Q1

ALLIANCE for Regenerative Medicine

2016

Quarterly Data Report

on gene and cellular therapies and the regenerative medicine sector

ALLIANCE for
Regenerative Medicine

The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

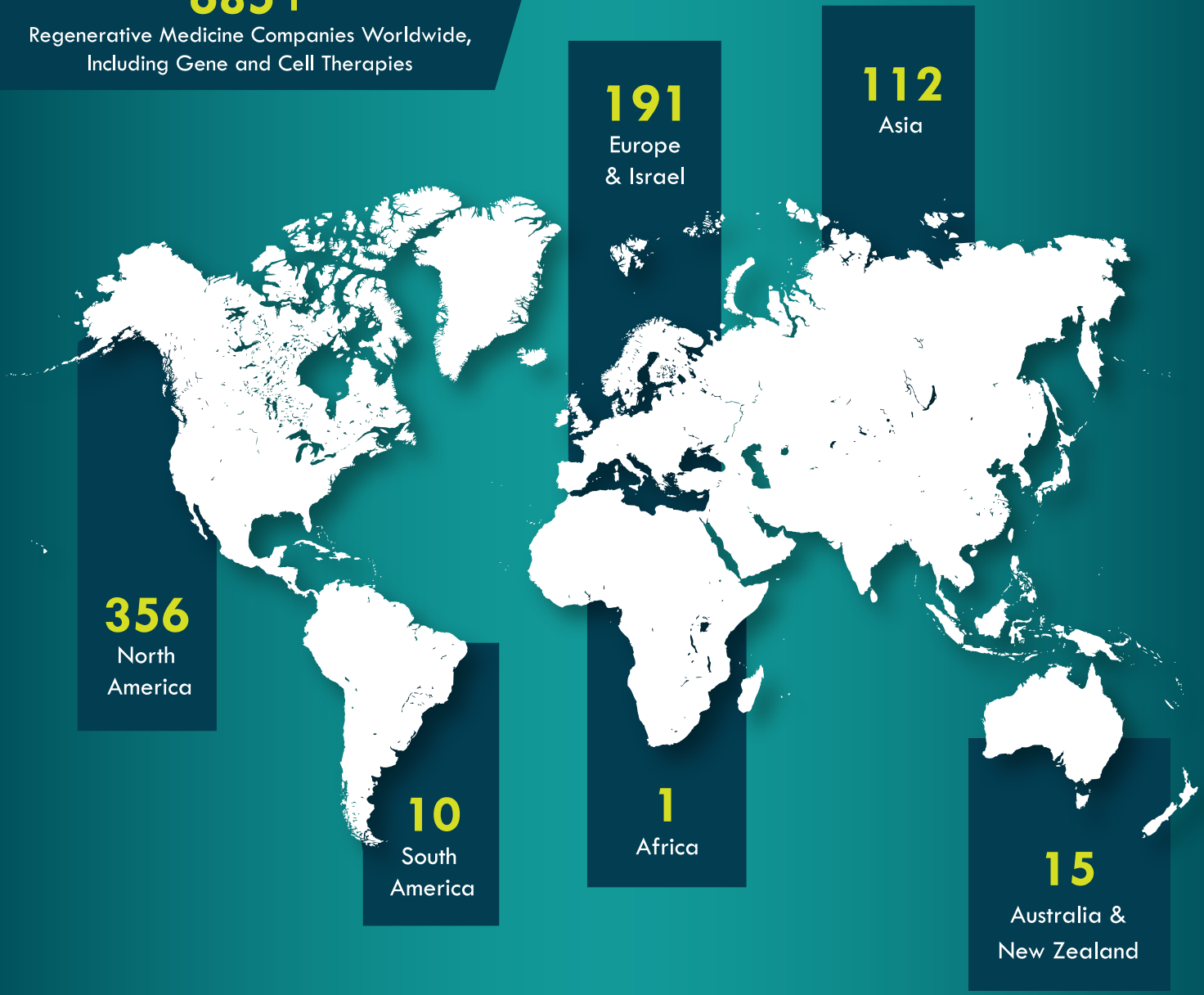
By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field.

