Analytical solutions and challenges for medicines manufacturing towards Industry 4.0

In February, KTN brought together members of the Medicines Manufacturing Challenge Community (MMCC) to discuss innovations that can help tackle data and analytics challenges. Delegates heard about exciting advances such as weighing molecules with light, virus laser detection, and computer-aided biology. Examples came from work on both small and large molecules and explored what could be learned from each. The meeting was organised jointly with the Centre for Process Innovation (CPI) and held at its National Biologics Manufacturing Centre in Darlington. The MMCC initiative is designed to develop the medicines manufacturing community - both by stimulating the uptake of innovations developed with support from the Industrial Strategy Challenge Fund, and by supporting consortium-building.

Key Points

- Analytics are becoming a barrier to advanced biopharma development and manufacturing.
- Process analytical technologies need to advance, so technology gaps and improvements should be identified.
- The biopharma industry needs to develop in-situ monitoring in real time, to realise the goal of an integrated, highly automated end-to-end process.
- AI will be a valuable tool, but industry must get the fundamentals of data gathering right.
- Projects should consider cyber security issues early on, where cloud-based applications are being used.
- There is a need for standards to drive innovation and keep the UK at the forefront of medicines manufacturing.
- The UK BioIndustry Association is developing a roadmap for analytics development, with a view to request a grant funding call for it.

Table of Contents

Challenges on the road to Industry 4.0

The biopharmaceutical sector is a prime candidate for the adoption of Industry 4.0 – the vision is of a fully automated plant, making medicines to exacting standards consistently. There's no shortage of data: as one of the most regulated industries on the planet, every step is scrutinised and the data analysed and reported on. But the industry has some obstacles to overcome to make that factory of the future a reality.

Thanks to advances in sensor and data analysis technologies, it has access to more data, and more complex data sets than ever before. However, scientists are often unable to acquire knowledge directly from measurements of a pharmaceutical molecule and instead have to make inferential measurements – often product, by product. Ultimately that affects the reproducibility of experiments and therapies, and drives a need for new sensors and analytics.

Allan Watkinson, Director of Biopharmaceutical Development at Covance, says analytics are becoming a barrier to advanced biopharma development and manufacturing. Other new medicines – the potentially transformative cell and gene therapies, are amongst the most complex drugs ever developed. Their dynamic nature makes it a challenge to manufacture them consistently and calls for new analytical techniques.

An initiative set up by the BioIndustry Association is trying to address that hurdle by exploring ideas to develop new analytics tools and techniques. It envisages a funding platform that could provide backing for promising ideas. Another industry challenge is data collection and management. There now exist many cloud-based platforms for data storage, and a plethora of machine learning tools to build process models. Matthew McEwan, one of the founders of Perceptive Engineering, explored the promise of AI in the biopharma sector. He stressed using AI was no different to any other modelling activity: "we have to attend to the fundamentals. And that is - are we collecting the right data? Is it sufficiently rich? Have I got the right model? And am I sufficiently validating that." And he warned firms to think carefully – and early on - about the cyber security aspects of cloud solutions.

Partnerships and community building to tackle industry challenges

The intention of the Medicines Manufacturing Challenge Community (MMCC) is to connect industry, and research and technology organisations beyond those who've already benefitted from the £146 million that has been invested through the Industrial Strategy Challenge Fund. As well as organising community building events, Marcel Kuiper Knowledge Transfer Manager for Health, says KTN is establishing a database of those involved in medicines manufacturing – now comprising 480 individuals from 235 organisations; supporting consortium building for grant applications; and assisting with those grant applications.

Current funding opportunities in the sector include a new initiative – Innovation Scholars Secondments for biomedical sciences, running initially over 3 calls in 2020. A grant goes to the organisation that seconds their employee, to enable it to backfill that role. While one of the paired organisations must be a company, secondments can be full or part time, and involve staff at junior or senior levels.

Kuiper also highlighted the Knowledge Transfer Partnership. This is a graduate recruitment programme running throughout the year, whereby a company partners with a university (or other research organisation) to employ a graduate on a defined project for which they'd benefit from new skills and the latest academic thinking.

