, Sanofi R&D and Armelle Martelet, Deputy Head of Structural Analysis Lab, Sanofi R&D – answer delegates' questions arising from the webinar, which was supported by SCIEX.

How easy is it to use SCIEX OS for setting up an acquisition?

SCIEX OS has very easy to use software. So, it is quick to setup

a method. You first create a project based on the kind of analysis, or a series of analysis, you want to perform. And then you will create your LC method, your MS method and then your batch and will assemble all this to do your acquisition. It is very user friendly.

Do you need to spend much time optimising parameters for the convolution of intact and subunits analysis?

We did not spend much time on optimisation of the convolution. There is a tool for the convolution. You need to mention the resolution you get and it works pretty well for the convolution. You can get an automatic calculation of your resolution, then usually use this range of resolution parameter to do the reconstruction of your spectra.

Also, there is a parameter that you can experiment with known as the time-being-to-send parameter, if it corresponds to the resolution

of your detection. So, you will increase this time-being-to-send parameter when you analyse intact proteins or even subunits. It will be decreased when you do peptide mapping, to adapt how often your detector is taking points, according to your mass range.

Did you optimise your source conditions in order to get a good signal for native SEC-MS analysis?

We didn't do anything before running this native SEC-MS method. We wanted to see if we could get something directly as it is. And it worked. We chose a de-clustering potential that was compatible with intact mass measurement and it was possible to get a good desorption already on that point. Perhaps, further, improvement would allow us to decrease the loaded quantity of Mab necessary to get the signal. But we are already happy with what has been achieved. 📧

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QA/QC

Quality Assurance (QA) is a wide concept and covers all aspects that could have an impact on the quality of prescribed pharmaceutical products. Anastasia Petropoulou, Radiopharmacy Technician / Clinical Scientist, University Hospital Bristol NHS Foundation Trust, focuses on some of the Pharmaceutical Quality Systems in relation to QA of manufactured medicines.

In terms of QA / QC, specifications and method / process capability are two sides of the same coin, writes Dave P Elder, JPAG Member and Dave P Elder Consultancy.



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Quality Assurance / Pharmaceutical Quality Systems in manufacturing medicinal products

Anastasia Petropoulou

Radiopharmacy Technician / Clinical Scientist, University Hospital Bristol NHS Foundation Trust, Radiopharmacy Department

BIOGRAPHY



ANASTASIA PETROPOULOU

AMRSC obtained a certificate in Health and Science followed by a BSc Hons degree in Pharmaceutical Science at the University of the West of England. She has gained experience in Quality Assurance / Quality Systems (QA / QS) by completing work in both pharmacy and the food industry. Anastasia has worked in Greece in the food industry as a Quality Assurance technician and in the UK pharmaceutical industry at Norbrook Laboratories Ltd in Northern Ireland and gained experience in testing raw materials as a Quality Control Analyst. She has also worked at NHSBT Bristol and the University Hospital Bristol NHS Foundation Trust, where she assisted in the production of parenteral nutrition and cytotoxic medicines. She currently works in Radiopharmacy as a Radiopharmacy Technician / Clinical Scientist where she applies PQS in the manufacturing process of radiopharmaceuticals.

Quality Assurance (QA) is a wide concept and covers all aspects that could have an impact on the quality of prescribed pharmaceutical products. The objectives of QA are: to ensure that the prescribed medicine competently provides the desired effect to the person taking it; to protect patients from accidentally being administered an incorrect or contaminated medication; and to ensure medicines comply with the regulation.

PHARMACEUTICAL Quality Systems (PQS) consist of eight pillars, which are designed to provide high quality finished pharmaceutical products, with QA and PQS working together in synergy (*Figure 1*). Pharmaceutical companies strive to provide high quality products to enable them to enhance their reputation, maximise profit and to provide high quality drugs to humans and animals. To meet these targets, they rely on well-designed PQS, which involve the coordination of quality through processes, with the aim of producing finished products of the highest quality.¹

It is worth noting that the European Medicines Agency (EMA) defines PQS as: "The degree of excellence processed by an item" and "Meeting the requirements of specific customers' needs".⁶

The general model of controlling quality involves standards. Those include: checking the value or degree of the set standards, checking the product for conformity and feeding this back into the initial system and checking stages.² The control of quality is an essential process and should be applied at all manufacturing stages; starting with the design, through to assembly of raw materials, in-process, post process and finally the finished products including stability testing. This explains why Quality Control is often described as being the most appropriate Total Quality Control (TQC) concept (*Table 1*).^{4,3}

This article will focus on some of the Pharmaceutical Quality Systems in relation to QA of manufactured medicines. As mentioned previously, the eight pillars of PQS constitute a good foundation for discussion (*Figure 1*).⁷

The application of a process performance and product quality monitoring system throughout



the product lifecycle is shown in *Table 1*.

This illustrates the most effective monitoring system that provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement, according to PQS Q10.⁵

Nevertheless, it is not possible to mention high quality finished pharmaceuticals without mentioning Good Manufacturing Practice (GMP) and Validation.⁵ It is well known that all manufacturing stages need quality assurance actions to ensure successful results; but how can they be achieved, and which is the most important action during all the manufacturing stages?

The answers can be found by applying GMP in each step of the manufacturing process.³ GMP is part of Quality Management that ensures products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification.³

Furthermore, it ensures the manufactured products meet the end-user's needs in terms of safety, quality and efficacy. GMP involves monitoring of processes, equipment, personnel and the environment in pharmaceutical companies.⁴

GMP is essential in all cases from initial drug trials to commercial launch. To obtain the best product, a manufacturer needs a system in place to ensure regular formulation, processing and composition.⁴ Without regulation of a manufacturing process, the consequences cause confusion that might escape notice in the first instance but at some later point will invalidate the safety of the product. This means someone will get harmed or it will cost the manufacturer money. However, the importance of patient safety is what drives companies to improve quality and prevent unnecessary expenditure on manufacturing.⁴

GMP applies to all types of pharmaceuticals. For example, a 'standard product' is one in which the unit operation and risk assessment of the end product suggests simple equipment ambient conditions; however, this doesn't mean that the system can be abused. GMP should be applied, and the product manufactured, according to highly-regimented and regulated procedures.⁴ On the other hand, sterile medicines require different processes and equipment.^{4,2} These types of manufacturing processes often include biotechnology derivatives; where the consistency and potency of bio-preparation, that needs validation and constant monitoring, is often highly variable but may also be associated with issues such as purity.² Sterile manufacture tends to be more vigorous in terms of equipment and specialised clean rooms. These specialised conditions and the nature of the drug itself often require additional staff training and a stronger reliance on the Qualified Person (QP) to sign-off.⁴

Figure 2 shows how Quality by Design embraces an integrated science and risk-based approach with continuous improvement for the entire product lifecycle.⁸ Process validation is needed to underpin confidence in the compatibility and coherence of each individual stage in a process of manufacture of pharmaceuticals.⁴ This represents the biggest part of the validation process in pharmaceutical products. However, cleaning and

FIGURE 1



LEFT: Eight Quality Systems contribute to the high quality of the finished pharmaceutical product⁷

It is well known that all manufacturing stages need quality assurance actions to ensure successful results; but how can they be achieved, and which is the most important action during all the manufacturing stages? ”

analytical validation are equally as important in manufacturing validation as in-process, or on-process, control. The aim is to ensure end-product suitability by fragmenting the process into modules with an appropriate consideration of risk and non-compliance to established standards.⁴ As such, the essential considerations of any validation of manufacturing should include:

- The importance of following and establishing an environment of GMP
- The site / building / equipment limitations, ➤

BELOW: Challenges in Implementing Quality by Design: An Industry Perspective⁸

FIGURE 2

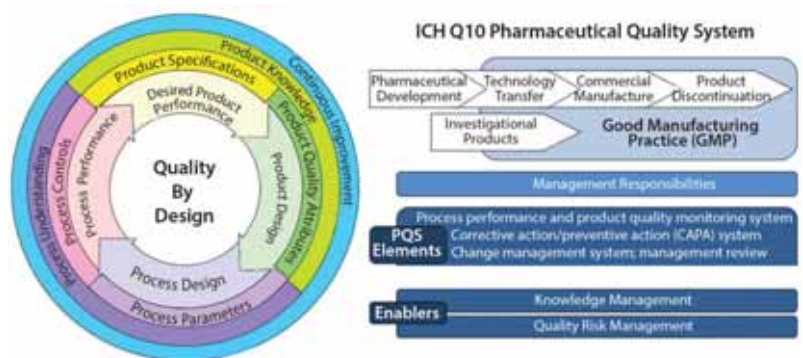



TABLE 1 Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within the state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

FIGURE 3



ABOVE: Quality Risk Management 

aspects associated with packaging / storage / handling of the product

- The complexity of routine production, provision of a suitable audit trail in terms of detailed reports and records.^{3,4}

Additional aspects of higher-end quality in a manufacturing validation include: the probability for consistency of manufacturing and the consequences of inconsistency. Another parameter in the validation process is the use of a pilot trial to identify the point of 'weakness' in a particular stage of a manufacturing process where particular attention is required.⁴ Pharmaceutical companies should have a system for implementing corrective and preventive actions arising from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, trends from process performance and product quality monitoring. A structured approach to the investigation process should be used, with the objective of determining the root cause.^{3,4}

A Quality Risk Management system (**Figure 3**) involves monitoring and assessing the system's or procedure's effectiveness. This mainly involves investigating deviations that have occurred during any step of the manufacturing process, or identifying other factors such as damaged or faulty raw materials, devices or equipment.

The root cause analysis is identified and documented and finally an evaluation is undertaken to confirm quality objectives were achieved and the quality of the product was not affected.² In other words, this system was built to ensure the quality of products by solving various issues or identifying risks and preventing the same happening again.


Risk management principles are used in many areas of business, including pharmaceuticals. The manufacturing and use of medicinal products, including its components, involves some degree of risk, whereas the risk to its quality is just one part of the overall risk.⁴ A robust quality risk management programme can ensure the high quality of pharmaceuticals by providing a proactive means of identifying and controlling potential quality issues during development and manufacturing. Effective quality risk management can provide regulators with greater assurance of a company's ability to deal with possible risks and can positively affect the level of direct regulatory oversight.^{4,6}

Efficient quality management results from the correct interfacing of quality control, quality assurance and quality improvement initiatives. It is achieved through acting on feedback from the people involved in the product supply chain. A quality cycle is a group of experts who meet with the aim of improving the quality of manufacturing processes, the environment, health and safety etc. Effective communication between the investors in the group can result in an improvement over and above those routine improvements.^{4,6}

Summary

In pharmaceutical manufacturing, QA is the parameter used to ensure prescribed medicine effectively produces the desired effect on the person taking it. The PQS, part of QA system, was designed to help manufacturers achieve the target for high quality finished pharmaceutical products; leading to the required level of drug regulations and providing efficacy and safety for patients.⁴ The parameters for approaching these targets include:

- The pharmaceutical product is designed to meet the need and performance requirements
- The process is designed to consistently meet product critical quality attributes⁸
- Processes, equipment, personnel and deviations are identified and controlled in an appropriate manner
- The whole manufacturing process is constantly monitored and updated to enable consistency in quality over time.

The application of Pharmaceutical Quality Systems in pharmaceutical products can extend to pharmaceutical development, which should facilitate innovation and continual improvement of prescribed medication.^{2,6} It is the tool with which to achieve product realisation by designing, planning, implementing, maintaining and continuously improving a system, to allow the consistent delivery of pharmaceuticals with appropriate quality attributes.^{4,6} 

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Specifications and method / process capability: two sides of the same coin

Dave P Elder

JPAG Member and Dave P Elder Consultancy

Specifications are defined as “a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described”.¹

BIOGRAPHY



DAVE ELDER has nearly 40 years of service within the pharmaceutical industry at Sterling, Syntex and GlaxoSmithKline. He is now an independent GMC consultant. Dr Elder is a visiting professor at King's College, London, and is a member of the British Pharmacopoeia. He is a member of the Joint Pharmaceutical Analysis Group (JPAG) and a member of the Analytical Division Council of the Royal Society of Chemistry.

SPECIFICATIONS establish predefined criteria of the expected quality of a product – Active Pharmaceutical Ingredient (API) or drug product – at that stage of their development. That is, there is, or should be, an expectation that specifications will evolve as process understanding and knowledge² increases.

Specifications are therefore a compilation of “critical quality standards [CQs] linked to overall product performance, which are proposed and endorsed by the applicant and reviewed and approved by the appropriate regulatory or pharmacopoeial authorities”.³ Despite decades of “harmonisation” initiatives, it is by no means certain that acceptance by one regulatory authority, eg. European Medicines Agency (EMA), will result in acceptance or approval by others, eg. FDA or Pharmaceuticals and Medical Devices Agency (PMDA).

Indeed, applicants often see different opinions from within the same EU regulatory region. Hence, the concept of a “universal specification” for a product is often aspirational in nature, rather than a realistic goal.¹

The link between specifications and the underlying critical process parameters (CPPs) and critical quality attributes, which are generated as part of a QbD-type (Quality by Design) submission^{2,4,5} have never been fully articulated, although all are part of the overall control strategy. Some commentators have expressed concern that ICH Q6A was never revised to more fully explain the inter-relationship.³

The application of ICH Q6A¹ during development, particularly early phase development, is one of the key challenges facing applicants and reviewers alike. In general, these guidelines were intended to be applied to marketing approval on new products, except for ICH M7(R1).⁶ This is sensible as knowledge of CQAs at this early stage of development may be very limited. Significant changes will be expected to

both the synthesis / process of the drug substance and to the formulation / process of the drug product as they proceed towards market.³ ICH M3(R2)⁷ does provide some clarity of the original intent. It states in connection with impurities: “The approaches for qualifying impurities and degradants are outlined in ICH Q3A(R2)⁸ and Q3B(R2).⁹ If specific studies are warranted to qualify an impurity or degradant, generally these studies are not warranted before Phase III, unless there are changes that result in a significant new impurity profile e.g., “a new synthetic pathway, a new degradant formed by interactions between the components of the formulation”.

However, the reality is that ICH Q6A guidance is often widely used during clinical development by both industry and regulators alike; often inappropriately, ie, requests for full details of impurities to be included on early phase clinical specifications. However, it is difficult to envisage the compilation of a specification for any early phase regulatory submission, e.g. investigational Medicinal Product Dossier (IMPD), investigational new drug (IND), without applying some aspects of the ICH Q6A guidance. Nonetheless, great care is needed to ensure that specifications are not constrained at an early stage based on limited data, especially if there is an intention to remove tests specified in early versions.

ICH Q6A does not include any discussions on process capability (Cp). However, it has become clear with the advent of QbD that a comprehensive understanding of the effect of variability of the process and supporting methodologies is required before robust specifications can be set. Process capability measures the output of an ‘in-control’ process by assessing the ratio of the process specification width (or range) to the spread of process values using standard deviation units. As the process capability improves, the variability

“Hence, the concept of a “universal specification” for a product is often aspirational in nature, rather than a realistic goal”

decreases, and it becomes more closely centred between the specification limits. A process where the majority of all measurements reside within the allowable specification range is a 6-sigma capable process³ (Table 1).

This assumes that the data are centred within the specification range, ie. 100% for API potency, ± 2% for specified range, ie. 98.0-102.0%. However, this is not typically the case; the presence of impurities means that the drug substance process is off-centred at 100-x%, where x is the total value of all impurities found in the process. This is reflected by the off-target process capability index (Cpk). A process with a Cp of 2 could have a Cpk of 1.5, which would equate to a failure rate of four defects in every million assessments. Thus, logically process capability or variability (including method variability), is one of the key parameters in setting robust specifications.

However, regulators have indicated that it is "not considered appropriate to add method variability as determined in analytical method validation to the variation seen in batch results as this variability is already included in the batch results and therefore will be counted twice".¹⁰ This perspective is predicated on the view that measurement uncertainty will always be smaller than batch variation. This is true if the sample size of the number of batches in question are sufficiently large reflecting the total population (typically a minimum of 30 batches).¹¹ In practice many new drug products will submit regulatory files with a limited number of batches, ie. three at commercial scale, accompanied by a number of development batches at smaller scale. This prompts the key question: "How will it be possible to ensure the variability of the production process is covered by the specification with limited number of manufacturing scale lots that are available at the time of submission?"³ Are these criteria replicated by the product's clinical experience or are the limits based on the cumulative process performance, or both?"¹⁰

Thus, if the specification is tightened during the review process and / or takes no account of process / method variability, this can turn a capable process into a non-capable process leading to OOS results or batch failures. Unfortunately, this is an increasingly common incidence during regulatory review, where reviewers consider that by further constraining the proposed specification they will make the process / specification more discriminating ensuring patient safety; simply, all that occurs are more batch failures of product that are of an acceptable quality.³

It is widely accepted that method variability is frequently greater than manufacturing process variability, particularly for API processes.¹²⁻¹³ Intermediate precision is the most appropriate method validation parameter for assessing Cp and

TABLE 1 Process Capability (Cp) and the Likelihood of Out of Specification (OOS) Consequences (adapted from Elder³)

Process Capability (Cp)	Standard Deviation Range (σ)	Probability that data are within specification limits	Occurrence of OOS Outcomes
1.00	6.00	99.73	1 in 370
1.25	7.55	99.98	1 in 5655
1.50	9.00	99.993	1 in 147160
2.00	12.00	99.999998	1 in 5.1 x 10 ⁸

should be taken into consideration when proposing any specification limits, or when assessing the capability of the method when the specifications are "constrained", as is the case for API assay, ie. 98.0-102.0%. Therefore, a specification of 100.0 ± 2% i.e. 4% range for a 3-sigma process is equivalent to a total variability of 0.67%. Thus the method variability needs to be at least half this value, ie. 0.34% (or less).¹³ The allowable method variability is further constrained as the true means of the specification is less than 100%, ie. 100-total impurities.

Thus, the supporting methods need to be 6σ capability (ie. show decreased variability) and hence the total method deviation is required to be ≤ one twelfth of the total allowable range or tolerance, ie. 0.17% (or less).¹³ Based on this significant high-performance liquid chromatography (HPLC) method variability, several commentators¹⁴⁻¹⁶ have expressed significant misgivings about the utility of the standard HPLC assay method to monitor drug substance quality. Kredla et al.¹⁷ commented that, "assay results are simply not stability-indicating [...] due to the large assay variability associated with them".

In the classical operating scenario, specifications have clearly defined acceptance and rejection zones (Figure 1).

