Alliance for Regenerative Medicine

September 12, 2023

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

Re: Docket No. FDA-2023-D-0559 for *Postmarketing Studies and Clinical Trials: Determining Good Cause for Noncompliance with Section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act*

Dear Sir/Madam:

The Alliance for Regenerative Medicine (ARM) is pleased to submit comments to the US Food and Drug Administration (FDA) in response to recently released guidance titled, *Postmarketing Studies and Clinical Trials: Determining Good Cause for Noncompliance with Section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act*.

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

General Comments

ARM appreciates the issuance of this draft guidance document, which provides helpful new information for sponsors on the factors FDA considers when determining whether an applicant has demonstrated good cause for failure to comply with the timetable for completion of postmarketing requirements (PMRs) for safety for drugs and biologics. Other beneficial contents of this guidance are the procedures for submitting an explanation for PMR noncompliance and identification of the potential advisory actions for noncompliance, which is information that has not been provided in previous guidance.

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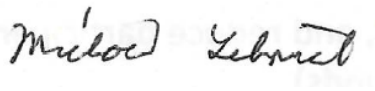
ARM finds many of FDA's expectations to be rational. However, we recommend the agency allow protocol amendments that are informed by evolving circumstances, especially for diseases with small populations. We specifically recommend allowing adjustment of PMRs based on evaluation of attrition, noncompliance, and refusals to enroll for modalities with lengthy and/or extensive PMRs, as described in more detail below. Doing so will assist in preventing noncompliance with safety PMRs and/or reasonably expanding the acceptable causes for noncompliance with them.

Thank you for your consideration of these comments and for your overall effort to provide guidance that will assist sponsors in the field of regenerative medicine. Below is a listing of line-by-line comments on this proposed guidance.

Sincerely,



Michael Lehmicke
Vice President, Science and Industry Affairs

Specific Line-by Line Comments: Section/Line	**Guidance Text**	**Rationale for Change or Comment**	**Proposed Change**
II. BACKGROUND			
Lines 74 – 77	"Once milestones are agreed upon, they are included in the action letter or postapproval letter acknowledging new PMRs. This original timetable serves as the basis for determining the status of the PMR, even if the applicant subsequently proposes a revised timetable."	Comments: It is unclear whether this statement implies that applicants should inform FDA if they anticipate missing an *original* milestone or have already missed an *original* milestone. Lines 294 – 296 state, "Applicants who have a revised PMR timetable who fail or anticipate failing to meet any of the revised milestones should also submit an explanation for FDA to evaluate." This	"Once milestones are agreed upon, they are included in the action letter or postapproval letter acknowledging new PMRs. This original timetable serves as the basis for determining the status of the PMR~~,~~ ~~even if the applicant subsequently proposes a revised timetable.~~ in annual reports. However, while a PMR may have a status of "delayed" based on the original timetable, applicants who have a revised PMR timetable do not need to inform FDA if they miss or

		statement implies that applicants do not need to proactively inform FDA if they have missed or anticipate missing an original milestone, and ARM requests clarification of this point, as suggested to the right. Additionally, statutes indicate not only that annual reporting to FDA on the status of PMRs requires inclusion of the status of the commitment based on the original schedule, but also that applicants should provide the most recent, previously submitted revision, if revisions have occurred, alongside the original schedule (21CFR314.81(b)(2)(vii)(a)(7) and 21CFR601.70(b)(7)). We suggest stating this requirement as well, here and/or in Section IVA, as noted below.	anticipate missing an original milestone, but rather if they miss or anticipate missing any of the revised milestones, as described in more detail in Section IV.
III. DETERMINING GOOD CAUSE AND FAILURE TO DEMONSTRATE GOOD CAUSE FOR PMR NONCOMPLIANCE			
A. Determining Good Cause for PMR Noncompliance			
Lines 128 - 148	"In general, FDA considers PMR noncompliance to be reasonable when it results from circumstances that meet the following criteria:	Comments: ARM appreciates that FDA indicates flexibility in these determinations by stating, "In general," and noting that FDA may also consider any other	"In general, FDA considers PMR noncompliance to be reasonable when it results from circumstances that meet the following criteria:

	• The circumstance is directly related to the missed milestone; AND • The circumstance was out of the applicant's control; AND • The circumstance could not have been reasonably anticipated and factored in at the time the original PMR timetable was finalized. In determining whether PMR noncompliance is reasonable under the circumstances, FDA may also consider any other available information that it deems pertinent. If any one of the aforementioned conditions is not met, in general, FDA will consider the noncompliance to not be reasonable under the circumstances and the applicant as failing to demonstrate good cause for the noncompliance."	available information that it deems pertinent (i.e., the totality of the circumstances). We encourage further flexibility, by deleting the last sentence, since the three listed criteria do not consider all available information that might be relevant to determining reasonableness under the circumstances. It would also be helpful for FDA to further indicate the types of information that might fall under "any other information" that can be factored into the totality of the circumstances.	• The circumstance is directly related to the missed milestone; AND • The circumstance was out of the applicant's control; AND • The circumstance could not have been reasonably anticipated and factored in at the time the original PMR timetable was finalized. In determining whether PMR noncompliance is reasonable under the circumstances, FDA may also consider any other available information that it deems pertinent. ~~If any one of the aforementioned conditions is not met, in general, FDA will consider the noncompliance to not be reasonable under the circumstances and the applicant as failing to demonstrate good cause for the noncompliance."~~
Lines 150-154	FDA will notify the applicant in writing of the determination of whether the applicant demonstrated good cause or failed to	Comment: ARM recommends identifying the time frame in which FDA plans to notify an applicant of the determination of whether the	FDA will notify the applicant in writing of the determination of whether the applicant demonstrated good cause or failed to demonstrate good cause for PMR noncompliance~~,~~

	demonstrate good cause for PMR noncompliance. The applicant could be subject to a warning letter followed by enforcement action for PMR noncompliance.	applicant demonstrated good cause for PMR noncompliance, to assist sponsors in adjusting timelines when necessary. We also suggest clarification that FDA will not issue a warning letter until after sponsor notification and provision of sufficient time to take appropriate action to correct or mitigate the circumstances that led to the PMR noncompliance.	within 30 days of receipt of the applicant's justification. After notification of PMR noncompliance and allowance of sufficient time for appropriate action to correct or mitigate the circumstances that led to noncompliance, t~~T~~he applicant could be subject to a warning letter followed by enforcement action for PMR noncompliance.
B. Examples of PMR Noncompliance FDA Would or Would Not Consider Reasonable Under the Circumstances			
1. Missed Final Protocol Submission Milestone			
Lines 191-192, 200 – 201, and 203 - 205	"PMR noncompliance associated with failure to submit a final protocol that FDA likely would not find reasonable under the circumstances includes the following: … • Submission of a proposed protocol that FDA considers unlikely to provide meaningful data about the safety issues or questions the PMR was intended to address	Comments: • Submission of a proposed protocol that FDA considers unlikely to provide meaningful data should first trigger FDA comments and an opportunity for the applicant to revise and resubmit the protocol. We would suggest only listing this example if qualifying it by adding "followed by the applicant's failure to amend the protocol" or similar. • An applicant's request to	"PMR noncompliance associated with failure to submit a final protocol that FDA likely would not find reasonable under the circumstances includes the following: … • Submission of a proposed protocol that FDA considers unlikely to provide meaningful data about the safety issues or questions the PMR was intended to address, in conjunction with the applicant's failure to amend the protocol • ~~Applicant's request to FDA to renegotiate the previously issued PMR (e.g., renegotiate the previously agreed-~~

