# A CELL THERAPY INDUSTRY TURNING POINT:

## How quality system audit standardization can increase collection capacity and reduce risk


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While recent therapeutic advancements in cell and gene therapy present hope for many patients, the rapid proliferation of these therapies is putting substantial stress on the infrastructure that supports the collection and processing of cellular starting material. [1] Left unaddressed, current processes risk overwhelming cell collection and processing sites and ultimately delaying the delivery of time-sensitive therapies to patients. [2,3]

What happens when innovative therapies and regulation create an environment that may overwhelm the infrastructure that companies rely on to collect cellular starting material? This is where breakthroughs can break down. And this is where companies may find themselves if the status quo continues.

**The development of standardized industry processes, including quality system audits (QSAs) of cell collection centers and cell therapy labs, can create immediate efficiencies for all stakeholders.**

QSAs—which assess compliance to FDA regulations 21 CFR Part 1271 Good Tissue Practices (GTP), 21 CFR Part 211 Good Manufacturing Practices (GMP) and operational practices—are similar across many cell and gene therapy products. [4] Yet, each cell and gene therapy company typically performs its own QSA for every collection center prior to the initiation of a clinical trial or commercial protocol at a site, and at regular intervals following site activation. With multiple cell and gene therapy companies using the same collection centers and cell therapy labs, the result is often multiple nearly identical, time-consuming audits at the site.

Collection slots at centers are limited, and each QSA forces collection center and lab staff members to shift time away from collecting and processing cells to focus on preparation, day-of and follow-up audit activities. The demand for collections and the need for audits are only expected to grow as more therapies enter the market, making current QSA practices unsustainable (Figure 1). [4]

