Q2

ALLIANCE for Regenerative Medicine

2016

Quarterly Data Report

on gene and cellular therapies and the regenerative medicine sector

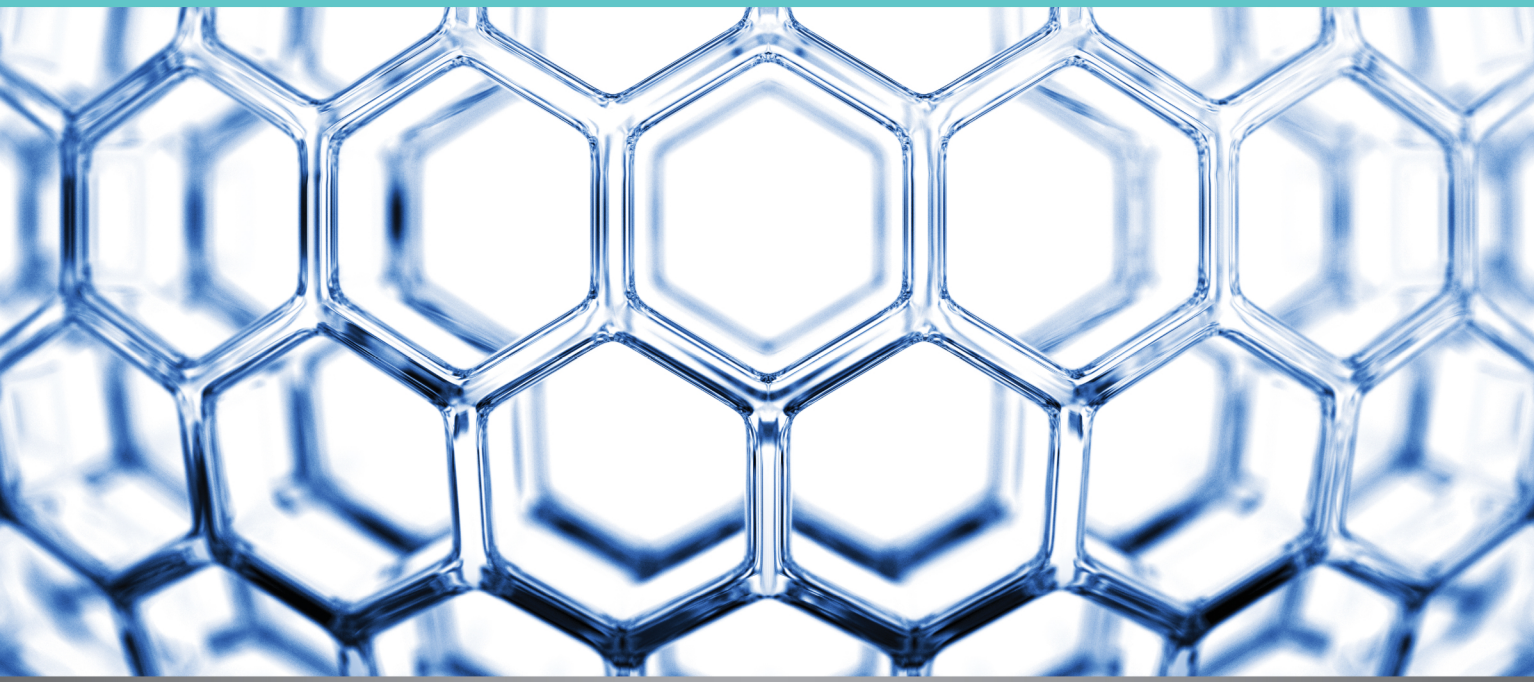
ALLIANCE for
Regenerative Medicine

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.....2-3

Financings.....4-5

Reimbursement & Market Access.....6-7

Clinical Trials.....8

Major Milestones & Key Data Events.....9

Establishment of Industry-Wide Standards.....10-11

Current Regulatory & Legislative Priorities.....12

Industry Overview

704+
Regenerative Medicine Companies Worldwide, Including Gene and Cell Therapies

Industry Overview

Q2 2016 took off with exciting prospects for companies active in gene therapy, cell therapy, tissue engineering and the broader regenerative medicine sector. Numerous deals, partnerships and key financings took place April through June 2016, highlighting the sustained interest in this expanding field.

