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Office of Science and Technology Policy  
RFI Response: Bioeconomy

*(Submitted via email to MBX.OSTP.WHBioeconomy@ostp.eop.gov)*

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to respond to your request for information (RFI) seeking input on the Bioeconomy. Specifically, ARM will focus our comments on: (1) the “policy or regulatory opportunities” that should be adopted to enhance patient access to regenerative medicines; and (2) government partnering recommendations to support the development of a skilled workforce.

### Introduction

ARM is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. Regenerative medicine is a rapidly evolving, interdisciplinary field that encompasses gene therapies, cell therapies and tissue-engineering products that are intended to augment, repair, replace or regenerate organs and tissues to cure or significantly change the course of chronic and life-threatening diseases.

ARM is comprised of more than 350 leading research-based life science companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. In the United States, ARM members have facilities in 33 states and globally, are in 25 countries. Since 2016 and through the second quarter of this year, global financing in the regenerative medicine sector has totaled an approximately \$32.7 billion. Importantly, these financings have consistently increased on a year-over-year basis – \$4.4 billion in 2016, \$7.7 billion in 2017, \$13.1 billion in 2018, and \$7.5 billion through the first half of 2019.

Our members are directly involved in the research, development, and clinical investigation of cell and gene therapy and tissue engineering products, including the submission of investigational new drug (IND) applications, 510(k) applications, Biologics License Applications (BLA) and other appropriate regulatory documents for such products to the FDA. ARM takes the lead on the sector’s most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

### Regenerative Medicine Pipeline

ARM is currently tracking 953 regenerative medicine companies worldwide that are conducting 1,071 clinical trials. Almost half of these companies are headquartered in the United States (521),

followed by Europe and Israel (233), Asia (164) with the remainder in South America, Australia, New Zealand and Africa. Of the 1,071 clinical trials, 366 are in Phase 1, 609 in Phase 2 and 96 in Phase 3.

While today there are just a handful of regenerative therapies available to patients, the pipeline is promising. The Food and Drug Administration has stated that it expects to be approving 10-20 regenerative medicine therapies annually by 2025. A study released this March by the MIT NEWDIGS FoCUS Project, entitled “Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System,” concluded that “Our analysis suggests that by 2030, up to 60 new cell and gene therapies could be launched, treating an expected 350,000 patients cumulatively and about 50,000 patients per year.”

***What specific actions could the U.S. Government take to reinforce a values-based ecosystem that will guide the transformation and expansion of the U.S. Bioeconomy, in both the short- and long-term? Please consider: a. Policy or regulatory opportunities and gaps throughout the continuum of basic science translation, product development and commercialization;***

As referenced above, we are on the cusp of unprecedented advances in how we treat and cure patients who are battling a variety of chronic and fatal diseases. The Institute for Clinical and Economic Review (ICER) has stated that “cell and gene therapies are starting to provide truly transformative advances for patients and their families, particularly those with conditions for which that has not been any effective treatment before.” While the science has advanced, current reimbursement models are not set up to meet the challenges of these single administration, curative/durable therapies.

Over the past several years, ARM has carefully analyzed the health care legislative and regulatory environment to determine the viability of certain alternative payment models that can be leveraged for these groundbreaking medicines. These payment models, including the use of value-based purchasing help address the fact that many of the one-time, curative treatments may realize their full clinical and economic value over time. Much of the current system, however, continues to pay for the quantity of services versus their value. ARM agrees with the July 17, 2018 comment by Department of Health and Human Services (HHS) Deputy Secretary Eric Hargin before the House Ways and Means Subcommittee on Health when he testified that current reimbursement models “(do) not necessarily translate to the modern health care system.” Regenerative medicine can transform the provision of health care in this country if new and innovative payment models are adopted by payers – both government and commercial.

