Alliance for Regenerative Medicine

February 10, 2023

Chiquita Brooks-LaSure, Administrator
Centers for Medicare & Medicaid Services
U.S. Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Ave, SW
Washington, DC 20201

Submitted via Sec303ASPdata@cms.hhs.gov

Dear Administrator Brooks-LaSure:

The Alliance for Regenerative Medicine (ARM) greatly appreciates that CMS hosted a Discarded Drug Refund Policy Town Hall, and we look forward to working with CMS to develop policies and processes that create transparency and predictability for manufacturers.

ARM is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM promotes legislative, regulatory, reimbursement and manufacturing initiatives to advance this innovative and transformative sector, which includes cell therapies, gene therapies, and tissue-engineering. Early regenerative medicine products have demonstrated profound, durable and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. Hundreds of additional product candidates contribute to a robust pipeline of potentially life-changing regenerative medicines and advanced therapies. In its 14-year history, ARM has become the global voice of the sector, representing the interests of 475+ members worldwide, including small and large companies, academic research institutions, major medical centers, and patient groups. As of year-end 2022, there were 1,457 regenerative medicine and advanced therapies developers worldwide sponsoring 2,220 clinical trials across dozens of indications, including rare monogenetic diseases, oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, and more.

ARM thanks CMS for its questions on how best to determine the applicable percentage needs of refundable drugs with unique circumstances. Specifically, ARM appreciates that CMS identifies and suggests certain product qualities for it to consider when evaluating unique circumstances. For example, CMS raises product classification, preparation instructions, route of administration, total vial fill volume, and specific formulations as potential grounds and reasons that a product has unique circumstances -- possibly warranting a higher drug discard applicable percentage (up to 100 percent).

ARM urges CMS to consider each of those product qualities as a unique circumstance warranting varying percentages because of their potential impact on things like manufacturing and distribution costs, patient access to the most appropriate clinical dose, and physician confusion.

Based on those reasons, and generally speaking, ARM believes that a categorical approach (as suggested by CMS) could provide the greatest certainty and predictability for manufacturers of products that share the attributes mentioned by the agency.

For example, given the very unique circumstances of cell and gene therapies, ARM urges CMS to categorize all cell and gene therapies as having unique circumstances based on their method of preparation and administration, and therefore apply the maximum applicable percentage of flexibility (of 100 percent).

Cell and gene therapies are typically one-time durable therapy treatments, representing a completely different treatment regimen than the currently listed top discarded drugs which require frequent and regular delivery of the product to a patient. The overwhelmingly one-time nature of these therapies requires that all potentially needed product be on hand and available for procedures. This is consistent with clinical trial data, FDA-approved labeling, and is clinically necessary.

For example, because a gene therapy seeks to modify or introduce genes into a patient's body, its delivery through particular vectors (like an adeno-associated virus - also known as AAV) may create antibodies in the treated patient, giving rise to immunogenicity concerns which could be associated with and preclude any re-dosing of the patient. Therefore, unlike other treatment modalities, AAV gene therapies and other similar therapies require that all dosing be completed in a single session because the goal of gene therapy is to create a durable treatment that prevents or potentially even cures the disease. ARM believes that CMS should treat this product classification as a unique circumstance and apply a maximum applicable percentage (100 percent) such that providers need only focus on providing the therapy to obtain the maximum therapeutic effect.

Similarly, cell and immunotherapies involve the administration of manipulated cells into a patient's body to grow, replace, or repair damaged tissue or stimulate the immune system for the treatment of a disease. As such, physicians should not be forced to risk performing an incomplete or ineffective procedure because of a limitation on the amount of available product, which is the natural consequence of applying such a discarded drug refund policy to cell therapies. Instead, to protect patient safety and maximize the potential therapeutic effect, cell therapies should always be considered as a unique circumstance under the discarded drug refund policy and applied the maximum applicable percentage.

Having a maximum applicable percentage applied to certain categories of therapies such as cell and gene therapies will provide manufacturers the ability to develop and distribute their therapies in the most safe and effective manner. In doing so, CMS will ensure that all patients can receive the necessary dose at the time of dosing.

In the alternative to a categorical approach for all cell and gene therapies, ARM urges CMS to consider cell and gene therapies administered in conjunction with a complex procedure, and/or those therapies distributed in vials with vial fill of 1mL or less, as unique circumstances warranting a drug discard percentage of the maximum appliable percentage (of 100 percent).

Withdrawing and administering exceptionally small volumes from a small vial leads to a higher percentage of drug discard due to fluid dynamics and losses in priming, or in drug transfer as part of the administration to a patient. Specifically, vial fill sizes of 1mL or less contain such a small amount of product that more than ten percent of liquid is required to ensure that the clinically appropriate dose is administered. In other words, every drop in these small vials is important for the effective and safe product delivery to patients. The additional volume beyond overfill, **when it exists**[1]**,** is needed to:

- account for drug that remains on the vial wall;
- compensate for vial adapter geometry that limits drug withdrawal;
- account for variation in filling equipment; and
- compensate for drug remaining in needles, syringes, and/or tubing during transfer.

Based on all these factors, we urge CMS to recognize that withdrawing and administering exceptionally small volume leads to higher percentage of drug utilization due to fluid dynamics, vial size, and losses in priming or in drug transfer as part of the administration to a patient. As such, drug utilization during priming and transfer is often necessary to achieve maximum clinical effect and should not be considered discarded drug.

ARM believes that this 1mL total vial fill volume contains a sufficient amount of product qualities to qualify as an unique circumstance such that CMS should assign the maximum appliable percentage (100 percent) for the drug discard refund policy.

Finally, certain products require complex methods of delivery which necessitate the utilization of variable product volume to successfully deliver the FDA-approved dose. We believe that any such product used during complex administration procedures should be included within the CMS unique circumstances regulatory provisions and applied the maximum applicable percentage; such products include those that require specialized equipment, multiple preparation steps, and/or multiple administration attempts. Factors that constitute procedural complexity leading to variable amounts of discarded drug include those that involve:

- tiny single use delivery mechanisms like microinjectors designed to deliver drops of drug product into tiny anatomical spaces of the body.
- multiple procedures to ensure successful drug administration (e.g. surgical procedure coupled with a surgical injection);
- variable and unpredictable patient characteristics which impact the physician approach to drug administration;
- variability of physician surgical approach due to patient characteristics, physician preference, or equipment used;
- equipment variability due to physician or facility preference; and

[1] Not all FDA approved ophthalmic products contain overfill.

- those that raise immunogenicity concerns.

As such, to maximize clinical outcomes of complex procedures that administer small quantities of active ingredient, CMS should recognize these class of products as having unique circumstances and also assign the maximum appliable percentage (100 percent) under the drug discard refund policy.

Sincerely,

/S/ Brett Logan

Brett Logan
Director, U.S. Market Access
Alliance for Regenerative Medicine