The Call to Cure
Biotech’s Mission: Halt Disease

Geoff MacKay, CEO of AVROBIO, which is developing potential single-dose lentiviral-based gene therapies for rare diseases.
When AskBio’s scientific founder, Dr. Jude Samulski, discovered how the Adeno-Associated Virus (AAV) could be safely used to deliver corrected genes to cells with genetic defects, it propelled one of the most exciting and inspiring fields in medical research today. Now the foundation for an entire industry, it also inspired the development of a world-leading gene therapy platform that includes the Pro10™ cell line, an extensive capsid library, and new methods for lowering the cost of delivery.

We know gene therapy is a highly complex business. But seeing the impact that gene therapy can have on patients suffering from incurable diseases fuels a never-ending passion to continually advance AAV gene therapy technology. We embrace the work that companies like Pfizer/Bamboo, Novartis/AveXis, and Roche/Spark are doing to advance gene therapy development as we all share a common goal: erase genetic disease.

We are a company on the forefront of the industry, guided by the vision and unparalleled expertise of Dr. Samulski, the founder of AAV gene therapy. We invite all researchers, advocacy groups, patients and their families to join us on this mission to advance promising gene therapies and to change the face of health care.

AskBio will work tirelessly to continually extend our own AAV technology platform. And we will collaborate with all in the field to find ways to safely and cost effectively get important gene therapies into the hands of those who need them most.

Sheila Mikhail
Chief Executive Officer/Co-founder

Asklepios BioPharmaceutical, Inc. (AskBio) is a privately held, clinical stage gene therapy platform company dedicated to improving the lives of children and adults with rare genetic disorders. AskBio’s gene therapy platform includes an industry leading proprietary cell line manufacturing process known as Pro10™ and an extensive AAV capsid library. Visit askbio.com to learn more.
A Look Back & Forward on Innovation

FORMER FDA COMMISSIONER SCOTT GOTTLIEB, MD, was on-hand at our parent company’s headquarters to help promote his keynote participation in MJH Associates’ inaugural oncology event, the OncLive® Global Expo, to be held in Orlando in October. While there, Gottlieb met with editors from MJH Associates’ publications, including Inside Digital Health, The American Journal of Managed Care, Medical Economics, Pharmacy Times, and Pharmaceutical Executive. Some of our questions overlapped, especially in the areas of biosimilars and generics, and real-world evidence. The following is a brief summary of Dr. Gottlieb’s views and insights on other topics.

Gene Therapies. The first topic is especially relevant with our August issue focus of cell and gene therapies (see coverage beginning on page 12). Dr. Gottlieb was asked about the effect of CAR-T medicines on the healthcare system. He noted that the current delivery system for CAR-T, which is heavily dependent on the institution that hospitalizes the patient and delivers the reengineered cells back into patients, is in dire straits and there needs thorough and well-thought decisions to be made. “Currently, those institutions are being underpaid on these therapies, and that is not sustainable,” he said. Gottlieb pointed to the fact that Medicare pricing doesn’t have a “checkbox” for CAR-T, only for injections, which is not what this is. This billing issue will negatively impact the downstream success of CAR-T therapies.

In addition, Gottlieb touched on the overall pricing issues with gene therapies as a potential socioeconomic problem for the US. He explained that private market insurance is designed to financially absorb high-cost therapies and procedures vis-à-vis large covered populations. On the other hand, Gottlieb said, if state Medicaid programs had to pay for one gene therapy administration of $1 million, as well as a heart transplant procedure in one year, that would be very tough on that state’s funds. Basically, private insurers can provide more access to newer therapies, but Medicaid, not so much. He said, “This could lead to a socioeconomic fracture. And that needs to be solved.”

A Short History on Innovation. Gottlieb elaborated on the foundation that paved the way for the current plethora of therapies in testing and available for rare and orphan diseases. And not just the Orphan Drug Act, which Gottlieb said allowed for additional incentives to develop those kinds of therapies. But he also drew from the knowledge accumulated during his tenure as a senior adviser to the administrator of the Centers for Medicare and Medicaid Services (CMS) in the early 2000s, when Part D benefit designs were being made. “Incentives were made in the way we designed the reimbursement model by creating a specialty tier in Medicare, which was done for a variety of reasons. But that specialty tier, where reimbursement was largely assured so companies could develop drugs targeted to rare, unmet medical needs that were going to be priced at a premium based on the value that they would deliver,” Gottlieb said. “By protecting that reimbursement, we drove incentives in the marketplace for product developers to design treatments targeted to those indications.”

Gottlieb said these constructs were created at a time when the major complaint was that drug companies were just developing me-too products and new iterations of already marketed drugs, but not a lot of innovation. “We made deliberate decisions to preserve reimbursement if you developed something truly novel for an unmet medical need,” he noted. “What happened was investors were rational and investment capital went very quickly into those spaces. And now we are seeing the fruits of that through a lot of really promising innovation that’s delivering real practical benefits for patients. Now the flip side is that the products are very costly.”

Pricing. Besides the socioeconomic fracture, the current pricing problem also casts a negative public perception on pharma. To Gottlieb, the crux of the issue is high out-of-pocket expense for the patient’s prescription benefit. He said, “Prices have continued to go up and patients are facing high out-of-pocket costs that are irrational, because these costs—at least in Medicare Part D—are tied to list price, which is largely not a real price and it’s not what the payers are paying. But the patients are paying out-of-pocket costs based on the list price and their liability is uncapped. There is no limit on what their costs can be in Medicare Part D, and that’s causing a lot of hardship. We need to make sure patients aren’t priced out of the products they need.”

You can look for more interviews with Dr. Gottlieb on our video channel in the near future. In the meantime, learn more about the OncLive® Global Expo, a three-day educational, innovative meeting that brings together an inclusive group of oncology professionals to collaborate on emerging trends and technologies in cancer care and research. See more here: https://www.onclive.com/expo/
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Cover Photo/Porter Gifford
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FDA Faces ‘Explosion’ in Growth of Gene Therapies

Agency focused on advancing testing and production methods, seeking input from other regions on common approaches

The recent approval of Novartis’s $2 million gene therapy Zolgensma, a one-shot cure that can prevent the death of infants from spinal muscular atrophy, reflects the emergence of a new world of effective treatments for critical conditions. Innovative therapies can replace, repair or inactivate a gene, either through direct administration of the product to the patient or by taking cells from the body, modifying them in culture, and returning them to the patient. Amidst some notable successes are many failed efforts, as scientists and innovators strive to advance novel technologies, while regulators adjust policies and practices to support these efforts. FDA officials are ramping up guidance development, streamlining oversight, and taking steps to advance manufacturing and clinical development of these cutting-edge treatments.

FDA’s Center for Biologics Evaluation and Research (CBER) has seen an “explosion” of growth in the cellular and gene therapy area, observed CBER deputy director Celia Witten at the Cell & Gene Therapy Products Symposium sponsored in June by CASSS (see https://bit.ly/30xHRx7). CBER’s Office of Tissues and Advanced Therapies (OTAT) received more than 400 investigational new drug applications (INDs) in 2018, many qualifying for breakthrough therapy status and the Regenerative Medicine Advanced Therapies (RMATs) designation for products providing evidence of treating, modifying, or curing a serious or life-threatening condition. For such therapies, FDA offers sponsors extra assistance in developing innovative testing and production methods, expedited review, and flexibility in meeting regulatory requirements.

FDA also is collaborating with regulators in other regions to devise common approaches and policies for developing and testing these innovative therapies around the world. The Cell Therapy Working Group of the International Pharmaceutical Regulators Programme (IPRP) has finalized a reflection paper on the nature and duration of clinical trials using cell therapies (see http://www.iprp.global/home). And a paper from the IPRP Gene Therapy Working Group discusses expectations for biodistribution assessments for gene therapy products. This analysis may provide a basis for the International Council for Harmonization (ICH) to develop a guideline on biodistribution studies of gene therapy vectors (see https://bit.ly/2xUr5gd).

To further advance standards for product development and assessment in this area, FDA is working with the National Institute for Standards & Technology (NIST) and has a contract with the Nexight Group to coordinate these efforts (see https://bit.ly/2Y3AHDk).

Early assistance

To discuss proposals for untraditional development programs for cellular and gene therapies, CBER officials encourage sponsors to utilize its INTERACT program (INITAL Targeted Engagement for Regulatory Advice on CBER products). This replaces pre-pre-IND interactions and offers early-stage informal consultation on product development, particularly for innovative devices, cutting-edge testing methodologies, and complex or novel manufacturing technologies. Such early discussion provides nonbinding advice and doesn’t replace the recommended pre-IND meeting for products further along the development pathway.

Manufacturers designing innovative production or development programs can gain additional advice and input from the CBER Advanced Technologies Team (CATT), recently formed to discuss and respond to queries from industry on advanced manufacturing and testing technologies (see https://bit.ly/2Y6KW-GW). Initial inquiries to CATT should briefly describe the technology, why it is novel and unique, its potential impact on product quality, and a summary of the manufacturing or development plan.

Expedited development and approval of cellular and gene therapies creates unique regulatory challenges and requires a “new paradigm,” said Steven Oh, deputy director of OTAT’s Division of Cellular and Gene Therapies, at the CASSS symposium. While these products still must meet quality standards, CBER
officials emphasize that they will exercise some flexibility on the type and extent of manufacturing information expected in a submission. Such leeway will depend on product characteristics, the seriousness of the condition being treated, the type of manufacturing process, the robustness of a quality system, and the strength of the risk-based quality assessment. And regulatory flexibility usually will be linked to agreement on postmarketing commitments and requirements.

These strategies for establishing appropriate and efficient pathways for bringing innovative drugs to patients so far have involved treatments for single-gene disorders that generally affect very small patient populations. The challenges will increase exponentially as developers seek products with multigenic targets that stand to involve millions of patients. Programs will need new approaches for clinical trials and for production scale-up, and prices will be scrutinized even more to ensure patient access to therapy.

While these products still must meet quality standards, CBER officials emphasize that they will exercise some flexibility on the type and extent of manufacturing information expected in a submission.

Will Congress enact curbs on drug pricing?

There is great enthusiasm on Capitol Hill and in the Trump administration for taking action to reduce outlays for prescription drugs, but the path forward is not clear. Multiple House and Senate Committees are weighing in on the issue with a range of measures that differ in style and substance. In the Senate, the Finance Committee and the Health, Education, Labor and Pensions (HELP) Committee look to build bipartisan support for broad legislative packages, while the House Ways & Means Committee and the Energy & Commerce panel are crafting reform measures with multiple provisions—some conflicting and overlapping.

Amidst all the proposals to expand patient access to affordable treatments are initiatives to maintain rewards for innovation, such as patent exclusivities and market-based pricing. A prominent administration proposal for bringing down outlays is to peg US prices to those of other industrial nations, such as the UK, Canada, and Japan. However, the White House has pulled back from that approach, which is strongly opposed by pharma, while also dropping plans to limit or alter rebates paid by manufacturers to pharmacy benefit managers.

Negotiating prices

A main Democratic proposal aims to authorize the government to negotiate prices on drugs covered by Medicare drug plans, and in some cases by private insurance. While Democratic leaders initially sought to limit negotiations to a short list of high-priced drugs, pressure from progressive party members to expand the scope of such negotiations prompted House Speaker Nancy Pelosi to agree to broader price negotiating authority. Some Senate Democrats also back government price negotiations, but diminishing support from the Trump administration has tamped down Republican interest.

Moves to permit drug importing have advanced at the state level, while also gaining broad support in Washington. Florida recently approved a program to bring in drugs from Canada for Medicaid and other state agencies and to authorize more general importing of drugs from outside the US. But, as with a similar law in Vermont, the Department of Health and Human Services (HHS) has to approve these programs, which has not occurred in the past with similar plans. This time, though, HHS secretary Alex Azar has backed import flexibility, and some expansion in drug importing is likely to be included in a drug pricing package.

Patent policy reform also may play a role in the drug pricing debate, as House and Senate Judiciary Committees look to devise patent reform measures likely to spur competition in the prescription drug market. Proposals call for curbs on “gaming” the patent system by drug companies looking to extend monopolies, and for the Federal Trade Commission to crack down on manufacturers that file multiple patents on a drug to delay competition.

Medicare spending caps

Then there are numerous proposals to reduce drug outlays by Medicare and Medicaid. Pharma companies and patient groups look to cap or limit out-of-pocket (OOP) spending by Medicare Part D beneficiaries and to spread OOP costs over the entire year. Industry also wants to provide copay assistance to Medicare beneficiaries, as occurs in the commercial market, and there’s interest in eliminating the current catastrophic phase of the Medicare drug benefit, retaining initial coverage and a catastrophic phase. Such approaches soften the impact of high drug prices on individuals, but without greatly undermining pharma pricing practices.
A round the industrialized world, the consensus is stronger every day that the future of healthcare is digital, and that effective data-sharing is pivotal to making it a reality. And in Europe, a genuinely innovative attempt to share genomic data across national borders is getting underway. But in the patchwork-quilt diversity of the old continent, every day is revealing just how much has to be resolved to make the concept work in practice.

A declaration of cooperation on cross-border access to genomic information, signed by nearly all the 28 European Union countries since 2018, is making some headway against multiple technical, administrative, and political barriers in pursuit of its goal of making one million genomes accessible in the EU by 2022. But it is still running into new impediments with each step that it takes, raising questions about the feasibility of its further targets for 2027 of seeing 100 million citizens with personalized health systems, and making data from 10 million citizens available for new discoveries.

The ambitions are noble, in terms of “supporting data infrastructure to advance research, disease prevention, and personalized health and care in key areas, including rare, infectious, and complex diseases.” The declaration speaks glowingly of how “the digital transformation of health and care and, in particular, the use of genomic medicine, will help health systems,” and ensure that the EU “remains competitive in the global race to advance personalized medicine.”

When the declaration was signed, its plan of opening up national and regional banks of genetic and other health data was hailed by EU officials as a game-changer for European research and clinical practice. “This initiative can boost the development of public health for the benefit of EU citizens,” said EU Commissioner for Health Vytenis Andriukaitis, vowing support for defining a governance model for cooperation, developing technical specifications, and promoting interoperability of registries and databases.