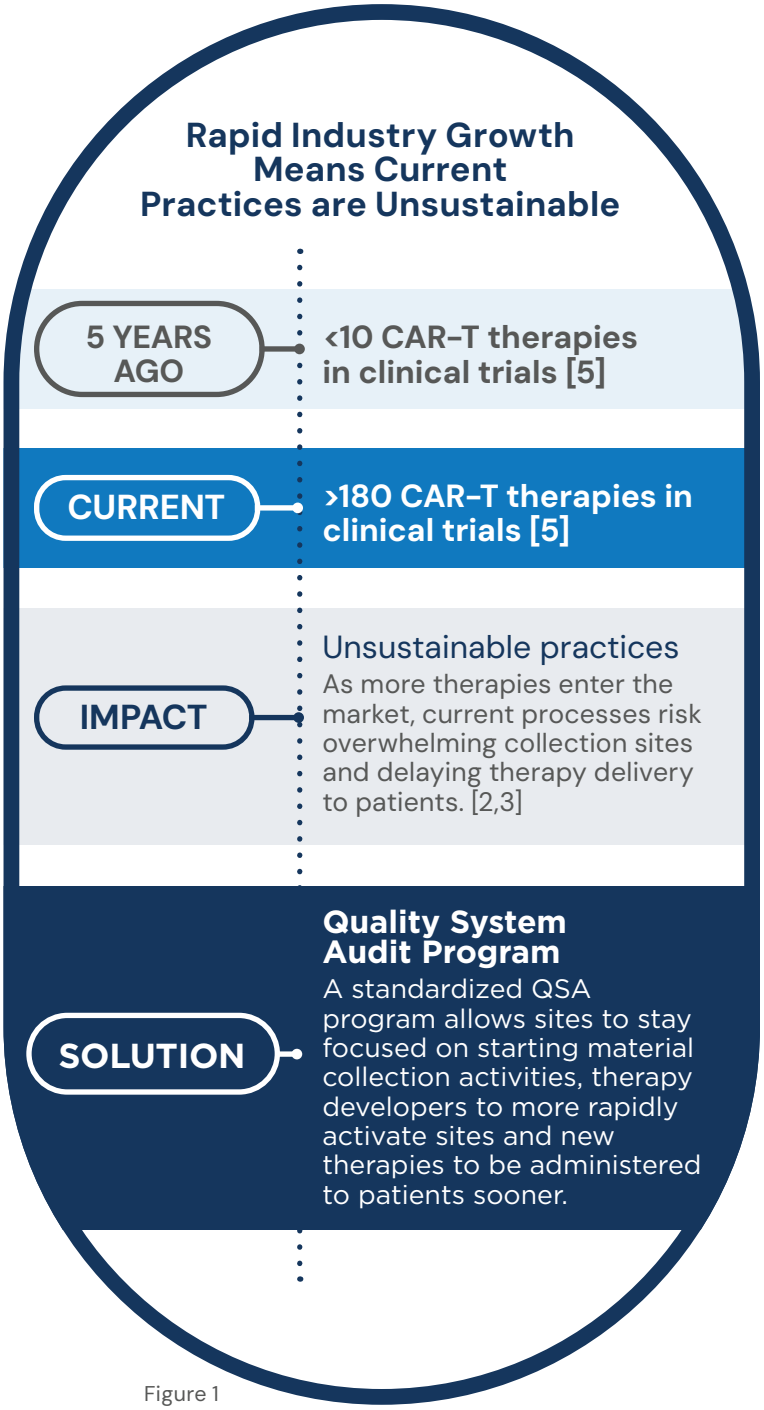



Figure 1

## The solution: Standardization through a QSA program.

This paper explores the challenges of the current QSA environment and the benefits that a standard QSA program offers cell and gene therapy companies, collection centers and labs, including:

- Time and cost savings
- Consistency in audit expectations
- Predictability in audit frequency and timing

## A statistical look at the current QSA environment

A QSA is a critical and necessary step to establish whether a cell collection center and cell therapy lab have the capabilities and processes in place to meet quality requirements and safely deliver high-quality starting material according to protocol. However, repeated QSAs by multiple cell and gene therapy companies at the same centers result in strained resources at collection centers and labs due to duplicative, and often overlapping, requirements for pre-, day-of and post-audit activities.

A September 2018 NMDP BioTherapies℠ survey of staff at the 112 apheresis and marrow collection centers in the NMDP℠ Network illustrates the issue: According to the survey, 40% of respondents said their center undergoes four or more audits and/or inspections annually, with 11% experiencing seven or more annually (n=87). In some cases, QSAs by different companies are occurring almost back to back when corrective actions noted in the first audit are still being addressed and implemented. This leads to overlapping findings, sometimes with conflicting resolution requests by companies. [4]

In addition to the frequency of requested audits, each audit is time consuming for collection center and lab staff. More than 60% of survey respondents said their center devotes 31 or more hours to audit activities

