Alliance for Regenerative Medicine

September 1, 2022

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 http://www.regulations.gov

Re: Medicare and Medicaid Programs; CY 2023 Payment Policies Under the Physician Fee Schedule and Other Changes to Part B Payment Policies; Medicare Shared Savings Program Requirements; Medicare and Medicaid Provider Enrollment Policies, Including for Skilled Nursing Facilities; Conditions of Payment for Suppliers of Durable Medicaid Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS); and Implementing Requirements for Manufacturers of Certain Single-Dose Container or Single-Use Package Drugs To Provide Refunds With Respect to Discarded Amounts. [CMS-1770-P]

Dear Administrator Brooks-LaSure:

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to comment on the Centers for Medicare & Medicaid Services' (CMS) proposed payment updates to the calendar year 2023 Medicare Physician Fee Schedule (Proposed Rule).[1] 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. With this focus, ARM is concerned that CMS only discusses one unique circumstance warranting a higher applicable discarded drug percentage. For reasons detailed below, ARM urges CMS to further define the statutory terms "unused and discarded," and apply its cited FDA guidance on vial fill more broadly[2] to certain weight-based dosed drugs and those delivered via a complex procedure in its assessment of when a therapy should qualify as a unique circumstance. Further, ARM urges CMS to similarly utilize its unique circumstances authority to apply either a 100 percent applicable percentage or permit the use of a JZ modifier for discarded drugs in connection with all cell, immune, and gene therapies in recognition of the specialized manufacturing and patient administration criteria of these therapies.

Early regenerative medicine products have demonstrated profound, durable and potentially curative benefits that are already helping thousands of patients worldwide, many of

[1] 87 Fed. Reg 45,860 (July 29, 2022).
[2] https://www.fda.gov/media/88138/download

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 13-year history, ARM has become the global voice of the sector, representing the interests of 450+ members worldwide, including small and large companies, academic research institutions, major medical centers and patient groups. As of year-end 2021, there are 1,308 regenerative medicine and advanced therapies developers worldwide sponsoring 1,200 clinical trials across dozens of indications, including rare monogenetic diseases, oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, and more.[3]

As discussed in previous comment letters, a large subset of these clinical trials focuses on the power of cell and gene therapies. These therapies are the first in a wave of new and exciting advanced therapies and technologies that are the next frontier in the fight against some of humankind's most devastating diseases and disorders. ARM is currently tracking the outcomes of approximately 897 cell-based immuno-oncology (cell IO) trials which includes CAR T therapies. In addition, ARM tracks hundreds of other clinical trials exploring the power of the immune system, particularly focused on T cells. ARM believes that the new and promising technology of using the patient's own immune system to fight disease provides the possibility that future treatments for many types of cancer, at its many stages, could be durable and curative.

Meanwhile, gene editing continues to advance as a therapeutic modality. There are currently 41 trials ongoing in gene editing, about one-third of which are in Phase 1 with the remainder in Phase 2.[4] Most of these trials (80%) use CRISPR technology, demonstrating the strong foothold this technology has established since the initiation of the first CRISPR gene-editing trial in 2019.[5] Many of these therapies have complicated delivery procedures and administration regimens for patients that can be compromised by discarded drug concerns.

ARM therefore urges CMS to use its unique circumstances authority to exclude the application of discarded drug policy to these therapies. In doing so, CMS will remove these concerns and provide predictability and certainty to the innovators in this sector and the providers who administer these therapies allowing them to focus on delivering the right amount of drug, to the right beneficiary, at the right time.

Executive Summary:

- *Under the Unique Circumstances Authority, CMS Should Apply 100 Percent Applicable Percentage or Permit the Use of the JZ Modifier for all Therapies That Can Only Be Administered Once Such as Cell and Gene Therapies.*
- *Vial Fill Amounts of 1mL and Smaller Should Be Assigned a 100 Percent Applicable Percentage or Assigned JZ Modifier*
- *Certain Complex Procedures Should be Assigned a JZ Modifier or 100 Percent Applicable Percentage*
- *The Applicable Percentage for Weight Based Drugs Should be Drug Specific*

[3] https://alliancerm.org/sector-report/2021-annual-report/
[4] Id.
[5] Id.

