Subject: Comment on FDA Draft Guidance for Industry Titled "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products"

Docket No. FDA-1995-D-0288

ARM is an international multi-stakeholder advocacy organization based in Washington, D.C. that promotes legislative, regulatory, and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM comprises more than 290+ leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. 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.

It is out of that dedication today that we submit our comments:

General Comments

We appreciate FDA's issuance of this guidance to assist applicants and manufacturers of certain licensed biological products in determining which reporting category is appropriate for a change in chemistry, manufacturing, and controls (CMC) information to an approved biologics license application (BLA) as specified in 21 CFR 601.12 (i.e., post-approval changes).

A general comment on this guidance is for FDA to harmonize with the ICH guidance's on this subject, and with recommendations from other regulatory agencies to promote international understanding for the process. For example, we recommend that this guidance, when finalized, be aligned with the ICH Q12 guidelines issued in September 2014.

In our review, we note that cellular, gene, and cell-based gene therapy are excluded as exceptions in certain sections, which are highlight in Attachment 1. We understand that these products are new to the landscape and will need more post-approval market experience to gain confidence and ascertain the categorization of post-approval change than other biological products. However, considering that this guidance may remain applicable for these products long after we have gained substantial post-marketing experience with them, we recommend FDA to assume a generally flexible, future focused approach. Specifically, we encourage FDA to recommend a risk-based approach for CMC changes that takes the level of evidence and internal quality systems into account in determining the appropriate reporting category for all post approval alterations.

Further, the guidance discusses the reporting categories of cellular, gene, and cell-based gene therapy products. It will be helpful for FDA to clearly define and distinguish these products with regard to gene therapy products in general, and cell-based gene therapy products specifically. As an example, on page 20 of the draft guidance appendix, the document categorizes change in the harvesting and/or pooling procedures that does not affect the method of manufacture, recovery, storage conditions, production scale or sensitivity of detection of adventitious agents as a change noted in the annual report. However, it notes that this categorization does not apply to cellular therapy and cell-based gene therapy products. It will be helpful to long term growth of the industry for FDA to clarify in the final guidance what kinds of gene therapy products are covered by these terms. Further, it would be useful to clarify that gene therapy products that are not cell-based, such as those that do not require *ex vivo* manipulations or removal of individual donor cells from body, will not be included in the listed exceptions in guidance appendix.

We look forward to publication of the final guidance and to providing FDA with our comments on future draft guidance supporting the development of regenerative medicine therapies. In particular, we look forward to contributing comments on potential future guidance documents on how changes in CMC to an approved application should be approached.

ARM appreciates the opportunity to provide feedback on this guidance. We also sincerely appreciate your time and consideration of our comments. We look forward to working with you in the days ahead.

Respectfully Submitted,

Michael Werner

Co-founder and Senior Policy Counsel

Alliance for Regenerative Medicine

ALLIANCE for Regenerative Medicine

Attachment 1 – Detailed comments on specific sections within "Chemistry, Manufacturing, and Controls Changes to an Approved Application":

Page / Section	Comment and Rationale	Proposed Change (if applicable)
3, III	Rename bullet point 6 'cell, gene, and cell-based gene therapy products' to the broader term "Regenerative Medical Products". Include specific examples of Regenerative Medical products in parenthetical as done with Plasma Derived Products	Change point to: • Regenerative Medical Products (e.g. cell replacement therapies, viral vector gene modifications, gene-modified cell therapies etc.)
5, IV	We commend FDA for inclusion of PAS clause in this section	
Appendix, pg. 20	Why do solely Cell and Gene Therapies require PAS for changes? Scale-out, if supported by a risk assessment should be classified as a CBE30.	Clarify or add role of risk assessment in assessing need for PAS.
Appendix, pg. 23	No context is given for why the analogous changes to a Gene Therapy master bank does not require PAS. The reporting category for generation of a new master bank for Gene Therapy products is not specified.	
Appendix, pg. 25	Clarification or examples needed for what constitutes a minor modification to an Approved Analytical Procedure	
Appendix, pg. 26	A qualifying statement is needed to help in understanding why a change from international to domestic standards cannot be performed under a risk-based assessment instead of PAS	
Appendix, pg. 28	Clarification is requested on reference to extension of shelf life	

	and the definition of an approved protocol. Can a BLA (post-approval of long-term stability) be used, or will a new protocol need to be developed for changes in shelf life and stability?	
Appendix, pg. 39	Consider including information regarding identity testing to support reporting the introduction of product(s) into a manufacturing area in an AR.	Add: …and specific identity tests exist to differentiate between all products manufactured at the facility.