The Future of Advanced Therapies:

Strategies to Evolve Global Health in a Post-COVID World

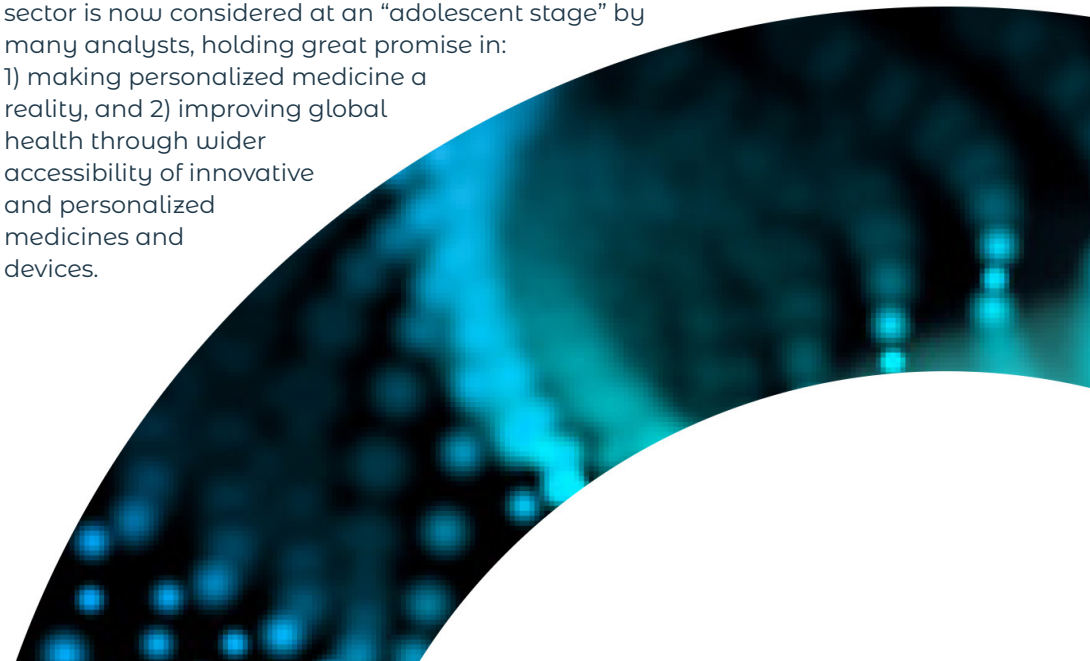
Introduction

Novel medicines based on genetic engineering, innovative cell-based therapies and tissue-engineered products are transforming the treatment and prevention of disease. These potentially curative cutting-edge therapies are generally developed for diseases with devastating consequences, when no treatment is available.

The contributions of such products, known in the European Union and the UK as advanced therapy medicinal products (ATMPs), or cell and gene therapy products (CGTPs) as they are called in the United States, take on new momentum as we examine the learnings that were gleaned during the COVID-19 pandemic. In light of the global health crisis, significant advances have been made in our understanding of how to get therapies to the patients that need them regardless of where they live, who they are, or what their socioeconomic situation might be – and to see the value of a treatment beyond a given patient treated.

Although we may never learn the full extent of the pandemic's economic, social and health impacts, we do know that COVID-19 has overwhelmed healthcare systems around the world and caused a ripple effect on the diagnoses and treatments of other diseases. The pandemic has also magnified certain disparities that have long been issues for certain populations. But at the same time, lessons learned from the pandemic have shown that accelerated development, without compromising patient safety, is possible for novel medicines. The pandemic has forced companies — and countries — to confront logistical and operational challenges to effectively distribute novel therapies, thereby mitigating and consolidating those challenges and, possibly, benefiting the treatments of diseases other than COVID-19 as well.

Innovations in medical science are complemented by advances in technology, bringing renewed hope for advancing the delivery of care. We stand at the threshold of a new era in how patients are treated and how disease and illness can be prevented and managed. The ATMP sector is now considered at an "adolescent stage" by many analysts, holding great promise in: 1) making personalized medicine a reality, and 2) improving global health through wider accessibility of innovative and personalized medicines and devices.



How Did We Get Here?

As early as the 1960s, scientists speculated that DNA sequences could be introduced into patients' cells to cure genetic disorders, and the completion of the Human Genome Project in 2003, which provided a complete blueprint of human DNA, was a major milestone in facilitating the development of gene therapy — particularly for treatments of genetic disorders. However, it was the success of chimeric antigen receptor T cell (CAR-T) therapy that really made gene therapy take off, and the past 20 years have seen a slow but steady stream of innovations.

But the path to exploiting the technology has been challenging despite decades of extensive activity on the parts of drug developers and regulatory agencies around the world. There has been great promise, but the sector has confronted a multitude of difficulties. For instance, scientific, clinical and regulatory uncertainties have been compounded by organizations' limited experience with the clinical and commercial uses of these innovative therapies. There is also the issue of limited manufacturing experience because these therapies are based on inherently dynamic biological systems. Finally, pricing and reimbursement and market access issues present additional hurdles for developers as they try to justify the costs to payers.

Minimizing Risks

With a model that is markedly different from conventional development paradigms — and one for which more-tailored approaches are needed — organizations must adopt multidisciplinary strategies that are designed to increase the overall success rates of development programs. The most important aspects of the planning? Start early. Anticipate and mitigate risk from Day One. Build bridges between quality, non-clinical and clinical disciplines. Make smart use of biostatistics. Adjust the plan as you go.

