March 4, 2014

Marilyn Tavenner
Administrator
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Avenue, SW - Room 445-G
Washington, DC 20201

Re: Policy and Technical Changes to the Medicare Advantage and Medicare Prescription Drug Benefit Programs for Contract Year 2015 (CMS-4159-P)

Dear Administrator Tavenner:

On behalf of the American Society of Transplant Surgeons, I am writing to object in the strongest possible terms to the proposal published by the Centers for Medicare and Medicaid Services (CMS) on Monday, January 6, 2014, to remove immunosuppressants from the list of six protected classes of drugs under Medicare Part D, effective in 2015 (the "Proposed Rule"). ASTS is an organization composed of more than 1800 transplant surgeons, physicians, and scientists dedicated to excellence in transplantation surgery through education and research with respect to all aspects of organ donation and transplantation so as to save lives and enhance the quality of life of patients with end stage organ failure.

Current policy ensures that transplant recipients have access to the most appropriate immunosuppressants by prohibiting Part D plans from restricting access through formularies. The Proposed Rule would enable Part D sponsors to impose formulary restrictions on these critical drugs, resulting in substantial risk of rejection, serious side effects, and other adverse drug reactions for Medicare Part D beneficiaries who are transplant recipients.

Background: Medicare Part D Coverage of Immunosuppressants

Immunosuppressant drugs are covered under Part B provided they are used in immunosuppressive therapy by a beneficiary who received a transplant covered under Medicare Part A. In all other situations, these drugs are covered under Part D. In 2007, 74,000 beneficiaries took immunosuppressants under Part B, and more than 80,000 beneficiaries took immunosuppressants under Part D.

For the most part, the standard of care for immunosuppressant therapy in kidney transplant recipients—the most common form of transplantation—is a combination of a calcineurin inhibitor and an antimetabolite (with or without a corticosteroid). The most commonly prescribed calcineurin inhibitor is a daily dose of tacrolimus (TAC), and the more commonly prescribed antimetabolite is a daily dose of mycophenolate mofetil (MMF). The first generic of tacrolimus was approved in 2009, and generics for MMF were approved in 2008. At this stage, it is estimated that the majority of recipients receiving any form of TAC and the majority of recipients receiving any form of MMF are receiving generics. In addition to TAC-based and MMF-based medications, other prescribed immunosuppressants include cyclosporine-based medications, mammalian target of rapamycin (mTOR) inhibitor-based medications, belatacept, azathioprine, and prednisone.

History of the Six Protected Classes Rule

The Medicare Modernization Act (MMA) created the Medicare Part D drug program in 2003, and, when CMS implemented the program, Congress urged the agency to cover "*all or substantially all*" medications within certain protected classes. As a result, CMS issued sub-regulatory guidance identifying six classes and categories of drugs (including immunosuppressants) that would not be subject to formulary restriction. Due to uneven implementation of this informal guidance, Congress enacted Section 176 of the Medicare Improvements for Patients and Providers Act (MIPPA), which established statutory protection for immunosuppressants and five other protected classes of drugs under Medicare Part D by requiring Medicare Part D drug plans to include in their formularies access to *all or substantially all* drugs in the six identified classes.

It is against this backdrop that the Affordable Care Act (ACA) provided CMS with authority to develop criteria to "identify, as appropriate, categories and classes of drugs for which the Secretary determines are of clinical concern." As such, Congress codified protected class status for immunosuppressants and the other five pre-existing protected classes of drugs and expanded protected status to *all* drugs within these six classes, although this codification is subject to the pending rulemaking.