	• Applicant's request to FDA to renegotiate the previously issued PMR (e.g., renegotiate the previously agreed-upon final study or clinical trial design), in the absence of critical new information making changes necessary."	renegotiate the previously issued PMR is not an example of a missed final protocol submission milestone, but rather is related to the next section of missed study/clinical trial completion milestone. ARM suggests removing it from this section. Additionally, ARM recommends that if this example is used in the next section, that FDA define what constitutes critical new information, to include the examples we provide in lines 218 – 231 of reasons for noncompliance that are reasonable under the circumstances.	~~upon final study or clinical trial design), in the absence of critical new information making changes necessary."~~
2. Missed Study/Clinical Trial Completion Milestone			
Lines 218 - 231	"PMR noncompliance associated with failure to complete a study or clinical trial that FDA likely would find reasonable under the circumstances includes the following: • Significant difficulties that are out of the	Comments: Estimating the number of patients who can be recruited for postmarket studies is difficult for rare diseases. If that number ends up being less than estimated, it could lead to noncompliance with PMRs, despite applicant efforts to	"PMR noncompliance associated with failure to complete a study or clinical trial that FDA likely would find reasonable under the circumstances includes the following: • Significant difficulties that are out of the applicant's control and could not have been

	applicant's control and could not have been anticipated and planned for with regard to subject recruitment for studies or clinical trials, including, for example, challenges in recruitment of individuals for reasons such as the following: – Adverse reactions of the drug added to the product labeling and/or the informed consent document for the study or clinical trial after a PMR was required that make subject enrollment in a clinical trial of the drug more difficult. – The availability of a new alternative therapy after an applicant's PMR was required that affects usage of the	estimate accurately and enroll on pace with requirements. In addition, the lengthy and/or extensive safety PMRs for some gene therapies may result in high patient noncompliance rates, or loss to follow-up, over the many years of required follow-up testing. We suggest these factors be provided as reasons for challenges in recruitment and retention that are out of the applicant's control that could not have been anticipated.	anticipated and planned for with regard to subject recruitment for studies or clinical trials, including, for example, challenges in recruitment and/or retention of individuals for reasons such as the following: – Adverse reactions of the drug added to the product labeling and/or the informed consent document for the study or clinical trial after a PMR was required that make subject enrollment in a clinical trial of the drug more difficult. – The availability of a new alternative therapy after an applicant's PMR was required that affects usage of the applicant's drug. – Small population size of the disease being treated, which may prevent recruitment of the number of subjects FDA initially required, within the period originally indicated. – Patient noncompliance, attrition, and refusals to enroll due to extensive long-term follow-up requirements for

	applicant's drug.		some types of products, such as gene therapies."
Lines 235 - 237	"Unexpected disruption or interruption in the supply (e.g., drug shortage, drug discontinuation) of the applicant's drug that is out of the applicant's control and delays the conduct of the study or clinical trial."	Comments: We agree that unanticipated drug availability is a reasonable circumstance for failure to complete a study or clinical trial. Examples of unanticipated supply issues should be expanded to include unavailability of critical reagents, materials, or components that are needed to manufacture the finished drug substance or drug product.	"Unexpected disruption or interruption in the supply (e.g., ~~drug~~ shortage~~,~~ or ~~drug~~ discontinuation of the drug substance, drug product, or any critical reagents, materials, or components needed to manufacture the drug substance or drug product) ~~of the applicant's drug~~ that is out of the applicant's control and delays the conduct of the study or clinical trial."
Lines 242 – 250	"PMR noncompliance associated with failure to complete a study or clinical trial that FDA likely would not find reasonable under the circumstances includes the following: • Inadequate subject recruitment for studies or clinical trials for which difficulties in subject enrollment should be unlikely (e.g., recruitment of healthy subjects for a drug-drug interaction trial or pharmacokinetics trial).	Comments: Difficulties in subject enrollment may occur for all types of subjects due to the inherent risks associated with clinical investigation, including healthy subjects who tend to derive little or no therapeutic benefit from participation. ARM recommends that FDA consider the totality of the circumstances to determine whether inadequate subject recruitment, and the resulting failure to complete a study or clinical trial, is reasonable under the	"PMR noncompliance associated with failure to complete a study or clinical trial that FDA likely would not find reasonable under the circumstances includes the following: • Inadequate subject recruitment for studies or clinical trials for which difficulties in subject enrollment should be unlikely (e.g., recruitment of healthy subjects for a drug-drug interaction trial or pharmacokinetics trial). However, the FDA will consider the totality of the circumstances to determine whether inadequate subject recruitment, and the