And, finally, but perhaps most important, initiate discussions with regulators early in development planning. Because ATMPs are complex biological entities, current regulations around them are also complex — and constantly evolving. Regulatory agencies should be involved throughout a development program so that they stay in lockstep and build their insights into the program. Ultimately, the goals are to build and execute an effective and efficient strategy that minimizes delays or risks of failure. That strategy should be built on an optimized regulatory approach and expedited pathways. Regulators are increasingly open to dialogue for immature and early programs, and they see their roles as enablers in addition to their more traditional roles as gatekeepers.

Developers of innovative therapies are charting new waters, therefore navigating these complex considerations can be challenging. But with proper strategic planning, organizations can clear the obstacles that lie ahead and move us closer to bringing ground-breaking, curative therapies to people in need.

Dr. Christian K. Schneider

Head of Biopharma Excellence and Chief Medical Officer

Disruption by Advanced Therapies

For decades, advanced therapies have held the promise of disrupting the ~$1 trillion global pharmaceuticals market. The promise is closer than we think as real-world results validate the science and as the technology improves.

The introduction of ATMPs has been a game changer for the treatment of severe conditions that today have no appropriate therapies or very limited treatment options.

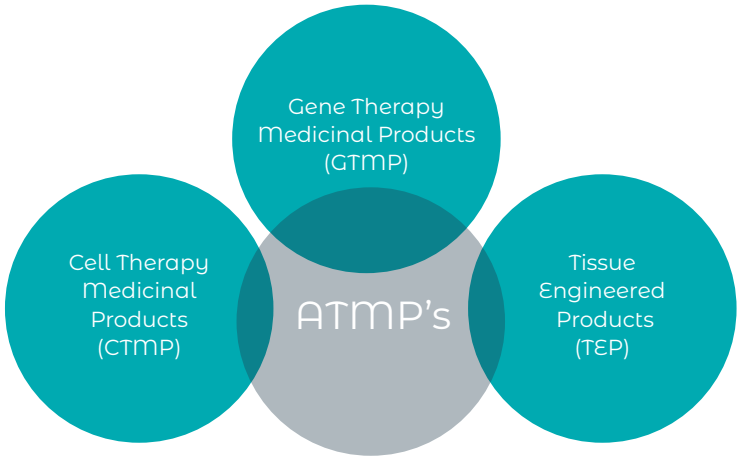
These therapies have literally transformed the industry and opened new routes for treating multiple types of cancers and incurable diseases. Genetic medicines for a range of diseases such as sickle cell anemia and several of the muscular dystrophies appear just in reach, and new science is galvanizing research.

For example, the current standard of care for hemophilia consists of frequent prophylactic infusions of plasma-derived or recombinant factor VIII for the patient's lifetime, to be monitored carefully and sometimes resulting in unwanted immune responses which impact the treatment success. In contrast, the promise of a cure for this common hereditary coagulation disorder with just one dose of gene therapy is tantalizingly close. This changes the outlook for these patients for life and allows us to witness a paradigm shifting moment in clinical research.

Because of the significant therapeutic potential of ATMPs for serious conditions – especially in comparison with conventional drugs – these advances bring us closer to diagnosing disease earlier, curing instead of treating illness, and delivering more personalized healthcare.

Changing the Care Paradigm

Consider for a moment the potential of gene therapy: Some of the first gene therapies are aimed at tackling monogenic disorders that are individually rare, but scientists believe there are between 6,000 to 10,000 monogenic diseases caused by defects in a single gene that – despite each being rare on a population prevalence basis – in total, impact approximately 300 million people globally.[1] The attraction of ATMPs is also its wider potential to treat other severe, and often chronic conditions – many of them with very limited alternative treatment options.



ATMPs Poised for Growth

By the end of 2020, nearly 1100 cell, gene- and tissue-based therapeutic developers worldwide had products in several different stages of clinical development, which represented an increase of about 100 developers compared with 2019[2]. Globally, there is a wide playing field with developers spanning non-profit organizations, hospitals, research centers, academia, startups, Big Pharma, spin-offs, and biotechs. These organizations tend to be innovation-driven and strongly science-based.

Among those new therapies that received approvals in 2020[4] were:

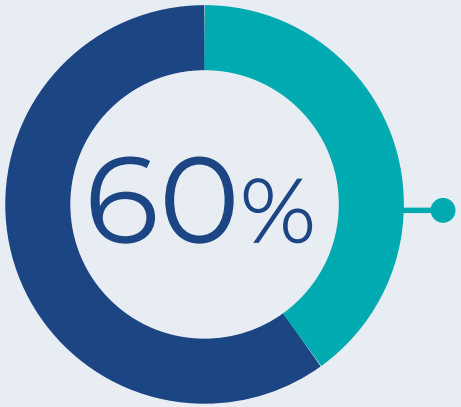
- Orchard Therapeutics' Libmeldy, a gene therapy to treat metachromatic leukodystrophy (MLD), was approved by the European Medicines Agency (EMA)

- Tecartus from Kite, a Gilead Company, was the first CAR-T treatment approved by the U.S. Food and Drug Administration (FDA) for relapsed or refractory mantle cell lymphoma

After those approvals, in early 2021 the FDA approved Breyanzi, a CAR-T therapy from Bristol Myers Squibb to treat adults with relapsed or refractory large-B-cell lymphoma. Currently a growing pipeline of therapies is nearing significant regulatory decision milestones, and the number of ATMPs reaching the market is expected to grow during the next decade.[5]

"Genetic medicine has the potential to usher in a third wave of healthcare innovation following in the footsteps of small molecule drugs (think medicine cabinet drugs like aspirin) and biologics..."