The Proposed Regulation

The Proposed Rule proposes to withdraw protected status for three of the current six protected classes of drugs, including immunosuppressants. In so doing, the Proposed Rule sets forth extremely stringent criteria for a drug class or category to meet in order to obtain or retain protected status. Under the Proposed Rule, a class or category of medication must meet both of the following standards to retain or obtain protected status:

- For a "typical individual," hospitalization, persistent or significant disability or incapacity, or death likely will result if initial administration (including self-administration) of a drug in the

category or class does not occur within 7 days of the date the prescription for the drug was presented to the pharmacy to be filled; **and**

- More specific CMS formulary requirements will not suffice to meet the universe of clinical drug-and-disease-specific applications due to the diversity of disease or condition manifestations and associated specificity or variability of drug therapies necessary to treat such manifestations.

In the Proposed Rule, CMS indicates that immunosuppressants meet the first of these standards but not the second. For this reason, CMS proposes to withdraw protected class status for immunosuppressants, thereby facilitating the imposition of formulary restrictions on transplant recipients' access to these critical drugs. With the changes proposed by CMS, access to immunosuppressants could be limited to only two medications in each class and category.

The sole rationale provided in the Proposed Rule for establishing such narrow criteria for protected class status and to so substantially modify longstanding Medicare policy is that, because drug manufacturers understand that formulary restrictions may not be imposed on medications that fall within the protected classes, they are generally unwilling to provide substantial discounts to Part D plans for these drugs. The Proposed Rule fails to discuss or otherwise take into account the potential for substantial increases in Part A or Part B costs in the event that inadequate immunosuppression results in organ rejection, hospitalization, or other adverse health consequences for Medicare Part D beneficiaries. Nor does the Proposed Rule explain the agency's reversal of its prior position that access to all or substantially all immunosuppressants is necessary due to the complexity of immunosuppressive regimens, the severity of the health consequences in the event that immunosuppression is ineffective, and variation in individual response.

ASTS Comments and Observations

The ASTS strongly urges CMS to refrain from authorizing Part D plans to impose formulary restrictions on Medicare patients' access to critical immunosuppressants. Immunosuppressants unequivocally meet **both** of the standards set forth for protected class status in the Proposed Rule. Moreover, allowing the imposition of formulary restrictions on the immunosuppressants available to Part D beneficiaries has the potential to result in dire health consequences for individual enrollees; to exacerbate an already critical organ shortage; to result in additional confusion and medication non-adherence; and to establish unjustified distinctions in coverage between Part D beneficiaries and those covered under Part B or private plans. In addition, authorizing such formulary restrictions has the potential to significantly increase, rather than decrease, overall patient and program costs.

A. Immunosuppressants Meet Both of the Proposed Standards for Inclusion in a Protected Class.

CMS correctly determined that immunosuppressants meet the first of the two standards proposed for inclusion of a drug class or category in a protected class: We most certainly concur that the first standard is met. Indeed, significant health consequences result if immunosuppression is not instituted within seven days of a prescription. However, CMS' determination errs in concluding that immunosuppressants fail to meet the second of the two proposed standards. In fact, there is a critical need for physicians to have the flexibility to individualize immunosuppressant therapy, both to protect against rejection and to minimize potentially serious side effects. Because individual patient response to various immunosuppressants is idiosyncratic and cannot be predicted, it is impossible for CMS to impose formulary requirements without unreasonably restricting access to those drugs that may be critical for individual patients.

CMS' conclusion that transplant surgeons do not need access to the full panoply of immunosuppressants to individualize therapy and ensure against rejection is based solely on the determination of a panel of CMS pharmacists and the CMS Chief Medical Examiner. It does not appear that the panel of pharmacists involved includes transplant pharmacists, nor does it appear that transplant physicians or surgeons participated in the panel deliberations. The Proposed Rule indicates that, because widely accepted treatment guidelines recommend subclasses of drugs rather than specific, individual drugs, the panel did not believe that every drug product should be required for inclusion on Part D sponsors' formularies.

Conversely, and quite inconsistently, CMS insists that the relevant treatment guidelines are sufficiently detailed to enable the agency to establish "additional, specific formulary requirements" without needing to require that Part D sponsors make all or substantially all immunosuppressants available to Medicare Part D beneficiaries.