The various pharmacopoeias are currently evaluating applying decision rules based on a probabilistic assessment that acknowledges measurement uncertainty (MU) and the role it plays in decision making, ie. Acceptance / rejection, ▶

“ This perspective is predicated on the view that measurement uncertainty will always be smaller than batch variation ”

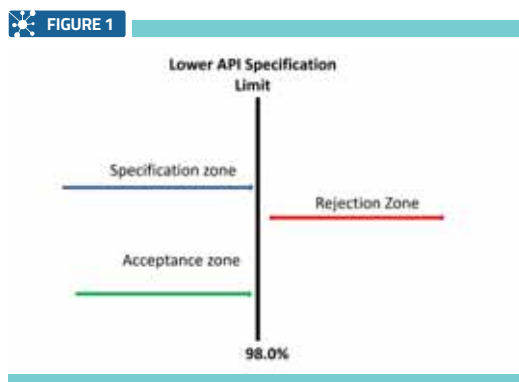
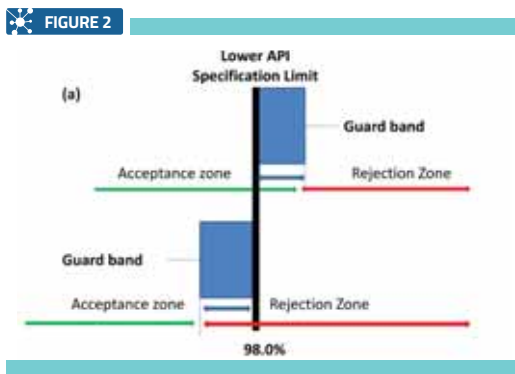


FIGURE 1

← LEFT: Specifications Complying with Simple Acceptance Criteria. Adapted from Ellison and Williams¹⁸

RIGHT: Specifications using Acceptance Criteria, (a) Relaxed acceptance (test for non-conformity), (b) Stringent acceptance (test for conformity). Adapted from Ellison and Williams¹⁸



based on compliance with a pre-determined specification.¹⁹ These decision rules support the decision-making process by, (i) assessing the measurement result, (ii) the specification limit (both current practices), (iii) the measurement uncertainty, (iv) and assessing the acceptable level of probability of making a wrong decision (where (iii) and (iv) are new approaches). These specification decision rules will introduce the concept of a "guard band" or "transition zone" between the acceptance and rejection zones within a specification.³ (Figure 2).

Within the specification "transition zone" a product will be considered non-compliant if the probability of either being above or below the designated upper or lower specification limit exceeds 2.5%. A target MU equivalent to σ equal

to 1.02 would meet these requirements. However, a bias will impact on this acceptance value. In the case of a non-centred specification or method bias of 1.0%, then σ needs to be reduced to 0.6%.³

An increasingly common situation that can occur in the QbD paradigm is the setting of specifications based solely on the clinically derived CQAs, without considering Cp arguments where Cp assessments clearly indicate that these proposed specification changes will make this a non-capable process, i.e. a 3-sigma process. The recent trend towards tightening dissolution specifications from the typically encountered Q=80% at 30 minutes, to the much tighter Q=80% at 20 minutes is a case in point. The intrinsically poor hydrodynamics of the dissolution apparatus at time points below 30 minutes ensures that there is significantly increased method variability for methods based on 20-minute (or lower) time points.²⁰ That is, the method becomes less robust, but not more discriminating.

A potential solution is to move towards the clinically-derived specification in managed stages, i.e. post-approval. Applicants would therefore generate data from a meaningful number of batches, i.e. 30 batches; allowing an assessment of the population variability and adjust the specification based on a revised Cp assessment.²¹ However, for some low volume products these large numbers of manufactured batches, i.e. ≥ 30 are still very aspirational.

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Current trends in detection of falsified medicines



Kathryn Lawson-Wood is an Infrared Technical Applications Scientist at PerkinElmer

There is global public health concern over the falsification of pharmaceutical products and the extent to which widespread distribution of substandard drugs has developed. These products are rarely efficacious and can lead to disastrous health consequences, including failed treatment, disability, and even death. Consequently, falsified medicines may negatively impact public confidence in health care systems, health care professionals and the pharmaceutical industry.

THE EU took steps to address these concerns through the introduction of the EU Falsified Medicines Directive (2011/62/EU) (FMD), adopted in 2011, setting out new measures to ensure that medicinal products in the EU are safe and that medicinal trading is properly controlled.^{1,2} 'Falsified' and 'counterfeit' medicinal products are closely related terms, which are commonly used interchangeably.

In the FMD, the term 'falsified' refers to any medicinal product with a false representation of its identity (including its composition, packaging, and labelling), source or history. Counterfeit medicines, on the other hand, are those that do not comply with intellectual-property rights or that infringe trademark law.²⁻⁴

Scale of the problem

The extent of counterfeiting / falsification is impossible to quantify. The Pharmaceutical Research and Manufacturers of America (PhRMA) states that it is greater in those regions where ineffective regulatory systems and market control exists.⁵ The World Health Organization (WHO) estimated that the prevalence of falsified drugs ranges from less than 1% of sales in developed countries, to over 10% in developing countries. In some regions, more than 30% of medicines on sale are falsified. Across the EU alone, it causes the loss of 4.4% of legitimate sales, the loss of €10.2bn in revenue for the pharmaceutical industry, and the loss of €1.7bn in government revenue.⁶

Technologies and application

Various analytical techniques are used throughout the industry for the

screening of falsified medicines, including Fourier-transform infrared spectroscopy (FT-IR), near-infrared spectroscopy (NIRS), Raman spectroscopy, and liquid chromatography-mass spectrometry (LC-MS).⁵ In the case of falsified drugs that are chemically very similar to the genuine product, authenticity may be determined by differences in the distribution of ingredients within the product using near-infrared microscopy.⁷

NIRS and Raman are often used as complementary techniques. Chromatographic techniques often require extensive sample preparation, have slow analysis times, and require extensive technical knowledge. NIRS, in comparison, is non-destructive, portable, rapid, and samples can be analysed through plastic bags and glass containers. Additionally, workflow-based approaches can be implemented to enable users of any background to perform the analysis. If a product is deemed falsified based on the initial screen using NIRS, it can then be subjected to further testing using a confirmatory method such as LC-MS.⁵

When combined with a chemometric algorithm, known as Soft Independent Modelling of Class Analogies (SIMCA), NIRS can be used to verify the identity of a material and detect falsified or suspect materials. SIMCA models the variation found within a collection of reference spectra for a given material.

An example screening application using NIRS is the detection of counterfeit statins. Statins are a class of drug used to lower cholesterol in patients. Approved in 1996 under the brand name Lipitor®, atorvastatin

was the most sold prescription drug in the U.S. from 2007 to 2011, with revenue generation of \$12.9bn in 2011. In late 2011, the expiration of the patent held by Pfizer allowed generic versions of the drug to emerge.^{8,9} Falsification / counterfeiting can apply to both branded and generic drugs and NIRS with chemometrics can provide a rapid and simple approach for their detection.

The Medicines and Healthcare products Regulatory Agency (MHRA) is inviting views on the proposed steps that the government intends to take to ensure the UK meets its obligations to transpose the provisions of the FMD requiring safety features to appear on the packaging of certain medicinal products.

Act now by completing a response form, which can be found at the link below. This consultation closes at 3pm on 23 September 2018.

<https://www.gov.uk/government/consultations/implementing-safety-features-under-the-falsified-medicines-directive> ■

References

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Virtual Trials: a more direct path to patients

Conducting virtual trials offers several key benefits, explains Josh Rose, Vice President, Global Head of Strategy, IQVIA. However, they need careful implementation and are not a ‘one-size-fits-all’.



TRADITIONAL clinical trials pose accessibility obstacles for patients, who often must travel long distances – as far as 50 miles or more – and make major time commitments for multiple trial-related site visits. This burden to patients can threaten clinical trial enrolment, with less than 5% of patients currently participating in clinical research,¹ 49% of participants dropping out before their study ends,² and new therapies taking an average of 10 years to reach the market.³

In addition, the U.S. Food and Drug Administration is increasingly requiring more patient diversity in pre- and post-marketing studies, owing to the fact that “medical products are safer and more effective for everyone when clinical research includes diverse populations”.⁴

The administrative and financial burden on sites can also prove challenging. Almost half of investigators do one study and never do another.⁵ Virtual trials can address these challenges.

Reducing patient burden to overcome barriers to participation

Virtual trials are designed to allow patients to participate from home, with the support of home health nurses. A patient-centric approach uses telemedicine to enable patient recruitment, gain informed consent, measure clinical endpoints, and monitor any adverse events from the patient’s home.⁶

This provides an innovative and more direct path to patients; taking trials directly to them, and offering a more attractive way for diverse and geographically distant individuals to participate.

The principal investigator is located remotely and supported by a virtual care team (Figure 1). This model provides for better physician oversight and round-the-clock data collection – rather than the infrequent site visits involved in

traditional clinical trials. This offers advantages for investigators, enabling them to ‘see’ more patients. Moreover, it reduces variability in assessments and data, and provides greater visibility into safety events. Investigators also benefit from technology to support tasks such as issuing alerts and notifications, scheduling, and reporting, which frees up their time to focus on research.

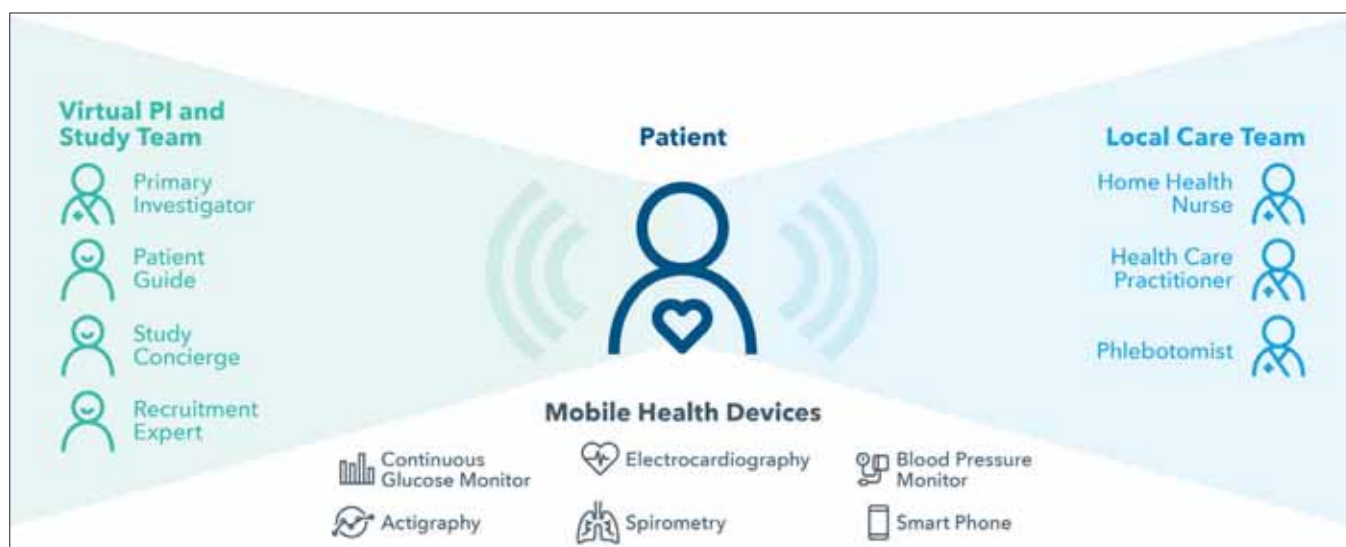


Figure 1: The virtual trial model puts the patient at the centre

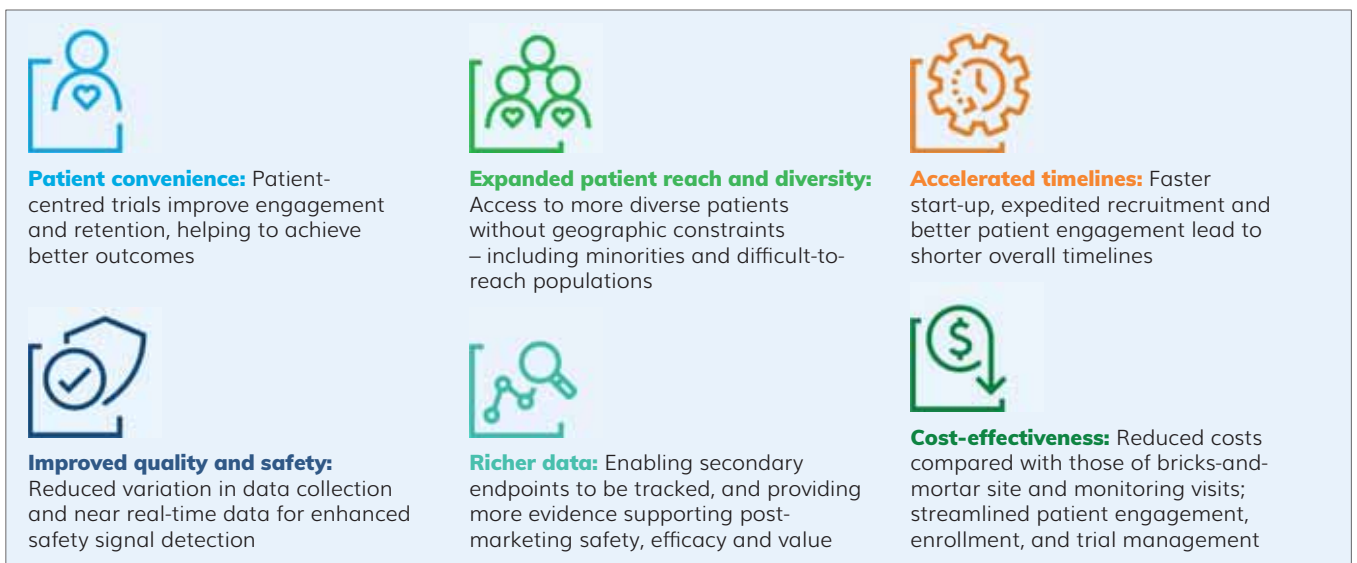


Figure 2: Benefits of virtual studies

The virtual approach

Virtual trials are not ‘one-size-fits-all,’ however. First, it is important to design a patient-centric protocol. The virtual approach works well with chronic diseases and less complex interventional and observational studies. Suitable study types include indications or protocols, where the investigational product has a known safety profile and endpoints can be assessed remotely. Initially, therapeutic areas such as endocrinology, Central Nervous System (CNS), dermatology, respiratory, gastro-intestinal, immunology, cardiovascular, and rare diseases present the best opportunities for a virtual approach.

This doesn’t mean we should totally rule out more complex indications where the burden on patients is very high. For these situations and more complex trials, elements of virtual and traditional trials can be combined in a hybrid approach. For example, this might be used to support long follow-up periods after innovative treatments such as cell therapies.

In other areas, virtual trials might not be a good fit. Examples include investigational products with an unknown safety profile, and protocols involving endpoint assessments that have not been validated for remote assessment. Studies where interventions must be conducted in a

structured setting – such as an intensive care unit or phase I unit – along with early-phase oncology and first-in-human studies, would typically not be suitable for a virtual approach.

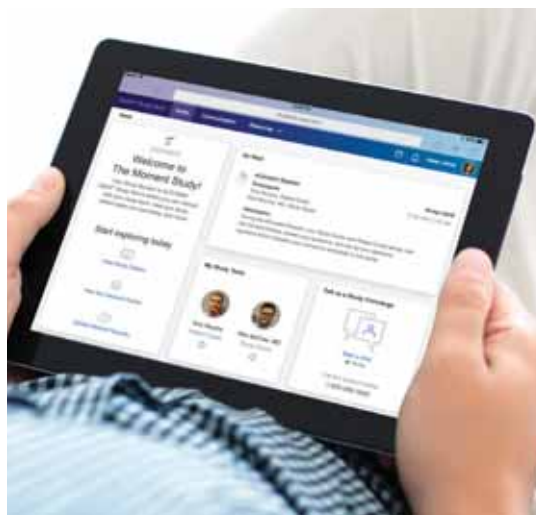
The benefits of conducting virtual studies can be summarised as delivering: improved patient convenience; expanded patient reach; access to more diverse patients; accelerated timelines; improved quality and safety; richer data; and greater cost-effectiveness. Read more information in **Figure 2**.

In conclusion, by focusing firmly on the patient, virtual approaches can potentially transform the research landscape, enabling better, faster and more efficient trials. They hold particular promise for less complex interventional and observational studies involving chronic diseases.

For patients, improved trial accessibility can expand clinical care options and boost retention.

For investigators, the ability to interact virtually with larger numbers of participants provides deeper insights from richer data and may reduce investigator turnover. Initial indications are that patient and investigator satisfaction is high. However, sponsors should keep in mind that virtual trials involve more than technology alone – they remain a complex endeavour that must meet regulatory requirements and demands in-depth clinical understanding.

IQVIA Virtual Trials is uniquely qualified to orchestrate the unique complexity of patient-centred virtual trials to accelerate the path to approval. Learn more by visiting <https://www.iqvia.com/virtualtrials>. ■



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THIS unique venue allows SciX to expand its technical programme, offer new workshops, and facilitate new networking opportunities. SciX attendees are likely to enjoy comfortable weather, as the event takes place for the first time in this beautiful Southern venue. The host hotel, the Atlanta Marriot Marquis, is situated in the heart of a lively downtown area, within easy walking distance to the Georgia Aquarium, the World of Coca-Cola museum, Olympic Park, and dozens of unique restaurants and bars.

FACSS also welcomes International LIBS 2018, which will be co-locating with the SciX conference this year.

The SciX conference is recognised for the strength and diversity of its technical programme and this year is no exception. The joint meetings of SciX 2018 will contain 130 sessions covering all fields of analytical chemistry. SciX 2018 will also host special programming to welcome our new member CLIRSPEC. The Sunday keynote speaker will be Dr Matthew Savoca, of the National Oceanic and Atmospheric Administration (NOAA) Southwest Fisheries Science Center and Hopkins Marine Station at Stanford University, who will speak on the analytical challenges of identifying microplastic debris and understanding their effects on marine wildlife.

