ALLIANCE for Regenerative Medicine

Subject: Comment on FDA Draft Guidance for Industry titled: "Evaluation of Devices Used with Regenerative Medicine Advanced Therapies"

Docket No. FDA–2017–D–6154

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:

Focusing on Regenerative Medicine

Subsequent to the enactment of the 21st Century Cures Act, and particularly Section 3024, we were pleased with the rapid implementation of the Regenerative Medicine Advanced Therapy (RMAT) designation by the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER). This rapid implementation already led to the designation of significant number of regenerative medicine therapies as RMATs. Similarly, we are pleased that CBER took the initiative to promptly generate the above-mentioned draft guidance for industry specifically focused on expedited programs for regenerative medicine therapies, including this guidance on the Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (RMATs).

We welcome the timely issuance of a draft guidance on this topic and recognize the complexities of / different pathways to be followed for the incorporation of a device into such therapy.

As outlined in the 21st Century Cures Act (Section 3034), this draft guidance was expected to address the following:

- How FDA intends to simplify and streamline regulatory requirements for combination device and cell or tissue products;
- What, if any intended uses or specific attributes would result in device used with a regenerative therapy product being classified as a Class III device;
- When FDA considers it necessary, if ever, for the intended use of a device to be limited to a specific intended use with only one particular type of cell; and,
- Application of the least burdensome approach to demonstrate how a device may be used with more than one cell type;

In general, the draft guidance provides information already available in other device or combination product specific guidance, without providing RMAT specific recommendations/examples. ARM would recommend that the guidance be more focused on RMAT specific recommendations only, with any references to general device guidances to be provided in an appendix. This change would be more in keeping with the view of the 21st Century Cures Act.

In Attachment 1, we provide a detailed comments section, where comments on each draft section of the guidance are provided with the goals of: 1) identifying the content that may be considered to address each of the topics specified above and 2) providing a description of the information that would be of interest to sponsors. We emphasize that it would be helpful if future iterations of the guidance include more specificity for Regenerative Medicine Advanced Therapies. Below are our general comments.

Please consider including the following concepts:

General approach/application of least burdensome principles

ARM appreciates the concepts specified in the General Approach section (Part III, p. 5), as the details were both comprehensive and easily understood. Furthermore, the 'least burdensome' principles articulated in Part III A (pp. 6-7) would benefit from examples specific to devices used with RMATs. The requirements for the 'least burdensome' approach are similar to current device regulation, but would a 'least burdensome' approach apply regardless of the main review division? For example, if a device used in a RMAT is being primarily regulated by CBER through an IND and ultimately a BLA process, would the device portion of review still follow a 'least burdensome' approach? Or is the 'least burdensome' approach paradigm reserved for products where CDRH will comprise the main, not consultative, review team (i.e., a IDE/510(k) or PMA approach)?

Available premarket pathways

A complex device may have design characteristics that need to be tested while the safety and efficacy of the underlying RMAT product is also being evaluated. In the Available Premarket Pathways section (Part III B (pp. 7-8)), additional IDE submission guidance would be helpful (e.g. when should an IDE submission be filed versus and alone or in combination with an associated IND for the RMAT product).

In this section, the guidance notes a "Q-Submission" can be submitted to gain general advice from CDRH on device development. ARM asks FDA to provide additional guidance from prior Q-Submissions into more comprehensive feedback, or feedback on sponsor best practices in the timing, contents, covered questions, and submission of these "Q-Submissions".

Necessary clinical evidence

The guidance did not contain any pre-emptive principles on how FDA will make a determination regarding the need for additional clinical evidence in support of a determination that reasonable assurance exists to find that the device is safe and effective for its conditions of use. For example, providing illustrative examples on how FDA will make this determination would be beneficial, but would still allow for the regulatory flexibility needed in these cutting-edge device RMATs.

Agency interactions for combination products

Given the complexity of various device pathways for combination products, it would be helpful if the Agency would consider a process to check on internal CDRH/CBER concurrence on the final marketing pathway for complex combination products. For instance, in the Combination Products section (Part IV (p. 10)), sponsors can request meetings and follow the given advice, but feedback may not be correct nor complete if appropriate divisions are not involved. This can lead to complete responses and information requests late during the product development cycle. Agency feedback on sponsor best practices would be helpful in this context. Additionally, an internal Agency process check, which could be part of an End of Phase 2 (EOP2) meeting or other similar development meetings, could help ensure that all Agency feedback is incorporated into final pivotal study designs.

Please consider providing recommendations for best practices or how to incorporate various FDA submissions and meetings into the overall product development timeline for both the RMAT product and the device. Separate development timelines for each constituent part (device and RMAT) often mean differing amounts of information are available on each component. Guidance from FDA would assist industry in managing the often-divergent timelines for RMAT and devices while ensuring timely and adequate feedback from all applicable review divisions (CBER and CDRH).

Transparency and predictability in regulatory decision-making

Please consider providing further clarification of, or provide a few case studies of, Agency expectations on engaging both CDRH and CBER to expedite device RMAT product development. For example, the timing of CBER's notification to CDRH for a consultative CDRH review is often not immediately communicated to sponsors. Consultative reviews are often not postponed until late in development, where issues can arise. Enhanced communication through notification of such consultative reviews would be helpful. Alternatively, should sponsors be encouraged to request such consultative reviews from their RPM early in device development for a product regulated under an IND?

Compatibility data

Finally, ARM appreciates FDA's inclusion of the concept that compatibility data from an originator device/RMAT may be leveraged for a second device that is similar to that of the originator (next to last paragraph on page 11). This concept allows for compatibility data

from an originator device/RMAT to be leveraged as appropriate and justified for the dataset, which supports an accelerated and streamlined approach for the development of device regenerative medicine therapies, in keeping with the goals of these guidances.

Additional references

In this draft guidance, FDA did not refer to human factors studies (and distinctions between the need for human factors work for medical professionals versus non-professionals) nor discuss change management, which can potentially have large impacts on the life cycle of RMAT devices. In regards to change management, device evaluation pathways utilized in the past have led to few post-approval change management submissions. However, even in the absence of any required FDA notifications of such post-approval changes, devices used with RMATs could require additional comparability and compatibility data (due to the potential for minor changes to unexpectedly effect product characteristics and dramatically change the product's overall safety and effectiveness). Best practices for post-approval change management under the myriad of submission routes possible for RMAT device products could be helpful.

Lastly, after the Agency issued this draft guidance, a new CDRH draft guidance on The Least Burdensome Provisions: Concept and Principles, dated December 15, 2017, became available. Should this guidance on the devices used with RMATs refer to this new CDRH guidance, and does the Agency expect the changes outlined in the CDRH guidance to impact this new guidance? Additionally, please consider outlining the application of the least burdensome approach specifically on the evaluation of devices used with RMAT products.

Lastly, ARM has some specific recommended changes, found in the table below.

ATTACHMENT 1 – Detailed comments on FDA Draft Guidance: "Evaluation of Devices Used with Regenerative Medicine Advanced Therapies"

Page (Section)	Comment and Rationale	Proposed Change (In red font)
Section II Scope **First Sentence**	For the sake of completeness, add reference to the definition of RMAT (as per section 506(g)(8) of the FD&C Act) and/or reference to the FDA RMAT designation webpage.	Modify to this Language: "This guidance applies to medical devices used in the recovery, isolation, or delivery of RMATs." To Read: This guidance applies to medical devices used in the recovery, isolation, or delivery of RMATs ***as defined in Section 506(g)(8) of the FD&C Act.*** *OR* This guidance applies to medical devices used in the recovery,

		isolation or delivery of ***Regenerative Medicine Advanced Therapies (RMATs). RMATs are defined in section 506(g)(8) of the FD&C Act, as including cell therapies, 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 (PHS Act) (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271). As FDA interprets section 506(g), gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy.***
Section II Scope	We recognize that the scope of the document is evaluation of devices used in the recovery, isolation or delivery of RMATs during development of RMATs. However, it will be helpful to clarify whether or not the concepts discussed will be applicable to other types of devices that may be involved during RMAT development, for example in vitro diagnostic devices (IVDs).	For investigational IVDs, it may also be helpful to clarify whether the new draft guidance *Investigational IVDs Used in Clinical Investigations of Therapeutic Products* will apply to RMATs. If it does, a cross-reference to that guidance and adding the guidance to the list of references that we recommend to add in an appendix would be helpful.
Section II Scope **First Sentence**	Clarification on FDA's position that isolation tools which are intended to be used within a direct patient setting are medical devices, while manufacturing tools used outside of a direct patient setting are general use equipment. Further examples may also be helpful.	*Isolation* is processing ***intended by the device manufacturer to be within a direct patient care setting*** that results in selection, separation, enrichment, or depletion of recovered cells or tissues that will become components of the final product;

		and
Section II Scope **Page 4, Second to the Last Paragraph**	This section only lists examples of devices that can be used with RMATs as devices intended for collection or processing of RMATs. It seems to be an omission that devices intended to deliver RMAT's or to facilitate the surgical procedure associated with RMAT's are not listed as an example of the "wide range of devices [that] may be used in conjunction with an RMAT."	Expand the list of example devices to include RMAT delivery devices, or devices used to facilitate RMAT surgical delivery.
Section II Scope **Page 4 Last Paragraph**	"The Agency does not consider scaffolds…" The agency has previously generalized the term for a device used in conjunction with a cell therapy as a "scaffold" (i.e. Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products). It would be helpful for sponsors engaged in the development of cell therapy products if the agency to provided more granularity around guidances for devices that deliver the cell therapy product that also provide a functional component to the RMAT. For example, are immuno-isolation devices also outside the scope of this guidance? Although the device is used to "deliver" the cells, both the device and cells are required for the intended therapeutic effect.	Modify this language: "The Agency does not consider scaffolds combined with a cellular product to be within the scope of this guidance." With respect to such scaffolds, they would generally not be considered solely a "device used in the delivery of an RMAT," because the scaffold is combined with the cellular product and provides more than a delivery function. Scaffolds also contribute additional functions such as physical support and/or reinforcement in or on the body. Both the scaffold and the cellular product are typically necessary for the RMAT to achieve its intended therapeutic effect or action." To Read: ***Devices which are implanted in combination with the RMAT, and which serve a function beyond delivery of the RMAT, are outside the scope of this guidance. Examples include (but are not limited to): scaffolds that are combined with a cellular product and contribute additional functions such as physical support and/or reinforcement in the body and***

		immuno-isolation devices that provide long-term protection for the implanted cells.
Section III **General Approach: Device Classification and Streamlining of Application of Regulatory Requirements** **Pages 5-6**	All of the information provided is already available in other guidance documents – there appears to be no information included that is specific to RMATs. Neither the device classification information nor the "least burdensome" information provided contains specific information for RMATs.	We interpret paragraph 3 as focusing on Topic 2 in General Comments – Uses or Attributes That Would Result in Device Being Class III. We request that FDA provide examples (if available) of devices used with RMATs that have been designated as Class 3 devices. Alternatively, the Agency could provide a flowchart that would help sponsors to facilitate their understanding of the device classification process.
Section III **General Approach** **page 5**	Guidance states "The appropriate regulatory evaluation pathway for devices used in the recovery, isolation, or delivery of RMATs and for Center jurisdiction for such devices may vary depending on the devices' technological characteristics and intended uses." It seems that the appropriate regulatory evaluation pathway should also depend on the risk level associated with the device. The following paragraph explains FDA's classification system but does not focus on the risk-based nature of the classification system.	Include language to explain the risk based nature of FDAs device classification system
Section III General Approach **Section A Least Burdensome Approach**	Section A generally discusses least burdensome principles. We note the need to update this section to include reference to more recently released CDRH guidance. There was the expectation that information would be provided on the least burdensome approach to demonstrate how a device may be used with more than one cell type.	We interpret this section as providing information relevant to Topic 4 in General Comments - Application of the least burdensome approach to demonstrate how a device may be used with more than one cell type Reference should be made to the most recent CDRH guidance.

	Information on this topic appears in Section V.	In a dedicated section of the guidance, we request that the least burdensome approach be specifically discussed for the evaluation of devices used with RMAT products.
Section III General Approach **Section B Available Premarket Pathways**	Section B describes the available premarket pathways for stand-alone devices.	It would be helpful to the diverse group of RMAT developers if this section could be moved (in addition to select information in Section IV) to an introductory section describing the available premarket pathways for both stand-alone and combination products.
Section IV Combination Products	There is only one statement (sentence 3) related to the use of separate marketing applications to allow for use of the delivery device to ultimately be labeled for use with multiple RMATs that have similar characteristics and administration requirements and one statement related to the simplification or streamlining of regulatory requirements (sentence 4).	We interpret this section as intending to focus on Topic 1 - How FDA intends to simplify and streamline regulatory requirements for combination device and cell or tissue products. See prior comments on moving the premarket pathways options to earlier in the document, perhaps in an introductory section. In this newly proposed introductory section, reference could be made to the opportunity for a drug/biologic sponsor to refer to a device master access file to utilize the device in an investigational setting. In general, it would be helpful for the Agency to provide examples of situations in which a simplified or streamlined approach has been taken in the approval of a device for use with an RMAT product.
Section IV Combination Products	The fourth sentence addresses the ability to fulfill regulatory requirements by simplifying or streamlining requirements by	FDA should address how the concept of reliance on data from RMAT studies can be utilized to reduce redundancy and

