Alliance for Regenerative Medicine

September 22, 2020

Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments for FDA Docket Number FDA-2019-N-5553: Annual Summary Reporting Requirements Under the Right to Try Act; Proposed Rule

ARM is an international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM promotes legislative, regulatory, and reimbursement initiatives to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. Early products to market 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 11-year history, ARM has become the voice of the sector, representing the interests of 360+ members worldwide, including small and large companies, academic research institutions, major medical centers, and patient groups.

General Comments

As the proposed rule states, "[t]he Right to Try Act amends the Food, Drug and Cosmetic (FD&C) Act to establish an option for patients who meet certain criteria to request access to certain unapproved medical products, and for sponsors and manufacturers who agree to provide certain unapproved medical products other than through FDA's expanded access program."

ARM maintains that company-sponsored expanded access programs, which involves IRB review and includes FDA oversight, provides the best framework for granting access to investigational drugs to patients that do not qualify for clinical trials. We also wish to highlight the initiatives undertaken by FDA (such as Project Facilitate and the Regan-Udall Foundations Expanded Access Navigator) which are aimed at improving accessibility to existing company-sponsored expanded access programs. While the expanded access program has detailed information for patients, physicians, and industry publicly available on the Agency's website, there is little guidance or formality to the definitions and processes to be utilized under the Right to Try Act.

In order to support adherence with the Right to Try (RTT) Act (hereafter called the Act) that became law on May 30, 2018, ARM member companies wish to ensure that implementation of the Right to Try (RTT) annual summary requirements, as outlined in the Proposed Rule, are aligned with those specified in the Act and are consistent with and do not impede other FDA reporting requirements. In this letter, we have responded to each of the Agency's requests for comment, in the order in which they appeared in the Proposed Rule. We are also providing an

alternative proposal for the format and content of the annual summary (Appendix 1) which we feel better aligns with the roles and responsibilities and requirements under the Act. Finally, we have highlighted areas where we feel additional clarity is required.

Response to FDA Requests for Comment

1) **Proposal for a Separate Process and Regulation [at 21 CFR 300.200] to meet Annual Summary Requirements under the Right to Try Act (Section IV, Introduction)**

   Given that the Act specifies that an investigational drug provided under the Act is exempt from IND requirements and FDA intends the annual summary to be submitted to the Office of the Commissioner (rather than the FDA Division with whom an IND applicable is filed), we understand the rationale and support FDA's proposal for a separate regulation and RTT annual summary.

   However, some ARM member companies expressed the position that a separate annual summary for RTT would be considered a regulatory burden (due to the need for new process development) and asked FDA to consider if there were ways in which the RTT annual summary and IND annual reporting processes could be synchronized (ex. aligned reporting periods and/or providing the RTT annual summary as an Appendix/Attachment to the IND Annual Report).

   In response #4, we recommend that the annual summary format and content be streamlined. In response #5a, we describe clarification that is needed to facilitate consistency in the preparation and provision of an annual summary.

2) **Definition of Manufacturer or Sponsor (Section IV, B)**

   The Act specifies that "The **manufacturer or sponsor** of an eligible investigational drug shall submit to FDA an annual summary of any use of such drug supplied under section 561B of the FD&C Act.

   The Act also specifies (in 561B (b) EXEMPTIONS) that "Eligible investigational drugs provided to eligible patients in compliance with this section **are exempt** from sections 502(f), 503(b)(4), 505(a) and 505(i) of this Act, section 351(a) of the Public Health Service Act, and parts 50, 56 and 312 of title 21, Code of Federal Regulations (or any successor regulations) ….". Moreover, the term "sponsor" is not defined in the Right to Try Act.

   For the purpose of this Act, and the annual summary requirement, ARM believes that the definition of Sponsor should be limited to the treating physician(s). While manufacturers may supply the investigational drug to the treating physician, Sponsors have the responsibility of overseeing its clinical use and monitoring the safety of the subject. In the case of drugs provided under the Act, that responsibility ultimately rests with the treating physician.

   Given the above position, we are proposing the following alternative definitions:

Manufacturer: The IND holder developing the investigational drug for commercialization who agrees to provide the eligible investigational drug under the Right to Try Act.

Sponsor: The investigator or treating physician who initiates the request for access to the eligible investigational drug under the Right to Try Act.

ARM believes that the Sponsor (as defined above) is in the best position to obtain the information provided in the annual summary. While the Act and proposed rule discuss reporting requirements for "manufacturers or sponsors", ARM believes that all reports should ultimately flow from manufacturers to the FDA. Manufacturers should have the opportunity to request data (in the proposed format) from sponsors (treating physician) for product provided under Right to Try and provide that information to FDA.

See response #4 for the rationale for manufacturer reporting.
See response #5b for comments on the proposed definition of serious adverse event.

3) Proposed Deadline for Submission of Annual Summary (Section IV, C)

We believe that the reporting timeframe for the initial report should not be retrospective to the date of the Act. It would be inappropriate to require retrospective reporting when entities did not know the content and format of the annual summary that would be required. Therefore, for the initial annual summary the reporting period should begin on the date the final rule is published and end on December 31 of that calendar year. In addition, to allow for data gathering, the time allotted for the initial annual summary should be extended from 60 to 90 days (by March 31 of the following year).

