

# Evaluation of Devices Used with Regenerative Medicine Advanced Therapies

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## Draft Guidance for Industry

**This guidance document is for comment purposes only.**

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of this guidance, contact CBER, Office of Communication, Outreach, and Development (OCOD) at 240-402-7800 or 800-835-4709. For questions about this document concerning products regulated by CDRH, contact the Office of the Center Director at 301-796-5900. If you need additional assistance with regulation of combination products, contact the Office of Combination Products at 301-796-8930.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
Center for Devices and Radiological Health  
Office of Combination Products  
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Contains Nonbinding Recommendations

*Draft – Not for Implementation*

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*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*

### I. INTRODUCTION

We, FDA, developed this guidance to provide you, device manufacturers, applicants, and sponsors engaged in the development of regenerative medicine therapies, with our current thinking regarding evaluation of devices used in the recovery, isolation or delivery of regenerative medicine advanced therapies.

Section 3034 of 21<sup>st</sup> Century Cures Act<sup>1</sup> (Cures Act) mandates that FDA issue guidance clarifying how FDA will evaluate devices used in the recovery, isolation, or delivery of regenerative advanced therapies, which FDA generally refers to as “regenerative medicine advanced therapies” or “RMATs.” Accordingly, this guidance discusses what FDA will consider when evaluating the devices used with RMATs. The Agency intends for this document, when finalized, to serve as a source of information about the Agency’s current thinking about a wide range of concepts related to the regulation of devices, as they apply to devices used in the recovery, isolation, and delivery of RMATs. Specifically, this guidance addresses how FDA intends to simplify and streamline its application of regulatory requirements for combination device and cell or tissue products; what, if any, intended uses or specific attributes would result in a device used with a regenerative therapy product to be classified as a Class III device;<sup>2</sup> the factors to consider in determining whether a device may be labeled for use with a specific RMAT or class of RMATs; 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.

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<sup>1</sup> Public Law 114-255.

<sup>2</sup> As explained in section III of this guidance, at this time, we are unable to provide a definitive list of intended uses or specific attributes that would result in a standalone device used with an RMAT being classified as a Class III device, but have instead addressed this requirement by providing information about characteristics of Class III devices. As we gain additional experience that would inform this aspect of the guidance, we intend to incorporate such information into the final guidance.

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FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA’s guidances means that something is suggested or recommended, but not required.

## II. SCOPE

This guidance applies to medical devices used in the recovery, isolation, or delivery of RMATs.

The term “device” is defined in section 201(h) of the Federal Food, Drug, & Cosmetic Act (FD&C Act) (21 U.S.C 321), as:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Under section 506(g) of the FD&C Act, a drug<sup>3</sup> is eligible for RMAT designation if:

- it is a regenerative medicine therapy as defined in section 506(g)(8) of the FD&C Act;<sup>4</sup>
- it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and

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<sup>3</sup> With respect to the RMAT designation program, references to “drugs” refer to human drugs, including drugs that are biological products, unless otherwise specified. For further discussion of the RMAT designation program, please see the guidance document entitled “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry,” dated November 2017, which when finalized, will represent the Agency’s thinking on the topic. As discussed in that draft guidance, a combination product (biologic-device, biologic-drug, or biologic-device-drug) can also be eligible for RMAT designation when the biological product component provides the greatest contribution to the overall intended therapeutic effects of the combination product (i.e., the “primary mode of action” of the combination product is conveyed by the biological product component).

<sup>4</sup> Section 506(g)(8) of the FD&C Act (21 U.S.C. 356(g)(8)), as added by Section 3033 of the Cures Act, defines a “regenerative medicine therapy” as including “cell therapy, 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 [42 U.S.C. 264] and [21 CFR Part 1271].”

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- preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition.

For the purpose of this guidance only,

- *recovery* means obtaining cells or tissues from a human donor;
- *isolation* is processing that results in selection, separation, enrichment, or depletion of recovered cells or tissues that will become components of the final product; and
- *delivery* refers to any method by which an RMAT is introduced onto or into the body of a human recipient, for example, infusion, injection, topical application, or inhalation.

*Combination product* includes:

- 1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- 2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- 3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- 4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.<sup>5</sup>

FDA recognizes that a wide range of devices may be used in conjunction with an RMAT. For example, the devices can be simple, low risk devices, such as a manual surgical instrument (e.g., scalpel) for recovering cells and tissue. Devices used with RMATs may also be complex, higher risk devices, such as an automated cell collection system that selects and processes specific cells for immediate return back to the patient. Additionally, devices used with RMATs can either be single entity devices or components of a combination product.

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

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<sup>5</sup> 21 CFR 3.2(e).

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the cellular product are typically necessary for the RMAT to achieve its intended therapeutic effect or action.

The use of general use equipment (e.g., centrifuges, cell washers, chromatography columns) in the manufacture of an RMAT outside of a direct patient care setting is reviewed under the Investigational New Drug Applications (IND)/ Biologics License Applications (BLA) for the RMAT. Therefore this guidance does not address such equipment. In addition, medical devices that are not used in the recovery, isolation, or delivery of RMATs are outside the scope of this guidance.

### **III. GENERAL APPROACH: DEVICE CLASSIFICATION AND STREAMLINING OF APPLICATION OF REGULATORY REQUIREMENTS**

The appropriate regulatory evaluation pathway for devices used in the recovery, isolation, or delivery of RMATs and for Center jurisdiction<sup>6</sup> for such devices may vary depending upon the devices' technological characteristics and intended uses. The devices' characteristics and intended uses are, in turn, generally based on the characteristics and conditions of use of the associated RMAT and the role of the device in the final product.

The classification of a device is a primary factor in determining the available premarket pathway for the device. The requirements for device classification are found in Section 513 of the FD&C Act (21 U.S.C. 360c).

