WHITEPAPER

Adapting QC Microbiology Labs for the Demands of Cell & Gene Therapies

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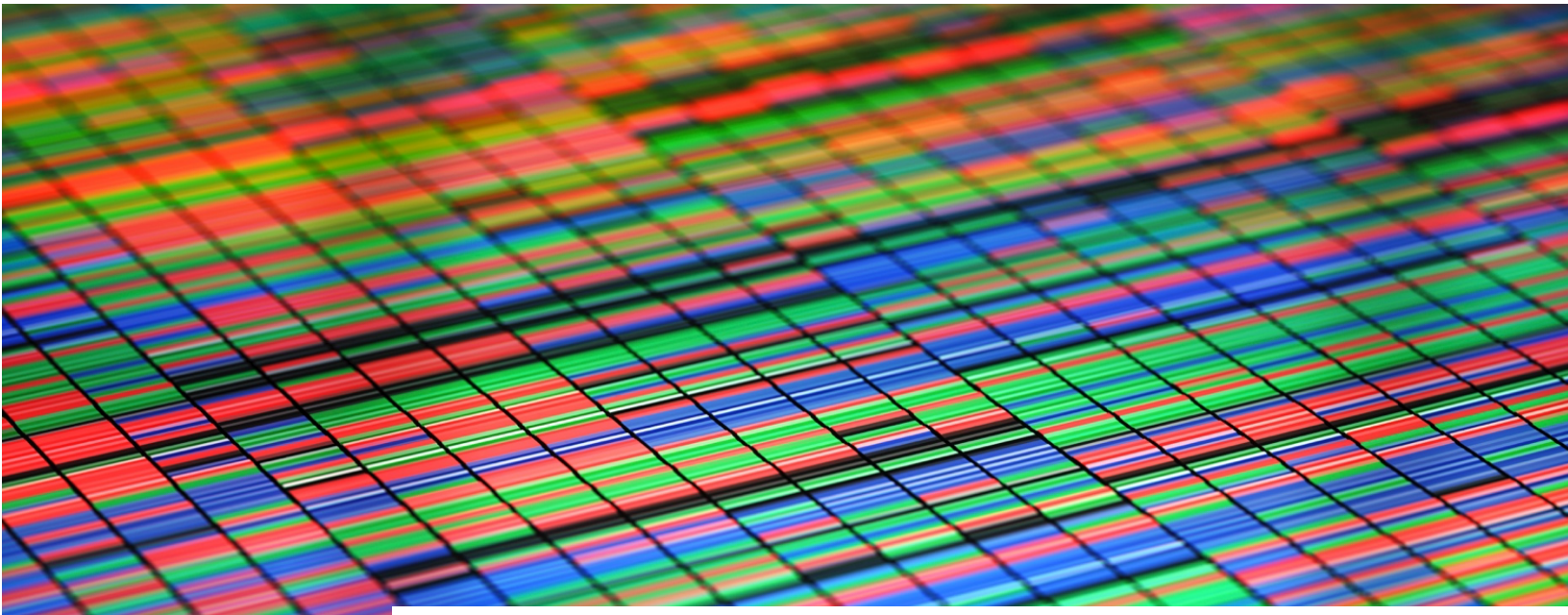

In this whitepaper readers will learn about:

- The distinct demands of cell and gene therapy QC microbiology
- The limitations of traditional QC microbiology workflows
- Automated rapid microbial methods (RMMs) and their advantages in cell & gene therapy manufacturing
- A real-world example of the pitfalls of traditional QC workflows
- The future outlook of QC microbiology regulatory guidance

After decades of research, the scientific and medical communities are just beginning to deliver on the promise of cell and gene therapies[i] (also classified as advanced therapy medicinal products or ATMPs[ii]). The coming wave of approvals and projected market growth indicate a rapidly rising demand for these life-altering therapies[iii,iv,v]

To make good on these exciting developments, ATMP manufacturers need to rapidly evolve their processes. Cell and gene therapies come with unique manufacturing challenges, including a drastic increase in quality control (QC) burden. Many of the most severe QC limitations occur within QC microbiology testing labs, which encounter:

- More complex manufacturing processes, with greater environmental, personnel, and bioburden monitoring needs
- Unique scale-up difficulties[vi] (especially for autologous cell therapies)
- Extremely rapid timelines, focused on reducing “vein-to-vein” time
- The requirement of QC microbiology testing for lot release

While challenging, careful planning and the introduction of advanced technologies into QC microbiology labs can open the door to productive and safe scale-up manufacturing. This whitepaper will discuss ATMP QC microbiology lab challenges and how automated approaches can resolve them, placing special emphasis on managing QC for the most complex cell therapies.