Value-based arrangements serve to link payments to performance in ways that account for both the cost and quality of care provided. The most basic value-based purchasing model may function essentially as a “money-back guarantee,” where the cost of the treatment would be refunded if the treatment does not meet certain agreed-upon clinical benefit endpoints for a particular patient or group of patients. One variation to this model is an initial or discounted payment upfront when the therapy is first administered, and to continue to evaluate clinical

outcomes and other measures to determine future payments for the remaining cost of the treatment. Both options present significant benefits when such treatments otherwise require a higher upfront investment for a one-time treatment, when in fact the eventual cost savings for a curative therapy accumulates over time. Manufacturers and payers may also consider “indication-based” pricing, with higher reimbursement rates when treatments pose a better therapeutic value for patients with certain medical conditions versus indications for which such therapies offer less of a benefit.

#### Impact of the Federal Anti-Kickback Statute

On August 27, 2018, the HHS Office of Inspector General published an RFI seeking input on the impact of the federal anti-kickback statute and the beneficiary inducements civil monetary penalty (CMP) on healthcare delivery. ARM took that opportunity to comment on the challenges these regulations pose for establishing value-based payment models.

ARM is supportive of the OIG’s efforts to reexamine the applicable regulatory safe harbors currently in place under the anti-kickback statute, but we are very concerned that the proposed change to exclude manufacturer price reductions in connection with the sale or purchase of a prescription drug under Medicare Part D or Managed Medicaid (unless the price reduction is required by law) would serve to also exclude arrangements involving the application of price concessions based on value. In addition, the very nature of value-based purchasing often requires that price concessions linked to value be applied after the point of sale, when clinical outcomes and other metrics can be measured. As such, the safe harbor proposed in 2018 to protect point-of-sale price reductions offers little benefit to – and could result in hampering – value-based purchasing arrangements here either.

We understand that HHS “does not intend for this proposal to have any effect on existing protections for value-based arrangements between manufacturers and plan sponsors,” and that the OIG has expressed interest in learning “the extent to which the proposed amendment and accompanying proposed safe harbor may affect any existing or future value-based arrangements.” Without more explicit protections in place to protect value-based purchasing, ARM believes that the 2018 Proposed Rule, if finalized, may have the unintended consequence of restricting the ability of manufacturers to offer value-based purchasing arrangements that involve any form of price concession or reduction after the point-of-sale. There are no current safe harbors in place that otherwise reliably protect the wide range of value-based arrangements and other payment models that could be employed for the federal reimbursement of regenerative technologies and therapies.

In addition, although the Proposed Rule focuses primarily on the use of rebates and price concessions in Medicare Part D and Managed Medicaid, we note that the OIG has also solicited comments on whether this amendment “should apply to prescription pharmaceutical products payable under other HHS programs,” for example, under Medicare Part B. Since regenerative technologies and therapies would more commonly be covered under programs other than Medicare Part D due to the methods of administration and sites of care, the extension of the proposed safe harbor exclusion to additional government health care programs will have an even

more pronounced, deleterious impact. ARM opposes further expansion of the applicability of the proposed safe harbor exclusion to any other HHS programs, until, at a minimum, the OIG is able to reliably assess the results under the Medicare Part D and Managed Medicaid programs.

*Recommended Anti-Kickback Safe Harbor for Value-Based Arrangements*

ARM previously submitted comments in response to OIG's annual solicitation of new anti-kickback statute safe harbors and special fraud alerts, as issued on December 27, 2017, as well as in response to the OIG's request for information on the anti-kickback statute and beneficiary inducement civil monetary penalty on October 26, 2018. As they are still applicable, we reiterate these points below.