- *CMS Should Establish a Comprehensive Dispute Resolution Process*
- *CMS Should Establish a Process for Identifying a Unique Circumstance Outside of Physician Fee Schedule*

I. Current Discarded Policy Differentiates Based on Administration

Historically, CMS has categorized discarded drugs into one of two categories, drug administered to the patient, or a drug discarded up to the labeled amount. Practically, this bright line definition had very little impact on the healthcare system because there was no refund attached to the discarded drug, as the Agency reimbursed providers and suppliers for the labeled amount. Specifically, CMS states in its Medicare Claims Processing Manual that "when a physician, hospital or other provider or supplier must discard the remainder of a single use vial or other single use package after administering a dose/quantity of the drug or biological to a Medicare patient, the program provides payment for the amount of drug or biological discarded as well as the dose administered, up to the amount of the drug or biological as indicated on the vial or package label."[6] The Agency further advises that effective January 1, 2017 when processing claims for drugs and biologicals local contractors shall require the use of the JW modifier to identify unused drugs or biologicals from single use vials or single use packages that are appropriately discarded and that this modifier, billed on a separate line, will provide payment for the amount of discarded drug or biological."[7] In this guidance CMS use the terms "unused" and "discarded" interchangeably. That is, this sentence supports the interpretation that "unused" drug is the same as discarded drug, which as ARM details below is not always the case. ARM believes the proper interpretation of the legislative text of the Infrastructure Investment and Jobs Act supports this view.[8]

There are circumstances in which active ingredient is part of the label but is not administered into the patient. This amount serves a critical role in the proper administration of the drug to ensure patient safety and should be considered used drug not subject to a refund. ARM believes that this is supported by the new law and CMS' own example offered in the preamble to the Proposed Rule. Therefore, given the new legal requirements of this statute, ARM believes that CMS is required to revisit the definitions of unused and discarded drug particularly as it relates to cell, gene, and immunotherapies, as well as those therapies administered via a complex procedure or extracted from small vial fills.

II. The Statute Requires CMS to Apply a Two-Step Process to Determine Discarded Drug

Section 90004 of the Infrastructure Investment and Jobs Act (Pub. L. 117–9, November 15, 2021) amended current law to require manufacturers to provide a refund to CMS for certain discarded amounts from a refundable single-dose container or single-use package drug. The refund amount is the amount of discarded drug that exceeds an applicable percentage, which is required to be at least 10 percent, of total charges for the drug in a given calendar quarter.[9]

[6] Medicare Claims Processing Manual, Chapter 17, § 40.
[7] Id.
[8] Section 90004 of the Infrastructure Investment and Jobs Act (Pub. L. 117–9), November 15, 2021.
[9] Id. at 46,056.

ARM believes that Congress established a clear definition of discarded drug in new Section 1847A(h)(1)(B), which is as follows:

> "For purposes of subparagraph (A)(i), with respect to a refundable single-dose container or single-use package drug furnished during a quarter, the amount of such drug that was discarded shall be determined based on the amount of such drug that was **unused and discarded** for each drug on the date of service."

ARM therefore believes that CMS must establish that the drug was both unused and discarded. This is clearly a two-step interpretive process, requiring the Agency to first define and apply the term "unused." If Congress wanted manufacturers to provide a refund on just "discarded" drug, then the word "unused" would simply not be in the law. Instead, the law would merely address the two categories set forth by CMS an administered drug and a discarded drug. Congress, however, added the term "unused" and based on the longstanding canon of statutory interpretation of "verba cum effectu sunt accipienda," every word and provision in the law is to be given effect. These terms are not interchangeable and must be recognized for their separate meanings.