SciX is also the venue for a large number of internationally-renowned award presentations. Unique to SciX is the FACSS Innovation Award session held on Thursday afternoon, featuring beer and a lively interactive format. Four abstracts will be selected, based on novelty, to compete in this session for the \$1,500 cash

award. Previous winners have presented groundbreaking research in optical reflection and waveguiding of sound, infrared theory and instrumentation, portable spectroscopy, 5D single particle-tracking in live cells, and inexpensive medical devices.

The exhibits feature the latest in instrumentation from the leading vendors in the analytical sciences. Lunches are provided for attendees in the Exhibits hall, with the "What's Hot" sessions, assembled by Exhibit chair Mike Carrabba, to learn about the latest products offered by vendors.

Education is a central mission of FACSS, and the SciX conference supports this goal through the technical programme and by offering short, intensive workshops. Taught by experts in the field, introductory, advanced, and / or hands-on technical short courses will be offered onsite encompassing the areas of Raman spectroscopy, laser-induced breakdown spectroscopy (LIBS), entrepreneurship, STEM (Science, Technology, Engineering and Mathematics) education, and chemometrics. Two exciting offsite workshops will be offered for the first time this year: hands-on forensics analysis (offered in conjunction with MVA Consultants) and Quality Control Testing of Beer (to be held at Sweetwater Brewery). Space is limited for all workshops.

By design, SciX remains a great conference for students. We feature a large number of student awards, special conference hotel rates for students, the opportunity for travel grants, networking events, scientific receptions, and even free lunch! There are also numerous volunteer opportunities that



students can participate in to increase their involvement in the conference and earn discounted registration.

The FACSS community has had a long relationship with many scientists in both industry and academia from Puerto Rico (PR). In recognition of this relationship, and in support of the rebuilding efforts after Hurricane Maria, FACSS is offering complimentary registrations for SciX 2018 for students enrolled at any PR university.

Lastly, SciX is about bringing people from the exhibits floor to the dance floor. The theme for the Wednesday night all-inclusive gala event is: 'The Great Science Fiction Exchange'. After a long day of exchanging scientific facts, put your knowledge of lasers and quantum physics to more entertaining use, as SciX warps into an alternate dimension for one night only. Dress up as your favourite science fiction character and add your distinctiveness to our collective, or just dance like an Ewok, as we assemble the armada to party like the Second Death Star just blew up! Resistance will be futile. So say us all. ■

AN INVITATION

We invite you to come and see why SciX is the Right Size, Right People, Right Conference. Visit our website, www.scixconference.com, to learn more and submit your abstract.



Quality assessment of biologics: higher order structure analysis using NMR



This webinar, organised in association with Bruker, will describe how 2D NMR can offer protein biochemists unprecedented analytical precision. Two sessions will be available on 27 September at 9AM (BST) and 4PM (BST). Please select your preferred time slot during registration.


WEBINAR delegates will learn how users of 2D NMR can obtain a unique fingerprint of a protein at an atomistic resolution by assigning just one spectrum. This non-destructive technique can also be combined with other complimentary techniques to gain even further insights into sample quality.

Examples of the spectral processing and statistical and chemometric analysis methods being developed to increase automation will also be described. Aside from enabling simultaneous analysis of large data volumes, the automation available today has almost advanced to the point that even non-experts will be able to acquire and analyse NMR spectra for decision making.

Delegates will also learn more about the following topics:

- 2D NMR spectral fingerprinting for higher order structure analysis of biologics



- Application to biologics in their formulated state for structural assessment
- Benefits of the advances in automated data acquisition and analysis
- Reproducibility and robustness for inter-lab precision
- Practical, easy application of 2D NMR in the biopharma space
- Bruker's latest instrumentation and software for 2D NMR analysis
- 2D NMR spectral fingerprinting for higher order structure analysis of biologics
- Application to biologics in their formulated state for structural assessment
- Benefits of the advances in automated data acquisition and analysis
- Reproducibility and robustness for inter-lab precision
- Practical, easy application of 2D NMR in the biopharma space
- Bruker's latest instrumentation and software for 2D NMR analysis. 



27 SEPT 2018



9.00AM (BST)
& 4.00PM (BST)

ABOUT BRUKER

Bruker is market leader in analytical magnetic resonance instruments including NMR, EPR and preclinical magnetic resonance imaging (MRI). Bruker's product portfolio in the field of magnetic resonance includes NMR, preclinical MRI, EPR and Time-Domain (TD) NMR. In addition, Bruker delivers the world's most comprehensive range of research tools enabling life science, materials science, analytical chemistry, process control and clinical research.

Bruker is also the leading superconductor magnet and ultra high field magnet manufacturer for NMR and MRI solutions.

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Quantitation of monoclonal antibody infliximab in human plasma by LC-MS/MS using Fab-selective limited proteolysis nSMOL technology

Alan Barnes¹; Aurore Jaffuel²; Neil Loftus¹

¹Shimadzu Corporation, Manchester, UK; ²Shimadzu France, Marne la Vallée, France.

Overview

- Infliximab was quantified from plasma by a novel enrichment technique using protein A/G bound resin beads from a commercial sample preparation kit.
- Nano-surface and molecular-orientation limited (nSMOL) proteolysis was performed using immobilized trypsin FG beads. This approach resulted in a selective digestion of the Fab region, which consists of peptides from the CDR region of monoclonal antibody (mAb).
- Three proteotypic peptides were selected for quantitation by LC-MS/MS with a detection limit of 0.25 ng/mL with a fast 8 min gradient using the Shimpack GISS column.

1. Introduction

Infliximab, commercially known as Remicade, is a chimeric IgG1 kappa monoclonal antibody (mAb), that targets tumor necrosis factor- α (TNF). However, a number of studies have identified a substantial proportion of patients (between 30-40%) who fail to respond to anti-TNF therapy. Current methods for monitoring infliximab are almost exclusively immunoassay based. In this study, we describe the use of nSMOL proteolysis, which selectively targets the Fab CDR region of infliximab, and LC-MS/MS quantitation.

2. Methods and Materials

Plasma samples were prepared using nSMOL kit (Shimadzu Corporation) and proteotypic peptides of infliximab quantified by LC-MS/MS MRM (LCMS-8060, Shimadzu Corporation).

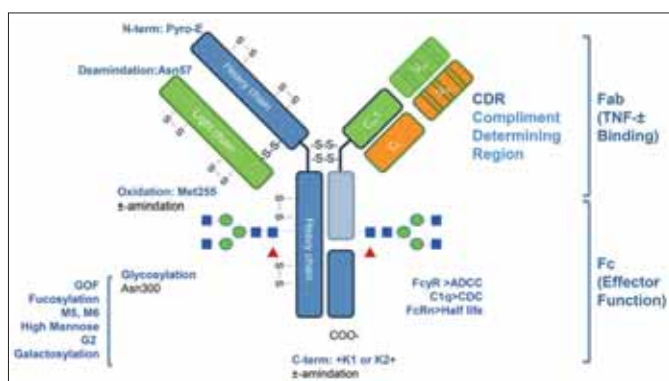


Figure 1. Schematic structure of infliximab.

Table 1. LC-MS/MS method for the analysis of infliximab in plasma.

Method/Parameter	Method/Parameter	Method/Parameter	Method/Parameter
UHPLC	Naxera LC system	LC-MS/MS	LCMS-8060
Analytical column	Shimpack GISS 1.9 μ m 50 x 2.1 mm C18	Ionisation mode	Heated ESI
Flow rate	0.4 mL/min	MRM Dwell time	30 msec
Solvent A	Water + 0.1% formic acid	Pause time	3 msec
Solvent B	Acetonitrile + 0.1% formic acid	Desolvation line	250°C
Binary Gradient	Time (mins) %B	Heating gas	10 L/min
	1.50 5	Drying gas	10 L/min
	5.50 45	Nebulising gas	2.8 L/min
	5.52 95	CID gas pressure	350 kPa
	6.33 95	Interface voltage	1.25 kV
	8.00 stop	Valve: FcV \rightarrow sample to MS	2.50 - 5.50 min

2-1. nano-Surface and Molecular-Orientation Limited (nSMOL) proteolysis

Infliximab Capture

Collecting monoclonal antibodies from blood or other biological samples using immunoglobulin collection resin

Protein A/G bound within 100 nm well resin beads specifically binds the Fc region of infliximab to the resin. As the Fc region is directly bound, the Fab region is then in the optimum geometry for tryptic digestion.

Selective Digestion

FG bead trypsin DARTTM: ferrite particles coated with poly-GMA (glycidyl methacrylate)

The nSMOL enables collection of IgG fractions in plasma via Fc regions, and selective proteolysis on Fv of antibody drugs using trypsin immobilized on the surface of nanoparticles.

This reaction field allows selection of quantitation peptides that reflect the structural characteristics of antibodies.

Antibodies have three CDRs respectively on each heavy and light chain, and the collected peptides using the nSMOL are mainly peptides including CDRs.

MRM detection of CDR peptides

Minimizing sample complexity for LC-MS/MS analysis

CDR peptides were enriched by centrifugal filtration then measured by LC-MS/MS with high specificity and sensitivity.

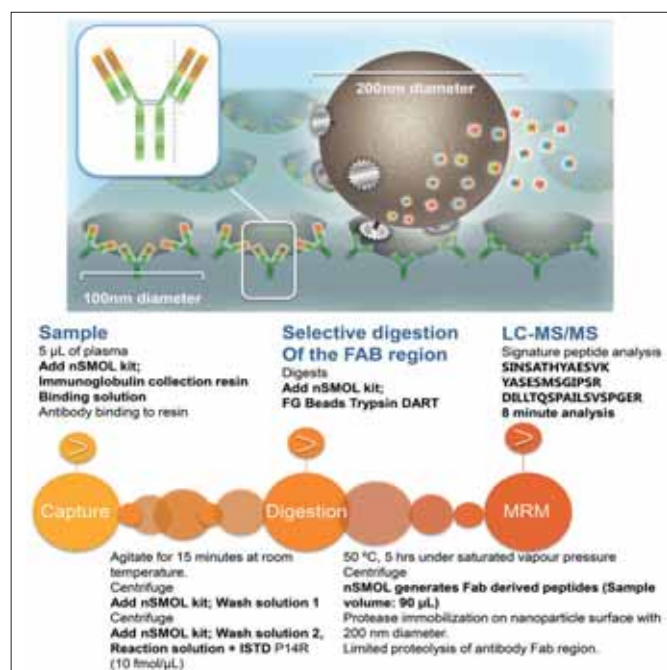


Figure 2. Schematic workflow for the selective proteolysis of the Fab region of infliximab via trypsin-immobilized nanoparticles.

3. Results

3-1. Peptide selection

Skyline software (MacCoss Lab, University of Washington) was used to perform in-silico protein digestion and predict candidate peptides and MRM transitions. Six proteotypic candidate peptides were evaluated and three selected for quantitation: SINSATHYAESVK, YASEMSGIPSR and DILLTQSPAILSVPGER (Figure 3) from Fab heavy and light chains respectively.

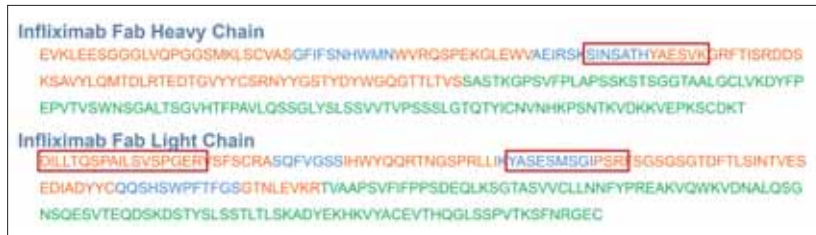


Figure 3. Amino acid sequence of infliximab Fab heavy and light chains. Green regions represent conserved peptide sequence, orange - unique sequence, blue – point of interaction of CDR with TNF α . Red boxes represent peptide sequences selected for quantitation.

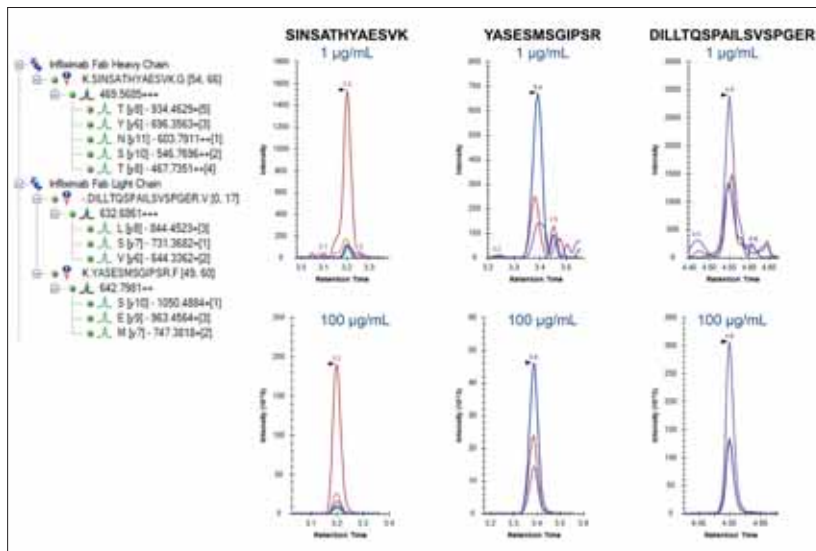


Figure 4. Skyline *in-silico* predicted proteotypic peptides of infliximab in plasma. SINSATHYAESVK, YASEMSGIPSR and DILLTQSPAILSVPGER were selected based on response, linearity and accuracy. Other peptides and quantifier/reference ions were evaluated but finally not selected due to either interference or insufficient sensitivity at the lowest calibration level.

3-2. Infliximab quantitation

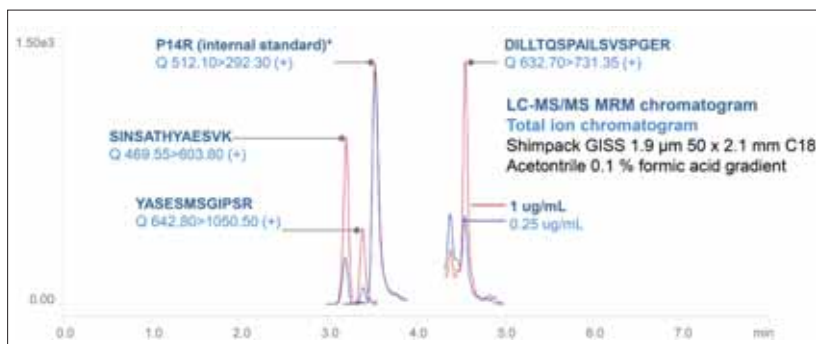


Figure 5. MRM chromatograms for 3 tryptic peptides for infliximab (1 µg/mL [Red trace] and 0.25 µg/mL [Blue trace] in plasma) and internal standard peptide P14R. *P14R internal standard (10 pmol/mL) XIC scaled to x0.05.

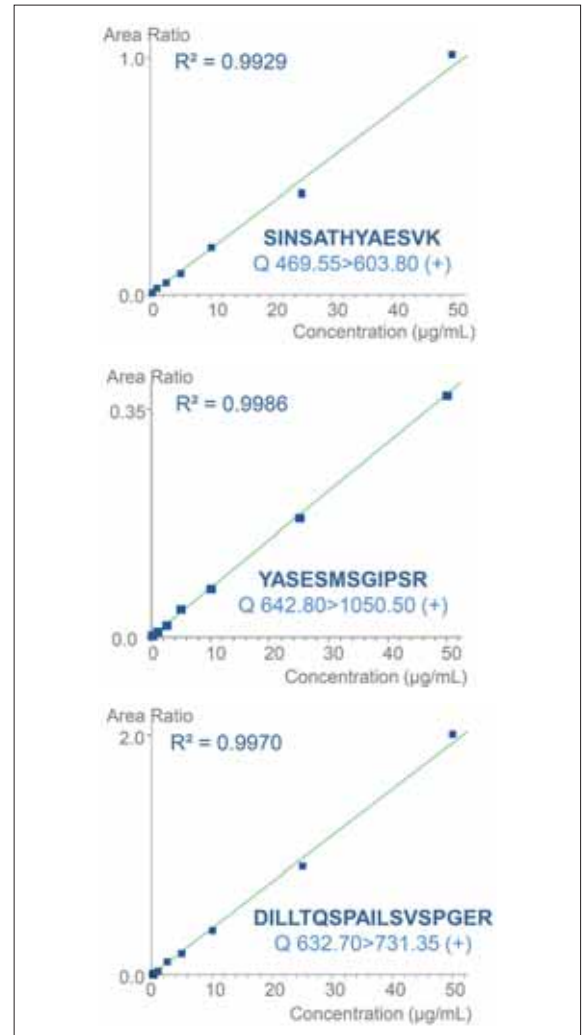


Figure 6. Calibration curves for each tryptic peptide. SINSATHYAESVK was selected for routine quantitation, performing better than YASEMSGIPSR and DILLTQSPAILSVPGER in terms of accuracy and sensitivity. Infliximab QC's also resulted in acceptable variance.

4. Conclusions

- To quantify infliximab in plasma samples nSMOL (nano-surface and molecular-orientation limited) was used to selectively digest the Fab region, which consists of peptides from the CDR region of monoclonal antibody (mAb).
- This approach results in higher selectivity as the technique is focused on specific signature peptides from the CDR region.
- In this work, SINSATHYAESVK was selected as the peptide for quantitation as a result of lower limits of detection and higher selectivity in patient samples.

5. References

- Iwamoto, N., Shimada, T. & Umino, Y. et al. (2014) Selective detection of complementary-determining regions of monoclonal antibody by limiting protease access to the substrate: nano-surface and molecular-orientation limited proteolysis. *Analyst*, 139, 576.

Postponement: the solution for biotech packaging

Dexter Tjoa

Director Corporate Strategy at Tjoapack

Postponement packaging, or late-stage customisation, is the supply chain practice of keeping a product in a standard format for as long as possible, only making it market specific – or even customer specific – at the moment demand arises.



BIOGRAPHY



DEXTER TJOA is the Director Corporate Strategy at Tjoapack. He is responsible for devising, implementing and evaluating the mid- to long-term strategies of the company and the services it offers, as well as overseeing the commercial department within Tjoapack. He has been with the company for three years, during which time he launched Meditraq, one of Tjoapack's sister brands, which offers contract serialisation services. He holds a BSc in Mathematics from the University of London and a MSc in Mathematics and Computer Science from the University of Oxford and has previously worked in the technology sector.
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LinkedIn: <https://www.linkedin.com/in/dextertjoa/>



LEFT: Implementing a postponement strategy can enable drug manufacturers to react quickly to changes in the market

THIS form of packaging has the potential to allow drug firms to supply products more efficiently and respond effectively to variable market demand. This article outlines how adopting postponement packaging could benefit the pharmaceutical industry, including catering for increasingly complex products, such as biotech drugs.