The rationale is not in dispute. There is broad agreement that digital applications and data have the potential to improve health and ease some of the well-known challenges faced by health systems: the budgetary pressure of ageing populations and chronic diseases, unequal quality and access to healthcare services, and shortages of health professionals.

The practical factors
But once the glow of the signing ceremony had faded, the real work began of identifying and solving the problems. Conspicuous among the challenges in whole gene sequencing were the different sequencing techniques commonly used, the lack of standardized measurements for data quality, quality of samples, or for storage, and the absence of clear methodologies for measuring the benefits.

The decision was made to tackle the deficiencies in both research and clinical practice, with a focus on capacity building, training, harmonization, policies for sequencing, intellectual property rights, interoperability, data governance, data quality control, patient engagement, ethics, and regulations.

Some best practices for genome sequencing practices were highlighted in national or regional initiatives such as the UK 100,000 Genomes Project, RD-Connect, and SciLifeLab sequencing facilities, and it was agreed that genomics data should be findable, accessible, interoperable, and reusable using a federated database model, in which every country keeps their data but provides controlled access.

But questions remain over the type of data to be accessed—minimum genomic data sets, variants, or full genome, and what type of clinical or wider healthcare data. And procedural questions came to the fore—not least, for the one million genomes to be used for research purposes, it will be critical to obtain consent, and therefore to move toward some harmonization of consent forms.

Across a series of meetings, officials from the participating countries have taken stock of their growing awareness of the opportunities, reviewed the divergences in their current practices, and chiselled away at the issues they confronted that impeded closer cooperation. They have been gratified to find some degree of commonality in sequencing techniques, data/sample quality checks, and data representation standards used, giving rise to optimism that interoperability should...
in principle be easier. Most countries, it has emerged, have standards for interpretation of sequences, and most link genomic data to other health data, such as demographic information, patient registries, clinical reports, or biobanks. Many countries also have genomic training of healthcare professionals in place, often with functioning accreditation systems.

**Drilling deeper**

To advance the work, the countries have set up a series of working groups exploring specific areas ranging from broad governance to ethics, and from privacy to the development of infrastructure.

They have also been holding discussions with an alphabet soup of organizations with a stake in this wide field, such as the European biobank and biomolecular organization BBMRI-ERIC, the European Bioinformatics Institute (EMBL-EBI), GA4GH Mission (the global alliance for genomics and health), or ELIXIR, the connection among national bioinformatics centers, which is currently linked to projects being conducted in the Czech Republic, Denmark, France, the Netherlands, England, Finland, Estonia, Scotland, Sweden, Slovenia, and Hungary.

The discussions are now, in the second half of 2019, moving on to defining genomics data and clinical information standards geared toward specific disease communities, designing common application programming interfaces to enable remote data discovery and access, and federated cloud computing environments with secure access to raw data and interoperable results.

And now the focus is shifting to ways of ensuring the maximum impact of data, and timely access to the data for the three principal groups envisioned: healthcare bodies, universities, and commercial entities. Effective data management and security are under study, and agreement is being pursued on standards that are persistent, stable, and fit for purpose. The working groups are aiming to demonstrate the potential benefits, iron out wrinkles in the chosen approaches, and develop incentives for the involvement of researchers and industry, as well as of citizens and healthcare providers. And over the rest of 2019 and 2020, a series of workshops and conferences are now being planned.

Questions remain over the type of data to be accessed—minimum genomic data sets, variants, or full genome, and what type of clinical or wider healthcare data at last drafting deliverables for the short, mid and long term, as the starting point for a road map for the entire project. They are also identifying experts, and aiming to map available genomic data sets on a national level, so as to understand how far there is to go toward the goal of more than one million human genomes.

**Funding and beyond**

The inevitable issue of funding also preoccupies the participants. Possible financial support is being explored via the EU’s research fund, Horizon 2020, and its successor program now being finalized, as well as through the EU’s regional development funds. Some of the European Commission’s own digital health strategies also offer hope of gaining backing. Member states will be approached for assistance. Guidelines will be drafted and published for Good Genomics Practice, covering sample management, data generation, and data analysis, and plans are afoot for a meta data structure that details the processing, sequencing, and analysis work carried out on samples.

But Europe is not alone in pursuing this course. There are plenty of other efforts underway around the world, and the window of opportunity for Europe is not going to be open indefinitely. One million genomes is a fine slogan and a worthy target—but it is only a start. 

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*The practical questions include whether extra efforts should be made to generate all the one million genomes through a self-standing new project, or whether it is enough to build on ongoing initiatives—for instance BBMRI already has 100 million samples. Decisions will also have to be made over what amount of clinical and phenotypic data would have to be linked to genomics data as a minimum for the data to count toward the ultimate goal.*
The Call to Cure

A pioneer in building businesses and innovation in gene-based medicine, including the first FDA-approved allogeneic cell therapy, Geoff MacKay, CEO of lentiviral-focused developer AVROBIO, discusses his most important quest to date—bringing gene therapy into the mainstream

By Julian Upton

Founded in 2015, AVROBIO (Cambridge, MA) is a clinical stage company developing potentially curative gene therapies with the goal to free patients from a lifetime of disease.

AVROBIO co-founder and CEO, Geoff MacKay, spent 11 years at Novartis in senior leadership positions within the Global Transplantation and Immunology franchise before becoming CEO of Organogenesis in December 2003. Organogenesis treated one million patients with living cell therapies and received the first FDA Center for Biologics Evaluation and Research (CBER) allogeneic cell therapy approval. MacKay went on to be the founding CEO of eGenesis, applying CRISPR Cas-9 gene editing to xenotransplantation. He also served as chairman of the board of MassBio, chairman of the Alliance of Regenerative Medicine, and Advisory Council to the Health Policy Commission for Massachusetts. Pharm Exec talked with MacKay about the evolution of his career and his vision to bring gene therapy into the mainstream.

PE: Could you share a little bit of background about your career and what led you to co-found AVROBIO?

GEOFF MACKAY: I spent more than a decade at Novartis in the 1990s in transplantation and immunology. At the time, Novartis was very enamored with the new emerging cell and gene space and had invested early, and I worked in that space. Eventually, Novartis realized that it was maybe a bit premature for them to commit. However, this experience gave me a glimpse of where the science was heading and I decided to leave big pharma and lead one of the early cell therapy companies, Organogenesis. Over a 10-plus year span as CEO of Organogenesis, I helped to build it into the leading cell therapy company in the world and got the first CBER approval for an allogeneic cell therapy. There are about 1.4 million patients in the world who have received cell therapy of any kind, and one million of
them received an Organogenesis cell therapy. It is still, in 2019, the only business that mass produces living cell therapies at such an industrial scale.

Eventually, Organogenesis grew into a marketing, sales, and manufacturing-focused company of 600 people and it was time for me to step back into more early-stage innovation. Just as cell therapy was the place to be 10 years prior, the gene therapy revolution was finally hitting; consequently, I was involved in starting up two gene-based companies. One, eGenesis, focuses on gene editing for xenotransplantation, is still a highly innovative Cambridge startup. But my main focus was AVROBIO, which I started in 2015 with two other founders.

PE: Was it difficult to make the transition from a big pharma to a biotech company after a decade?

MACKAY: In the Cambridge biotech ecosystem, many people go from pharma to small biotech. I think the critical success factor is to take all the immense learnings from pharma but simplify them and make them less bureaucratic. I can’t imagine a better school than spending a decade in Novartis. The challenge is, how do you simplify all of that “best practice” training into something that is faster-paced and more streamlined? I think if you have that as a mindset, you can really succeed in making the transition from big pharma to biotech.

PE: How have you seen the gene therapy field change and grow? What point are we at now?

MACKAY: Part of the catalyst for forming AVRO in 2015 was the immense excitement around the clinical validation that was hitting the field at that time. This includes CAR-T, which can be considered ex vivo gene therapy targeting oncology indications. Going back five years, the validation for gene therapy for rare disease applications, from companies like GSK and Bluebird Bio, was really exciting and the future of gene therapy was coming into clear focus.

Now moving ahead to 2019, there is a critical mass of energy and early-stage trials that are really taking hold and advancing the field. Medical practice is about to be dramatically transformed based on the hundreds of new gene therapies that are currently in clinical trials. I don’t really know what the precise definition of a tipping point is, but it seems we’re well beyond it right now.

PE: Can you explain what a lentiviral approach to gene therapy is, and what its advantages are?

MACKAY: A key point is that it’s individual therapy. We collect the patient’s blood and select out their own CD34 hematopoietic stem cells. We then give those stem cells an upgrade by transducing them with our lentiviral vector, which is an inactivated and highly modified virus that delivers the normal, healthy gene into the cells. Next, we cryopreserve these modified cells, so they have a long shelf life to conveniently ship back to the clinic. Those modified cells are thawed and then rein infused back into the patient via a straightforward, one-time administration of the gene therapy. The mechanism is such that these modified cells migrate to the bone marrow, where they will engraft. The ultimate impact on disease comes not from those engrafted cells, but from their daughter cells. The progeny of these gene modified CD34 hematopoietic stem cells turn into the blood lineage, which both produce and distribute the active therapeutic protein throughout the body.

To me, the real value of lentiviral gene therapy is apparent when properly matched to a disease with a particular set of needs. If what is required is a full systemic distribution of an active protein for the life of a patient, that really is the sweet spot for lentiviral vectors. In fact, over 200 patients have been treated with lentiviral-based gene therapies across a growing list of monogenic rare diseases, with long-term follow-up going out as much as 10 years or more.

PE: Beyond the clear advantages of one-time versus chronic treatment, what are the benefits to patients?

MACKAY: In the diseases that we target, lysosomal storage disorders, the one-time gene therapy is potentially a tremendous advantage because today’s standard of care is biweekly infusions for the life of the patient. That means a major disruption of the patient’s life. Freeing up the patients from

FAST FOCUS

» Geoff MacKay helped launch two gene-based startups in 2015, eGenesis and AVROBIO, which he established with two other founders. His main focus was AVROBIO, where he remains CEO and president today.

» From March 2012 until April 2014, MacKay was chairman of the board of MassBio, an association of 600 biotech companies, universities, academic institutions, and other organizations. He was also board chairman for the Alliance for Regenerative Medicine from January 2013 until December 2014.

» AVROBIO is developing an investigational gene therapy, AVR-RD-01, in Fabry disease, and has additional gene therapy programs in other lysosomal storage disorders, including Gaucher disease, cystinosis, and Pompe disease.
these biweekly infusions has a tremendous positive impact on quality of life.

One of the biggest potential advantages of gene therapy is that it addresses the main unmet need that today’s standard-of-care enzyme replacement therapy (ERT) slows down disease progression but does not halt it. The major goal of our gene therapy approach is to halt disease progression. The scientific rationale for why we believe this is possible relates to the pharmacokinetics of enzyme delivery. ERT requires an infusion every two weeks and yet is gone from the blood within 12 hours. This implies that the majority of time in between infusions, the patient may have insufficient enzyme in distribution. The whole premise of gene therapy centers on delivering 24/7 protection of enzyme, as opposed to this stop-start method with today’s ERT.

The whole premise centers on delivering 24/7 protection of enzyme, as opposed to this stop-start method with today’s ERT.

which a genetic defect causes a patient not to produce normal levels of an important functional enzyme. Our clinical studies are still ongoing, so the results are not yet completed; to date, we’ve seen what we believe to be a consistent readout across our first eight patients showing improvement in multiple surrogate biomarkers and functional endpoints. We are fortunate that Fabry is a well-studied disease with established primary and secondary endpoints. Although much further study is required, we are more excited with every step forward in building a growing body of evidence of the therapeutic potential of our gene therapy for patients with Fabry disease.

**PE:** Obviously, you will continue to be dependent on clinical results, like all companies, but, if there are “bumps in the road” along the way, how do you deal with that from a leadership perspective?

**MACKAY:** Bumps in the road are par for the course in biotechnology. Science is complicated and rarely progresses in a linear fashion. We have focused on rapidly building our company and creating a pipeline of investigational gene therapy candidates. Pushing forward, we have a constant focus on talent acquisition as well as properly financing our company. Since we formed AVRO, we have secured a strong financial position, partially enabled by a successful IPO in 2018.

I couldn’t be more proud of the leadership team that we’ve built. Our leaders include the original founders of AVRO and executives that joined us in the start-up phase, who were instrumental in getting us to where we are. More recently, we strengthened our executive team, bringing in top-tier industry veterans who we really think are the best in the world at what they do.

**PE:** There’s an ongoing discussion around the pricing of these kinds of treatments. What is your feeling on how payers are evolving in terms of accepting one-time treatments and their relatively high prices?

**MACKAY:** One-time, single-dose gene therapies have the potential to save the healthcare system a fortune by offsetting enormous lifelong costs of care. How to implement a value-based payment system is an evolving and complicated discussion. All of us, in society, are going to have to make an assessment as to what we’re willing to do for one-time curative gene therapies. Regarding lysosomal storage disorders, the decision may be quite a bit easier because today’s standard of care is extremely expensive. The lifetime cost for a patient with Fabry disease, for example, is $14 million.

Gene therapy not only has the potential to free up the patients from ongoing infusions and hopefully provide a better clinical outcome, but can also save the healthcare system many millions of dollars for every patient dosed. The first wave of gene therapy companies is proposing various innovative risk-sharing models with payers. The diseases that AVRO are targeting have very concrete, easy-to-calculate health economic benefits with a payback within a few years, almost independent of how they are priced.

**PE:** How much is your attention focused on the manufacturing and commercialization challenges for gene therapies to achieve future success?
MACKAY: This is our top priority. From the very first day of starting AVRO, we wanted to be the company that solves many of the bottlenecks around large-scale commercialization of gene therapies. We have been keenly focused on answering the questions: “how do you scale up?”—“how do you industrialize?”—“how do you deliver convenient cost-effective gene therapies that the healthcare system can really adopt?”—“how do you reach patients around the world in need of your medicine?”

The platform we have created, called plato™, is designed for commercial-stage production of our gene therapies. We view plato as leading the field in transitioning to large-scale bioreactors; fully automated manufacturing, and advanced vectorology refinements. Since 2015, we’ve been focused on preparing plato for the clinic. This required a real mobilization of our team and I am happy to say that, in the first half of 2019, we received multiple regulatory clearances around the world that enable us to incorporate plato into both our Fabry and Gaucher clinical development programs.