The plain meaning of the word "use" is to "deploy (something) as a means of accomplishing a purpose or achieving a result," by contrast "unused" drug must therefore mean drug that had no purpose or that was not deployed to achieve a result. In establishing a difference between unused and discarded, ARM urges CMS to recognize the plain meaning of the word "unused" to conclude that active ingredient that is used to safely administer an appropriate dose without being administered into the patient is considered used product and not subject for a refund. ARM believes that Congress chose the word "unused" to imply that the liquid was not instrumental in assuring that a safe and effective dose was administered to the patient, and then it is discarded. Under that scenario, it seems reasonable for manufacturers to pay a refund on that amount. If, however, the liquid served a useful purpose to safely administer the clinical dose, this liquid should not be considered for a refund. For example, there are small vial fills that contain active ingredient, beyond overfill, that is in the vial to assure that the appropriate dose is withdrawn and then administered to the patient consistent with the FDA approved required dose. Additionally, gene vectors are engineered, and cell and immunotherapies are designed to deliver the necessary genes and immune cells for treating the disease. These processes, as detailed below, result in specified amounts of biologicals that are all used as part of the safe administration of active ingredient.

Finally, CMS recognizes the distinction of used for a clinical purpose versus "unused" by citing an example of a drug that is reconstituted with a hydrogel and administered via ureteral catheter or nephrostomy tube into the kidneys where there is substantial amount of reconstituted hydrogel that adheres to the vial wall during preparation. In this example, CMS proposes that the drug amount that adheres to the vial wall (and not able to be extracted from the vial) and must be discarded perhaps inappropriately leads to a higher percentage of discarded units billed with the JW modifier.[10] In response, CMS proposes a 35 percent drug discarded percentage. ARM

[10] Id.

supports this higher percentage and believes it complies with Congressional intent. ARM urges CMS to establish a policy that any drug that is needed and "used" to safely administer active ingredients to patients is NOT considered "unused" and therefore not subject to a refund.

III. Under the Unique Circumstances Authority, CMS Should Apply 100 Percent Applicable Percentage or Permit JZ Modifier to all Therapies Designed to be Delivered One Time Such as Cell, Immune, and Gene Therapies.

Cell, gene, and immunotherapies 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 beneficiary. The overwhelmingly one-time nature of these therapies requires that all potentially needed product be on hand and available for all procedures, consistent with clinical trial data and FDA-approved labeling. For example, gene therapy seeks to modify or introduce genes into a patient's body with the goal of durably treating, preventing, or potentially even curing disease, including several types of cancer, viral diseases, and inherited disorders. Gene therapy approaches include replacing a mutated gene that causes disease with a functional copy; introducing therapeutic proteins to continuously fight disease; or delivering a new, correct copy of a gene into the body.[11] Gene therapy may be performed in vivo, in which a gene or therapeutic protein is transferred to cells inside the patient's body, or ex vivo, in which a gene is delivered to a patient's extracted cells outside of the body, which are then transferred back into the patient .

Typically, gene therapy developers introduce genes or proteins into patient cells using vectors, which are often deactivated viruses. Deactivated viruses are designed to be unable to make patients sick but serve as the vehicle to transfer the new genetic material into the cell. Viruses that have been used for human gene therapy include retroviruses, adenoviruses, herpes simplex, vaccinia, and adeno-associated virus (AAV).[12] Other ways of introducing new genetic material into cells include non-viral vectors, such as nanoparticles and nanospheres.

Gene therapy techniques can also be used to genetically modify patient cells ex vivo, which are then re-introduced into the patient's body in order to fight disease, an approach known as gene-modified cell therapy. This approach includes a number of cell-based immunotherapy techniques, such as chimeric antigen receptors (CAR) T cell therapies, T cell receptor (TCR) therapies, natural killer (NK) cell therapies, tumor infiltrating lymphocytes (TILs), marrow derived lymphocytes (MILs), gammadelta T cells, and dendritic vaccines.[13]

The delivery of AAV gene therapy may create antibodies in the treated patient, giving rise to immunogenicity concerns which could preclude re-dosing. Unlike other treatment modalities, AAV gene therapies and other similar therapies generally require that all dosing be completed in a single session. Similarly, cell and immunotherapies are 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.