The postponement principle

The idea behind implementing a postponement strategy is to enable drug manufacturers to react quickly to changes in the market. In keeping products market-agnostic until there is a specific market requirement, companies can lower working capital by reducing their finished goods inventory. They can also avoid the waste produced by repackaging products that have previously been prepared for another market or in compliance with a regulation that has since been updated.

Rather than finalising a product and moving it to its relevant country, the product can be partially

prepared and then stored in a centrally located warehouse until such time as it's required. At this point, it can be tailored accordingly and shipped in days or even hours.

Despite being relatively new to the pharmaceutical industry, postponement is not a new concept; rather an adaptation of various lean manufacturing concepts from other sectors. For example, the automotive industry has been effectively employing a postponement strategy for over a decade – only assembling and shipping vehicles to dealers when an order comes in. This provides an effective means of managing the differences between bulk manufacturing and real-time market demand.

Adoption and suitability

To date, the adoption of postponement across the pharmaceutical supply chain has been limited, mostly because implementing such a strategy requires a change in industry mindset. However, given the potential cost, resource and

time savings associated with postponement, there could be significant advantages for companies who choose to operate in this way.

The European market is a particularly good use case for postponement packaging, owing to the vast number of differing requirements. Both language and regulations surrounding artwork design differ from one country to another, particularly following the introduction of serialisation regulations. As a result, should demand for certain medicines arise in one part of Europe, supply that was previously intended for another country may need to be repackaged. Hence, there is a tendency to over supply to each market, which generates a lot of waste.

Postponement allows manufacturers to prepare products for Europe up to a certain point, adding country-specific requirements, such as leaflets in native languages, at a later stage.

Using postponement for biotech products

A postponement strategy can also be particularly useful when packaging small volume or orphan

up and down more easily to meet unpredictable demand; for example, in tender markets. Consequently, this allows companies to reduce time to market and fulfilment cycles by several weeks, as they need not wait for additional supply to be sourced or manufactured. This ultimately means that medicines arrive with patients more quickly and also helps drug manufacturers make cost savings and reduce working capital.

Potential hurdles

The main hurdles that companies will face regarding the implementation of postponement are developing a suitable process and handling market agnostic stock that may not be visually identifiable. There is also the not inconsiderable matter of capital investment associated with purchasing machinery and centralising warehouse operations. Contract packaging organisations (CPOs) can help companies trial the postponement process for their products and then fully implement a strategy, while reducing the need for a large upfront investment.



drugs, for which market demand is difficult to predict. With an increased number of large-molecule biotech products entering the drug pipeline, companies are faced with the challenge of ensuring these medicines are readily available without generating excessive amounts of high value product that might never be needed.

In addition, a number of biotech products have high fragility, meaning they require very short packaging cycles to preserve their efficacy. Implementing postponement packaging makes it easier for companies to handle these medicines efficiently as they do not need to be packed until they are required. It also provides companies with a unique opportunity to pack on a patient-by-patient basis.

Implementing postponement: the benefits

Implementing postponement offers manufacturers more flexibility. The ability to respond to market demand can offset common problems associated with order forecasting and demand planning, such as waste, stock shortages and tight timelines. It can also allow them to scale their operations

As is the case with serialisation implementation, information flow is also a potential challenge. Supply chain partners will need comprehensive and regular insight into customer forecasting data to ensure there is sufficient stock in the centralised warehouse. This will require suppliers and customers to work together far more closely.

Final thought

There are huge supply chain improvements to be enjoyed as a result of implementing a postponement strategy, but it involves completely altering traditional operations. As such, in order for companies to fully realise the benefits, a shift in mindset is required in the industry. While implementation will not be without its hurdles, it's important to consider not only the potential savings that will result from waste and inventory reduction, but also the huge benefit to the patient: a guarantee to receive the right medicine, on time. Proper expertise and processes are absolutely vital, making CPOs with experience of postponement packaging ideal partners for companies looking to explore this type of strategy. 📧

“ *Despite being relatively new to the pharmaceutical industry, postponement is not a new concept; rather an adaptation of various lean manufacturing concepts from other sectors* ”

← **LEFT:** Supply chain partners will need comprehensive and regular insight into customer forecasting data to ensure there is sufficient stock in the centralised warehouse

“ *This ultimately means that medicines arrive with patients more quickly and also helps drug manufacturers make cost savings and reduce working capital* ”



Understanding current CFR 21.11 and data integrity requirements

This webinar focuses on what topics pharmaceutical manufacturers need to consider when sourcing new analytical equipment in order to comply with data integrity and 21 CFR Part 11 / EU Annex 11. Supported by SUEZ, the webinar will take place on 2 October 2018 at 3pm BST.



02 OCTOBER 2018



3.00 (BST)

KEYNOTE SPEAKER:



DANIEL KELLNER-STEINMETZ
EMEA Application
Lead UPW / CV, SUEZ

Daniel Kellner-Steinmetz is the EMEA Applications Specialist for SUEZ. He has eight years of experience in the Quality, Manufacturing, and Training areas of the pharmaceutical industry. Most recently he served as the Global Product Quality Lead for several commercial products at Shire (formerly Baxter) in Vienna. Daniel holds a Bachelor of Science in Biomedical Engineering.

WHEN replacing ageing analytical equipment, key concerns centre on whether the replacements will comply with data integrity and 21 CFR Part 11 / EU Annex 11 requirements.

Common questions from pharma and biopharmaceutical manufacturers include: is the new technology compliant with auditor expectations? Can we get the right data saved the right way in the right place? Can we use USB devices?

These are just some of the questions that arise – often with concern or even panic – due to the large workload that may go along with the implementation of equipment.

This webinar will provide detailed information on what is required. It will also help managers avoid misinterpretation of the regulatory requirements, which might waste time and lead to unnecessary expense.

Also under discussion will be the 'new' term data integrity and how the right digital records can help compliance.



Sievers TOC Analyzers are designed to help increase efficiency while complying with data integrity guidance. In this webinar we will discuss how Sievers instruments can help you comply and how the Sievers Lean Lab solution can help make your lab testing for USP and compliance faster, more efficient, and more reliable.

The keynote speaker will be Daniel Kellner-Steinmetz, EMEA Application Lead UPW/ CV, SUEZ.

Webinar delegates will be able to put a question to Daniel at any time during the

webinar, using the computer control panel.

ABOUT SUEZ

SUEZ (formerly GE Analytical Instruments) specialises in pharmaceutical water quality monitoring and cleaning validation. The company combines Sievers Total Organic Carbon (TOC) Analyzers with certified reference materials, vials, and technical support to help you improve process control and achieve compliance. The SUEZ solution also includes pharmaceutical service plans and validation support packages.

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BPSA European Single-Use Summit highlights polymer-based bio-processing and cell and gene therapies

This unique event, focused on polymer-based bio-processing and cell and gene therapies enabled by single-use technologies, takes place in Barcelona, Spain between 26-28 September.

A KEY theme of the Bio-Process Systems Alliance (BPSA) Second International Single-Use Summit will be the innovation and commercialisation of the next generation of opportunities in single-use processing and cell therapies.

The Summit includes a mix of technical and European regulatory topics that highlight the critical need for innovation in the polymer-based bioprocessing industry, to accelerate and advance life-saving cell-growth and cell-harvested immunotherapies.

The BPSA-sponsored Barcelona Summit will feature a unique blend of technical and innovation topics for company leaders across the globe with a business stake in single-use systems as users and providers.

Conference topics will include: the current business climate for single-use, EU regulatory insights, market growth potentials, as well as the positive attributes of single-use systems, which make them safe, reliable, cost-effective and sustainable.

A range of industry-leading speakers will share their knowledge of the topics under discussion. Keynote speakers include:

- Barbara Paldus, General Partner, Sekhmet Limited, who will deliver a forward-looking perspective on biotechnology, bioprocessing, cell, gene and tissue therapy advances. Barbara will also discuss how 3D printing,

high-speed quantum computing and nanotechnology will feature in the creation and delivery of advanced medicines, replacement organs and immunotherapies

- Uwe Gottschalk, Chief Scientific Officer, Lonza (Switzerland), who will describe single-use in the context of personalised medicine paradigms
- Cesar Trigueros, Chief Science, Viralgen (Spain), who will address the market potential and supply of viral vectors, which is currently far below demand
- Jose Castillo, Chief Technology Officer, Univercells (Belgium), who will consider innovations in micro-facility flexible manufacturing projects
- Nino Mihokovic, Quality of Medicines Specialist, EMA (UK), who will address the European Medicines Agency (EMA) perspectives and experiences with polymer-based bio-processing systems.

A panel discussion will be dedicated to closed systems and integrity assurance.

Topics under discussion include the assurance of CCI, including principles around Quality Risk Management (QRM), Quality by Design (QbD), quality and process control, and integrity testing practices.

Further panel discussions will focus on a variety of topics impacting the industry. For example, Cristina Amorim, Thermo-Fisher Scientific and chair of the BPSA



26-28 SEPTEMBER 2018



BARCELONA, SPAIN

Sustainability Council, will facilitate a discussion of plastics and sustainability.

The Barcelona Summit will also highlight the global impact of single-use on modern medicine – real, potential and imagined. Kevin Ott, BPSA Executive Director, said: “The Summit is not only focused on the proven effectiveness of legacy plastic bioprocessing platforms, but also on the ‘next wave’ of business opportunities, with an eye toward GMP [Good Management Practice], workforce excellence and sustainability.”

The event, to be staged at the Crowne Plaza in Barcelona, is expected to draw delegates from Spain, France, Belgium, Netherlands, USA, UK, Canada and Eastern Europe. Registration and hotel information can be viewed at www.bpsalliance.org. ■

ABOUT BPSA

The Bio-Process Systems Alliance (BPSA) was formed in 2005 as an international corporate member association dedicated to encouraging and accelerating the adoption of single-use manufacturing technologies used in the production of biopharmaceuticals and vaccines. For more information, visit www.bpsalliance.org.



www.bpsalliance.org

From cell process to fill finish: how single-use evolved into an essential downstream technology for biopharma and the role of BPSA in education around risk management for users

Single-use adoption for downstream manufacture of bio-pharmaceuticals is growing – fast. Looking back only a decade, single-use components, mostly ‘dumb’ multi-layer plastic bags, were novelties, used primarily in bio-tech as disposable commodities used to accelerate experimental drug development more efficiently, ie, to ‘fail faster.’ Kevin D. Ott, Executive Director, Bio-Process Systems Alliance explains.



BPSA's mission is to encourage and accelerate the adoption of single-use manufacturing technologies used in the production of pharmaceuticals and vaccines

TODAY, the novelty has transformed into a necessity, as sophisticated polymeric bio-processing systems enter the forefront of drug, vaccine and soon, cell and gene therapy commercialisation – all driven by the desire and need to deliver cures for acute and chronic diseases. Using sterile disposable plastic systems designed around performance, safety and cost helps enable that goal.

Starting around 2013, single-use began to emerge rapidly as the ‘go-to’ platform in the downstream production of precision

medicines – ie, custom therapies targeted at smaller patient populations. This was a necessary performance-driven and needs-based shift from large-scale stainless steel facilities to low-capital cost ‘flexible facilities’ with smaller footprints as enabled by single-use. The advent of integrated single-use Systems (with a capital S) is still changing (and will continue to change) how large-molecule therapies and vaccines are manufactured. Soon, single-use will also be integral to the manufacture of cell, gene and tissue therapies. Plastic-based

disposable bio-processing is here to stay and, by all accounts, will continue on a 6% to 8% compound annual growth rate (CAGR) curve for the indefinite future, according to available data, notwithstanding the staggering potential in the gene therapy areas.

While utilisation of disposable polymeric one-use systems is essential and critical to drug production, inherent in disposable systems are risk factors that were necessarily identified and addressed. This has enabled BPSA, through significant



BPSA organises a host of conferences, technical working groups and other meetings, such as the BPSA Summit in Washington, DC, pictured here

educational initiatives to respond to the many technical concerns with plastic-based systems, covering the decades between 2005 and 2017.

At its core, for those who might be questioning risk – it is about the safety of the drug product for the patient. Period. There is no room for error. And, there is still much to be done as the end users of single-use systems begin to assay how to implement these innovative, flexible manufacturing platforms more safely and more effectively.

It's been said that the transition between old and new is never elegant or seamless. But in the case of single-use, BPSA served to smooth that transition. BPSA is a unique non-profit voluntary corporate association of users, suppliers (both component

suppliers and large system integrators), test laboratories, and educational institutions built around the mission of accelerating the adoption of single-use, worldwide.

To that end, BPSA is a host of conferences, seminars, and task-specific technical working groups, aimed at informing and educating around the promise and now delivery of the benefits of single-use. It is our pleasure to partner with European Pharmaceutical Review in this endeavour.

Those who are perusing this issue of European Pharmaceutical Review, and wish to avail themselves of some of the technical highlights published over the past decade by BPSA are encouraged to visit www.bpsalliance.org. There, you can read and download (no pay wall) in-depth white papers and technical guides covering the 'risk reefs' that the single-use industry navigated as it set its course to successful implementation as a downstream processing tool. Highlighted on the BPSA site are tutorials, white papers and current good manufacturing practice (cGMP) guides (not standards) addressing the challenges that industry, through BPSA, had addressed on an international basis, with ample partnering, that has had a big hand in the acceleration of the downstream adoption of Single-Use Technologies (SUTs).

These concerns include extractables and leachables testing regimens, integrity assurance, change notification principles and recommendations, and particulate identification and control. There are others. We do hope as you learn more about the utility of single-use systems and their comprehensive benefits across the board, you will lean on *EPR* and on BPSA as your clearinghouses for timely information for and about the business of single-use. ■

BIO-PROCESS SYSTEMS ALLIANCE (BPSA)

Bio-Process Systems Alliance (BPSA): www.bpsalliance.org is an industry association whose mission is dedicated to encouraging and accelerating the adoption of single-use manufacturing technologies used in the production of pharmaceuticals and vaccines. BPSA facilitates education, sharing of best practices, development of consensus guides, and business-to-business networking opportunities among its member company employees. Kevin D. Ott, Executive Director, BPSA can be contacted at otk@socma.com.

ORGANISATION DETAILS

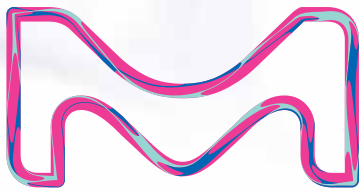
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WEB: bpsalliance.org
SOCIAL MEDIA: Facebook, LinkedIn and Twitter



Bio-Process Systems Alliance
 Advancing Single-Use Worldwide



An infographic guide produced by BPSA



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Novel single-use tangential flow filtration capsules for downstream bioprocessing

In this Spotlight on Single Use, David Beattie, Vice President BioProcessing R&D, Merck explains the mode of operation and benefits of its Pellicon® Capsules.

What new single-use processing device is your company offering?

Merck offers Pellicon® Capsules: novel single-use tangential flow filtration (TFF) devices engineered for ease-of-use, process flexibility and improved product and operator safety in manufacturing monoclonal antibodies, antibody-drug conjugates and other biologics. These efficient, spiral-wound TFF filters perform like Pellicon® cassettes, complementing our many products and services related to TFF and ensuring the quality, availability and safety of life-enhancing drugs.

What distinguishes your device from those of your competitors?

Our Pellicon® Capsule is first of its kind. Its holderless design simplifies installation and enables post-use containment for safe removal. The capsules are provided gamma-sterilised and with preservative-free water for reduced preparation time. These features facilitate setup, minimise risk, save time and conserve resources.

What are the main benefits of the Pellicon® single-use capsule for TFF systems?

The chief benefits are speed, flexibility, process economics and safety.

■ Plug-and-play

The holderless design simplifies connection to a single-use system by reducing installation efforts and operator errors that may cause integrity failures. Encapsulation enables a closed, disposable flow path for post-use containment with easy, safe device removal and reduced risk of operator exposure and product cross-contamination.

■ Ready to use in minutes

The gamma-sterilised filter eliminates pre-use sanitisation. The capsules are supplied in preservative-free,

reverse-osmosis water, which reduces flushing volumes. Time and fluid savings improve batch turnaround and process economics.

■ Proven performance and scalability

Pellicon® Capsules offer the high performance and linear scalability of Pellicon® cassettes. Capsules have the same robust, regenerated cellulose Ultracel® composite membrane for optimum product recovery and a turbulence-promoter feed channel screen that provides high mass transfer and flux for superior performance.

When implementing a single-use capsule for tangential flow filtration, what factors should be considered?

Ultrafiltration is often the last crucial bioprocessing step; biomanufacturers require final purity. End users of single-use capsules for TFF require proven, scalable filtration products from a reliable manufacturer that first must secure the quality of their drug substance, and also offer efficiencies to accelerate processing speed.

How can the Pellicon® single-use TFF filter affect capital and start-up costs of designing and commissioning a new manufacturing facility?

Pellicon® Capsules' manufacturing benefits include: improved batch turnaround, process flexibility and operator safety with reduced capital costs. The efficient design reduces installation efforts and simplifies operation, requiring minimal preparation and conserving time and resources associated with cleaning and validation. Reduced water and caustics use, utility costs, equipment downtime and unproductive labour save resources and footprint. Improved batch turnaround enhances facility throughput to cost-effectively increase speed to market.

Do manufacturers need to replace all stainless technology to take advantage of the benefits of single-use systems?

No, manufacturers can apply single-use technology incrementally. Pellicon® Capsules are simple to integrate into existing facilities without major investments in new equipment. The linearly scalable capsules facilitate transitioning from cassettes, easing process development and validation for current Pellicon® product users. Once manufacturers experience the benefits of single-use bioprocessing, they often look to use it more. Our technical experts can answer questions about applying single-use systems to streamline processes.

What are your sustainability practices?

We recognise that every product has environmental impact and engage in life cycle analysis to minimise it. Pellicon® Capsules have substantially lower energy and water requirements than reusable TFF filters, eliminating the need for extensive cleaning and sanitisation between batches. They also reduce operator and environmental exposure to toxic chemicals. ■

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Harmonise and thrive – a solution for navigating the challenges in every phase of the pharma lifecycle

In this webinar, keynote speaker *Tiffany Gabriel*, Senior Business Consultant at Abbott Informatics, explored some challenges encountered and how a Laboratory Information Management System (LIMS) can provide solutions to help overcome those challenges.