CMS' rationale for concluding that immunosuppressants do not meet the second of its proposed "protected class" criteria is unsupportable for several reasons. First, the panel specifically references only a single guideline, the 2009 treatment guidelines for the Long-Term Treatment of the Liver Transplant Patient, and notes that this guideline does not recommend specific drugs within each of the classes over any other in the same class. The panel concludes that CMS' current formulary review requirements based on treatment guidelines would capture immunosuppressants in all the classes of drugs delineated in the guideline, and, on this basis, the panel concludes the current beneficiary protections are sufficient.

Unfortunately, the panel draws an incorrect conclusion based on its review: While this guideline does outline recommended immunosuppressant therapy in terms of the classes of drugs generally included in an effective immunosuppressant regimen, this guideline does not suggest or imply that individuation of immunosuppressive regimens within these classes is not required. In fact, it is precisely because different recipients react differently to the drugs within each class that specific drugs are not recommended by the guideline. The same is true of other treatment guidelines that specify the

recommended immunosuppressive regimen in terms of the classes of drugs and not in terms of specific named immunosuppressants.

Second, in fact, the need to individualize immunosuppressants to meet individual patient needs is well recognized in the clinical literature, in clinical guidelines, and in the statements of professional associations. Immunosuppressive medications are not interchangeable. They are prescribed in combinations tailored to meet the unique needs of the individual transplant recipient in order to achieve sufficient immunosuppression while minimizing the toxicity associated with individual agents. Restrictive formularies limit physicians' ability to prescribe the right combination of medications to protect the recipient from organ rejection and other serious side effects. This delicate balance was recognized in the original decision to include these medications under protected status.

Transplant physicians devote a significant portion of their training to learning the nuances of recipient-centered immunosuppression. A major focus of transplant physicians' attention to transplant recipients is dedicated to individualizing the post-transplant immunosuppressive regimen. One of the largest areas of transplant research is directed toward comparison of different immunosuppressive drugs and regimens. All of these efforts are based on the need to prolong transplant graft survival and to decrease the multitude of life-threatening side effects caused by immunosuppressive agents. Each patient has a unique risk for rejection and for untoward effects of immunosuppressive drugs. Access to all available drugs permits choice of a regimen that minimizes side effects such as renal failure, diabetes, hypertension, hyperlipidemia, neurotoxicity, bone marrow suppression, gastrointestinal toxicity, and others. It is precisely such access to a growing number of immunosuppressive agents and attention to individualizing regimens for each patient that has been a major contributor to improved transplant organ and patient survival. Any barrier to nuanced immunosuppression will lead to worse patient outcomes.[1,2]

Third, it is unclear how CMS can reasonably and simultaneously conclude that BOTH (1) the recommended protocols for immunosuppression are so general that they "only recommend subclasses of drugs rather than specific individual drugs" AND (2) that these very same protocols are sufficiently detailed for the agency to formulate "additional specific formulary requirements" that are sufficient to account for individual variation among transplant recipients. In fact, it is precisely because individual reaction to immunosuppressants is virtually impossible to predict that applicable treatment guidelines do not specify individual drugs but rather formulate recommendations in terms of drug classes and sub-classes. It is extremely difficult for us to understand how CMS can formulate "additional, specific formulary requirements" when those expert in the field, including highly trained and experienced

[1] American Journal of Health-System Pharmacists, Volume 69 (2012), article ID 110624; http://www.ajhp.org/content/69/22/1961.full.pdf+html?hw-tma-check=true

[2] The New England Journal of Medicine, Volume 351 (2004), article ID 033540; http://www.nejm.org/doi/pdf/10.1056/NEJMra033540

transplant pharmacists, physicians, and surgeons, have concluded that it would be unreasonable to do so in the face of the vast variation in transplant recipients' reactions to the array of immunosuppressive agents currently available.

B. **Limiting Access to the Full Range of Immunosuppressants Available to Transplant Recipients Has the Potential to Endanger Patients**.