PE: We hear about “industrializing” gene therapy manufacturing and “commercial scale” manufacturing. What does that entail exactly? What are the foundational issues that need to be addressed?

MACKAY: Peter Marks, director of the Center for Biologics Evaluation and Research (CBER), has made the point at many recent meetings that he is completely confident that gene therapy will succeed clinically. What keeps him up at night, and what he is very outspoken about, is the need to upgrade and to improve quality and consistency related to manufacturing. Of course, that’s very well aligned with the focus that we’ve had at AVROBIO since we began the company.

Vector scale-up, cell bioprocessing, and related analytical criteria are all challenging topics that require immense focus. Locking in major CMC elements early and developing internal capabilities to implement smaller process changes is key. In fact, companies that don’t prioritize this from day one may not succeed. It is worth noting that the CBER division of FDA has really risen to the occasion and provides tremendous leadership to the emerging companies in our field. What industry needs from regulators is clarity and consistency, and FDA has been a beacon of light as standards are being established.

PE: Do you envision reaching the required manufacturing level by the time you’re approaching commercialization?

MACKAY: Yes. Having dosed eight Fabry patients to date and with our other clinical programs advancing as planned, our thoughts and energy are now geared toward launch readiness. We are already establishing manufacturing solutions in North America, Europe, and Asia in order to meet global demand. The scale-up requirements are significant, and the automation and vector innovations deployed within our plato platform give us confidence in our belief that we will be able to treat thousands of patients at the point of commercialization.

PE: What is your long-term vision for bringing lentiviral gene therapies to a broad range of patients?

MACKAY: We’re highly focused on the first wave of gene therapy candidates in our pipeline because we believe, if the profile holds, they will be truly transformative to patients suffering from lysosomal storage disorders. There are about 30,000 patients across the four rare diseases in our pipeline, and today’s standard of care generates about $4 billion of annual revenue. Beyond this first wave, we believe that the optimization around our plato platform lends itself well to expanding into more indications.

We wanted to be the company that solves many of the bottlenecks around large-scale commercialization
Mapping Out the Future of Cell and Gene Therapy

Despite the emergence of approved treatments in the field, the cell and gene therapy space remains fertile territory for growth, exploration, and discovery. How applying a data-driven model may be the best way to approach this complex ecosystem and assess the innovations of tomorrow

By Lital Aravot

Each passing year, the success of cell and gene therapy becomes clearer, more widely covered in the media, and is increasingly the focus of a rapidly growing society of researchers. Making sense of this extensive ecosystem is no small feat, but by using a data-driven approach, the life sciences industry can get closer to determining what the future holds for cell and gene therapy.

The idea of inserting a gene into a patient’s cells to treat or prevent disease has emerged as one of the most exciting areas of biotechnology. Its buzz can be attributed to the hope these therapies hold for patients with rare and often deadly inherited diseases; the scientific promise and intrigue of gene editing; and the business opportunity that these revolutionary therapies with lucrative price tags hold.

But what do we really know about cell and gene therapy? What proverbial gold will be found at the end of this rainbow?

What we know

The plethora of medical conditions that cell and gene therapies are being evaluated for is ever expanding, however, oncological disorders remain the most commonly explored. Last year’s Nobel Prize in Medicine awarded to a pair of cancer immunotherapy researchers marked an important milestone in the development of such therapeutics. The works of Dr. James P. Allison and Dr. Tasuku Honjo uncovered the role of checkpoint...
inhibitors in the body’s immune response to cancer. Checkpoint inhibitors work by re-engaging the checkpoints on T-cells, which are the cells within the immune system that fight cancer. When cancer cells shut down these checkpoints on T-cells, they are unable to fight off the cancer cells.

Through their work, Allison and Honjo deciphered exactly how cells were interacting so they could fine-tune methods to recruit and control the immune system in fighting cancer. Their findings scientifically bolstered the foundation of a new principle for cancer treatments: immunotherapy.

The researchers’ discoveries ultimately led to a new class of drugs that has already resulted in lasting remission in several patients. The first drugs to make it to market based on the Nobel Prize winning research include Yervoy, Opdivo, and Keytruda. Allison discovered the checkpoint inhibitor CTLA-4 (the target of Yervoy) and Honjo discovered the checkpoint inhibitor PD-1 (the target of Opdivo and Keytruda).

These breakthroughs helped expand the field of T-cell therapy, which by 2017, notably delivered the first approvals of CAR T-cell medicines Kymriah and Yescarta, which treat blood cancers.

Where we are today
Cell and gene therapy provides an almost unlimited source of innovation. These therapies offer personalization and show potential relevance across multiple conditions, as evidenced by recent product approvals for spinal muscular atrophy (Zolgensma), inherited retinal dystrophy (Luxturna), and beta thalassemia (Zynteglo), a rare genetic blood disorder. Across most of the diseases being tested, competition is low despite an increasing amount of therapeutic potential and advanced maturity.

Making sense of this extensive ecosystem can be a difficult task; however, by using a data-driven approach of exploring the cell and gene therapy space, one can potentially map out the opportunity areas to determine where the future of cell and gene therapy is heading.

At Signals Analytics, for example, to prioritize opportunities, we’ve broken the ecosystem down using three key parameters:

» Therapeutic potential. The therapeutic potential of the cell and gene therapies being evaluated for treating the medical condition: this indicates how much preclinical and clinical scientific evidence exists and, more importantly, its growth rate and percentage of “positive” signals, such as successful clinical trials.

» Maturity. The maturity of the specific cell and gene therapies was evaluated for treating the medical condition: this provides insight into how close to market these solutions are. A launched drug is indicative of a mature solution, while a research paper indicates a less mature solution.

» Competitive landscape. How competitive the space is for treating this medical condition with cell and gene therapies (see Figure 1 on page 18).

We’ve also mapped out four cohorts in which innovation is taking place:

» Saturation. These are diseases and supporting therapies that have proven scientific value, are at later development stages, and have already garnered interest from entities in the space.

» Establishing. The establishing opportunities are those that have already developed baseline confidence through scientific evidence and medium to high solution maturity. In this cohort, the level of competition varies, and this can be attributed to their being niche markets or for which scientific breakthroughs are still on the brink of discovery.

» Promising. The promising opportunities that are largely untapped in terms of competition; however, work remains to be done to establish their therapeutic potential and develop these solutions into later-stage clinical entities.

» Nascent. In the last cohort, for the brave at heart, are the very early projects, those just beginning to exhibit scientific potential. Presented ahead are learnings from this breakdown, and what will likely be some of the most innovative efforts that will reach the market in the next three to 10 years.

Saturation
In response to the opioid public health crisis, there has been a natural shift toward newer, natural, and non-addictive alternatives for treating pain. Simultaneously, there is growing research into cell and gene therapy treatment options for patients with neuropathic pain who respond poorly to opioid and over-the-counter analgesics.

Of these recent innovations is a cell therapy targeted specifically for treating the pain experienced in musculoskeletal conditions, mostly osteoarthritis, by using mesenchymal stem cells (MSCs) from adipose tissue. These cells promote the body’s natural healing
Gene Therapy

by reducing inflammation, promoting tissue repair, and reducing scarring, and can relieve neuropathic pain when injected directly into an affected joint or tendon.

Australian regenerative medicine company Regeneus is developing a portfolio of innovative cell-based therapies with an initial focus on osteoarthritis. Progenza, its allogeneic off-the-shelf adipose-derived MSCs, are currently being evaluated for reducing knee pain and improving cartilage volume in osteoarthritic patients.

Progenza differentiates itself from other MSC therapies since it includes cell secretions, which improve the functionality of the MSCs post-thawing. In addition, the company claims that the use of MSCs from adipose tissue assists in scaling the manufacturing of these cells.

While more research is needed to establish that such an approach would also be applicable for solving the opioid crisis, early positive signals are emerging for the use of stem cells for opioid therapy, according to a 2018 study by the Cleveland Clinic. In its study, MSCs transplantation showed long-lasting and consistent opioid tolerance (OT) and opioid-induced hyperalgesia (OIH) in rat and mouse models. These results indicate that stem cell therapy may be able to prevent and reverse OT and OIH, which are key issues faced by patients prescribed to opioid therapy.

Huntington’s disease, a relatively rare genetic condition, remains incurable, and this is despite the medical advances that have taken place in the neurological space. The disease is typically inherited and caused by an autosomal dominant mutation in either of an individual’s two copies of a gene called Huntingtin (HTT). When mutated, the result is an abnormal protein which gradually damages cells in the brain.

Some of the key research efforts around this disease are targeted at establishing safe and efficient methods for lowering total or mutant HTT expression in the brain. One research group from Jinan University has been evaluating how CRISPR/Cas9-mediated inactivation can effectively deplete mutant protein aggregates and attenuate early neuropathology. Simultaneously, uniQure has been testing ways to suppress mutant protein expression by using engineered microRNAs targeting HTT transcripts that are delivered by the adeno-associated viral vector AAV5.

Research into Huntington’s disease is still developing; however, its advancement is sure to be supported by the growing body of research and grants focusing on cell and gene therapies for treating this rare disease.

Promising

This opportunity cohort is about five to six years away from potentially reaching the market and comprises innovations at preclinical or very early Phase 1 clinical trials. The top medical conditions being evaluated include oncological disorders such as endometrial cancer, chronic myeloid leukemia (CML), and soft tissue carcinoma, and immunological and infectious diseases such as...
Sjogren’s syndrome, tuberculosis, hepatitis B virus, and urinary tract infections, among others.

Of particular interest is the application of cell and gene therapies for treating cystic fibrosis (CF) patients who experience persistent lung infections, which limit their ability to breathe over time. In these patients, a defective gene causes a thick and sticky buildup of mucus in the lungs, pancreas, and other organs.

Gene therapy is an ideal treatment method for CF, and this major shift in medicine allows for the correction of the underlying genetic cause of a disease such as CF as opposed to merely treating its symptoms. The process typically involves packaging healthy genes into altered viruses, which then act as a vector to deliver a dose either into the bloodstream or the disease affected area. However, in the lungs of these patients, bacteria collect in the airways and biofilms form, which present an additional barrier to penetrate the afflicted area with immune cells, antibiotics, or gene transfer technologies.

One of the most innovative and attractive areas we expect to see reaching the market for CF patients are various uses of nanoparticles for pulmonary delivery of tobramycin. Both these findings could be an encouraging alternative to the currently available CF therapy options.

**Nascent**

This group of opportunities is the furthest away from hitting the market. There are still likely eight to 10 years before these innovations come to fruition; however, it’s also a fertile ground to test new concepts. The key medical conditions being evaluated in this cohort are ulcerative colitis (UC) as well as a variety of pulmonary disorders such as respiratory failure, pulmonary edema, and pulmonitis.

As this space is bolstered with even more scientific evidence, we can anticipate a more narrowed focus of R&D efforts, which will enable the maturation of these therapies in patients who are refractory to current standard therapies. This research group has established autologous GMP-ready regulatory T-cells for Treg-based cell therapy.

Additional innovative efforts for treating UC can be seen in the use of nanoparticles to deliver anti-inflammatory relief to the bowel. A research group at Georgia State University is focusing on using nanoparticles that are capable of colitis tissue-targeted delivery and site-specific drug release that will overcome the challenges of oral drug delivery. Some of these challenges include the instability of drugs in the gastrointestinal tract, low targeting of disease tissues, and severe adverse effects. Nanoparticles may offer a unique and therapeutically effective system that addresses these issues.

**What’s next**

As is true for many new ecosystems, the cell and gene therapy space is booming with extensive evaluations of multiple diseases, formats, and technologies—resulting in a few anticipated treatment approvals and launches in recent years. As this space matures and is bolstered with even more scientific evidence, we can anticipate a more narrowed focus of R&D efforts, which will enable the maturation of these therapies. Until then, we’ll bask in the rays of all this scientific ingenuity but continue to take a data-driven approach.
High-Stakes Manufacturing: Mitigating the Risks

How to navigate the production and reimbursement intricacies of bringing regenerative medicines from bench to bedside

By Mo Heidaran and Richard Macaulay

Regenerative medicines—which are treatments that repair or replace the body’s own damaged or diseased tissues using cell or gene therapy, or tissue engineering—can treat severe, incurable, or chronic diseases that do not respond to conventional drugs.

Complete remission/response rates in clinical trials for the first two FDA-approved CAR T-cell medicines to treat cancers of the blood, Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), reportedly ranged from 54% to 81%—results previously unheard of in the clinical settings studied. And Luxturna (voretigene neparvovec), a single-treatment gene therapy for patients with previously untreatable progressive vision loss due to an inherited genetic mutation, was approved by FDA after data showed it provided a working copy of the mutated gene, restored vision, and improved sight.

With at least 20 more new gene therapy products in late-stage development and more than 100 companies working on CAR T-cell therapies, the field of regenerative medicine is exploding. Despite the exciting science and huge potential, developing regenerative medicines is difficult. Manufacturing can be lengthy, complex, and costly, especially when it involves genetically modifying and processing cells or genes. That’s because:

» Even small changes in manufacturing processes can negatively impact product quality and clinical outcomes.
» Some products are approved at small scale, but commercial scale operations require manufacturing controls to be in place.
» Shortages of high-quality ancillary materials (such as growth factors, nutrients, and reagents) are a major constraint.

Although regenerative medicines often qualify for expedited regulatory pathways, speeding development and review times, use of these mechanisms requires less clinical data. Curative therapies often show positive benefit-risk ratios after tests in a small number of patients—and their clinical benefits and production costs support high price points. However, sponsors must launch these products in a cost-constrained healthcare marketplace where payers want more data about benefits and side effects, not less, and may not fully reimburse until they have it.

Strategies to mitigate risks

1. Identify the clinically relevant quality attributes for cell and gene therapy products. Making changes to the process/product is an inevitable part of continually improving a product, especially for cell and gene therapies. However, manufacturers of these products often introduce major manufacturing changes—such as scale-up and automation—very late in the product’s development lifecycle. This is risky because even small changes in manufacturing processes can potentially affect product quality, effectiveness, and ultimately, commercial success. That’s why FDA and other regulators strongly advise manufacturers to analyze and understand precisely the critical quality attributes (CQAs) of their drug.