4) Proposed Annual Summary Submission Content (Section IV. D)

In the proposed rule, FDA says that because drugs and biologics applicants take responsibility for monitoring the safety of their products, the Agency expects they would be able to meet reporting requirements. FDA also notes that producers of investigational drugs should be able to provide FDA with required information. While we believe that the sponsor (physician requesting access) should be involved in supplying data for the annual summary, we can appreciate that they would only be able to report on their experience. However, the manufacturer (IND holder), who authorized access, would be in the best position to report on all access granted for the product.

While we appreciate the Agency's provision of a potential format for the Annual Summary. However, we believe that the format/content outlined in the Proposed Rule:

- asks for more information than is required by the Act, and
- does not take into consideration that there are no defined requirements for safety reporting under the Right to Try Act. That is, it assumes that the same level of information would be available in a serious adverse event report from the sponsor (treating physician) as would be available in a clinical trial (MEDRA term, severity

from pre-defined AE criteria). Whether the manufacturer or sponsor (treating physician) are responsible for reporting, this content is inappropriate.

Therefore, we have proposed an alternative for the format/content of an annual summary which is restricted to required information (see Appendix 1). We would also suggest that the sponsor should be responsible for providing required information to the manufacturer to facilitate their completion of the annual summary.

5) Additional Considerations or Clarification Needed

a) Process Clarity and Update of FDA's Right to Try website

At the present time, the mechanism by which a physician makes a request to the manufacturer of the investigational drug or biological product under the Right to Try Act is not defined. For example, an academic investigator may inquiry about access to an investigational drug and there may be ambiguity as to the intended purpose of this request (it may be for an investigator initiate study or RTT use). We request FDA consider clear criteria on how a request for access under RTT is submitted to a manufacturer.

At the time the final rule is issued, we recommend that the FDA RTT website be updated to provide information on the definitions and expectations related to the sponsor (physician) and manufacturer (IND holder).

b) Further Definition of Annual Summary Expectations

1) No Access Granted Means No Report

We interpret the last sentence in Section IV. Introduction of the Proposed Rule to imply that an annual summary <u>is not</u> required unless access under the Act has been granted during the reporting period. We ask that this be clearly stated in the Final Rule. For example, "the manufacturer or sponsor is only required to submit an annual summary if a request for access has been granted in the reporting period".

2) Annual Summary to Cover Only Initial Grant and not Continued Use

It is not clear whether an annual summary need only report on new access granted within the reporting period or if there is an expectation that ongoing use from a prior reporting period (which would, for example, impact on the total number of doses supplied) would need to be described in yearly annual summaries until the product is no longer being administered to any patient granted access. The final rule should provide clarity on this point.

c) Definition of Serious Adverse Event

As stated previously, the Act specifies that "Eligible investigational drugs provided to eligible patients in compliance with this section **are exempt** from sections 502(f), 503(b)(4), 505(a) and 505(i) of this Act, section 351(a) of the Public Health Service Act, and parts 50, 56 and **312 of title 21**, Code of Federal Regulations (or any successor regulations) ….".

We would like to emphasize that it is not necessarily the case that Sponsors (defined by ARM as the investigator responsible for and who initiates the request for access) will have conducted clinical trials and have experience with utilizing the definitions for serious adverse event or serious **suspected** adverse reaction provided under 21 CFR 312.32. As noted, ARM has proposed alternative reporting format and content in the attached.

We have no objection to the provision of the criteria outlined in 21 CFR 312.32 (paraphrased below) to articulate circumstances that should be considered serious.

*Definition of Serious

1) Death
2) Life-threatening
3) Inpatient hospitalization or prolongation of existing hospitalization
4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect
5) Based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the above outcomes

d) Use of Clinical Outcomes

The Act describes select circumstances where use of clinical outcomes may occur. However, the proposed rule does not indicate how the Secretary (FDA Office of the Commissioner as delegate) intends to meet the obligation to report on the number of drugs for which clinical outcomes were utilized.

ARM members are particularly interested in understanding how the Secretary (FDA Office of the Commissioner as delegate) plans to inform sponsors that they have determined that use of such clinical outcome is critical to determining the safety of the eligible investigational drug.

Conclusion

The regenerative medicine sector is the next frontier in the fight against some of society's most devastating diseases and disorders. These therapies have just begun to demonstrate their power to improve patient lives, but there is still much work to be done. ARM is looking forward to continuing to work with FDA, and other key stakeholders, to address the policies needed to advance the sector so that these cutting-edge treatments can meet their potential and be accessible to patients in need.

Thank you for the consideration of our recommendations.

Sincerely,

Robert J. Falb
Director, U.S. Policy and Advocacy

APPENDIX 1

A) SPONSOR CONTRIBUTION TO ANNUAL SUMMARY

NAME:

REPORTING PERIOD:

Total Number of Patients Treated:

Uses For Which Drug Was Made Available:

Any Known Serious* Adverse Event:

*DEFINITIONS TO BE UTILIZED FOR SERIOUS^=

1) Death
2) Life-threatening
3) Inpatient hospitalization or prolongation of existing hospitalization
4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect
5) Based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the above outcomes

B) MANUFACTURER ANNUAL SUMMARY

Manufacturer:

Name of Drug:

Applicable IND number:

Use Explored Under IND:

Annual Summary Date:
Report 1: 31 March in the year the final rule is published
Report 2: 31 March of subsequent calendar year (repeat for subsequent reports)

Annual Summary Reporting Period:
Report 1: Date of Final Rule – End of Current Calendar Year
Report 2: Subsequent Calendar Year

Total Number of Patients Treated:

Total Number of Doses Supplied:

Uses For Which Drug Was Made Available:

Any Known Serious Adverse Event: