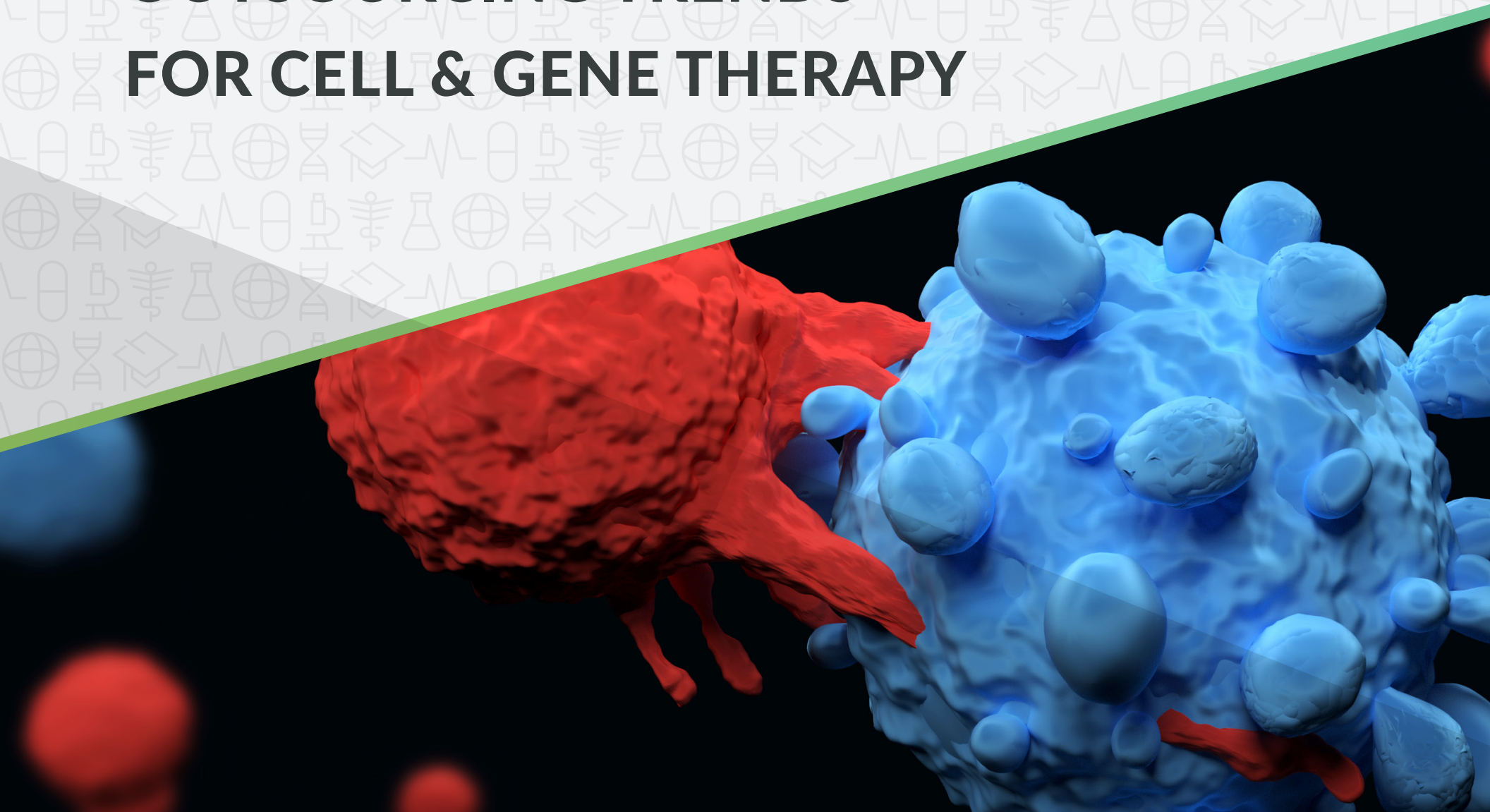
cell & gene

OUTSOURCING TRENDS FOR CELL & GENE THERAPY



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CDMO SELECTION: HOW TO KICK OFF A GAME-WINNING PROJECT

RAY SISON
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In my outsourcing experience, the transition from procurement to execution is always rushed. Often, critical activities like negotiating the master service agreement (MSA) take longer than expected, signatures are held up or purchase orders do not materialize. As a result, the project is behind before it even begins. Amidst tying up loose ends from the contracting phase and setting up the operational functions of the project, it is a tense yet exciting time for both the project sponsor and the CDMO. However, there is danger during the transition phase. In the rush and excitement, key connections vital to the success of the project can be missed. This will lead to miscommunication and misunderstanding — and eventually a strained relationship. Excitement can quickly give way to distress. Don't let this happen.

I have discussed the CDMO selection process in previous articles, ranging from request for proposal (RFP) development through negotiation and closing. This article explores the execution phase of outsourcing with a focus on the context and planning of the kickoff meeting. At this meeting, the handoff from the existing procurement team to the operations team will require close attention. Consider the following resources, inputs, and outputs:

- **People:** Who will be on the project teams? What are their respective roles and span of control?
- **Information:** What information will the teams need in order to create the deliv-

erables in accordance with the project objectives?

- **Process:** What processes need to be utilized or established within each organization in order for them to progress the project?
- **Materials:** What materials will be needed and/or produced? How much and when?
- **Technology:** What technology, equipment, or capabilities will be required to execute the scope of work (SOW) and where does it reside?
- **Documentation:** What are the data, documentation, or other outputs related to the SOW and its objectives?
- **Financial:** What is the timing of spend, initiation costs, fees, penalties, or other financial triggers associated with the SOW?

Let's examine each in further detail.

INCLUDE NEW TEAMS AND STAKEHOLDERS

At kickoff, both the sponsor and CDMO will field new or modified teams and stakeholders. Note which procurement team members are exiting or will step back from active participation to become stakeholders. They maintain the project history and can recount important information about the selection process and original project objectives. Onboarding project managers (PMs) should be able to tap them as resources as needed.

Table 1: Project Team Transition for Technology Transfer and Scale-Up

Procurement

Sponsor	CDMO
Technical Lead	Business Development
QA Lead	Quote Writer
Regulatory	Manufacturing Head
Purchasing	PM Director
Executive/Management	Executive/Site Management
	Analytical Head

Operations

Sponsor	CDMO
PM	PM
Technical Lead/s	Manufacturing Leader
QA – Staff	Packaging Leader
	Analytical Leader
	QC Leader
	Stability Coordinator
	QA Representative

Note that a PM is listed for both the sponsor and CDMO. It is highly advisable for the sponsor to assign its own PM as a single point of contact and coordinator of all sponsor-related activities associatedwith the project at the CDMO.

The takeaway from the example above is that contracting activities are typically exercised at a higher level and with a different set of personnel than the operations team — notably on the CDMO side. Resources that will be executing the SOW will operate at a granular level and may not be aware of overall project objectives, priorities, or strategies discussed and negotiated during procurement.

INFORMATION MUST FLOW IN ALL DIRECTIONS

While the kickoff is a formal transition, the transition will have already started at several key points prior to this. Compile any key learnings from previous interactions and use the meeting to communicate them to the operations team. At the CDMO, the team may not be able to put their daily activities into the context of the larger program or they may not have visibility into other critical workflows, e.g., clinical, regulatory, commercial, etc. The new teams will have varying and limited levels of familiarity with each other, their processes, and/or their capabilities. This is normal. In a well-planned kickoff meeting, take the opportunity to reintroduce the project. Strive to create a level playing field and a common knowledge base.

Key points of information exchange may include:

1. **First contact** – The first information exchange begins the dialogue between the sponsor and the eventual CDMO. Any usable ideas or strategies from this point forward should be conveyed to the operations team.

2. **RFP development/SOW** – Scope development represents a high level of information exchange, refinement, and detailed sequences, as well as groups of activities. This will directly inform the CDMO project plan and its integration into the global program plan.

3. **Site Visit Capabilities Assessment** – Information exchange regarding facilities, equipment, process, and personnel will set expectations with the sponsor. In-depth technical discussions and preliminary project risk assessments may have been shared

during the visit. Sponsor technical leads will likely have taken part in the site visit. These findings should be revisited and re-evaluated, especially if any of the assumptions have changed.

