Q3

ALLIANCE for Regenerative Medicine

2016

Quarterly Data Report

on gene and cellular therapies and the regenerative medicine sector

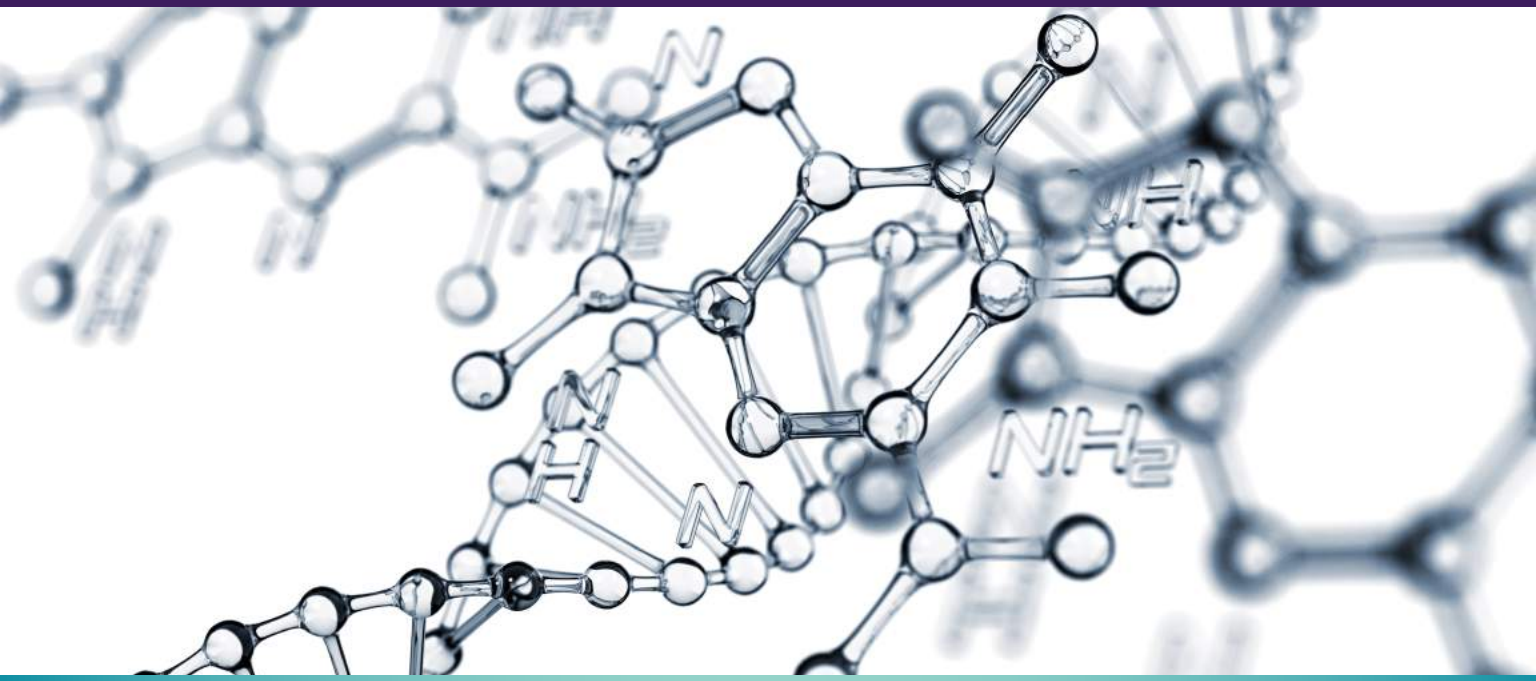
ALLIANCE for
Regenerative Medicine

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

734+
Regenerative Medicine Companies Worldwide, Including Gene and Cell Therapies

Industry Overview

Financing and deal making activity among companies active in cell and gene therapy, tissue engineering and the broader regenerative medicine sector remained strong, moving forward at a lively pace in Q3 2016. We saw an increase in initial public and secondary offerings, as well as private and venture financing deals and a series of promising partnership and acquisition activities we believe will fuel growth in this sector through 2016 and beyond.

