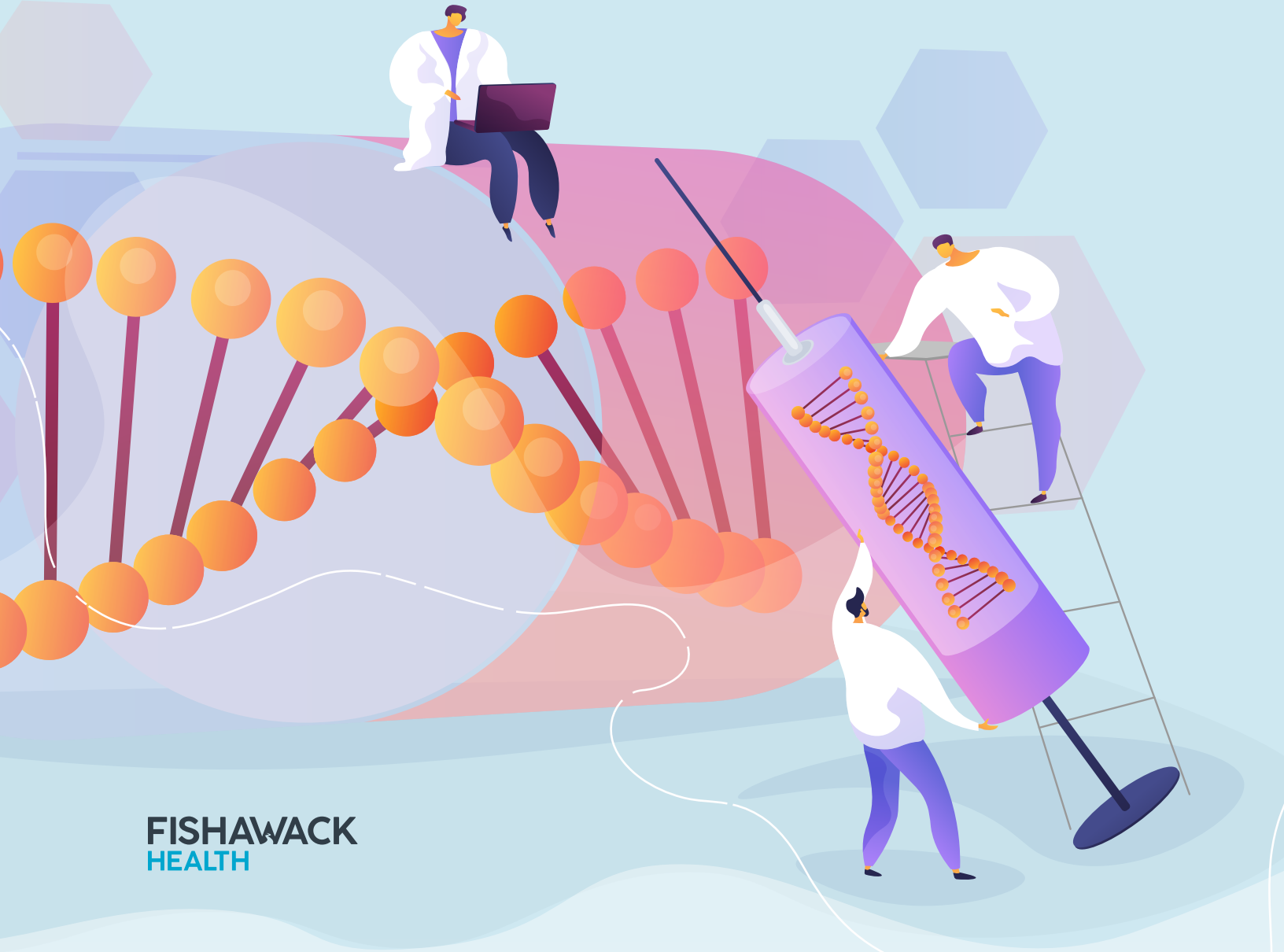


FISHAWACK HEALTH

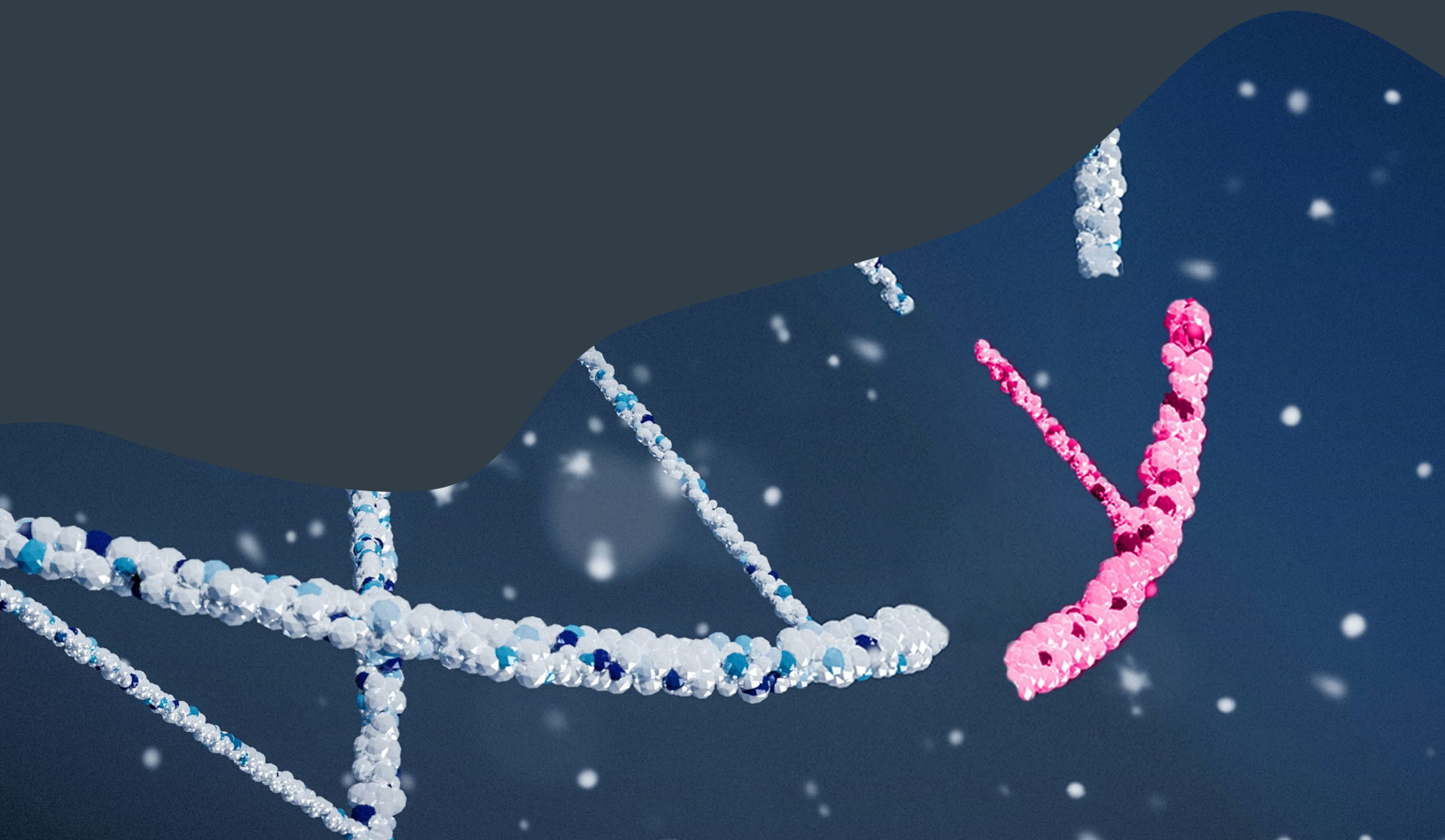
THE FAST-PACED FUTURE OF CELL AND GENE THERAPIES

- US policy changes impacting commercialization of cell and gene therapies
- AstraZeneca's pioneering cell therapies for chronic diseases
- 6 trends shaping the future of personalized medicine
- Commercial insights on CRISPR technology for beta-thalassemia
- Simplifying the high science for your stakeholders

November 2022

FISHAWACK HEALTH

CONTENTS



FISHAWACK HEALTH

INTRODUCTION

The fast-paced future of cell and gene therapies

Cell and gene therapies represent a paradigm shift in the development of pharmaceutical products. Not only do these treatments often promise to cure disease, they also represent an evolution in the manufacture and delivery of products. As a result, cell and gene therapies are synonymous with complexity.

Manufacturers developing cell and gene therapies face a steeper climb to commercialization compared with traditional biopharmaceutical products. While there is significant innovation in this space, few cell and gene therapies reach the market. Additionally, those that do have been marred by supply chain and manufacturing challenges, along with healthcare infrastructure barriers, including a lack of treatment sites for administering therapies. These factors affect the scalability of these products and the patient and healthcare professional experience.

Add to this a fast-paced global policy and regulatory landscape in which policymakers and regulators struggle to upskill fast enough to keep up with the evolving high science. Payers require more support than ever to understand the novel data and make decisions regarding these therapies.

Patients and healthcare professionals alike are entranced by the promise of the treatments but require support in understanding the risks and benefits of novel cell and gene therapies.

Understanding the barriers and risks early in drug development is paramount for ensuring these therapies deliver on their promises for patients.