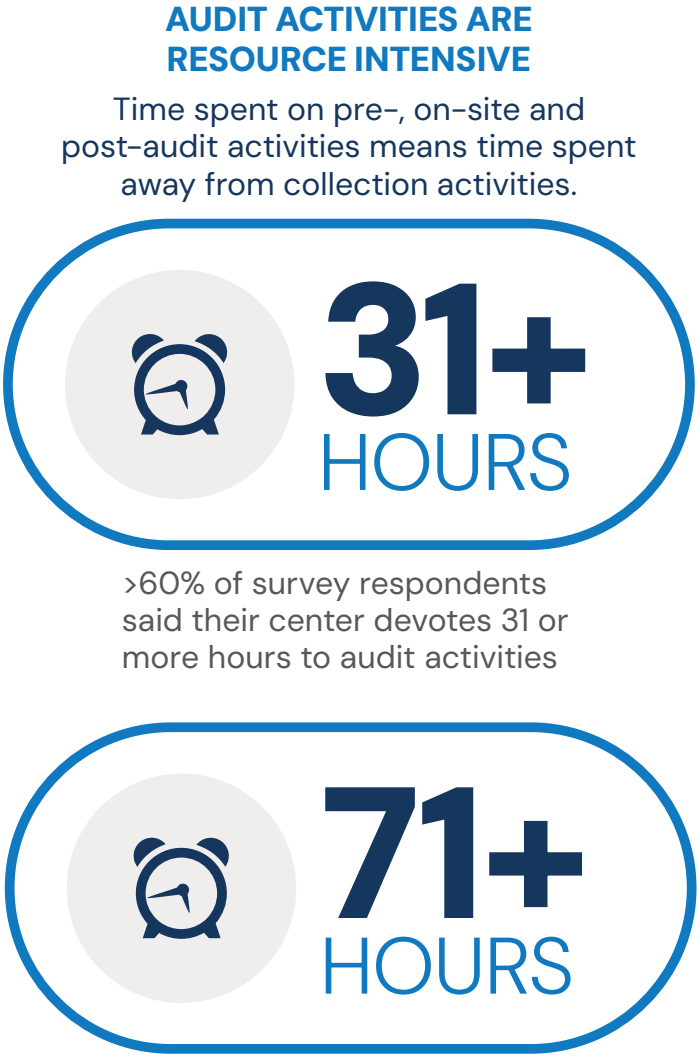



Figure 2:
Results from NMDP BioTherapies survey of NMDP Network apheresis and marrow collection centers.

(i.e., pre-audit, during the audit and post-audit), with 31% spending 71 or more hours on these activities (n=83) (Figure 2).

As the amount of time dedicated to audit activities increases, staff have less time to spend on the collection of high-quality cell therapy source material.

## Benefits of a standardized QSA program

A standardized QSA program allows one organization to audit each cell collection center and cell therapy lab one time over an established timeframe, such as every two years (Figure 3). Audit results can be licensed from the auditing organization, alleviating the necessity for multiple companies to conduct individual, yet similar, audits at the same sites. The auditing organization provides cell and gene therapy companies with an on-site audit checklist—including notes and supporting documentation reviewed—audit report with findings and an audit closure letter.

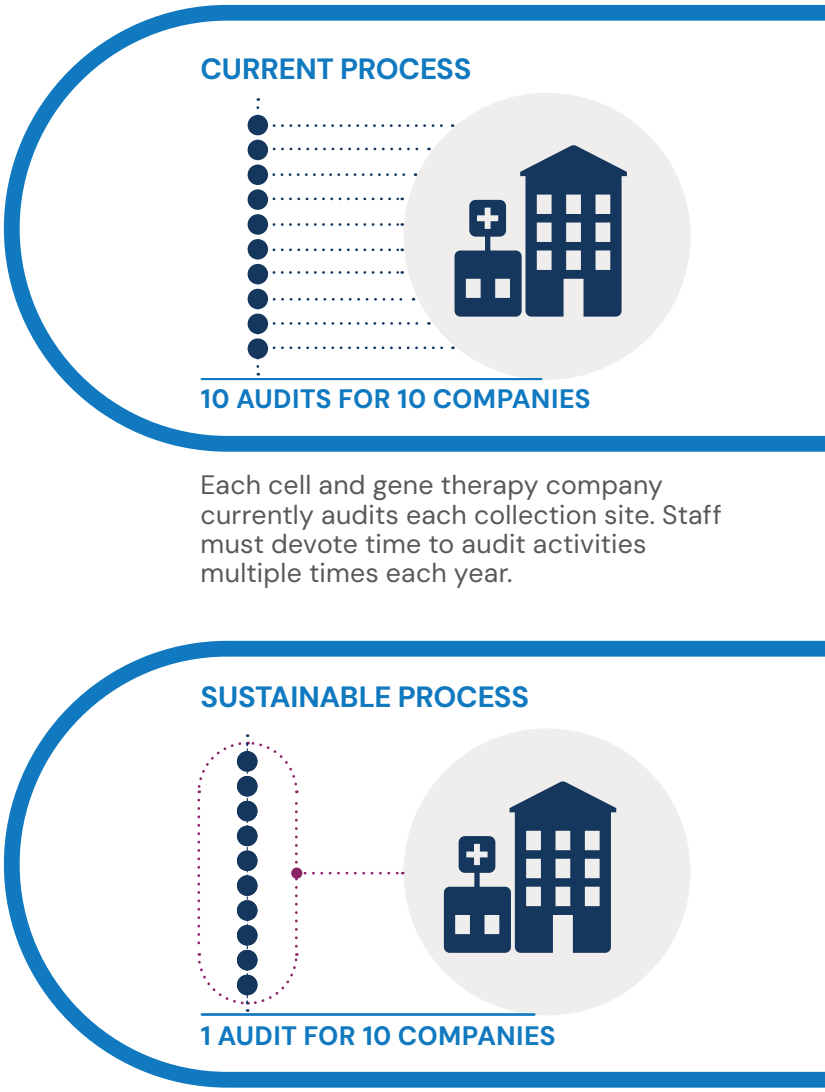
**The result:** Therapy developers can more rapidly move sites from qualification to activation and save costs associated with building the internal infrastructure to hire and train specialized auditors. In addition, collection centers and labs spend less time on audit activities and more time collecting high-quality starting material for therapy manufacturing and delivery to patients.