4. **Kickoff Prep** – In the weeks prior to the kickoff, the PMs need to be assigned and must work together on the agenda, administrative items, information exchange, and procurement of long lead time items.

AGREE ON PROCESS AND RESPONSIBILITIES

The MSA and quality technical agreement (QTA) are source documents for the responsibilities, representation, and warrants of each party. It is a best practice to have negotiators of these documents lead a high-level review of salient negotiated points affecting the execution of the MSA or defining responsibilities and specific activities from the QTA. Agreement by both parties is needed on how to operationalize provisions of the MSA and QTA, e.g., change orders, reserving manufacturing slots, ordering materials, deviations, dispute resolution, etc. I find that this topic fits well during a discussion of administrative items that are routinely covered during the kickoff meeting.

EARLY PROCUREMENT OF MATERIALS

Because procurement of materials can often involve long lead times, it is an activity typically initiated weeks before the project kickoff. This requires assigning personnel, exchanging information, and establishing processes well ahead of the kickoff and will require some form of prepayment. In order to expedite project initiation, sponsors and CDMOs now routinely begin preliminary work prior to final execution of contracts. With agreement from both parties, some activities can be initiated on the basis of a letter of intent, purchase order, consultation agreement, limited SOW, etc. Be sure to understand the risks associated with initiating activities under a letter of intent, purchase order, or other arrangement short of a fully executed MSA and QTA.

Material flow outputs, e.g., engineering batches, clinical trial materials (CTM), registration batch manufacture timing and coordination will obviously be part of the kickoff agenda. The CDMO PM will be responsible for building realistic timelines based on requirements and expectations communicated to them during the kickoff meeting.

IDENTIFY ALL NECESSARY TECHNOLOGY

During the capabilities assessment visit, the CDMO will have identified equipment, manufacturing lines, personnel, and skillsets applicable to the SOW and project. If additional equipment, materials, or capabilities are needed, they need to be identified and included in the project activities. All resources that are heavily used will need to be reserved and coordinated. This includes personnel.

Ray Sison
VP Pharmaceutical Outsourcing and Tech Transfer
Xcell Strategic Consulting

SET EXPECTATIONS FOR DOCUMENTATION

Well-written proposals will identify documents that are the deliverables for each phase of work. Consider these on par with material flow outputs and set expectations for quality, format, content, etc. When reviewing the SOW during the kickoff, create a checklist of deliverables and expected completion dates. If the operations team identifies additional deliverables or required adjustments that are not included in the SOW, these should be negotiated as part of the SOW.

INCLUDE FINANCIAL PROJECTIONS

Typically, financial triggers and timing are not included in the kickoff agenda. However, both parties need to be clear on invoicing and payment processes, fees, penalties, pass-throughs, and other arrangements detailed in the MSA. Many sponsors benefit from receiving a timing of spend projection from the CDMO based on the timeline and anticipated milestones.

After taking a methodical approach to preparing for project initiation and the kickoff meeting, the sponsor should be proactive and generate an agenda to discuss with the CDMO setting expectations.

An example agenda for the meeting may look something like this:

AGENDA

- Introductions
- Sponsor Presentation
  - Company
  - Project Background and Context
  - Objectives/Priorities
- CDMO Presentation
  - SOW Review and Deliverables
  - Project Assessment/Technical Discussion
- Administrative
  - MSA/QTA Review
  - Communication
- Site Tour
- Open Discussion/Next Steps

KICKOFF MEETING BEST PRACTICES

- **Be present.** Given the breadth of topics and importance of information exchange, do not forgo the opportunity to meet personally with the operations team and build rapport from the start.
- **Be proactive.** Develop an agenda and use it for preliminary talking points to set expectations for the kickoff meeting.
- **Staff up.** Recognize that personnel will be changing and that the newcomers will not have the benefit of accumulated knowledge gained in preceding months. Set a level playing field for all team members. Assign a PM prior to kickoff and well ahead of contract execution if timing is critical to coordinate activities with the CDMO.
- **Build on what's done.** Use the MSA and QTA as a basis to assign responsibilities and to develop processes between companies. Review the SOW to highlight project deliverables and agree on strategy and rationale.

To summarize, considerable effort has been expended by both the sponsor and CDMO throughout the selection process. Transitioning to contract execution should be methodical, regardless of the rush and eagerness to move the project forward. In preparing for the kickoff meeting, a sponsor should take a methodical approach and work with the CDMO in a proactive way to script the kickoff meeting to effectively communicate the accumulated knowledge from the procurement teams to the operational teams.

ABOUT THE AUTHOR

Ray Sison is VP of Pharmaceutical Outsourcing and Tech Transfer at xCell Strategic Consulting. He began consulting in 2011 after recognizing a need for expertise in pharmaceutical outsourcing among the discovery- and clinical-stage pharma companies he served as a business development representative for Patheon and MDS Pharma Services. Based on his experience, Sison provides insight to the CDMO's business and operations, helping his clients negotiate and achieve better outcomes. Additionally, he has developed sound processes and templates to streamline CMO procurement to save time and cost. In this series of articles, as well as online webinars, he continues to share best practices and case studies, helping improve the outsourced business model.

CAR T-CELL THERAPIES: CURRENT LIMITATIONS & FUTURE OPPORTUNITIES

ANAMIKA GHOSH, PH.D. &
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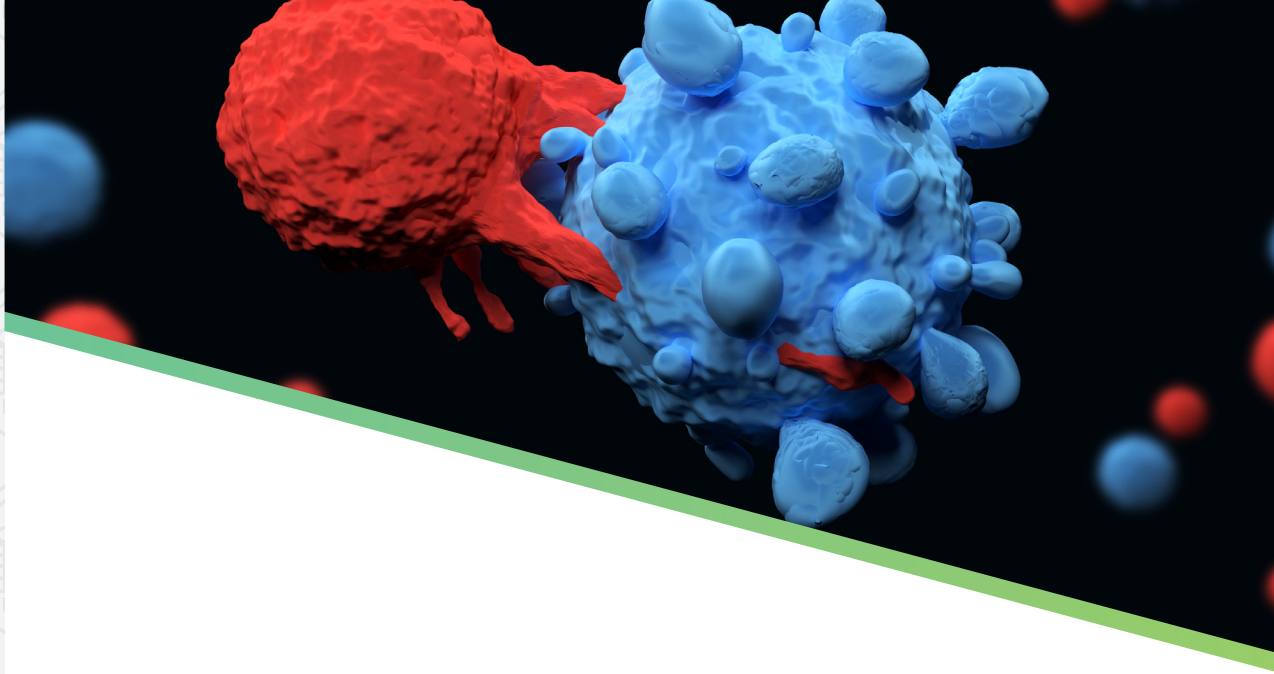
DRG ONCOLOGY



A novel and exciting approach to cancer treatment, CAR T cell therapies bring forth a new paradigm in cancer immunotherapy, wherein a patient's own T cells are bioengineered to express chimeric antigen receptors (CARs) that identify, attach to, and subsequently kill tumor cells.

