



February 5, 2019

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-N-4000
“Framework for a Real-World Evidence Program; Availability”

Dear Sir or Madam:

The Alliance for Regenerative Medicine (ARM) is pleased to submit these comments in response to the framework issued by the Food and Drug Administration (FDA) for a Real-World Evidence (RWE) Program (Framework Document).

ARM is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the FDA. ARM takes the lead on the sector’s most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

FDA intends that the RWE Program will be multifaceted, involving demonstration projects, stakeholder engagement, internal processes to bring senior leadership input in applying the framework, and guidance documents to assist developers interested in using real-world data to develop RWE to support FDA regulatory decisions. ARM commends FDA’s commitment to stakeholder engagement as it works to address these issues and looks forward to continued participation in these efforts.

Comments

FDA's Framework Document references section 505F of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as the basis for FDA's RWE framework. Section 505F, along with section 505(c)(5) and section 351(a)(2)(E) of the Public Health Service Act, address the potential use of RWE to help support the approval of a new indication for an already-approved drug or biological product.

We note that FD&C Act section 506(g)(7) refers to another use of RWE: the use of RWE to satisfy post approval requirements for a Regenerative Medicine Advanced Therapy (RMAT) granted accelerated approval under FD&C Act section 506(c):

Post approval requirements - The sponsor of a regenerative advanced therapy that is granted accelerated approval and is subject to the post approval requirements under subsection (c) may, as appropriate, fulfill such requirements, as the Secretary may require, through—

(A) the submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence, such as electronic health records[.]

FDA's Framework Document does not cite section 506(g)(7) and does not address whether FDA intends the framework to apply to RWE submitted to FDA to fulfill post approval requirements for accelerated approvals of RMAT products. ARM requests that FDA clarify whether the RWE Framework Document addresses the use of RWE for these post approval uses, and if the Framework does apply, ensure that special considerations for RMAT products are incorporated. We acknowledge that for RMAT products receiving accelerated approval, FDA would be in discussion with the RMAT sponsor about confirmatory studies well before accelerated approval of the RMAT. Those discussions provide full opportunities for FDA to develop and implement appropriate regulatory policy for post approval uses. However, the current Framework does not account for such RMAT application and may lead to confusion or misapplication.

Although FDA commits to issuing certain guidances under the Framework Document, guidances that address RWE broadly may not adequately address issues specific to the use of RWE in support of the efficacy of RMAT products. The following are examples of issues that may require a different approach in the RMAT context.

The Framework Document suggests that FDA will need to review many data sets before the Agency would be prepared to accept RWE developed in an observational setting in support of an efficacy determination.¹ This suggests that FDA will undertake a prolonged and detailed review,

¹ For example, the Framework Document quotes Fralick et al. with apparent approval, "to establish a meaningful baseline, the FDA will need many sets of randomized clinical trials with prospectively designed, nonrandomized analyses to match the populations included in randomized clinical trials across a range of lineal questions, each investigated with a set of designs and methods following rigorous epidemiologic principles." Framework Document at 12 (referencing Fralick, M., Kesselheim, A.S., Avorn, J., and Schneeweiss, S. (2018). Use of Health Care Databases to Support Supplemental Indications of Approved Medications, *JAMA Internal Medicine*, 178(1): 55-63. doi:10.1001/jamainternmed.2017.3919).

potentially lasting years before FDA is able to accept RWE as proof of efficacy in a supplemental application. However, there is an urgent need to bring RMAT products to market. Many RMAT products are likely to be approved under accelerated approval, and the development of standards and acceptable data sources to satisfy post approval requirements to confirm those accelerated approval is also an urgent matter.

1. The examples discussed in the Framework Document refer to analyses of large numbers of patients – 11,712 in an example of randomized controlled trials integrated into health care systems.² The initial studies of RMAT products supporting accelerated or even full approval may be quite small, and the disease or condition treated may be rare. Post approval studies for those receiving accelerated approval may be much smaller, and present different issues, than the large population analyses discussed in the Framework Document. It will be important to capture, in the proposed guidance, the critical data elements that FDA will wish to see incorporated into RWE studies for RMAT designated products, independent of study denominator size. For example, will the FDA request more focus on RWE regarding safety elements versus efficacy and duration of response of RMAT designated products? Without this clarification, sponsors may submit plans and make early investments on study design that don't meet FDA standards and lead to unwanted delays for all stakeholders. Also, it would be helpful to clarify whether it is conceivable to use RWE to support manufacturing optimization.
2. The Framework Document states that data from other countries may be a valuable source of Real World Data (RWD), which may provide RWE, while noting that “[u]sing data from other countries might require analyses that consider the differences in medical practice, health care delivery, and data reliability and relevance compared to the United States.”³ We applaud the agency for recognizing the utility of data from other countries. We encourage FDA to consider the limitations in obtaining data from other countries to satisfy post approval requirements for RMAT products, particularly when small numbers of patients are available to be studied. Therefore, a more tailored approach to leveraging non-US data should be carefully considered, justified and appropriately analyzed.
3. We also note that the Framework Document states that FDA is considering issuing guidance on the use of RWD to generate external controls, such as historical controls. ARM urges FDA to prioritize this guidance document and consider expanding the scope of the use of historical controls beyond trials supporting additional indications for approved drug and biological products. Patients receiving regenerative therapies such as cellular and gene therapies often suffer from devastating diseases with little or no available treatments. A requirement to conduct a Natural History Study (NHS) to provide evidence for a historical control can be time consuming and burdensome for sponsors. Patients may even resist enrollment, viewing the NHS as an impediment to their access to a new therapy. The use of RWD to develop historical control data could shorten the timeline for development of groundbreaking new regenerative therapies.

² Framework Document at 11.

³ Framework Document at 16.

4. Registries become an important source of RWE and are increasingly used by patients, professional and industry organizations. Registries are used in many different contexts, may be set up differently, as disease or product registries, and are not specific to RMAT. However, due to the nature of RMAT and the possibility of more frequent approvals under accelerated schemes, RWE and registries are particularly important for these products. ARM suggests that the FDA consider issuing more guidance about establishing registries as a tool to collect RWE. We refer to the EMA discussion paper on “Use of patient disease registries for regulatory purposes – methodological and operational considerations” which has been released on 8 November 2018 and under open consultation until 30 June 2019 as a reference for considerations to include in guidance in an effort towards convergence. An FDA guidance on the design and use of registries to address its practical design, operational issues, evaluation principles as well as quality indicators, source verification and control mechanisms would be helpful. A convergence of processes and requirements with Europe and other regions on RWE and the use of registries would be beneficial to all ATMP developers. We propose that this topic be added on the agenda of the FDA/EMA bilateral meetings. Previous work in this area, such as the Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness issued by the ISPOR-ISPE Task Force or the AHRQ publication, “Registries for Evaluating Patient Outcomes: A User’s Guide” could also be reviewed and integrated in the guideline.

Thank you for our consideration,



Director, U.S. Policy and Advocacy