ARM's comments proposed a safe harbor that includes specific protections to provide firm guidance to a wide range of stakeholders wishing to enter into value-based arrangements, while still protecting federal health care programs from overutilization, increased costs, or other abuses that would impact patient freedom of choice and access to quality care. This is especially critical if the OIG were to implement the Proposed Rule as currently drafted. ARM's proposed safe harbor provides for the following:

1. The terms and conditions of the value-based arrangement, including the time period for the measurement of the clinical outcomes and metrics, are fixed prior to the purchase.
2. The purchase price for the health care item or service would be disclosed by the buyer and the seller to Medicare and Medicaid as required by law.
3. The value-based arrangement insulates patients from undue financial burden, so that the patient shares in any beneficial adjustment to the purchase price of the health care item or service and is "held harmless" for any increase in price to the buyer.
4. Any ancillary items or services used solely or primarily for the measurement of clinical outcomes necessary to determine payment or other terms under the value-based arrangement cannot be separately billed by the buyer or seller.

On October 9, the HHS OIG unveiled new proposals reforming the anti-kickback statute (AKS) that focused on provider-based arrangements. While they did not include any safe harbors for pharmaceutical value-based payment arrangements, ARM was pleased to note that HHS Secretary Alex Azar stated that "We are working on protections to enable value-based outcome payments for pharmaceutical products."

**Recommendation:** The Administration should adopt the ARM-recommended AKS safe harbor as outlined above that will allow for establishment of value-based payment models for regenerative medicine products in federal health programs so that patients can have access to these groundbreaking therapies.

***In what ways can the U.S. Government partner with the private sector, industry, professional organizations, and academia to ensure the training and continued development of a skilled workforce to support the growth of the Bioeconomy?***

The importance of a skilled, robust domestic workforce for the Regenerative Medicine industry cannot be overstated. This rapidly growing industry employs individuals in numerous roles, which have different educational and training requirements.

**The Need for Skilled Personnel**

Currently, cell processes such as the production of autologous Chimeric Antigen Receptor T Cells (CAR-T) involve manually intensive operations. Although there are efforts to automate in this space it is unclear how many parts of the process can be automated. In most cases manufacturing equipment has not been standardized, which is an impediment to full automation as different equipment from different manufacturers may not be compatible. It is likely that most newly approved cell therapy processes will involve at least some manual steps for the foreseeable future (at least 5-10 years). Even if automation becomes the industry standard, regulatory constraints make it difficult to change a production processes (i.e. from a manual process to an automated one) once a therapeutic has been approved

Most manufacturing personnel in the industry have university degrees in the biologic sciences. The special skills they need, such as cell culture and aseptic technique, are currently not taught at trade schools or through vocational technical training. Many of these individuals spend a relatively brief time in these roles before moving on to other technical or managerial positions, which is the primary reason why they obtained the degrees. The net result is that it is difficult to retain individuals with the right skill sets in these positions.

Individual therapeutic developers and academic centers largely bear the burden of training manufacturing personnel in the specialized skills that are required. This can take as long as 2-3 months and involves significant risk in that these individuals can leave the company for other opportunities.

**Recommendation:** The Administration should encourage vocational training and certification programs for Cell and Gene Therapy manufacturing, and provide appropriate funding through organizations such as NIIMBL (<https://niimbl.force.com/s/about-niimbl>), and via grants to training programs at regional academic centers.

**CBER Staffing Needs**

The Center for Biologics Evaluation and Research (CBER) is the division of the Food and Drug Administration which is responsible for evaluating sponsor applications for Cell and Gene Therapies. This includes requests for a Regenerative Medicine Advanced Therapy Designation (RMAT), Investigational New Device Applications (INDs) for clinical trials and Biologic License Applications (BLAs) for commercializing these therapies. The relevant number of RMAT requests and IND and BLA submissions are shown in table 1.

Table 1 – CBER Cell and Gene Therapy Workload<sup>1,2</sup>

Fiscal Year	2017	2018	2019
RMAT	31	47	37*
IND	246	215**	Data not available
BLAs***	7	4	Data not available
Breakthrough Designation	8	6	Data not available

\* Current as of 10/11/2019

\*\* Through July 11, 2018

\*\*\* Office of Cell and Gene Therapy only

US Food and Drug Administration (FDA) officials have said they expect this pace to continue, adding to the 800 active INDs for such products already filed with the agency. As noted earlier, by 2025 they predict the agency will be approving between 10 and 20 cell and gene therapy products annually.