AveXis lead the financing pack with its $168.6M (includes all shares, exercised in September or October) in a follow-on public offering to fund ongoing clinical efforts for its gene therapy candidate, AVXS-101, for the treatment of spinal muscular atrophy. Additional financings included Audentes Therapeutics' $85.1M IPO; GenSight Biologics' €45.2M IPO; and Argos Therapeutics' $50M follow-on offering. In addition, Histogenics, Caladrius Biosciences, Fibrocell and Fate Therapeutics all received private placements to continue to fund their respective growth and development.

Partnership activity was robust this past quarter, with the continued trend of smaller upfront payments and high milestone rewards. In a deal potentially worth $1B+, bluebird bio and Medigene signed a strategic R&D collaboration and licensing agreement for TCR immunotherapies. Takeda signed a licensing agreement with TiGenix for ex-U.S. rights to Cx601, with TiGenix receiving €25M upfront with the potential of €355M in milestone payments. Ono Pharmaceuticals will pay €11.25M upfront with €270.75M in potential milestone payments to develop Celyad's allogeneic NKR-2 T-cell therapy in Japan, Korea and Taiwan.

On the M&A front, Allergan acquired RetroSense Therapeutics for $60M (with future commercialization and regulatory milestone payments possible) for its RST-001 gene therapy program. BioCardia and TigerX signed an agreement to merge, giving the combined company an estimated $23M to support ongoing Phase III development of the CardiAMP cell therapy for heart failure. Tissue regeneration company Derma Sciences acquired BioD, which is developing allografts to aid in wound healing, for $21.3M upfront with the possibility of an additional $56.5M in milestone payments.

The news was not all good, however. In late August, Novartis announced plans to close its Cell and Gene Therapy Unit, although the company maintains a commitment to file their cell-based immuno-therapy pediatric r/r acute lymphoblastic lymphoma (ALL) program for approval with the U.S. FDA and EMA. In addition, Juno's Phase II CAR-T ROCKET clinical trial in the treatment of adults with relapsed or refractory B cell ALL was briefly put on clinical hold due to three fatalities – days later, the FDA approved the trial to resume, with a modified preconditioning regimen.

We continue to be impressed with the sustained growth, financial investment and ever-increasing collaborations across the broader regenerative medicine spectrum. We look forward to the future as these financing milestones translate into additional clinical results that have the potential to change the lives of so many patients.

– Patricia Reilly
Executive Director – Medtrack

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

Informa Business Intelligence,
Pharma and Healthcare

Financings

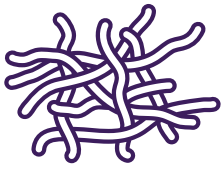
Total Global Financings

TOTAL GLOBAL FINANCINGS

$3.5B raised YTD 2016
$952.3M raised Q3 2016

GENE & GENE-MODIFIED CELL THERAPY

$2.01B raised YTD 2016
$607.4M raised Q3 2016



TISSUE ENGINEERING

$168.9M raised YTD 2016
$80.5M raised Q3 2016

CELL THERAPY

$1.9B raised YTD 2016
$316.8M raised Q3 2016

Total EU Financings

TOTAL EU FINANCINGS

$378.9M raised YTD 2016
$155.8M raised Q3 2016

GENE & GENE-MODIFIED CELL THERAPY

$262M raised YTD 2016
$97.6M raised Q3 2016

CELL THERAPY

$180.7M raised YTD 2016
$76.6M raised Q3 2016

Examples of key financings: Q3 2016

IPOs:

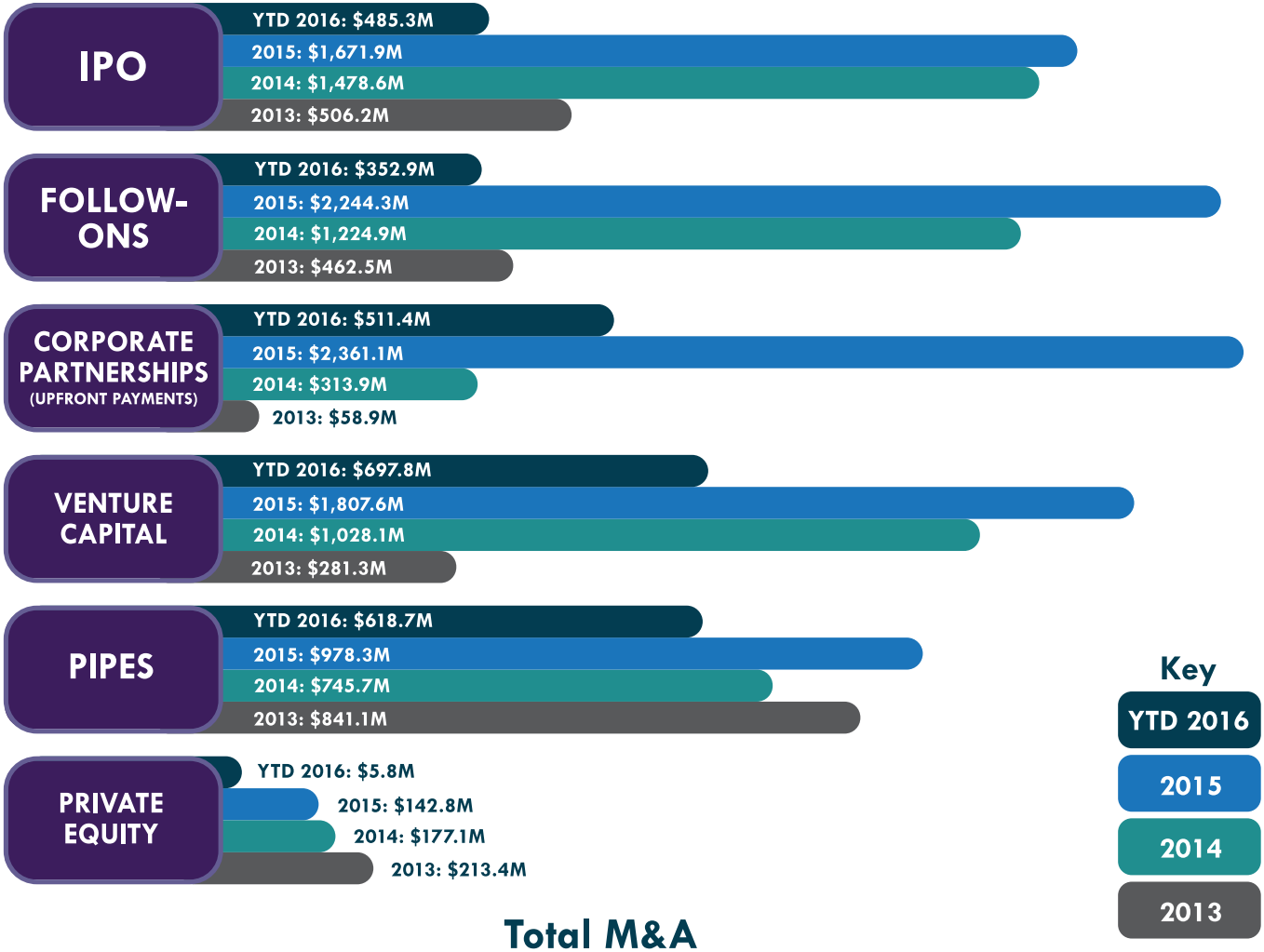
- **Audentes Therapeutics IPO raises $85.1M –** August 20, 2016
- **GenSight Biologics IPO raises €45.2M –** August 11, 2016
- **Cellect Biotechnology Ltd. IPO raises $8.4M –** August 3, 2016

Corporate partnerships, acquisitions and other financings:

- **bluebird bio and Medigene establish $1B+ strategic T Cell receptor (TCR) immunotherapy research and development collaboration and licensing agreement, $15M upfront –** September 29, 2016
- **Pfizer acquires Bamboo Therapeutics in $645M deal, with $150M upfront –** August 1, 2016
- **Takeda and TiGenix enter into €355 million licensing agreement for ex-U.S. rights to Cx601 for treatment of complex perianal fistulas in patients with Crohn's disease, €25 million upfront to TiGenix –** July 5, 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



Total M&A

Sector Commentary: Large Pharma Perspective

Sven Kili
Vice President,
Head of Cell Therapy Development
GSK

At GSK, we believe cells as medicine have a strong future. We are investing significantly in the development of world-class R&D and commercial supply capabilities for cell and gene therapies with the vision that these technologies will stand alongside the more commonly used small molecule and biopharmaceutical approaches in the development of medicines.