FROM discovery to manufacturing and testing, each phase comes with a unique set of data management challenges. Automated data management software, such as STARLIMS, can help organisations achieve regulatory compliance and quality data management throughout the product's lifecycle.

The webinar – Navigating data management challenges in the pharmaceutical lifecycle – which took place on 12 July 2018, covered five key topics:

- How LIMS offers a solution to data management challenges
- How it handles information; organisation, tracking, scheduling, and monitoring functions
- Advanced analytics capabilities for critical business decision-making
- Data security and regulatory compliance features
- Unique functional benefits of STARLIMS solutions within each phase of

the pharmaceutical product lifecycle.

Here, we review some of the key questions answered in the webinar by the keynote speaker, who has more than 13 years of experience in the LIMS space, holding many roles from business analyst to project manager and now technical sales.

What is the biggest benefit of implementing a LIMS for a pharmaceutical customer?

Abbott Informatics' STARLIMS offers the pharma and biotech sector a scalable, web-based laboratory information management system with 21 CFR Part 11 compliance-capable features, including: audit trail, electronic signatures, and chain of custody functionality to simplify quality control processes.

The benefits of such a solution can be realised from different perspectives.

Having LIMS in place goes beyond data management – it helps you keep up with the compliance regulations. You can get products to market

faster; without compromising on quality or safety.

What return on investment can STARLIMS provide to a generic pharmaceutical manufacturing business?


These would be the same benefits as in other pharma organisations – maintain batch traceability, audit trails and compliance to regulations. Generic pharma manufacturing companies must still perform R&D activities and development work, which requires flexibility in testing workflows. Investing in a LIMS means having a tool that will help you meet compliance at your disposal, providing you with the ability to trend and track manufacturing processes at the touch of a button. It also offers the ability to make proactive decisions; for example, with the use of STARLIMS Advanced Analytics.

The ability to include 'What if?' scenarios in capacity planning can have a big impact on the business. The use of intuitive predictive analysis tools can help you drill

down into your lab data and identify trends and patterns, enabling you to make better decisions more quickly.

How difficult is it to setup a view of LIMS data using Advanced Analytics?

STARLIMS Advanced Analytics features help organisations transform data into actionable insights, allowing you to map out laboratory processes, find bottlenecks and improve laboratory operation across the board. You can create personalised dashboards and colourful visualisations, so that you can view and assess the lab operations from a fresh perspective, highlight issues and act proactively.

We offer a comprehensive training course to customers on the Advanced Analytics features and capabilities, providing them with the knowledge to configure the dashboards and visualisations to their needs. Customers can also download pre-built dashboards available at STARLIMS Content Library and tweak to their requirements, providing the opportunity to use content already available without the need to build anything from scratch. 

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BIOPHARMA PROCESSING & DEVELOPMENT

Biopharmaceuticals require high-quality standards, high initial investments for approval and introduction into the market as well as continued investment in manufacturing, according to André C Guerra, PhD Student, School of Engineering, Newcastle University and Jarka Glassey, Executive Vice President of the European Society of Biochemical Engineering Sciences.

The particle size of Active Pharmaceutical Ingredients (API) has a significant effect on a drug product's manufacturability and performance. Understanding the importance of diversity of particle size methods is key, writes Edislav Lekšić, Team Leader of Physical Sciences, Almac Group.

Unlocking the potential of new technologies, such as Lab-on-a-chip, can cut manufacturing costs and boost product development, explains Nasr Esfahani, Senior Design Engineer on microfluidic devices, Orphidia Ltd.



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Machine learning in biopharmaceutical manufacturing

André C Guerra

PhD Student, School of Engineering, Newcastle University and Marie Curie Early Stage Researcher in EU H2020 MSCA ITN BIORAPID

Professor Jarka Glassey

Executive Vice President of the European Society of Biochemical Engineering Sciences

The biotechnology industry is expected to increase the production of new biopharmaceuticals.¹ Biopharmaceuticals require high-quality standards, high initial investments for approval and introduction into the market as well as continued investment in manufacturing.^{2,3}



BIOGRAPHY



ANDRÉ C. GUERRA is a PhD Student at the School of Engineering, Newcastle University and Marie Curie Early Stage Researcher in the EU H2020 MSCA ITN BIORAPID (<http://bio-rapid.eu>). His main interests are in applied predictive modelling for bioprocess manufacturing, including the development of AI and IoT applications for the biopharmaceutical industry. The main focus of his project is to develop a general modelling framework for rapid bioprocess manufacturing monitoring

IN ORDER to achieve profitable and sustainable manufacturing of biopharmaceuticals, bioprocess and bioproduct development must be planned and executed concurrently throughout the production lifecycle.⁴ Currently, bioprocess development is a critical bottleneck for the successful implementation of innovation obtained during bioproduct development.⁵ The majority of host-cell screening, initial conditions, material attributes and bioprocess parameter in-depth optimisation, as well as the

identification of relationships between critical process parameters (CPP) and critical quality attributes (CQA), happens at an early stage of development during the implementation and execution of design of experiments (DoE) towards the established quality by design (QbD) paradigm.^{4,6}

Process modelling is required in order to achieve the aforementioned goals.⁷ Product and process development have been largely accelerated by the development of representative models in the past, mainly in the domain of product discovery

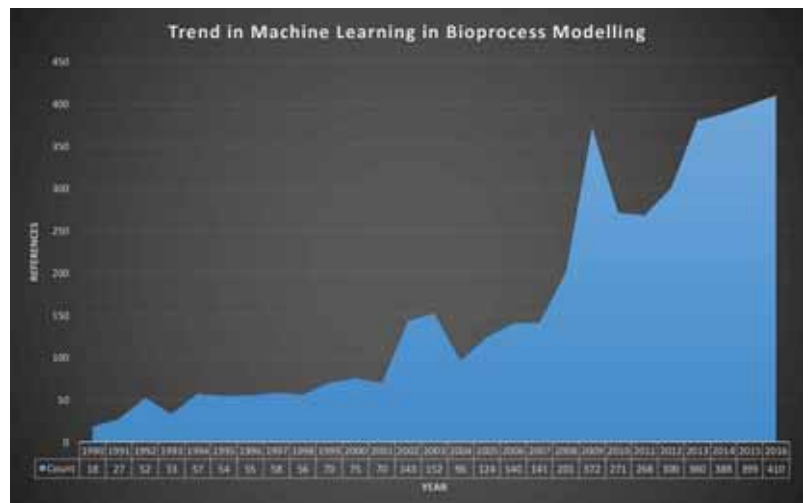
and development. However, with the drive-force behind Industry 4.0, the ubiquitous application of process models in flexible, autonomous, scalable biotherapeutic drug manufacturing platforms is expected.^{1,8} For instance, process modelling will be crucial in advanced biotransformations catalysed by *in vitro* synthetic (enzymatic) biosystems.⁹

Nevertheless, current biopharmaceutical manufacturing still requires continuous process / product assessment and evaluation, since different sources of variation – such as environmental disturbances, slow process drifts (ie, fouling, cell / inhibitors / activators activity loss) and process disturbances (ie, feedstock quality / impurities, step / grade inputs, manual sampling) – may influence process outcome.^{4,10} Several factors contribute to the varying yields still observed in large-scale biopharmaceutical manufacturing, such as the difficulty in balancing biosynthesis of pharmaceuticals with the inherent cell physiology conditioned by the operating conditions.¹¹

All bioprocesses exhibit nonlinear, dynamic behaviours to some extent, which depends on unknown reaction kinetics with time-varying parameters. A variety of factors – including a lack of mechanistic understanding of these biochemical kinetic reactions and instrumentation for online measurements (especially for CQAs); the complex interactions between multiple variables with varying degrees of correlation; time-delayed and scale-dependent bioprocess responses – all introduce new challenges for biotechnologists to build trustworthy representations of the process and product state in the form of a process model.^{4,10,12}

A process model is a mathematical representation of the relationships between process operating parameters and process outputs / state or product quality attributes. Models can describe a single process unit operation, ranging from upstream to downstream unit operations, or provide a holistic representation of the whole process.¹² Mechanistic models, relying on first / fundamental principles and phenomenological assumptions, are typically parameterised empirically. The applicability of such mathematical process models, typically composed of a system of differential equations, has been demonstrated in the development of improved strategies for DoE, monitoring and control strategies.^{12,13} Advances and advantages of mechanistic modelling for biopharmaceutical manufacturing have been reported;^{11–16} however, mechanistic models have several limitations. For example, the lack of necessary model resolution to predict biopharmaceutical CQAs¹⁶ and the static representation of dynamic (scale and time-dependent) parameters.¹⁵ Currently, mechanistic models are reportedly used

FIGURE 1



in the monitoring and control of bioprocess outputs, based on the feed rate of raw materials,^{14,16,17} but the controllability of specific CQAs (such as glycosylation of monoclonal antibodies) is yet to be fully evaluated.¹⁷

Statistical, data-driven or machine-learning models rely on inferences based on collected data. The use of modelling approaches in bioprocessing has increased steadily over more than 20 years (Figure 1). Machine learning models can be subdivided into supervised and unsupervised learning algorithms, depending on the presence or absence of process output data in observations, respectively. Supervised learning algorithms are commonly used for the quantification of CPPs or CQAs and assessing their interdependency, while unsupervised learning algorithms are commonly used in classification applications. Several applications have been reported using these modelling approaches, summarised below:^{10,12}

- Soft sensors – real-time estimation of CPPs / CQAs, based on other real-time measurements and online parameter estimations
- Mode of operation selection – based on the classification of current process measurements into a discrete mode of operation to select appropriated monitor and control mechanisms
- Chemometric models – extract information present on multidimensional spectra into metabolite concentration estimations
- Multivariate data analysis – for the post-mortem analysis of the variation of Process Analytical Technology (PAT) instrumentation measurements in-process (such as identification of golden batch operation conditions)
- Multivariate statistical process control – for process / product state monitoring and failure

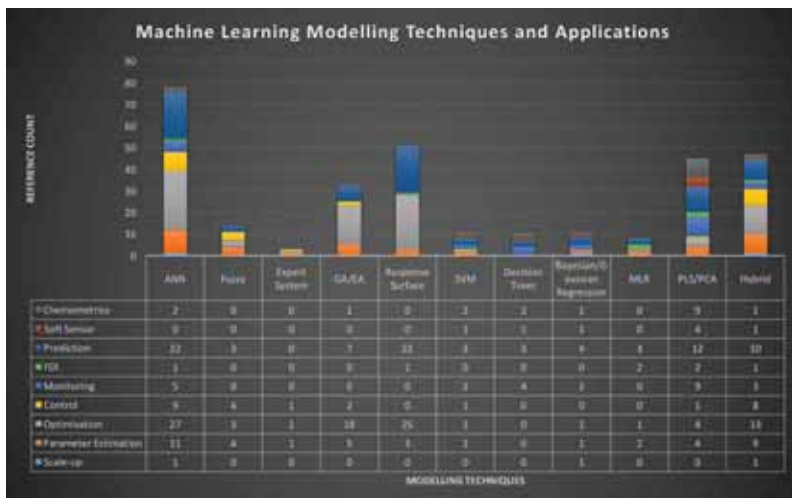
↑ ABOVE: Evolution of the number of peer-reviewed publications resulted from the query “Bioprocess Machine Learning” from Google Scholar [03/10/2017].

BIOGRAPHY



PROFESSOR JARKA GLASSEY is currently the Executive Vice President of the European Society of Biochemical Engineering Sciences (ESBES) and Vice President Technical of the IChemE. She is based at Newcastle University and her expertise is in Quality by Design, process analytical technologies and bioprocess modelling. The main emphasis of her research is on using advanced modelling techniques for (bio)process development for biologics and small molecules.

FIGURE 2



ABOVE: Distribution of different modelling techniques over the most common applications Google Scholar references in bioprocess operation / bioproduct manufacturing for the period [01/01/2017; 03/10/2017]. Modelling techniques and applications were assessed individually for both “bioprocess”, “biopharmaceutics” and “monoclonal antibody” search terms.



detection and identification to detect when the process is deviating from its normal / optimal behaviour and source causes

- f) Process state-observers – estimate the entire process state, based on real-time input variable measurements
- g) Dynamic simulations – for exploring process parameter settings and optimisation of dynamic operating conditions as well as uncertainty and sensibility analysis
- h) Closed-loop, adaptive, model-predictive control – predicts the process state for different control actions and acts accordingly.

Given the current availability of faster and more practical modelling packages, several modelling approaches have been recently applied to biopharmaceutical process / product modelling in the above mentioned areas (Figure 2). Artificial Neural Network (ANN) appears to be the most commonly-used modelling approach, due to its ability to capture non-linear relationships in dynamic systems, as well as to estimate parameters of other models.

Latent Variable methods, such as Partial Least Squares (PLS), may provide better solutions for multivariate regressions of PAT instrumentation data, given their ability to determine correlations between thousands of multi-dimensional variables at once. Recursive partitioning algorithms (or ‘tree’ models) are commonly used as classification models for root-cause analysis.¹⁸ However, the majority (>70% – data not shown) of applications found in literature report pattern recognition (classification) applications for early-stage biopharmaceutical product development.

Several disadvantages of data-driven models in biopharmaceutical industry have also been


reported.^{10,18,19} The lack of representative datasets (different batches describing all possible sources of variability) for model development, testing and validating may limit their ability to generalise over wider operability regions. Black-box model parameters are difficult to interpret and, due to the complexity of models, not readily stored and integrated into interpretable knowledge (with rare exceptions).

Furthermore, these models have several disadvantages regarding the uncertainty of predictions outside the calibration space (extrapolation), inside the calibration space when insufficient observations are available for model development (overfitting), and collinearity (correlation-causation) effects, which only become apparent with the introduction of more data to model.¹⁰ Another challenge in biopharmaceutical manufacturing process lies in the collection of valid modelling data. Biopharmaceutical manufacturing data include multi-modal, multivariate data, noisy and missing values. The effective pre-processing of raw data into ‘ready-to-model’ data is time-consuming and may introduce artifacts or loss of information. Recently, modelling in the QbD approach was extensively reviewed resulting in several considerations including Good Modelling Practices.⁴ The main challenges and opportunities for process modelling in biomanufacturing development and operation include:

- Higher transparency of model methodologies and assumptions
- Improved criteria for quantitatively comparing model candidates
- Sensitivity analysis of model predictions with respect to changes in input variables
- Generalised uncertainty analysis strategies, for the quantification prediction error and noise variability effects on model outputs
- Reproducibility, replicability of the results and the stability of the model to data updates
- Feasibility and flexibility analysis, which also takes into consideration the inherent uncertainty of model parameters during the normal process operation to define better control spaces
- Clarity on the explicit integration of domain expertise with black-box modelling approaches (hybrid semi-parametric models as a viable option)
- Dynamic and adaptive DoE for multi-process unit operations
- Scale-independent models and the evaluation of scalability of model parameters across different scales
- Real-time predictions and analysis, to support RTR (Real Time Release) of biotherapeutic drugs.

“Several factors contribute to the varying yields still observed in large-scale biopharmaceutical manufacturing”

Although the biopharmaceutical industry may be reluctant to embrace machine learning as a standard tool for bioprocess development – due to the potential catastrophic consequences of faulty products – biopharmaceutical manufacturing is presenting us every year with innovative

applications and case studies. The technological progress in machine learning and computing will inevitably lead to broader applicability of these techniques and such case studies are important in providing the community with useful benchmarking material. 

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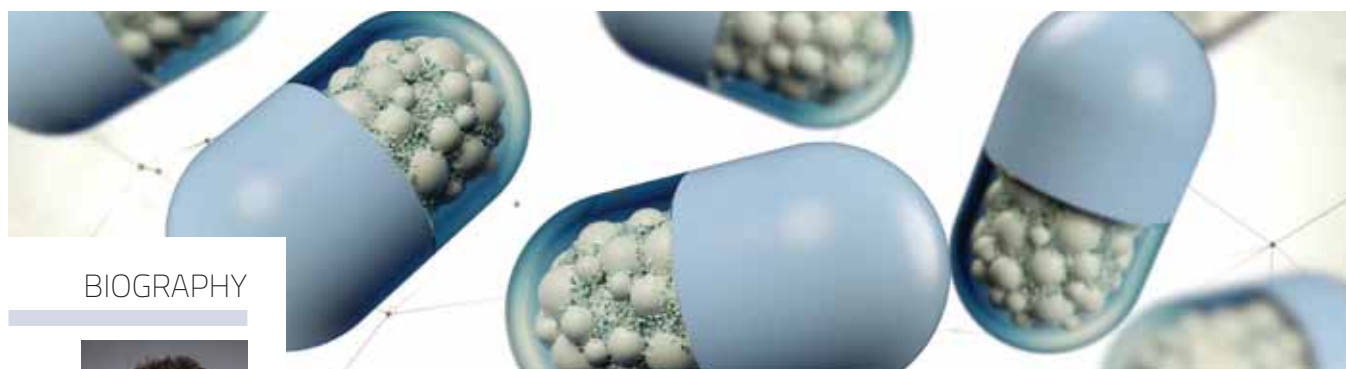
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Understanding the importance of diversity of particle size methods

Edislav Lekšić

Team Leader of Physical Sciences, Almac Group

The particle size of Active Pharmaceutical Ingredients (API) has a significant effect on a drug product's manufacturability and performance. With respect to manufacturability, particle size can affect compatibility, flowability and blend uniformity; with respect to product performance it can affect solubility, dissolution, and bioavailability.



BIOGRAPHY



DR EDISLAV LEKŠIĆ is the Team Leader of Physical Sciences at Almac Sciences. He has worked in the pharmaceutical industry for the past 12 years, with expertise in solid state chemistry related to API target selection, crystal surface property, scale-up and production troubleshooting. He has been involved in preformulation work and development of complex systems such as solid dispersions and cocrystals. For several years he has worked closely with patent law authorities contributing to aspects of IP. He has a strong GMP background and experience related to XRPD and PSD method validation and transfers. Edislav received a PhD in supramolecular chemistry from the University of Zagreb.

WHILE most manufacturers employ methods to control particle size prior to product release, particularly if the API is not soluble, they do not always consider the impact of particle size on product manufacturability (**Figure 1**).¹ We recommend the monitoring of particle size at all manufacturing stages, as doing so will contribute to the understanding of, and ability to control, the process and ensure quality and consistency in batches. Different methods will be needed for monitoring particle size at different points in the process.