Novartis' Kymriah, the first ever such therapy to receive regulatory approval for the treatment of B-cell acute lymphoblastic leukemia (ALL), a hematological malignancy, entered the U.S. market in August 2017 and was followed in October 2017 by Gilead/Kite Pharma's Yescarta — also a CAR T cell therapy — targeting diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), subtypes of non-Hodgkin's lymphoma (NHL). Kymriah was subsequently granted an FDA label expansion to include its use in patients with DLBCL in May 2018. Geographic expansion soon followed, with Kymriah receiving marketing authorization from the EU in August 2018 and from Japan's MHLW in March 2019 for treatment of B-cell ALL and DLBCL and Yescarta receiving EU approval in August 2019 for treatment of DLBCL and PMBCL.

The landmark approvals and clinical success of Kymriah and Yescarta opened new and encouraging avenues for developers of cellular immunotherapies. Research in the field

of CAR T cells has progressed rapidly, and novel technologies to address areas left unaddressed by Kymriah and Yescarta have started streaming into the research arena.

This article aims to focus on the barriers to widespread commercial adoption of the currently available CAR T cell therapies and how these weaknesses are presenting opportunities for developers of the next generation of CAR T cells.

LIMITATIONS DIRECTLY AFFECTING PATIENTS

LIFE-THREATENING ADVERSE EVENTS

Close patient monitoring is a crucial part of the treatment protocol for both Kymriah and Yescarta, as the therapies are associated with high-risk side effects such as cytokine release syndrome (CRS) and CAR T-related encephalopathy syndrome (CRES). CRS, a type of systemic inflammatory response, is typically characterized by high fever, lower-than-normal blood pressure, and difficulty breathing. CRES, a toxic encephalopathic state, often manifests with symptoms of confusion and delirium, seizures, and cerebral edema. Administration of CAR T cells must be followed by strict adherence to patient safety protocols to ensure that proper measures are taken to immediately manage these high-risk side effects.

WAIT DURING VEIN-TO-VEIN TIME

The manufacturing process of autologous CAR T cells requires leukapheresis, followed by extraction of patients' T cells, transportation to the manufacturing facility, genetic engineering to incorporate CARs, and transportation of the finished product back to the treatment center. The highly personalized therapy is then administered to the patient. The period in between, referred to as vein-to-vein time, ranges between three and four weeks for both Yescarta and Kymriah. This period can be daunting for the patients awaiting treatment and renders these CAR T cells unsuitable for patients with rapidly progressing disease.

TREATMENT IS RESTRICTED TO HEAVILY PRETREATED PATIENTS

Patients must have progressed on at least two lines of systemic therapies to be eligible for Kymriah or Yescarta treatment. Heavily pretreated patients can be weakened by

progressing disease and prior therapies and thus be unable to withstand the severe side effects of CAR T cells. Thus, the eligible patient pool to qualify for these therapies gets further limited to heavily pretreated patients with good performance status.

Anamika Ghosh
Lead Analyst
Decision Resources Group

LIMITATIONS DIRECTLY AFFECTING HEALTH-CARE PRACTITIONERS

COMPLEX PATIENT REFERRAL PATHWAY

Because of the complex nature of the therapy and its associated high-risk side effects, access to CAR T cells is highly regulated, being available only at certified centers. Primary care oncologists must refer eligible patients to CAR T cell therapy specialists, a process that hinders the widespread adoption of CAR T cell therapy. To offset this complexity, Gilead is now training its oncology representatives to inform physicians about CAR T cells, encourage identification of Yescarta-eligible patients, and help them with patient referrals.

Dana Gheorghe
Associate Director, Oncology Team
Decision Resources Group

ACCREDITATION OF CAR T-CELLS SPECIALTY CENTERS AND TRAINING OF HOSPITAL STAFF

The FDA mandates CAR T cells be available only through a restricted and regulated program, in certified centers and administered by trained healthcare providers (HCPs) who adhere to risk evaluation and mitigation strategies (REMS) guidelines. Training of HCPs is a mandatory step toward getting a center certified as a CAR T cell specialist center. The long training process and the increasing demand for CAR T cells, however, are increasing patient waiting lists as new centers await certification.

LACK OF CLARITY IN PLACEMENT OF CAR T CELLS IN TREATMENT PRACTICE

Novel drug classes with limited clinical data, such as CAR T cells, require research to ascertain some practical aspects of patient treatment in the commercial setting. Some

physicians are skeptical about prescribing CAR T cells, as they are unsure about this therapy's place in the treatment algorithm and its impact on further lines of therapy.

LIMITATIONS ASSOCIATED WITH COMPLICATED MANUFACTURING PROCESS

FAILURE IN PRODUCTION

Being a highly personalized therapy, the complex, multistep process of generating autologous CAR T cells increases the risk of production failure, an event that delays and, in some instances, even denies access to the therapy.

Commercial Scalability Challenges

With each product representing a fresh manufacturing batch, the production of autologous CAR T cells that meet commercial demand and anticipated label and geographical expansions, while maintaining product quality and clinical equivalence, remains a challenge.

LIMITATIONS DUE TO EXCEPTIONALLY HIGH THERAPY COST AND COMPLICATED PAYER POLICIES

In the United States, CMS recently raised reimbursement of the total cost of CAR T cell therapies from 50 percent to 65 percent, effective from 2020. Treating physicians, however, maintain that given the extremely high cost of therapy (ranging between $373,000 and $475,000 per infusion) and patient management (which can go as high as, and sometimes also over, $0.5 million), the reimbursement gap remains unsustainable and is a huge impediment to patient access. Novartis offers outcomes-based pricing for Kymriah (only for the treatment of B-cell ALL) — an agreement that ties the therapy's clinical success to its payment. However, this arrangement does not include the hospital expenses associated with the therapy. While the access and reimbursement policies are being ironed out, the queue of patients waiting for insurance clearance is continuing to grow.

OPPORTUNITIES & DEVELOPMENTS

Despite the challenges listed above, the overall attitude about CAR T cells is decidedly positive. Investors are convinced that CAR T cells are a revolutionary cancer treatment. While physicians indicate that the safety issues that are synonymous with CAR T cell therapy are a huge concern and call for an urgent solution, research is already underway to devise solutions that can address the pain points of the currently available CAR T cells. Some noteworthy concepts and developments are discussed below.

IMPROVING SAFETY

Advanced Safety Mechanisms

Being "live" drugs, many of the safety issues of CAR T cells are attributed to the difficulty in controlling the cells' proliferation and activation, which can lead to symptoms of an immune system in overdrive. Various companies are employing novel techniques to address this problem. Researchers are working on tunable CAR T cells whose proliferation, concentration, activation, and elimination can be regulated with an inducer agent. For example, Juno Therapeutics' lisocabtagene maraleucel contains a truncated form of epidermal growth factor (EGFR), EGFRt, that enables rapid elimination of these CAR T cells using cetuximab, an EGFR inhibitor. Bellicum Pharma's CAR T cell candidate, BPX-601, employs an inducible MyD88/CD40 activation switch, and the therapeutic effect and level of activation of BPX-601 can be modulated by regulating the concentration of a small-molecule inducer, rimiducid. Similarly, Autolus' AUTO-2 and AUTO-4 can be turned off by administering monoclonal antibody rituximab. Autolus is also developing next-generation CAR T cells for solid tumors that incorporate a suicide cassette called rapaCasp9 that is controlled by rapamycin, a compound with a better tissue penetration and faster effect than rituximab.