Drawing on our experience working with biopharmaceutical innovators on the commercialization and launch of cell and gene therapies, we have developed a series of articles on the evolving landscape, which we present in this publication.

Read on to learn about:

- An interview with Professor Francesco Dazzi, Medical Lead Cell Therapy, BioPharmaceuticals R&D at AstraZeneca, on the company's novel cell therapy pipeline for chronic diseases
- Patient and market access insights on leveraging CRISPR technology for hematologic diseases
- The evolving policy and regulatory landscape for cell and gene therapies
- Trends shaping the future of personalized medicine
- Steps for communicating the complex science to a variety of stakeholders

Better health happens when we connect.

Get in touch to learn about our experience developing powerful strategies and solutions that drive the successful commercialization of cell and gene therapies.

DEVELOPING A VALUE STRATEGY FOR CELL AND GENE THERAPIES

Last month we published a report detailing expert advice for developing value, evidence, and access strategies that resonates with a growing network of stakeholders in complex therapy areas. Many of the points raised and advice given are highly relevant for those launching cell and gene therapies, so we recommend reading the report in tandem with this one. **Read it here.**

US policy changes impacting commercialization of cell and gene therapies

In this Q&A, Kylie Stengel, Policy Consultant, and Mark Von Eisenburg, Market Access Consultant, explore FDA challenges at each stage of the product life cycle—from preclinical to post-approval—and share their insights on the changing US regulatory and policy reforms impacting commercialization of cell and gene therapies.

*By **Amiee O'Driscoll**, writer*

The cell and gene market is evolving at lightning speed. Since the approval of the first CAR-T therapy in 2017, more than 20 cell and gene therapies have been approved by the FDA.[1] This includes six CAR-T and four gene therapies. Today, the pipeline is filled with hundreds of these novel candidates, often designed to treat therapeutic areas with high unmet need and limited alternative treatments.

This has led to a dynamic landscape in which the FDA has struggled to upskill in the complex science and the rising demand for regulatory expertise. As a result, it is now turning to legislative and/or regulatory updates to help expedite approvals.

> As of May 2022, there were roughly 500 unique cell and gene products in Phase 1, 2, and 3 trials

In turn, biopharmaceutical companies are compelled to think critically about evidence generation to meet the approval and post-approval demands of various stakeholders, including regulators and payers, as evidence of novel cell and gene therapy effectiveness may be more pivotal to approval and coverage decisions, while also being harder to obtain in a traditional clinical trial setting.

Manufacturers will need to employ a robust strategy and implement meticulous planning procedures early in the drug development process to account for the evolving regulatory and policy landscape. This includes an increased focus on areas such as health equity, patient-focused drug development, and clinical trial diversity.

Avalere Health, which joined Fishawack Health in June 2022, is a leading healthcare consulting firm based in Washington DC. Avalere's team of more than 200 advisors offers vast experience and expertise in federal policy and policy developments across all 50 states.

Offering services in market access, due diligence, and transformation, Avalere partners with life science companies, providers, and others to bring unique solutions to intricate healthcare challenges. Combining Avalere Health's experience with Fishawack Health's global capabilities results in unparalleled global insights and expertise within the cell and gene product life cycle.

We heard from Avalere Health representatives Kylie Stengel, Policy Consultant, and Mark Von Eisenburg, Market Access Consultant, who shed light on the key FDA regulatory challenges and the impact of US policy changes at each stage of the cell and gene product life cycle. They focus on the impact on product developers, highlighting considerations that will equip companies to plan effectively.

> 36% of pipeline products are for orphan diseases, but 7% are expected to treat larger and more prevalent patient populations. ... As more of these products come to market, there will definitely be some implications for budget impact and payer financing

> While there's support for the (accelerated) approval pathway, ... some stakeholders have recently expressed concerns that standards around timelines for sponsors to complete confirmatory studies are not strict enough
>
> ***Kylie Stengel**, Policy Consultant*

There are a significant number of cell and gene therapies in the pipeline at various stages of development. Can you tell us what trends you're seeing?

Kylie: As of May 2022, there were roughly 500 unique cell and gene products in Phase 1, 2, and 3 trials. Most of these are early stage; around 70% are Phase 1, 22% are Phase 2, and around 7% are Phase 3 trials. Based on our analysis, just over 75% of these pipeline therapies are cell therapies, including autologous and allogeneic cell therapies. In the other corner, we have in vivo and ex vivo gene therapies. These products will be administered in different settings of care, including inpatient, outpatient, and physician offices. And we're even seeing a few pipeline therapies that could be available in the pharmacy setting. So there are definitely some different implications for product reimbursement depending on the setting in which these therapies are administered.

Unsurprisingly, given the products we've seen come to market to date, over half of the cell and gene pipeline is for oncology indications. But we're also seeing pipeline products with indications across a variety of therapeutic areas, including ophthalmology, hematology, metabolic disorders, and immunology. These will be treating patient populations across different payer markets, including Medicare, Medicaid, and commercial markets. Additionally, MIT's NEW Drug Development Paradigms consortium (now part of Tufts Medical Center) estimates that, excluding those for oncology indications, about 36% of pipeline products are for orphan diseases, but 7% are expected to treat larger and more prevalent patient populations for conditions such as cardiovascular disease. As more of these products come to market, there will definitely be some implications for budget impact and payer financing.

> In the preclinical phase, one of the core issues the cell and gene market still faces is lack of cohesion across stakeholders when it comes to classification of products

***Mark Von Eisenburg**,*
Market Access Consultant

These statistics raise some questions around the FDA, including its ability to keep up with application reviews. Can you tell us about some of the FDA regulatory challenges?

Mark: It's an important consideration, and there are many potential challenges a product developer might face. It really does depend on where in clinical development they might be and whether or not that manufacturer has prior experience to leverage during those developmental phases. In the preclinical phase, one of the core issues the cell and gene market still faces is lack of cohesion across stakeholders when it comes to classification of products. We're operating with emerging biotechnology in which combinations of novel technologies and complex manufacturing processes might be intermingled between a gene therapy and a cell therapy or aspects of both. Another challenge is that we don't want the novelty of technology to force riskier or inefficient policies or regulatory processes. However, from what we see now, the technology will outpace some of the regulatory precedents, which aligns with the historically reactionary manner in which review expertise is gained for novel technologies.

Similarly, in the preclinical phase, you need to think about where the expertise might lie at the FDA. This is an important consideration because we think about cell and gene therapies being regulated by the Center for Biologics Evaluation and Research (CBER). But there are instances, for example, with RNA therapeutics, where biologics are regulated by the Center for Drug Evaluation and Research (CDER), because that's where the FDA expertise is, so planning review teams is an additional challenge.

We see the FDA working on its current thinking regarding CAR-T–specific cell therapy, as well as gene therapy–specific manufacturing guidance. Although these publications might provide areas of clarity for product sponsors, there's still a need for best practices when it comes to this early stage of development.

On the legislative front, do we see any movement as it intersects with preclinical or early-stage regulatory challenges?

Kylie: The House draft User Fee Amendment or UFA reauthorization bill released in May 2022 would have required the FDA to convene a public workshop on the best practices for generating scientific data to facilitate the development of human tissue and cellular-based products. Additionally, the draft Cures 2.0 legislation would require the FDA to submit a report to Congress on the FDA's challenges related to cell and gene products in the next 10 years and what's needed to address those challenges. This bill is still proposed in the US House of Representatives and has yet to be considered. However, now that the User Fee program has been advanced into law (on September 30) without additional policy riders being included, some provisions specific to cell and gene therapies will become law before their impact is felt.

> The challenge of generating powered data for a small patient population is a key issue for many cell and gene therapies that are under development

Now that we've discussed the preclinical phase, can you highlight some of the core challenges in the clinical phase?

Mark: The first that comes to mind has to do with this topic of patient-focused drug development. This relates to a push we've seen recently—fueled by some learnings from the COVID-19 pandemic—for getting accurate representation in your trial population. The challenge of generating powered data for a small patient population is a key issue for many cell and gene therapies that are under development. We need to see innovative methods for continuous monitoring of patients for use of real-world data and standardizing this into real-world evidence to assist on both the pre- and post-market sides of evidence generation.

Additionally in the clinical phase, we think about the concept of FDA-expedited development and approval pathways. There are quite a few of these and they are particularly relevant to cell and gene therapies, which often treat diseases that have high unmet medical needs or are serious and life-threatening. Gene therapies often have expedited designations to assist not only with their product development but also their product review timelines and level of evidence required.

It's worthwhile to note that of all drugs approved by CDER (which include some biologics) between 1992 and 2021, 58% of them have had at least one expedited designation. So it's common to have an expedited designation to help fulfill these unmet medical needs. That said, tailoring an effective evidence-generation plan at the clinical phase so that your ongoing evidence generation remains informative into product life cycle is a challenge that cell and gene therapy manufacturers might face at a higher rate than other manufacturers.

When it comes to patient-focused drug development and expedited pathways, is there any legislative movement that we're seeing regarding these topics?