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[11] https://alliancerm.org/technologies/gene-based-medicine/

[12] https://www.fda.gov/consumers/consumer-updates/how-gene-therapy-can-cure-or-treat-diseases?utm_medium=email&utm_source=govdelivery

[13] https://alliancerm.org/technologies/gene-based-medicine/

A variety of different types of technologies can be used in cell, gene, and immunotherapies, most of which require that all dosing be completed in a single session; all the active ingredient is used for and intended for that beneficiary and therefore should be excluded from a refund.[14]

The unique nature of these treatment modalities, which often prevents any re-dosing of a patient, requires that the maximum potential needed product – consistent with clinical trial data and FDA labeling – be available for each procedure administration. Patients should not be exposed to, and physicians should not be forced to risk performing an incomplete and ineffective procedure because of a limitation on the amount of available product; this could be an unintentional consequence of applying a rigid, inflexible discarded drug policy to gene, cell, or immune therapies. Instead, to protect patient safety and maximize the potential of therapeutic effect, cell and gene therapies should have a 100 percent applicable percentage under the discarded drug policy. This will ensure that all patients can receive the necessary dose at the time of dosing. In that regard, there may be circumstances where a cell, gene or immunotherapy is administered to a patient over a course of time. The time variable can, however, be interrupted by a patient-physician decision to discontinue receiving therapy. ARM urges CMS to consider this process as used drug as well and exclude this entire regimen from the refund requirement.

In the alternative, CMS could instruct providers to use the JZ modifier for all claim forms for a cell and gene therapy administration given their unique nature, giving physicians the ability to treat all patients confidently and correctly without jeopardizing patient health or treatment effectiveness.

IV. Due to Unique Circumstances Certain Vial Fill Amounts and Weight Based Dosed Therapies Should Also Have Higher Applicable Percentages

A. Background

Beginning January 1, 2023, manufacturers of single source drugs and biologicals (drugs) are required to provide a refund to CMS for certain discarded amounts from a refundable single-dose container or single-use package drug.[15] The refund amount is the amount of discarded drug that exceeds an applicable percentage, which is required to be at least 10 percent, of total charges for the drug in a given calendar quarter.[16] There are, however, exceptions to this requirement. Specifically, the statute provides, and ARM encourages CMS to codify in regulation, that a refundable single dose container or single-use package drug does not include a

[14] ARM notes that USP has not published permissible vial fills for cell, gene, or immunotherapies such that ARM believes that CMS cannot rely on USP guidance on overfill or otherwise for these cutting-edge therapies. https://www.drugfuture.com/pharmacopoeia/usp35/PDF/0765-0784%20%5B1151%5D%20Pharmaceutical%20Dosage%20Forms.pdf
USP

[15] Id. at 46,056.

[16] Social Security Act (SSA) §1847(h)(3)(B)(i)(II).

radiopharmaceutical or imaging agent, certain drugs requiring filtration, certain new drugs, and those drugs with "unique circumstances" as determined by the Secretary.[17]

In discussing its authority to increase the applicable percentage for any drug with unique circumstances, CMS states that "[w]e expect that for most drugs supplied in single-dose containers, the amount of drug indicated on the vial or container reflects the amount of drug that could potentially be administered to a patient."[18] In support of this conclusion, CMS cites FDA guidance, which provides that "for drugs in ampules or vials intended for injection, the declaration of net quantity of contents on the label is considered to express the minimum quantity of contents and that variation above the stated measure must comply with the excess volumes set forth in the United States Pharmacopeia (USP)."[19] CMS further states that "[i]n this guidance, FDA recommends that single-dose vials should not contain a significant volume beyond what would be considered a usual or maximum dose for the expected use of the drug product.[20]

ARM believes the Agency should not overly restrict the application of its unique circumstances' authority given the many types of modes of administration, classes of drugs and vial sizes that providers use to treat a diverse Medicare beneficiary population. CMS should therefore broaden its applicability of this authority to the examples stated below. In doing so, ARM believes that CMS will preserve appropriate access to society's next generation of cutting-edge therapies.