CQAs are essential for the development of meaningful prod-
uct specifications, which is how sponsors establish and ensure manufacturing quality and consistency. But identifying product-specific and clinically relevant CQAs is highly complex for regenerative medicines and requires a systematic, iterative approach.

2. Establish commercial-scale manufacturing controls prior to licensure. Historically, FDA has set the bar high for the chemistry manufacturing and controls (CMC) readiness of a licensed product. Sponsors must demonstrate the finished product can be manufactured consistently at commercial scale in accordance with a predetermined set of release specifications, and product quality can be maintained for the duration of its shelf-life. However, for cell and gene therapy products, FDA has been flexible as to what constitutes reasonable and scientifically-justified quality controls and metrics. In some cases, products are approved at small manufacturing scale and manufacturers sometimes struggle to meet their own proposed release specifications post-approval.

Manufacturing controls must be established at commercial scale prior to licensure if sponsors are to ensure regenerative medicines are available to patients. To achieve this, CMC should be embedded in clinical development in a way that makes process validation and control a priority earlier in the product lifecycle than ever before.

Manufacturers should automate the entire process, or at least attempt to automate distinct unit operations which are critical to consistent manufacturing of a high-quality product.

3. Support public-private consortia focused on producing ancillary materials. Manufacturers of gene therapies struggle to procure essential ancillary materials in a sustainable, cost-effective manner. Establishing a reliable supply chain requires not only following the Current Good Manufacturing Practices (CGMPs) for materials, and vendor qualifications and quality agreements that are required for marketing authorization, but also ensuring the long-term reliability of the supply chain.

There is a significant shortage of high-quality ancillary materials in the market today. This shortage—expected to worsen as increasing numbers of regenerative medicines are commercialized over the next decade—is due to the limited availability of natural resources, the cost of manufacturing, and susceptibility to many outside threats and competition.

The lack of ancillary materials can’t be addressed by private industry alone and will likely require sustained intervention from international agencies and governmental authorities. Sponsors establish and ensure regenerative medicines are commercialized in the market today. This shortage—expected to worsen as increasing numbers of regenerative medicines are commercialized over the next decade—is due to the limited availability of natural resources, the cost of manufacturing, and susceptibility to many outside threats and competition.

4. Consider alternative reimbursement schemes. Therapies that cure or reverse diseases can generate substantial downstream cost savings for healthcare systems and thus can be cost-effective at very high per-patient prices.

For payers, determining the reimbursement value of a single-treatment therapy with curative potential is challenging since that requires the entire cost of treatment be paid upfront. It is especially difficult if there is uncertainty about efficacy due to lack of long-term follow-up data or real-world evidence (RWE).

In response to this challenge, payers have increasingly turned to new contracting arrangements, including performance-based reimbursement, indication-specific pricing, dynamic pricing, and budget caps, which have been extensively used for regenerative medicines. For example:

- Strimvelis, an ex vivo stem cell gene therapy to treat rare disease ADA-SCID, known as “bubble boy syndrome,” was launched in Italy with a full “money-back guarantee.” The €594,000 per patient cost of treatment will not apply if it doesn’t work.
- In the US, Kymriah was launched with an outcomes-based approach. The Centers for Medicare and Medicaid Services (CMS) was to pay only for patients who respond to Kymriah by the end of the first month ($475,000 per responder). In both England and Germany, Kymriah is subject to a dynamic pricing agreement where temporary reimbursement has been granted pending collection of real-world and clinical trial data.
- In January, BlueBird Bio proposed a leasing-type agreement for Zynteglo, a putative curative therapy for beta-thalassemia approved in Europe in June. Although there have been notable failures—such as the UK’s risk-sharing scheme for multiple sclerosis drugs—nontraditional reimbursement strategies and pay-for-performance schemes are realities for which developers now must plan.
In Europe, legislation relating to medicines based on genes, tissues, or cells dates back nearly 20 years, and was reinforced by specific European Union regulation that came fully into effect nearly a decade ago—but still today there are only a tiny handful of these products on the market.

This limited outcome belies years of extensive and intensive activity among drug developers and regulators: between 2009 and 2017, 500 clinical trials were recorded with products of this type (known in European terminology as ATMPs—advanced therapy medicinal products). But all of this resulted in only 19 market authorization applications to the European Medicines Agency (EMA), and only 10 ATMPs received a marketing authorization. In addition, three companies later withdrew their product, and one discontinued product marketing, all citing commercial reasons, according to the most recent published survey conducted among companies (see https://bit.ly/32ArS3s). The latest official EU figures also show that the EMA’s first recommendation for approval of an ATMP containing stem cells was issued only in 2014, and since then there was only one more in 2015, two in 2016 and two in 2017, and three in 2018: Kymriah and Yescarta, the first two CAR T-cell therapies in the EU, and Luxturna, for inherited retinal dystrophy caused by RPE65 gene mutations.

The slow progress does not derive uniquely from a lack of legislation or regulatory guidance.

No shortage of regulation
The EU’s specific legislation classifies further into three main types: gene therapy medicines, somatic-cell therapy medicines, and tissue-engineered medicines. In addition, “combined” ATMPs may contain one or more medical devices as an integral part of the drug, such as cells embedded in a biodegradable matrix or scaffold (detailed definitions are set out in Regulation (EC) No 1394/2007; see https://bit.ly/2LYWANM).

Since 2011, the EU’s centralized authorization procedure has been adapted with defined and customized technical requirements, and specific and strict requirements relating to risk management and traceability (including retaining data for a minimum of 30 years after product expiry). EMA conducts the single evaluation and authorization procedure, and continues to monitor their safety and efficacy. A specialist Committee for Advanced Therapies (CAT) provides the scientific assessment. It delivers a draft opinion on a product’s quality, safety, and efficacy and transmits it to the EMA’s Committee for Medicinal Products for Human Use (CHMP), EMA’s main scientific body, which produces a recommendation as the basis for the European Commission to make the final decision.

Easing market access?
In addition to its obvious intention of guaranteeing the highest level of health protection for patients, the EU legislation was designed explicitly to ease access to the entire EU market, to ensure wide availability of approved products, and to promote the competitiveness of European companies in the field.

But an official review of the ATMP regulation in 2014 concluded that while it had protected patients from unsound treatments, it found shortcomings across manufacturing, early and later phases of development, the marketing authorization process, and the postmarketing setting.

The EU response was to confirm that it was committed to supporting the development of ATMPs and was determined to “ensure that the regulatory framework supports—and not hinders” their development. This response took concrete shape with an EU action plan agreed in 2017, aimed at streamlining procedures and meeting developers’ specific requirements more smartly (see https://bit.ly/2M0Qv3d). The plan was updated in April and again in November 2018.

Efforts have also been made by regulators to reduce administrative burdens and adapt manufacturing requirements to the specific characteristics of ATMPs: a specific GMP framework for ATMPs was created, and EMA has organized specific training sessions for national inspectors to align their approaches. An updated guideline
on “Quality, preclinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)” was published in 2018. And development of a guideline on quality, non-clinical, and clinical requirements for applications for clinical trials for ATMPs has been underway for more than a year now, and is due for finalization by late 2019. An updated guideline on “Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (CHMP/GTWP/671639/2008)” was released for public consultation in July 2018 for a period of one year, with the aim of helping to clarify regulatory expectations. The aim is to finalize this revision in late 2019 as well.

Adapted guidance on Good Laboratory Practice for ATMPs has also been developed to help in approval of clinical trials or granting of marketing authorization in cases where GLP-compliant preclinical studies are not feasible. And an EMA Q&A on the risk-based approach for ATMPs that have not been subject to substantial manipulation was published in 2017 to explain how this can provide flexibility and reduce requirements in a marketing authorization application depending on specific risks.

Last year also saw an update to the procedural advice on evaluation (see https://bit.ly/2Lr630F) and a draft revised guideline on safety and efficacy follow-up and risk management (see https://bit.ly/2YcNyD6).

But work on more than 100 guidance documents has more to be done as EMA prepared for Brexit—including the guideline on the comparability for ATMPs, which will address a recurrent issue for almost all ATMP developments where manufacturing changes take place during the product development.

Practical assistance
In parallel to the evolution of regulation and guidance, there is plenty of work among regulators aimed at assisting the emergence of ATMPs.

EMA increasingly gives scientific support to developers in designing pharmacovigilance and risk management systems for ATMPs, through early dialogue with multidisciplinary or multi-stakeholder expert teams. EMA procedures for scientific advice are also being streamlined, including by strengthening interaction between EMA’s committees with responsibilities for ATMPs. And increased interaction between EMA and EUnetHTA is underway on product evaluation, to increase understanding of health technology assessment, regulatory processes, and clinical-added value of ATMPs.

ATMPs are constantly on the agenda of the EMA-linked Innovation Task Force, a scientific, regulatory, and legal forum for early dialogue with applicants. The legislation also created incentives, including fee reductions for scientific advice and for marketing authorization, with particular significance for smaller firms and for hospitals.

Advanced therapies feature in the latest call for proposals under the EU’s Innovative Medicines Initiative public-private research program, with €45 million offered in support for projects that accelerate research into advanced therapies for rare diseases, or support the development of engineered T-cells to fight cancer. The funding is a recognition that “developing ATMPs is highly challenging,” said the announcement in late June. The specific aim is to advance understanding of the factors that trigger an immune response to ATMPs, and develop tools to study them. Regulators will also be involved, to ensure the tools and data generated by the project are in line with their expectations and needs for assessment. The focus will be on rare diseases caused by a single gene mutation, although it is expected that many of the project’s findings will be applicable to other diseases.

ATMPs feature prominently in the reinforced EU-US collaboration on medicines, with senior officials from the Commission, EMA, and FDA acknowledging the “similar regulatory challenges on both sides of the Atlantic,” and agreeing to encourage early parallel scientific advice and to strengthen collaboration on common scientific approaches on regulation.

Unfulfilled potential?
EMA’s own recently published regulatory strategy for 2025 spells the dilemma out clearly. It identifies cell-based therapies at the top of the list of the “transformational research that is having a significant impact on the regulatory science agenda.” ATMPs “have great potential to address unmet medical need,” it goes on.

But “the number of applications for approval has been, however, very limited,” it remarks, and “despite ongoing efforts in this area, more remains to be done to address current challenges and those that will rise from emerging technological advances in the ATMP field.”

It is work in progress in Europe—but a lot of work lies ahead. ☛
In December 2017, Spark Therapeutics became the first company ever to have a gene therapy approved in the US. Luxturna, its one-time treatment for adults and children with inherited retinal dystrophy caused by RPE65 gene mutations (a rare genetic disorder which causes vision loss and usually leads to blindness) has since received approval in Europe.

Spark was founded in March 2013 as a spin-off from Children’s Hospital of Philadelphia (CHOP) to advance and commercialize CHOP’s decades-long research into treating blindness. In February this year, drug giant Roche announced it would be acquiring the gene therapy company for $4.8 billion, a deal that Spark CEO Jeffrey D. Marrazzo said would help “accelerate the development of more gene therapies for more patients with more diseases and further expedite our vision of a world where no life is limited by genetic disease.”

At this year’s Veeva 2019 Commercial & Medical Summit in Philadelphia, Veeva Co-founder and President Matt Wallach introduced Marrazzo as someone who “basically knows more about commercializing a personalized medicine than anyone on the planet.” Their subsequent fireside chat chronicled Luxturna’s journey so far, from the initial controversies around pricing to its role as a milestone in the ongoing advancement of gene therapy. Here, Pharm Exec presents highlights from that conversation.

Matt Wallach: Let’s talk through the different innovations associated with Luxturna and how they happened in practice. If we start with pricing, the drug is $850,000, or $425,000 per eye—and that tends to be the headline. Can you talk about how you came up with the price?

Jeff Marrazzo: One of the first things to clarify is that Luxturna is a one-time price. We already today have five years of follow-up data in patients in the Phase III study who received a single dose and are still benefiting at the same level as they were before. We have patients even in the Phase II study who either self-reported or their physicians have reported that they’re [benefiting after] more than a decade. So, there is data that supports the idea that a one-time treatment can have a long-term, durable effect. What
we were trying to do was to think about how, under the current healthcare system, do you take all of the future benefit that you are hopefully going to deliver to a patient, potentially for the rest of their life, and bring that back to a single charge.

Now, that is not the way I think we should be paid. Ultimately, we should be paid on a recurring basis subject to continued performance of the therapy. We should be standing behind these types of products if we believe in them, which we do, but our system is not yet set up to do that. That was one of three different things we did at the beginning. We announced not just the price, but [also] that we were willing to offer partial rebates back [if] the drug didn’t work initially or if it didn’t show sustained effect at around 36 months.

Second, we offered two different ways in which this type of therapy, which is administered by providers, could come to market. One is the traditional way that we all know as “buy and bill.” The second way is to offer a direct model where we would structure a relationship directly with the payer and ultimately not require the hospital to take possession of the therapy and the financial obligation of that, but also for the payer to avoid what has become a huge copay? The thing that has been consistent with the data that we’ve seen in the Phase III study. We wanted to see if we could test the way the system operates with a number of novel ideas. We wanted to see if we could test the way the system operates with a number of these models, all with an eye toward ensuring access for patients administered drugs would be reimbursed.

**MW:** How about what the patients would expect that. You don’t know until you get actually into the real world, but we’ve been extremely pleased by that. We’ve had three patients that have gone through this outcomes-based rebate structure. As far as I’m aware, we have not paid any rebates, which again, is considered change in policy.

**MW:** How many of the times that the drug has been administered did it go through the traditional model, and how many times did you eliminate the middle man and go direct to the payer?

**JM:** Last year in the market it was roughly about 65, and 35 times we used the direct model and not the traditional model—a little more than half. I think that tells you a little bit about where payers, and to some extent hospitals, are perhaps looking to where the future might land in terms of the way these types of provider-administered drugs would be reimbursed.

**MW:** How much has actually been paying when it’s covered? Is it fully covered? Is there a huge copay?

**JM:** One of the great successes is the fact that we came out with a number of novel ideas. We wanted to see if we could test the way the system operates with a number of these models, all with an eye toward ensuring access for patients. The thing that has been most gratifying to me is the fact that to date, as far as I’m aware, there is still no patient that does not either have insurance coverage or a path to insurance coverage.