Separately, industry is leading on the development of a Community for Analytical Measurement Science, for both research and training. Julian Braybrook representing CAMS, said the initiative aims to address fundamental problems and ensure analytical scientists have the skills needed by industry. New academic posts are being created this year and next; while E-learning modules will be rolled out in 2020, covering core laboratory skills both in chemistry and the biosciences. A range of webinars is also planned.

Allan Watkinson explored issues the industry faces:
- the sums required for cell therapy treatments are unsustainable;
- the manufacturing of ATMPs is much more complex than for small molecules; and
- industry is still trying to get to grips with how it can harness digitalisation and Industry 4.0.
- there are skills shortages to address if the UK is to be a major centre for excellence for advanced therapies.

“analytics are becoming a barrier to advanced biopharma development and manufacturing”

Expensive cell and gene therapies are not only complex to engineer but often have a short shelf-life, so industry wants to see the vision of real-time release testing become more of a reality. “It's pointless having something which you need to release immediately and then have to do 21 days plus for sterility testing,” suggests Watkinson. He doesn’t see regulators abandoning QC release testing entirely, but ideas for more autonomous manufacturing could reduce the need for it.

One of the technology gaps the industry has to address is analytics, which are becoming a barrier to advanced biopharma development and manufacturing. Process Analytical Technologies (PAT) have not advanced as far as the industry would have wanted. A roadmap towards the ideal manufacturing process of the future requires PAT in order to implement medicines manufacturing in a more “cost-effective process knowledge manner that evolves into adaptive manufacture and finally Industry 4.0 – where we’ve got almost autonomous manufacture,” suggests Watkinson. That drive, towards flexible and smaller-volume manufacturing – and potentially personalised medicines – highlights the importance of *in situ* measurement for process understanding and for monitoring and control, says Alison Nordon, at Strathclyde University. “If we want to be able to have a fully Integrated end to end process…. we have to have *in situ* measurements in real time to allow automated control.” She adds that “a combination of *in situ* measurements, software sensors and the process model - the digital twin model simulations - are all going to be important for Pharma 4.0.”

A cross-industry workshop run by the UK BioIndustry Association (BIA) has explored ideas to develop future analytics, and tried to identify gaps in the current armoury. It concluded that the key to moving forward with analytics is to “really understand what your CQAs [critical quality attributes] are, then you can say what aspects of existing technologies need to be improved – whether that’s cost, speed or sensitivity”, and where new analytics technologies need to be developed. There is, Watkinson added, a need for “solid standards”.

The workshop also explored setting up a network - or virtual hub – to allow developers to come together to generate ideas for the future, and a joint industry and government funding platform that would assess proposals emerging from it.

Managing Analytical Data

Key points

- Data has to be structured and made accessible, if it is to be analysed.
- AI will be a valuable tool, but industry must get the fundamentals of data gathering right.
- Projects should consider cyber security issues early on, where cloud-based applications are being used.
- Companies should think about how a machine learning tool will be supported in future

Matthew McEwan, who leads the Applications Engineering Team for formulated products at Perceptive Engineering, used his experience across different industry sectors to try to sift out the reality from the hype when it comes to AI and modelling.

What is machine learning? It's the automation of building a model, says McEwan. Just as in manually building a model, “you need to collect high-quality, rich training data to build your model; you need to identify and parameterise it with training data that has an appropriate structure; and you need to validate that model sufficiently so that you trust that it works.” But, he explains “you also need to tell the algorithm a bit about what the world is like”. This process is called feature engineering, but it’s a rate-limiting step because an expert needs to examine the data, to explore what’s important – for example, which part of the process is sensitive to which parameters. Deep learning seeks to eliminate this stage by giving the algorithm enough examples for it to figure out the important features for itself. He gave an example of shampoo manufacturing process, for which he used data from about 40-50 batches to construct a model.

Applying deep learning would, he estimates, have required data from 800-1000 batches. And while the technology is “massively exciting …. it's very, very hard, at least in the process analytic space that we're working in to ever have enough data to be able to apply that sort of technique.”