B. Vial Fill Amounts of 1mL and Smaller Should Be Assigned a 100 Percent Applicable Percentage or Assigned JZ Modifier

CMS states that "[w]e expect that for most drugs supplied in single-dose containers, the amount of drug indicated on the vial or container reflects the amount of drug that could potentially be administered to a patient."[21] While this might be the case for many vial fill amounts, ARM believes that there are certain circumstances where the contents of the vial are used to ensure that the appropriate amount of active ingredient is injected into the patient and therefore should not be considered discarded drug. For example, vial fill sizes of 1mL or less only contain drops of liquid and each drop counts, as they are used as part of the administration process. Specifically, the additional volume beyond overfill in these tiny amounts is used to:

- account for drug that may be encased on the vial wall,
- compensate for drug that cannot be withdrawn due to vial adapter geometry,
- manage expected variation in filling equipment,
- compensate for dead volume remaining in needle and syringe during transfer, and
- account for a drop or two of drug that may be unintentionally dispelled due to pressure changes that can be quite significant in small vials.
- basic fluid dynamics require more drops to execute clinical effect.

[17] 87 Fed. Reg. at 46,061.
[18] Id. at 46,061.
[19] 21 CFR 201.51(g); https://www.fda.gov/media/88138/download
[20] Id.
[21] Id. at 46,061.

The FDA considers in its vial fill the amount of liquid required and used to express a needle and to account for dead volume in the transfer, and so should CMS because this active ingredient served a useful purpose. ARM urges CMS to recognize that withdrawing and then administering exceptionally small volume leads to higher percentage of drug discarded due to loss in the transfer or priming of the administration. These drops are not significant volume beyond what would be necessary to achieve maximum clinical effect and should not be considered discarded drug. These drops serve an important function to properly administer appropriate dose. They are not "waste," the drops do not remain in the vial, and certainly cannot be used for another beneficiary.

As mentioned above, CMS does state an example of a unique circumstance that might require a higher "applicable percentage" of exempted discarded drug that is very similar to the 1mL vial fill or less situation. Specifically, the Agency describes as an exception a drug that is reconstituted with a hydrogel because there is a substantial amount of reconstituted drug that adheres to the vial during drug preparation. CMS concludes that "the drug adhering to the vial wall (and not able to be extracted from the vial) must be discarded, which leads to a higher percentage of discarded units billed with the JW modifier."[22] As stated above, this is also an issue for vial fill sizes of 1mL or less in terms of necessary liquid in the vial used to achieve a clinical effect. The additional volume in the vial is meant to be sufficient to permit withdrawal and administration of the labeled volumes. Each drop of liquid in the vial is used and is necessary for the clinical outcome desired, and like the hydrogel example, should not be considered discarded drug.

Fluid dynamics does not allow for a smaller vial or the assurance that the appropriate dose will be administered to the beneficiary. ARM does not believe manufacturers should pay a refund on a vial size for which it basically cannot control. Consequently, CMS should assign a 100 percent applicable percentage to vial fill sizes less than or equal to 1mL or assign the JZ modifier.

C. Certain Complex Procedures Should be Assigned a JZ Modifier or 100 Percent Applicable Percentage

Similarly, ARM believes that discarded drug resulting from a complex drug administration procedure should have a higher applicable percentage. For example, any product used during complex administration procedures, defined as those that require specialized equipment, multiple preparation steps and/or multiple administration attempts, should qualify because these techniques often utilize extra product to ensure proper dosage. The amount of product is dependent on unpredictable variables such as patient characteristics, physician surgical approach, choice of equipment, and/or if priming is required (for example hold-ups in syringe, tubing, and cannula, and product loss due to drip tests and multiple administration attempts). This variability should not be considered discarded drug.

Like small vial fills, novel and complex processes are typically designed to deliver drugs most efficiently and effectively to a wide range of patients. Extra amounts of active ingredient are required and used to achieve these objectives. Classifying these amounts as discarded drug

[22] Id.

would significantly hurt the commercial viability of the specific process. As such, any product used during complex administration procedures, defined as those that require specialized equipment, multiple preparation steps and/or multiple administration attempts, should be assigned a JZ Modifier or 100 percent applicable percentage.