Importantly, through at least the balance at the end of last year, we had patient assistance programs that were being implemented to cover all the out-of-pocket costs for the patient under the commercial market. That means that a patient, a family doesn’t have to choose between their pocketbook and their child’s vision or their own vision. And that, ultimately, is what we were trying to accomplish.

**MW:** So, despite what is reported in the headlines—“$850,000”—the patients and their families actually didn’t pay anything. They had insurance. You have a rebate offer out there—have you had to pay any kind of a rebate?

**JM:** We’ve had three patients that have gone through this outcomes-based rebate structure. As far as I’m aware, we have not paid any rebates, which again, is considered change in policy.

**MW:** There are patients all over the country. There are eye surgeons all over the country—around 1,800. How did you cover the nation?

**JM:** We’ve had to establish and build a rather complex supply chain because we need to get a medicine that is required on a chronic recurring basis to patients at the right time and the right place and in the right conditions, e.g., frozen. If you can bring the patient to the therapy, as opposed to bringing the therapy to the patient, it works. Ultimately, we selected 10 treatment centers around the US and now have contracts and established relationships with them. All 10 of them have been operational and treated...
Tackling patient access to offset the challenge of declining ROI in drug development

Protocol complexity — impacting the speed and cost of clinical development

Assessing burden on the patient and site to stress test the impact on patient recruitment

Discussion around the increasing cost of drug development has dominated industry forums for many years, largely because of the challenge that the biopharmaceutical sector has had with many of the blockbuster drugs going off patent. However, it is only in the last few years that commentators have started to reflect on whether the reaction to this challenge has actually increased the complexity (and consequently the cost) of drug development rather than improving the situation. Protocol development has historically been in the hands of the scientists and therapeutic experts at Biopharma with high sensitivity to input from external sources, but could there be an alternative approach? Biopharma organisations are looking for innovative solutions to improve efficiency in clinical development, are they looking in the right place for a solution? Could additional insight support a better way to increase predictability in therapeutic testing and reduce costs? Research shows that protocols are becoming increasingly more complex. This increases time and cost and also importantly, burden on patient and investigators alike without necessarily gaining improvement in outcomes. By analysing data collated across multiple studies and a wide spectrum of therapeutic areas and indications, it is possible to gain insight that can be used to vary the protocol and positively enhance patient access and decision making.

Patient power and dynamics — Focusing on unmet needs

The patient has always been at the centre of drug development, but the patient journey has changed and is still actively evolving with increasing access to more information online and the support of patient advocacy groups. Industry research has shown patients still largely prefer to hear about clinical trials from their healthcare professionals; however, that doesn’t stop them researching their condition on the web and being able to have more informed conversations with their doctors. The appointment of senior roles in biopharma with a focus on patient interactions is hardly unexpected as organisations address this changing dynamic and the need to get closer to this important stakeholder, to give patients what they need rather than what pharma thinks they want. Developing drugs for unmet need that will really make a difference to patient lives seems like an obvious objective but the best intentions may not always deliver on this and sceptics suggest that pharma companies are not focusing enough on therapeutic areas and indications that are most acute. For example we are all too aware of the challenges of an ageing population and the increase in Alzheimer’s disease where there is an acute need for therapies. The question is whether pharma is investing enough to tackle challenging areas of research such as CNS, where if there were successful outcomes it would be beneficial to patients, society and to pharma in the long run.

Virtual trials — extending the reach of clinical trials — Democatising trials for greater access

Having to conduct a clinical study exclusively through investigator sites limits a sponsor’s access to patients, as patients need to take into account the proximity to the nearest site for visits. Increasingly, sponsors are looking at ways to decrease patient burden and the frequency of visits to site through virtual trials. This is especially true for non-interventional studies but is also possible for pre-approval studies. Virtual studies can make use of a combination of devices, sensors, and home nursing services, all of which contribute to making them more convenient for the patient and truly patient centric. This is not a totally new phenomenon with many organisations arguing that they have been bringing studies to the patient in various forms or hybrid trials for many years. What is new and improving all the time is the emerging technology that will enable a more holistic approach from the outset, such as enabling sites to conduct telehealth sessions with patients, new forms of sensors and wearables to capture data and all of which contribute to making them more convenient for the patient. These trials will extend the geographical radius, extending the outreach for patient recruitment and also improving the options of clinical trials as a care option for the patient.
In good hands

Site and Patient Solutions
ICON’s focus on understanding and engaging with patients throughout the journey of a clinical trial improves patient recruitment and retention.

- Leveraging patient insight based on health information collaboration, patient surveys and forums to gain better understanding of patient motivation and engagement
- Highly targeted recruitment and retention strategies that improve patient communication and compliance

Increasing predictability in patient recruitment.

ICONplc.com/patients
somebody within the first 12 months. What we’re able to do in that instance is bring together highly specialized individuals who know how to diagnose and treat these patients that require a surgical procedure to deliver Luxturna. It’s also an important part of ensuring the highest quality care. Now it’s possible because we bring the patient to the therapy.

**MW:** Can you tell us about the people in the field supporting the medication?

**JM:** We don’t have sales reps. We looked at the question that was in front of us and said, okay, what are the critical things that we need to be able to accomplish in order to make sure that this medicine makes its way to patients? Certainly, access was critical. We have a team that focuses on both the commercial and the government side of the payer space. We also have a team of people that support the education of the medical community. Keep in mind, this wasn’t just the first approved gene therapy—it was the first pharmacologic agent ever approved for any inherited retinal disease (IRD). So, we had a whole community of physicians that did not have much experience with this pharmaceutical product.

However, we did have a large number of those that were dealing with products related to macular degeneration. The medical education was a huge piece of it. And we have a team that does that both internally as well as in the field. But we go beyond this to focus on driving the diagnosis. We have a team of what we call “genetic diagnostic liaisons,” who really work to try to help physicians get access to simple, free genetic tests that can help diagnose.

**MW:** Because Spark pays for it?

**JM:** Correct. We thought that was really important because we heard very loud and clear from the patient community that prior to the approval of Luxturna, and even post, there was no pharmacologic treatment for any inherited retinal disease. And there’s more than 200 different genetic subtypes of it.

So, the insurance wasn’t covering even the diagnostic information that patients were yearning for. It wasn’t simple to get, it was complex to try to understand. We’ve put systems in place to cover that for patients. We have a team that focuses on that and then there’s a team that interacts with each of those 10 treatment centers. It all comes together in a very highly collaborative model where all of those pieces and parts of the organization have to work together in service of that individual patient and his or her family.

**MW:** You had a certain set of expectations and the team worked for years to come up with all of these innovations. What were some of the things that stuck out and that you were not expecting?

**JM:** On the positive side, I was extremely pleased with the speed in which we got coverage. I can’t tell you the number of conversations I had with many different stakeholders, not least those on Wall Street, who said, “This is not going to be easy. You’re not going to get access. You’re not going to get covered. Insurance is going to push back on it.” I think the speed was one of the biggest upsides and most pleasant surprises, how quickly we got up to now 85% commercial insurance coverage within just a couple of quarters.

We want to make happen more quickly. There are good reasons why the government is taking its time and thinking it through. But these are the types of reforms that need to happen, where we can get paid over time and we can put more than a partial rebate at stake and stand more behind our product. I think that’s ultimately the best way for these therapies to make their way to market.

**MW:** You said there were 200 different genetically-caused issues or mutations that trigger some form of blindness. What have you found about the number of patients? How big was the market when you started?

**JM:** Based on the epidemiologic research that had been done before we launched, we would project up to around 6,000 patients around the globe that might have these types of mutations, with 1,000 to 2,000 of those in the US. But we knew Luxturna is a single-use treatment for patients with inherited retinal dystrophy caused by the RPE65 gene mutation.
going in that while that is what the epidemiologic data projected, it certainly wasn’t the number of patients that had a confirmed genetic diagnosis. Comparatively, other countries do more in terms of coverage of genetic testing.

**MW:** There’s no reason for someone to get a genetic test for blindness if there’s no treatment.

**JM:** Right. That’s certainly the rationale that a payer would look at it and say, “We’re not going to spend hundreds of thousands of dollars on that.” We thought a very small percentage of those patients actually had a genetic test, which is why we put so much effort, even pre-approval in the appropriate way, trying to gather more information about the genetic subtypes of patients with IRDs to inform all of our research and development efforts. Also now, post-approval, we have a specific test targeting people who have RPE65 mutation.

We’re really only four quarters in (as of May) and we’re still finding new patients that didn’t know they had a particular mutation. To be clear, Luxturna is only indicated for one of those 200 odd genetic subtypes.

**MW:** Is it possible that Luxturna could work for the others?

**JM:** No, we wouldn’t expect that it would because it is targeted specific for RPE65. We know the bits and bytes of code that make up the RPE65 gene, and that’s what we’re delivering to the back of the eye.

**MW:** How do you actually deliver it? What is the process?

**JM:** Essentially, we use a disarmed virus. It’s something called adeno-associated virus, essentially something that causes the common cold. It’s not pathogenic. We strip it of some of its properties that would allow it to replicate in a way that you wouldn’t ideally want, but we keep the properties that allow it to be infectious. It is basically a carrier that ultimately delivers the genetic material, the correct copy of RPE65, to the cells in the back of the eye. The virus, or the viral-like particle, infects the cells and drops its DNA inside. Instead of dropping in the viral DNA, it drops in the normal copy of RPE65. It’s done through a surgical procedure and takes about 45 minutes. It is under general anesthesia and the surgeons do one eye at a time. About a week or so later, they’ll do the second eye.

With the scientific tools that we have today and the way the mode of action is working in these types of therapies—whether it be gene therapy, gene-modified cell therapy, or gene editing—I think we are headed to more specific therapies. The technology itself is very targeted, but that doesn’t mean the drug is necessarily aiming at a “specialty market.”

I think one of the next phases for genetic medicine—gene therapy being one of those—is the broader application of these to many other types of disorders. For instance, we’re all very excited about some of the work that we see continually emerging in our lab around neurodegenerative conditions. We’re working on some rare conditions, diseases like Batten disease, but we’re also working on things like Huntington’s disease, which doesn’t have any disease-modifying treatment today and is actually one of the more prevalent conditions.

You could also imagine applying this to an even broader spectrum of more common neurodegenerative conditions. If you think about the history of the last 20 or 25 years, we’ve tried to apply different technologies to various neurodegenerative conditions. One of the major issues has been the blood-brain barrier; we can’t repeatedly administer something systemically and get enough of it to cross the blood-brain barrier. What if you could take that concept and apply it directly to the brain through a one-time injection? It opens up real potential in a variety of different areas.

**MW:** Do you have any parting words for people in sales and marketing operations and in medical about how they can get themselves prepared for these developments?

**JM:** I think that this generation, this century of science, is going to force us into real creativity on how we ultimately commercialize.
Gene Therapy

Cost Climate Change: A Case Study
Four takeaway messages from the Zolgensma pricing storm

By Hervé Liliu

‘m sure by now everyone has seen the headlines:
World’s most expensive therapy,” “astronomical,” “casino culture”
The May announcement by Novartis of the list price of its new gene therapy for spinal muscular atrophy (SMA), Zolgensma, sparked a plethora of heated reactions. $2.15 million was the figure. Now, a couple months later, it is time to look back at the story and try to answer one simple question: was this a storm in a teacup or a tropical cyclone?

Here are four takeaway messages from the drama that unfolded that may offer an answer.

1. Time is of the essence
The sticker-shock that stemmed from the Zolgensma list price reveal has eclipsed the question that really matters—the question of time. A 1, 2, 3, or 10 million-dollar investment doesn’t mean much if there is zero information regarding the timespan of the expected return. We have to state the obvious here that on one hand, it’s a gene therapy that is a one-time treatment requiring a considerable upfront investment, and on the other hand, there are a host of chronic therapies that require smaller investments spread over a period of time. Taken separately, those chronic treatments might seem more affordable, but cumulated over time, they can become far more expensive than Zolgensma’s single shot.

To me, the question of “for how long should those chronic treatment costs be cumulated to make a fair comparison between Zolgensma and the current standard of care?” trumps the question of the price tag. Novartis has opted for 10 years. In its press release, the company claimed that the set price was “50% below 10-year treatment costs for genetic pediatric ultra-rare diseases (estimated at $4.4 million to $5.7 million).” That could be considered a bit of a cryptic claim in the absence of information relating to the products included in the analysis. So, through mining Inbeeo’s pricing database,

Methods and Limitations of Analysis
All treatment costs for the orphan-drug products used in this analysis were calculated based on the respective Federal Supply Schedule (FSS) price as of June 1, 2019, obtained from the Office of Procurement, Acquisition and Logistics (OPAL) at the US Department of Veterans Affairs. The wholesale acquisition cost (WAC) price for Zolgensma was obtained from a press release issued by Novartis.

Information on dosing and frequency of administration was obtained from the respective label/prescribing information file downloaded from the FDA. To estimate the bodyweight of patients treated with products whose dosing regimens are dependent on bodyweight, weight-for-age data tables for males and females (ages 2 to 20 years) from the Centers for Disease Control and Prevention (CDC) were used. In brief, for each one-year age bin (2 to 3 years, 3 to 4 years, etc.), the reported bodyweights within the age bin (e.g., the bodyweights reported for months 24.5 to 35.5 in the case of the 2-to-3-years age bin) were averaged and the resulting value was chosen to represent the bodyweight for an individual in said age bin. For the purpose of this analysis, the absence of a gender-bias was assumed for all diseases/conditions treated with the selected orphan-drug products (i.e., all calculated bodyweights represent the average between a male and female individual in the corresponding age bin). Treatment costs were calculated for the 5th, 10th, 25th, and 50th bodyweight
we extracted a sample of 10 products that might actually meet the criteria of comparability, including Biogen’s Spinraza, as the only other disease-modifying therapy approved in SMA (see Table 1).

We then estimated the cumulative treatment cost they would generate over different time periods (see Figure 1 on page 32).