Kylie: As mentioned, clinical trial diversity has been a big focus. Again, the House draft UFA reauthorization bill would have required product sponsors to submit diversity action plans to the FDA about the planned clinical trial enrollment and how that aligns with the treatment population. Additionally, the draft Cures 2.0 legislation would require the US Government Accountability Office to study barriers to clinical trial participation for underrepresented patient populations. It would also require the Department of Health and Human Services to implement a public awareness campaign around clinical trials, particularly for minority populations, as well as requiring sponsors to collect standardized patient experience data. Related to expedited development, the draft Cures 2.0 legislation would also expand the timing for when sponsors can request expedited designation, particularly around regenerative medicine advanced therapy and breakthrough designation.

Can you tell us what challenges companies might anticipate in the review phase?

Mark: Technology is moving forward linearly and application numbers are increasing, and we've seen some prospective movement on the part of the FDA and other industry stakeholders to try to plan for this bump in applications, for instance, in the Prescription Drug User Fee Act (PDUFA) VII commitment letter. There are more resources for CBER review staff, but generating appropriate review teams for these novel technologies is still a challenge because you need to cherry-pick where the expertise lies across centers. Having resources for a staff bump in PDUFA is great, but you still need to have the talent to fill those spots.

Additionally, it is important to plan ongoing evidence generation—especially if you are pursuing expedited regulatory pathways and if you know confirmation of clinical benefit is going to be needed down the road.

Finally, can you touch on the post-approval life cycle management phase?

Mark: We've mentioned ongoing evidence generation needs, but this confirmation of clinical benefit and other post-marketing commitments might be especially important for approval products with unknown or unconfirmed effectiveness profiles. Sometimes you'll have a Risk Evaluation Mitigation Strategy requirement, to monitor safety signals; other times, clinical studies to determine long-term outcomes. This brings us back to the topic of engaging with the FDA in a more dynamic manner or potentially even engaging with other regulatory agencies to align that evidence-generation strategy from the clinical phase all the way through into the product life cycle. There is room for changes to how data are sourced and stored in the post-approval environment, whether it be in registries, in databases that group technologies by their platform (eg, mRNA products), or other methods.

One thing we haven't explored in detail is the accelerated approval pathway. Can you tell about its relevance to cell and gene therapies?

Kylie: The accelerated approval pathway allows for an expedited approval of drugs that treat serious conditions and fulfill an unmet medical need, and that's based on a surrogate endpoint. While there's support for the alternative approval pathway as a way to bring these therapies to patients more quickly, some stakeholders have recently expressed concerns that standards around timelines for sponsors to complete confirmatory studies are not strict enough, in addition to other concerns related to this more limited clinical trial data.

Earlier in 2022, we saw a few stand-alone bills introduced in Congress that would implement stricter requirements for accelerated approval drugs. Generally, these bills would give the FDA greater authority when it comes to market withdrawals and allow the FDA to specify the conditions for confirmatory studies. However, we've seen bills that go a little further, for example, the Accelerated Approval Integrity Act. That bill would put time limits on the number of years a product could be on the market before completing confirmatory trials.

> We have seen prominent figures ... argue that reforms are needed as soon as possible to address uncertainty about risks and benefits

The House draft UFA reauthorization legislation did include some provisions related to accelerated approval—specifically, the legislation would have allowed the FDA to specify the conditions for confirmatory studies, including allowing it to specify that the post-approval studies need to be underway at the time of the accelerated approval. The bill would have also required product sponsors to disclose accelerated approval on the product label.

These accelerated approval provisions were not included in the May draft Senate version of the UFA reauthorization bill. The continuing resolution, enacted on September 30, that reauthorized the User Fee program did not include any of these accelerated approval provisions or other previously considered policy riders. However, the accelerated approval pathway is likely to still be an area of focus for policymakers and one to keep watching closely. We have seen prominent figures, such as FDA Commissioner Robert Califf, argue that reforms are needed as soon as possible to address uncertainty about risks and benefits. These views echo the recommendations made by the FDA's Oncology Center of Excellence, which call for better quality and efficacy of data.

PREPARE FOR THE CHALLENGE AHEAD

As cell and gene therapies continue to show more clinical success, the FDA will need to enhance its guidance and expertise. In the meantime, biopharmaceutical companies need to keep up with the latest regulatory precedents and legislation and plan their pathways accordingly.

Central to this is developing an understanding of the regulator as a stakeholder with complex evidence gaps and disparate knowledge, which requires new forms of communication and dynamic engagement.

By conducting robust planning early on, manufacturers can better anticipate potential barriers and drive highly focused decision-making to ensure products progress smoothly across the pipeline and patients can more quickly access life-changing treatments.

Get in touch to find out how we can support you in commercializing your cell and gene product or pipeline.

WEBINAR: NAVIGATING THE CELL AND GENE THERAPY MARKET ACCESS LANDSCAPE

On December 7, 2022, our Policy, Value, Evidence, and Access team members will host a new webinar revealing further insights on the cell and gene therapy landscape.

Join us for:

- Updates on the evolving global cell and gene landscape
- Advice on overcoming market access challenges that present as key barriers for cell and gene therapies

Register today.

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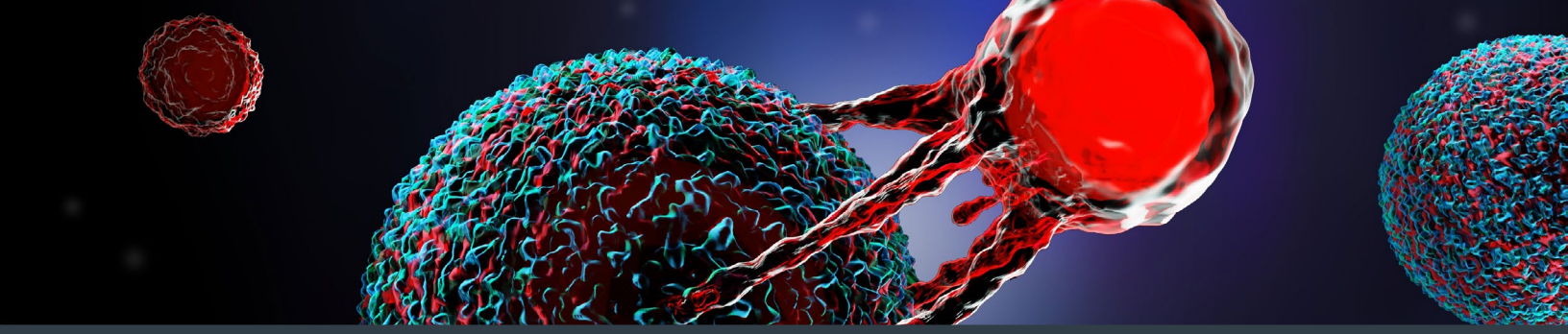

AstraZeneca is pioneering novel cell therapies for some of the world's most common chronic diseases

Fishawack Health sat down with Professor Francesco Dazzi, Medical Lead Cell Therapy, BioPharmaceuticals R&D at AstraZeneca, to learn about the company's groundbreaking cell therapy pipeline in cardiovascular, renal, and metabolic diseases and in immunology and discuss why developing cell therapy for a large patient population requires a different approach.

*By **Natasha Cowan**, Senior Corporate Communications Manager*

During the last five years, we have witnessed an explosion in cell therapy innovation. Significant advances in the understanding of disease biology and major innovations in gene editing, protein engineering, and cell culture technology have created a highly fertile scientific environment in which cell therapy research is flourishing. As an early innovator in cell therapy, AstraZeneca BioPharmaceuticals is now investigating the potential of this exciting technology across cardiovascular, renal, and metabolic diseases and immunological diseases.

This represents a paradigm shift for cell therapy. Across the industry, much of the research in this area has concentrated on developing treatments for complex cancers and rare diseases, which generally target small patient populations.

AstraZeneca is developing potential groundbreaking treatments for some of the most prevalent diseases in the world. Not only is it meeting significant unmet need, but it also is breaking new ground in these disease areas.

> Leveraging its cross-functional expertise from oncology, the company is exploring the removal of disease-causing or dysfunctional cells using engineered immune cells, such as CAR-T cells.

> You must take a different approach to clinical research, rebalancing the focus not just on the product, but on the patient, because the patient's biological makeup may completely transform the outcome

***Professor Francesco Dazzi**, Medical Lead Cell Therapy, BioPharmaceuticals R&D, AstraZeneca*

Leveraging its cross-functional expertise from oncology, the company is exploring the removal of disease-causing or dysfunctional cells using engineered immune cells, such as CAR-T cells. Its innovative pipeline includes engineering Treg cells, which act as "natural brakes" in the immune system and control the activity of other immune cells. These Treg cells are engineered using CRISPR gene-editing technology with the aim to treat inflammatory diseases. Using functional genomic screens, its scientists are identifying potential targets that they want to engineer in the cells. The company is also exploring a next-generation off-the-shelf CAR-T therapy for immunological diseases.

The challenges when developing cell therapies in this area are substantial. The treatments are complex, costly, and difficult to manufacture and scale. For example, primary human Treg cells are notoriously difficult to work with at scale. To understand which pathways to regulate, the team is conducting a whole genome-wide screen and full RNAi screen to extract granular details on the markers, pathways, and regulators necessary to control the immunosuppressive functions and stability of Tregs.

Adding to the complexity is that cell therapies are living treatments. Here lies the challenge and the intrigue for Francesco Dazzi, AstraZeneca's new Medical Lead for cell therapy and the research and development team at AstraZeneca BioPharmaceuticals.