Stuart Loren, Managing Director,
Fort Sheridan Advisors LLC and Karmin Capital



of the development of ATMPs in Europe is executed by research centers and hospitals – many of which lack commercial capability.[3]

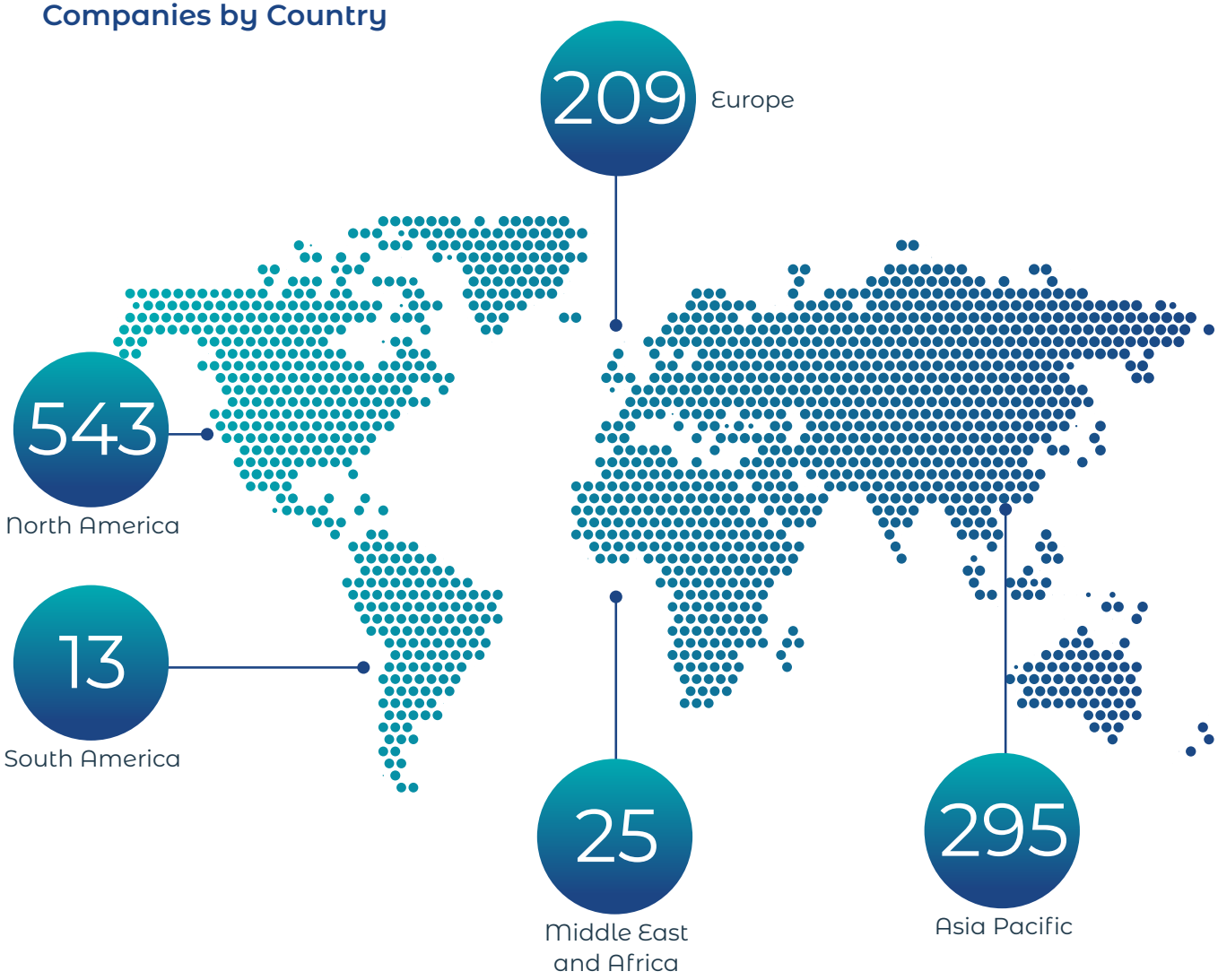
Snapshot

By the end of 2020, there were 1220 clinical trials ongoing, with 152 of those trials in Phase 3 — supporting FDA and EMA predictions that they will approve 10-20 cell and gene therapies each year by 2025.[6]

Clinical Trials by Technology Type and by Indication in 2020.[7]

423 trials are using Gene Therapy technology, 419 are using Cell based IO, 368 using Cell therapy, and 10 using tissue engineering. The majority of trials are in oncology (n = 554), followed by indications for neurodegenerative diseases (n = 94), monogenetic diseases (n = 87) and infectious diseases (n = 73). More than half (n = 685) are phase 2 trials, 383 are phase 1 trials and 152 are phase 3 trials.

Companies by Country



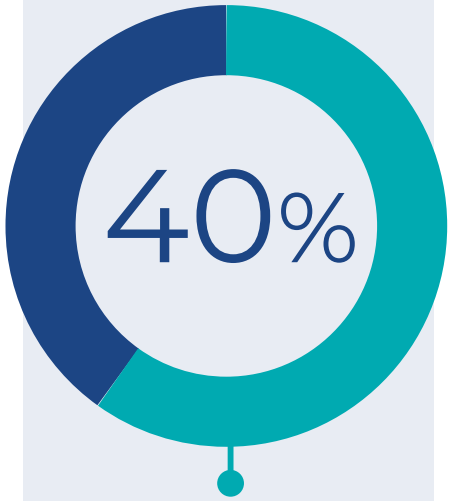
Source: Alliance for Regenerative Medicine

The Pathway to Commercialization

Clinical results have been encouraging, but there have also been setbacks in the development of ATMPs during the past 20 years, including some high-profile failures caused by serious safety issues, including deaths, and clinical data integrity issues. Yet, with setbacks have come learnings. Organizations are finding ways to work with regulators and accept that risk is part of the reality of developing innovative and highly complex therapies. The efforts are all about identifying and mitigating these risks, and to put them into context with the benefits.