Third Paragraph – Sentence 4	reducing redundancy in data requirements. However, the guidance only applies the streamlining to the device constituent part (the example of using RMAT clinical trial data to support the device regulatory requirements) and not streamlining the RMAT requirements/review by utilizing RMAT device data and trials. Furthermore, this streamlining of the device requirements is <u>only</u> applied when the device has a stand-alone device filing, not a device-led or biologic-led single application filing (PMA or BLA).	streamline RMAT device reviews when the RMAT studies are filed to a combination product BLA or combination product PMA. FDA should also address how the same streamlining can occur with information from the RMAT device filing for the RMAT filing (either as a combination product BLA or a stand-alone RMAT BLA). If the latter is not appropriate for this guidance, which may be limited to interpretation of policy application of section 3034, then at minimum, the Agency should state in this guidance where and when it will convey such policy in future guidance(s).
Section V **Factors to Consider For When a Device Can Be Used With Only One Particular Type of Cell-Based RMAT or More Than One Type of Cell-Based RMAT**	As stated above, FDA intended that this document address "the factors to consider in determining whether a device may be labeled for use with a specific RMAT or class of RMATs;" and "when a device may be limited to a specific intended use with only one particular type of cell; and application of the least burdensome approach to demonstrate how a device may be used with more than one cell type." Section V does give some high level information on how compatibility issues could result in device market authorization being limited to use with a specific RMAT, and there is a general statement on how "experience gained over time" may allow for identification of delivery device characteristics that could support general labeling for these devices. However, these statements do not address the "least burdensome approach" for obtaining market authorization for stand-alone delivery devices.	This section appears to address Topic 3 and some of Topic 4 as outlined in the General Comments section, without addressing the application of the least burdensome approach. Further information specific to the least burdensome approach for RMAT delivery devices is necessary, especially when it is deemed that only specific labeling is supported, and the market authorization of the standalone device must be linked to the approval of a specific RMAT. While this may be more obvious for a combination device, in a case where the delivery device is not manufactured by the company sponsoring the RMAT trial, the device pathways are often unclear and convoluted.

Section V **Factors to Consider For When a Device Can Be Used With Only One Particular Type of Cell-Based RMAT or More Than One Type of Cell-Based RMAT**	There are examples of existing general use devices (e.g. syringes and needles) that are used to deliver RMATs in all stages of clinical development as well as commercial use (e.g. Luxturna PI advises to use off-the-shelf subretinal injection cannula , sterile needles and syringes). These general use-devices are typically Class I, exempt, and as such neither general nor specific indications for use. The manufacturers of these devices have not been required to demonstrate compatibility with a single or multiple RMATs as a condition of marketing. In contrast, Section V of the RMAT guidance indicates that a device manufacturer would be responsible for ensuring compatibility between cells and delivery device, and that a device manufacturer may be required to assess interactions for each new device-RMAT combination. Based on the above-mentioned examples, device manufacturers have previously not been held to this standard. This approach seems to penalize Sponsors for innovating devices for RMAT therapies by restricting the use of devices to a single product and requiring further RMAT-specific testing to incrementally establish the use of a device with more than RMAT. This is counter to least-burdensome principles. Sponsors should be able to develop delivery devices for RMATs in the same way they are developed for other devices intended to deliver "typical drugs." This places an unnecessarily high burden on the device Sponsor, and	Consider revising Section V such that RMAT devices are held to the same standard as currently marketed devices that may already be in use for RMAT collection or delivery. That is, to allow Sponsors to specify a range of operating specifications or functionalities (for example, viscosity or cell diameter) that can be cleared as general use, as opposed to requiring iterative clearances/submissions depending on RMAT. Additionally, we would like FDA to clarify where the responsibility lies for establishing compatibility/safety when a device is used with a RMAT product(s).

	one that is not placed on delivery devices already on the market. FDA should allow sponsors of delivery devices to set forth acceptable operating ranges, as proven by bench test data; and to obtain general indications for use based on that range, rather than requiring sponsors to obtain RMAT-specific clearance for delivery devices and then incrementally expand the indications for use.	

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,

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Alliance for Regenerative Medicine