POWERS

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ATTORNEYS AT LAW

MEMORANDUM

To: Kim Gifford
Diane Mossholder
From: Diane Millman
Peggy Tighe
Re: 21st Century Cures bill; Provisions of special interest to ASTS
Date: December 1, 2016

As you know, it appears that the 21St Century Cures bill (the "Cures Bill") will soon be law, and this bill includes a number of provisions strongly supported by ASTS. In particular, the Cures Bill includes a provision that authorizes CMS to exclude transplant-related readmissions from the readmission penalties, and we plan to monitor CMS' implementation of this provision through regulation. The bill also includes a provisions related to another ASTS priority area--anti-microbial research-- that may be of interest, as further described below.

In addition, the Cures Bill includes a number of provisions that may impact the TTI project and other provisions of interest as highlighted below. A firm memo summarizing all of the provisions in the bill accompanies this memo.

I. Provisions that may impact the development of new immunosuppressant drugs and other drugs relevant to transplantation

Over the past few years, ASTS has been concerned about the relatively slack development of new transplant-related drugs and has focused some attention on the extent to which the FDA regulatory environment inhibits the approval of new drugs relevant to the field (and the approval of transplant-related extra-label indications of approved drugs). Many provisions of 21st Century Cures address FDA regulatory reform and a number of these provisions may be of particular relevance to ASTS.

A. Facilitating Approval of Extra-Label Indications.

We understand that a number of drugs approved for non-transplant indications are clinically useful and in fact commonly used for transplant indications. While extra-label indications are common and well accepted, the fact that usage is "off-label" may inhibit coverage; preclude manufacturers from disseminating potentially useful clinical information; and complicate the task of obtaining FDA approval of new pharmaceuticals. (With respect to this last consideration, we understand that the standard of care for immunosuppression may involve the extra-label use of approved drugs and because extra-label indications of approved drugs cannot be used as "comparators" in clinical trials of new drugs, appropriate new drug trials are difficult to design and implement.)

In this regard, it is useful to note that a number of provisions of 21st Century Cures may help facilitate more expeditious and less costly approval of extra-label indications of new drugs. For example:

Sec. 3022. Real World Evidence.	• Requires FDA to evaluate the use of real world evidence to help support the approval of a new indication for a previously approved drug and to help support or satisfy post-approval study requirements
Sec. 3031. Summary Level Review.	• Allows FDA to rely upon qualified data summaries to support the approval of an application for a new indication of an already approved drug. • Sponsors of the application still must submit all information to FDA.

Other provisions of the bill are intended to facilitate responsible communication by drug companies of scientific and medical developments, including off-label uses of approved drugs.

B. Surrogate Endpoints

Based on prior discussions, we understand that the development of new transplant-related drugs has been hampered by the lack of clinically relevant, definable, and realistic clinical trial endpoints. Section 507 of the Cures Bill includes a process for the FDA review and approval of "drug development tool(s)" which may include biomarkers (defined to include a surrogate endpoint), "clinical outcome assessments[1]" or other "method[s], material[s], or measure[s] that the Secretary determines aid drug development and regulatory review". A "drug development tool" may be used for the purpose of supporting approval of a new drug or for the purpose of supporting investigational use of a drug and may facilitate the more expeditious approval of drugs in areas, such as transplantation, where traditional clinical endpoints have been cumbersome or unworkable. Surrogate endpoints are also encouraged for the purposes of approving drugs for the treatment of rare diseases (Section 3012) and accelerated approval of "Regenerative Advanced Therapies (Section 3033). Section 3034 of the bill establishes that devices used with a regenerative therapeutic product will be considered moderate risk devices, unless the FDA determines otherwise, while Section 3036 requires the FDA to consult with stakeholders and others to establish standards that support regenerative medicine and advanced therapies.

In light of the benefits afforded to regenerative medicine and advanced therapies under the bill, it might be worthwhile for ASTS to give some thought to whether any transplant-related therapeutic advancements, such as islet transplants, reperfusion technologies, or other transplant-specific technological advances would meet the statutory definition of "regenerative medicine therapies":

> DEFINITION.—For purposes of this section, the term 'regenerative medicine therapy' includes cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations.

[1] This term is defined as "a measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions that also includes a patient-reported outcome.

C. Antimicrobial Resistance

The Cures Act includes a number of provisions related to anti-microbial resistance, which may be of interest to ASTS. For example,

Sec. 3041. Antimicrobial Resistance Monitoring.	• Requires reporting from CDC and FDA on information and data regarding human resistance to antimicrobial drugs. • Requires CDC to distribute educational materials related to antimicrobial stewardship programs or practices to health care facilities, such as long-term care facilities and community and rural hospitals. • Requires CDC to provide a mechanism where health care facilities can report antimicrobial data that will be made available to the public.
Sec. 3042. Limited Population Pathway.	• Provides FDA with the flexibility to approve antimicrobial drugs based on a limited population if the drug treats a life-threatening infection. • If FDA approves a drug based on a limited population, the labeling and advertising of an antimicrobial drug shall contain "Limited Population" along with a proprietary name of the drug. • Gives FDA the authority to review and approve promotional materials of a drug approved based on a limited population at least 30 days prior to drug dissemination.

II. Non-FDA Provisions of Interest

There are a number of non-FDA related provisions of interest in the Cures Bill. The first authorizes Medicare beneficiaries with ESRD to enroll in Medicare Advantage Plans. The provision, Section 17600 of the bill, excludes organ acquisition costs, including Part A and Part B costs associated with acquisition of an organ from a living donor, from the amounts paid to Medicare Advantage plans for ESRD beneficiaries that enroll in them, and provides for separate Medicare payment for organ acquisition costs.

The second provision of interest (Section 4009) clarifies that a manufacturer's provision of peer-reviewed journals, journal reprints, journal supplements, medical conference reports, and medical textbooks is not reportable under the Sunshine Act, and also includes a specific exemption from disclosure:

> (I) for speaking at, or preparing educational materials for, an educational event for physicians or other health care professionals that does not commercially promote a covered drug, device, biological, or medical supply; or ''(II) that serves the sole purpose of providing the covered recipient with medical education, such as by providing the covered recipient with the tuition required to attend an educational event or with materials provided to physicians at an educational event.

We hope that this memorandum is useful to you. Please let us know if you have any questions, or if a summary of the provisions of interest to individual researchers would be of interest to you.