Improving On-Target/Off-Tumor Targeting And Overcoming Risk Of Resistance Due To Antigen Loss

Tumor plasticity leading to loss or modulation of antigen is one of the primary tumor escape mechanisms that results in development of resistance to antineoplastic therapies. To overcome this risk, researchers are developing bi-specific [e.g., Autolus' AUTO-2 (TACI/BCMA-specific), AUTO-3 (CD19/CD22-specific)] and multi-targeted

[e.g., Celyad's CYAD-01 (NKG2D receptor-specific)] CAR T cells. It is expected that such multi-targeted CAR T cells will have better on-target/off-tumor specificity and will thus have lesser side effects than single-targeted CAR T cells.

EXPANDING THE SCOPE OF TREATMENT

Going Beyond CD19-Targeting

Both Yescarta and Kymriah are CD19-targeting CAR T cells, and many emerging CAR T-cell therapy developers are continuing to focus on this antigen. CD19, a target expressed mostly on B-cells, has served as an excellent target for the first generation of successful CAR T cells; however, researchers are gradually beginning to shift their focus to other tumor antigens with the aim of expanding the scope of cancer treatment beyond B-cell hematological malignancies. Some of the most advanced and noteworthy of this new wave of CAR T cells are bluebird bio's bb2121 (BCMA-specific for multiple myeloma), Mustang Bio's MB-102 (CD123-targeting for AML), and Juno Therapeutics' JCAR018 (CD22-targeting for follicular lymphoma and B-cell ALL).

Treating Solid Tumors

Solid tumors are undeniably a much larger market (and hence, attractive to investors) than hematological malignancies, and being able to launch a successful CAR T-cell therapy in a solid tumor indication represents a holy Grail. Achieving success in solid tumors, however, is an enormous challenge because of target antigen heterogeneity, a general lack in specific cell surface antigens, physical barriers (like dense stroma or obscure tumor location), and immunosuppressive microenvironment. One of the approaches being adopted to overcome some of these challenges is intratumoral delivery of CAR T cells [e.g., Mustang Bio's MB-103 for glioma, Leucid Bio's 4ab T1E28z+ T-cells for squamous cell carcinoma of the head and neck (SCCHN)]. Other researchers are focusing their efforts on well-established solid tumor antigens (such as CEA-targeting CAR T cells by Sorrento Therapeutics for metastatic liver tumors and Novartis' mesothelin-targeting NIU-440 for various mesothelin-positive cancers). To improve tumor targeting and potency, development is also focused on multi-targeted CAR T cells, such as Aurora BioPharma's AU-105 (HER2/CMV antigen targeting) or multifunctional CAR T cells [e.g., Celyad's CYAD-01 (NKG2D receptor-specific) and Baylor College of Medicine's GD2-targeted Epstein-Barr virus-specific cytotoxic T lymphocytes (CTLs)].

Off-The-Shelf CAR T Cells To Address Logistic Challenges And Waiting Periods

Most of the logistic challenges associated with the complex manufacturing process of the current generation of autologous CAR T cells will likely get addressed with allogeneic, off-the-shelf CAR T cells. Allogeneic CAR T cells are generated from healthy donor cells that are better in both quality and quantity than cells derived from patients. These CAR T cells will be readily available for patients, thus reducing the gap between prescribing and administering the therapy. This would be especially beneficial for patients with rapidly progressive disease. Additionally, as each batch of allogeneic CAR T cells could be used to treat multiple patients, the overall therapy costs would diminish, and the scalability challenges would be overcome. However, anticipated safety challenges, like graft-versus-host disease (GvHD) and immune rejection, cannot be disregarded. Developers of allogeneic CAR T cells are testing various gene editing techniques to generate universal CAR T cells. For example, CRISPR Therapeutics' CTX-110 employs clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 multiplexed gene editing technique to eliminate T cell receptor (TCR) and major histocompatibility complex class I (MHC-I) expression, thereby minimizing the risk of GvHD and recognition and rejection by a patient's own T cells. In Servier/Allogene Therapeutics' UCART19, TRAC and CD52 genes are disrupted, thereby allowing administration in non-HLA (human leukocyte antigen)-matched patients.

INCREASING POTENCY

Increasing CAR T Cells' Persistence With Defined Cell Composition

Biological characteristics of different subsets of T cells can be exploited to attain distinct characteristics in CAR T cells. For example, Poseida Therapeutics' P-BCMA-101 is enriched in T-stem cell memory (Tscm) cells. Tscm cells are long-lived, are multipotent, and gradually produce T-effector cells; these properties are anticipated to render CAR T cells with more durable therapeutic response than the current CAR T cells, which are composed largely of the short-lived T-effector cells. Baylor College of Medicine is employing NK-T cells (GD2-targeting, IL15-expressing CAR NK-T cells) that are known to co-localize with tumor-associated macrophages (TAMs) and can effectively permeate into solid tumor tissues. City of Hope and NCI are collaboratively developing CAR T cells based on T-central memory (Tcm)-enriched CD8+ T cells that are known to have

better persistence and migration potential to secondary lymphoid tissues than standard T cells.

Overcoming Immunosuppressive Tumor Microenvironment

Tumors with immunosuppressive environs, referred to as immunotherapy-cold tumors, present a particularly difficult challenge for immunotherapies. To address this challenge, CAR T cell developers are coming up with novel mechanisms to combine CAR T cells with pro-inflammatory cytokines. One of the techniques being employed to offset the side effects of systemic administration of cytokines is the incorporation of the cytokine gene within the CAR T-cell construct. An example of such an approach is Juno Therapeutics' MUC16-targeting, IL12-secreting "armored" CAR T cells – JCAR-020, currently in an early-phase trial in solid tumors. Another interesting concept being tested by Baylor College of Medicine is the TGFβ-resistant (TGFβ being an immunosuppressing cytokine) HER2-targeting, Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes (EBV-specific CTLs).

Combination With Immune Checkpoint Inhibition To Overcome T-Cell Exhaustion

Immune checkpoints can attenuate the activity of CAR T cells and quicken T cell exhaustion. CAR T cell developers are addressing this challenge by testing the combination of CAR T cells with immune checkpoint inhibitors (e.g., Autolus' AUTO-3 in combination with Merck & Co.'s Keytruda), by incorporating an immune checkpoint inhibitor-secretory gene within the CAR construct (e.g., Marino Biotechnology's PD1 shRNA-expressing iPD1-CD19-eCAR T cells), or by creating immune checkpoint-resistant CAR T cells (e.g., Innovative Cellular Therapeutics' dominant negative PD1 CAR T cells, ICTCAR-014).

CONCLUSION

CAR T cells show immense potential, but they also face substantial challenges to more widespread adoption. Since their launch, sales of Yescarta and Kymriah have been increasing at a relatively slow pace, with barriers such as reimbursement, patient selection and access, and manufacturing issues hindering their commercial success. These hurdles will need to be overcome in order to fully capitalize on the potential of these

therapies. Nevertheless, encouraged by the clinical activity demonstrated by Kymriah and Yescarta, researchers have turned their focus to immune cells other than T cells, such as macrophages and NK cells. While researchers are fine-tuning cellular immunotherapies with novel concepts or technologies, the medical community is eagerly waiting for the therapy that can address all the limitations of the currently approved CAR T cells.

ABOUT THE AUTHORS

Anamika Ghosh is a lead business insights analyst in the Biopharma Oncology team at Decision Resources Group (DRG). She has expertise in various solid and hematological malignancies, and various immune-oncology drug classes, such as immune checkpoint inhibitors and CAR T cells. She has over six years of experience in the field of oncology market research and in providing strategic insight solutions for oncology. Ghosh received her Ph.D. in life sciences from the International Centre for Genetic Engineering and Biotechnology (ICGEB) and her M.Sc. in biomedical sciences from the University of Delhi.