Increased QC Micro Lab Testing and The Need for Automation

All drug companies rely on QC microbiology testing. These are designed to carefully assess site and product contamination risks through bioburden and environmental monitoring. While many use compendial growth-based methods[vii,viii,ix] these traditional workflows tend to be highly manual, creating bottlenecks as the number of tests increase. If not addressed, these bottlenecks can delay contamination detection, investigation, and resolution – with real-world consequences. Microbiological safety is a critical quality attribute for patient well-being.[x,xi]

Relative to traditional biologic drug manufacturing, ATMP production can require significantly more bioburden and environmental monitoring. This is particularly true for cell therapies and even more so for

autologous ones, like CAR-T (Figure 1). Process complexity and less mature biomanufacturing approaches can lead to greater manual handling, which increases contamination opportunities[xii]. The dependence on manual manufacturing processes also means that you have more personnel to train and monitor, which both rely on QC microbiology testing. “In traditional filling lines, you probably only have two people in the room per shift. In cell therapy manufacturing, you could have a significant larger number of personnel in the room due to the manual nature of the process,” [xiii] says Irving Ford an experienced CAR T manufacturing Quality professional. “With more people, there's more personnel monitoring, but you still need rapid time to results.”

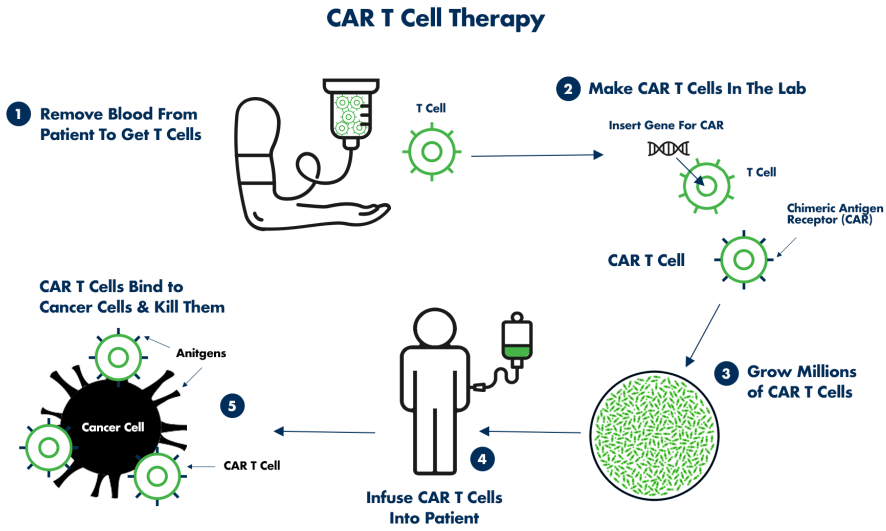

Figure 1: CAR-T Cell Therapy Production Process from Vein-to-Vein

A single lot often has multiple steps inside sterile hoods, stretching across several days. This may include cell separation, introduction of a viral vector (gene therapy) to modify those cells, culturing cells to required volumes, harvesting, and fill-finish. Each step requires viable and non-viable microbiological monitoring of air, surface, and personnel samples. While requirements vary, microbiological monitoring for certain processes can involve more than 100 samples and analyses per lot.

For autologous therapies, microbiological testing increases even more significantly since one lot serves just one patient. If a company must scale-out an autologous cell therapy to remain commercially viable, they will likely need to produce multiple lots per week. For example, one operation (name withheld for commercial reasons) aims to produce 60 lots per week. At this volume, their QC microbiology lab could

need to perform several thousand growth tests per week. That's far too many for a manual process to handle efficiently.

> ***For autologous cell therapies, each lot is manufactured for just one patient. As a result, to manufacture 60 lots for 60 patients in a given week, a QC microbiology lab could need to perform several thousand growth tests in seven days. That's far too many for a manual process to handle efficiently***

The urgency of these therapeutic procedures can make batch loss due to contamination a matter of life and death. This acute connection to a patient's life can put significant strain on the employees performing the manufacturing process and the QC microbiology analysis, especially when combined with increases in testing volume.

While errors are relatively rare, this pressure can lead to employee anxiety, burnout, and turnover that negatively impacts commercial viability. The human impact in this high-stakes environment cannot be overlooked, as the pressure and stress can lead to more costly errors, data integrity gaps, contamination, and QC failures[xiv] – along with turnover of experienced staff.