The advent of cloud computing and storage is enabling us to archive and historise huge amounts of data, but McEwan cautions that firms need to think about cyber security very early on. “If you're saying we built this brilliant application, how do we make it cyber secure? If you're asking that question at that stage, you have just bought yourself a recipe for a big, long overrun.” However, robust and resilient measures for cyber security have to be balanced with access, so as to avoid what he calls the “infinity bucket” – a black hole for data. “It’s about politics …and its about control. But we, as a modelling community, need to sell the benefits of what we're trying to do, why we need access to this data. Otherwise, why did you bother in the first place?”

“in terms of being able to do machine learning, life has never been more democratic”

A related point is the landscape for cloud implementations of machine learning, with hundreds of providers of various components of a technology stack. “In terms of being able to do machine learning, life has never been more democratic. There have never been more tools out there that are accessible to more people than what we have at the moment.” Set against that are questions of the future supportability of all the different platforms, all constantly being updated. What’s required are some standards to ensure interoperability between all the different technology stacks.

“we have not really mined the best of industry 3.0, before we even start on 4.0”

Machine learning is a tool – but there are many others, says McEwan. “Our model structures need to scale with the style of data that we've got. And if you've not got much data, don't try and throw a complicated model structure at it, because it will likely end in tears.” He argues that “certainly in the

pharma space, I can see that we have not really mined the best of industry 3.0, before we even start on 4.0".

The industry is generating vast amounts of data, and while there is no shortage of storage options, that data has to be structured and made accessible so it can be analysed.

Opvia and Synthace have both developed platforms for structuring and analysing data. "Five to ten years ago it was super-easy to do everything in spreadsheets …... But now you've got gigabytes of data, I'd argue Excel is no longer the right tool for the job, " suggests Opvia co-founder Will Moss. Having more data with increasingly disparate sources creates its own problems – not least, of reproducibility. It also requires new skills. Getting all the data together with the context (who ran the experiment and when, for example), in a clean final format "is not a data science problem, that's a data engineering problem," he asserts.

"now you've got gigabytes of data, I'd argue Excel is no longer the right tool for the job"

Moss argues that trying to adopt blanket new processes for data management across an organisation can be high risk. He suggests that the "best way to get people excited about the opportunities of data is to pick a really small area, probably somewhere where you're generating a lot of data and collaborate really closely with that team to show end to end value. So that team can then go from paper based processes to a properly fully digitally automated process."

Once people see it's worthwhile, he adds, it's then easier to take the next steps and roll it out across an organisation. Opvia, says Moss, will "allow you to figure out the process to go from the lab to a standardised and clean data set." The system provides both context and version control, "so as you work with that data, you can see what you've done with over time."

Synthace makes software to programme both lab and data automation. Markus Gershater, Chief Scientific Officer and co-founder describes their concept as "computer-aided biology". Synthace started life as a bioprocess optimisation company, very keen on Design of Experiments. But it discovered that doing linear modelling manually was "too tough, and trying to programme automation to do it was also tough." That's because the same DoE is usually not run twice. "So it means that all that effort you put into programming the automation is then wasted as you go on to the next iteration of your experiment," explains Gershater. So Synthace now develops software to help programme the automation so that it's flexible and can be repurposed. The data processing workflow is also modular and can be reconfigured as needed.

Alongside others, Marc-Olivier Baradez at the Cell and Gene Therapy Catapult used Synthace's Antha platform to capture and structure all its datasets, to allow analysis and model building as it tested a PAT strategy for lentiviral vector manufacture. The sheer complexity of the molecules means

that it is a huge challenge to produce them to a high level of consistency. “You need to understand what to measure; what it means in terms of the physiological and biological activity of the cells; and how to do these measurements in real time – either for process control, or in the context of Design of Experiments for process optimisation,” says Baradez. The team implemented real-time *in situ* Raman spectroscopy and measured viral titres in real time, both at 5 litre and 50 litre scale. It now has a wealth of data that it hopes will allow them to come up with the biological insights to improve the manufacturing process.

One of the challenges for the biologics industry is to identify drugs that are going to fail, earlier in the development process. Lewis Wharram, a development scientist at CPI, described the work he and colleagues had done on the BioStreamline project to develop decision making tools for monoclonal antibodies. Starting with 200 candidates, 50 antibodies were selected based on experimental data and then characterised by biochemical and biophysical methods. This provided information on the molecular features that would provide the best chance of developability success, as well as manufacturing platform fit and meeting storage stability requirements.