In April, the University of Pennsylvania joined with the Parker Institute for Cancer Immunotherapy to accelerate development of new treatments for cancer, backed by a $250 million gift from the Institute. This announcement was closely followed by UPenn's news of the first proposed human clinical trial using CRISPR-Cas9 technology to disrupt the genes for PD-1 and native T cell receptors in a small trial for patients with myeloma, sarcoma or melanoma who stopped responding to treatment.

In addition, Biogen announced an up-to $2B research deal with UPenn to develop therapeutic candidates using both new AAV gene delivery vectors and genome editing targeting eye, skeletal muscle and the CNS.

Industry partnerships picked up the pace in Q2 with several dozen announced. Regeneron and Intellia Therapeutics joined forces in a $125 million licensing deal to advance CRISPR/Cas9 technology with a focus on liver diseases. Celgene will pay $50 million to develop Juno's CD19 (CAR-T cell) program outside the U.S. and Takara's RetroNectin technology, which facilitates highly efficient gene transduction by retrovirus vector, has been licensed to Kite Pharma. Kite also entered a partnership with Cell Design Labs, which is exploring 'on/off switches' in cell signaling for Kite's CAR-T cell programs.

Several early-stage financings rounds took place in Q2, including Kite's participation in Cell Design Labs' $34.4 million Series A financing and Homology Medicines, touting a new approach to gene editing, secured $43.5 million in a Series A funding. Other notable financings went to Agenovir (CRISPR/Cas9 and other nucleases to treat persistent viral infections), AiVita (stem cells), Orchard Therapeutics (gene therapies for orphan diseases) and Nouscom (immunotherapies). TxCell raised $22.47 million in private placement, and signed an agreement with Lubeck Institute of Experimental Dermatology for CAR-Treg-based cellular immunotherapy for bullous pemphigoid, a rare autoimmune disease. Organogenesis, which specializes in wound care, raised $30 million from existing investors for portfolio expansion and company growth. OvaScience closed a $57.56 million public offering of common stock and Lion Biotechnologies raised $100 million in private placement funding. In IPOs this quarter, Intellia Therapeutics raised $124 million to support their proprietary CRISPR/Cas9 gene editing technology.

Mid-year, we're seeing numerous signs of sustained momentum for the industry, with some highly-anticipated milestones to come. We look forward to what further advancements 2016 has in store.

– Patricia Reilly
Executive Director – Medtrack

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

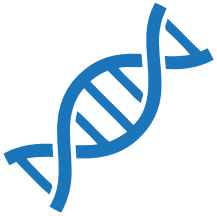
Informa Business Intelligence,
Pharma and Healthcare

Financings

Total Global Financings

TOTAL GLOBAL FINANCINGS

$2.5B raised 1H 2016
$1.3B raised Q2 2016



GENE & GENE-MODIFIED CELL THERAPY

$1.3B raised 1H 2016
$753.4M raised Q2 2016

TISSUE ENGINEERING

$88.1M raised 1H 2016
$39.9M raised Q2 2016

CELL THERAPY

$1.5B raised 1H 2016
$785.6M raised Q2 2016

Total EU Financings

TOTAL EU FINANCINGS

$227.1M raised 1H 2016
$161.7M raised Q2 2016

GENE & GENE-MODIFIED CELL THERAPY

$152.6M raised 1H 2016
$129.1M raised Q2 2016

CELL THERAPY

$108.6M raised 1H 2016
$58.7M raised Q2 2016

Examples of key financings: Q2 2016

IPOs:

- **Intellia Therapeutics IPO raises $124.2M –** May 11, 2016

Corporate partnerships & acquisitions:

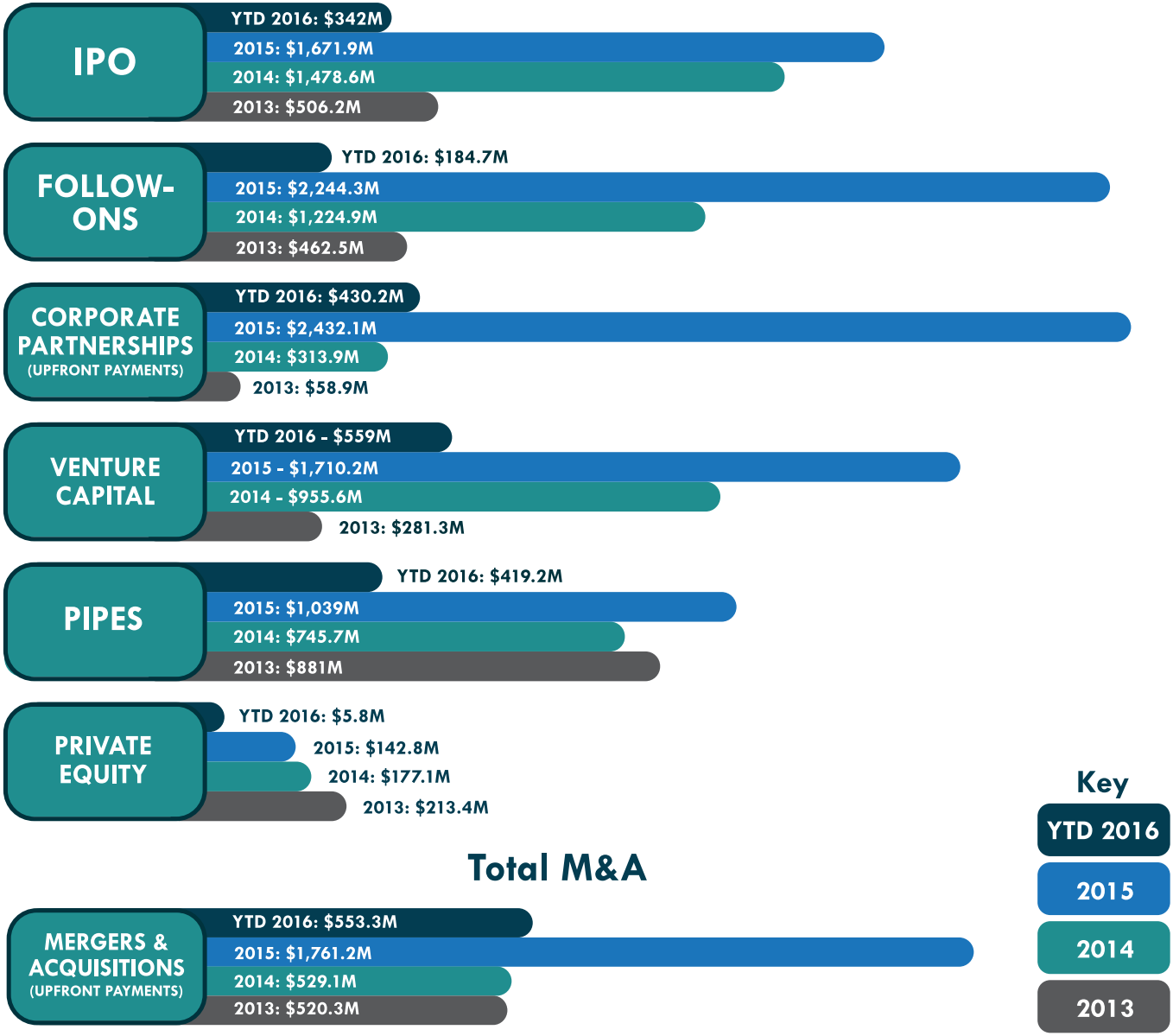
- **Lion Biotechnologies raises $100M in private placement –** June 8, 2016
- **Biogen announces up to $2B collaboration with University of Pennsylvania on multiple gene therapy programs, includes an upfront payment of $20M –** May 16, 2016

EU deals & financings:

- **CRISPR Therapeutics raises additional $38M as part of Series B financing –** June 24, 2016
- **TxCell raises $22.47 million in private placement –** June 17, 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.*

Total global financings by type, by year



Reimbursement & Market Access

Sector experts provide their insights on reimbursement and market access issues for disease-modifying and potentially curative therapies with short-duration dosing regimens.

