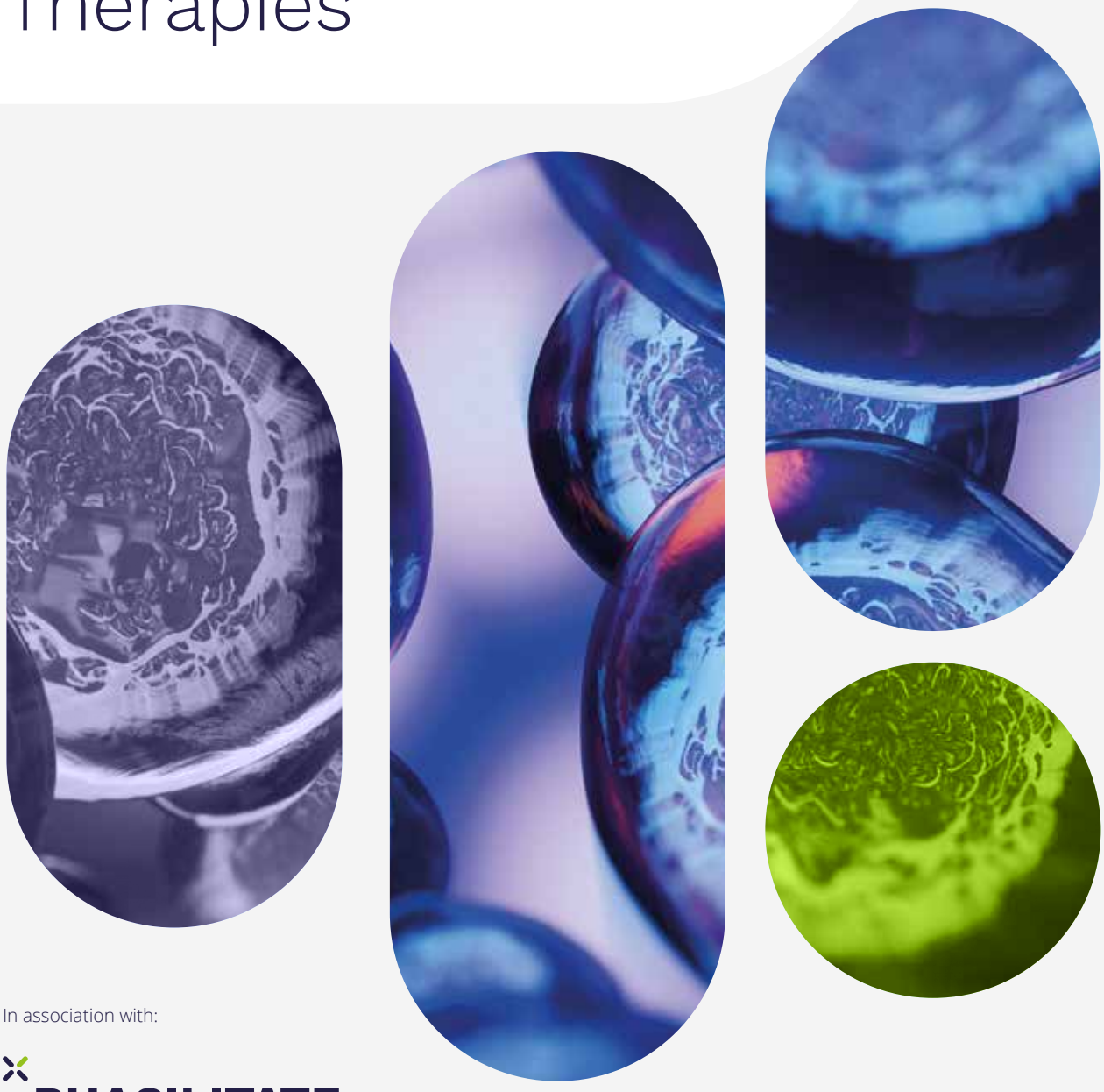
bio-techne®

The Role of Analytics in Reproducibility and Regulatory Approval of Cell and Gene Therapies



In association with:

PHACILITATE

Contents

Introduction

The potential of the cell and gene therapy industry is prohibited by the current costs and logistics of harvesting a patient's cells, processing them at a centralised location and delivering them back to the patient. To create change, both technology and manufacturing-model innovation are required. Analytics, real-time monitoring and data are going to be essential in reducing CoGS and improving access to and commercial viability of therapies.