Broadly speaking, our analysis confirms Novartis’s claim of a 50% discount vs. other treatment costs for genetic pediatric rare diseases over 10 years. However, it also reveals that the variability of—and thus the uncertainty around—treatment costs grow considerably after 10 years. A five-year comparison seems more reasonable, with Zolgensma’s acquisition price being close to the median cost in our sample. Anything shorter than that puts Zolgensma under a less favorable light. This is why time is of the essence—a gene therapy price tag is only relevant in the context of how durable its benefit for the patient will be.

2. Cash doesn’t grow on trees

The question of the considerable upfront investment that will bring benefits over time is not a trivial one. In business, it is called “cash flow management,” and there are percentile, and the data shown in Figure 1 represent the 50th bodyweight percentile. The patient’s age at the initiation of treatment was assumed to be 2 years for all comparators (first age bin: 2 to 3 years), unless the respective label/prescribing information specified that patients must be older to be eligible for treatment. In these cases, the lowest eligible age (among the pediatric population) was used as the patient’s age at the initiation of treatment, and treatment costs were calculated from that age onwards.

The treatment with Zolgensma was assumed to be paid upfront as a lump-sum. However, payment in instalments and/or an outcomes-based payment scheme (akin to the pricing scheme Bluebird Bio announced for Zynteglo) cannot be excluded. For the purpose of this analysis, treatment with Zolgensma was assumed to be curative (i.e., no further treatments required during the lifetime of the patient) or that at least no further treatment is required during the 10-year period after the initial intervention (NB: mean time since treatment of Phase I patients is 3.7 years, with a range of 3.3 to 4.3 years, as of May 2019).

Costs associated with the administration of Zolgensma or the comparator products used in this analysis (e.g., for IV infusions) were omitted (i.e., all reported costs represent drug costs only). Future treatment costs for the comparator products (i.e., costs in Year 2 and onwards) were not discounted. An FSS price for Zolgensma is not yet available, and any discounts on the WAC price the manufacturer might be offering are unknown.

Sample Product Comparisons

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brineura&lt;sup&gt;a&lt;/sup&gt;</td>
<td>cerlipase alfa</td>
<td>To slow the loss of ambulation in symptomatic paediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)</td>
</tr>
<tr>
<td>Cholbam®</td>
<td>cholic acid</td>
<td>Treatment of biliary acid synthesis disorders due to single enzyme defects; adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders</td>
</tr>
<tr>
<td>Crysvita®</td>
<td>buromab</td>
<td>Treatment of X-linked hyposphatemia (XLH) in adult and pediatric patients 1 year of age and older</td>
</tr>
<tr>
<td>Kanuma®&lt;sup&gt;b&lt;/sup&gt;</td>
<td>sebelipase alfa</td>
<td>Treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency</td>
</tr>
<tr>
<td>Mopsevi®</td>
<td>beta-glucuronidase</td>
<td>Treatment of mucopolysaccharidosis VII (MPS VII, Sly syndrome) in pediatric and adult patients</td>
</tr>
<tr>
<td>Spinraza®</td>
<td>nusinersen</td>
<td>Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients</td>
</tr>
<tr>
<td>Strensis®&lt;sup&gt;c&lt;/sup&gt;</td>
<td>asfotase alfa</td>
<td>Treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)</td>
</tr>
<tr>
<td>Symdeko&lt;sup&gt;d&lt;/sup&gt;</td>
<td>tezacaftor/ivacaftor</td>
<td>Treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor</td>
</tr>
<tr>
<td>Takhzyro®</td>
<td>lanadelumab</td>
<td>Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older</td>
</tr>
<tr>
<td>Vимizим®&lt;sup&gt;e&lt;/sup&gt;</td>
<td>elosulfase alfa</td>
<td>Treatment of mucopolysaccharidosis type IVA (MPS IVA; Marquio A syndrome)</td>
</tr>
</tbody>
</table>

Table 1. Orphan-designated products selected from Inbeeo’s pricing database that may meet the criteria of comparability with Zolgensma.

### For personal non-commercial use
Paying as little as $5 for a power yoga class sounds like a wiser investment than a $2,000 annual gym membership that includes “all-you-can-eat” classes, and driving around town in the newest German car for $20 a day must be a bargain as compared to cutting a $40,000 check. They are the same product and at the end of the day will cost the customer the same amount of money, but the narrative affects the value perception—permanently. This is known as price anchoring, and it is pretty powerful. From the moment you have established a $2.15 million price anchor in the mind of your customers, it is difficult to move away from it.

4. No one is ready for what’s coming

With the not-so-great price anchoring, it is suggested here that Novartis was not fully prepared for the Zolgensma story. But who is? Surely not payers. Let’s take a look at the dominant pricing frameworks in the US and the EU and try and assess their level of readiness.

In the US, the dominant model remains utilization management via brand tier placement, using negative financial incentives to nudge patients and prescribers toward preferred brands and generics. Co-insurance continues to be on the rise, meaning it becomes customary to charge patients 10%, 20%, or more of the final bill.

The sums at play with Zolgensma are, of course, mind-boggling. And with pharma companies blaming insurers for not passing the negotiated rebates on to the consumer, you can be sure this issue will not go unnoticed with a treatment like Zolgensma. Copay cards will come in as short-term fixes, but they cannot hide the deficiencies of a system at risk of losing all connection to the reality of value.

In Europe, the dominant framework remains that of the incremental cost-effectiveness ratio (ICER). It is affected by some well-documented methodological issues, but if oversimplified to what may be the most acute ones, they are two-fold. Firstly, the desire to summarize outcomes related to chronic disease in one universal measure—the quality-adjusted life year (QALY), which is something that is incredibly personal and individual. And, secondly, the way time and uncertainty are handled in cost-effectiveness models. Some recent product launches have clearly put those weaknesses in the spotlight, in particular in the orphan-drug space. But assessing the lifetime cost-effectiveness of a $2.15 million product based on two single-arm open-label studies of 35 patients combined promises to be quite the challenge. One can only imagine the dramatic effects of the sensitivity analyses when varying the proportion of patients being able to walk or sit thanks to the treatment, something that could possibly take the ICER down from several million to virtually zero.

much to be written

It is clear that this is just the beginning of a story that is unfolding before our eyes, as confirmed by the recent list price disclosure of Zynteglo, Bluebird Bio’s gene therapy against transfusion-dependent beta-thalassemia. Claiming that Zolgensma is the most expensive treatment in the world is misleading. But claiming that the product is “expected to save costs to the healthcare system” in its approval press release is a leap of faith given how little we know about its long-term benefit-risk profile.

The only certainty is that pricing frameworks on both sides of the Atlantic need a profound change to be ready for gene and other advanced therapies. And by profound change, a reworking from the ground up, not applying Band-Aids through installments or ICER threshold modulations.

With an estimated 10,000 currently known monogenic diseases according to the World Health Organization, the likes of Zolgensma and Zynteglo are prototypes of what payers are truly facing—not a few isolated storms, but an irreversible climate change.

Hervé Lilliu is Director, Inbeeo

Figure 1. Cumulative wholesale acquisition cost (WAC) of treatment with selected orphan-designated products in the US compared with Zolgensma’s $2.15 million figure.
Managing the Clinical Trial Minefields

The field of gene medicine has a history filled with hope and tragedy, successes, and cautionary tales. The world’s first gene therapy was approved in Europe in 2012, only to be taken off the market five years later due to regulatory and commercial barriers. Now, almost seven years after the first approval, gene therapy clinical development is thriving. And the path to patients in R&D settings, and ultimately to market, continues to evolve as new milestones are met and newcomers abound.

This is good news for those with rare diseases and unmet medical needs, but for these new options, the trajectory from concept to trials to approval and commercial availability is a uniquely complex, but not impossible, pathway.

New therapeutic reality

“Once just a theory, gene therapies are now a therapeutic reality for some patients,” Dr. Scott Gottlieb, the former FDA commissioner, wrote in July 2018 when announcing steps the agency was taking to support development of new drugs.

Gottlieb, at the time, pointed to the approvals of Kymriah, Yescarta, and Luxturna. And since then, there’s been additional approvals, an encouraging sign considering the scarcity of gene therapy drugs and the enormous effort and expense involved in conducting human trials. Still, Gottlieb cautioned, there is much we don’t understand about how these products work, how to administer them safely, and whether they will continue to work properly without causing adverse side effects in the long term. Accordingly, the then-commissioner issued six scientific guidances intended as the basis of “a modern, comprehensive framework” for advancing the field of gene therapy while ensuring that new products meet the agency’s standards for safety and efficacy.

Three of the documents focus on disease areas where gene therapy is seen as having especially strong potential: hemophilia, retinal disorders, and rare diseases. The other three are updates to existing FDA guidance on manufacturing issues; targeting these compounds’ safety, quality, potency, and purity; testing of retroviral vector-based gene therapy products; and the design of long-term follow-up observation of patients.

What is emerging here, on the part of the entire drug development community, is a shift in emphasis. After a slow start, gene therapy has moved beyond the theoretical realm, and it’s widely accepted that many new treatments in this space will appear on the market in the relatively near future.

Advice for sponsors

So how do we proceed? The answer is carefully, with a lot of deliberation and planning and proper stakeholder engagement. Here are some things sponsors should consider.

- Early and open dialogue with the regulators is imperative. These discussions should include the development plan, endpoints (including the potential use of any biomarkers and/or disease-specific clinical outcome assessments), study design (including the use of placebo or an acceptable control, where appropriate), the number of studies under consideration, patient numbers, and plans for long-term follow up.

- Procurement of orphan-drug designation and/or approval for one or more of the agencies’ expedited programs (e.g., breakthrough therapy or RMAT with the FDA or PRIME designation with the EMA) will facilitate this access and collaboration.

- Upfront planning and compliance with the agencies’ instruction for determining and validating new endpoints should be incorporated in the development plan. Of note, the FDA released in December draft guidance for industry titled Biomarker Qualification: Evidentiary Framework.

- With respect to endpoints, it’s important that they are as meaningful to patients individually as they are significant clinically. Therefore, early engagement with the patient community to obtain the patient/family perspective on the disease, identify relevant endpoints, ensure feasibility of clinical trials and specific study designs, and incorporate patient experience data should be prioritized.

- Advanced therapy medicines are notoriously expensive, and payers are very concerned with managing the potential financial risk and impact of gene therapies. Consequently, a combination of existing and new approaches to reimbursement will need to be considered. Sponsors need to understand, as early as possible, what data and value claim payers will need, and they must focus on generating a value statement and health economics story early—and, where needed, build a collection of this data into the clinical plan.

— Angi Robinson is the Vice President of Rare Diseases & Pediatrics at Premier Research
Three Tips to Managing Multiple Agency Partners

If my 20 years in this industry have taught me anything, it’s that pharma marketers have a high-stress, complex job. Physicians are harder to reach, value chains have become more nuanced, and patients are playing a bigger role in their care decisions than ever before. Simultaneously, technology and data accessibility have raised the bar on what consumers expect.

The demands on today’s pharma marketers are only growing. To deliver on those demands, many of them rely on external partners. But it isn’t as simple as hiring a single agency; a complex digital landscape requires an equally complex ecosystem of partner agencies.

Managing these multiple vendors requires extensive coordination, and can result in frustration when communication falls apart. These three practices are key to navigating today’s multiplayer agency landscape—and getting more value from each of your external vendors.

Be direct with expectations
Working with multiple vendors means that there are a lot of cooks in the kitchen. If you want to avoid confusion-induced project delays, be frank about expectations with your marketing partners from the get-go. Whether you’re working with two vendors or five, you can avoid conflict by giving each of them access to critical information.

» How you’ll work together. Get everyone in the same room and outline how internal and external stakeholders will partner. Distribute an agency collaboration model that clearly illustrates the realm of your brand team, agency of record (AOR), digital production agencies, and specialty partners.

» Who has the final say. If there’s duplicative expertise at the table, avoid conflicts of interest by naming a product or initiative leader as the final decision-maker.

» Roles and responsibilities. Make sure everyone is apprised of clear guidelines regarding who’s going to do what (and when). Don’t forget to define interdependencies.

Clear the air
When you’re managing several marketing vendors—not to mention your own direct reports and relationships with other team members—it’s easy for wires to get crossed. Implement best practices in project communications with the following steps.

» Identify a source of truth. Multiple stakeholders reporting on project status make tracking progress difficult. Designate a key channel, such as your project management collaboration platform, as the single source of truth. Require all contributors to report progress through that channel in real time.

» Create a communication protocol. Help your external partners understand the communication chain of command, including escalation paths and final decision-making authorities. Define a standard workflow for how team members communicate with clients.

» Don’t delay when the direction changes. It’s common to want to delay communicating changes in the project timeline or scope to outside partners before you have everything cleared internally, but when the stakes are high, the sooner you get everyone on the same page the less room for confusion and chaos there will be.

Get real about metrics
Establishing measures of success before you sign on the dotted line is essential. Not only will you learn what metrics and data your vendors and partners are capable of communicating, you’ll provide a more concise picture of what you expect them to deliver.

» Create shared goals. Agencies are rarely siloed by channel; for example, your AOR, digital production agency, and media buying agency may all play a key part in reaching your digital display ad goals. Ensure that all vendors are working toward the same business priorities, and determine how their success will be measured.

» Provide transparent insight. Timely feedback is essential for all stakeholders. Determine key reporting benchmarks, who is responsible for each, and set deadlines as to when they should be reported.

» Think about the intangibles. To ensure a successful engagement, go beyond the numbers, setting the standards high by sharing your organizational core values. When your agencies and vendors have an understanding of your company culture and values, it gives them a clear picture of how you expect to do business.
Market dynamics are changing rapidly. Cost pressures are driving pharma manufacturers to generate evidence that demonstrates product value. While we’re seeing more drugs approved than ever before, R&D organizations continue to struggle with designing evidence-generation strategies that improve patient access to medications.

To that end, in the age of value and affordability, pharma R&D arms can leverage FDA’s final guidance on pre-approval information exchange, otherwise known as PIE, to engage with payers earlier in the development process (ideally prior to a drug’s Phase II clinical trials), with the overarching goal of favorable coverage and reimbursement decisions since PIE was issued in June 2018.

Instead of nibbling around the edges of PIE, R&D organizations can embrace FDA’s final guidance by working hand in hand with payers earlier in the development process (ideally prior to a drug’s Phase II clinical trials), with the risk-adjusted net present value can be leveraged to find the appropriate balance of trial designs that go beyond achieving regulatory milestones alone.