In fact, the ups and downs of the sector sum up the state of play for gene-therapy research. To succeed commercially and bring promising drug candidates to market, organizations must understand that conventional development paradigms often don't apply, as the lack of standardized models point to more tailored approaches being needed.

That means that as early in the clinical process as possible – ideally even earlier – organizations need to formulate strategies that consider an integrated drug development plan designed to scale up seamlessly, that engage the right commercial resources early on, and that rethink traditional payment models in partnership with payers.



of ATMP product failures are among those developed by small companies as compared to failures among medium- or large-sized companies (17%).[8]

Equally important are the major regulatory considerations as the landscape moves away from specific guidance to more general guidance that mandates all manufacturers and developers bringing a drug to market base their decisions on Quality Risk Management, which focuses on the risk to patients.

With several different pathways to market, early planning is key. And though it may be tempting to focus on speed-to-market, organizations must prioritize *efficiency* over speed while ensuring that decisions made in early development phases don't create challenges further down the line.

In these exciting times of accelerating scientific breakthrough, realizing an ambitious vision rarely follows a linear path. By necessity, commercializing an innovative therapy will require a highly dynamic management approach.

5 Strategic Imperatives to Accelerate Commercialization

With ATMPs, there are many complexities to consider in the commercialization process. Patient populations are smaller and more targeted and even though that means product quantities can be low, they also have very specific logistical requirements. For example, manufacturing considerations and patients' lives can depend on the speed at which a product moves from the bedside to the facility and back again.

Although ATMPs might be potentially transformative, pricing for advanced therapies may ultimately prove prohibitive for some payers. At the same time, the underlying quality, regulatory, and manufacturing guidelines that apply to traditional drug development must still be considered – and those guidelines can be nuanced depending on country or region, which makes them challenging to navigate.

The key to success? Organizations must anticipate and mitigate risk from Day One and consider the following 5 strategies:

1 ASSESS

Conduct a risk/benefit assessment focused on reducing the risk of failure at every point of the development lifecycle.

2 PLAN

Develop an Integrated Product Development plan that spans organizational disciplines.

3 SCALE

Consider models for manufacturing and ways to incorporate good manufacturing practices early in the research phase.

4 ACCELERATE

Pursue innovative regulatory pathways to accelerate time to market.

5 PRICE

Look beyond the science to understand the market landscape that will shape the future and drive market access and pricing strategies.

Conduct a Risk/Benefit Assessment

To ease the financial burden, reduce risk associated with the regulatory process, and accelerate time to market, organizations should develop a strategic plan focused on issues that can lead to failure at every point of the development lifecycle.

Risk – and benefit – is in the eye of the beholder, and that holds true particularly with innovative therapies. While encompassing huge potential that could lead to curative options for genetic disorders or the treatment of diseases that are currently difficult or impossible to treat and where the unmet medical need is high, they also come with significant known and unknown risks, many of which are unique to this product class. These include issues such as donor identification and traceability and ensuring cell quality during collection.

The challenge is that developing therapies with only limited funds does not leave room for any misstep – either foreseeable or unforeseeable. The risk/benefit assessment should be designed as a gate to go/no-go decisions at each stage of development. Sometimes, the "go" will require a change in direction so the process should be agile with an eye toward risk identification, evaluation, and mitigation. That agile approach should apply not only to the biological activity of the ATMP, but also the quality attributes, the manufacturing process steps, and the therapeutic administration procedures.

Risk Mitigation Starts with the Patient Population and Healthcare Professionals

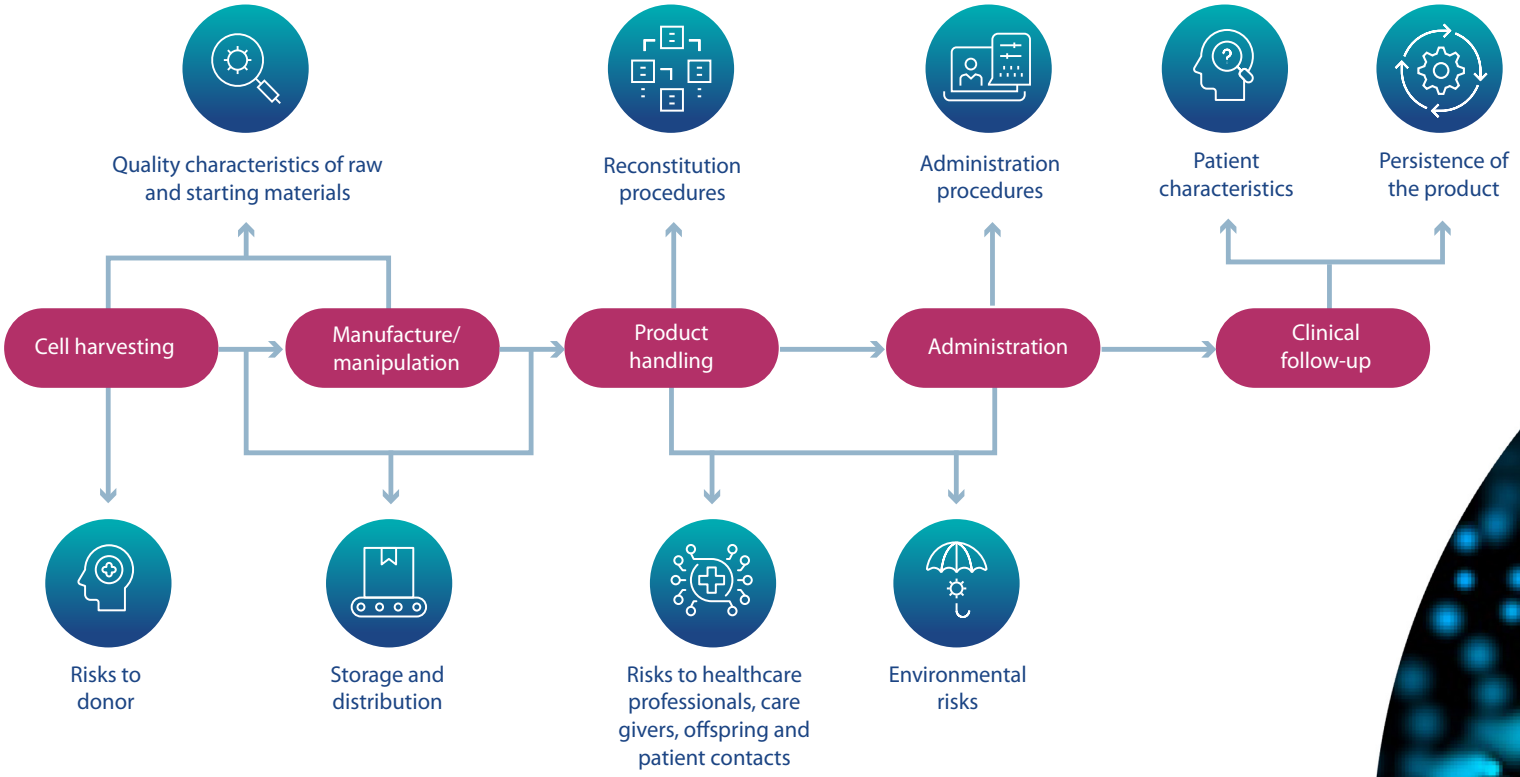
Risk identification should be considered across all areas of development and should focus primarily on safeguarding patients and minimizing risks to healthcare professionals and caregivers. In the context of ATMPs, safety takes on a different meaning as a risk to one segment of the patient population can mean a long-awaited, life-saving cure to another.