alliancerm.org

Table of Contents

Industry Overview

685+
Regenerative Medicine Companies Worldwide, Including Gene and Cell Therapies



Industry Overview

While financial markets in the first quarter of 2016 had a significantly slower start than the previous year, companies active in cell therapy, gene therapy and other regenerative medicines disclosed an array of strategic acquisitions and partnerships, as well as several notable IPOs in our sector.

Astellas Pharma completed its $379 million acquisition of Ocata Therapeutics, and, in addition, Juno announced that it had acquired AbVitro, offering the opportunity to use a single cell sequencing platform to enhance the recognition of cancer antigen targets as well as to help assess cancer patients' immune systems while they undergo treatment. Further, Spark Therapeutics acquired its longtime collaborator Genable Technologies in an agreement that includes the orphan drug RhoNova, designed to treat rhodopsin-linked autosomal dominant retinitis pigmentosa. Editas Medicine raised $108.6 million in 2016's first U.S. IPO. Also in this quarter, AveXis, Inc. raised $95 million in its February IPO, and MaxCyte raised $15 million on the London stock exchange.

At the start of January, Japan's Healios K.K. and Athersys, Inc. entered into a partnership and license agreement, which includes using Athersys's MultiStem cell therapy to treat ischemic stroke. In February, Baxalta signed a $1.7 billion deal with Precision Biosciences to develop CAR-T therapies for novel targets in oncology, with an upfront payment of $105 million to Precision Biosciences. Also in February, Celgene licensed bb2121 from bluebird bio, Inc., an autologous CAR-T cell product targeting B cell maturation antigen, in a deal worth $10 million.

Q1 saw a number of agreements between regenerative medicine companies and academic, government or non-profit organizations. Early in the quarter, GE Healthcare and FedDev Ontario announced a $40 million (CAD) investment into the Centre for Commercialization of Regenerative Medicine's center for advanced therapeutic cell technologies in Toronto. In addition, ImmunoCellular Therapeutics signed an agreement with University of Maryland focused on the potential to improve the efficacy of dendritic cell, T-cell and combination immunotherapies for cancer; AGTC agreed to work closely with the BCM Foundation to hunt for the key to Blue Cone Monochromacy and Kiadis Pharma and the Leukemia & Lymphoma Society agreed to work towards the development of Kiadis's ATIR101 as an adjunct treatment. Also, the National Institute of Allergy and Infectious Diseases will be testing Pluristem's allogeneic mesenchymal stem cell product PLX-R18 as a treatment for acute radiation syndrome. And this is just to name a few!

As Q2 picks up speed, we look forward to tracking the evolution of the expanding number of companies active in this sector, new partnerships among the more established groups and the initiation of new clinical trials and funding for numerous diseases with no cure.

– Patricia Reilly
Executive Director – Medtrack

– Nancy Dvorin
Managing Editor – IN VIVO, Start-Up and Medtech Insight

Informa Business Intelligence,
Pharma and Healthcare

Financings

TOTAL GLOBAL FINANCINGS

$1.2B raised Q1 2016

GENE & GENE-MODIFIED CELL THERAPY

$519.6M raised Q1 2016

TISSUE ENGINEERING

$48.2M raised Q1 2016

CELL THERAPY

$766.8M raised Q1 2016

Total EU Financings

TOTAL EU FINANCINGS

$65.4M raised Q1 2016

GENE & GENE-MODIFIED CELL THERAPY

$23.5M raised Q1 2016

TISSUE ENGINEERING

No recorded financings in Q1 2016

CELL THERAPY

$49.9M raised Q1 2016

The gene and cell therapy and the broader global regenerative medicine sector had several notable financing events in Q1 2016, despite a downturn in the overall financial markets:

Examples of key financings: Q1 2016

IPOs:

- **Editas Medicine IPO raises $108.6M** – *February 8, 2016*
- **AveXis, Inc. IPO raises $95M** – *February 10, 2016*
- **MaxCyte, Inc. IPO on London Stock Exchange raises $15M** – *March 29, 2016*

Corporate partnerships & acquisitions:

- **Baxalta signs $1.7B agreement with Precision Biosciences, Inc., $105M upfront** – February 25, 2016
- **Celgene exercises $10M option with bluebird bio for CAR-T cell therapy** – February 17, 2016
- **Healios K.K. and Athersys, Inc. enter into $240M partnership for treatment of stroke using Athersys MultiStem Therapy, $15M upfront** – January 8, 2016

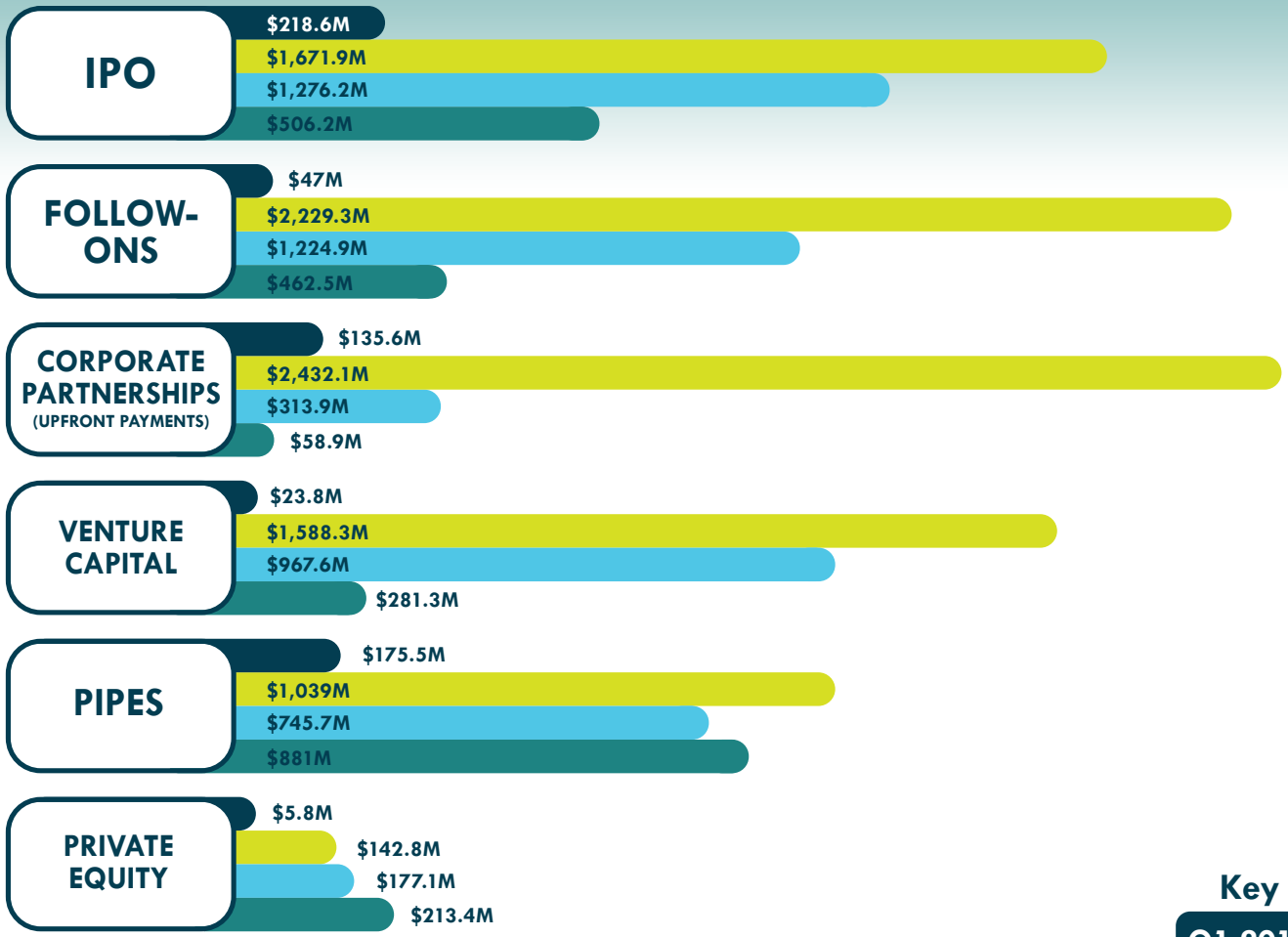
EU deals & financings:

- **GSK and Miltenyi Biotec establish cell and gene therapy collaboration, includes discovery program for CAR-T cell-based oncology therapies** – March 16, 2016
- **TiGenix raises €23.75 million in private placement to advance Cx601 marketing authorization approval process in EU** – March 10, 2016
- **Adaptimmune and GSK expand their strategic immunotherapy collaboration to $500M from $300M** – February 2, 2016

**Total amount raised represents sector-wide figures; please note that some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups.*

Financings

Total global financings by type, by year



M&A: Q1 2016

Key

- Q1 2016
- 2015
- 2014
- 2013

Patient Outreach & Education

Jennifer Kim Cutie
Associate Director,
Patient Advocacy
Voyager Therapeutics

Just as each patient's journey is unique, every patient group or organization has its own history, focus and expertise, and therefore each group's priority issues may differ. Early conversations with patients and patient organizations are crucial in the development of novel therapeutics. Ultimately, our goal is to create therapies that provide meaningful, positive change in the lives of patients and their families.

We are able to gain a great deal of information from reviewing publications and speaking with clinical and scientific experts, but without the direct input of patient groups and patients, we are missing vital pieces of the puzzle. Patients have a unique and critical fund of knowledge around the day-to-day experience of living with a disease that lends real world perspective to our efforts, and their presence serves as an important reminder of the people behind our everyday work.

Michele Rhee
Head of Global Patient Affairs
bluebird bio

The primary objective of the patient advocacy and affairs function within bluebird bio is to do our part to address the unmet needs of our patient communities. Our function works in the overlap between the patient community's unmet needs and the company's strategic goals. This transparency and clarity around our patient advocacy creates a trusting basis for all interactions and collaborations, allowing us to partner in more creative and out-of-the-box ways, which means that we have the potential to have more impact and help more people.

Julie Venners Christiansen
Head of Global Patient Advocacy,
Gene Therapy, R&D
Rare Disease Unit
GSK

Patient advocacy groups have a common goal with the scientific and pharmaceutical industry in that they want effective, innovative therapies brought to market that will offer a better life for patients. In the gene therapy area, GSK has focused on alignment with patient advocacy groups that can result in positive outcomes for the patient/family caregiver, such as the need for family respite care and early diagnosis tools such as newborn screening.

Patient Outreach & Education

Jean Walsh
Patient Advocate, Ambassador
Friedreich's Ataxia Research Alliance

The ARM Roundtable for Rare Disease further reinforced my growing understanding of the importance of patients and caregivers in the process of finding regenerative cures and treatments. I was overwhelmed by how many people there were, all with diverse backgrounds and skills, committed to regenerative cures and treatments. There are a lot of people collaborating to help rare disease patients!

Barbara Wuebbels
Vice President, Patient Advocacy
Audentes Therapeutics

We have engaged with patient communities since the first week we opened our doors as a company. Patient engagement is very valuable in developing new therapeutics, as it is critical to find out what patients and/or parents really want a new drug or treatment to do for them, or to what lengths they're willing to go for a clinical trial. In some cases, it may be entirely different from what the company thinks they want!