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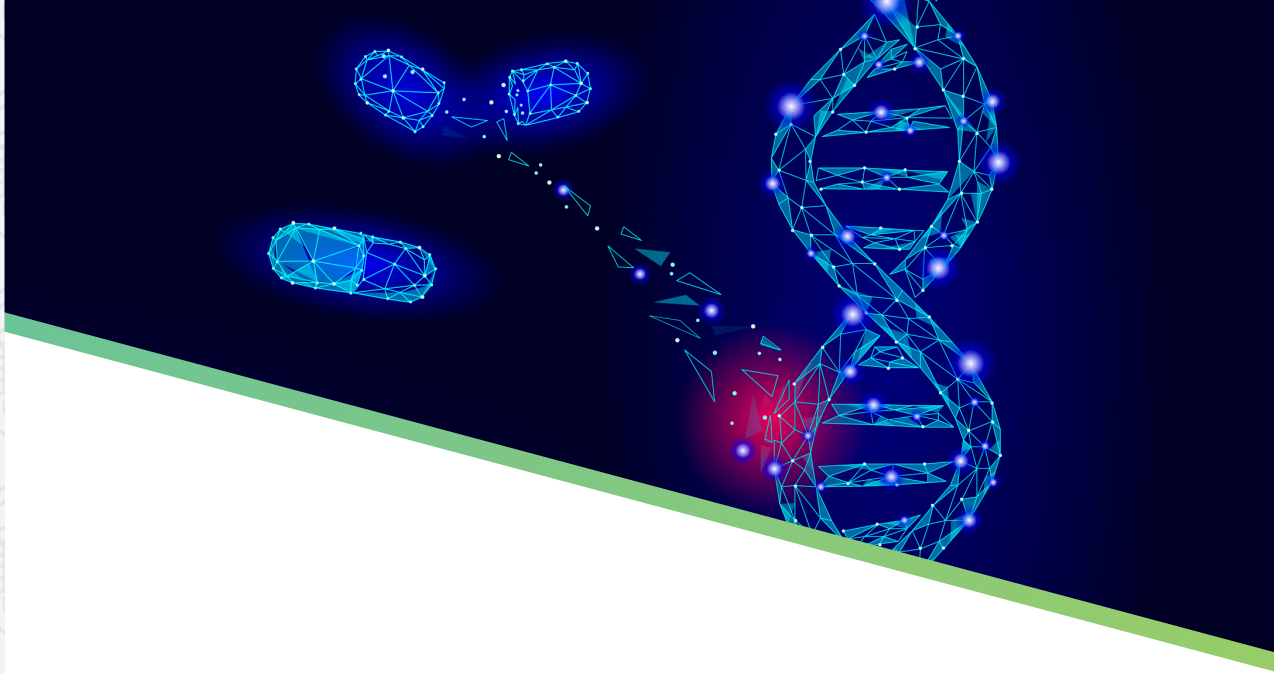
ADAPTIMMUNE'S DEEP DIVE INTO MANUFACTURING & PROCESS DEVELOPMENT

ERIN HARRIS, EDITOR-IN-CHIEF
CELL & GENE



In Part 1 of our two-part series with Adaptimmune, CEO James Noble, who has announced his retirement since the publication of this article, provided thoughtful insight on the status of combatting solid tumors as well as the ongoing pricing issue affecting the cell and gene therapy sector. Here, along with John Lunger, SVP, Manufacturing and Supply Chain, and Mark Dudley, SVP, Product Development at Adaptimmune, we dig deeper into the topics discussed in Part 1 — we shed granular light on how pricing will affect manufacturing; we talk outsourced versus in-house manufacturing and more.

NEW METHODS OF MANUFACTURING

In Part 1, Noble discussed how the pricing of cell therapies will come down because the cost of manufacturing will decrease and there will be completely different manufacturing methods. So, what are these different methods of manufacturing? Lunger explains that Adaptimmune is constantly assessing new technologies for their applicability to their manufacturing process and supply chain. "Technical innovation in equipment (bioreactors), supplies (media) and information management (bar coding and "big data" analytics) are improving manufacturing process as well as the safety and potency of the cell product," he says. "New equipment and rapid data analytics enable the implementation of automated operations, increasing process reliability and through-

put. Process improvement to “close open steps” and digitally capture data reduce the sterility risks to our product, which cannot be sterile filtered, and reduce vein-to-vein time by simplifying product release. Future efforts aim at the adoption of cutting-edge technology for cell separation, gene transfer, activation, and characterization that may reduce the dose while improving potency.”

John Lunger
SVP, Manufacturing and Supply Chain
Adaptimmune

Lunger goes on to explain that these new manufacturing methods will allow Adaptimmune to have a less manual, more robust process, which will enable them to become more efficient and provide increased control over a complex manufacturing process. “New technologies are scalable without increased manual oversight. New analytic tools enable rapid understanding of cell product potency, and improvements of manufacturing methods that capitalize on the new understanding.”

Mark Dudley
SVP, Product Development
Adaptimmune

Note that both cell and gene manufacturers and equipment manufactures are developing these new methods. However, the need for and the offer of new manufacturing and processing technologies are evolving rapidly and constantly, which requires cell and gene therapy manufacturers to be able to quickly and effectively assess new technologies for their applicability to their own products.

In terms of coming to market, Dudley explains that Adaptimmune has the capability to have multiple processes for multiple trials. For example, the process for its SPEARHEAD-1 clinical trial incorporates several process improvements compared to the Ph1 trial of the ADP-A2M4 product. These result in decreased time for vein-to-vein manufacturing execution, improved reliability of product release, and increased understanding of each individual product prior to administration. The SURPASS trial will be using a process with some changes from our SPEARHEAD-1 process that will further reduce vein-to-vein time, increase product potency, and reduce costs of goods associated with manufacturing.

With the “One Patient, One Batch” nature of autologous cell therapy, Adaptimmune is always examining the opportunity to improve its processes while maintaining the high quality standards required by GMP, as well as finding the best and most rapid way to introduce these improvements to manufacture products for our clinical trials and in the future for our marketed products.

But, how will these new methods help decrease the cost of manufacturing? Lunger explains the current process changes improve CoGs in several ways. “First, automation will enable more throughput with the same/less direct labor. Second, simplifying the process and reducing “open steps” will enable a decrease in the manufacturing and “vein to vein” cycle time. As a result, more patient batches can be processed in a given period with greater reliability. Third, optimizing the inputs of raw materials, in particular high cost materials such as the viral vector, will reduce direct costs per patient batch. And finally, improving product potency allow the reduction of total cell dose to achieve equivalent clinical outcomes, reducing manufacturing costs.”

Lunger also states that when it comes to estimating how these new methods will decrease the price of cell therapies, specific numbers are hard to estimate. “If you look at the reduction in CoGS that biologics/MaBs have experienced from the early days of the technology to now, we believe we could anticipate similar improvements,” he says. Biologics manufacturing typically generates inventory that can be stockpiled for CMC risk mitigation. Autologous cell therapies always rely on a “just in time” approach for which a production run is typically the only product available to a patient. Despite these divergent manufacturing approaches, several lessons from biologicals can be applied to autologous C> treatments. A phase-appropriate quality control strategy, prospective capacity/demand planning, and “quality by design” principles were developed before C> products and are important to apply in an integrated C> manufacturing and supply network.

FROM ACADEMIA TO COMMERCIALIZATION

It’s a tremendous challenge to scale-up cell and gene therapies from an academic setting to commercialization. “Cell and gene therapy is a complex process, and since it is still new, there is relatively little expertise in the market,” Dudley states. “Therefore, our advice would be to start early to develop the manufacturing and supply capability,

either internally or externally, while establishing a culture that embraces nimble, "fit-for-purpose" quality lifecycle management (QLM) principles. Exploratory clinical trial sponsors (including academic sites) should fully integrate CMC and clinical operations to enable the most rapid product development. Clinical sponsors should maintain flexibility to improve the process and product while de-risking the supply chain and scaling manufacturing. Commercial activities require optimized supply execution in global markets and should engage patients and physicians to improve the "customer" experience. This approach is working well for Adaptimmune." "Hindsight is always 20/20, but the one thing would you have done differently from the start with manufacturing is that we would have likely invested even earlier in our CMC growth and internal capability development," says Lunger.

THE PROS AND CONS OF WORKING WITH PARTNERS

Adaptimmune currently has dedicated space and personnel set up with two CMOs: PCT Hitachi in the Navy Yard (Philly) and the Cell and Gene Therapy Catapult in the UK. These are two different models. "While PCT Hitachi is a more traditional CDMO, where their staff do the manufacturing on their equipment, C> Catapult in the UK is more of an incubator model, where they support innovation by providing the facility and some infrastructure, but the manufacturing is done with Adaptimmune people and equipment," states Dudley. "The C> Catapult approach enables us to develop the organizational capability for internal manufacturing, potentially at our own facility in the future, without the initial infrastructure investment. Another difference between what we do with each is that we are developing viral vector manufacturing at C> Catapult, whereas with PCT Hitachi is SPEAR T-cell drug product manufacturing. External CDMOS, when combined with internal capability provide some level of flexibility and supply risk mitigation. This is something to consider carefully for autologous cell therapy products."