3. Lay the foundation for RWE partnerships. FDA has embarked on the journey to include the use of RWE as part of the regulatory paradigm. The agency leverages advancements in analytics as well as the explosion of disparate data sets that span electronic health records, laboratory tests, wearable devices, and insurance claims data via its new RWE Framework. At the same time, value-based partnerships, such as risk-sharing agreements and data-sharing partnerships, are on the rise but fail to demonstrate tangible results to policymakers. By engaging earlier with payer organizations, pharma manufacturers can set the foundation for a streamlined negotiation and implementation process. They can also explore the use of novel clinical endpoints and integrate data sets earlier in the development process.
WHAT

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Spain

HEALTHCARE LIFE SCIENCES & REVIEW

ON THE MOVE?

With Spain now enjoying an economic rebound, pharma and medtech multinationals are seeing the country as a top-tier investment destination once more thanks to a much-improved market access scenario, high quality, but affordable manufacturing capabilities and an enviable clinical research base. Today the country stands proud as the tenth largest pharma market in the world with a valuation of some EUR 26.15 billion (USD 29.55 billion) in 2017 according to BMI.

“For the past three years, the overall value of medicine sales in the hospital segment expanded at a rate of 3.3 percent while retail sales increased 2.2 percent... I genuinely cannot think of any other European market that has enjoyed an analogous growth trajectory,” enthuses Humberto Arnés, the director general of Farmaindustria, Spain’s leading pharmaceutical industry association.

B. Braun CEO Jesús Donado adds, “In the past two years, we have seen a recovery, not only economically, but in terms of investment into the health system.” He does, however, caution that “while investment levels have grown from their position five years ago, we still remain behind other comparable European countries, so there is still a distance to go.”

Meanwhile the life sciences industry has been consolidating its status as a critical growth engine for the national economy. “The pharma segment alone is contributing over 40,000 high-skilled direct jobs of which more than 12 percent are in R&D and the industry now makes up almost a quarter of innovative technology in the country so it’s becoming a real dynamo for economic prosperity,” exclaims Javier Hidalgo, CEO and president of Tedec-Meiji.

Equally exciting is the bold way that Spain seems to be attempting to transition over to the new era of value-based outcomes, personalized precision therapies and integrated healthcare. “There’s certainly a lot going on over here right now,” observes Margarita Alfonsel, general secretary of the country’s medtech association, FENIN.
MANUFACTURING PLATFORM OF CHOICE

It is perhaps emblematic of Spain’s rising stock as a pharmaceuticals powerhouse that the country is fast cementing and rounding out its positioning as a tier one drug manufacturing destination. Indeed, Big Pharma multinationals are now routinely including Spain in their global production and supply chains with Pfizer’s plant in San Sebastián de los Reyes, Madrid, notable for being the company’s only global facility that manufactures, packages and distributes recombinant products for the treatment of hemophilia A and B. Further, Bayer’s API site in La Felguera, Asturias generates the entire group’s acetylsalicylic acid, the active component of Aspirin.

The burgeoning esteem in which producers hold Spanish manufacturing is also evident from the fact that the country now hosts the largest stem cell plant in Europe and one of the top three globally, a platform recently bequeathed to Japanese outfit Takeda following the acquisition of Genetrix for some EUR 500 million (USD 560 million).

“Possessing this site, here in Spain, is a matter of immense pride given the sheer operational sophistication and scale of this platform,” confides Takeda’s general manager Stephanie Granado.

Another Japanese group, Tedec-Meiji, has also been betting big on the strategic importance of Spain, having identified the outskirts of Madrid as the optimum location to situate two large industrial factories comprising the centerpiece of its worldwide supply network. “When you factor in cost-quality ratios, manufacturing in Spain is considerably cheaper than it would be in Switzerland or Germany, and yet we can still produce top notch, reliable products fit for export anywhere,” elaborates Tedec-Meiji’s Javier Hidalgo.

There are, indeed, a plethora of factors rendering Spain-based manufacturing so appealing right now. “Firstly, being able to have factories within the EU is a major advantage and, as part of that, Spain offers a strong quality-price differential. Spain enjoys a much better track record in meeting the expectations of GMP and EMA regulations than Eastern European states, you have the 5th largest European pharma market on the doorstep that can soak up any overproduction, and a steady supply of affordable, but top caliber science-educated human capital,” enthuses Manuel Ramos Ortega, chairman of Catalan contract manufacturer, Labiana.

Also notable is the variety of manufacturing forms in Spain from the most sophisticated biologics to very basic items. For instance, HC Clover, more commonly known as ‘Aplicaps,’ has managed to grow a veritable global business empire in the contract manufacturing of soft gelatin capsules from a vantage point near Madrid. “Our original idea was to be producing different pharmaceutical forms, but we noticed a real market gap in the supply of capsules and had some well-known MNCs requesting assistance. In the space of under two years we had built a market of over 150
million capsules supplying the pharma, dietic and cosmetic sectors,” recounts CEO, José Luis Martín Guinea.

Nowadays, the company has a manufacturing capacity of in excess of 1,800 million capsules per year and a portfolio of over 900 different products. The business originally started out based in Portugal, but Spain was identified as the most logical destination for establishing the manufacturing facilities. “Our competitive advantages are our rapid reactions – usually we can develop a product ready for placement in a market within a timeframe of three months – and our pro-activeness in identifying creative and practical solutions for our clients’ needs such as the design of a gastro-resistant capsule. To achieve these two points we have been tapping into Spain’s high-level talent pool,” he explains.

“Of course, ultimately we follow whatever we consider to be the most compelling business case,” confides Martín Guinea, noting that his firm recently took the unprecedented step of signing a joint venture for a new plant in Brazil. “We have been exporting some seven million capsules from Spain to Brazil every month for over four years. However with the devaluation of the Brazilian Real against the Euro, it became rather expensive and once you add in the costs of customs tariffs, it was becoming complicated so we needed to act,” he says.

ON THE RADAR OF MEDTECH TOO

For the medtech industry, as well, Spain is becoming an important platform in the supply chain landscape of some of the biggest MNCs, with R&D capabilities, more often than not, integrated into the mix as well. “Not only has Spain
Spain’s generics segment – characterized by comparatively low penetration rates of 42 percent in volume, 24 percent in value and beset by market distortions such as the mandated absence of a clear price differential between the reference medicine – is generally considered a tricky niche to master where many big brand multinationals have tried and failed. Since its arrival on the local market back in 2010, however, Accord Healthcare’s rise has been little short of meteoric: to the point where the Spanish affiliate now dominates the hospital generics space boasting one of the highest ratios of profitability with the lowest working capital.

“Sometimes success is about being in the right place at the right time and there were two strokes of good fortune for the affiliate. Picking up some synergistic hospital products from Stada and then acquiring Combino in both Spain and Portugal provided us with a great level of portfolio breath,” admits managing director and executive vice president for global licensing, Marc Comas.

“I always knew that if we were to launch injectables in the hospital space, we would make a success of it. The move actually maintain 2768 personnel in country because of this high level of industrial activity which includes our most important factory worldwide for the production of injection needles,” discloses CEO Jesús Donado.

“We are actually expanding our facilities and moving to a 30,000 m2 facility with a new factory. The challenge is not simply to expand our production but to upgrade the technology by introducing full automation for our fabrication of needles. As a center of excellence, we must bear this in mind, continuing to provide not only quality products, but also economically efficient products in terms of price point,” he attests.

Furthermore, Accord has managed to position itself as much more than a conventional generics outfit. “We always look at how the originator product can be improved. There are many things that can be done in the generic space which will constitute an improvement for the product, such as if we can bring bio-betters and not only biosimilars,” reveals Comas. “What matters is not only a competitive price, but having the products always available. There are so many shortages that have rendered price as no longer the most important factor. Instead, security of supply and having a product to sell is more valuable than having a product that is periodically unavailable,” he opines.

As the Spanish market, along with its peers across Western Europe, braces itself for the introduction of latest generation, high sophistication, but costly therapies, the Ministry of Health has been busy rolling the so-called “Valtermed” system which aims to “secure optimal information for the appropriate decision-making in the macro, meso and micro management of pharmaceutical provision across the different stages of the drug cycle.”

“You definitely get the sense that the country is learning... I am not sure that many other markets are really prepared either, but the positive thing is that the Spanish are keen to catch up and align with emerging trends in
The ‘Rare Disease – Precision Medicine’ Nexus

Spain’s ability to properly address rare disease remains heavily dependent on the health system’s competencies in data collection, processing and sharing. “The current diagnosis period for rare diseases in Spain stands at a median of five years, so there is considerable scope to do better,” argues Sobi’s general manager, Aurora Berra. “A fundamental part of this identification process is registries, which unfortunately Spain does not yet have, unlike peer markets such as the UK and Italy... Philosophically, everyone from policy makers to payers love the concept of personalized medicine, but prerequisite infrastructure like nationwide registry processes simply have to be implemented first,” she affirms.

“The primary obstacle is Spain’s decentralized system of authority where power resides in the regions so that data for a specific rare disease will actually be dispersed across 17 different incompatible regional registries all of which collate the information in different ways,” laments Alba Ancochea, director of FEDER, an institution that groups together Spain’s 337 rare disease patient organizations.

For its part, Sobi is doing what it can to better educate the national and regional administrations. “Pharmaceutical companies know the steps that must be taken to identify patients and must be more proactive at sharing this knowledge, explains Berra. Meanwhile the company is simultaneously working alongside patient groups, national associations and physicians to grow awareness in hemophilia.

Berra is also on the board of Foundation29, which seeks to leverage artificial intelligence in designing diagnostic models to lower the time period of identification of rare diseases in Spain. “By analyzing particular symptoms and phenotypes of certain diseases, we will help the physician to diagnose rare diseases earlier,” she explains.

Another stark fact is that although the European Commission has approved 53 orphan drugs, only 18 are securely reimbursed in Spain. “I think the overall understanding of rare diseases by specialists in Spain is improving, but the question is, do orphan drugs receive market access at a faster rate than other innovative medicines? Probably not. In many countries, there are bespoke regulatory processes for orphan drugs and, in my opinion, there should equally be a specific budget dedicated towards these treatments,” concludes Berra.

medical advancement. I consider the Valtermed platform to be a strong indicator of that on-going endeavor,” muses Stefanie Granado, general manager of Japanese drug maker Takeda.

“Valtermed is essentially a mechanism for gathering data and real-world evidence for evaluating the health outcomes of products which have a big impact on the budget. We consider this a positive step towards value-based healthcare, though we will monitor its implementation closely as we are keen to ensure the system does not in any way delay price reimbursement, which remains one of our outstanding concerns,” cautions Javier Urzay, deputy director of the innovative drug developers’ association, Farmaindustria.

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“We do recognize, nonetheless, a sincere willingness on the part of the authorities to put the welcome mat out for breakthrough therapeutic innovation... since 2013, there has been a drive to compile reports on therapeutic positioning (IPTs) which offer evaluations of the clinical value of new products and their positioning in the market based on clinical differentiation. These reports are constructed by the Agency together with the regions, and represent a decent starting point for the reimbursement procedure,” confirms Urzay. “Though there is still some way to go to turning these tools into a high-speed vehicle for bringing innovation to market,” he qualifies.

“Medicines must be continually evaluated in real-time, and the only way to do this is by using RWE. It should be a mandatory tool from early phases and market approval to pricing and post-reimbursement and this will help us to really understand the true value of a therapy. We are already utilizing big data, but this is mostly for pharmacovigilance and understanding the patterns of a medicine’s use in primary care to search for unknown adverse effects,” explains María Jesús Lamas, director of the Spanish Agency of Medicine and Health Products (AEMPS), whose evaluations are passed to the Ministry of Health, who determine, firstly, if the medicine should be reimbursed using public funds and under which conditions, and secondly, the pricing of the product.

That’s not to suggest that absolutely everyone is optimistic though. ‘Frugal innovators,’ in particular, voice concern that their own incremental design improvements tend to be neglected and overlooked in favor of blue-sky, disruptive discoveries such as CAR-T and that the true value of their offerings is thus not always being factored into the assessment criteria when adjudicating price and reimbursement.

Take, for example, Nordic Pharma’s NORDiMET® Methotrexate Autoinjector Pen for rheumatology. “This is an incremental innovation in the sense that the compound within the device is well established, but that doesn’t diminish the fact that this represents a game changer for the patient experience and triggers clear co-benefits. This is because the ultra thin five-bevel needle causes causing reduced trauma to the patient’s body, while the double click mechanism helps ensure the complete dose has been injected, thus giving confidence to and empowering patients,” contends the company’s general manager for Iberia, Rafael Mella.

“Sadly the health authorities are not taking into consideration that this mature compound, which is already within the Spanish reference pricing envelope, is being administered in an innovative way by our injector pen, so in the end, it is being priced at the same level as inferior medical devices; with no differentiation between our design and older devices,” he laments.

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The logical next step in shifting the paradigm towards the healthcare of tomorrow will be to join forces to enact value-based schemes with industry players working hand in hand alongside healthcare providers, regulators and practitioners to co-create arrangements such as risk-sharing agreements based on results being met,” recommends Jesús Sobrino, UCB’s area head for Iberia and the global leader of the Belgian multinational’s ‘Patients Experience Program.’

With its unorthodox business model and dynamic corporate culture Aspen is very much expected to introduce some color and flair to Europe’s fifth largest pharma market. “We are certainly not your typical industry actor. Unlike an R&D-driven drug developer, we grow inorganically through acquisition with the aim being to quickly internalize other companies’ products that have not managed to attain full potential,” explains Miriam Rodríguez, general manager for Iberia. “Moreover, we tend to focus on technically complex products in specialist areas and distinguish ourselves through our abilities to reap strong performance from post-patent molecules and to optimize product lifecycle management,” she adds.

Normally when pharma companies engage in M&A activity, the task revolves around the acquisition or meshing together of entire companies, resulting in a lengthy process of sorting out the component parts to divest or merge. Aspen, however, is fundamentally different. “We opportunistically seek out synergistic products, business lines or portfolios that we can rapidly digest and absorb, internalizing the production as quickly as possible. Our work cycle is thus considerably shorter than the majority of our competitors,” confides Rodríguez.