For example, we once designed a trial involving a new treatment, which, we believed, carried some potential risks. We thought the young participants' parents should stay in proximity to the clinical site for the duration of the trial, about 48 weeks. The parents quickly told us they could not do that because of work and other family obligations. With this in mind, we redesigned the trial so that they only stayed for 12 weeks, which is the maximum medical leave. If we had not met with parents, we would never have enrolled the trial!

Clinical Trials

669
Clinical trials underway at the end of Q1 2016

Ph. I: 200
Ph. II: 401
Ph. III: 68

Current Clinical Trials by Therapeutic Category: Q1 2016

- Nearly 40% of current clinical trials are in oncology
- More than 12% are in cardiovascular

Major Milestones & Key Data Events

Examples of major milestones and key data events: Q1 2016

- U.S. FDA grants orphan drug designation to Adaptimmune's T-cell therapy targeting NY-ESO for treatment of soft tissue sarcoma – March 30, 2016
- BioMarin receives European orphan drug designation for BMN 270, first investigational AAV-factor VIII gene therapy for patients with hemophilia A – March 24, 2016
- Dimension Therapeutics receives positive opinion for European orphan drug designation for DTX301 for the treatment of ornithine transcarbamylase deficiency – March 17, 2016
- TiGenix announces positive 52-week phase III results of Cx601 in complex perianal fistulas in Crohn's disease patients – March 7, 2016
- First allogeneic cell therapy product launched in Japan by Mesoblast licensee JCR Pharmaceuticals – February 24, 2016
- Mesoblast announces its proprietary Tier 1 mesenchymal stem cell product candidate remestemcel-L demonstrated increased survival in children with acute GVHD – February 21, 2016
- One-year results from phase II stroke study of Athersys MultiStem cell therapy demonstrate a significantly higher rate of complete or nearly full recovery – February 17, 2016
- Amarantus receives orphan drug designation from the U.S. FDA for Eltoprazine in the treatment of Parkinson's disease levodopa-induced dyskinesia – February 10, 2016
- U.S. FDA grants breakthrough therapy designation for Adaptimmune's affinity enhanced T-cell therapy targeting NY-ESO in synovial sarcoma – February 9, 2016
- Asterias Biotherapeutics receives orphan drug designation for AST-OPC1 for the treatment of acute spinal cord injury – February 4, 2016
- Immunocore's IMCgp100 granted orphan drug designation by U.S. FDA for the treatment of uveal melanoma – January 25, 2016
- Dimension Therapeutics announces orphan drug designation of DTX301 for the treatment of ornithine transcarbamylase deficiency – January 6, 2016

Industrialization & Manufacturing

Sector leaders offer their insights on industrialization requirements for the sector, logistical and manufacturing challenges and how their respective organizations are addressing these issues.

Cindy Collins
CEO, Purification & Analysis
and Cell Therapy
GE Healthcare

The biggest issue in manufacturing, I believe, is addressing the potential for errors by de-risking the process. As the patient's cells progress from the first to the last unit operation in a multi-step process, it becomes more and more precious, because the investment made to create the therapy accrues at each step and offers the potential to treat or cure the patient. Any product or technology that helps to remove the opportunity for error along the cell processing workflow, whether that risk is one of loss, contamination or mix-up, will help cell therapy become mainstream. To accomplish this, tool providers like GE are increasingly inventing more closed, disposable, connected and automated work-flows that reduce errors within the production process. And part of that automation are digital solutions that can not only provide walk-away production, but could also provide predictive analytics and integration of analytics, quality systems and documentation.