However, if the risks pay off, they could make a significant contribution to preventing some of the leading causes of morbidity and mortality worldwide.[1]

NEW MUSCLES FOR FAILING HEARTS

"Cell therapies for regenerative medicine are completely different than a molecule," explains Francesco. "You develop a molecule to target a particular molecular structure, but a cell has billions of molecules, billions of receptors, billions of functions, and this clearly makes things very complicated. You must take a different approach to clinical research, rebalancing the focus not just on the product, but on the patient, because the patient's biological makeup may completely transform the outcome."

In May 2022, AstraZeneca, along with researchers from Procella Therapeutics and the Karolinska Institutet, published their findings from a groundbreaking investigational study that demonstrated a new cell therapy approach for heart failure. The study illustrated, for the first time, that human ventricular progenitor cells can promote regeneration of healthy cardiac tissue after a heart attack, improve cardiac function, and reduce scar tissue.[2] Evidence in preclinical models shows that when the cells are injected, they can engraft, multiply, and develop into beating ventricular cardiomyocytes, replicating those in a healthy heart.[3]

"The holy grail of tissue repair is to have a progenitor cell, which will hopefully be able to graft and repopulate the area that has been damaged. In our preclinical studies, we have injected the cells in the infarcted areas, and they have grafted beautifully," says Francesco.

The study represents a milestone in the treatment of heart failure, especially for older patients who may not be able to withstand surgery, and provides new hope to millions of patients with end-stage heart failure who face agonizing waits for heart transplants. However, developing and scaling a treatment of this nature is a complex challenge.

> In our preclinical studies, we have injected the cells in the infarcted areas, and they have grafted beautifully

SCALING UP

Understanding the potential routes for administration and scalability early on are important considerations when developing a cell therapy. This is illustrated by the supply chain shortages and infrastructure challenges that have left acute lymphocytic leukemia (ALL) patients waiting for months without CAR-T treatments.[4]

Manufacturers developing the next generation of cell therapies therefore need to carefully consider the real-world application of these complex treatments and the market dynamics from the preclinical phases.

CAR-T therapy to treat patients with ALL is only suitable for a few hundred patients per year.[5] AstraZeneca's ambitious target is to offer a treatment for chronic diseases that could be viable for larger patient populations.

As a result, the company is carefully considering its strategy early on. The first step is to rigorously define the patient population. This includes a focus on patient stratification and developing molecular classifiers to understand the subpopulations of patients that will respond to the treatment.

"After patient selection, another hurdle is the administration modality," Francesco says. "What is the best approach to maximize cell engraftment and persistence, and how should the cell transplant be distributed? Is an in situ injection better than an intravenous administration? For example, some injuries can affect a tiny part of the heart or a large part of the heart, and even a small injury could impact overall function. At the same time, you need to think about how you scale cell manufacturing, because if you don't have an efficient scale-up system, you need to make decisions early on."

BRINGING IN THE PATIENT VOICE

AstraZeneca was drawn to Francesco because he not only has more than 25 years' experience working in regenerative medicine as a clinical academic focused on hematopoietic stem cell transplantation—including working on the only successful regenerative therapy using established stem cells to totally repopulate bone marrow and blood formation—but also because he remains a practicing clinician and can offer the patient and clinician perspectives at the earliest stages of clinical development.

Francesco was drawn to the resources, infrastructure, and competencies a top 10 biopharmaceutical company could offer, including its proximity to the University of Cambridge. "Because of the lack of resources, as an academic, the most you can do is treat a small cohort of patients. It's exciting to have every single component on hand and to be able to take a complete approach. That means there are endless possibilities and opportunities to make a difference to patients," he explains.

His passion for patients is shaped by his work treating those with leukemia and his involvement in trials for genetic diseases, which have taught him about the value of improving a patient's quality of life. As a result, he is helping to ensure their voices and experiences are considered from the preclinical stages, including to improve the design of clinical trials.

"Quality of life is extremely important—it's almost as important as if you are cured. A decent improvement makes a massive difference," he explains. "For example, I've been involved in a couple of trials for epidermolysis bullosa. It's a genetic condition in which children develop vesicles all over the place—it's torture for them.

"There was very little we could do, but the treatment could reduce the itching. Some people might think, 'So what? You can scratch an itch,' but as soon as they scratched it, they would develop massive ulcers. So even reducing the change of dressing to once every day, rather than three and four times per day, was a small step forward that could make a big impact."

Here, it is important to deliver meaningful results for patients and clinicians, as well as the regulator. By gaining patient insight prior to the clinical trials, manufacturers can better understand their unmet needs and build measures to show marked improvements in quality of life, which can be differentiating for clinicians, payers, and regulators.

These metrics are being reviewed more closely by regulators and payers. For example, the UK National Institute for Health and Care Excellence has spent several years reevaluating and improving its quality-of-life measures.[6] In 2019, the organization published its first scientific advice on including patient perspectives in study design, illustrating the importance of providing data on outcomes that patients value.

Meanwhile, the FDA is publishing a series of guidance documents to support manufacturers in systematically collecting data on the patient voice, addressing challenges around the heterogeneity of data, and methods used to evaluate patient experience.[7]

"Years before the trial, you can start discussions with patients on their major unmet needs to begin building different metrics to measure improvements as a result. You just need to ask the right, specific questions early on," Francesco says.

A PIONEER IN INNOVATION

AstraZeneca's biopharmaceutical pipeline is filled with cell therapy innovations that could transform patients' lives. Alongside innovations in the area of heart failure, the company is researching how to expand and stabilize Treg cells to combat autoimmune diseases, investigating restoring liver function using human biliary epithelial cells, and looking at growing kidney organoids for chronic kidney disease.

One area Francesco is particularly interested in is exploring better ways to uncover targets for cell therapies, which would improve clinical trials and speed up scientific discovery. "One of the limitations is that preclinical models are only a model of the disease. They are beautiful, but the question is always: Do they have a real impact on patients? Safety and ethicality will always be paramount, but there is a need to think differently, push boundaries of experimental medicine, and develop a better understanding from patients, samples, and disease," he says. "In cell therapies, the target and patient subgroups remain to be precisely identified. If we could identify these, then success is more likely.

"So many times in cell therapies we see an amazing product that could potentially do something incredible like rebuild an organ, but once injected you can't even find it. There is an immense opportunity but only if tackled from every angle."

The challenges ahead are undeniable, but the future looks bright for AstraZeneca's biopharmaceutical pipeline and offers a glimmer of hope for patients with debilitating diseases.

"A lot of companies talk about being leaders in the field, but to actually be a leader in the field at a company that has this knowledge about cell therapy and resources to back it up means the opportunities are endless," says Francesco. "There is a real possibility to make a difference for patients, and it's incredibly exciting to really see this come to fruition."

Get in touch to learn how our teams at Fishawack Health can support you in developing a successful early commercialization strategy for your cell therapy.

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6 trends shaping the future of personalized medicine

Senior Consultant Leah Carlisle explores the key trends discussed at the 16th annual Personalized Medicine Conference, providing expert analysis and key recommendations for biopharmaceutical innovators.

*By **Leah Carlisle**, Senior Consultant*

With precision medicines accounting for at least 25% of FDA approvals in the last 7 years, personalized healthcare is far from niche.[1] Personalization is one of the foundations of modern healthcare, advancing how we realize better outcomes for patients and society.

Related forces like value-based care and patient empowerment are bolstering the movement towards personalization. At the same time, the COVID-19 pandemic has disrupted the health landscape—illuminating inequities, spurring technological innovation, and further elevating the role of human behavior in health.

Bringing together a wide array of stakeholders—from the pharmaceutical and diagnostic industry to providers, payers, patients, and clinicians—is crucial for exchanging perspectives and ideas in this changing landscape. This is just what the Personalized Medicine Coalition did at its 16th annual conference, "From an Enterprise to an Era," in May 2022.

Read on for our key takeaways from the rich conversations at the conference and learn what they mean for innovators working to continue advancing personalized healthcare.

1. WE HAVE COME A LONG WAY OVER THE PAST DECADES TO ADVANCE PRECISION MEDICINE—WE HAVE A STRONG BEACHHEAD TO EXPAND FROM, BUT STILL A LOT OF EXPANSION TO DO

In looking to the future, many speakers balanced the challenges preventing the advancement of personalized medicine with the progress made to date. Regulatory approaches have come a long way, driving accelerated approvals and the use of novel trial design such as N of 1 studies—clinical trials focused on a single patient. Advancements like CAR-T and rare disease phenotype-based interventions have benefited patients across the globe—proving we are well beyond personalization being a fad.

The Cancer Moonshot℠, led by President Joe Biden, has also spotlighted the benefits of personalized healthcare and provided essential funding to accelerate scientific discovery, foster collaboration, and improve data sharing.

Additionally, developments in companion diagnostics and multicancer panels have driven collaboration between drug developers and testing companies, and the demand for and adoption of value-based medicine has elevated the importance of personalization.

On the horizon, the impact of personalization is expanding across diseases. Researchers are detecting more cancers early and broadening their focus to therapy areas such as psychiatry, which often uses trial and error.

However, systemic progress is often slower. Reimbursement paths are often ill-defined, digital solutions struggle to deliver outcomes data at scale, and health systems in countries like the USA are not as set up for prevention and staying well. The life science sector has the opportunity to become a changemaker, starting with groups like the self-insured and employers who can champion a preventative focus.