CMOS VS. IN-HOUSE MANUFACTURING

As expected, in-house manufacturing versus CMO is a bit of both and something else entirely. "Autologous products must obviously be thought of differently than allogeneic, but even more so when you consider autologous products in the cancer field,

compared to other therapeutic areas," says Dudley. "The reason is that rapid manufacturing cycle time and flexibility, to work around patient treatment schedules, is paramount to successful trials and products, because patients currently treated with our therapies are heavily pre-treated and need access to treatment options quickly." In addition, the ability to access new technologies to improve manufacturing operations and product efficacy, and the rapid implementation of process improvements are key to cell and gene therapy success. Being in control of these activities is enabled by in-house capabilities.

BIGGER, BETTER, FASTER — HOW TO BRING THERAPIES TO MARKET QUICKLY AND COST EFFECTIVELY

Lunger and Dudley state that a difficult issue for cell and gene therapy is a need to better understand the mechanism of action for cellular immune products. "Development of a simple potency assay that predicts therapeutic safety and efficacy would enable developmental activities and regulatory filings to help scale commercial manufacturing," they explain. "Inexpensive and reproducible analytical tools that enable correlative studies, biomarker identification, and product improvements would accelerate cell and gene therapy adoption and technology dissemination."

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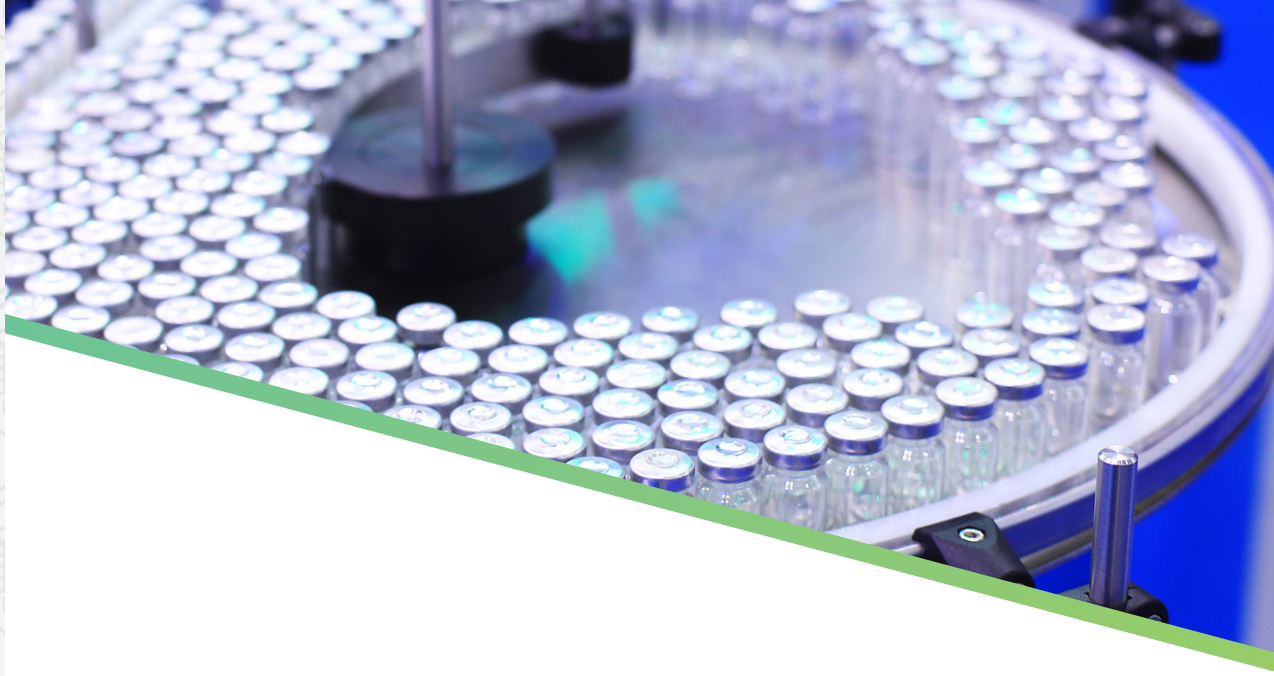
Erin Harris is chief editor of Cell & Gene and a contributing editor to Life Science Leader magazine. She studied English and psychology at Lafayette College and has 20+ years of experience in B2B publishing. Erin spent 10 years covering and reporting on the adoption of information technology from a B2B perspective. She's written on technology topics ranging from Big Data and analytics to security and e-commerce. In each case, her reporting centered on innovations that improved operational efficiencies, fostered interdepartmental collaboration, or enhanced supply chains. Currently, she writes actionable information for professionals involved in the development and commercialization of cell and gene therapies. She covers the entire product lifecycle from basic research to commercialization. Erin has interviewed executives from Fortune 500 as well as startups. She has moderated panel discussions and has spoken at numerous industry events from large conferences to niche forums.

DEVELOPING AND MANUFACTURING CELL & GENE THERAPIES: DO BIOPHARMA METHODS APPLY?

MARK F. WITCHER, PH.D.



Cellular and gene therapies, sometimes called advanced therapy medicinal products (ATMPs), represent a very rapidly emerging field of biotechnology with tremendous promise for future therapeutic applications. A reasonable question is: Are the methods used for developing the current generation of biopharmaceuticals, monoclonal antibodies, hormone replacements, etc., applicable to the next generation of biotech ATMPs? Or more importantly, can the similarities and the differences between the two generations of products be used to build methods that improve the development and commercialization of all types and future generations of biopharmaceutical products? In my opinion, while there are significant differences, the basic principles for developing both are nearly identical, requiring a clear understanding of the primary development and manufacturing goals for all biopharmaceutical products.

The two generations have significant differences in their business and reimbursement models, life cycle durations, patient selection, methods of administration, supply chain issues, etc. However, some very significant similarities can be identified. Both involve extremely complex products manufactured through very complicated processes. Both have a significant number of critical quality attributes (CQAs) that determine a product's safety and efficacy. But, very importantly, both have unknown and unmeasurable product attributes that can be classified as unknown-CQAs (U-CQAs) that very likely also have a significant impact on the product's safety and efficacy.[1] Control of U-CQAs can likely only be achieved by

careful control of the manufacturing processes over the pre-clinical, clinical, and commercial manufacturing life cycle to assure control of the processes' behavior and performance as both the CQAs and U-CQAs are produced. The level of U-CQAs is likely even higher in cellular and gene therapies because of the complex nature of the cellular products and the more intricate and semi-random incorporation of the gene therapy products into the patients' genetic structures.

Thus, all biopharmaceutical products have the same manufacturing problems that can best be solved using the same approaches and methods during their development and manufacturing life cycles, including a product's path through the regulatory approval processes. Although different therapies will likely reach different kinds of product attributes, the methods used to follow the paths can be essentially the same. The industry as a whole will be far more effective if it uses the same methods for all types of biopharmaceutical products. Methods based on sound science and basic engineering principles will be far more effective in solving very complex problems and providing effective communication platforms with regulatory agencies.

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For an industry that is unfortunately largely currently focused on compliance[2] as a design criterion, the new generation of ATMPs can present a wide variety of problems because many compliance standards have not yet been identified or established. Further, compliance standards beyond vague good manufacturing practices (GMPs) may never be desirable because of the complex, ever-changing definition of these products. In addition, these products may separate out into large multifaceted families of therapies based on genetic and epigenetic differences between groups of patients and various diseases.

If the industry can focus on prospectively building appropriate methods for achieving excellence rather than seeking compliance with poorly defined guidelines to address the fundamental life cycle challenges, the industry can more effectively achieve high product quality. If common methods based on sound principles are identified and widely used, the biopharmaceutical industry may also greatly reduce the development time for new products.