Aaron Dulgar-Tulloch
Director, BridGE@CCRM
(CCRM-GE Healthcare Partnership)
CCRM

Translating a therapy from the clinic into industrial-scale manufacturing is a complex and time-consuming process. BridGE@CCRM is focused on addressing these challenges by bringing therapy manufacturers and technology developers together to drive speed and consistency through collaborative process and technology development. The resulting processes will be simplified and integrated, reducing commercialization time and improving product quality.

Thomas Fellner
Head of Commercial Development,
Cell Therapy
Lonza

The biggest manufacturing challenge is scaling the processes without losing product quality. In some cases this scaling requires significant changes to manufacturing platforms. For instance, moving from 2D to bioreactors and the concomitant use of appropriate downstream solutions. These changes are challenging not only from a hardware and know-how perspective, but also from a product comparability perspective.

For these reasons, Lonza is putting a lot of effort into developing scalable platform solutions for allogeneic and autologous therapies, while having the know-how and analytics in place to address product comparability issues. As the field develops, using scalable platforms from the start (pre-clinical and early clinical), will result in fewer comparability issues.

Industrialization & Manufacturing

Richard Grant
Global Vice President,
Cell Therapy
Invetech

Each company's process has its own challenges, but common to all is choosing scalable technologies that can be closed and that will meet or exceed the outcomes of the manual process in performance and repeatability. Planning for commercial scale should focus on not getting locked in to manufacturing processes that will cost too much to replicate or cannot scale to meet commercial volumes. It is important to focus on matching equipment capacity and utilization to optimize the organization's ability to operate to maximum efficiency.

Invetech analyzes the current (and intended) manufacturing process, identifies the best scalable manufacturing solutions by integrating off-the-shelf equipment and custom-design systems to deliver an optimized manufacturing process. The aim is to automate and close as many steps as possible and interface with software systems to facilitate electronic batch record keeping.

Alex Vos
CEO
PharmaCell

As a Contract Manufacturing Organization, PharmaCell is heavily engaged in autologous and allogeneic cell therapy manufacturing. We are convinced that a strong push to automation in autologous and to bioreactor-based 3-D cell culture solutions for allogeneic will be key to develop cost-effective therapies.

Over the years PharmaCell has been working with clients particularly in late-stage, early-commercial programs to develop end-to-end cross-border supply chain solutions. This integrated perspective from the starting material (e.g. apheresis or biopsy) to the bed-side is critical as doctors and hospitals expect an "Amazon-like" experience also for these highly complex therapies, specifically as they themselves may feel relatively uncomfortable handling these challenges. In moving from clinical to commercial manufacturing, cellular assay validation and availability of high-throughput patient scheduling systems are further issues that need to be addressed as well. PharmaCell has worked in a number of projects on these issues and now has integrated these perspectives in our work flows.

Stephen Ward
Chief Operating Officer
Cell & Gene Therapy Catapult

One of the key barriers to the growth of the cell and gene therapy industry is the ability to grow cells reliably and cost effectively at scale. The approach of the Cell and Gene Therapy Catapult (CGT) is broadly two fold: firstly, to invest in process and analytical systems and toolkits that can be deployed to generate robust and controllable processes that deliver products at a cost that is commensurate with reimbursement reality, and secondly, to provide access to large-scale GMP facilities with a capacity to deliver products for pivotal clinical trials and early commercial supply. The UK is strongly positioned for early clinical phase manufacturing and the large-scale capacity center will help in growing a UK-based global industry.

The large scale manufacturing center, which is currently being constructed and will be managed by CGT, will open in mid-2017 and will be used by companies for the manufacture of late phase clinical trial and initial commercial supply of both cell and gene therapies. The concept of a supported and controlled-environment facility for multi-collaborator use at scale is of great interest to industry, as it enables them to retain control of their process without the capital investment of an own build. Companies are also attracted by the idea that the capabilities and services of CGT, including process and analytical development as well as regulatory and clinical support are readily accessible.

Current Regulatory & Legislative Priorities

Global reimbursement issues – advancing specific proposals to promote coverage, coding and payment policies that facilitate development of and patient access to gene and cellular therapies and other regenerative medicine products.