“This, in turn, has a big impact on the corporate culture because our staff have to be comfortable with constant change. Ordinarily, change is considered scary within an organization and human nature resists doing things differently. In Aspen, by contrast, we thrive on change and our workforce has to be ready to embrace and adapt to brand new portfolios at virtually a moment’s notice.”

“Fragmentation can be a real asset when you’re trying to pilot innovative market access strategies, measure outcomes in more creative ways and ultimately devise pay-for-performance agreements... Always the biggest challenge for these sorts of innovative access schemes is to collect consistently good quality data to measure outcomes and this is logically far easier to determine at an account or regional level,” he points out.
The Business Development ‘Snipers’: Innovative Out-Licensing Strategies

Barcelona-based Noventure – part of the Ferrer group – has achieved dramatic success since appointing former Almirall COO Luciano Conde as CEO in 2015. Thanks to its unique technology and equally unique out-licensing strategy, the firm has grown from selling around one million packs of its products per year to an expected five million in 2019.

Noventure’s technology has, in Conde’s words, “an innovative mode of action – ‘the barrier effect’ – which mechanically protects the function of the epithelial mucosa.” These mucoprotectors can prevent a wide variety of diseases generated by pathogenic microorganisms, allergens or toxic environmental particles.

The company’s products – classified as medical devices – are in general not reimbursed and offer health solutions without carrying out a pharmaceutical action. As Conde notes, “our products are a good alternative because, in pharmaceuticals, indications are becoming more niche and more costly to develop and sell. On the other hand, traditional open care markets are genericized and more unpredictable. That is why many companies are shifting towards self-medication, an area where they control their destiny and are not dependent on bureaucratic decisions around pricing or reimbursement.”

However, rather than marketing their products themselves, Noventure targets potential partners who may have a gap in their portfolio in a certain region. As Conde explains, “We act as snipers in the market and target our partners with a business proposition. This is working well, as shown in our high business development success rate – last year we signed products in 41 territories.”

Fellow industry veteran José Luis Fumanal, Noventure’s VP of sales and marketing, adds, “we show prospective partners that they could make a concrete healthy profit without increasing their fixed costs, enhancing their profitability at very little cost.” He continues, “This simple approach changes the perspective of the discussion as we are not just selling them what our product offers technically, but how it may benefit them by fitting in with their portfolio and promotional strategies with minimal effort.”

As an example, Fumanal points to Noventure’s “agreement with Zambon in Italy. We offer them our product in urology to complement their leading product lines, and by sharing with them the commercial fit of our product in their strategy, the agreement was fast to set up. Similar examples of a synergistic agreement have been set in Austria, the Scandinavian countries, and other territories.”

A REGIONAL OUTLIER

Some ambitious and pioneering decentralized authorities, such as the region of Catalonia certainly appear to be forging ahead with the transition at considerably faster pace than their counterparts in other provinces. “Catalonia, is unequivocally one of the most active regions in terms of adopting new business models and overhauling methods of purchasing,” claims Maria Vila, regional vice president of Medtronic.

“When the cardiovascular unit of one hospital in Catalonia recently published a public tender, instead of wishing to purchase defibrillators, the objective of the contract was rather to select a partner who could assist with the treatment of the patients with defibrillators. Consequently, Medtronic is now undertaking the remote monitoring of patients that have a defibrillator implanted. There is a percentage of the budget that is only received if some clinical, management, and efficiency outcomes are met such as decreasing the number of un-needed hospitalizations,” she recalls. “This is the genuine face of value-based healthcare!”

“There is a steadfast desire on the part of all stakeholders to fashion a new ecosystem where personalized precision medicine can flourish and go mainstream,” declares Alba Vergés, minister of health for Catalonia. “In view of the high up front price points for many of these supposedly high-added value therapies, it obviously makes sense to strike the sorts of performance related remuneration mechanisms that hold companies liable for results, so that is precisely what we are trying out and hopefully, if all goes to plan, we can become a bit of a showcase role model that others will one day seek to emulate.”

MEDTECH: IN THE DRIVING SEAT

In many respects, it is the medtech segment that lends itself most easily to a value-based healthcare model in that outcomes for engineered solutions are more predictive than for drugs. It therefore comes as little surprise that it is the medical device developers and healthcare systems integrators that find themselves positioned right on the fault line between the classic and future worlds of medical science, and with the most to offer in terms of helping Spain to accomplish the transition.

Examples abound of medtech developers attempting to harness the Spanish healthcare system as a proving ground to roll out holistic, and in some cases turnkey, offerings that...
extend well beyond the mere provision of medical devices. “We identify an excellent opportunity to become a genuine strategic partner to hospitals, delivering comprehensive solutions from the vial to the vein that ensure the administration of the correct therapy to each patient,” reveals BD group’s Lourdes López Jiménez.

Johnson & Johnson has even developed a program called ‘Care Advantage’ which focuses on value-based healthcare to drive value results along with enhanced clinical and patient satisfaction. “We did this because we realized Spanish hospitals and institutions are not only demanding that we develop top-notch products, but also expecting that we contribute to increasing their efficiency and clinical outcomes, alongside improving the patient experience,” recalls country head, Rocco de Bernardis. “Recognizing that Spain is afflicted with one of the highest rates of obese children in Europe – 19 percent of boys and 17 percent of girls – and conscious that a full seven percent of all healthcare spending in Spain is related to obesity, we have been scoping in on the deployment of bariatric surgery as a tangible and effective way to reduce the chronic disease burden and alleviate financial stress on the healthcare apparatus,” he adds.

Gremlins in the Machine?

That does not imply that everything is plain sailing, however. On the contrary, implementation of these grand visions can be a tortuous and risk strewn process not for the faint hearted or those without deep pockets. Many medtech actors fret that prevailing public tendering channels in many provinces are no longer fit for purpose and more often than

**More Than Just a CRO**

In 2018, INC Research and inVentiv Health merged to create Syneos Health, which now stands as the industry’s only fully integrated biopharmaceutical solutions organisation which includes one of the world’s top three global clinical research organisations (CRO) as well as a contract commercial organisation (CCO). Rosa Gonzalez Galindo explains what sets Syneos apart from its competitors.

Gonzalez Galindo notes three key points that set Syneos apart as a service provider. She asserts that, “The first is our biopharmaceutical accelerator model that allows us to support clients across the entire drug development and commercialization continuum”. Gonzalez Galindo adds, “Because our clinical and commercial experts live under the same roof, they are able to constantly share real-world knowledge and insights that lead to getting the job done better, smarter and faster increasing the likelihood of regulatory approval and maximizing commercial success”.

The second key strength relates to Syneos Health’s organizational structure, which actually mirrors that of their clients in the pharmaceutical industry, with dedicated specialists in various therapeutic areas. As Gonzalez Galindo states, “we have dedicated business units focused on CNS, Oncology and General Medicine. All employees in each of the business units, from the business unit head to the clinical research associates (CRAs) are specialized therapeutically.”

Gonzalez Galindo concludes by outlining Syneos Health’s third differentiator, ‘The Trusted Process’. She explains, “this is our proprietary, metrics-driven methodology initially developed to manage all aspects of a clinical study. This unique, four-step approach delivers faster results while maintaining data integrity and reducing operational risk and variability”.

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**SPANISH MEDTECH MARKET EVOLUTION**

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not prove counterproductive. “Public sector procurement, which constitutes some 75 to 80 percent of health system contracts, generally takes place in the form of single product tendering which is thoroughly ill suited to our ambition of serving up integrated solutions involving multiple customers and entire chunks of the care continuum,” observes B. Braun’s Jesús Donado.

“One of the challenges we still commonly encounter is having to quantify the savings our solutions will bring in order to justify added-value to the authorities, particularly in the public sector where the financial boundaries are strictly defined and there are few clear-cut ways to track and prove the full scope of performance benefits delivered,” admits Beckman Coulter’s Herraez.

“I do not know of any country that can do this well, and Spain is no exception. The inconvenient truth is that the public system struggles with measuring healthcare outcomes, and even healthcare costs so it becomes very difficult to assess performance in an objective manner,” concurs Maria Vila of Medtronic, “The first step is therefore finding ways to demonstrate to the authorities that we can truly create value, and then the second step is to actually manage to sell them that value,” she insists.

In the eyes of many, the primary bottleneck compromising the system’s ability to measure end outcomes, calculate total costs and thus fairly adjudicate comparative value, tends to be the absence of an enabling digital infrastructure where data can be systematically compiled, interpreted and shared. “Value based care ultimately hinges upon good data hygiene and harnessing the power of big data firstly requires it to be collected, and to be standardized into a particular form... One of the barriers we run up against in Spain is that every single hospital produces their own data in their own idiosyncratic way and until this can be ironed out an a decent level of interoperability can be attained, the prospects of wholesale progress remain slight,” stresses Jaime Vives, general manager of Roche Diagnostics.

BUILDING AN INNOVATION HUB

With a robust manufacturing footprint and respectable sales growth in place, Spain is now looking towards creating a stronger innovation ecosystem.

Nowhere is this more apparent than in the region of Catalonia. As Biocat CEO Jordi Naval points out, “more than 60 percent of all the healthcare and biotech innovation happening in Spain is taking place in Catalonia.”

Melqui Calzado, general secretary of Catalonia Bio and Health Tech, an association representing biotech, pharma, medical devices, and e-health companies in the region, feels that three key topics will be crucial to further promoting the development of innovation in Catalonia. “The first is innovation itself, as the biotechnology sector can only move forward with innovative products.” Calzado continues, “The second topic is entrepreneurs, not only in regard to start-ups, but also mindset. A scientist can be working for a big pharmaceutical company and still have an entrepreneurial mindset.” He concludes, “The third topic is networking. We have 160 odd members and we are constantly looking to generate opportunities for them to collaborate and learn from each other.”

For Biocat’s Naval, what Catalonia lacks is executives. He explains, “In Catalonia, money is not the major challenge; neither is science, administration, or framework. There are excellent professionals at the regulatory and operational level, however, the region needs more CEOs and CMOs; serial entrepreneurs and business leaders in the biotechnology industry.”

Beyond Catalonia, Cristina Garmendia, whose biotech firm Genetrix was acquired by Takeda in 2018 for EUR 520 million, reasons that Spain’s financial institutions are not yet commensurate with the level of innovation coming out of the country. She notes that, “What we need is for our scientific power to drive economic growth. The issue that persists in Europe, particularly in Spain, is the lack of financial institutions to keep up with the fast growth of science and research. Therefore, it is crucial to expose start-ups to national and international venture capital (VC) because a company can’t go from public subsidies to bank loans, they need an intermediate system to improve the financial chain.”

Success stories such as Genetrix are critical to attracting further investment into Spain’s innovative biopharmaceutical industry according to Joël Jean-Mairet, general partner at VC fund, Ysios Capital.

These success stories, “are key, as they will attract more VC to the market,” he suggests. Jean-Mairet is optimistic about Spanish innovation’s current growth trajectory, stating that, “in terms of human capital, Spain faces the same challenges as other European countries. In our experience, professionals enjoy Spain and, once you can guarantee large funding rounds and disruptive innovation, the top talent will follow. In the last few years, we have been getting more and more calls from international VC firms asking about top local companies, indicating that Spain is now firmly on the VC map for life sciences.”
The Shrinking Disconnect in Digital Therapeutics

There is rapidly growing and sizeable evidence which shows that innovating is the most important factor in pharmaceuticals. The industry is a field which itself has developed and evolved on the basis of disruption and innovation.

Digital therapeutics (DTx) are at the cutting edge of this new disruptive tech-led industry. They form part of the wider jigsaw of patient support and treatment services that are seeking to enhance and optimize medicine and medical treatment for those at its center—the patients.

In my former role as a Governmental advisor for the US Patient Protection and Affordable Care Act—also known as Obamacare—I helped to provide insights on how new technologies could be used to improve and reform the US healthcare system. These kinds of digital interventions enable better patient outreach, sign-up rates, and, crucially, the ability to capture real-world data (RWD).

As evidence-based interventions, driven by state-of-the-art software programs, DTx contribute to the prevention, management, and treatment of a plethora of medical conditions and illnesses. By their very nature, they also have the ability to capture RWD on usage, engagement, disease progression, healthcare outcomes, and therapeutic efficiency—and in doing so, can demonstrate value to patients, payers, and healthcare providers.

Integral to the successful roll out of DTx is the need for a solid digital therapy management platform. Such a platform integrates the tools and support needed for the holistic treatment of the patient’s condition.

These platforms can help to empower patient self-management, enhance clinical care coordination, and capture RWD.

By integrating behavioral science into these platforms, we can also get a better understanding of both the needs of the patient and of their clinicians, when particular treatments are prescribed.

I believe that the pharmaceutical industry is now slowly getting up to speed on digital interventions. What, in the past, was a software solution developed by startups, has now become the core focus of attention of much larger industry players who are realizing the importance, both from a financial and public health perspective, of producing better outcomes for patients.

The reality is that life science companies require RWD, and relevant statistics that show the value delivered to the healthcare system beyond what can be seen through clinical trials alone. As a result, there has been an increased focus on digital technologies that can generate data to demonstrate value. For the pharma industry, this has meant a shift in viewing digitally-enabled interventions from a “nice to have” to a “must have.”

Challenges

Until recently, there has been a disconnect between startups, pharma companies, and payers. Going forward, partners working together on DTx will need to agree on their definition of, and the opportunities in DTx.

It is crucial to put the patient at the center of any solution that is provided—imagine yourself as a patient with hypertension who is taking four different drugs to manage your condition. Assuming each of the drugs is supported by an app, patients will not want to be using four different apps.

For DTx to work at scale, and to gain broad adoption by patients, they need a solution that will combine the various elements of their treatment to support them to effectively manage their condition and achieve the best possible healthcare outcome.

Crystal ball gazing

One thing is certain, we will continue to see regulatory bodies and industry associations adapt and define the evolving DTx space for some time to come.

Recent examples include the FDA’s Digital Health Innovation Action Plan, the Digital Therapeutics Alliance, and the Digital Medicine Society.

There is now a real opportunity for pharma companies to think about breaking down the historical barriers between them to collaborate in designing digital solutions that put the patient, their journey, and their experience at the center. It is here that digital therapy management platforms can play the most important role.

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healthcare technology leadership

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