## Time and cost savings

Using a QSA program saves time for collection centers and labs, as well as the therapy developers.

In the September 2018 survey of apheresis and marrow collection center staff, 36% of respondents cited an increase in demand for apheresis and/or marrow collection services for cell and gene therapies as the biggest challenge currently facing their centers (n=94).

### QSA Program Use Benefits Both Collection Centers and Therapy Developers




Each cell and gene therapy company currently audits each collection site. Staff must devote time to audit activities multiple times each year.

One QSA program audits each collection site every two years. Cell and gene therapy companies license audit results. Staff focus on cell collections instead of audit activities.

Figure 3

To meet the demand, staff members at centers must be able to focus their attention on patient care. When cell and gene therapy companies license audit results from a QSA program rather than conducting individual QSAs, center staff members can spend their time harvesting quality cellular starting material for therapies, as opposed to preparing for and enduring multiple audits throughout the year.

For cell and gene therapy developers, licensing audit results through a QSA program can save weeks to months of time in the site qualification process, allowing the site to begin collecting starting material for therapy manufacture faster. Typically, sites receive a four- to six-week notice that an audit will occur, which allows time for the site to prepare. The onsite audit itself takes one to two days. The auditor provides the audit report to the center within 30 days after the audit, and centers must respond with a corrective action plan and implementation date within 30 days (15 days for critical errors).

In addition, companies would eliminate the need to invest in building an internal infrastructure to hire and train highly specialized auditors, which saves time as well as salary, benefits and travel-related costs (Figure 4).

## Consistency of audit expectations

Using a QSA program to license audit results provides increased clarity of expectations for collection centers and labs, minimizing the resources needed for pre- and post-audit activities.

Because U.S. cell and gene therapy companies typically audit for compliance with Food and Drug Administration GTP and/or GMP regulations, every auditor should be auditing to the same standards. However, collection centers and labs have reported receiving requests from companies for quality plans and standard operating procedures (SOPs) to review that

### QSA PROGRAM MODEL PROVIDES COST SAVINGS TO COMPANIES

COMPANY AUDIT PROGRAM

**$500,000–$700,000**

$5,000–$7,000 per audit
x
100 collection sites

QSA PROGRAM

**$350,000**

$3,500 per audit
x
100 collection sites

**POTENTIAL SAVINGS**
**$350,000**

A cell and gene therapy company can license audit results for approximately half the cost of building its own infrastructure and save on salary, benefit and travel-related costs. In many cases, the audit results are immediately available which saves time during site qualification.

Figure 4

diverge from these standards, resulting in additional preparation activities, as well as overlapping findings with conflicting corrective action requests.

A standard QSA program improves consistency and efficiency in at least two areas:

1) document review
2) corrective actions

## Document review

Prior to the audit, most cell and gene therapy companies request a review of documents, including quality plans and SOPs, to increase efficiencies the day of the audit.

**The problem:** Not every company requests the same pre-audit documentation, which means sites cannot package a standard set of materials to send.

Many companies are requesting slight modifications to SOPs, which requires recollecting the documents from various departments for each audit.

Use of a QSA program would allow cell and gene therapy companies and centers to work with the auditing organization to develop a standardized, comprehensive set of documents required for audits, reducing the need for repetitive, time-consuming work.

## Corrective actions

For collection centers and labs that undergo multiple audits throughout the year, inconsistent findings and corrective action requests are creating inefficiencies and confusion.

For example, a center is in the process of addressing findings from Company X's audit when Company Y arrives to conduct its own audit. Companies X and Y cite the center for the same finding. However, Company Y asks for a slightly different corrective action than what the center was already in the process of implementing for Company X.

The findings may require minor changes, such as language in an SOP, or a major change in process that requires many staff members to plan and implement. In either case, staff need to be retrained on each change, and changes must be reported to the companies that completed prior audits.