The decision of when to monitor particle size – and using what method – depends on how relevant the particle size is to the product. There is great diversity in the particle-size distribution (PSD) methods that can be used on the same material during drug product development, depending on what property is being measured. Programme leaders and manufacturers are often confused by the array of PSD methods, as there is no general PSD method listed in pharmacopoeias. This article explains the different PSD methods that are based on laser diffraction and clarifies their potential applications in different project phases and for different purposes (**Figure 2**).

The source of the diversity in PSD methods

The wide diversity of PSD methods stems from differences in their technical aspects (instrument parameters), their purpose (process monitoring at different project stages) and their relation to drug performance (primary particles, agglomerates).

The need for different method parameters is understandable. The common parameters that can vary in the wet dispersion method are pump speed, obscuration, and sonication time. There are different acceptable values for these parameters for smaller (eg, Dv90 less than 10µm) or larger particle sizes. While larger particles would require a higher pump speed to ensure efficient dispersion (preventing sedimentation inside the measuring cell), special care needs to be taken when setting the obscuration limits for samples characterised by small particle size to avoid phenomena such as multiple scattering.^{2,3}

Should the method parameters change in a Good Manufacturing Practice (GMP) environment, it will most likely result in a new method that requires fresh validation – unless the method's robustness was demonstrated under those parameters during the original validation. The idea of using one selected PSD method with the intention of covering a wide range of particle sizes – for example, where different API grades

are targeted or when PSD methods support the micronisation of trials – presents a challenge.

There might be more than one PSD method suitable for determining the particle size of a given batch. For example, in the early stage of development, one might want to use a generic PSD method for monitoring the process. The term generic here refers to the method parameters that might be suitable, based on the particle size as observed under a microscope, eg, the default. By monitoring different samples during the early R&D phase using one or more generic methods, one can see trends in the changes in powder bulk properties and learn about the influence of process change on the particle size and morphology in general. Any difference in process (synthesis, scale up, and process optimisation) or improvement (such as reactor size, and increase or decrease in crystallisation temperature) might lead to differences in crystal growth or the formation of the agglomeration of different strength and sizes.

At a certain project stage, it is desirable to develop a fit-for-purpose method. Such methods are suitable for monitoring release or manufacturing processes, such as drying and milling. Often, the drying process is not properly monitored with respect to how the particle size and shape of those particles change during the course of the drying process. Thus, this is a production step that can potentially cause issues related to poor macroscopic property of the bulk. Milling is a critical step in the production of APIs because it significantly alters the physical property of the batch (eg, kinetics of solubility). It can also reduce the stability of the material because the increase in hygroscopicity, due to higher surface area or amorphous phase formation, can trigger secondary agglomeration formation upon storage.

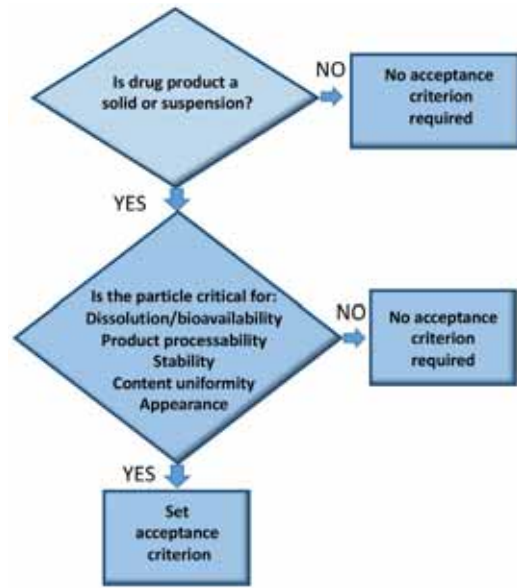
PSD methods are process related and, most likely, the method parameters should be fine-tuned to support PSD and morphology changes until the process for synthesis and isolation of a given API is fixed. This can then be followed by validation, depending on the project's clinical phase. Continuously monitoring PSD and collecting data (which also involves microscopic analysis) is part of an Analytical Quality by Design (AQbD) approach to building a robust method that will be easy to validate when required (Figure 3).⁴

GMP methods

Release

The PSD method selected for use in the release should be in line with the Quality Target Product Profile (QTPP), which is part of a Quality by Design (QbD) approach to product development. The QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality.⁴

FIGURE 1



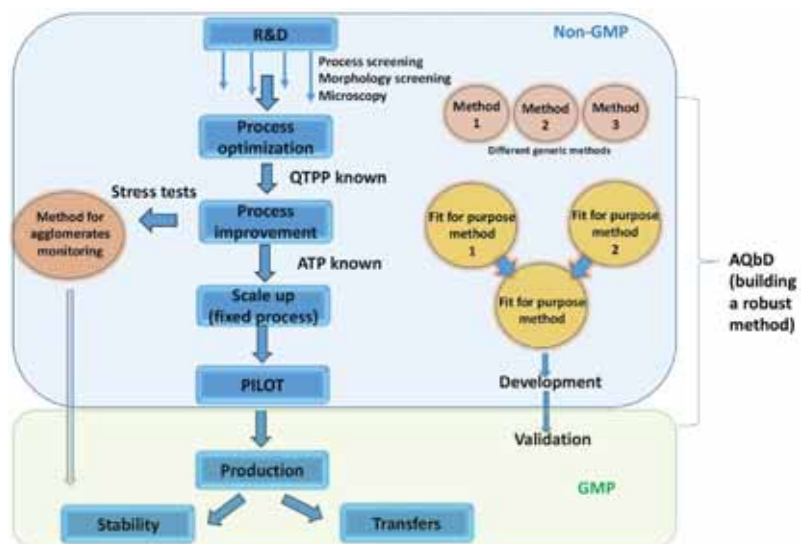
LEFT: Decision tree on when to consider testing for particle size

“The need for different method parameters is understandable”

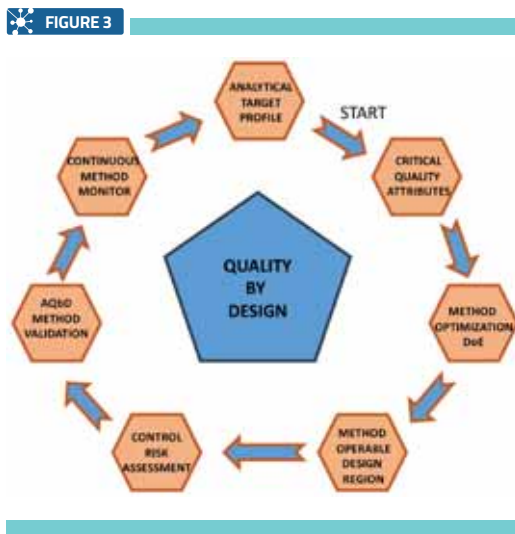
These product characteristics can be achieved by measuring primary particles or agglomerates in the sample. In most cases, due to low water solubility, PSD methods are used to measure primary particles (single crystals) in the bulk, as there is direct correlation between particle size and kinetics of solubility. In the case of crystalline material, it is to be expected that API consisting of smaller particles will show faster kinetics of solubility, which might influence bioavailability. Inhaled drug products comprised of fine and homogenous powders of primary particles characterised by narrow distribution are important for successful particle deposition and product

BELOW: Different PSD methods with different purposes can be employed at different project stages

FIGURE 2



RIGHT: Analytical quality by design, referring to constant monitoring and method development, to build a robust method



efficiency. In most cases, production batches consist of a mixture of primary particles and agglomerates. Agglomerates are objects in which more particles are joined together and act as one. Their degree of hardness is often different, which increases the sample's heterogeneity. Further discussion is required to understand formulation type as the presence of agglomerates might have a significant role in terms of solubility, formulation performance, and content uniformity. In such cases, measuring the agglomerates might be desirable. Agglomerates formation might be created intentionally to improve the process, such as through an increase in filterability time.

Stability

In general, treating the PSD method as a default quality test in an official GMP stability study should be an exception rather than a rule. There are two main reasons for this:

- Any resulting increase in particle size does not necessarily reflect a quality issue
- The PSD method might not be feasible after the powder macroscopic property has been changed.

The main purpose of the stability study is to determine the shelf life of drug substances and drug products by stressing the samples. However, changing the macroscopic property of the powder under stability conditions, such as particle size via agglomeration formation, might not be relevant for the quality aspects of a given compound. Out-of-precision (OOP) results could occur due to sample inhomogeneity and the small sample quantity used for each stability point testing.⁵ Out-of-specification (OOS) or out-of-trend (OOT) results found by executing the stability protocol might not have any meaningful influence on

the quality of the product. For instance, weak agglomeration formation that can be detected with a suitable PSD method during stability testing will generate results that will trigger an OOS investigation in a GMP environment. The results could be misleading as this change might not be relevant for the product quality, given that formed agglomerates will be destroyed by wet granulation.

In addition, stress conditions created by temperature and humidity changes can significantly alter the macroscopic properties in the bulk, such as powder flow and powder cohesiveness. An existing (eg, dry dispersion) method may no longer be suitable because the method's measurement parameters were optimised during method development on the batches of the same compound, but with different macroscopic properties. This indicates the need to have different PSD stability methods in line with the QTPP, which may differ from the release specifications (for instance, omitting the sonication step during sample preparation). Changing the method to adjust the parameters in a GMP environment is not easy to justify, causes lengthy delays in reporting the results, and might be quite expensive for manufacturers. Instead, the influence of agglomerate formation during storage and its impact on drug product performance should be examined in the early stages of drug development, and sensitive methods should be developed accordingly.

Batch-to-batch comparison methods

When a batch is comprised of agglomerates of different strengths, or when a batch is characterised by fragile crystals with poorly expressed crystal habit, methods that support batch-to-batch comparisons might be suitable. When agglomerates of different strengths are present in the bulk, they cause material to be heterogeneous and therefore challenging to sample homogeneously. Fragile crystals break randomly, making it difficult to achieve a plateau during sonication, which is needed to define full sample dispersion. Batch-to-batch comparisons do not provide real particle size (eg, primary particles), but particles formed upon application of certain method conditions (eg, stress caused by sonication) serve to differentiate among batches.

Conclusion

During the project development more than one PSD method might be employed as PSD methods are sensitive to chemical process changes. As a final release test, a PSD method is selected to ensure consistency and quality directly related to known product performances, while PSD results obtained during a stability programme contribute to the determination of a drug product's shelf life.

“ In most cases, production batches consist of a mixture of primary particles and agglomerates ”

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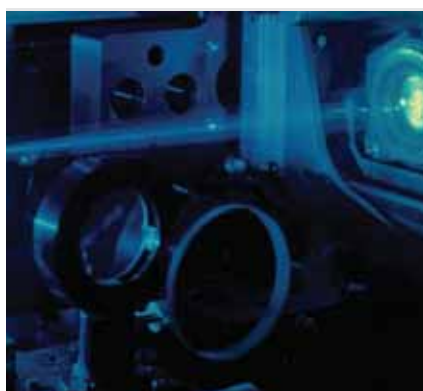
Raman spectroscopy enables Advanced Process Control in upstream bioprocessing

The Food and Drug Administration's (FDA's) Quality by Design (QbD) and Process Analytical Technology (PAT) initiatives brought a paradigm shift to using *in situ* PAT instead of grab sampling / off-line analysis.

PAT and QbD are strongly encouraged by regulatory agencies for their recognised benefits of increased scientific understanding, improved process efficiency, and consistent product quality. QbD and PAT initiatives support bioprocessing and emphasise the importance of real-time analysis in biopharmaceutical manufacturing. Implementation of PAT and QbD principles are driving innovation in the way biopharmaceutical companies operate.

Raman spectroscopy is an established PAT in small-molecule pharmaceuticals and bioprocessing, from the laboratory to manufacturing.¹ In bioprocessing, Raman spectroscopy provides an *in situ* and real-time analysis of multiple biochemical attributes without sample extraction from the bioreactor. In mammalian cell cultures, a single *in situ* Raman probe measures glucose, lactate, amino acids, and cell viability.^{2,3} An *in situ* Raman measurement is representative of the process, that supports advanced process control (APC) strategies necessary to realise high-yield production and ensure consistent product quality. Raman-based feedback control allows for in-process corrections so that output variability is reduced, even with variable inputs. And, the high specificity of Raman spectroscopy enables cross-scale model transfer without significant model rework.^{4,5} These features have been harnessed by industry leaders to realise yield improvements, ensure robust process understanding and apply APC to impact product critical quality attributes (CQAs).

A recent study by Berry et al. describes rapid generation of Raman-based feedback control of glucose during a CHO cell bioprocess to optimise the product's glycation CQA.⁶ Significant glucose control was achieved after only two calibration



In bioprocessing, Raman spectroscopy provides an *in situ* and real-time analysis of multiple biochemical attributes without sample extraction from the bioreactor

steps and eight concurrent bioreactor runs. Raman-based feedback control supported a targeted concentration condition or a stepwise condition, demonstrating Raman as a robust method to integrate into a controller of an industrially relevant bioprocess. Other recent studies have demonstrated that Raman spectroscopy is compatible with a non-linear model predictive controller and that Raman-based feedback control of lactate in cell cultures increased yield up to 85% over the historical process.^{7,8}

The biopharmaceutical industry will continue to see developments in yield improvements, novel platforms, perfusion-based manufacturing, PAT for downstream processes, and original approaches to manufacturing facility design. Working closely with industry groups and leaders, we ensure that Raman spectroscopy meets not only the scientific application needs but also facility and engineering requirements. Raman spectroscopy has demonstrated value in biopharmaceutical

manufacturing, from scientific understanding to process control.

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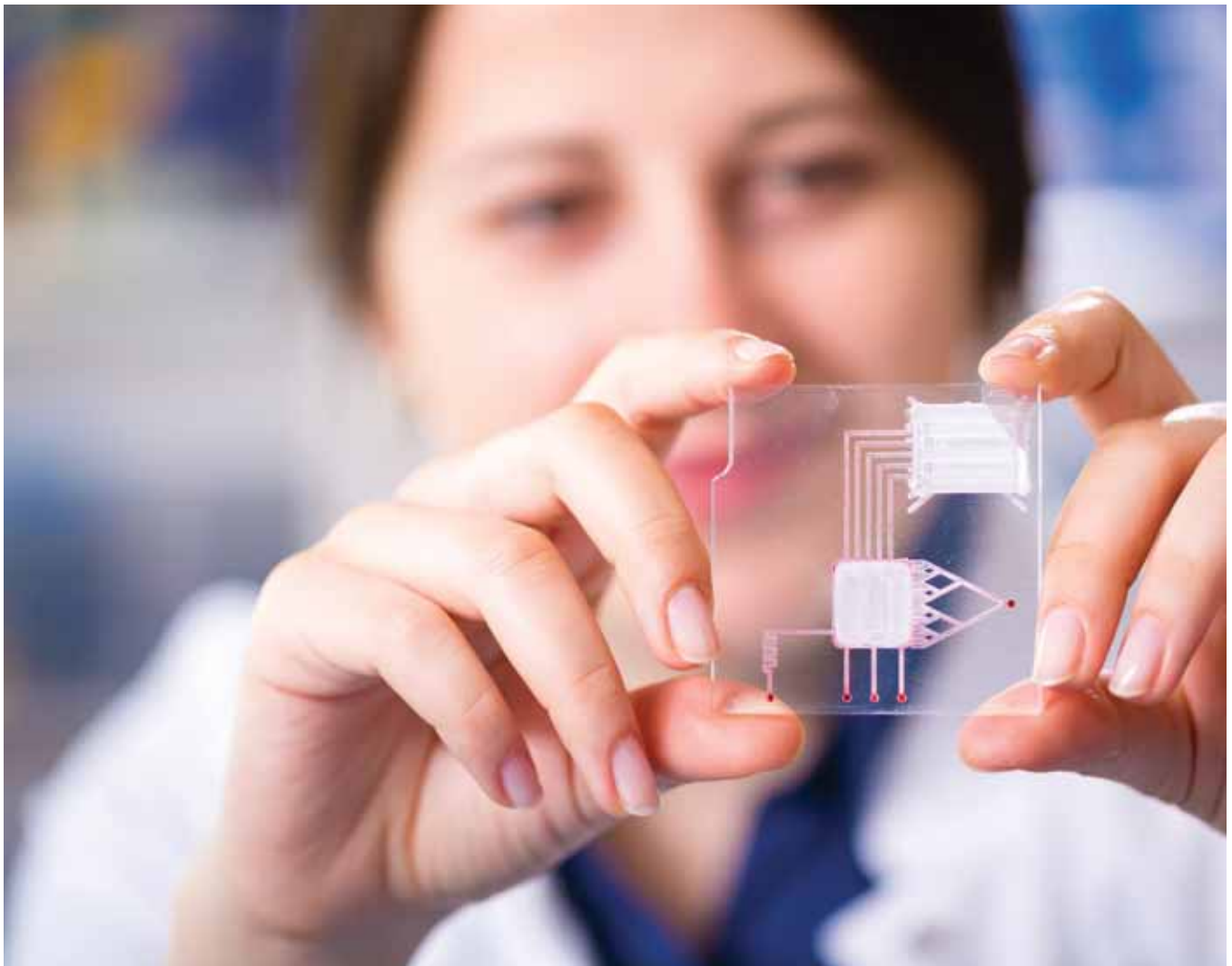
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Unlocking the potential of new technologies, such as Lab-on-a-chip, to cut manufacturing costs and boost product development

Nasr Esfahani

Senior Design Engineer on microfluidic devices, Orphidia Ltd

The investigation and development of new drugs is a time-consuming and rigorous process with many challenges. Every step and each new method is developed with the intention of bringing effective medicines to patients in the shortest possible time, while ensuring the highest possible level of safety. Good product design, as well as good manufacturing practice (GMP), can lead to more efficient development. Aside from the mass manufacturing process, the integrity of the bioprocess itself may also limit product quality in the final stage.



NEW TECHNOLOGIES such as Lab-on-a-chip (LOC) have economic advantages of lowering the costs of manufacturing processes and improving the efficiency and accuracy of product development. Lab-on-a-chip is currently one of the most powerful technologies employed, with huge potential to impact healthcare, medicine and biopharma. After much development over the past quarter of a century – and with commercialisation starting to take off¹ – the ability to shrink sample quantities to micron levels has the potential to speed up the study of many drugs designs and biopharma products. For example, LOC enables automated liquid injections using microchannels down to 50µm in width to transfer picolitre amounts of liquid in milliseconds.