> We must harness the voices making a positive impact to drive urgency among stakeholders like policymakers

Our take: *A sense of progress can often spur further action. Although focusing on the challenges ahead is beneficial, we should balance this with sharing personal stories and data on our achievements to date. We must harness the voices making a positive impact to drive urgency among stakeholders like policymakers. We must also conduct research and provide forums to uncover and share learnings from diseases in which personalized medicine is more advanced to inform activities in other therapy areas. Collaboration, patient engagement, and behavioral science will help address some of the systemic challenges at play.*

2. WE ARE INCREASINGLY MOVING FROM PRECISION MEDICINE TO A MORE HOLISTIC VIEW OF PERSONALIZED HEALTHCARE

Genomics remains essential to the past, present, and future of precision medicine. A "multi-omic" view, however, is becoming front and center—incorporating other biological factors such as proteomics and metabolomics.

In Q2 2021, CB Insights reported approximately 50% quarter-over-quarter growth in "omics" funding.[2] Panelists highlighted the need to continue investing in the technology to combine multi-omics analysis into one platform—there is progress being made here, but the technological capability is not present yet.

Biological data need to be layered with clinical, social, environmental, and other personal data so we can personalize healthcare, not just medicine. Deep, broad data are multidimensional, considering information such as personal values, lifestyle, social determinants of health, environmental concerns, and emotion-centric data about mental health.

Innovative companies are increasing investment in capturing this data longitudinally—looking at the patient experience over time and analyzing clinical trial and real-world data together.

> Evidence-generation efforts should look at a breadth of factors early to ensure studies capture these multifaceted data and technology platforms can integrate them

Our take: *This multidimensional approach is encouraging and involves viewing a patient as a whole person whose health is impacted by more than their medication. Evidence-generation efforts should look at a breadth of factors early to ensure studies capture these multifaceted data and technology platforms can integrate them. Human-centered–design approaches are valuable for ensuring we are capturing this data in a way that removes, not adds, burden for patients and healthcare professionals.*

3. SILOS ARE THE ENEMY OF PERSONALIZATION—COLLABORATION IS KEY

The topic of collaboration came up in nearly every conference session, highlighting the unprecedented nature of partnerships in the life science industry. Today, academic centers are more willing to share data, including bringing in more evidence on the social determinants of healthcare. The Tempus and Yale SalivaDirect™ effort, which mobilized the academic, government, public, and private sectors to drive broad equitable access to COVID-19 PCR tests, is one of many examples of this.

As Kite Pharma CEO Christi Shaw said in her opening keynote, advancing personalized medicine is a "team sport" that requires tough decisions and collaboration. She highlighted the need to identify what you are exceptional at and work with the academic community, dive into translational research, and share between centers to continuously improve.

Multistakeholder engagement is central to collaboration, including working with trusted community sources to ensure patients and doctors understand the value of personalized medicine. This includes less typical healthcare professional audiences such as pediatricians and ER doctors, who need to understand the situations in which biomarker testing can benefit their patients. Diverse thought leaders, such as doctors and patient advocacy groups, should be engaged early to design trials, help find patients, and more. Additionally, nonprofit disease groups can and should take a leadership position in building and maximizing partnerships.

> Cocreation with multistakeholder audiences drives genuine collaboration and ensures patients, healthcare professionals, and other key voices have real input from the start

The landscape is full of innovation, so there is no need to build everything from scratch; instead consider partnering to fast-track advancements. Common protocols and collaborative models, as well as data standards and interoperability, can help fuel partnerships enabling speed and constant iteration.

Our take: *When planning an initiative, build collaboration into the roadmap and chart all the relevant stakeholders from the earliest phase. Cocreation with multistakeholder audiences drives genuine collaboration and ensures patients, healthcare professionals, and other key voices have real input from the start and can see the value of the initiative. Collaboration can be easier said than done, so teams should prioritize an early assessment of internal culture, processes, and platforms to identify and solve challenges up front.*

4. GENUINE PATIENT-CENTRICITY AND PATIENT ENGAGEMENT DRIVE LEADERSHIP AND PROGRESS

Patient-centricity has long been a buzzword in the healthcare industry, but the reality is that business demands and systemic constraints can limit follow-through. Today, patients are more empowered, and healthcare players are increasingly moving past lip service to meet their needs. Patient-centricity is often a long game and means making the hard decisions to put patients over short-term profits—for example, deprioritizing "me-too" treatments in favor of novel innovations that meet significant unmet needs or that make a meaningful improvement compared to the available options. These priorities, of course, require genuine buy-in from the top of the organization.

Consumer engagement empowers patients to demand personalized care and seek referrals and second opinions where needed. An engagement strategy can include investing in services and resources to support patients, such as patient navigators and ambassadors, and partnering with patient advocacy groups to deliver emotional and practical support such as finances and transportation.

Identifying and eliminating frictions in the patient and caregiver experience and pinpointing where patients get lost in the process are vital for creating patient-centric experiences. One way to highlight these barriers is by thinking about your offering in terms of an end-to-end audience journey.

The most innovative companies think of themselves as testing service companies, not solely diagnostics providers, and prioritize caring for patients before, during, and after biomarker testing. They build a sense of community and purpose between patients and facilitate story sharing, while ensuring engagement is bidirectional—cocreating and genuinely seeking input from patients at every level of product or service development and commercialization, from clinical trial design to marketing.

These companies also invest in educating the community in a language they can understand, said in multiple ways, and with formats such as webinars that allow for time to digest and learn. They understand that a focus on the patient experience also includes ensuring transparency and simplicity around data use and informed consent, including developing a feedback loop that returns data and information to participants, as programs like All of Us do.

Our take: *Community collaboration and patient-centricity are a business imperative as much as it is a moral one. The practices above are critical, from cocreation to experience mapping. Bringing the patient and caregiver voice into drug and service development and supporting them across their journey must be a priority for any initiative. Patient impact should be measured as part of ROI calculations alongside the business impact, with leadership considering longer timelines that allow teams to measure the correlation between the two key performance indicators.*

5. HEALTHY EQUITY CANNOT BE AN AFTERTHOUGHT

The COVID-19 pandemic highlighted the detrimental impact of global inequities in healthcare and beyond. Cost and accessibility continue to be societal issues, and there is a huge focus on ensuring innovations can be accessed by all the people who need them, not just the wealthy.

Companies continue to work hard to drive diversity and inclusivity by building increasingly diverse data sets that reduce bias in algorithms and evidence. Post-launch, innovative drug developers are gathering and publishing real-world evidence in specific populations so patients can see how others like them responded to therapy.

However, it is not enough to generate evidence to show the impact on underrepresented populations. The industry must also take steps to ensure the policies and systems that govern data are informed by a diverse community and that social determinants of health are a part of the data ecosystem.

> We can't truly personalize healthcare if we only have the data and insight to do so for the groups of people who traditionally are included in the health system

Community engagement is vital for ensuring diverse communities understand and benefit from novel treatments. As Randy Burkholder, former Vice President of Policy and Research at PhRMA, explains, "It's up to us to make sure that public trust in science does not itself become an undruggable target." Solving issues of mistrust begins with educating the community on the impact of diseases and collaborating with diverse populations to build authentic and relevant educational programs.

Reaching patients where they are and mitigating financial, psychological, and logistical burdens will ensure drug developers can reach the whole patient population while building trust in underserved groups. Leading drug developers are therefore expanding clinical trials into the community and investing in transportation and local and at-home care to ensure all patients can participate.

Our take: *We can't truly personalize healthcare if we only have the data and insight to do so for the groups of people who traditionally are included in the health system. The public eye is on us, and leadership, or a lack thereof, will be noticed. A health equity lens must be applied to every initiative and activity—from who we include in market research to the eligibility criteria of our trials. And it must cover a range of characteristics, from neurodiversity to race and ethnicity to ability status—and the intersectionality between them. At times, this may require tradeoffs in budgets and timelines. However, there are genuine business benefits, such as reaching a broader audience and providing a more personalized care experience that improves outcomes.*

6. WE NEED TO MATCH MEDICAL SCIENCE WITH IMPLEMENTATION SCIENCE

Dr Janet Woodcock, Principal Deputy Commissioner, US Food and Drug Administration, opened the second day of the conference by saying: "You can't just put innovations out there and expect the system with people stressed out of their minds to pick it up. We need to (ensure we are) translating these advances down to people." Science and technology are advancing more quickly than people can understand and adopt. As many physicians struggle to keep up with growing demands, patients miss out on personalized care options because of suboptimal testing practices at various stages of the journey, from test to referral and treatment decision.

Innovations need to be both accessible to the patient and painless for the doctor. By taking a behavioral science approach to understanding stakeholders' drivers and entrenched behaviors, we can make the process as easy and accessible as possible.

> "There is a massive and urgent opportunity to harness the principles of behavioral and implementation science

Clinical decision support can drive clarity, providing only the right information at the right time at the point of care, such as alerts specific to a patient's medications, genomics, and metabolism.

Christ Hospital in Ohio, for example, has developed multiple chatbots to educate and flag patients, triggering referrals for activities such as screening, and is working on creative ways to show the financial impact of such programs.