Process monitoring

Key points

- Academics and industry are developing new techniques to monitor and improve processes.
- A combination of *in situ* measurement, new sensors, and process modelling are all going to be important for Pharma 4.0.
- Exciting new sensor technologies are being invented to address challenges from quality control to understanding complex protein assembly.

Geoff Smith, Professor of Pharmaceutical Process Analytical Technology at De Montfort University is applying established electrical techniques to a new area of process analytics for freeze drying.

“you don't know if it's the process or the formulation [or both] that ultimately is stabilising the protein”

Complex APIs and biologics present stability challenges that have led to a growth in the use of freeze drying for final product formulation, as well as a demand for more effective freeze drying techniques. Smith showed how applying electrical impedance and dielectric spectroscopy techniques can allow industry to capture process information, that current process analytical techniques don’t. Freeze drying “is a complicated process, done on a very large scale. There's lots of heterogeneity within the system; there are issues around scale up and keeping the product within its performance criteria..... so there's a lot of effort to try and understand the process better.” At present “you don't know if it's the process or the formulation [or both] that ultimately is stabilising the protein,” he explains.

He described a small-scale system, using a micro-electrode array that can fit inside a standard freeze drying microscope. It’s been modified with the addition of an impedance spectrometer. The set-up, developed in partnership with Biopharma Process Systems and funded by Innovate UK, provides objective assessments of thermal processes – such as crystallisation, glass transition and collapse temperature – for small-scale formulation development. Having an optical system also means its possible to observe other behaviours, like crystallisation. Now the group is looking for funding to develop the system so it can handle multi-well measurements, thus delivering the first ever high-throughput screening tool for freeze-drying product and process development.

“We can measure almost everything you need to know within the freeze-drying process.”

The second approach is for process understanding. Through-vial Impedance Spectroscopy (TVIS) was also developed with Innovate UK funding. Electrodes are attached to individual vials, and these in turn are connected via thin wires to the TVIS spectrometer. While they’re looking at new methods of mounting the electrodes on the vials, Smith doubts the system will ever be wireless. The advantage of the technique, he says, is that direct measurements can be made in batch systems, rather than relying on modelling to predict (for example) drying rates and ice interface temperatures.

“We can measure almost everything you need to know within the freeze-drying process.” The benefit of this new process understanding would be that the industry would potentially get energy and efficiency savings.

Alison Nordon, in the Department of Pure and Applied Chemistry at Strathclyde University, applies optical spectroscopic techniques for *in situ* monitoring of a range of pharmacological processes - from the very initial stages of API synthesis through to production of the final dosage form. The aim of the two centres she works with (tackling process analytics and continuous manufacturing) is to apply developments in spectroscopic tools to both improve existing processes and to develop new ones. She gave two examples of work they’d carried out. In the first, near infrared (NIR) spectroscopy was used to monitor the blending of an API, where the mixing end point is usually based on experience. The team, at the Centre for

Process Analytics and Control Technology (CPACT), used NIR spectroscopy to produce mixing profiles of different active ingredients.

“data analysis and in-situ measurements go hand in hand to improve processes”

In parallel, they ran a data analysis project to establish a calibration-free endpoint detection method. This worked on the assumption that at the start of the mixing process “you've got a heterogeneous distribution of particles which are moving, and therefore if you measure spectra continuously, you'll get high variation. And then as you move towards the endpoint, you should reach a homogeneous distribution. So your spectral variation should be much lower – and that should be indicative of the endpoint,” explained Nordon. One of the researchers developed a moving window algorithm to assess spectral variation over time to determine when the mixing end point had been reached.

The researchers on the team deployed the research technique at GlaxoSmithKline, allowing the company to have continuous verification of their blending process. It led to an 80% reduction in blend time – saving both energy and costs at one of its manufacturing sites. Nordon stressed that data analysis and *in situ* measurements go hand in hand “to improve current processes, but also to look at new ones”.