LOC can also automate the process by directing the right amount of liquid at the right time using micropumping and microvalves. The flexibility of the design of these devices allows the transfer of benchtop lab bioprocesses (such as filtrations and membrane-based filter technologies) to LOC, especially in the cell separation field. For example, instead of using lengthy laboratory-based techniques and image processes to roughly estimate the number of cells in a sample, LOC – by means of a simple manufactureable microstructure in the form of a polymer with enough hydrodynamic and surface properties – can sort and / or accurately count a large number of cells in a shorter amount of time.² From a biopharmaceutical product development point of view, if such a device can be commercialised to accurately sort and / or filter cells, it could revolutionise health and diagnostic fields – such as perfusion bioreactors for continuous manufacturing of monoclonal antibodies³ and / or cell population heterogeneity and morphology analysis.⁴ When looking more in depth to design and development in the biopharmaceutical industry, there are several main aspects to be considered: these include design criteria, order of importance, quality, concentration, productivity, yield / conversion and type of bioreactor, as well as the material to be used.⁵ All these aspects can change depending on the biological processes being developed, such as anchorage dependence or suspension adapted and temperature gradients.

Looking at which tools have been used in the past decade to speed the process of technology transfer into manufacturing, we perceive two main directions: Process Analytical Technology (PAT) and the development of platform technologies. The well-established quality axiom that "quality cannot be tested into products but should be built-in or should be by design" is now being applied with PAT, as the operative mechanism of assuring quality, reducing failures and

“ LOC can also automate the process by directing the right amount of liquid at the right time using micropumping and microvalves ”

mitigating deviation during manufacturing.⁵ Additionally, thorough awareness of the manufacturing process and development path that led to it allows for flexible management of change. Computational modelling appears to enable more accurate analysis in the field, which can help the product advance more quickly. These trending analysis tools are still not sufficiently well adapted to real samples or clinical conditions of testing, but nevertheless PAT is likely to add value to process understanding and reduce the risks associated with the impact of seemingly small process changes, such as the change of a vendor for a process ingredient.⁵

Platform technologies are manufacturing operations that should be applicable to more than one biopharmaceutical product, with the desired effect of eliminating the process of reinvention for each new product and reducing manufacturing investments. The multidisciplinary field of LOC can cooperate to develop core technology programmes off the process-development path. New technologies such as LOC, which need to provide cost savings, faster production, safer products and other benefits within the supply chain, can be introduced systematically.

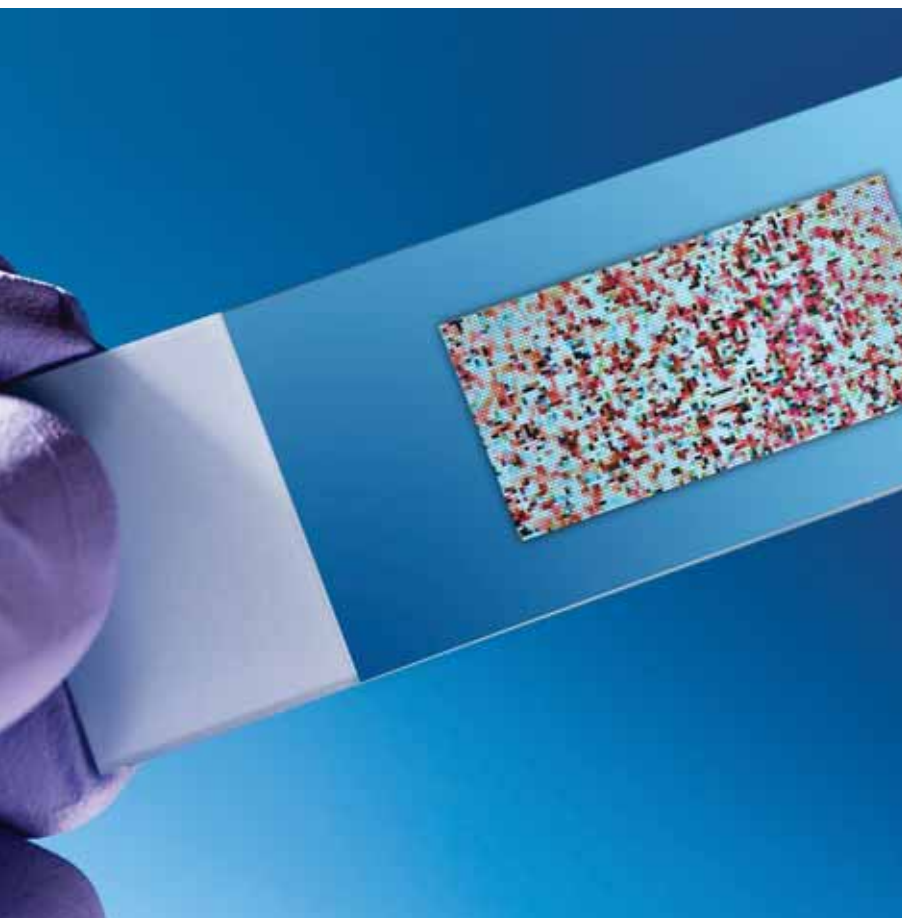
It is important to emphasise the need to speed up the development of LOC technology with more industrialised methods and regulations on mass manufacturing standards. As with every new technology, there are unknown challenges in the design process, as well as the manufacturing line, for a prototype to reach approval level. Traditionally, many industries follow the approach of "do it right the first time". However, being a new technology, LOC follows a more scientific approach, which can be challenging due to the restrictions of the more technical industrial approach. Traditional methodological routes are still used in the field of manufacturing, which block or slow down the process (injection moulding, optimisation of process and restriction of materials that adapted with this method). These routes are often not the best way to efficiently optimise the product development stage that aims to reach the market. In the absence of a good manufacturing practice being established, the accurate design cannot be proved biologically; hence, the manufacturing process will likely take a long time and, in many cases, will fail.


Another important aspect is the development of a production process, as well as the ▶

BIOGRAPHY



DR NASR ESFAHANI is a designer in microfluidic and lab-on-a-chip devices with a strong interest in design for manufacturing and mass production. Nasr is passionate about creation and innovation in science and engineering, which have led him to be involved in the development of high-tech revolutionary products over the past 10 years. In 2014, he received his PhD in Engineering from the University of Hull, after being awarded a doctoral scholarship to investigate mass manufacturing strategies for lab-on-a-chip devices. He has worked in the Institute of Innovation and Product Design at the International Manufacturing Centre of the University of Warwick in collaboration with Silson Ltd. He then joined a team of scientists as a PostDoc, to develop microfluidic platforms for dose-on-demand positron emission tomography (PET) tracers at University of Hull. Currently, he is working as senior design engineer on microfluidic devices at Orphidia Ltd.



ABOVE: Lab-on-a-chip can enable the automation of manufacturing processes 


“ Computational modelling appears to enable more accurate analysis in the field, which can help the product advance more quickly ”

building of a production plant, which must be available for clinical phases. The diagnosis and biopharmaceutical industry must invest heavily in process engineering and plant construction, particularly in the fields of manufacturing, to provide valuable devices or prototypes on time for clinical studies. An example of this is organ-on-a-chip (devices that can model the effects of a drug directly into one part of body). However, it is unknown whether this product will ever reach the market and some devices will not easily lead to a return of R&D costs – especially in start-ups, as they have to invest a lot on developing technology to adapt to current standards. Ideally, one would start investing into a commercial plant when the phase of clinical study data becomes available. However, phase III clinical material must come from the commercial plant and the production process must meet regulatory requirements (for

example, for the European Medicines Agency (EMA) and GMP standards).⁶ Therefore, many companies must develop new concepts that start process development and engineering right after the first results of clinical phase I studies.

In general, the time required for clinical studies can be long and, in many cases, design will fail by not providing the required accuracy. At the same time, the regulatory requirements are growing, so the clinical testing time may even increase. The time needed for phase III clinical development depends on the type of device designed for the developed drug and the experimental readout.

Overall, development of the LOC field still lacks financial investment due to the lack of expertise and / or manufacturing technology that could help to better produce the desired product. Often researchers working with LOC fail to recognise the technical challenges that exist when engineering a product and the activity of many companies is based on pure research, with a focus on patients, being determined to create meaningful therapies but lacking the product development component. In terms of the regulatory approval level, LOC devices are still at an early stage and the majority does not even reach commercialisation level, as most of them were not designed with this aim, but rather for scientific research (such as PhD projects). At universities, large amounts of money have been spent in LOC. Most of the projects, however, do not have an industrial aim, as this can be time consuming and development of the devices tends to finish once the project reaches the solution stage. Therefore, without any direction towards high volume manufacturing, it would be hard to standardise and tune these projects within market and industry.

In conclusion, biopharma needs to update some traditional methods. Too often nowadays, industries such as high-tech start-ups fail at the stage of regulatory approval and product marketing. Merged technologies such as LOC, which are still not fully introduced into industry and adapted within current standards and regulations, also need to be established. If biopharma requires a boost for faster development, one solution would be significant investment into the advance of design and manufacturing to allow new technologies to deliver new products more quickly. 

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Achieving insights from connected R&D workflows

As R&D workflows become more sophisticated, companies are faced with the challenge of managing multiple types of complex data from a larger number of systems. Labs are turning to the latest digital technology as a strategic enabler of innovation across the various research disciplines and stages involved in drug development.

ALEC WESTLEY, Senior Leader of Technical Sales at Thermo Fisher Scientific, addresses questions asked by labs making the move to cloud-based data management platforms, who want to gauge the benefits of implementing an extensible lab informatics platform and how these digital technologies can help overcome the issue of increased data complexity.

This follows *European Pharmaceutical Review's* webinar – Creating a connected ecosystem to gain insights across R&D – which took place on June 28, 2018 and was supported by Thermo Fisher Scientific.

With R&D workflows often reliant upon multiple systems spanning several different departments, how can modern informatics platforms help to better integrate processes?

Pharmaceutical R&D workflows generate large amounts of data that must be managed across the development pipeline, from concept and research through to scale-up and manufacture. Many modern laboratories rely on electronic laboratory notebooks (ELNs) and databases to capture and organise this data. However,



ELNs are commonly assigned to specific processes and used across multiple research areas, teams and facilities, which can make data sharing difficult. Consider protein identification, for example, which is used downstream of molecular biology and cell culture processes in the development of biologics. These workflows involve protein selection, purification, analytics and verification steps. Separate point solutions for each process can inhibit their broader integration and limit organisational productivity. Robust, integrated informatics solutions are essential to ensure that these complex workflows function efficiently.

In most cases, existing systems do not need to be abandoned to put in place

platforms that connect all processes, instruments and workflows. Data from ELNs and databases can typically be integrated into new systems to create fully connected digital ecosystems. Platform-as-a-service (PaaS) solutions that are based on a modular framework, such as Platform for Science, can be seamlessly incorporated into current systems in a manner that meets an organisation's needs. If an entire system overhaul is required, a complete replacement solution can be implemented to seamlessly transition existing data; if only specific features are required, for instance, to allow organisations to take on new capabilities, modular PaaS solutions enable the integration of new parts into

the existing system without the need to replace the fundamental infrastructure.

Enhancing or replacing an existing system with an integrated digital platform improves efficiency by enabling instruments and devices to upload data directly to secure user accounts. Moreover, these platforms can increase lab productivity by facilitating data management for R&D pipelines, experiments and inventory logs. Legacy instruments can be connected using cloud services within the platform to maintain control of experimental data from any location. The latest integrated platforms connect the wide scope of biology performed in R&D labs such as qPCR, next-generation sequencing, mass spectrometry and

synthetic biology to help organisations achieve a comprehensive overview of their entire workflow.

Can R&D workflows be customised using new digital solutions?

Customising R&D workflows provides better control over standardised processes and can improve organisational efficiency. Customised workflows are an important feature of a complete digital solution and this can be achieved via a data-driven approach or a decision-point approach. With a data-driven approach, researchers can automate processes along the R&D pipeline by linking actions using workflow configurations. This creates a series of data-driven criteria and allows samples and their associated data to move to the next assay in the chain. Alternatively, a decision-driven approach gives more control to users, allowing them to determine which steps are needed based on variable conditions. Either approach gives organisations the flexibility they need to build complete workflows.

Pharmaceutical workflow-specific applications provide a set of best practice configurations and industry-standard templates that work on top of data management solutions such as laboratory information systems (LIMS), ELN and scientific data management systems (SDMS). These can help to standardise individual steps across a workflow for small molecule discovery, genomics, biobanking and pharmaceutical development. In addition, integrating accessible products and apps into a platform gives organisations full access to data across the R&D pipeline, resulting in an open and stable

next generation ecosystem.

When customising workflows, important decisions must be made around which users will have access to systems and data. Using cloud-based solutions, there are essentially no limits to the amount of data that can be stored or the number of individuals who can use the platform. When sharing information with other users, laboratories or software partners, full project-level or specific data-level visibility can be set depending on the needs of each user.

What kinds of data can be accessed using a system like the Platform for Science and how can certain data types help with organisation, sharing and decision-making?

Pharmaceutical and biopharmaceutical workflows involve the generation and use of a wide range of structured, unstructured and reference data. Data management platforms really come into their own by integrating all these types of data into a single system. ELNs, for example, result in the creation of unstructured data, which can make finding specific information time-consuming and inefficient. With an integrated platform, this data can be easily associated with structured data, enabling searching and mining of both data types. Structured data supports further workflow analysis, allowing users to track and trend assay results, or compare findings to reference information.

Since all data in a comprehensive data

management system can be mined and cross-referenced with other information across that workflow, these systems allow users to quickly join the dots between different data sources, improving decision-making capabilities. Any structured data such as text, analytical run sequences and data files can be easily searched, accessed and mined for further analysis and trending. In this way, the latest platforms are encouraging innovation and driving productivity. Integrating instrument-driven processes with focused apps, automated sample tools and equipment monitoring solutions allows users to maintain control while also gathering insight and intelligence through end-to-end workflow visibility.

Moreover, when it comes to accessing and sharing this data, cloud-based systems make data retrieval significantly easier. By helping users to quickly exchange files and share large data sets in the cloud, cloud-based data sharing can strengthen collaboration, whether that's within an organisation or with external partners. Sharing data in this manner can shorten the time between research phases since upstream and downstream users have real-time access to data.

What benefits do cloud-based services provide in comparison to on-site systems?

The cloud supports an R&D ecosystem that is open to everyone. Cloud-based systems offer enhanced performance and stability, and enable full scalability

as an organisation grows. Their flexible and extensible design supports easy changes in process structure to keep pace with evolving workflows. Moreover, by eliminating the costs associated with maintaining hardware and performing system upgrades, cloud-based solutions are also a more affordable solution than on-site systems.

Whether cloud or on-site platforms are used, major upgrades can be scheduled on a regular basis, typically every 12–18 months. Smaller modular upgrades can be scheduled as needed. However, a benefit of cloud-based services is the delivery of upgrades by the service provider, requiring significantly less investment of internal resources. Some solutions, such as Platform for Science, include system validation and Health Insurance Portability and Accountability Act (HIPAA) compliance with upgrades, saving time in comparison to on-site upgrades, which typically require manual validation.

Security features for on-site systems must generally be developed and implemented in-house. These must include appropriate measures to identify and mitigate risks in each facility, as well as complying with regulations across all servers and sharing functionalities. In contrast, many cloud service providers also have security functionality built in. Platforms such as Amazon Web Services include secure VPN access, firewalls, data backup and recovery, all of which are handled with encryption by Amazon. These solutions significantly reduce the burden on individual organisations. 

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Beyond this we’ve also seen huge innovations in terms of process improvements – advances in flow chemistry, AI, 3D dosage printing and continuous manufacturing are pushing the manufacturing



Orhan Caglayan
Brand Director
CPhI Worldwide

sector forward at a rapid rate. Innovation in the active pharmaceutical ingredient (API) R&D arena has seen the development of several promising stereoselective catalytic platforms which promise to simplify API production in the future. Strategic approaches to API and finished dosage form (FDF) manufacturing are also changing, exemplified by the recent acquisition of Halo Pharma by Cambrex which sees the company acquiring capabilities to manufacture drugs on an end-to-end basis.

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Highlights of this year's event

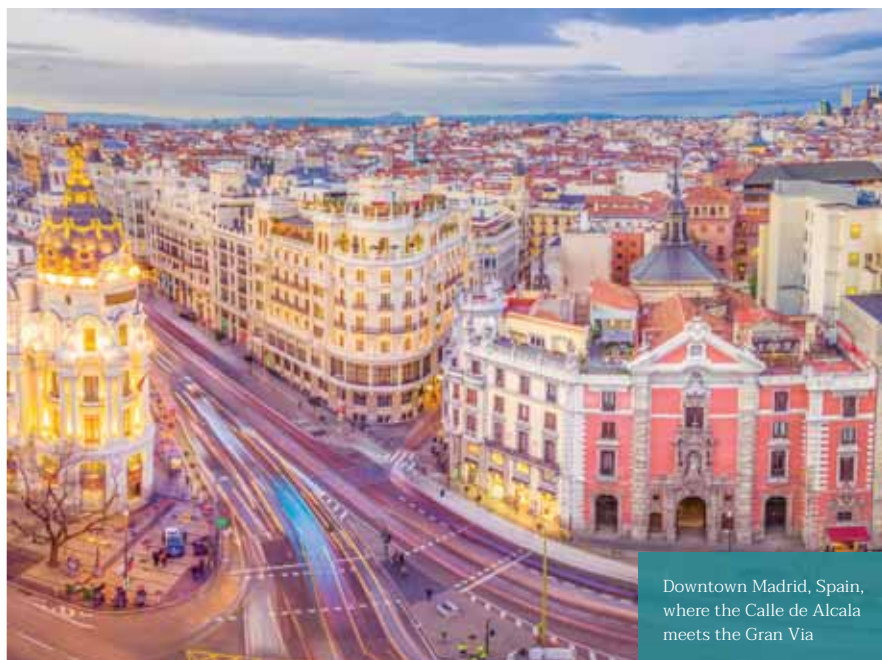
After last year's success, CPhI Worldwide will return on the 9-11 October 2018, at IFEMA, Feria de Madrid, Spain. The forum will attract pharmaceutical executives from all over the world come together for three days of collaboration, information dissemination and discussions that will shape the future of the industry. Building on last year, which saw a record 45,000 senior pharma professionals in attendance, CPhI Worldwide 2018 will host more than 2,500 exhibitors in 20 easy-to-find zones covering the entire supply chain – from ingredients, APIs, excipients, to contract services, packaging, machinery and more.