Digital health is making it easier to meet patients closer to home, but it isn't without its challenges. When implementing a new technology or platform, having all relevant stakeholders input into plans from the start will enable buy-in and participation. Additionally, the biopharmaceutical industry can learn a lot from sectors that have already adopted technological advancements, such as behavioral health, gaining insights on how to ensure the technology meets stakeholders' needs and matches their patterns of behavior.

Our take: *There is a massive and urgent opportunity to harness the principles of behavioral and implementation science to define goals for how you would like stakeholders to act, understand the range of drivers and barriers to those desired actions, define, and—critically—rigorously test interventions to achieve these goals.*

FROM NICHE SCIENCE TO THE FOUNDATIONS OF MEDICINE

The personalized healthcare community is energized and innovating at great speed, not only in terms of the science and technology required for personalization but also in terms of collaboration and consumer-centricity, which are essential for realizing the potential of personalized medicine advancements. The innovations and approaches that the community are championing are becoming a fundamental, not a niche, part of healthcare broadly—and all of this was excitingly spotlighted at this year's long-awaited Personalized Medicine Coalition conference.

Get in touch to find out how our consultants, medical communications and marketing experts, and policy and market access specialists can unite to help you advance your personalized healthcare efforts.

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The promised land of gene therapy: Commercialization of novel gene-editing technology in beta-thalassemia

With transformative treatments that leverage CRISPR technology, there are many challenges to overcome throughout the journey of development through to patient access. We interviewed a researcher at a top 20 pharma company, multiple patients, and our own market access experts for their insights into the process, obstacles, and opportunities for biopharmaceutical companies to meet patient needs and achieve success in the market.

*By **Samhita Sen**, Marketing Executive, and **Kunal Chopra**, Medical Writer*

Gene therapies and research into them have grown immensely in recent years, offering more novel tools in regenerative medicine to fight disease, including rare diseases and genetic disorders. In the last decade, there has also been rapid development and interest in CRISPR/Cas9 technology and other gene-editing tools that could offer transformative avenues to deliver gene therapies for patients and families affected by devastating diseases such as sickle cell disease and thalassemia.

Beta-thalassemia is a rare blood disorder caused by a genetic defect in hemoglobin. Several manufacturers are developing novel treatments for the disease, including Vertex, which has partnered with CRISPR Therapeutics to develop a gene-editing treatment for beta-thalassemia and sickle cell. In October 2022, the companies announced their plan to file exagamglogene autotemcel, the CRISPR/Cas9 gene-edited therapy, for a rolling review with the FDA.[1] Novartis also recently inked an up-to $1.5 billion deal with Precision Biosciences to support its development of one-time treatments for beta-thalassemia and sickle cell.[2] The move marks a continuation in its ongoing commitment to exploring gene-editing technology.

Despite the surge of interest from both scientific and financial stakeholders, there remain numerous unique challenges at every step of this new frontier. From developing and financing the therapy in a timely manner to market access challenges due to the lack of maturity and extensive evidence, and explaining the complex science to physicians and patients, there are a variety of hurdles to overcome before bringing this type of technology to market. And while regenerative and curative therapies are often greatly lauded, there are also challenges in treating affected patient populations, including cost, accessibility, side effects, and other associated risks.

Earlier this year, the US Food and Drug Administration (FDA) approved the first potentially curative gene therapy to treat beta-thalassemia.[3] While multiple companies have been working to bring transformative technologies such as CRISPR to market, approval will require further consideration around the many concerns and challenges of each stakeholder at every step. From the research and development stage all the way to patient access and treatment, remaining considerate of the populations that will ultimately be the end-users and testament to the technology's success is vital.

BRINGING IN THE PATIENT PERSPECTIVE

Diagnosed with beta-thalassemia at six months old, Amar has had regular blood transfusions every few weeks for the majority of his life. As a child, he found himself falling behind others his age. "I always felt I was playing catch-up, through school, work, life—always making up for lost time," he says.

Now in his 4Os, he reflects on both the physical and mental impacts of the disease. He says, "As I'm getting older, my body is deteriorating, and it raises concerns for my future and what my life expectancy will look like. The disease has triggered other health conditions, including osteoarthritis, hypogonadism, and diabetes. It's a constant challenge, both physically and mentally," he says.

Zeb's six-year-old son is affected by thalassemia and experiences a drastic mental and physical decline after his second week post-transfusion. "His mood, his happiness, his appetite, it all shifts. And when he gets his transfusion, he is so much happier again," Zeb says.

Patients often become quite resilient in the face of their disease, but the effects of beta-thalassemia can be fatal. And although both Zeb's son and Amar have relied on Exjade® to stave off the iron overload that comes with regular blood transfusions, both patients are constantly trying to manage their disease. "At one point, I remember I was having 18 tablets daily. When I was told my bone density was deteriorating, I was placed on bisphosphonate medication administered intravenously. I was prescribed a large dose of strong painkillers. In addition to this, I had iron chelation therapy issues, painful intramuscular testosterone injections, vitamin D tablets, and now I have the continuous glucose monitoring patch for diabetes," says Amar.

All the individuals interviewed shared that the necessity of regular transfusions disrupted their schedules, forcing them to take time off from school, work, or holidays to maintain a healthy level of hemoglobin. With this comes the financial burden of the treatment regimen itself, plus potential extraneous expenses such as hospital fees, transportation, and parking.

> Although the technology may offer a transformative solution, it will be difficult to balance the promise with the reality of cost

Although existing treatment regimens are time intensive and have an estimated lifetime cost from $720,000 to over $5 million, a curative therapy would need to be evaluated to understand the risks and costs to the patient, along with the benefits.[4,5] From its price point to potential side effects, there are many reasons that might lead a patient to view the curative option as unviable.

Instead, most patients endure a lifelong treatment regimen involving symptom management, pain relief, and blood transfusions. CRISPR technology could offer a safer, more accessible, and life-changing method of gene therapy for these patients if the price point is set within reach.

As a one-time dose, any gene therapy for thalassemia involving CRISPR technology aims to reduce, if not eliminate, the need for blood transfusions, thereby greatly shortening the time required for treatment. This outcome would also reduce the financial burden of the disease and potentially other health issues that can occur as a result of thalassemia as well. For patients, however, there is much more to consider.

When bringing gene-editing tools to patients, biopharmaceutical companies will need to address patient needs and alleviate concerns by ensuring equitable access, healthcare professional education, sharing real-world evidence and patient-reported outcomes to offer accurate and representative data for the patient population. On top of this, they will also need to find ways to equip patients with a comprehensive understanding of the value of the technology, side effects, risks and benefits, and other key considerations to inform their decision-making process.

A TRICKY BALANCE OF ACCESS AND REVENUE

Five years on from the first gene therapy approved by the FDA, there are plenty of ongoing scientific advancements in the gene therapy space, including potentially transformative treatments in the pipeline for patients with rare diseases and limited options for treatment. This year, Bluebird Bio's new beti-cel treatment for patients with transfusion-dependent thalassemia was approved by the FDA following its unanimous support for the one-time gene therapy earlier in the year.[6]

"However, the market access challenges for regenerative medicines need to be considered alongside the opportunities they bring," says Dr Sanjeev Gogna, Senior Director at PRMA Consulting, a member of Fishawack Health. With a potential cost of up to $3 million per dose, the newly approved beti-cel therapy is out of reach for patients without the means to afford it. The only other curative option for patients with beta-thalassemia thus far has been allogeneic hematopoietic stem cell transplantation from a matched donor, which is difficult to find. Both cost and accessibility remain primary concerns with these options.

"The complex production process and the higher acquisition cost coupled with limited or immature data also mean that, although the technology may offer a transformative solution, it will be difficult to balance the promise with the reality of cost," says Sanjeev. The immense cost of producing a viable therapy for a small patient population necessitates setting a high price point. Biopharmaceutical companies working in this space will need to balance their profit margin with the goal of bringing curative therapy to as many patients as possible.

> While CRISPR Therapeutics' and Vertex Pharmaceuticals' gene therapy candidate, exa-cel, also shows promise, there is still room to improve the evidence package and value presented for health technology assessment (HTA) bodies to consider it a viable option

He says, "As this technology scales, we can anticipate major challenges to the value assessment. For any company operating in this space, it's important to understand how health technology assessment (HTA) bodies will balance the tradeoff between precision, maturity of evidence, high up-front costs and affordability, and how this relates in general to decisions over value."

Generating sufficient data can be a challenge with a small patient population. HTA bodies making decisions about potential benefit value robust evidence to show efficacy and safety. So innovative methods for continuous monitoring of patients, accurately representing the patients in trial population to align with the treatment population, some use of real-world data, and tailoring the evidence-generation plan early at the clinical phase can all help ongoing evidence-generation needs through to move past approval. This also helps ensure that patients and the communities advising patients are equipped with as much data as possible to make informed decisions about their treatment options and regimen.

> "(CRISPR therapy is) more precise and easier to use than other gene-editing tools and can really give the patient a better shot at a healthy life

The late-stage clinical data presented by Bluebird Bio indicated that 89% of patients achieved transfusion independence and lacked serious adverse side effects beyond two years post-infusion.[7] While CRISPR Therapeutics' and Vertex Pharmaceuticals' gene therapy candidate, exa-cel, also shows promise, there is still room to improve the evidence package and value presented for HTA bodies to consider it a viable option.[6] Sufficient evidence can also help justify the risk-benefit balance for reimbursement agencies and payer bodies considering the therapy from a regulator perspective. "Hence, developing a strong evidence package is essential to maximize commercialization opportunities," says Sanjeev.