The industry basically needs two types of methods for developing complex manufacturing processes. The first is a method for managing the manufacturing process' life cycle. This approach was initiated using ICH Q8 and the FDA's 2011 Process Validation Guidance[3,4] and further expanded by using lifecycle process development and validation (LPDV) concepts.[5,6] LPDV is built around four basic questions: What, How, Will it work, and Did it work? These four questions are basic requirements for all processes and provide a universal framework that can be used to develop fundamentally sound methods required for manufacturing complex products using complicated processes.

When supported by a well-structured design space (ws-DS) and quality by design (wQbD), LPDV provides an effective tool for managing all types of process life cycles, especially the difficult problem of controlling U-CQA.[6] LPDV focuses on building control strategies within the ws-DS for controlling both the CQAs of the final product and the process' behavior over the development life cycle to assure successful commercialization of the product conceived and initially tested in early clinical trials.[1]

The second method uses quality risk management (QRM) tools initially described by ICH Q9.[7] However, the methods recommended in Q9, such as FMEA (failure modes and effects analysis), etc. have proven to be ineffective.[8] These methods do not properly address the risk's uncertainty of knowledge levels and probability of occurrence. [9,10] If the risks are viewed as being caused by input threats passing through a process to produce a risk consequence, a more structured approach is accessible for quickly assessing risks as part of a system risk structure (SRS).[9] The uncertainty of the structured risks can then be assessed using prospective causal risk models (PCRMs) to estimate the knowledge level and likelihood of the risk consequence's occurrence.[10] While SRS and PCRM might provide better approaches for managing risks, the biopharmaceutical industry and regulatory agencies must work diligently on better QRM methods to quickly and efficiently assess, manage, accept, and communicate the wide variety of risks necessary to make both proteins, ATMPs, and future generations of biopharmaceuticals.[11]

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Mark F. Witcher, Ph.D., has over 35 years of experience in biopharmaceuticals. He is currently a senior consultant with Brevitas Consulting. Previously, he worked for several engineering companies on feasibility and conceptual design studies for advanced biopharmaceutical manufacturing facilities. Witcher was an independent consultant in the biopharmaceutical industry for 15 years on operational issues related to: product and process development, strategic business development, clinical and commercial manufacturing, tech transfer, and facility design. He also taught courses on process validation for ISPE. He was previously the SVP of manufacturing operations for Covance Biotechnology Services, where he was responsible for the design, construction, start-up, and operation of their $50-million contract manufacturing facility. Prior to joining Covance, Witcher was VP of manufacturing at Amgen.

CDMO SELECTION: 3 QUESTIONS TO SAVE TIME AND REDUCE STRESS WHEN REVIEWING AN MSA

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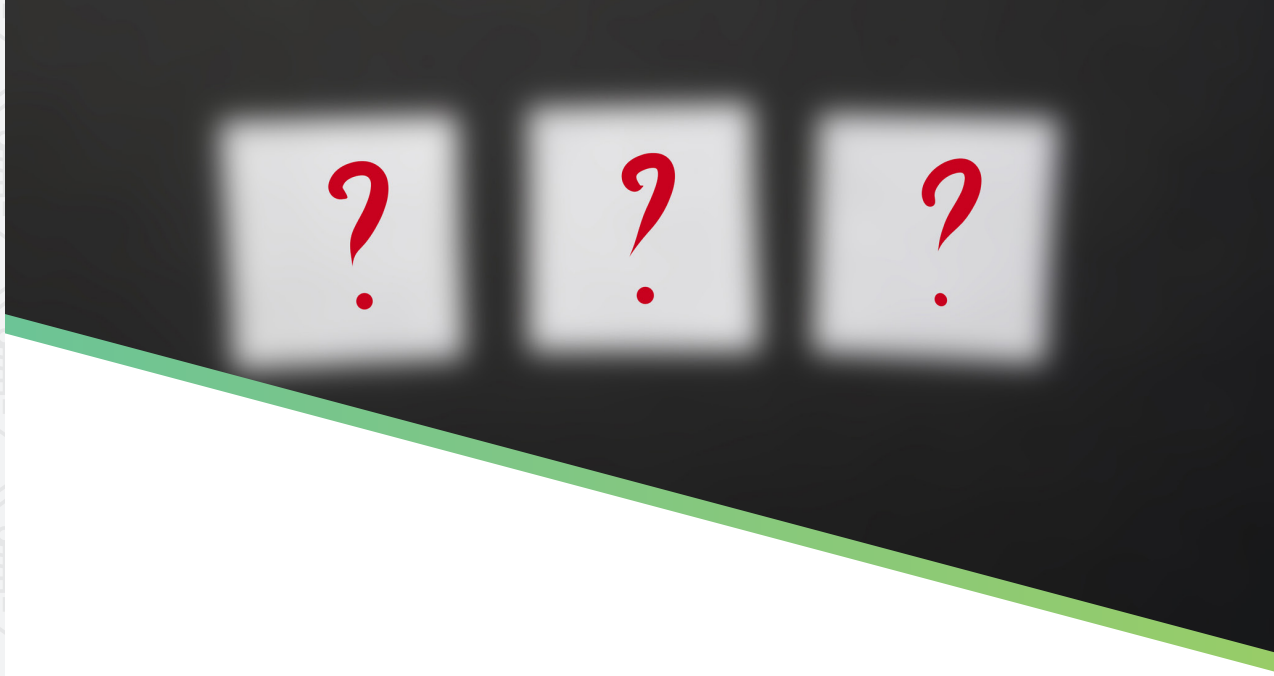

Whether because of unfamiliarity or lack of resources, master service or supply agreement (MSA) execution can be time consuming and difficult. At any given pharma company in the development or clinical stage, the leadership team and investors prioritize patients, therapies, and trial results. Equally important to success is a drug product supply chain for manufacturing, packaging, and distribution. Selecting CDMOs to support clinical trials that can also drive product launch is a challenging but critical task for many companies with novel compounds, e.g., highly potent drugs such as cytotoxics, biologics (including gene/cell therapies), and aseptically manufactured products. But unlike specialty and large pharma, startups typically do not have sophisticated procurement teams responsible for CDMO partnering.

Having negotiated for both buyers and sellers, I've developed shortcuts and best practices to help save time whenever a 55-page document hits my inbox and only one month is in the timeline for contract negotiation. First, understand that ***an MSA is not a novel, read from front to back. It is a functional legal document that provides operational, financial, and legal guidance*** that will be referenced as needed throughout the term of the agreement. My perspective represents the technical and operational functions leading the CDMO selection. Rely on your Quality, Regulatory, Legal, and other stakeholders to contribute in their respective areas of expertise.

NEGOTIATION STARTS BEFORE YOU RECEIVE THE MSA

Negotiation starts with the request for proposal. In a competitive bidding process, stipulate up front that in order to be a finalist (primary or backup), a bidder must provide an MSA template in Microsoft Word outline format with all internal references hyperlinked. If their template isn't already formatted this way, they will thank you for it later. This will allow anyone to create a table of contents (ToC) quickly if it is not included and to move through the document with ease. It also eliminates reformatting when sections are added/deleted and it updates all references automatically, reducing turnaround time on both ends.

Use the ToC or top-level outline view from the primary and backup bidders to get a general sense of structure and to determine if any critical sections are missing from either template. This benchmarking is the first level of comparison and can be scored as part of the overall evaluation. If timing is the top priority, the primary bidder may be determined based on the quality and anticipated negotiation effort of the MSA.

FOCUS ON EACH FUNCTION SEPARATELY

After the preliminary comparison, read each MSA three times. That's right, it sounds counterintuitive, but, as stated above, the MSA serves three broad functions and should be read with a focus on each in turn. Keeping each function separate allows you to identify and group sections and then to agree/disagree/comment in a logical flow.