	• Failure to complete prespecified and feasible interim data analyses that are considered relevant to inform appropriate completion of the study or clinical trial."	circumstances. ARM also suggests that FDA should determine whether interim data analyses are "feasible" only after considering an applicant's explanation for a missed PMR milestone, and that FDA use wording such as that to the right to clarify this intent.	resulting failure to complete a study or clinical trial, is reasonable under the circumstances. • Failure to complete prespecified and feasible interim data analyses that are considered relevant to inform appropriate completion of the study or clinical trial. The FDA determines whether an interim analysis is feasible after evaluating the applicant's explanation of the circumstances."
IV. PROCEDURES			
A. Reporting on the Status of a PMR			
Lines 281 - 283	"As described in section II., Background, FDA considers the submission of the annual report required under 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70, as applicable, containing all of the elements set forth in 505(o)(3)(E)(ii) as satisfying the periodic reporting requirement under section 505(o)(3)(E)(ii)."	Comments: This would be an appropriate place to clarify that in annual reports, the original timetable serves as the basis for determining the status of the PMR, even if the applicant subsequently proposes a revised timetable, and that applicants should provide the most recent, previously submitted revision, if revisions have occurred, alongside the original schedule (21CFR314.81(b)(2)(vii)(a)(7) and 21CFR601.70(b)(7)).	"As described in section II., Background, FDA considers the submission of the annual report required under 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70, as applicable, containing all of the elements set forth in 505(o)(3)(E)(ii) as satisfying the periodic reporting requirement under section 505(o)(3)(E)(ii). Applicants should be aware that annual reporting to FDA on the status of PMRs requires inclusion of the status of the commitment based on the original schedule. If revisions have occurred, applicants should also provide the most recent, previously submitted revision, alongside the original

			schedule (21CFR314.81(b)(2)(vii)(a)(7) and 21CFR601.70(b)(7)).”
B. Submitting an Explanation for PMR Noncompliance or Anticipated Noncompliance			
Lines 294 - 296	“Applicants who have a revised PMR timetable who fail or anticipate failing to meet any of the revised milestones should also submit an explanation for FDA to evaluate.”	Comments: To assist in clarifying the statement in lines 74- 77, ARM recommends adding clarification to this statement as well, to indicate that applicants are not required to inform FDA of the missing of *both* original and revised milestones, only revised milestones.	“Applicants who have a revised PMR timetable who fail or anticipate failing to meet any of the revised milestones should ~~also~~ submit an explanation for FDA to evaluate but do not need to submit an explanation to FDA if they fail or anticipate failing to meet original milestones.”
Lines 301 – 302 and 305 - 309	“FDA determines whether an applicant has demonstrated good cause for noncompliance with a PMR milestone in the timetable only after the applicant has missed the milestone date. … Before the applicant misses a milestone, FDA can assess whether it finds that the applicant has provided sufficient justification for the anticipated delay (i.e., anticipated failure to meet a future milestone). FDA plans to notify an applicant of its determination that an applicant has failed to provide	Comments: The time frame in which FDA will review a submitted Explanation for PMR [Anticipated] Noncompliance should be specified, since this paragraph is unclear. An overly prolonged FDA review period can challenge the submission of adequate additional justification or adjustment of milestones, in the event FDA determines insufficient justification for delay was submitted. FDA should identify its communication method for its determination of whether sufficient justification of delays	“FDA typically determines whether an applicant has demonstrated good cause for noncompliance with a PMR milestone in the timetable only after the applicant has missed the milestone date. … Before the applicant misses a milestone, FDA can assess whether it finds that the applicant has provided sufficient justification for the anticipated delay (i.e., anticipated failure to meet a future milestone). FDA plans to notify an applicant of its determination that an applicant has failed to provide *sufficient justification* for the *anticipated* delay in meeting the PMR milestone. FDA will communicate its

	sufficient justification for the *anticipated* delay in meeting the PMR milestone."	has been submitted (e.g., email, formal letter/notification).	determination of whether sufficient justification has been provided through a [*communication type (e.g., email, formal letter/notification)*] within 30 days following receipt of the Explanation for PMR [Anticipated] Noncompliance."