CMS' Proposed Rule appears to be premised on the assumption that transparency, appeals, and other Part D protections are sufficient to ensure that the imposition of formulary restrictions on the availability of immunosuppressants will not increase organ rejection or otherwise endanger Medicare beneficiaries. We strongly disagree. In fact, finalizing the Proposed Rule in its current form holds substantial risk for highly vulnerable transplant recipients covered under Medicare Part D.

Inadequate immunosuppression causes organ rejection, subsequent need for risky treatments, often transplant organ loss, and sometimes patient death.[1,2] Contrary to CMS' assertions, current transparency, appeal, and other procedural requirements are not sufficient to ensure Medicare beneficiary access to individualized immunosuppressant regimens in the face of formulary restrictions. The CMS appeals process generally available to Medicare beneficiaries under Parts A and B is undeniably broken, and, while Part D appeals are generally resolved a bit more expeditiously, it is our understanding that most cases are not heard within the 10 days required by Medicare rules. Eliminating protected status not only for immunosuppressants but also for far more frequently used anti-depressants and anti-psychotics would unquestionably swamp the already beleaguered appeals system, and appeals filed by the (relatively few) Medicare Part D transplant recipients likely would be lost in the quagmire.

In fact, limiting access to immunosuppressants based on formulary restrictions would further complicate the already formidable task of managing complex post-transplant immunosuppression regimens. In 2007, the Government Accountability Office (GAO) found that the percentage of beneficiaries whose kidney transplants failed roughly doubled when increasing the timeframe from 36 months following the transplant to seven years. GAO notes in its report:

> (w)hile a lack of health insurance is one reason transplant recipients may stop taking their medication, studies have reported that there are numerous other reasons for medication noncompliance, including avoidance of adverse side effects associated with immunosuppressive medications and difficulty following complex treatment regimens.

Placing further obstacles in the path of elderly transplant recipients covered under Part D by imposing formulary restrictions on critical immunosuppressants unnecessarily increases the risk of life-threatening organ rejection.

The relatively recent availability of a number of important generic immunosuppressants further suggests that this is not the time to facilitate the imposition of formulary restrictions on immunosuppressants. From the approval of the first generic MMF and TAC in July 2008 and August 2009, respectively, through 2012, 10 generic manufacturers of MMF and four generic manufacturers of TAC emerged. The use of generic immunosuppressants has grown steadily and substantially since they became available, and the use of generics is now substantial. Widespread availability of generics has the potential to substantially decrease the cost of immunosuppression both for payers and for patients, undermining the need to withdraw protected status for these drugs to achieve cost savings. Moreover, the relatively rapid increase in the number of generic products available has increased patient and provider confusion, and clinical repercussions of switching to and among various generics have not been studied in depth. The issues related to generic substitution may be compounded by the impact of multiple switches between generic formulations due, in part, to insurance coverage arrangements. Further, monitoring of patient reaction to such switches is difficult since, under current generic substitution practices, the transplant team may not be notified that a patient's immunosuppressant has been switched to a generic, or switched from one generic to another. Patient confusion has been linked to decreased patient adherence,[3] and patient adherence is critical in preventing organ rejection. In short, the imposition of formulary restrictions on the availability of specific immunosuppressants by various Part D plan sponsors would substantially complicate effective immunosuppression for a vulnerable patient population during a time of significant transition and rapid advancements in drug therapy in the field of immunosuppression.

C. Imposing Formulary Restrictions on the Availability of Immunosuppressants Has the Potential to Increase, rather than Decrease, Medicare Costs.

Not only does the imposition of formulary limitations on immunosuppressants have the potential to increase the risk of organ rejection and other complications, it has the potential to increase, rather than reduce, overall program and patient costs for the Medicare program.

First, if this policy contributes to rejection of even a limited number of organs, the increased system costs would be substantial: In 2010, The United States Renal Data System (USRDS) estimated annual per beneficiary Medicare expenditures in 2010 to be $87,561 for a beneficiary receiving hemodialysis (the most common form of dialysis treatment) and $32,914 for a beneficiary with a functioning kidney transplant.