D. The Applicable Percentage for Weight Based Drugs Should be Drug Specific

As mentioned above, in implementing the discarded drug policy CMS quotes FDA's guidance to manufacturers "that single-dose vials should not contain a significant volume beyond what would be considered a usual or maximum dose for the expected use of the drug product."[23] ARM appreciates that CMS refers to this guidance and urges the Agency to apply this concept to weight based dosing. Consistent with this FDA guidance, companies design and manufacturer vials to account for variability in body weight and body surface area, which is typically much more efficient, practical, and financially prudent than producing many different vial sizes.

By design, dosing variability exists for therapies that are weight-based; yet CMS doesn't address this fact. There is much greater than ten percent variability in weight and body surface area amongst Medicare beneficiaries that CMS ignores in implementing its discarded drug policy. It is not practicable for companies to manufacturer many different vial sizes for weight-based purposes. Even if this were to occur, it is not reasonable to expect pharmacies and hospitals to stock many different vial sizes for weight-based therapies.

For some one-time durable gene therapies, a package of vial sizes may be specifically tailored by the manufacturer to a patient's weight as reported by the provider, meaning no wastage should occur without a deviation from treatment guidelines and incentivizing such a deviation could have safety and efficacy implications for patients. For these reasons, ARM believes that a uniform standard for weight-based drugs is inadvisable. As such, ARM urges CMS to reconsider its approach to applying the discarded drug policy to weight-based dosing by establishing a process that examines each weight-based drug and establish a refund policy for only those extreme outlier circumstances. Manufacturers should not have to pay a refund for developing vials that can serve the overwhelming majority of beneficiaries, only the extremes shall be eligible for refund.

V. CMS Should Establish an Appeals Process Within its Dispute Resolution Process to Include a Manufacturer's Applicable Percentage or Exclusion Request

In the Proposed Rule, CMS proposes to establish a dispute resolution and appeals process specific to the implementation of Section 90004 of the Infrastructure Investment and Jobs Act. We agree with the Agency that such a process will facilitate smoother implementation of the discarded drug refund requirement and recommend that CMS finalize this policy.

To further streamline implementation of the statutory requirements, ARM recommends that CMS broaden the dispute resolution and appeals process to cover disputes related to the agency's denial of a requested higher "applicable percentage" or exclusion for a particular drug.

[23] https://www.fda.gov/media/88138/download

Presumably, CMS would make these determinations as part of the annual rulemaking process. Expanding the scope will provide CMS with the vehicle and the opportunity to recognize and address, like it did with the determination of charges and the refund amount, the potential for error in making these determinations, and give manufacturers the opportunity to address the dispute in a consistent manner.

By expanding the scope of the proposed dispute resolution process beyond challenging erroneous refund calculations as proposed, CMS would contribute to a more robust and predictable regulatory framework and "aid[s] in the successful implementation of [the discarded drug refund requirement]".[24] To provide the Agency and public with certainty, such a dispute resolution process could be made available to manufacturers for a limited amount of time (e.g., 60 days) after issuance of the final rule. In the absence of such an opportunity, manufacturers would need to wait until the next rulemaking cycle to have the issue considered by the agency; for manufacturers unable to wait that long, this delay may result in unnecessary and costly challenges to the determination.

The proposed regulations already contemplate and outline the basic process that could be adopted to address a different but equally important need (rebate calculation). Without such a process, CMS and manufacturers face the possibility of ongoing confusion over how to linearly address problems that arise during and after a "unique circumstances" determination, which CMS could alleviate by proactively implementing a process to address such complaints. This discretionary determination is made by analyzing groundbreaking drug therapies and the complex calculations required for their safe and effective administration, thus it merits as much opportunity as possible for CMS to consider any factual disputes and for manufacturers to thoroughly explain all aspects.

This recommendation complements CMS's intention to establish good policy by creating a streamlined and expedited dispute resolution process for other parts of the provision. ARM urges CMS to broaden the dispute resolution and appeals process to cover disputes related to the agency's denial of a requested higher "applicable percentage" or exclusion for a particular drug.

Additionally, because of the confidential proprietary commercial information contained in each dispute report, ARM further urges CMS to confirm that the dispute resolution process will be confidential and that none of the reports issued to manufacturers during the dispute will be public. ARM also recommends that the appeal and dispute processed be conducted by individuals who were not involved in the original decisions.