Nordon also works on continuous manufacturing and advanced crystallisation at CMAC. Here *in situ* measurement is being used to develop process understanding, as well for monitoring and control purposes. “We're also using the data that we get to develop and validate some of the process models,” says Nordon. A big part of the research is focused on the development of a digital twin. Raman spectroscopy has been used to monitor the production of different polymorphic forms of molecules in real time. With a combination of Design of Experiments (DoE) and *in situ* measurements “we can understand how the different factors affect which polymorphic form we get for different types of molecules.”

The process monitoring work is also driving innovations in measurement techniques. CPACT has been working with the University of York to try to increase the sensitivity of low field NMR (nuclear magnetic resonance), using hyperpolarization methods (to alter the magnetic properties of materials). “We want to have methods that have got high molecular specificity but are also very sensitive so we can potentially look at some more online measurement of trace components, which our optical techniques often struggle with,” Nordon explains.

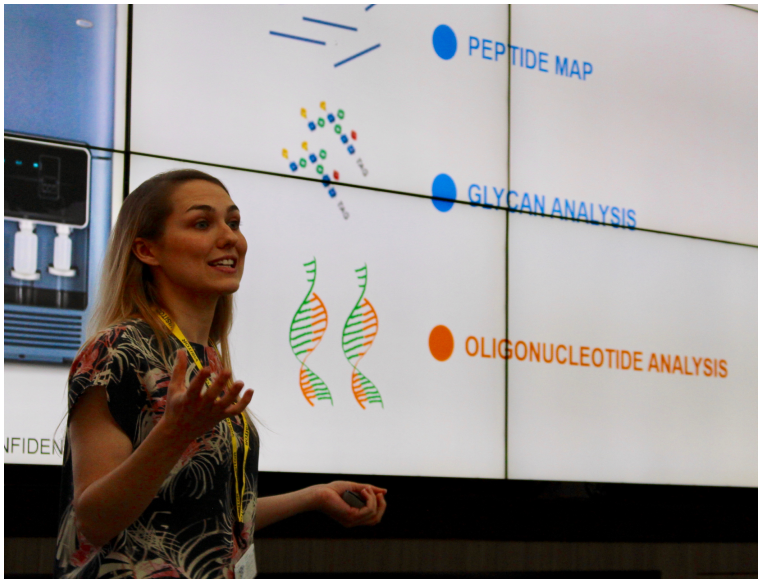
Chris Spencer, a scientist at AstraZeneca’s Cell Culture and Fermentation Science team contrasted the recent advances in mobile phone technology with the lack of progress in bioreactor technologies “which generally still have the same probes they did 20 years ago.” He has been looking at how to improve bioreactor systems and to integrate PAT. “Where we’d like to be is having a fully standalone 3-5 litre bioreactor system where we monitor all of

our key process parameters - essentially to have a system that largely runs itself." Any system would also need to be scalable. What's required are online (or at line) analytics and robust feedback to a bioreactor control system. "Where we are currently is nowhere near this and we've got a lot of problems to solve before we get anywhere near it".

On top of that, any system would have to be able to be integrated into systems from multiple vendors and be easily used by a range of scientists across the business. Spencer described the work he and colleagues did with University College London, to assess four commercially available systems that would potentially allow monitoring of key process parameters in bioreactor systems. No available system fully met their requirements - amply demonstrating the sort of gaps the industry hopes new funding can close. Work is underway to develop a bespoke Raman plate reader system.

In his presentation, Matthew McEwan alluded to the need to democratise sensor technology, to make it more widely available and less costly. Both Waters Corp and Microsaic have developed bench top mass spectrometer systems to help speed up decision making. Pira Ragulan,Technical Sales Specialist at Microsaic Systems, described the miniaturised mass spectrometer it has developed for bioprocessing applications. Early work with CPI has demonstrated that it's possible to detect metabolite profiles for different IgG cell cultures, as well as to identify favourable and unfavourable conditions in a bioreactor.

Heidi Gastall, Senior Applications Chemist at Waters, described a complementary system for use in process development and quality control, that's robust enough to be used by non-experts. Its use would enable biopharma researchers to make decisions without having to wait for results to come back from specialist labs. Gastall says analysis can be done on (for example) proteins down to the glycan level. The system also allows multiple attributes to be monitored at the same time.