BUILDING A STRONG FOUNDATION FOR AMBITIOUS ENDS

Gene editing opens up a world of possibilities for innovative cellular therapies that are both safe and effective, as shown in autologous CAR-T products, which have become safer as a result of gene-editing technology.[8] "CRISPR therapy is big for debilitating disorders that are monogenic or caused because of one gene mutation," says Manisha Padmakumar, Postdoctoral Researcher at UCB in Belgium. "It's more precise and easier to use than other gene-editing tools and can really give the patient a better shot at a healthy life."

Other methods such as lentiviral transduction can have serious side effects as it is less precise in how it places the gene of interest. Zinc-finger nucleases and TALENs have also been compared as powerful gene-editing tools but tend to involve a more painstaking process to manipulate and engineer than the Cas9 method.

"Gene therapy is very powerful, but then health insurance is still figuring out how to deal with it," says Manisha. "For example, for most citizens in the European Union, there is heavily subsidized healthcare funded by the social security system so as to not create an economic disparity in access to health insurance. But how will they afford the millions it will take to fund this kind of one-time treatment for a single patient?"

The higher cost of researching, developing, and producing a viable gene therapy is often passed on to patients and providers, causing difficulty in getting coverage and reimbursement for the therapy.[9] Thomas Klima, Chief Commercial Officer at Bluebird, told Endpoints News that Bluebird's approved beti-cel therapy is no longer marketed in Europe due to the lengthy pricing process and financial negotiations that payers were not ready to accept.[3] Instead, biopharmaceutical companies need enough profit to balance the immense investment put into this type of treatment.

This can put the therapy out of reach for some patients. "For companies, it's difficult to get CRISPR therapy into the pipeline at all because of the small patient population and the profit base," says Manisha. "Now, people are thinking of counterapproaches that attack the problem differently, such as creating off-the-shelf therapy options, which can work for some cancers."

> "The healthcare provider should always have a genetic counselor or a team of geneticists. … It should ultimately be a team effort because one person cannot have all the answers or insights

For some, the mindset around gene editing is focused on the risks and ethical concerns, posing a challenge for biopharmaceutical companies looking to market their product. Manisha says, "The mindset has to change. We are so used to taking off-the-shelf pills that injections initially seemed scary. Then, injections became commonplace and cell transplants were the unknown. People are still getting to a place where they accept new technology, but it will take some time."

Building the foundation of data early can help later in the pipeline, but this also requires being careful with research and development. "With social media, if even one instance doesn't produce a good result, it can have a huge social impact on people's perception, leading companies to give up gene therapy from their portfolio. Instead, there needs to be more care and expense towards research to avoid this outcome," says Manisha. "We might see an amazing result in the lab, but long-term follow-up on every clinical trial is very important, and we are seeing that more and more throughout the life-span of the patient."

KEEPING THE FOCUS ON THE PATIENT FIRST

As the healthcare landscape shifts toward a more patient-centric outlook, some companies are now working in collaboration to combine their expertise in different parts of the pipeline.[10] With this comes a shift toward greater transparency, accountability, social responsibility, and an emphasis on the value of patient lives.

With collaboration and patient outcomes in mind, Manisha says, "The healthcare provider should always have a genetic counselor or a team of geneticists if they are treating a patient with a genetic mutation. It should ultimately be a team effort because one person cannot have all the answers or insights." Patients and caregivers are increasingly becoming advocates and experts in their own disease, more so than some physicians. Including them in research and outreach to understand their disease better could be an effective way to engage the patient communities and needs earlier in the pipeline, build a stronger case for the treatment based on those insights, generate data throughout the process, and work to actively change the public perception of gene therapy with robust evidence and education.

Once the therapy is available to patients, its success in the market will hinge on whether patients make the choice to use it. Taking this into consideration, biopharmaceutical companies will need to find cost-effective ways to scale up and meet patient needs. "I look into how much testing has gone into it, how long the trials have been going on for, the potential side effects, and weigh those against the benefits," explains Amar. This information is most manageable for patients when broken into bite-size chunks of content. For example, specific information that helps manage expectations around the novel and complex treatment journey could be invaluable for patients considering the life-altering treatment.

Sharing real patient stories and other useful information alongside this type of content, and doing so using a variety of channels to reach all the relevant communities, could go a long way to building a more comprehensive understanding of the new technology.

As many individuals within the patient community become advocates themselves, providing information to better understand the science, risks, and benefits through multiple avenues could be helpful as they conduct their own independent research. This includes taking a robust approach to educate and engage healthcare professionals.

Zeb says, "The information my wife and I get is mostly from conferences or online. My wife is quite proactive, so we research what's available. We were expecting more information from our consultants but found they didn't know much more than us."

Educating the healthcare professionals involved in the care of patients with rare diseases is difficult but necessary as they are integral to improving patient outcomes and advising patients and their communities to make the best decisions for the patient's short- and long-term health.

Consultants are the medical experts liaising with and helping patients make the right decisions for their treatment journey. They need to be able to convey information accurately and in layperson's terms. In some cases, this may include finding an individual or advocacy group to help break down the medical jargon and language. This extra step helps ensure patients, regardless of language or cultural background, are fully informed about their options. Without the relevant information and understanding, patients may not be open to alternate treatment options such as novel gene therapies.

A CONNECTED APPROACH TO COMMERCIALIZATION

With this exciting new technology in the pipeline, it is vital to take the full life cycle into consideration, thinking about the patient experience up front and implementing a connected approach from the start.

From competitive market analysis, first-to-market strategy, and gene delivery to patient identification and post-treatment planning, Fishawack Health offers a wide breadth of experience and services in the rare disease and regenerative medicines space for gene therapies. With the goal of developing a sustainable business model that keeps all stakeholders in mind at every stage, we offer our integrated services to support our clients' needs wherever they are in their commercialization journey.

While many companies are not yet ready to begin the commercialization process, there is still enormous potential for strategic input. In particular, keeping the end in mind and working with a multidisciplinary view is crucial to success as the applications of CRISPR-based gene editing for revolutionizing the treatment options and experience for rare and inherited diseases grow. Ultimately, translating the value of the treatment and process in a way that overcomes both the fear of the unknown and the perceived cost burden will be of great value as more treatments are made available.

Our expertise in this area spans over 150 projects completed in the last five years, including projects in CAR-T therapy, gene therapies, and rare diseases, along with working with companies across the spectrum, from emerging biotechs to top 20 pharmaceutical companies. With unique obstacles and opportunities at every step with CRISPR-based gene editing, companies in this space will need to take care in how they approach the market and position their CRISPR-based therapy to all stakeholders at each step of the commercialization process.

Interested in how we can help you combat the challenges in commercializing your cell and gene therapy? Contact us.

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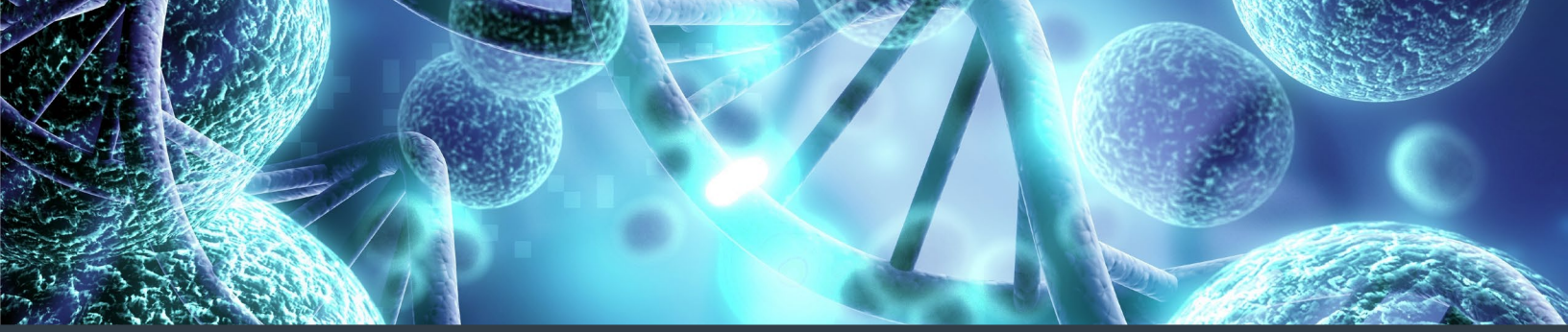

Making the complexity of cell and gene science simple for your stakeholders

Learn from our medical communication experts the steps you need to take to ensure your audience understands the high science you want to communicate

*By **Catriona Marshall**, Manager, Medical Communications and Business Development, and **Amy Jackson**, Executive Director, Medical Writing*

Mutations in the gene encoding adenosine deaminase (ADA; a key enzyme of the purine salvage pathways) cause the autosomal recessive disease severe combined immunodeficiency (SCID). When ADA function is absent or impaired, the toxic metabolites adenosine, 2'-deoxyadenosine, and deoxyadenosine triphosphate accumulate in cells, causing severe lymphocytopenia affecting T- and B-lymphocytes and NK cells.

Hang on, you've lost me. What does that ACTUALLY mean? And how useful was that little piece of text? It all depends on your level of scientific and medical knowledge of your audience.