VI. CMS Should Establish Clear Criteria and Definitions for When a Therapy Qualifies as a Unique Circumstance.

In finalizing the discarded drug policy, ARM urges CMS to clearly define some initial criteria that the Agency believes satisfies the unique circumstance criteria. Specifically, are there classes of products, modes of administration, or disease states that the Agency believes categorically contain unique circumstances necessitating a higher applicable percentage? ARM's comments detail many of these examples, and ARM believes that CMS' final rule should

[24] 87 Fed. Reg. at 46052.

establish a framework that further guides industry on how CMS will apply its unique circumstances authority.

Second, CMS should establish a process for the manufacturer to engage CMS on the applicability of these criteria to any particular drug. Specifically, CMS should develop an application process for manufacturers to help understand whether a product's vial size, complex procedure or delivery mechanism qualifies as a unique circumstance. This predictability and transparency will materially help manufacturers understand CMS' policy, inform vial development, and avoid unnecessary discarded drugs.

In constructing the application and appeals processes, CMS should explicitly build in, as appropriate, the ability for the agency and innovator manufacturers to consult with relevant expert agencies and other organizations, including the Food and Drug Administration and the United States Pharmacopeia. This is consistent with recommendation 2-2 contained in the Congressionally mandated, CMS-commissioned 2021 report conducted by the National Academies of Sciences, Engineering, and Medicine, *Medications in Single-Dose Vials: Implications of Discarded Drugs.*[25]

As CMS and manufacturers work together to implement the new law designed to reduce, to the extent practicable, the amount of drug product not actually delivered to patients, there will be numerous issues of first impression that will arise and need to be resolved. Many of these novel questions will relate to gene and cell therapy products as the science in this area continues to evolve and the pipeline grows. In order to help facilitate the development and delivery of these potentially life-altering therapies, it will be constructive for CMS and innovators to have the benefit of the most informed thinking of leading technical experts as it fashions, refines and applies its new policies and procedures.

VII. Issues Related to Average Sales Price

As CMS does not publish all manufacturer submitted Average Sales Price (ASP) data on the ASP drug pricing file, "there are likely billing and payment codes payable under Medicare Part B that would meet the proposed definition of refundable single-dose container or single-use package drug that are not found on the ASP drug pricing file or the JW modifier data published on the CMS website."[26] ARM agrees that these drugs are included in the discarded drug policy but urges CMS to publish the ASPs of these drugs on the ASP drug pricing file and publish JW modifier data published on the CMS website. By providing this transparency, providers and manufacturers will be better prepared to transition to and comply with this new policy. ARM believes that if CMS collects a rebate on discarded drug, it is only fair that the drug's JW modifier data and ASP also be published.

CMS states that the refund amount is calculated as the product of the "total number of units of the billing and payment code for such drug that were discarded during such quarter; and

[25] The National Academies Press 2021, Washington, D.C. https://doi.org/10.17226/25911, Recommendation 2-2, p.56.
[26] Id. at 46,058.

the payment limit amount for the refundable single-dose container or single-use package drug."[27] CMS states that it will use 106 percent of the ASP as the payment limit amount. ARM, however, believes that if sequestration is in place the payment limit amount should be 104.3 percent of the ASP consistent with Congressional intent of this being only a refund program.

VIII. Conclusion

ARM is confident that meaningful improvements in clinical outcomes and cost reduction can be accomplished through regenerative medicine technologies. ARM believes that the field of regenerative medicine has the potential to heal people and bend the health cost curve toward lower long-term costs and higher quality outcomes. This trend is already evidenced by several approved and marketed first-generation regenerative medicine products that are demonstrating both clinical and cost reduction value. Accordingly, we could substantially reduce overall healthcare expenses by reducing hospital care, the need for physician, clinical and professional services, nursing, and home healthcare.

We thank CMS for its many proposals and statements in the Proposed Rule and look forward to working with CMS to establish policies that promote appropriate access to regenerative medicine therapies in both the near term and long. Please free to contact Brett Logan (blogan@alliancerm.org) with any questions.

Sincerely,

/S/ Brett Logan

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

[27] Id. at 46,061.