A QSA program can provide all stakeholders with a clear understanding of the standards they will be held accountable to during the audit. Centers would only need to take corrective actions once, eliminating the need to report back to and receive approval from multiple companies.

> **"Each company that has a commercial product will accredit each program independently. There may be different criteria. It can be confusing, labor intensive and difficult to manage, and it is not always obvious which standard you need to meet for which company. As more companies develop cell therapy products, that's going to be even more complicated."**
>
> David Porter, MD
> Director, Cell Therapy and Transplantation
> University of Pennsylvania

## Predictability of audit frequency and timing

Multiple, independent audits throughout the year result in substantial scheduling complexity for collection centers and labs, which often have limited visibility into the frequency or timing of new audits.

To ensure sites continue to meet quality standards and requirements, companies typically audit collection centers and labs every two to three years, in addition to the initial audit for site qualification. As a result,

centers can expect to experience the same influx of overlapping audits year after year.

The audit schedule under a QSA program would be much more predictable, allowing sites to plan resources accordingly.

It is important to note that a QSA program would not replace the inspections by accrediting organizations such as the Foundation for the Accreditation of Cellular Therapy (FACT), AABB or The Joint Commission. Those inspections, which review for compliance to the accrediting body's standards rather than compliance with FDA regulations, already occur on a regular schedule. [6-8] A QSA program, which audits for FDA GTP and GMP regulatory compliance,

is intended to reduce the number of regulatory audits and increase the predictability of when audits will occur.

## Challenge to using a QSA program

There are situations where specific audit needs that are not part of a standard QSA will be required—for example in the area of intellectual property (IP) requirements.

In those situations, a short, supplemental audit strictly focused on those IP areas conducted by either the company owning the IP or by the QSA program could be undertaken. This would be less disruptive and time consuming for the site than a full audit.

While there are challenges involved in implementing a standard QSA program in the industry, the status quo is not sustainable. Standardization can reduce the resource burden that collection centers and labs are experiencing and help ensure high-quality therapies are delivered to patients.

## Conclusion

Industry implementation of a standard QSA program offers many benefits to cell and gene therapy companies, cell collection centers and cell therapy labs, including:

- Collection center and lab staff spend less time on audit preparation and follow-up and more time providing patient care and collecting and processing cell and gene therapy starting material.
- Therapy developers are able to more efficiently move sites from qualification to actively collecting and processing starting material by leveraging the pre-conducted audit for quality compliance.
- Therapy developers realize cost efficiencies because they do not need to invest resources in building the infrastructure to hire and train highly-specialized, certified auditors.

In order for standardization efforts to keep pace with the rapidly growing industry, key stakeholders—including cell and gene therapy companies, collection centers and labs, transplant (infusion) centers, regulatory agencies and organizations like NMDP BioTherapies℠, the Standards Coordinating Body, FACT and AABB—must collaborate.

We are at a turning point as an industry. With more life-changing cell and gene therapies in clinical studies and becoming commercially available for patients, it's critical to find opportunities to standardize and ensure sustainability of the industry. By working together to develop standardized processes that will reduce pressures on the infrastructure, we can overcome our challenges and achieve our common goal—saving more lives through cell and gene therapy.

# AUTHORS

## Heather Steinmetz, MPH

Heather Steinmetz, MPH, is the quality assurance (QA) manager for UCLA Health's Hematologic Malignancy/Stem Cell Transplant (HM/SCT) Program. She works in collaboration with the Hemapheresis Unit, Stem Cell Lab and Adult & Pediatric Clinical Transplant Program to ensure regulatory compliance is incorporated into all aspects of the HM/SCT Program.

She has served as the operational lead implementing all FDA approved CAR-T therapies within the HM/SCT Program. Steinmetz has worked within the hematopoietic stem cell transplant field throughout her career. She began her career at NMDP[SM] where she spent four years as a donor coordinator guiding unrelated donors through donation. She joined UCLA in 2010 as a CIBMTR® (Center for International Blood and Marrow Transplant Research®) coordinator.