At present, there is a serious lack of purpose-built bioprocessing technologies for cell and gene therapy manufacturing. Those that are available are mostly based on legacy MAbs technologies that have not changed in decades. For example, there is a huge need for more point-of-care technology that will allow the processing of autologous therapies at or near the hospital site. However, this kind of distributed-manufacturing network doesn't fit regulatory and licensing models.

There has been some promising regulatory innovation from regulatory stakeholders. In August 2021 the UK's MHRA set out a new framework for point of care manufacturing (POC), known as the 'Control Site' concept. The aim is to link this new regulatory framework to existing regulatory systems to provide reassurance that point-of-care products meet the same level of safety, quality and efficacy as conventional medical products. In practice, this means that a network of sites could be under one license rather than having to license each manufacturing site individually.

The FDA also published draft guidance 'Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products' in the first quarter of 2022 that also adresses multisite manufacturing and testing, with a particular focus on comparability.

Quality is also a significant barrier to delivering therapies via a distributed manufacturing network. The difficulty is in the time needed for quality control and QP release at the end of the manufacturing process, so alternative or additional control measures are required to provide assurance of product quality for supply. This is where real-time, remote monitoring sensors and analytics come into their own. If this level of remote control and transparency is achievable then this kind of distributed manufacturing model will be possible.

However, manufacturing analytics is something of an elephant in the room. While manufacturing process suitability and efficiency are now firmly front of mind and being addressed, the conversation around analytics, particularly in-line and real-time, is taking place in hushed tones.

Analytics deserves its time in the spotlight for a few reasons. First, is a recent string of highly publicised, late-stage review issues from the FDA that were mostly due to CMC-related causes. In particular, Iovance and Sarepta's cases were linked to potency assays; could these have been avoided with the effective application of analytics to better characterise the product through critical quality attributes (CQAs)?

Second, there were some very telling public comments made by Peter Marks, director of the Center for Biologics Evaluation and Research at the FDA, at the World Medical Innovation Forum in 2021. It is reasonable to derive that product characterisation is a huge priority for the FDA and without robust, mechanistic assays, approval will be out of reach.

> **"Pick something. Pick some quality of the cell. Pick something that you think might correlate and measure that," he said. "We'll take any offers that are reasonable."**

According to Marks, cell and gene therapy developers haven't always done a good job constructing tests early on that allow them to consistently measure their products as they move from early testing into larger clinical trials and, eventually, to the FDA.

> **"It sounds almost sing-songy," he added. "But many times developers get very excited about the fact that their product produces an important effect that they don't worry as much about reproducibly making that product."**

The FDA is considered to have the highest bar when it comes to regulatory requirements for assays and their guidelines: 'Potency Tests for Cellular and Gene Therapy Products' are now over a decade old, so what's preventing developers from designing mechanistically relevant assays?

This report examines the above question, focusing on:

- The identification and measurement of appropriate CQAs
- The value of fit for purpose analytics technologies
- What the future of CGT manufacturing analytics should look like

Chapter 1

Defining Your Critical Quality Attributes and What Needs to be Measured for Successful Regulatory Submissions

Can you measure too much?

The clue is in the name; CQAs are critical for the successful development of cell and gene therapies. A strong set of carefully selected CQAs can demonstrate safety, reproducibility, lot-to-lot consistency and, ultimately, pave the way to regulatory approval.