If COVID-19 has taught us anything, we now understand that risk also extends to the public arena. There is now the added concern about perceived public risk with the advent of innovative therapies. The ability to communicate the science of benefit versus risk in a way that can be well understood and accepted by the public at large is a critical potential roadblock that needs to be managed.

While many risk minimization activities are routine measures, additional tools and approaches specific to ATMP-related risks may be necessary. These could include offering specialized training for experienced physicians at selected, accredited centers, as well as providing targeted educational materials for physicians, pharmacists, patients, caregivers, family members, and other relevant stakeholders.

Risk management extends through post-authorization as organizations collect safety and efficacy data obtained in "real-time" settings from post-authorization safety studies (PASS) and post-authorization efficacy studies (PAES). The objectives, as well as the extent and duration of the individual PASS and PAES, are decided on a case-by-case basis. These depend on the specific characteristics of particular ATMPs as well as the intended indication and the resulting scientific uncertainty, the important risks or missing information, as determined during the risk identification exercise.

The Decision-Making Tree



Decision Points

What are the risks to donors?

- What are the medical and surgical procedures (leukapheresis, pre-medications) that may present safety concerns? How will they be mitigated?

What risks are there related to raw and starting materials?

- Transmission of diseases through viral, bacterial, or parasitic infections
- Tumorigenicity related to proliferation and/or differentiation capacity of cells
- Use of biologically active substances during the manufacturing process

What are some of the patient-specific risks?

- What is the potential impact of previous or concomitant therapies on the treatment? Or impact of treatment on previous or concomitant
- What is the potential impact of unrelated viral infections?
- What is the implication of unwanted immunogenicity and its consequences?

Are there any risks to healthcare professionals, care givers, or other stakeholders?

- Are there risks of virus or vector shedding and related risks of transmission?
- Is there a risk of fetal transmission caused by genetic transformation of the germ line?

What are some administration procedure risks?

- What medical or surgical procedures related to the administration of an ATMP present risk to the patient, healthcare professional or caregiver?
- Are there specific risks inherent in repeat administration?

Develop an Integrated Product Development Plan

In order to quickly adapt to new knowledge as development progresses, organizations should have an agile plan that spans key organizational disciplines.

For advanced therapies, the transition from research and development (R&D) to the clinical stage can be laden with landmines. While R&D focuses on identifying promising product candidates, drug development requires a diligent approach across various disciplines in a highly regulated environment to bring promising drug candidates to the commercial stage. On this path, an integrated product development plan (IPDP) is an extremely useful tool to increase the overall success rate; however, it can also be one of the most under-estimated aspects of a company's planning.

For a holistic approach to the creation of an IPDP, all development disciplines such as manufacturing, nonclinical and clinical development as well as regulatory affairs need to be involved. Even for early-stage programs, commercial aspects such as targeting specific countries for commercialization, the competitive environment as well as pricing /reimbursement aspects should all be considered. The IPDP is a living document that will get continually updated as development progresses, promoting organizational prioritization and decreasing time-to-decision.

When developing or applying regulatory tools for accelerating Covid-19 vaccines and treatments, regulatory authorities around the world have gained considerable experience in using these for biotherapeutics where these are warranted. This will not be an "automatic option" for all treatments – therefore, it is important to design the IPDP in a way that explores, from early on, how its set-up can also accelerate the development from a regulatory perspective.

Key elements of an integrated drug development plan

Start with the End Goal in Mind

The goal can be visualized in the form of a target product profile (TPP).

- the value proposition under consideration of the competitive environment
- target indication(s)
- target countries or regions and pricing
- identified population(s) for development, including desired efficacy and safety profile, route of administration, and dosing strategies

Plan Now or Pay Later

Rushing from research to development without a full understanding of the target is a dangerous proposition. Organizations must go through the exercise of defining the target product with the realization that this will be a starting point only, and that the IPDP will adapt as the science evolves. More importantly, through upfront structured planning– even while acknowledging things will change – the company will avoid road bumps and move faster as it progresses toward commercialization.