GSK has been involved in the cell and gene therapy space since 2010, working with Fondazione Telethon and the Ospedale San Raffaele, acting through their joint San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), a world-leading research center for stem cell gene therapy in Italy. We also established our Rare Disease Unit in 2010, and have since built a team of cell and gene therapy and rare conditions experts dedicated to understanding and creating new medicines. Our goal is to apply the knowledge and expertise we're gaining in this area to develop innovative cell and gene therapy solutions for a greater number of patients, including those with rare and ultra-rare diseases and limited or no approved treatment options, as well as other, more prevalent conditions, including cancer, chronic auto-immune and metabolic disorders.

Making this technology a reality for patients requires specialized skills and experience in order to rapidly progress these novel technologies, establish new production techniques, engage regulatory authorities on development and registration strategies and follow-up, address logistical challenges in the supply chain and identify ways to cost effectively scale-up a very complex scientific process. We recognize the advantages of working with external experts and collaborators within the cell and gene and rare disease community, and in working collaboratively with regulators and academic institutions to address these needs.

Through our collaboration with SR-TIGET, we applied our product development expertise to optimize a manufacturing process that was previously only suitable for clinical trials into one that is robust and suitable for commercial supply. In 2016, Strimvelis became the world's first approved ex-vivo gene therapy for patients with ADA-SCID. This milestone brings GSK, and the broader cell and gene therapy industry, closer to using a patient's own cells to treat the root cause of disease, enabling follow-on projects for other rare diseases such as Metachromatic Leukodystrophy and Wiskott-Aldrich Syndrome, for which we are currently developing gene therapies.

The ability to make such a large difference in a patient's life with a single administration therapy is very exciting; however, the business model remains untested and very complex. We have had discussions with payers and reimbursement agencies to discuss the value proposition and mechanisms of payment, and will continue to engage with these groups in preparation for the launch of the other indications to ensure the greatest potential availability of these gene therapies to patients.

Andrea Hunt
Vice President
New Products TA Lead
Gene Therapy, Neuroscience,
Oncology & Ophthalmology
Shire

Though the field as a whole continues to emerge and advance, we believe gene therapy technology truly has the potential to transform medical care, offering patients a durable, multi-year effect. Our investment into this field of research is part of Shire's continued efforts to advance innovation in hemophilia—one of the company's primary areas of focus.

Our broad R&D strategy is driven by a combination of internal expertise and external collaborations, enabling us to bring together the best scientific abilities, as well as the technical and operational capabilities to usher in promising advancements through the development process to commercialization.

In this category in particular, deep technical and manufacturing expertise is critical to bringing the technology to commercial scale. Leveraging our decades-long heritage in hemophilia with a wide range of proven direct factor replacement treatments, along with our extensive history of manufacturing biologics and complex therapeutic products, is essential when introducing novel technologies and new therapeutic classes.

801
Clinical trials underway at the end of Q3 2016

Ph. I: 266
Ph. II: 467
Ph. III: 68

Current Clinical Trials by Therapeutic Category: Q3 2016

- More than 43% of current clinical trials are in oncology
- More than one in 10 are in cardiovascular