Josh J. Carlson
Assistant Professor
Pharmaceutical Outcomes
Research and Policy Program
University of Washington

Addressing reimbursement and market access issues for gene and cell therapies brings up various challenges related to several key factors: new mechanisms of action, unfamiliarity among decision-makers, high upfront costs, method of administration and current lack of long-term data.

This particular moment in time is crucial when it comes to identifying and addressing challenges, as well as leveraging the many opportunities these products represent. Many of these products are expected to enter the market in the near-to-immediate future, but few are presently on the market and none with a large market share. Therefore, appropriate planning and discussion can facilitate informed and reasoned decision-making when it comes to coverage and reimbursement.

In this context, early and frequent discussions with the end users of data and products to best understand their needs as well as consideration of innovative coverage and reimbursement strategies, including coverage with evidence development and performance-based risk-sharing may help address these challenges and smooth the path toward clinical use.

Eric Faulkner
Vice President,
Precision and Transformative
Technology Solutions,
Evidera
Executive Director, Genomics,
Biotech and Emerging Medical Technology
Institute of the National Association
of Managed Care Physicians

The debate about how to deal with potentially curative therapies is driving global focus to all regenerative therapies right now. Some vanguard transformational products are beginning to hit the market and stakeholders see hundreds more on the way. How they are handled from a pricing and reimbursement perspective will influence how later products are addressed.

There are four key issues that make value demonstration and market access planning more complicated for regenerative therapies:

- Novelty and uncertainty – these are truly new and transformative therapies for which stakeholders have limited experience and significant uncertainty around outcomes
- Curative or long-term effect potential, which most therapies do not have to consider
- However, you have to prove it: this space stretches us in terms of how we think about characterizing clinical and economic benefits, presenting both opportunities and challenges
- Current global reimbursement and payment systems were not built with regenerative therapies in mind, requiring manufacturers to be more diligent, creative and consider all options

Continued on page 7

Continued from page 6

Global stakeholders are just at the tip of the iceberg in terms of thinking about how to address regenerative and single administration, potentially curative therapies. We are also in the midst of seismic transformation of global health systems to address value and cost dimensions of care. As these changes take place, the door for new ideas on how to address these transformative technologies is open. Now is a key time to be around the table as the "rules of the road" for reimbursement of regenerative medicine products are currently under consideration in the global arena.

Ted Slocomb
Vice President,
Commercial Planning
Audentes Therapeutics, Inc.

A rich pipeline of clinical stage products currently exists. They have the potential to be transformative for many rare, deadly and costly diseases. Patients should have the earliest opportunity to benefit from these innovations; it is therefore important that adoption of these new therapies not be hindered.

It is also critical that the first launch of these new products, such as AAV gene therapy and gene-modified cell therapies, set a strong precedent by demonstrating real world effectiveness and value. This should encourage a view of these products that acknowledges their long-term value, which will be central to establishing a successful reimbursement model.