Novel sensors and techniques

A new tool in the bioanalytics space is mass photometry – developed by a University of Oxford spin out, Refeyn. To develop its new approach to analysing molecules, Refeyn has exploited the idea that if light is shone on a single molecule, some of the light will be scattered. The amount of light scattered is reasonably directly correlated to the mass of the molecule. Chief Marketing Officer Matthias Langhorst explains that it's taken ten years of optimisation to develop an instrument, which can be thought of as "as a very, very high sensitivity interference reflection microscope." The breakthrough "was a way to selectively attenuate the reflected light, which in comparison to the light scattered by a single molecule is still massive. By attenuating that - without affecting our protein - we get a quantifiable signal."

The advantages over other existing technologies are that no labelling is required so the samples don't have to be modified, and the system is compatible with a wide range of buffers. It can be used in many biological systems including membrane proteins and DNA, for example. The technique provides information on all sub-populations in a sample – including anything that shouldn't be there. Application areas extend from quality control to understanding mechanisms of complex protein assembly.

John Hales from the Department of Biochemical Engineering at University College London introduced two analytical technologies that he says will have a role in characterising new biopharmaceutical products, in alleviating the burden on analytical labs and in the digital transformation. The first that they're pioneering is virus laser detection. The virus laser is made up of a scientific instrument and a bio recognition probe that can be used to find target biomolecules and also to generate a laser signal. To monitor a bioprocess, the virus laser would be connected at line between different stages of the bioprocess and used to make sensitive measurements of product or impurities in close to real time. So any problems could be detected and rectified immediately, rather than an entire batch of medicine having to be thrown away after testing at the end of the process - as happens now. Hales has funding through the EU's ATTRACT programme, to develop demonstrator units and probes.

The second technology being explored is Decay-associated chromatography. This is being used to make label-free measurements of the levels of protein directly in mixtures. Hales explains: "typically in chromatography, it's quite difficult to assess the identity or the purity of a protein within a peak, but using this technology, you can de-convolute the signal. He showed an example of how they'd used the technique to trace the elution profile of two different proteins, even when there was almost complete overlap of elution profiles. Hales thinks it would also work well to distinguish between empty and full adeno-associated virus (AAV) particles – and is looking for a partner who could provide samples.

Lauren Wilson, Senior Development Scientist at Allergan, described how her company is tackling the analytics challenges of working with adeno-associated viruses (AAVs) for gene therapy treatments. Allergan's UK R&D sites work on biologics – designing, developing and delivering drug substances for clinical trials. The fact that AAVs aren't associated with any human disease, and can facilitate long-term gene expression makes them desirable vectors for gene therapy. Interest is growing in a range of serotypes due to their targeted tissue specificities. "As these products are fairly novel, you can imagine generating a commercial manufacturing process and the associated analytics is not without its challenges," says Wilson. Different process analytical techniques are required throughout the production process. "We've got very good at measuring viral titre infectivity and some of the process and product residual testing. But what we do find more challenging is monitoring how our virus is packaged and also aggregation levels of AAV particles."

There are several issues with packaging: the virus particles don't package DNA very efficiently, and they can package DNA that is different to the trans gene – leading to a high level of heterogeneity. There are two choices of technique - Cryogenic Transmission Electron Microscopy (cryoTEM) and Analytical Ultracentrifugation (AUC). Both have challenges around the sample concentrations and purity that are required, and have to be outsourced which adds to cost and extends turn-around times.

The second challenge is that different AAV types have different propensities for aggregation. Available analytical methods of Dynamic Light Scattering (DLS) and Size Exclusion Chromatography (SEC) also have pros and cons. "We wanted a method by which we could visualise our viral particles throughout the process, to help us overcome these challenges."

The team's chosen route was a mini transmission electron microscope (miniTEM) from Vironova. The advantages, says Wilson, are that it can be used by a non-microscopist, and requires low sample volumes. Allergan is predominantly using it for assessments of aggregation, but it is also able to deduce whether virus particles are empty or full by staining the sample. Assuming empty particles are more susceptible to breakage, they become internally stained; whereas full particles remain intact. This provides a valuable screening tool, before sending samples for outside analysis via cryoTEM. They've used different staining techniques to enable assessment of aggregation and empty:full ratios, and compared results using the different techniques. She concludes that miniTEM has been a "great analytical tool", although challenges still remain to characterise viral particles.