Examples of major milestones and key data events: Q3 2016

- *Fate Therapeutics receives FDA Orphan Drug Designation for ProTmune in allogeneic hematopoietic cell transplantation* – September 26, 2016
- *Kite Pharma announces positive topline KTE-C19 data from ZUMA-1 pivotal trial in patients with aggressive non-Hodgkin lymphoma* – September 26, 2016
- *Cellular Dynamics International, a FUJIFILM company, announces launch of iCell Hepatoblasts to enable research into therapies that stimulate liver regeneration* – September 22, 2016
- *bluebird bio's LentiGlobin investigational gene therapy for transfusion-dependent beta-thalassemia is accepted into European Medicines Agency's PRIME Program* – September 21, 2016
- *Alliqua BioMedical announces commercial introduction of Interfyl Connective Tissue Matrix* – September 19, 2016
- *Asterias Biotherapeutics announces positive efficacy data in patients with complete cervical spinal cord injuries treated with AST-OPC1* – September 14, 2016
- *Sangamo BioSciences receives Orphan Drug Designation from U.S. FDA For SB-FIX, first application of therapeutic* in vivo *genome editing* – September 6, 2016
- *GenSight Biologics receives Orphan Drug Designation from the European Commission for product candidate GS030 for treatment of retinitis pigmentosa. The EMA also granted Advanced Therapy Medicinal Product classification to GS030* – September 1, 2016
- *MolMed S.p.A. receives Conditional Marketing Authorization from the European Commission for Zalmoxis, the first immunogene therapy for adults with high-risk haematological malignancies* – August 22, 2016
- *iCell Gene Therapeutics announces U.S. FDA has granted Orphan Drug Designation for its chimeric antigen receptor engineered T-cells for the treatment of peripheral T-cell lymphoma* – August 11, 2016
- *Spark Therapeutics announces new positive data from continuation of Phase 3 trial of voretigene neparvovec, its most advanced product candidate, for treatment of inherited retinal disease* – August 10, 2016
- *Mesoblast Phase 2 trial results of MPC-300-IV show dose-related improvements in biologic refractory rheumatoid arthritis* – August 9, 2016

Continued on page 9

Major Milestones & Key Data Events

Continued from page 8

- *Bellicum announces the European Commission has granted Orphan Drug Designation for both its lead T-cell therapy product candidate BPX-501 for treatment in hematopoietic stem cell transplantation and activator agent rimiducid for treatment of Graft vs. Host Disease* – August 4, 2016

- *Cesca Therapeutics announces promising 40-month follow-up results of patients enrolled in critical limb ischemia study* – August 3, 2016

- *Abeona Therapeutics announces initial subjects in ongoing Phase 1/2 Sanfilippo Type A gene therapy trial demonstrate encouraging early biopotency signals* – August 2, 2016

- *Agilis Biotherapeutics announces FDA Orphan Drug Designation for treatment of Friedreich's ataxia* – August 2, 2016

- *REGENXBIO receives FDA Rare Pediatric Disease Designation for RGX-121 gene therapy for treatment of Mucopolysaccharidosis Type II* – August 2, 2016

- *Takeda and TiGenix announce 24-week results of the Phase 3 ADMIRE-CD trial investigating Cx601 in the treatment of complex perianal fistulas in patients with Crohn's disease* – August 2, 2016

- *Caladrius Biosciences receives FDA Fast Track Designation for CLBS03 to treat recent onset type 1 diabetes* – July 28, 2016

- *uniQure presents updated clinical data in patients with severe hemophilia B demonstrating up to nine months of sustained levels of Factor IX activity and therapeutic effect* – July 27, 2016

- *Adaptimmune receives Orphan Drug Designation in the European Union for its NY-ESO SPEAR T-cell therapy for treatment of soft tissue sarcoma* – July 26, 2016

- *Spark Therapeutics and Pfizer announce FDA Breakthrough Therapy Designation for SPK-9001 for the treatment of hemophilia B* – July 21, 2016

- *AveXis receives U.S. FDA Breakthrough Therapy Designation for AVXS-101 gene replacement therapy for spinal muscular atrophy type 1* – July 20, 2016

- *BrainStorm announces positive top line results from the U.S. Phase 2 study of NurOwn in patients with amyotrophic lateral sclerosis* – July 18, 2016

- *Organovo and Roche Researchers publish data demonstrating superiority of 3D bioprinted human liver tissues in assessing drug-induced toxicity* – July 11, 2016

Sector Commentary: Investor Perspective

Reni Benjamin
Senior Biotechnology Analyst
Raymond James & Associates, Inc

When we think about the cell and gene therapy space as a whole, 2015 vastly outperformed 2016 in terms of financing opportunities. However, we don't believe that is due to investors' disdain for the cell and gene therapy space – on the contrary. The broader biotech space took a significant hit at the beginning of the year and the negative sentiment carried over into the cell and gene therapy sector.