The overarching goal is to know your product inside out and as early as possible, but deciding exactly what to measure is a challenge. Can you measure too much and exactly how much is enough for regulatory submission and approval? The comments from Peter Marks above indicate that almost anything will be considered, but the important thing is that the CQAs must be mechanistically relevant, i.e. you must be able to demonstrate the mechanism of action in order to get regulatory approval. A good example is gene expression; the delivery of a gene is not enough, its expression is not enough, but how does it fold and how does it work in action? That's the level of characterisation needed.

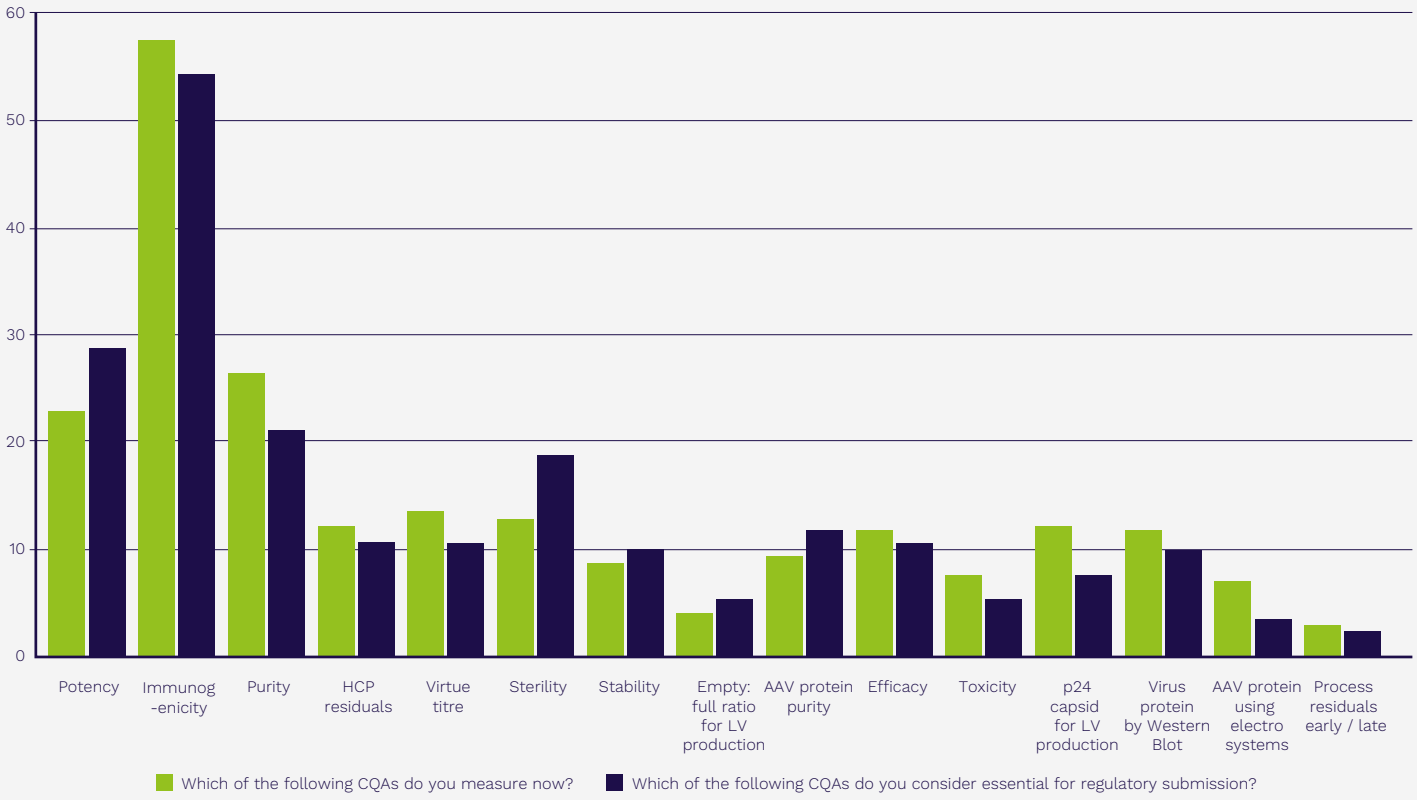
Understanding where any off-target activity might occur is central to building a picture of your therapy's mechanism of action, it can then be determined if and how this can be measured.