Standards

Key points

- Standards are key to boosting innovation
- The MHRA is working to improve reproducibility, and on developing standards for biologics and ATMPs.
- Too few advanced analytical characterisation methods for biological molecules are PAT compatible.

Standards can lead to knowledge sharing, and innovation. They can help cut waste and costs, by minimising time spent on trial and error. They can also boost trade – both domestic and international.

“Standardisation is important. If you get it wrong, it can be a barrier. But if you get it right, there's lots of evidence that standards can improve productivity and performance,” says Julian Braybrook, Director of Measurement Science for the National Measurement Laboratory at LGC. “If you think about increasing the efficiency of your process - about the way you can standardise the process to take out the variables, all these elements form part of [improving] productivity performance.”

Indeed Gary Kemp, Principal Scientist at the MHRA, said that while the agency’s number one focus is to protect public health, supporting and enabling innovation are very high on its list of priorities. Kemp’s role at the MHRA is focused on the production of quality standards at the British Pharmacopoeia (BP).

The BP provides documentary and physical reference standards that are publicly available, and are used in over 100 countries. “The development of clear guidance and tests to support the introduction of new technology and processes avoids each organisation having to reinvent the wheel each time. So if we can set a minimum quality standard to meet for industry there's a clear regulatory hurdle there, which enables innovation from the sector.”

But while thousands of labs might use the same highly prescriptive method, there are issues of reproducibility. The BP is trying to get to grips with reproducibility issues in some of the methods it specifies. The first initiative centres on Quality by Design (QBD). “Can we apply the same concept to

analytical methods, as the method itself can be seen as a process?" One concept it's explored is that of an analytical target profile, which would "define the performance criteria of a method" as opposed to the rigid method parameters it currently specifies. That would be complemented by additional method information from its work on DoE.

Such an approach, he explains "not only ensures that the analytical methods in the standards are robust and fit for purpose," but also "facilitates the adoption of innovative analytical technologies, because the standard is performance-based and it's flexible."

A second area of work is in Biologics – both in terms of standards development, and engagement with industry and other international agencies. Here it's exploring: (i) performance standards that could define method performance in terms of accuracy and precision; and (ii) class-based standards. Rather than a standard applying to one particular product, it could be applied across a class of molecules – for example, monoclonal antibodies The MHRA hopes to have some recommendations towards the end of the year.

A second area involves the standardisation of advanced therapy medicinal products (ATMPs). This is at a much earlier stage of development. Asked how such complex therapies could be standardised, Kemp said it was early days but there was some thinking emerging on creating non-mandatory standards, and guidance documents. What was crucial, he stressed, was to maintain international harmonisation so as to avoid any unnecessary barriers.

Braybrook chairs the British Standards Institute Committee on Regenerative Medicines Products, and wants to know where the UK should be leading on standardisation in this sector. “We have a wealth of very high end analytical characterisation methods [that] allow us to build an understanding of our products.” However, most are not PAT suitable. Those that are suitable are “largely around biomass and they're largely about metabolites. So we’ve got a long way to go if we're thinking about transferring from the ‘what happened?’ to ‘how do we make it happen’ and ‘how do we predict what happens’.”

The US he said, has already identified its industry’s needs and challenges – and the UK had to do the same. Potential areas for work include raw materials and production equipment, through to analytics, testing and product quality. Some activities are underway in terms of documentary and physical standards.

Braybrook also described work underway at the National Measurement Laboratory (NML). Protein higher order structural analysis is one component of the regulatory requirements for the development and manufacturing of biopharmaceuticals, and while “there are a lot of methods available, there's no real guidance on which technique to use at any one time,” he explains. So the NML has been examining how to address that challenge. He presented two reference protocols using a high-end technique - hydrogen deuterium exchange mass spectrometry - as the benchmarking platform, “to induce control and characterisation into the structural changes.” In turn, that allows developers to monitor method validation, and look at sensitivity to structural changes.