But there are also other unique considerations that come with ATMPs. At the core, the "traditional" clinical development paradigm is simply not applicable to these organizations. Agility is crucial as key decision points pop up along the way. Notably, chemistry, manufacturing, and control (CMC)-related issues have been at the center of several high-profile late-stage review issues during 2020; in fact, as far back as 2018, former FDA commissioner Scott Gottlieb commented that, unlike traditional drug reviews where 80% of FDA review is focused on the clinical portion of the company's application, the reverse is true when it comes to cell and gene therapy where the emphasis is on product manufacturing and quality.[9]

The key to Successful Drug Approval

Comparison of the route and time required for fast (1) and slow (2) companies to achieve their goal

Components of the IPDP Across Disciplines

Quality

Outlines the proposed manufacturing approach as well as the control strategy for the drug substance and the drug product.

Keep in mind:
Manufacturing can start at bedside; don't underestimate the complex end-to-end logistics chain.

And remember:
Consistent quality is a pre-requisite for a ATMP to function consistently in the patient.

Nonclinical

Outlines the proposed in vitro and in vivo studies planned to address pharmacology, safety and toxicology.

Keep in mind:
In vitro data can deliver useful information later in the development process.

Clinical

Outlines at least the first-in-human study and, depending on the stage of development, calls for further clinical studies — up to approval and beyond for potential follow-up commitments.

Keep in mind:
Clinical development can often outpace CMC development, presenting CMC with challenges to meet development needs and meet regulatory compliance and timelines.

Regulatory

Presents the regulatory tools that are available in the target territories and assesses the suitability and most favorable timing of these tools for the product candidate. The IPDP typically comprises the regulatory interaction strategy, dedicated regulatory programs as well as submission strategies.

Keep in mind:
Regulatory agencies can provide valuable input and advice and should be involved early and frequently throughout the development program.

Decision Points

Do you have a defined target in mind?

- What is the vision for the way the ultimate product is intended to be developed for commercialization?
- What is the TPP?
- Have you considered the value proposition, given the competitive environment?
- What are the target countries or regions?

Have you considered the manufacturing approach?

- For manufacturing, will you involve contract manufacturing organizations (CMOs) or do you plan on building your own manufacturing capability?
- What will be the source of raw materials?
- Have you planned for specific regulatory requirements for cell sources and testing requirements?

Have you outlined the nonclinical part of the IPDP?

- How does the drug work and for how long?
- Are there relevant animal models available for pharmacology and safety assessment?
- What are the appropriate doses and regimens?
- What are the potential safety concerns and uncertainties?
- How can the risks and uncertainties be mitigated when progressing to the first in-human clinical studies?

Have you defined the components of your regulatory strategy?

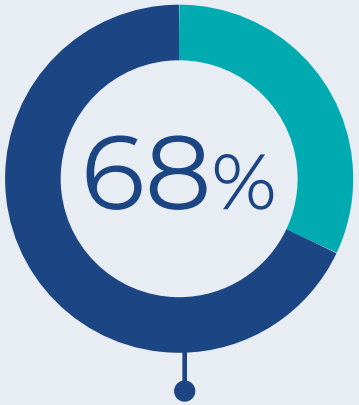
- Have you outlined the regulatory tools that are available in the target territories?
- Have you assessed the suitability and most favorable timing of these tools for the product candidate?
- Have you considered regulatory interaction strategy, dedicated regulatory programs and submission strategies?

Prepare for Scale with a Sustainable Commercial Process

Innovators must overcome manufacturing challenges – the greatest being one of scale. Few manufacturers have found the transition from lab-based research to a sustainable commercial process to be straightforward.

Manufacturing has been a bottleneck for many ATMP organizations. A well-constructed **regulatory strategy** should include the considerations necessary to optimize manufacturing processes for commercial good manufacturing practice (GMP) production early in the research phase — while that approach is still adaptable. It will also help build flexibility into the process so that new technologies can be embraced as they become available.

Those pursuing accelerated regulatory pathways, such as EMA PRIME in Europe or one of the FDA's expedited development and review pathways, have to know how they will eventually manufacture the therapy — by designing the path to commercialization right from day one. In many cases, moving the therapy from the lab to scaling it for supply to patients, which means producing a sterile drug product in sufficient quantities, has been challenging. One of the biggest misconceptions on the part of ATMP manufacturers in early-stage trials is that they do not need to be GMP compliant; in fact, the product still needs to be manufactured in compliance with all the principles of GMP from the moment the therapy is administered to human patients.



of novel drug approvals in the US in 2020 used at least one of FDAs expedited development and review pathways to speed approvals.[10]

Many in industry today consider the "Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products", within Part IV of Eudralex Volume 4, a summary document issued by the European Commission, to provide the best current GMP guidance document on the production of ATMPs.

In fact, many of the FDA's ATMP-related papers align with it, giving manufacturers a fairly standard mechanism from which to develop their regulatory strategy, whatever their technology platform. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) also provides a valuable resource for ATMP innovators by harmonizing inspection practices and GMP standards from 53 regulatory authorities around the world.

5 Top Considerations When Transitioning to Commercial Manufacturing

1

Prepare for operational readiness.

To ensure they are ready to scale up and that they are not burning cash as they do, organizations must align their manufacturing readiness with the regulatory pathway, the patient population, and the dosing they are pursuing.

2

Determine how you'll manufacture.

Manufacturing can start at bedside; don't underestimate the complexity of the end-to-end logistics chain. Decide early on whether you will build your own manufacturing facility or work with a specialist manufacturing organization.

3

Prioritize safety.

The consequences of a product contamination event are dire. The facility, material and personnel flows, cleaning and decontamination protocols, the way utilities are set up, and the contamination control strategy, must all be designed according to a robust Quality Risk Management (QRM) strategy that protects the workforce, product, and importantly, the patient.