728
Clinical trials underway at the end of Q2 2016

Ph. I: 223
Ph. II: 439
Ph. III: 66

Current Clinical Trials by Therapeutic Category: Q2 2016

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

Examples of major milestones and key data events: Q2 2016

- Pluristem reports data showing PLX-PAD cells effective in treating Duchenne muscular dystrophy – June 22, 2016
- Adaptimmune receives positive opinion for Orphan Drug Designation in EU for SPEAR T-cell therapy targeting NY-ESO for treatment of soft tissue sarcoma – June 20, 2016
- Fate Therapeutics announces FDA Fast Track designation for ProTmune for the reduction of incidence and severity of acute GvHD in patients undergoing allogeneic hematopoietic cell transplantation – June 20, 2016
- Sangamo BioSciences announces FDA clearance of IND application for SB-913, ZFN-mediated genome editing treatment of MPS II – June 20, 2016
- AGTC announces Orphan Medicinal Product Designation in the EU for gene therapy to treat X-linked retinitis pigmentosa – June 7, 2016
- Kite Pharma grants access to EMA's Priority Medicines (PRIME) regulatory support for KTE-C19 in the treatment of chemorefractory diffuse large B-cell lymphoma – June 1, 2016
- GSK's *ex-vivo* stem cell gene therapy Strimvelis receives European Marketing Authorization to treat very rare disease ADA-SCID – May 27, 2016
- Abeona Therapeutics announces FDA allowance of investigational new drug for Phase I/II clinical study with ABO-101 gene therapy for patients with Sanfilippo syndrome type B – May 24, 2016
- Bone Therapeutics announces further positive efficacy in ALLOB Phase I/IIA delayed-union fracture trial – May 17, 2016
- Caladrius Biosciences receives Orphan Drug Designation for CLBS03 to treat type 1 diabetes – May 12, 2016
- European Commission grants Cytori Therapeutics Orphan Drug status to a broad range of Cytori cell therapy formulations when used for the treatment of hand dysfunction and Raynaud's Phenomenon in patients with scleroderma – May 10, 2016
- Cellectis announces second baby with leukemia remains in remission six months after UCART19 T-cell treatment – May 6, 2016
- Agilis Biotherapeutics announces Orphan Drug Designation approval in Europe for treatment of Angelman syndrome – May 4, 2016
- Kite Pharma announces FDA Orphan Drug Designations for KTE-C19 in five additional indications: primary mediastinal B cell lymphoma, mantle cell lymphoma, follicular lymphoma, acute lymphoblastic leukemia and chronic lymphocytic leukemia – May 2, 2016
- Fibrocell receives Orphan Drug Designation from the FDA for FCX-013 for the treatment of localized scleroderma – April 25, 2016
- BioMarin provides encouraging preliminary data on first eight patients in hemophilia A gene therapy program – April 20, 2016
- Juno investigational CAR T cell product candidates JCAR018 and JTCR016 demonstrate encouraging clinical responses in patients with B-cell and mesothelioma cancers – April 20, 2016
- Kiadis Pharma presents positive data on the primary endpoint of its single dose Phase II trial with ATIR101 – April 4, 2016
- Mesoblast cell therapy shows disease-modifying effects on knee osteoarthritis – April 1, 2016

Establishment of Industry-Wide Standards

Leading company experts provide commentary regarding the need for the development and implementation of agreed-upon industry-wide standards to advance this sector.

Jessica Carmen
Director of Business Development,
Cellular Therapies
MaxCyte, Inc.

In the emerging markets encompassed by regenerative medicines, including gene therapy, cell therapy, tissue engineering and cell-based drug discovery, there are currently too few standards associated with the measurement of these novel therapeutic modalities. Industry-wide standards will allow for all technologies in the space to be more successful, adhering to the old adage "a rising tide lifts all boats." Such standards enable sponsors of new therapies to use pre-specified protocols and/or reference materials to measure their products in order to ensure product safety and manufacturing consistency.

The most urgent need with respect to standards development is the measurement assurance and establishment of reference standards for gene therapies. This includes the reliable and consistent measurement of nucleic acids as well as the establishment of reference standards for viral therapies. Additionally, a broadly used method of cell counting and viability would also of great value in the development of regenerative medicines. Together, these standards would help developers safely and consistently introduce genetic material into cells and facilitate the quantification of cells prior to administration to patients.

To address the need for industry-wide standards creation, ARM is in the process of establishing a Standards Coordinating Body (SCB). Its mission is to serve as a source of knowledge and expertise to enable more efficient and successful clinical and commercial development of cellular/gene & regenerative medicine therapies and cell-based drug discovery through development of international standards for areas including measurement assurance. The SCB's primary goal is to serve as a coordinating body for all activities associated with the establishment of standards for regenerative medicines. This will allow for the efficient establishment and dissemination of standards and standards related activities as well as reduce the chances for duplicate efforts.