Bringing Automation into the QC Microbiology Lab

To solve the challenge posed by high-volume and high-pressure QC microbiology testing, cell and gene therapy companies are turning to automated approaches that drastically cut down the amount of manual labor. More specifically, microbiologists are adopting automated rapid microbial methods (RMM) to increase throughput, accelerate time-to-result, and reduce the burden of paper management.

> ***"Taking away the human aspect and letting robotics take over is a huge advantage."*** — ***Irving Ford, an experienced CAR T manufacturing Quality professional***

Incorporating automated RMM systems that perform bioburden and environmental monitoring can drastically improve a site's scalability. Thus, ATMP manufacturers can better manage the increased testing volume associated with scale-out manufacturing of many small lots. This is especially true if the sample plate tracking, loading, incubation, colony counting, analysis, and data management are all automated in a single system **(Figure 2).**

Ford indicated that adopting automated RMM systems, including the Growth Direct, into QC microbiology labs should be a "day one decision." Ford cited the elimination of paper management as being key to his calculation. "An ultimate goal for a cell therapy lab is to become 100% paperless." Filling out, organizing, storing, and then later manually reviewing print information is highly inefficient and massively reduces QC microbiology throughput.

Echoing that point, Marc Glogovsky, Senior Consultant for Microbiology at ValSource, LLC, says that the benefits of automated RMMs are maximized if those systems integrate with laboratory information management system (LIMS). For cell and gene therapies, "data integrity is key." QC microbiology labs need to be able to easily "track all of the information collected and tie it to specific patient batch." With many batches and patients to manage, you really don't want to rely on manual organization and paper.

As an added benefit, individual employees won't need to manage the pressure of manually performing these tests and analyses, which reduces fatigue, burnout, and human error. Instead, microbiology teams can devote their time to performing higher value work, like identifying contaminations, performing investigations, and resolving issues. In practice, organizations may find the automation also helps keep their teams lean, without sacrificing productivity.

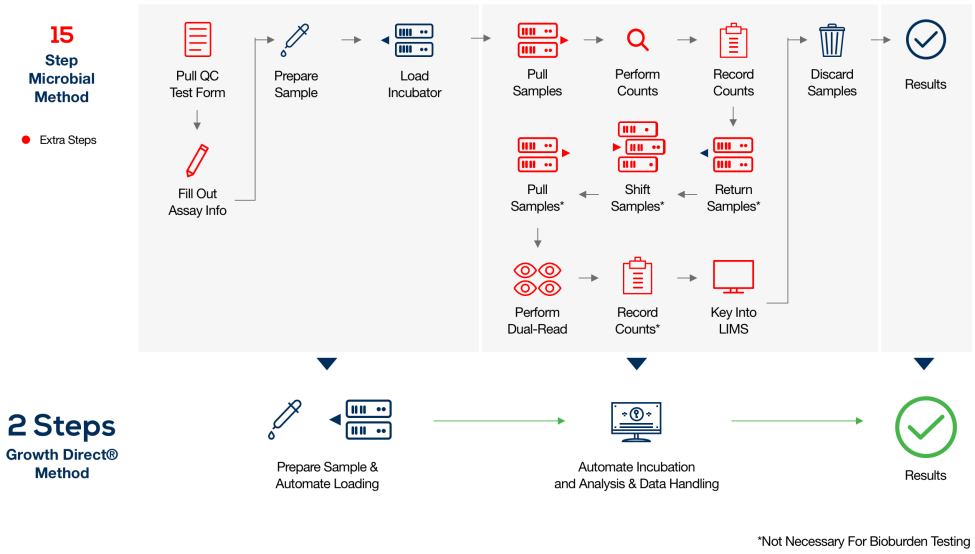

Figure 2: QC Microbiology Workflow Comparison: Traditional Method vs Growth Direct (an automated RMM)

Adapting to Expedited Timelines

Cell therapies are less stable than other biologic modalities. They demand speed throughout the processes to ensure product activity and avoid spoilage. Adding to this urgency, these therapies are often used to treat individuals with aggressive cancers that can't afford to wait on lengthy production cycles. For autologous therapies, some patients even stay at the hospital after their cells have been collected, awaiting their final life-saving dose. Any delay or misstep means those patients must remain in the hospital longer, while running the risk that time may expire. For this reason, cell therapy manufacturers are constantly focused on reducing the total "vein-to-vein" time, which includes cell extraction, manufacturing, QC, and then patient infusion (Figure 1).