CPhI's practical one-to-one matchmaking programme, Live Pharma Connect, allows delegates to connect with exhibitors online before the event, and facilitates meetings during their visit to ensure key connections can be established. The easy-to-use system is supported by an automatic matchmaking function, eliminating the need to manually search databases to find the right business connections.

Co-located events

Away from the pharmaceutical ingredients hall, attendees will also have access to co-located events, allowing them to easily locate exhibitors who are ready to meet their business needs:

ICSE connects the pharmaceutical community with contract service providers – with representatives from clinical trials services, logistics providers, data management, Contract Research



Downtown Madrid, Spain, where the Calle de Alcalá meets the Gran Vía

Organisation (CROs) and contract development and manufacturing organisations (CDMOs). Jim Miller, former President of Pharm Source, will present on the outlook of CDMOs and consider the “what ifs” the industry faces over the next five years.

InnoPack allows buyers to investigate the latest innovations in pharma packaging solutions, including anti-tempering devices, drug-stable barrier solutions and single dose applicator systems. An indispensable workshop, run by Victor Bell, president of Environmental Packaging International (EPI) – global environmental packaging

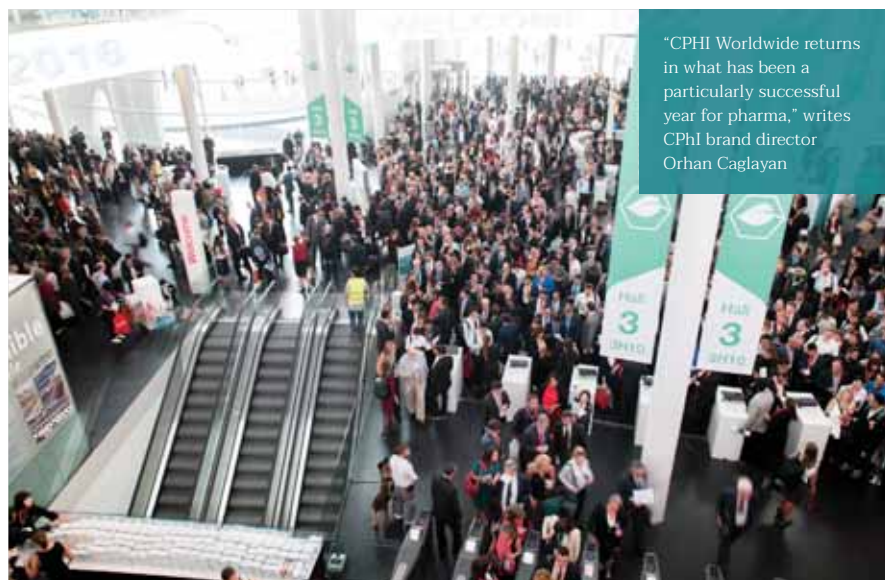
and product stewardship consultants, will discuss today's common packaging goals and how companies are taking actions to meet them – with a particular focus on overcoming the sustainability crisis.

P-MEC Europe features international exhibitors and manufacturers from pharmaceutical equipment companies focused on instrumental analysis, measuring and testing technologies, materials testing, laboratory and quality control.

Finished Dosage Formulation (FDF) brings together every aspect of the finished dosage supply chain, from Big Pharma and CMO to in / out licensing and dossier specialists. A panel discussion around ‘Creating a Sustainable Market’ will see industry thought-leaders come together to examine how the world's market is predicted to grow over the next decade. Meanwhile, presentations on the rise of biosimilars and next-in-class biologics by Uwe Gudat from Fresenius Kabi, and Roman Ivanov from BIOCAID will decipher the rules, regulations and barriers surrounding these increasingly valuable products.

Introducing... bioLIVE

In a year that has seen rapid advancements in the biologics field, UBM will host pioneers from the bio-industry – including top industry execs, R&D's innovative thinkers and bio-service providers – at a new event adjacent to CPhI Worldwide, **bioLIVE**. ▶



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CPhI Worldwide | Hall H3, Stand 3H35

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Industry thought-leaders will exhibit their most ground-breaking ideas and technologies, ready to grow partnerships in the most efficient way.

Focused on examining the intersections between business and biotech, **bioLIVE** will also host special sessions on the potential roles of AI, the emergence of cell and gene therapies, and the bioprocessing and biomanufacturing innovations that are shaping the industry. Of particular interest, we will welcome representatives from the National Institute for Bioprocessing Research and Training (NIBRT), who will discuss tackling the work force shortage – a challenge which presents significant hurdles to innovation in the bio-industry.

Eric Langer, President and Managing Partner of Bioplan Associates looked forward to the event, saying, “There is great potential in bringing the bio community together – running at the same time as CPhI Worldwide. The launch of **bioLIVE** will help accelerate the development of the bio supply chain, improve knowledge exchange, and create a more collaborative bio/pharma environment.”

Beyond the exhibitions

Beyond the exhibitions, delegates will have access to the latest pharma news in the media gallery. A series of Pharma Insight Briefings will provide a go-to space for pharmaceutical professionals looking to

explore emerging therapeutic areas and new business opportunities. In these in-depth, high value seminars, unbiased information on trends, industry developments, and the latest regulatory insights will be shared – encouraging attendees to develop strategies that will grow their business. Key insights include:

Addressing an unmet need: a special session on How pharmaceutical industry professionals can extract clues from data routinely collected on products and processes will be presented by Mike Tobyn of Bristol-Meyers Squibb.

Quality by Design: A presentation by Amina Faham of the International Pharmaceutical Excipients Council will discuss how strategic drug design can save time and money in the production of safe and effective consumer drugs.

The presentation on Brexit ‘The wider implications for the pharmaceutical sector’ will provide insights into how the European pharmaceutical market may change after the UK’s exit from the European union.

Representatives from IQVIA will present an exciting session on ‘The digital future, and what this means for pharma’.

Meanwhile, a snap-shot of the most interesting, innovative products coming to the market can be found in the Innovation Gallery. For a more in-depth look, register for an Innovation Tour, where the CPhI exhibition floor will be explained with inside information on API selection and successful generic formulation development.

A Country Pavilion Roundtable (Tuesday, 9th October) will provide



Primary Packaging Solutions

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SciLabware Limited, a company of DWK Life Sciences, is one of the world's leading manufacturers of **high quality glass vials, dropper assemblies and plastic bottles**, providing primary packaging solutions to diagnostic and pharmaceutical industries across the globe.

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- Custom packaging including labelling, printing and flow wrapping
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Stand 4A60  Visit our stand to find out more **9th - 11th October 2018** Feria de Madrid, Spain



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Email us with your questions enquiries@scilabware.com

Visit SciLabware at CPhI

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Working closely with our customers, our team is dedicated to developing and delivering a packaging solution tailored for your project. We provide our customers quality solutions, meeting their highest demands with our expertise and broad WHEATON® product portfolio; including ampoules, dropper pipettes and assemblies, glass and plastic bottles and a comprehensive range of vials and closure systems.

Our focus is to design and develop complete solutions to the daily challenges in life science, personal care, diagnostics and pharmaceutical packaging markets. Our flexible approach to every project means our customers benefit from a single source supply partner with exceptional customer service.



Nemera is on show at CPhI

Nemera always puts patients first, designing, developing and manufacturing drug delivery devices for the pharmaceutical, biotechnology and generics industries.

Nemera's services and products cover several key delivery routes:

- Ophthalmic (multidose eye droppers for preservative-free formulations)
- Nasal, Buccal, Auricular (pumps, valves and actuators for sprays)
- Parenteral (auto-injectors, pens, safety devices & implanters)
- Dermal and transdermal (airless & atmospheric dispensers)
- Inhalation (pMDIs, DPIs)



Nemera provides the most comprehensive range of devices in the industry, including off-the-shelf innovative systems, customised design development and contract manufacturing.

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SHOW PREVIEW

attendees with the opportunity to network and discuss issues surrounding import and export strategy, regulation, industry growth, new markets and the challenges faced by the pharmaceutical market across the globe. The half-day round tables will be chaired by UBM representatives and will be followed by a press briefing and networking opportunities – making this an invaluable opportunity to learn about and integrate in to target markets.

The CPhI's Women in Leadership Forum (Wednesday, 10th October) will return for the fifth year, in what has been described by delegates as a "wonderful opportunity to think outside of the box, in an industry dominated by men". Serving as an exceptional networking opportunity, the forum allows women to share their experiences, expertise and leadership techniques. For the first time, men will also be welcomed to join their female colleagues at this event to facilitate conversation around how men and women can work together to diversify pharma.

Additionally, CPhI will this year play host to the Big Data & Machine Learning Summit – Europe (Wednesday, 10 October) in collaboration with The Innovation Enterprise. Covering key topics such as the role of big data in the supply chain and analytics in drug development and discovery, this conference will bring together the most forward-thinking researchers and data scientists to discuss their latest findings.



Beyond the exhibitions, delegates will have access to the latest pharma news in the media gallery and elsewhere

Awarding Excellence

Following the success of last year's awards, a greatly expanded CPhI Pharma Awards Gala Dinner (Tuesday, 9 October) will take place in a glitzy ceremony at the Eurostar Madrid Tower, with 500 influential pharma guests expected. Among the most famed accolades in the pharma industry, former winners of the CPhI Awards feature a 'Who's who' of pharma executives. A total of 17 commendations will be awarded this year to celebrate the innovation and skill shown

in the pharma industry today with many applications are expected, after more than 200 awards last year.

Stay connected on site

Prospective attendees of CPhI Worldwide are invited to explore the event planning tools available online for a smoother experience. Remember to download the CPhI Worldwide App – which provides exhibitors and attendees with a timetable of the day's activities, a list of exhibitors ▶

The Puerta del Sol square is the main public space in Madrid



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CPhIworldwide Stand No: 3G76

Providing unique endotoxin detection reagents for every user and every method

Long recognised as a world-renowned supplier of high purity chemicals, FUJIFILM Wako Chemicals U.S.A. Corporation proudly introduces its new line of PYROSTAR™ ES-F reagents, instrumentation and consumables for the specific determination of bacterial endotoxin. This line represents the culmination of more than 30 years of research and development dedicated to providing customers with endotoxin-specific products for every user and every method.

FUJIFILM Wako invites you to visit the company at CPhI Worldwide, Hall H3, Stand 3H35, to learn more about its products and discover how FUJIFILM can provide solutions to support all of your endotoxin testing needs.

PYROSTAR™ ES-F

The PYROSTAR™ ES-F series of reagents represents a uniquely endotoxin-specific line of Limulus Amebocyte Lysate products, which are formulated to be used qualitatively as a Gel-Clot reagent or quantitatively as a Kinetic-Turbidimetric reagent without the worry of interference from beta glucans. All lysates are matched with control standard endotoxin.

Limulus Color KY

The Limulus Color KY series includes both multi-test and a single-test configurations, each designed for time-based chromogenic

analysis, using a synthetic substrate which produces a yellow colour and can specifically detect endotoxin with the highest sensitivity available in the market today.

Toxinometer® Measurement System

The Toxinometer® Measurement System is a computer-driven kinetic incubating tube reader with fully integrated and CFR compliant software, that is extremely user-friendly and easily expandable. Depending on the number of samples to be processed, the state of the art expansion modules can be connected to allow for endotoxin testing in a wide range of fields and sample quantities.

Endotoxin Testing Accessories and Specialty Kits

Includes FUJIFILM Wako's premier line of endotoxin-free pipette tips, test

tubes, caps and lysate reagent water.

In addition, FUJIFILM Wako has developed an endotoxin-free Extracting Solution for use on medical devices and containing human serum albumin that is capable of extracting endotoxins which cannot be extracted in water or saline solution. They also provide the Limulus PS Single Test kit that incorporates an affinity resin suspension designed to overcome product interference by adsorbing potential endotoxin in samples while washing away the inhibitory components.

FUJIFILM
Value from Innovation

CPhIworldwide Hall H3 Stand 3H35



CPhI 2018 is expected to build on last year's event, which attracted a record 45,000 senior pharma industry professionals

and their hall location. Meanwhile, CPhI Online provides pharma news to help keep up-to-date on recent trends in preparation for the conference.

CPhI and bioLIVE Annual Report

Reflecting CPhI's work to provide opportunities to learn about new trends, business insights and prospects, the eagerly anticipated CPhI Annual Report will launch its sixth edition following this year's CPhI worldwide event. This highly-regarded

report will include a collection of essays from industry experts on the hottest topics and most pressing issues.

As always, the report will include the results of this year's CPhI Global Pharma Index, which this year will include questions on the up-and-coming bio-industry. Attendees are encouraged to submit their answers to the survey here (<https://www.surveymonkey.co.uk/r/M6ZJJSW>) before the event to enable CPhI to provide the most accurate and beneficial information in the report.

Finally, we are striving to encourage our partners to follow corporate social responsibility practices, and this year our official charity partner is the International Medical Corps UK. The International Medical Corp delivers life saving healthcare in emergencies for people affected by disaster or conflict. They work around the clock, not only to rebuild lives and communities in some of the most dangerous places on earth, but are determined to pass on essential skills to local hands. A number of charity sponsorship options are available, with added promotions at the event, and delegates are also encouraged to consider how they can best use their skills by offering in-kind products or services to benefit Global Angels. To learn more about our charity packages, please visit <https://www.cphi.com/charity>.

Hosted in the landscape of one of Europe's burgeoning biotech and pharma hubs, CPhI Worldwide promises to be an unmissable opportunity to discover the latest and most innovative advancements, catch up with old contacts and form vital new partnerships that will push the industry to the next level. ■



Host city Madrid, with its Gran Via Street, offers a wealth of attractions to visitors



Register online for
CPhI Worldwide 2018 at:
www.cphi.com/europe

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and innovation from across the
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Coming up in the
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ISSUE 05 OCT 2018

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Advances in automated performance verification for UV / VIS spectrophotometers

This webinar, supported by Mettler-Toledo GmbH, Switzerland, focuses on the latest developments in automated performance verification for UV / VIS spectrophotometers. Taking place on 17 October 2018 at 15.30 BST, webinar delegates will be updated on the benefits of automated performance verification plus a range of other topics.



17 OCTOBER 2018



15:30 BST

KEYNOTE SPEAKER:



DR HANS-JOACHIM MUHR
Head of Strategic Product Group UV / VIS, Mettler-Toledo GmbH, Switzerland

Dr Hans-Joachim Muhr has a PhD in Chemistry and an Executive MBA. He has 15 years' experience in project innovation management, global sales and marketing for titration automation products. He also has six years' executive management responsibility in analytical instrument businesses (UV / VIS, Thermal Values).

IN ASSOCIATION WITH:



REGULATED environments require the regular performance verification or qualification of UV / VIS spectrophotometers. Instrument performance is the main factor directly affecting the accuracy and repeatability of measurements. So, it is important that this is regularly monitored regularly, and that documentary evidence is provided. Optical performance verification is conducted to the widely accepted guidelines described in the U.S. and EU Pharmacopeias. The recommended tests include: the check of photometric accuracy and repeatability, wavelength accuracy and repeatability, instrument resolution as well as stray light measurement.

Since the procedure for comprehensive performance verification is intricate and time consuming, there are great benefits of integrating it into the analytical workflow and having it automatically executed.

The first section of this webinar will assess the positive impact of automation on workflow efficiency,

and security in optical performance verification, of UV / VIS spectrophotometers with certified liquid reference materials assessed against manual execution. It will be shown that automatic optical performance verification, which is the major part of the qualification of UV / VIS spectrophotometer, can comply to data integrity requirements.

Stray light, or stray radiant energy, is a common confounding factor in spectrophotometric measurements. It is defined as light from a source other than that of the instrument's, and significantly affects linearity, especially at higher analyte concentration or absorbance respectively.


In the second section of this webinar, the impact of stray light on result integrity is presented, and methods for measuring stray light, according to the current and previous versions of the USP are presented and assessed.

The third and final section of the webinar discusses the importance of trained users who use a qualified

UV / VIS spectrophotometer in an analytical laboratory. Correctly trained, experienced users make fewer errors and avoid expensive follow up costs. Application-relevant, practical tips and hints will be presented, which help to avoid measurement errors in routine use.

The keynote speaker will be Dr Hans-Joachim Muhr, Head of Strategic Product Group UV / VIS, Mettler-Toledo GmbH, Switzerland.

Attend this webinar to learn:

- Benefits of automated performance verification
- Positive aspects of using certified liquid reference materials
- Data integrity compliance in optical instrument qualification
- The impact of stray light on measurement performance and methods to determine it accurately
- How to avoid measurement errors in routine use of a spectrophotometer. 

REGISTER NOW

europeanpharmaceuticalreview.com/webinars

EVENTS DIARY

Keeping you up to date with forthcoming events in the industry



september

october

november

20 Thermo Fisher Scientific Knowledge Culture Workshops

Date:
20 September 2018
Location:
Cramlington, UK

09 CPhI Worldwide

Date:
9-11 October 2018
Location:
Madrid, Spain

04 ISPE Annual Meeting & Expo

Date:
4-7 November 2018
Location:
Philadelphia, United States

09 bioLIVE

Date:
9-11 October 2018
Location:
Madrid, Spain

04 APPS PharmSci 360



Date:
4-7 November 2018
Location:
Washington DC, United States

23 Medicine Quality & Public Health Conference



Date:
23-28 September 2018
Location:
Keble College, UK

15 PDA Pharmaceutical Microbiology Conference

Date:
15-16 October 2018
Location:
Berlin, Germany

21 SciX 2018: The Great Scientific Exchange

Date:
21-26 October 2018
Location:
Atlanta, United States

06 PDA Outsourcing & Supply Chain – A 360° View

Date:
6-7 November 2018
Location:
Seville, Spain

26 BPSA European Summit

Date:
26-28 September 2018
Location:
Barcelona, Spain

31 Lab Innovations 2018

Date:
31 Oct 2018-1 Nov 2018
Location:
Birmingham, UK

20 PharmaLab 2018

Date:
20-21 November 2018
Location:
Düsseldorf/Neuss, Germany

PDA Europe Conference, Exhibition, Education

The Parenteral Drug Association presents:

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Register by
26 August 2018
and SAVE!

27-28 November

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The Human Data Science Company™
at **iqvia.com/success**