We believe that financing opportunities remain available from both private and public investors all the way to strategic investments. So far this year, those companies, gene therapy companies in particular, that have generated positive clinical trial data have been largely successful in financing their ongoing development. It's also worth noting that it's possible we haven't seen as many financings as 2015 because companies may have taken advantage of last year's valuations to fill the coffers; these companies may find themselves without the need to rush into a financing this year.

That being said, the cell and gene therapy space faces numerous clinical, regulatory and reimbursement challenges that can materially impact the current financing environment: 1) trials need to show a statistical and clinical benefit and no large safety issues; 2) need for continued work with regulatory bodies on a global scale; and 3) continued outreach to payers to design innovative reimbursement methods.

What keeps us confident that we can overcome these hurdles is a combination of the speed at which scientific knowledge is expanding; the appetite from both large pharma and large-cap biotech to acquire or partner assets rather than develop them in-house; the demonstrated ability of companies in this space to learn from failure and develop multiple shots on goal; and the current interest rate environment, fostering investment in an effort to chase meaningful returns.

If all goes well, 2017 should be a great year for financing the cell and gene therapy space. And, assuming the currently trajectory of clinical progress and dealmaking continues, we believe 2017 should be materially better than 2016. We anticipate that, over the next two years, the cell and gene therapy space is likely to have several potential approvals from the lead CAR-T and gene therapy players. As investors, we would view the approval of one or more of these products as a significant positive for the space, as such an approval would demonstrate to investors in development and commercial stage companies alike that both clinical and regulatory challenges can be overcome.

Current Regulatory & Legislative Priorities

U.S. presidential election. ARM will conduct outreach to the new Administration and transition team, focusing in particular on how the election results will impact ARM's regulatory and reimbursement 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, including identifying potential policy and legal impediments to coverage and reimbursement; conducting formal analysis of payment models to facilitate access and adoption; and 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. In September 2016, the SCB and NIST entered into a memorandum of understanding, the first step in an SCB-NIST public-private partnership. The SCB aims to build a coalition that will include other partnerships with other federal agencies and international standards organizations. The initial work plan will be released in Q1 2017 to coincide with the formal launch of the SCB.

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

- 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. In September 2016, ARM submitted comments in response to the European Commission's targeted multi-stakeholder consultation on the draft guidelines Good Manufacturing Practices specific to ATMP. ARM recommends the EC provide ATMP-specific guidance as an annex to the EudraLex Volume 4 of the "Rules Governing Medical Products in the European Union," rather than as a standalone document, which may lead to disparities in GMP standards, among other concerns.

EU hospital exemption. Hospital exemption has vastly different interpretations and levels of enforcement in the various EU Member States. ARM is currently preparing a position paper to be published in Q4 2016 outlining several recommendations to ensure that patients are protected from unnecessary risks and that hospital exemption could not be used as a way to circumvent the applicable legal instruments for the marketing of safe and efficacious medicinal products.

Continued on page 12

Current Regulatory & Legislative Priorities

Continued from page 11

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.

FDA draft guidance on minimal manipulation. In September 2016, ARM submitted comments and presented at the public hearing in response to the FDA's draft guidance on minimal manipulation and homologous use on human cell and tissue products. ARM requested further explanation on the requirements for product characterization and related claims for each type of product, including examples of how FDA will define and apply key terms, including "minimal manipulation," "homologous use" and "main function" when evaluating various technologies.

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. In September 2016, ARM submitted comments responding to the PDUFA VI Goals Letter, emphasizing the importance of hiring sufficient and qualified staff to meet the increasing number of cell and gene therapy IND and BLA applications to be filed in coming years.

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.

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ALLIANCE for Regenerative Medicine

Alliance for Regenerative Medicine
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