> Knowing your audience and developing engaging content in different formats is the key to explaining complex science

FOR THE GENERAL PUBLIC

This paragraph would be simply dismissed—it's impenetrable. For the more scientifically and medically literate, it may translate into "a mutation causes SCID, which sounds like bad news, a bit like AIDS."

FOR A NONEXPERT HEALTHCARE PROFESSIONAL (HCP)

The key piece of information about lymphocytopenia may provide a bit of extra context about how the disease could impact patients, with the gravity of the condition extrapolated from the name (severe! [and] combined! immunodeficiency disease).

FOR THE EXPERT

The paragraph is probably redundant. You aren't telling them anything they do not already know, and you're possibly taking up valuable time.

Clearly, communicating your message in the right way for your target audience is key, and although we all have access to vast amounts of information at our fingertips, the job is not straightforward. This is especially true for complex and targeted cell and gene therapies with novel modes of action that leverage novel biomarkers and complex delivery methods.

The science behind these therapies is at the cutting edge of healthcare innovation, and there is a wide range of understanding (from none to highly literate) across both patient and healthcare professional populations that must be considered when planning a communication.

For patients, regulators, payers, and healthcare professionals alike, questions are also raised about the robust nature of the data—especially for accelerated approvals. As a result, conversations around the risk and benefit of these therapies become more challenging: Digestible communications are needed to help those who are not experts in the science make (the right) decisions.

THE IMPORTANCE OF KNOWING YOUR AUDIENCE

Knowing your audience and developing engaging content in different formats is the key to explaining complex science to nonexperts. **What do we mean by knowing your audience? There are many things to consider, which may include:**

- Who are they and what is their role in the patient journey?
- What is their likely level of knowledge?
- What information do they need to know?
- What are their attitudes and beliefs likely to be?
- Who might they be influenced by?
- What is their preferred learning style?

The answers to these questions will vary by therapy area, treatment, and stakeholder. The latter two will be addressed through development of an omnichannel communications plan, but the others need to be considered while developing the content.

> 50% of patients treated for relapsed or refractory diffuse large B-cell lymphoma felt that caregiver involvement was important for supplementing their understanding of treatment options

THE PATIENT VOICE

More than ever, patients are at the forefront of what we do—be it ensuring their voices are heard in the drug development process or that communications are tailored to their needs. After all, if patients do not understand their diagnosis, treatment options, and likely outcomes, their voices are effectively muted, so our clients are increasingly asking us to help with patient-focused communications.

We tailor information in medical communications much like we do when we are not at work, almost subconsciously. We've all been there. A family member who knows that you do "something medical" asks you to explain information from their doctor. They've looked online but they still have questions. Can you help? Well, of course, but you know they aren't experts in the area, and you need to think carefully about how much information they need at this point. Some diagnoses are life-changing (read, -ending), despite the number of promising new gene therapies, for example. Information needs to be conveyed in ways they will understand and can act upon.

Going back to our industry, when writing for patients, the main aim is to optimize readability; that is, how easy it is to read and understand the text. You can assume minimal medical knowledge. This can be done by shortening sentences, reducing the number of long words, using punctuation effectively, and ensuring that the flow and structure are logical and compelling. Considering what the reader actually needs to know is also helpful, because as well as taking out complex details, you may need to add additional clarification on points that may not be obvious to a layperson. That said, it is often useful to signpost readers to a further source if they would like to find out more about a particular topic.

If we revert to our example from the start of the article and apply these principles, we can produce a much simpler, but still accurate, description:

Severe combined immunodeficiency (SCID) can be caused by a reduction in a protein called adenosine deaminase (ADA). ADA removes toxic molecules from the blood, so if ADA doesn't work properly, toxic molecules build up. In turn, this reduces the number of infection-busting white blood cells in the blood, impairing the immune system. This means that people with this condition are more likely to get very ill from any infections they pick up.

ADA-SCID is very rare—it occurs because of a genetic mutation, which must be inherited from both parents for the disease to be present.

When considering the lay audience, it's important to remember that many patients depend on caregivers. These individuals may require information beyond that needed by a patient, such as how to help the patient, signs and symptoms to monitor, and when they should call for medical help, along with facilitating shared decision-making.

This is highlighted by recent research by Avalere Health (part of Fishawack Health), which found 50% of patients treated for relapsed or refractory diffuse large B-cell lymphoma felt that caregiver involvement was important for supplementing their understanding of treatment options. However, few tailored materials existed to help caregivers provide support.

Developing insight on, and understanding of, caregiver communities and creating materials to support them in their roles as a trusted voice in decision-making is therefore essential, especially for complex cell and gene therapies that can be difficult to understand.

> In a recent project, our scientific team was asked to find a way to explain the mechanism of action of a complex oncology therapy to patients and nurses

Another tool that can really help us when communicating to the lay audience is visuals. Infographics are all around us, like signs outside shops, road signs and markings, and those clever animations in television documentaries to explain how the jet engine works or why huge skyscrapers don't fall over. What we can learn from all of these is that simple visuals can be very effective. If done well, they can have a wide appeal.

Take CAR-T therapy for example:
An infographic showing T-cells being taken from a patient, being manipulated to create the treatment, and then being injected back into the patient is more likely to resonate with the lay audience than a paragraph of text.

ENGAGING THE NONEXPERT HCP

In the medical communications setting, expertise can be harder to define. Modern medicines increasingly include specific molecular targets, meaning that both disease pathogenesis and treatment mechanisms of action are highly complex. A few examples are the use of gene therapy to deliver treatments, targeting enzymes involved in repairing damaged DNA, targeting molecules found on specific cells involved in the disease, and therapies that only work if a genetic mutation is present. In such cases, only relevant research scientists and highly specialized HCPs would be considered experts. This highlights the importance of truly understanding your audience, including their level of understanding and, crucially, what it is they need to know before you start writing.

Everyone has a different learning style and capacity for absorbing information. The VARK questionnaire[1] was developed by Neil Fleming in 1987 after he noticed a difference in the way that people responded to being given a simple task, such as giving directions to a local landmark. The questionnaire assesses a person's preferred learning style by considering four categories: visual, aural, read/write, and kinesthetic learning. It stands to reason that by taking this into account and creating content in different formats, we can increase our chance of a given person receiving and understanding the information that they need.

We can make infographic-style plain language summaries and graphic abstracts for key research papers so that patients and nonexpert HCPs can have real engagement with the studies and data behind their disease or treatment.

Short, animated videos (2D or 3D) and podcasts are ideal for those who like to watch or listen (rather than read), with podcasts being perfect for those who like to multitask—running and learning at the same time, for example!

However, there are some cases when you need to do more—the communication still isn't quite right for your audience. This is where you have to look outside the box and perhaps devise an analogy that everyone will understand.

EXPLAINING A NOVEL MODE OF ACTION IN ONCOLOGY

In a recent project, our scientific team was asked to find a way to explain the mechanism of action of a complex oncology therapy to patients and nurses. The drug works by inhibiting repair of single DNA strand breaks in cancer cells, which ultimately leads to the death of those cells. So they considered that there were three situations: cells with no DNA damage, cells with damage to one strand of the DNA that could be repaired, and cells with damage to both strands of the DNA, which would ultimately die. Proteins in the cells can sense the second situation and repair the DNA, unless the drug stops them doing so.

The analogy that the team came up with was that of boxes of items on a factory production line. The boxes (cells) travel along a production line, and a sensor detects those containing defective items. Those that are bent (single-strand DNA damage) are removed from the production line and repaired before being replaced on the line (DNA repaired, cell lives). Boxes containing broken items (double-strand DNA damage) that can't be mended are permanently removed from the production line and accumulate as trash (cell death).

If the factory worker turns off the sensor (by using the drug) that detects the bent items (that can usually be repaired), then they will just be classed as defective and accumulate with the broken items (resulting in increased death of cancer cells).

This was visually represented as an infographic showing the cell biology and the analogy side by side; feedback was positive, and the materials have been used by nurses to help explain how the drug works to patients and their carers.

GUIDING DECISIONS THAT MATTER

We've talked about how to ensure that HCPs and their patients can understand the complex science around a disease and its associated therapy, but of course that is only part of the story. Each individual material may be part of an omnichannel plan that provides appropriate, but complementary, information to all relevant stakeholders.

In this way the content we develop can support shared decision-making and enhanced HCP-patient relationships.

So to summarize, these are our top tips for writing for a nonexpert audience: Before you start writing anything, know who your audience is and their level of understanding, keep it simple, use images, and, if all else fails, find an analogy to real life that is easily understood.

If you'd like help with communicating complex science to a wide range of audiences, contact us at newbusiness@fishawack.com.

Reference

1. Fleming N, et al. *Educ Dev.* 2006;7.4:4-7.

FISHAWACK HEALTH

Established in 2001, Fishawack Health (FH) is a purposefully built commercialization partner for the biopharmaceutical, medical technology, and wellness industries. Our 1,500+ experts combine their knowledge and expertise across our core disciplines—Medical; Marketing; Policy; Value, Evidence, and Access; and Consulting—to create the connections that make better health happen.

We partner with our clients to navigate the complex and rapidly changing healthcare ecosystem. Together, we realize the potential of strategies and solutions to accelerate innovation that improves lives.

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