- Identifying potential policy and legal impediments to coverage and reimbursement
- Conducting formal analysis of payment models to facilitate access and adoption
- Outreach to U.S. CMS, private payers and EU HTA bodies and reimbursement agencies

Advocating for ARM's provisions to be included in congressional efforts to streamline the drug development and review process to ensure patient access to safe and efficacious regenerative medicine products. This includes:

- *Development of standards for gene and cellular therapies and the regenerative medicine sector.* The U.S. Senate Committee on Health Education Labor and Pensions (HELP) recently passed legislation that calls on FDA to work with stakeholders to develop standards for regenerative medicine. The lack of standards has been identified by FDA, ARM members and others as a key obstacle to product development, evaluation and review. This will support ARM's efforts to establish a standards coordinating body to develop and implement material and process standards essential to the timely advancement and approval of new regenerative therapies to treat major unmet medical needs.
- *A modified role for the NIH-Recombinant DNA Advisory Committee (RAC)* to ensure the streamlined oversight of gene therapy clinical trials.
- *Combination products.* ARM advocates for reforms to optimize the review process for combination products or other situations when more than one review center at FDA is involved in product evaluation and review. ARM is supportive of U.S. Senator Johnny Isakson's (R-GA) Combination Products Innovation Act, now a part of the Senate's Medical Innovation package.
- *Potential new pathway to market.* ARM will continue to work with policymakers to improve the efficiency of the approval pathway for regenerative medicine and advanced therapies products. ARM supports a predictable and transparent regulatory pathway to market for safe and efficacious products and will be working to develop policies to further that objective.

International regulatory convergence – ARM is working to establish and maintain a predictable and efficient regulatory review and approval process in the U.S. and EU to promote greater international harmonization.

Input to the EU public consultations on the new Priority Medicines Scheme (PRIME); the Commission notice on Articles 3, 5 and 7 on Regulation (EC) N°141/2000 on orphan medicinal products.

- In addition, ARM is drafting a white paper on environmental risk assessments for GMOs.

Standards development – ARM and the members of the international regenerative medicine Standards Coordinating Body (SCB) steering committee are preparing an initial work plan for the group to address important near-term requirements. The group is also working with NIST and other federal agencies to finalize a public–private partnership model to support these activities.

- ARM is participating in and providing support to the ISO TC-276 global deliberations on standards for biological products, which includes a significant focus on analytics — cell counting and cell characterization, as well as standards to support bioprocessing and manufacturing activities. The international working groups are meeting the week of May 9 in Washington DC.

Gene editing & related bioethics issues – ARM is working closely with the National Academy of Sciences (NAS), and has provided a detailed industry perspective on the state of commercialization of somatic cell gene editing technologies. This information will be included in their upcoming consensus report to be released by EOY 2016.

PDUFA reauthorization recommendations – The current Prescription Drug User Fee Act (PDUFA) version V is set to expire in 2017.

- ARM has convened a working group to discuss ARM's goals for the reauthorization.

ARM will comment on and help to shape FDA's draft guidance on minimal manipulation and homologous use on human cell and tissue products. ARM will also present at the FDA public meeting in September 2016.

Special thanks to our data partner:

informa

Informa is one of the world's leading knowledge providers. We create and deliver highly specialized information through publishing, events, training, market intelligence and expertise, providing valuable knowledge to individuals, businesses and organizations around the world.

Informa provides authoritative research and analysis and up-to-the-minute business news, comment and events for all sectors of the healthcare, medical and life sciences communities. Informa Business Information (IBI) is one of the world's leading providers of industry and drug news, analysis and data to the global pharmaceutical industry.

ALLIANCE for Regenerative Medicine

Alliance for Regenerative Medicine
Contact: Lyndsey Scull | Senior Director, Communications | lscull@alliancerm.org
alliancerm.org