Issues relating to adequate CQA measurements, in particular potency assays, and analytics have been the underlying causes of a few high-profile setbacks for cell and gene therapies recently, for example:

- **Sarepta's SRP-9001:** the FDA requested further potency assays during a Type C meeting in 2020
- **Iovance's Lifileucel:** BLA filing was pushed back due to required potency assays to characterise Iovance's TIL therapy
- **Mesoblast's Ryoncil:** better characterisation of product CQAs were required to support clinical data, particularly in terms of comparability between lots

> **"We often don't know our mechanisms of action well enough or exactly what's giving the clinical readout. Is it on-target or off-target activity? An obvious example is the FDA rejection of Mesoblast's remestemcel-L, which resulted partially from a lack of a demonstrated relationship between quality attributes and clinical performance. In addition to significant clinical reservations, the FDA needed more evidence that the assays and attributes being used by Mesoblast are sufficient to ensure the manufacturing process produces consistent batches of acceptable quality."**
>
> Anthony Davies, Founder and CEO, Dark Horse Consulting

Q2. Which of the following CQAs do you measure now?



One conclusion that can be drawn from this data is the focus and high priority that is being put on immunogenicity assays over potency assays, both in terms of what is being measured currently and what is thought to be necessary for regulatory approval. Just 29% think that potency assays are essential for regulatory approval. This is at odds with the real-world examples already discussed and the fact that a validated potency assay is required for BLA approval (as per section II B of the FDA guidance document).

What's really necessary is a matrix of assays and that is somewhat reflected in this data. A matrix approach affords a few shots at goal without having to measure everything or too much, as this can set viability thresholds and parameters too high, resulting in batches not being released.

There is a somewhat elusive balance to strike between measuring too much, measuring the attributes that are truly critical and giving the regulators the data they need. Ideally, refining what needs to be measured long-term can be done through the development process along with defining the product and its mechanism of action.

Analytical tools and technologies are a frontrunner solution, particularly in a field where the product can change so easily due to changes in the process.

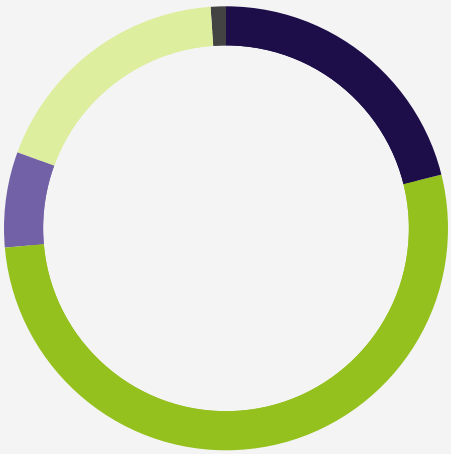
Chapter 2

Does Effective Analytics Contribute to Reproducibility and Regulatory Filing?

Understanding analytics needs and bottlenecks

Fundamentally, there isn't enough understanding of the relationships between products and their process, which can lead to inconsistencies between batches and affect reproducibility. Different analytical tools can provide insights that help developers to overcome these comparability and characterisation challenges. There are also financial implications; the cost of therapies will always remain high if huge amounts of unnecessary testing are needed due to a lack of understanding of a product's mechanisms of action.

Prior to this paper, Bio-techne and Phacilitate conducted a survey to provide insight into the industry's perception and use of analytics technologies. The vast majority of the industry has implemented manufacturing analytics to some extent with only 25% stating that they haven't or haven't even considered it yet. Technology and knowledge are deemed to be the two areas in most need of innovation, i.e. the right analytics technology doesn't exist yet and there is not enough knowledge to implement and operate it.