Here are three questions you should continually ask yourself during review:

1. **Operational:** *What am I buying?*
2. **Financial:** *How am I paying?*
3. **Legal:** *What happens if (when) things go wrong?*

In your first pass, take on an operational perspective and

Ray Sison
VP Pharmaceutical Outsourcing and Tech Transfer
Xcell Strategic Consulting

read only sections that make mention of products and services. As the owner of the relationship, drug product development (technical) or supply chain (operations) teams must live with the agreement after it is signed. From a supply chain viewpoint, look at anything related to product or information flow. Be sure that your expectations are clearly reflected in the document and, if not, add comments. Remember that what is being bought could be a good or service, but it might also be data, reports, documents, or other output that will support a filing. Identify all references to goods or services and map them to your organization. Reflect on any previous technical and operational experience you have had with outsourcing and how you interacted under normal circumstances to obtain the deliverables outlined in the quotation.

In your second pass, look only at sections or subsections that discuss the financial aspects of the relationship. In development projects, there are up-front payments, monthly and milestone payments, and then there are the triggers for each. For commercial supply, there are forecasts, orders, release, shipping, etc. Each may trigger some level of payment. Be clear on the definitions for what constitutes the trigger for payment and comment accordingly. Other fees, pass-throughs, and penalties will be mentioned. Weigh in on what you are willing to accept, reject, or modify. From a supply chain viewpoint, look at anything related to money or information flow.

For the third pass, channel everything and anything you can recall that has ever gone wrong with a project and what happened in the aftermath. Read the sections that address abnormal circumstances and calibrate the fairness of the CDMO's position. Would the document provide useful guidance for your previous experiences? Are penalties/remedies reciprocal where appropriate? Your legal and regulatory colleagues should provide heavy input in this aspect. Agree on how to prioritize negotiation points. Be prepared to cite specific examples of real-world experiences to drive your points when negotiating with a CDMO. Few attorneys have ever been in a lab, warehouse, or manufacturing floor and thus they will have little context for the contract language. This is where operational input will be most valuable during negotiation.

Product/Service		Payment		Disputes	
Scope	Capacity	Quotations	Yield	Delay	Notice
Representations	Inventory	Amendments	Discount	Shortage	Claims
Warrants	Materials	Forecasts	Credit	Deviations	Breach
Responsibilities	Storage	Minimum Orders	Fees	Deficiency	For Cause
Term	Shipping	Volume	Penalty	Discrepancies	Audit
Performance	Acceptance	Orders	Adjustments	Non-conformance	Remedy
Obligations	Data / Records	Cancellation	Invoicing	Disputes	Resolution
Requirements	Qualification	Change Orders	Payment	Errors	Damages
Cooperation	Inspections	Price	Conversion	Defects	Liability
Filings	Intellectual Property	Currency	Costs	Failure	Indemnity
Forecasts	Confidentiality	Shipping	Pass Through	Reject	Insurance
Reservations		Delivery	Reimbursement	Recalls	Cancellation
		Acceptance	Expedited	Re-work	Termination
			Exclusivity	Re-performance	Risk

Table 1: Search Keywords for MSA Functions

BEST PRACTICES, PREPARATION REDUCE CYCLE TIME

After completing the three passes, here are a few best practices to prepare for MSA negotiation and reduce review cycle time:

1. Check any references to the quality agreement and ensure that it is properly aligned.
2. Skim the backup MSA for context and further benchmarking.
3. Keep a running tab on key negotiation points under each function to include in the body of an email when forwarding the document for internal review. This allows the internal stakeholders to focus their review and helps to set the agenda for negotiation.

The technical or operations lead is usually the person driving the CDMO selection process and receives the MSA directly from the CDMO. As the first reviewer, the ability to effectively process the document and then pass along meaningful comments and negotiation points will set the stage for developing an internal strategy. While it is not unusual for Legal to take the lead in contract negotiations, as owner of the relationship the project lead should be at the table providing clear guidance and subject

matter expertise. The concepts in this article can help you better prepare for the negotiation and ultimately tip the balance. If negotiations hit an impasse, be prepared to move to the backup bidder. Obviously, nobody wins every battle, so bear in mind that the goal is to protect your company's interests while not hindering progress toward company objectives. Strike a balance, close the deal, and get ready for project kickoff.

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Ray Sison is VP of Pharmaceutical Outsourcing and Tech Transfer at xCell Strategic Consulting. He began consulting in 2011 after recognizing a need for expertise in pharmaceutical outsourcing among the discovery- and clinical-stage pharma companies he served as a business development representative for Patheon and MDS Pharma Services. Based on his experience, Sison provides insight to the CDMO's business and operations, helping his clients negotiate and achieve better outcomes. Additionally, he has developed sound processes and templates to streamline CMO procurement to save time and cost. In this series of articles, as well as online webinars, he continues to share best practices and case studies, helping improve the outsourced business model.

3 BUSINESS CHALLENGES FROM THE CDMO'S PERSPECTIVE

ERIN HARRIS, EDITOR-IN-CHIEF
CELL & GENE

Partnering with a CDMO that marries innovation with technical, regulatory, and manufacturing experience can be cell therapy and gene therapy companies' best opportunity for scalability and yet their biggest hurdle. From process development through commercial supply and all the steps in between, cell and gene therapy companies expect CDMOs to meet an understandably high bar.

I recently had the opportunity to take a quick trip down 76 East to WuXi AppTec located in Philadelphia's Navy Yard. I toured WuXi's Manufacturing suits, which is where they company does its Viral GMP production. I also toured their Testing suites, which includes the WuXi's Testing and GMP production building. The tours were informative and helped me shape my questions for the second half of my visit, which was a sit down with WuXi's SVP and Global Head of Wuxi Advanced Therapies, Felix Hsu.

Hsu and I had a great conversation around the CDMOs perspective on manufacturing, and I feel the outcomes of our conversation can benefit our readers. Here's why.

He and I talked about the top challenges WuXi's clients bring to the table. As you research and visit CDMOs that can potentially execute your vision, consider how you and your team can address these three challenges. Does any of this sound familiar?

1. TIME.

Hsu assured me that WuXi's clients often have more money than time. Or, clients have developed a platform and sometimes expect to accelerate this platform without a well-characterized process — or very little process in place. Accelerated timelines to meet an IND date won't always work for the CDMO in these circumstances, and the timelines are often aggressive or unrealistic.

Erin Harris
Editor-In-Chief
Cell & Gene

2. STOP TINKERING.

Hsu stressed that how things work in an academic setting is different from how they work for GMP manufacturing. And, so, scientists sometimes have a difficult time accepting that they cannot continue to work on process and must stop making changes to move forward with GMP manufacturing.

3. NO LAST-MINUTE CHANGES.

He explains that sometimes clients struggle to determine exactly what they want or need in terms of the assay development in the timeframe needed. As always, time is a major factor and manufacturing is one of the biggest decisions your organization will make. Academic labs vary greatly from manufacturing environments and have greater flexibility; CMDOs often cannot allow last-minute changes to the process and/or raw materials if they are to meet tight deadlines.

What has your experience been with partnering with CMDOs and how has your organization learned?

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Erin Harris is chief editor of Cell & Gene and a contributing editor to Life Science Leader magazine. She studied English and psychology at Lafayette College and has 20+ years of experience in B2B publishing. Erin spent 10 years covering and reporting

on the adoption of information technology from a B2B perspective. She's written on technology topics ranging from Big Data and analytics to security and e-commerce. In each case, her reporting centered on innovations that improved operational efficiencies, fostered interdepartmental collaboration, or enhanced supply chains. Currently, she writes actionable information for professionals involved in the development and commercialization of cell and gene therapies. She covers the entire product lifecycle from basic research to commercialization. Erin has interviewed executives from Fortune 500 as well as startups. She has moderated panel discussions and has spoken at numerous industry events from large conferences to niche forums.

ABOUT US

Cell & Gene provides actionable information to professionals involved in the development and commercialization of cell and gene therapies. Through the original editorial published on the site — both staff-written and contributed (by subject-matter experts) — Cell & Gene facilitates the sharing of insights on challenges, trends, and best practices in this burgeoning field. Cell & Gene's editorial scope spans the entire product lifecycle from basic research to commercialization, including:

- Discovery and R&D
- Clinical trial design, recruitment, execution, and analysis
- Regulatory affairs and quality systems
- Process development and manufacturing
- Outsourcing and supply chain
- Logistics strategies
- Market access and payment/reimbursement

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