For many cell therapy manufacturers, QC microbiology ends up being a primary bottleneck. This is typically due to the requirement of product sterility for lot release of cell therapies, especially since terminal sterilization is not possible for living therapies.[xv] Traditional compendial sterility tests require 14-day growth periods to confirm sterility, creating the longest lead time for any required QC microbiology tests.

Speeding Up Lot Release Using Rapid Microbial Methods

To relieve the bottleneck created by compendial sterility testing, QC microbiologists have adopted rapid sterility tests to provide faster results (approx. 5-7 days vs. 14 days).[xvi] While 14-day growth cycles in both aerobic and anaerobic conditions must still be completed, regulatory agencies accept these alternative approaches as interim sterility tests for lot release, provided the methods have been carefully validated. To supplement interim sterility tests, regulatory authorities require detailed risk assessments and mitigation plans to help protect against non-sterile injection.[xvii]

For cell therapy manufacturers using interim sterility testing methods, both raw material and in-process bioburden with environmental monitoring become even more important for mitigating risk. If a lot is being released early using an interim sterility test, manufacturers need to have more confidence that their process and manufacturing environment are contamination free.

According to Ford, "*Sterility is not the be all end all. Regulatory bodies expect you to have an overall contamination control program. The sterility test is just one point in the overall process. The better control you have over the process from start to finish, the better it is for your end result.*

> ***"If there is nothing in your bioburden up front and there's nothing in your environmental monitoring, chances are that there's nothing in your product. If your environmental monitoring is showing counts on your employees or in an air sample, then that throws doubt on your product." – David Jones, Ph.D. Director of Technical Marketing and Industry Affairs at Rapid Micro Biosystems***

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In fact, the EU's new GMP Guidance Annex 1 suggests that batch records for environmental monitoring need to be completed before the product is released.[xviii] Even if that policy is not yet enforced, the industry and regulatory bodies are headed in this direction to enable accelerated timelines that treat patients sooner, while limiting additional risks.

Collectively, this means that bioburden and environmental monitoring programs can themselves become bottlenecks. This is another reason why cell and gene therapy organizations may adopt high-throughput rapid microbial methods (RMMs), particularly automated RMMs, to help perform these analyses. With RMMs, data can be collected and analyzed more quickly, which enables better monitoring and faster issue detection. As a result, microbiologists can get in front of contamination challenges, reduce their site's collective risk, and cut down sterility failures.

Having these analyses performed by an in-house RMM with full LIMS integration can also save precious time. When relying on an outside contractor, sites may end up waiting hours or days for the results to be transferred, integrated, and reviewed. With an in-house RMM connected directly to a LIMS, manufacturers receive count results more directly and quickly, avoiding delays in batch release and sign-off.

Looking Ahead at ATMP QC Regulations

Microbiology QC is a cornerstone of patient safety in the cell and gene therapy manufacturing process. However, the unique needs of these new modalities can quickly overwhelm traditional QC microbiology workflows. Though the entire industry is struggling with these challenges, no organization wants to deal with downstream impacts created by QC microbiology complications.

As a cautionary example, the FDA issued two Form 483's to two different sites, a legacy Juno Therapeutics site in Bothell, Washington and a contracted Lonza facility in Houston, Texas, producing Bristol Myers Squibb's CAR T-cell therapy product, lisocabtagene maraleucel (liso-cel). Issues in microbiological contamination control and QC microbiology were cited in both.[xix,xx] In one case, the FDA randomly inspected environmental monitoring plates and discovered discrepant colony enumeration results.[xxi] While the FDA ultimately approved liso-cel in 2021[xxii], it likely contributed to costly approval delays.

In this case, the site actually performed correct quality control measures by having environmental monitoring plates counted and then verified by a second count. Yet, human error can occur—even when doubled-checked—especially when testing volumes and tight timelines mount in the lab. For this reason, regulatory agencies like the FDA continue to call for improved QC and greater investment in modern automation and control systems. [xxiii,xxiv]

Since the US FDA and other regulatory agencies will continue to keep a close eye on ATMP manufacturers, organizational leaders can help their company stay ahead of the curve by investing in their QC microbiology lab. Specifically, implementing an RMM technology that introduces automation to microbiological testing procedures—including plate enumeration, data management, and issue identification—will offer profound returns and helps avoid regulatory missteps.

If you have additional questions about how to improve your QC microbiology lab's efficiency or want to speak with an expert about our Growth Direct automated RMM system, Contact Us Today!

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