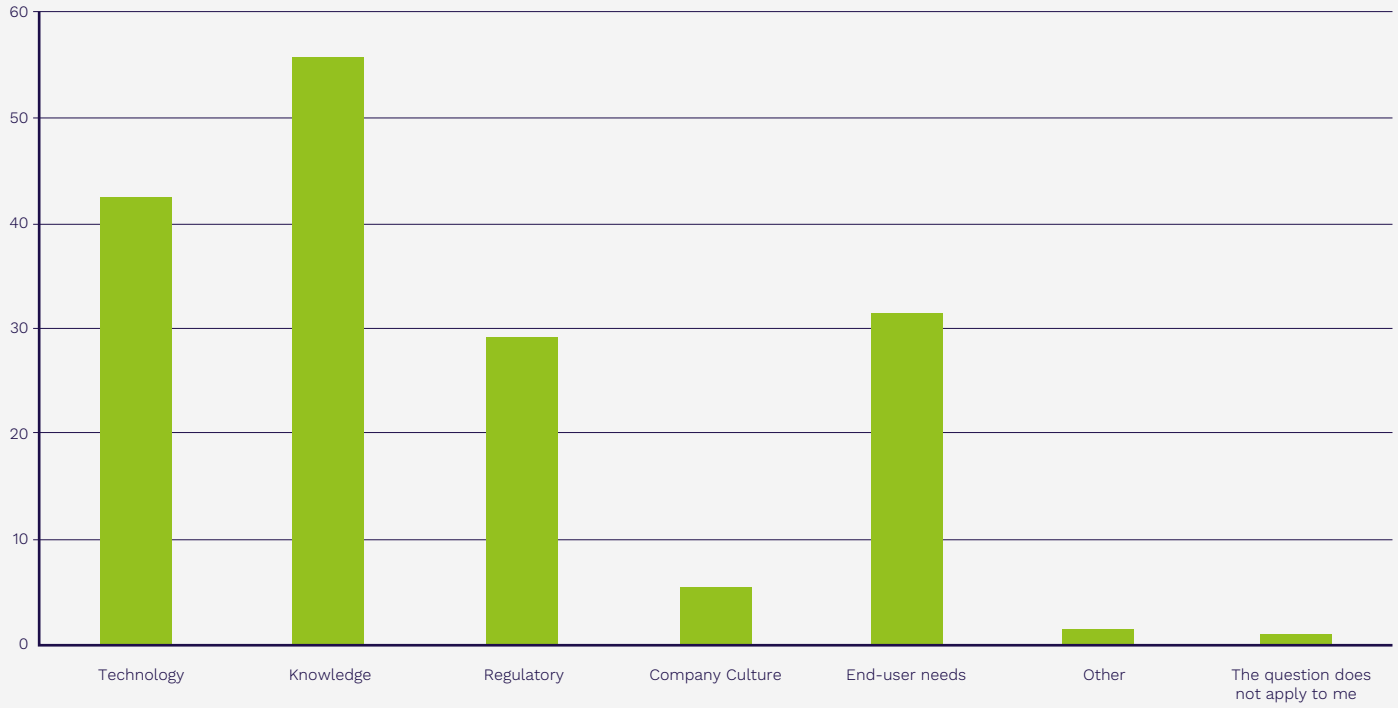
Q8. To what extent have you implemented analytics into your manufacturing processes?

- Very
- Somewhat
- Not at all
- Haven't considered it yet
- This does not apply to me

"It's critically important that appropriate analytical methods are employed which ensure quality attributes match acceptance criteria for the intended application. Consequently, determining effective analytics for use in regulatory filings must be a collaborative effort between stakeholders and regulatory bodies."

Diane Wotta, PhD, Sr. Dir. Global Quality Assurance, Regulatory Affairs & Safety.

Q9. Where is innovation needed to make analytics an effective viable solution for commercial-scale manufacturing?



The real value of fit-for-purpose analytics technology has not been realised but the potential gains could be transformative for the cell and gene therapy industry and for patients worldwide. We've distilled the aanlytics value proposition down into three main areas - reproducibility, operability and batch release.

Reproducibility

Reproducible data and manufacturing processes underpin informed decision-making during clinical development and regulatory pathways. Reproducibility of the end product itself is, of course, essential for approval and is becoming a common shortfall during the regulatory review process.

Analytics tools have a leading role to play in developing validated assays that are easily understood, interpreted and cost-effective, which is key to regulatory success. More specifically, analytics can help define binding and function in potency assays.

When considering a multisite manufacturing model, analytics data contribute to standardisation across sites and reduce process variability, which is directly proportional to reproducibility and lot-to-lot consistency.

Operability

The 'human factor' is an obvious source of inconsistency. A combination of analytics and automation makes new techniques and processes easier to transfer, as oftentimes, whoever develops the test or process isn't running it day to day and others need to be trained to get the same results. This is even more important when scaling up and operating a distributed manufacturing model.

Integrating analytics into a manufacturing process results in requiring less skilled operators and you then have access to a wider labour pool. This solves another challenge holding back CGT's success; 73% of the industry say their main bottleneck is finding the right QC talent.

Analytics tools can also allow remote operation capabilities, so operators don't need to be in any one lab or location.

Batch release

Today, there are 920 active cell and gene therapy clinical trials for solid tumours, which seems a sure sign that developers are now looking towards therapies that cover large, global populations. The manufacturing scales needed for these kinds of indications could lead to a new bottleneck; testing for batch release.

Allogeneic products are slightly less challenging, as they're manufactured in one big batch and the QC process is more like the traditional pharma model. However, large-scale autologous products or a distributed manufacturing model could succumb to a batch release backlog.

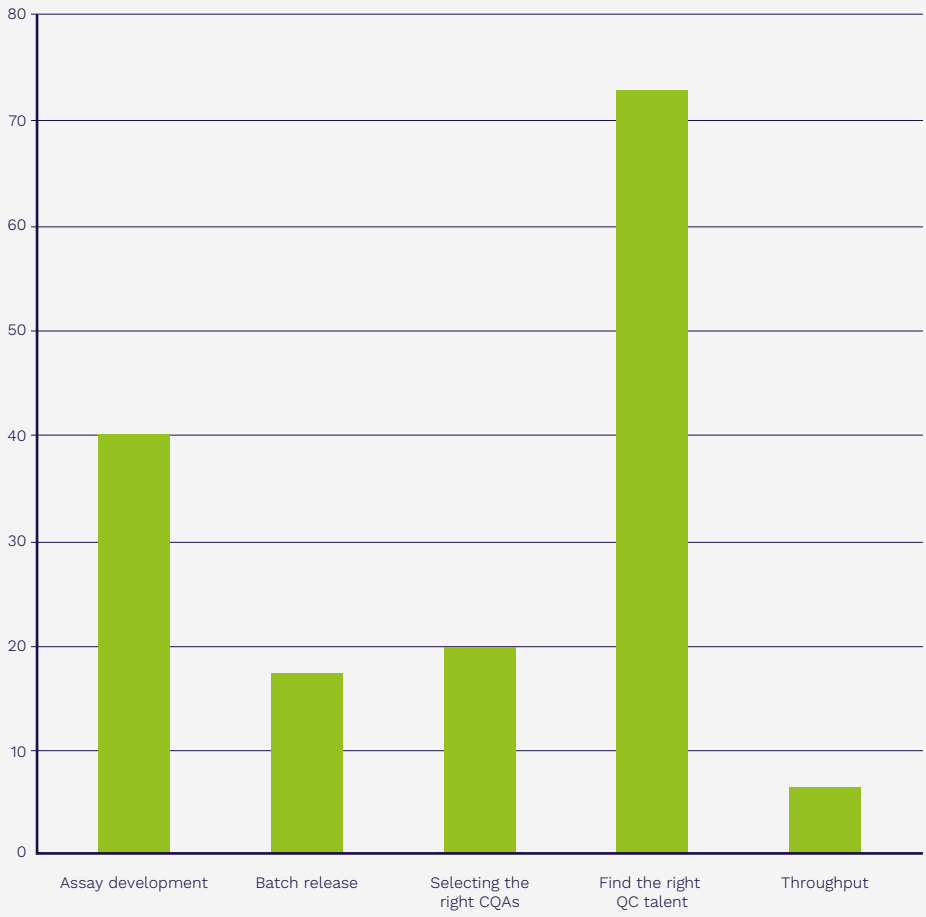
With larger scales and batches comes the digitisation of manufacturing and supply chain infrastructure in the form of tools like manufacturing execution systems. This digitisation has a knock-on effect on batch release in that it reduces the number of QC and QP personnel needed as there are fewer manual requirements. Also, practices like 'review by exception' can be implemented and allow auto-release of batches.

Analytics has a significant role to play within this infrastructure. In conjunction with automation tools, they will be more powerful and can achieve faster - potentially real-time and online - assessments of release criteria and potency testing. Analytical data could also be analysed using AI applications to make QP sign off more automated.

Bottlenecks and challenges

While there are plenty of advantages to be gained through the use of analytics, there are some limitations and challenges that still need to be addressed to increase the opportunities of this technology even further.

Q1 What are your biggest QC-related bottlenecks?



For instance, regulatory authorities are yet to define their requirements on where and how to use analytics technology. While there are some national technical guidelines from the US and British Pharmacopeia, NIST is looking at standardisation and ISCT have some relevant consensus panels, regulatory guidance remains an important cog in this analytics wheel.

The fundamental cost-benefit analysis often comes into question. Many organisations and individuals see the benefits of analytics technology but have a hard time accepting the costs. There is also the question of how to scale up these analytical techniques once they are defined.

Chapter 3

Designing the Optimal, Scaled Analytics Model

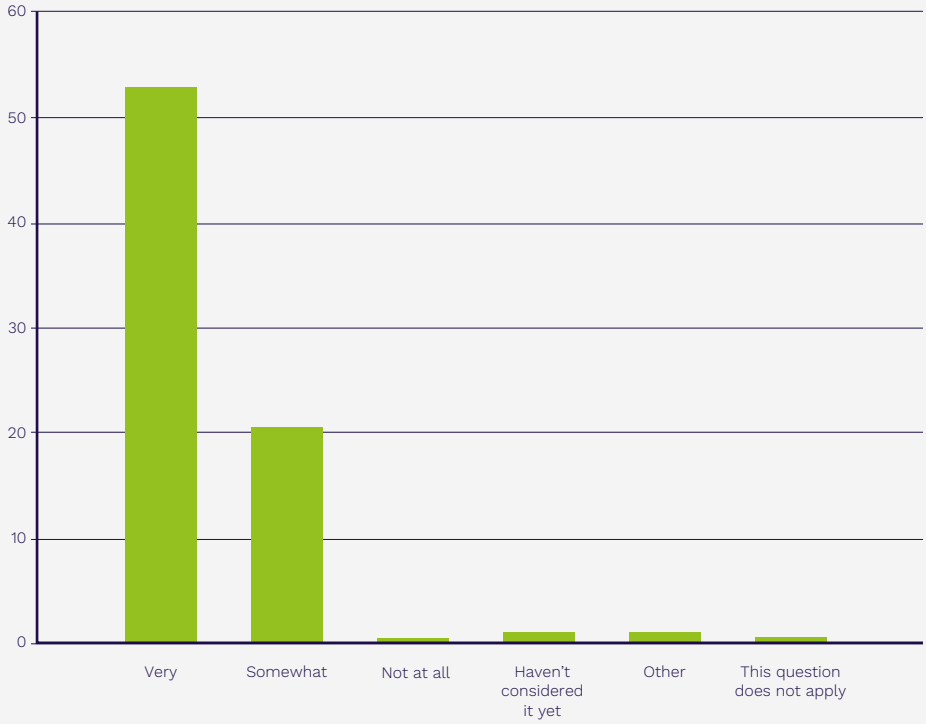
The future analytics paradigm

If current analytics technology isn't fit-for-purpose and the right technology doesn't exist yet, but there is huge potential, it begs the question - what does an optimal, scaled analytics model look like? As an industry, we have the opportunity to create a vision for the ideal analytics paradigm that would improve manufacturing outcomes. As standardisation eludes many facets of the cell and gene therapy industry, it might be helpful to consider this brave new world of analytics in modular elements, for example, sensors, batch release, infrastructure and software, real-time, in-line.