4

Build in flexibility.

In order to deliver a new breed of curative therapies that have never before existed, companies must anticipate potential problems that have never before been faced—and that takes a tremendous degree of flexibility. Facilities must be flexible enough to adapt and integrate new technologies and processes quickly and efficiently.

5

Respond with agility.

With patients' lives and investors' expectations hanging in the balance, today's ATMP manufacturers must pursue innovative design-build solutions that can move their product from concept to operation within just a few years.

Decision Points

Do you have a plan to properly manage the facility and equipment?

- Have you considered the requirements for the design, operation and maintenance of a classified cleanroom facility?
- Do you understand classifications and what they mean?
- Have you accounted for the fact that you will likely need to keep the facility operational even when you're not manufacturing?
- Have you factored the operations into your cost estimates?
- Have you considered the suitability of CMO operations in terms of product recovery when product volumes are already low; e.g., product gets held up in manufacturing systems and can be an expensive impact on yield?

How will the decision on where you manufacture potentially impact your go-to-market plans?

- Have you considered where your manufacturing facility will be established and how that will impact the regulatory process?
- Have you factored timelines to implement quality management systems into launch plans?

Do you know what the regulatory authorities expect?

- Do you have a good understanding of what the authorities will expect when it comes to GMPs and QMSs?
- Do you know the minimum requirements for a QMS, for quality risk management, for product development and for production and quality control as they relate to GMP principles — from respective starting materials through to production of the finished product?
- Have you considered how product sterility will be maintained during manufacturing when many of the traditional methods of sterilization are not suitable for ATMPs or CAGTs, such as filtration and heat?

Have you considered how the product you manufacture will affect your plans?

- Viral vectors: How challenging will they be for scale and safety?
- Autologous cell therapies: What are the considerations for cost, scale-out and variability, including potential for batch failures?
- Allogeneic cell therapies: Key is scale-up, but what challenges exist for ensuring product comparability as the manufacturing process gets developed?

Navigate Regulatory Pathways to Accelerate Commercialization

It takes far more than a decade at a cost in excess of $1 billion to bring a new drug to market. A well-thought-out regulatory strategy is important to increase the success rate at the time of submission.

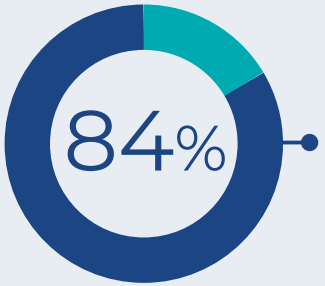
An effective regulatory strategy is a key ingredient for successful drug development and approval and an integral part of the **risk assessment.** The strategy aligns the regulatory activities involved in bringing a product to market with the drug development process and business strategy.

There are distinct aspects to the regulatory plan – all happening in parallel – which should evolve as development progresses: 1) documenting the goal, which can be visualized via the **TPP**, 2) keeping pace with competitive therapies, 3) maintaining regular checkpoints with regulatory agencies, and 4) considering regulatory pathways, depending on markets or regions, indication areas, and classification of the therapy. The regulatory strategy should evolve along with development and as new information about the competitive environment, study results, and interactions with regulatory agencies progress. Deciding on the pathway to commercialize a therapy starts with a strategic framework.

Planning is crucial. Consider this: Phase 3 clinical trial success rates hover around 50%.[12] That's a remarkable proportion considering that the majority of development costs have already been spent at this advanced stage. Therefore, it is imperative to have an effective regulatory strategy in place as soon as the drug development program begins.

Move beyond the science and assess the anticipated impact the therapy will have on the patient population. Consider:

- Is there another drug on the market that is just as good? Is our therapy going to have the market impact that is expected? Where relevant, what is the risk of non-intervention (doing nothing), and how can that help in defining the anticipated benefit from early on?
- Are stakeholders going to stay with what they already know? If a treatment already exists, are stakeholders likely to be willing to change to something that may be very different? Have you planned for every scenario?



success rate of marketing authorization applications that have complied with clinical trial design recommendations from regulatory agencies compared with 43% of non-compliant programs.[11]

Formalize interactions with regulatory agencies – the sooner the better.

Organizations will need to demonstrate that products warrant additional attention from regulatory authorities. For example, EMA PRIME helps optimize the development and accelerated assessment of medicines of major public health interest. The scheme is based on enhanced interaction and early dialogue with medicine developers. The interaction starts as a conversation with the rapporteur, who will eventually be the person reviewing the Marketing Authorization Application. This gives the company the opportunity not only to present the clinical information, but also to educate the agency so that before they review the filing, agency officials understand exactly what the product does and how it is manufactured.

Determine how the therapy will be manufactured – and plan right from the start. Regulators have to understand operational readiness.

Aligning manufacturing readiness with the regulatory pathway is essential to ensure money and time is not wasted. In pursuing any expedited regulatory pathways, for example, organizations will need to know how they will manufacture the therapy. A hard-learned lesson from past failures is that moving from discovery in the lab through scale up and on to qualification of a manufacturing process that is reliable and robust, allowing the therapy to be manufactured at sufficient levels for consistent patient supply is a whole different story. Developers will need to work out details like minimizing the potential for contamination and the maintenance of sterility in products manufactured for early clinical studies in human patients – challenges just not present in the lab – to ensure they have a sterile drug product in sufficient quantities.

Quality and regulatory planning go hand in hand. There are multiple risks for organizations that don't plan properly and find themselves rushing toward commercialization. These can include:

- Pricing implications: The cost of construction, maintenance and operation of an appropriate classified cleanroom facility; or, alternatively, the cost of engaging an appropriate Contract Manufacturing Organization that has the relevant expertise.
- Impact on milestones: To hit a milestone, companies may need to play catch-up or prepare in advance to comply with the nuanced regulations in different territories.
- Quality implications: Are there sufficient timelines to implement the QMS?
- Scalability challenges: How will the therapy be administered to the patient in a compliant manner? What is required to make sure that it's safe?