Second, there are numerous other mechanisms built in to Part D that have the potential to limit costs without impeding access to these critically important drugs. For example, Immunosuppressive drugs are already subject to pre-approval requirements and "tiering."

[3] Journal of Transplantation, Volume 2013 (2013), article ID 897434; http://www.hindawi.com/journals/jtrans/2013/897434/#B14

Third, it is unclear whether the cost of immunosuppressants under Part D is substantially out of line. According to the USRDS, in 2010, Medicare expenditures for Part B immunosuppressive drugs were $4,008 per transplant recipient.[4] Only four immunosuppressants have differences of more than $2,000 between annual Part B and Part D beneficiary spending: Thymoglobulin, oral Prograf, Cellcept, and oral cyclosporine. The difference between the total price in Part B and the total price in Part D is smaller for these drugs than for other high price drugs, such as hormonal suppressants, and the three branded products all have Part D prices within 20% of the Part B price.

D. **Other Public Policy Considerations Support the Retention of Immunosuppressants in the Protected Class**.

The imposition of formulary restrictions on immunosuppressants has the potential to result in unsupportable distinctions in the coverage afforded to Medicare beneficiaries under Part D and other transplant recipients. Under the Proposed Rule, Medicare Part D beneficiaries potentially would have much more limited access to immunosuppressant therapy than those insured under the state exchanges. For example, Medicare formulary rules would enable Part D sponsors to offer only two immunosuppressants in each class or subclass. Based on the preliminary 2012 EHB-benchmark plan designs across all states, each state would require health plans offered in the exchanges to cover drugs in the "immunosuppressive agent" classes. Roughly half of all states would require at least 20 different immunosuppressive drug products to be covered in health plans offered through their state's health insurance exchanges. The total number of drug products in the immunosuppressive agent class may not be much larger than 20, which may suggest that if CMS' current formulary rules were applied, Part D plans would be authorized to limit access to immunosuppressants more severely than roughly half of the state exchanges.[5]

Moreover, under the Proposed Rule, Medicare beneficiaries covered under Part D would have considerably more limited access to immunosuppressants than those covered under Part B. Under current law, immunosuppression is covered under Medicare Part B if the initial transplant was covered by Medicare in a Medicare-approved facility, while Medicare Part D covers immunosuppressive drugs for those Medicare beneficiaries whose initial transplant was not covered by Medicare. It clearly makes no sense to provide more limited flexibility in immunosuppressive regimens for some Medicare beneficiaries than for others, based solely on whether the initial transplant was covered by Medicare.

[4] US Renal Data System, *USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Bethesda, MD, 2012, Table K.b, http://www.usrds.org/reference.aspx. This figure is for individuals with Medicare as a primary payer only.

[5] For more information on the EHB prescription drug coverage methodology, see http://www.cms.gov/CCIIO/Resources/Data-Resources/Downloads/ehb-rx-crosswalk.pdf. An estimate of the total numbers of immunosuppressant drug products available is 21. This estimate was gathered from the CMS Formulary Reference File Alignment File by grouping unique identifiers (RXCUIs) with the same active ingredient.

Furthermore, such a policy would foreclose any future administrative efforts to consolidate coverage for immunosuppression under one of the two programs.

For all of these reasons, ASTS strongly urges CMS to refrain from finalizing the Proposed Rule and to retain immunosuppressants as one of the protected classes of drugs under Medicare Part D: Immunosuppressants do in fact meet the two "protected class" criteria proposed by CMS; allowing formulary restrictions has the potential to endanger Medicare Part D beneficiaries who are transplant recipients and to increase costs; and the current formulary review process used by CMS has the potential to result in less access to critical immunosuppressants for Medicare Part D beneficiaries than for recipients who obtain coverage through the state exchanges or under Medicare Part B. We strongly urge CMS to reconsider this counterproductive and potentially dangerous proposal.

Sincerely yours,

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