CBER is currently experiencing a critical staff shortage. The Director of CBER, Peter Marks, has estimated that staff will need to grow by 25-50% in the next year, and double within the next several years in order to keep pace with the increasing number of sponsor applications for these life saving therapies. These staffing needs are particularly acute in the Office of Tissues and Advanced Therapies.

Staff shortages present the additional risk of overstressing the individuals who have experience reviewing these applications, possibly resulting in turnover of key staff.

**Recommendation:** The Administration should take action to ensure that CBER is able to hire the sufficient number of staff with the appropriate education and skills set to support the review of the increasing number of Regenerative Medicine IND and BLA submissions. We urge the Administration to support initiatives to provide sufficient funding.

### Educational Needs

The United States is recognized as having the finest higher education system in the world. Academic institutions such as the University of Pennsylvania, Stanford, the University of Texas

<sup>1</sup> PDUFA performance reports: <https://www.fda.gov/about-fda/user-fee-performance-reports/pdufa-performance-reports>.

<sup>2</sup>[https://cdn.ymaws.com/www.casss.org/resource/resmgr/cell&gene\\_therapy/2018\\_CGTP\\_GavinDenise.pdf](https://cdn.ymaws.com/www.casss.org/resource/resmgr/cell&gene_therapy/2018_CGTP_GavinDenise.pdf)

and many others are on the forefront of the regenerative medicine revolution. A particular strength of US academic institutions is their strong connection with medical institutions, which facilitates communication and collaboration among physicians and basic and translational scientists. These university affiliated hospitals also provide the critical mechanism by which patients in need can access these treatments. The first CAR-T cell therapy to be approved in the world, Kymriah, was developed at the University of Pennsylvania and licensed to Novartis, which is fully commercializing the product. The Children's Hospital of Philadelphia developed Luxturna, a recently approved gene therapy for inherited retinal disease, which was licensed to Spark Therapeutics in 2013. Spark is commercializing this therapy.

In the regenerative medicine industry, we are witnessing innovation in an academic setting, followed by licensing technologies to startup companies, which are then acquired by more established companies. This model is a proven creator of jobs and spurs economic growth. Recognizing this, some academic institutions, such as the New Jersey Institute of Technology (NJIT), are specifically developing graduate level programs focusing on regenerative medicine.

**Recommendation:** The Administration should encourage the ongoing efforts of higher education institutions in the regenerative medicine space.

***In what ways can the U.S. Government partner with the private sector, industry, professional organizations, and academia to establish a more robust and efficient Bioeconomy infrastructure?***

#### Technical Standards Development

Given that the regenerative medicine is in its infancy, it is not surprising that there is a lack of standardization. The lack of standards inhibits progress in various ways. One example is the process by which cells are collected from the patient for CAR-T cell therapies (Apheresis or leukapheresis). This process is performed in a clinical setting, and different institutions use different protocols and different equipment. This presents serious logistical problems for therapeutic developers who are typically working with several different hospitals. Inconsistencies in the starting cellular material lead to variable quality, increased costs and in some cases result in an unusable product at a time when the patient needs it the most.

A lack of standards in the industry also increases the regulatory burden. Therapeutic developers are forced to develop their own proprietary standards, which then must be evaluated by the FDA on a case by case basis. While this may be appropriate in some cases there is sector-wide agreement that the entire industry would benefit from standardization in such areas at starting and ancillary materials, cell characterization, cryopreservation, and labeling (to name just a few).

Several organizations are active in the development of standards in the regenerative medicine industry, including: the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB) (<https://www.standardscoordinatingbody.org>), NIST, and USP. These groups require ongoing funding to sustain these efforts.

**Recommendation:** The Administration should continue to provide funding through the appropriate channels for organizations developing and facilitating adopting of standards in the regenerative medicine space.

Thank you for your consideration. If you have any questions, please do not hesitate to contact us.

Sincerely,



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