When is too soon?

The first interaction with regulatory agencies should be held early enough but be sure you are sufficiently prepared. Early enough means allowing time to incorporate the advice into the further development program. Sufficiently prepared means the sponsor should have a clear enough understanding of their product and program supported by initial data.

Decision Points

What should you consider from the authorities' standpoint?

- How will the regulatory authority interpret the filing?
- What does the regulatory authority expect, and does the filing include the necessary information about manufacturing practices and QMSs?
- Are you prepared to defend and adapt the filing?
- Have you considered the nuances in regulatory requirements from region-to-region so you don't end up with disparities?

Have you considered what happens after conditional marketing authorization?

- Are you prepared to collect long-term data and build the data into your plan early on?
- Given that ATMPs do not collect comprehensive data from large patient populations, what will the authorities expect?
- What if you plan to manufacture in one region but to distribute in another?
- If retesting is required, how will it be managed without consuming large proportions of a GCTP batch?
- Have you researched the financial impact if a patient needs a second — or even a third — therapeutic treatment?

How do you balance clinical rigor with safety considerations?

- What is the right balance of getting the required clinical data but at the same time not putting patients at risk?
- Is there enough due diligence to show that the therapy is reasonably safe?
- Was there inappropriate handling of safety related aspects?
- Were safety signals thoroughly assessed? Are these related? Predictable? Limited? Reversible?

Have you considered potential failure points?

- Insufficient proof of product rationale, e.g., knowledge gap between anticipated mechanism of action and the pathophysiology of the disease.
- Insufficient magnitude of clinical effect, statistically or clinically, including if the product may or may not work better in certain subgroups of patients (disease phenotype, treatment-naïve, or certain stage, for example).
- Methodological flaws in the pivotal study design, e.g., lack of comparator or inappropriate endpoints and/or determination thereof.
- Lack of an integrated approach across disciplines.

Initiate Market Access and Pricing Planning

The key to unlocking market access is the ability to look beyond the science to understand dynamics and the competitive landscape that will shape the future and drive value.

In the growing, yet nascent, space of ATMPs, the challenges start early on when trying to reconcile the technology, the therapeutic objectives, and the regulatory requirements for commercialization. The implications go far beyond regulatory compliance, as they can affect the go-to-market strategies and associated revenue streams. To gain market access, developers must be able to demonstrate clinical and economic evidence to providers, healthcare decision-makers, and importantly, payers.

Historically, market access for a therapy depended almost exclusively on efficacy and safety. These factors are still critical, but today, clinical differentiation and its effects on healthcare outcomes and resource utilization and optimization require more comprehensive approaches.

Organizations must analyze the competitive landscape and determine how the new therapy comparatively improves patient outcomes, how it reduces the burden on the healthcare system as a whole, and whether it is worth its price. Given the complexities of the ways healthcare is paid for depending on the market, it's crucial to understand who will finance the therapy and the mechanisms by which the care will be reimbursed.

This is especially challenging with ATMPs where there may be alternative therapies that are available without the high price tag. Developers must assess value through the lens of the payer. If, for example, current therapies don't necessarily cure you, but they offer some quality of life at an affordable price, payers may opt to stick with current approaches for treatment. Developers must expand their strategies to take a more holistic view of patient treatment and provide better real-world evidence, therefore offering a stronger value proposition for decisionmakers. This planning must begin at the onset of an idea during the proof-of-concept phase.

For payers and market access stakeholders, the value proposition encompasses the optimal combination of disease need, clinical efficacy, and economic impact to achieve market access at an optimal price and in the appropriate setting. This requires that the manufacturer is able to validate and communicate the need for treatment and the value of utilizing the therapy in question in the right setting and for the right patient.

All these considerations need to be factored in when assessing value and price. Equally important to planning are policy discussions and advocacy for a particular treatment pathway. Organizations should begin advocacy efforts to ensure their therapeutic approach can be discussed, potential roadblocks navigated, and price negotiations can occur well before the therapy is ready for market.

Navigating Emerging Payment Models

In the United States, with its various public and private payers, multiple payment models are emerging. Among them are:

Outcomes-based contracts, which reimburse when the treatment successfully achieves a predetermined clinical endpoint.

Installment payments, which are spread out over a predetermined time period.

Risk pooling for curative therapies where public and private payers set aside a portion of healthcare budgets into a dedicated fund.

The subscription or so-called "Netflix" payment model where the payer pays a fixed annual subscription fee to the manufacturer for unlimited access to drugs.

Decision Points

Do you have a compelling value proposition?

- Have you considered the political and social implications for your therapy, which could affect market acceptance?
- Have you planned for the ways the therapy will be administered and the toll it will take on patients, caregivers, and other stakeholders?
- Do you require certified centers to extract samples? Who are your donors? How will these factors impact pricing?

Does your economic model incorporate ALL costs?

- Have you estimated the total, all-in costs from collecting samples at the bedside to getting the therapy back into the patient?
- Have you incorporated the societal or environmental impacts into access strategies?
- Have you researched the financial impact if a patient needs a second – or even third – therapeutic treatment?

Have you assessed competitive therapies?

- How does the commercial landscape look and how does your therapy compare?
- Do you have a compelling case for the medical need, and is there a competitive advantage?

Have you considered the unique healthcare payment models in each market?

- Have you determined who is going to be financing the therapy and how they evaluate the long-term effects of the therapy?
- Does the payer have an interest in investing in curative therapies versus chronic treatments?
- Have you considered how to estimate higher cost burdens from the long-term treatment of chronic diseases?

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