While reviewing and reporting patient status to the CIBMTR registry, she learned key elements fundamental to the success of the HM/SCT program. She transitioned her donor and patient experience into the QA manager role providing a cohesive understanding of the entire program.

Steinmetz received her Master of Public Health from Touro University California.

## Amy Hines, RN, BSN

Amy Hines, RN, BSN, is the Director of Collection Experience for the NMDP. She works with senior leadership to develop the strategy for the growth of the NMDP-owned network of apheresis facilities and is responsible for the implementation of that strategy. Hines was an instrumental member of the NMDP team that planned and launched the NMDP Seattle Collection Center in January 2020.

She joined NMDP[SM] in 2013 managing the NMDP Apheresis and Collection Center Network of more than 90 apheresis center and 80 collection center partners. She then became the Director of Collection Network Management for NMDP BioTherapies[SM]. In this role, Hines oversaw the performance of apheresis centers and cell therapy labs in the Collection Network, and ensured their ongoing compliance with FDA and international standards and criteria, industry best practices, and appropriate regulatory and accrediting entities.

Hines has spoken about the challenges apheresis centers are facing and then need for standardization during multiple conferences and webinars, including Cell and Gene Therapy World U.S. 2018, the Adoptive T-Cell Therapy: Development track of the Immuno-Oncology Summit 2018, Phacilitate: Leaders World 2019 and World Advanced Therapies & Regenerative Medicine Congress 2019.

She has nearly 20 years of experience in the cellular therapy field, starting her career as a stem cell transplant registered nurse. She received her Bachelor of Science in Nursing from Grand Valley State University in Allendale, Mich.

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## Richard Smith

Richard Smith is an independent consultant for NMDP BioTherapies[SM]. Based in the U.K., he primarily supports new business development efforts in Europe.

Smith has extensive experience as a clinical scientist. Most recently, he worked as a global senior scientist for Terumo BCT, where he supported immunotherapy clients with technical and operational questions about apheresis and the optimization of the protocol for specific purposes. He worked with transplant physicians, engineers and scientists to design and implement study protocols, including first-in-human and pre-registration activities through post-market surveillance work.

Since 1996, he has worked internationally with biotechnology and engineering companies, specializing in the clinical and scientific support of medical devices used in cellular therapies and stem cell medicine. He continues to publish and present on a variety of cell separation and processing technologies.

Smith received his education and training at Southampton University Hospitals NHS Trust in the department of Haematology and Serology.

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# About NMDP BioTherapies℠

NMDP BioTherapies works with cell and gene therapy companies, cell collection centers and cell therapy labs to ensure the highest quality cellular therapy starting material is available to manufacture life-saving cell and gene therapies for patients in need.

Our organization is in a unique position to bridge the gap between stakeholders to find common ground that can lead to more efficient, standardized processes and, ultimately, better therapies for patients. Through NMDP℠, we have more than 30 years of experience managing the global supply chain for the first cellular therapy: hematopoietic stem cell transplantation and have enhanced our capabilities to also support the growing market for cell and gene therapies.

During that time, we built a Network of more than 110 U.S. apheresis and marrow collection centers and 180 transplant centers; developed relationships with donor centers, transplant centers and registries in 46 countries outside of the U.S.; and grew the NMDP Registry℠ into the largest and most ethnically diverse listing of potential donors and umbilical cord blood units in the world. This has allowed us to successfully manage more than 92,000 cell therapies worldwide.

As the cell and gene therapy industry has evolved, an increased number of therapies require autologous or allogeneic cells as starting material. Our experience has provided us with a unique understanding of the complex needs of the cell and gene therapy industry, as well as collection and transplant centers.

Our Quality System Audit Program (QSAP), for example, brings a standardized approach to audits. Our American Society for Quality-certified auditors evaluate collection centers and cell therapy labs for compliance with GTP, GMP and other applicable regulations. QSAP allows cell and gene therapy companies to license quality system audit results from NMDP BioTherapies, efficiently move centers and labs from qualification to activation, and minimize the audit burden on collection centers and cell therapy labs.

In partnership with the Standards Coordinating Body, we are actively engaging industry, clinical and accrediting agencies in discussions to promote the development of standardized processes—and accelerate access for patients to the life-saving cell and gene therapies they need.

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NP21389; FEB 2024