Elena Kfoury
Director, Business Development
& Strategic Alliances
Axiogenesis Inc.

Agreed-upon and consistently reproducible quality standards facilitate discussion with regulatory agencies, enabling cutting-edge bench science to translate into actual therapies and technologies for patients in need.

While innovation is the hallmark of an evolving field, the standardization of products and processes is a critical driver of true growth in many markets. There are several reasons: 1) by speaking a common language, vendors and customers improve communication through the supply chain, facilitating confidence in the science itself; 2) statistical methods can be applied to reduce manufacturing variability and improve quality, providing customers with a reliable source for technology to benchmark for their own internal processes; 3) formal and practical training becomes easier as there is a transparent reference point to assess further iteration of technology and process.

Establishment of Industry-Wide Standards

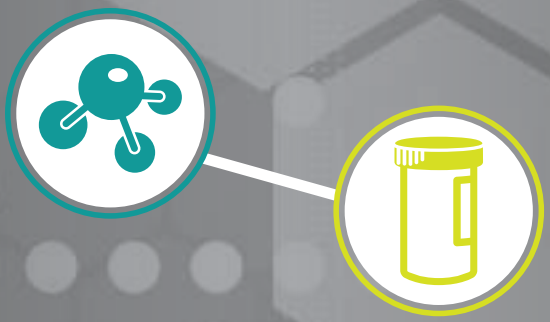
Jiwen Zhang
Senior Director,
Regulatory Affairs, Cell Therapy
and Regenerative Medicine
GE Healthcare

Harmonized standards are essential for international commerce and trade, global product development and successful commercialization and market access. Regulators, including FDA, have indicated the important role of standards, including their ability to complement existing regulations and guidances, while addressing numerous issues related to manufacturing, nomenclature and testing.

To ensure these agreed-upon standards are created and implemented in a coordinated fashion across countries and regions, standards development activities need to be conducted in an international setting. The International Standards Organization (ISO), International Council for Harmonisation (ICH) and other standards developing organizations (SDOs) provide such mechanisms where our industry needs to engage and lead efforts.

The mission of ARM's proposed Standards Coordinating Body (SCB) is to support the development, dissemination, education and implementation of standards and related deliverables for cellular and gene therapies and regenerative medicine, as well as cell-based drug discovery industries. Numerous standards projects have been initiated, underscoring the critical need for contributions from subject matter experts to develop and make these standards published and adopted for implementation.

The SCB is designed to serve as a source of knowledge and expertise, not only providing input into individual SDO projects, but also ensuring a comprehensive organizational overview of standards currently being developed worldwide. Additionally, the SCB will coordinate and organize upstream and downstream SDO activities with regards to standards education, dissemination and implementation.



Current Regulatory & Legislative Priorities

Global reimbursement issues. Advancing specific proposals to enable market access and favorable reimbursement policies for gene and cell 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

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 for cell therapy, reference standards for *in-vivo* and *ex-vivo* gene therapies, tissue engineering and drug discovery. The group is also working with NIST and other federal agencies to finalize a public-private partnership model to support these activities.

Optimizing current regulatory and review pathways to ensure patient access to safe and efficacious regenerative medicine products. This includes:

- ARM continues to work closely with FDA to identify opportunities for improvement and optimization.
- 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.

EU GMP for ATMP consultation. The European Commission has published a new targeted multi-stakeholder consultation on the draft guidelines Good Manufacturing Practices specific to ATMPs. ARM is developing its response for submission in Q3 2016.

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 and the existing regulatory framework. This information will be included in the NAS upcoming consensus report to be released by EOY 2016.

PDUFA reauthorization. The current Prescription Drug User Fee Act (PDUFA) version V is set to expire September 2017. ARM has convened a working group to discuss ARM's goals for the reauthorization and will provide a statement to be submitted at the upcoming mid-August public meeting.

FDA draft guidance on minimal manipulation. 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.

National Academies Forum. ARM has been invited to be a member of the NAS Forum on Regenerative Medicine. The Forum will examine regulatory and reimbursement issues.

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