In-process, real-time

Recent data show that in-process monitoring is either somewhat or very important to a staggering 92% of the industry. So, the demand for effective in-line monitoring is huge and would indeed form part of an ideal analytics set-up.

Q10 How important is in-line process monitoring to you?



A combination of in-process controls and real-time monitoring presents huge potential and could be instrumental in being able to predict the successful manufacture of cell and gene therapies. This would require a massive shift in both manufacturing and analytics technology simultaneously, meaning suppliers of both would need to work together, which isn't necessarily a seamless endeavour but certainly in the realms of possibility. One important step will be to establish exactly where in-process analytics can and should be applied throughout a given production process and what the ideal upstream and downstream applications might be. At the moment, this kind of analytics setup is mainly being applied to culture monitoring; the use of sensors in bioreactors is very established.

More in-line sensors in the production system overall could provide a readout of product quality before the end of the production process. One ideal scenario would be the ability to have full knowledge of product quality at the end of the process, so that additional costly and time-consuming tests are not needed to determine quality. This kind of detail and approach would increase reliability, reduce cost and make operations more effective overall.

There is one final piece of the puzzle. The combination of in-process and real-time analytics is essentially meaningless without a feedback loop to improve the manufacturing process as a whole and also to allow any necessary adjustments to the product to ensure batch release. This also requires an effective escalation pathway to manage adverse events in real-time.

> **"Bioprocessing 4.0 and IoT are going to be central to the future of cell and gene therapy manufacturing, where data is collected and stored at every touchpoint. This, coupled with effective, positive feedback loops will further improve the efficiency of manufacturing."**
>
> Cenk Sumen, CSO, MaxCyte

- Consideration of sample size requirement and sensitivity - depends on cell and how viable or productive the cell line is
- More sampling is generally a good thing, bringing sampling and QC into the process is beneficial
- Bring it all into the production suite and empower operators to make decisions

Smart manufacturing

An ideal paradigm for analytics in cell and gene therapy has to involve smart manufacturing, which will provide insights into process development and quality. As we move towards bioprocessing 4.0, big data, AI, ML and IoT will all play a role. Ideally, integrating IoT into bioprocessing will allow many applications to share data that can all be pooled into a common batch record. This could be done through current, specialist software like Autolomus' offering or using automated passive data collection approaches in a closed system. All of this can improve traceability, which will be important for regulatory submission. Data collection and analysis throughout the production process will ultimately drive manufacturing and release decisions in real-time.

Given the amount of data generated by our industry, we've been extremely slow to adopt AI and ML, which are well-suited to repeat processes like GMP manufacturing. Better data collection and management infrastructure are needed to realise the potential of smart manufacturing and start taking advantage of the kind of analysis that can ultimately lead to more robust and predictable outcomes.

Continuous validation is another component of this ideal future analytics and bioprocessing 4.0 paradigm. As the industry moves towards therapies for global populations and mass indications like diabetes, QA/QC and batch release as it is currently would never allow us to serve this volume of patients. Using analytics tools, sensors and better data management could allow for continuous validation and help overcome the throughput and cost challenges here.

All of this proves that these technologies are not only nice to have, but they are also critical.

bio-techne®

Bio-techne (www.bio-techne.com/) are a leading provider of tools and reagents to support cell and gene therapy GMP manufacturing and analytics. This report is a thought leadership and educational exercise aimed at heads of manufacturing, supply, operations, process development, CTO, CSO, i.e. those tasked with solving strategic and technological challenges

In association with:

PHACILITATE

We connect industry leaders in advanced therapies through our inspiring conferences, vibrant communities and market intelligence. Find out more and join the Phacilitate network at www.phacilitate.com