Section 513(a) of the FD&C Act (21 U.S.C. 360c(a)) establishes three classes of devices based on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness: Class I (general controls), Class II (special controls in addition to general controls), and Class III (premarket approval in addition to general controls). Although a device's intended uses and technological characteristics are considered during classification, FDA has no predetermined list of intended uses or specific attributes which would result in a device used with an RMAT (or any device) to be classified as a Class III device. As a general matter, Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential unreasonable risk of illness or injury, and for which there is insufficient information to determine that general and/or special controls would provide reasonable assurance of safety and effectiveness.<sup>7</sup> Further, under section 513(f) of the FD&C Act (21 U.S.C. 360c(f)), postamendments devices (devices that were not in commercial distribution before May 28, 1976, the date the Medical Device Amendments were enacted) are classified in Class III unless FDA classifies or reclassifies them into Class I or II, or

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<sup>6</sup> See Guidance for Industry and FDA Staff: [Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](https://www.fda.gov/RegulatoryInformation/Guidances/ucm126052.htm), dated July 2007. Available at <https://www.fda.gov/RegulatoryInformation/Guidances/ucm126052.htm>.

<sup>7</sup> Section 513(a)(1)(C) of the FD&C Act; 21 U.S.C. 360c(a)(1)(C).

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determines that such a device is “substantially equivalent” (SE)<sup>8</sup> to another device for which premarket approval is not required.<sup>9</sup> Thus, a postamendments device may be subject to regulation as a Class I or II device in certain circumstances, including when:

- the device is within a type of device that has been classified into Class I or II and FDA has found the device to be SE to a device within such type;
- the device is within a type of preamendments device that is unclassified and FDA has found the device to be SE to a device within such type; or
- FDA has classified or reclassified the device type in Class I or II in accordance with sections 513(f)(2)<sup>10</sup> or 513(f)(3) of the FD&C Act (21 U.S.C. 360c(f)(2),(3)).

#### **A. Least Burdensome Principles**

FDA applies the level of regulation necessary to provide reasonable assurance that a medical device is safe and effective for its intended use. In accordance with the “least burdensome provisions” of the FD&C Act,<sup>11</sup> the least burdensome principles apply to FDA requests for information related to (1) demonstrating a reasonable assurance of device safety and effectiveness in PMAs<sup>12</sup> and (2) determinations of substantial equivalence for devices with technological characteristics that differ from those of the predicate device.<sup>13</sup>

In conducting premarket review of a medical device, FDA requests information that is necessary to make a determination of whether the statutory standards for marketing authorization are met in accordance with the least burdensome principle. Based on the least burdensome principle, the term “necessary” means that FDA considers “the minimum required information that would support” (1) “a determination by [FDA] that an application provides reasonable assurance of the safety and effectiveness of the device”<sup>14</sup> or (2) “a determination of substantial equivalence between a new device and a predicate device.”<sup>15</sup>

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<sup>8</sup> Substantial equivalence is defined at section 513(i) of the FD&C Act (21 U.S.C. 360c(i)). FDA generally evaluates substantial equivalence on the basis of a premarket notification submitted pursuant to section 510(k) of the FD&C Act (21 U.S.C. 360(k)). Certain devices are subject to a statutory exemption from the 510(k) premarket notification requirement (see sections 510(l) and (m) of the FD&C Act (21 U.S.C. 360(l) and (m))).

<sup>9</sup> A preamendments device for which premarket approval is not required could be a preamendments device that has been classified into Class I or Class II, a preamendments device that has been classified into Class III but for which a regulation under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring the submission of an application for premarket approval (PMA) has not yet been issued, or a preamendments device that has not yet been classified.

<sup>10</sup> This process is referred to as “De Novo” classification, and is described in more detail below.

<sup>11</sup> The FDA Modernization Act of 1997 (FDAMA) added two provisions, commonly known as the “least burdensome provisions,” to the FD&C Act; related provisions were added to the statute by the FDA Safety and Innovation Act of 2012 (FDASIA) (Pub. L. 112-144) and the Cures Act.

<sup>12</sup> Sections 513(a)(3)(D)(ii) and 515(c)(5) of the FD&C Act, 21 U.S.C. 360c(a)(3)(D)(ii), 360e(c)(5).

<sup>13</sup> See section 513(i)(1)(D)(i) of the FD&C Act (21 U.S.C. 360c(i)(1)(D)(i)).

<sup>14</sup> Section 515(c)(5) of the FD&C Act (21 U.S.C. 360e(c)(5)).

<sup>15</sup> Section 513(i)(1)(D)(ii) of the FD&C Act (21 U.S.C. 360c(i)(1)(D)(ii)).



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Additional information related to how FDA intends to apply the least burdensome provisions is available in the following FDA guidances (“Least Burdensome Guidances”) that discuss the principles with which the recommendations discussed in this guidance are consistent:

- The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, dated October 2002. Available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm>.
- Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA; Final Guidance for Industry and FDA Staff, dated November 2000. Available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073679.htm>.

### **B. Available Premarket Pathways**

The appropriate premarket submission pathway for a given medical device is determined by the risks associated with the device as well as the level of regulatory controls necessary to provide a reasonable assurance of safety and effectiveness. The available submission pathways (e.g., premarket notification (510(k)), De Novo classification (De Novo) request, Premarket Approval (PMA) Application, or Humanitarian Device Exemption (HDE)) are briefly discussed in sections III.B.1 -4.

When clinical evidence is necessary to support marketing authorization of a medical device, an investigational device exemption (IDE) may be necessary.<sup>16</sup> An IDE allows the investigational device to be used in a clinical study in the United States in order to collect safety and effectiveness data. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device. FDA has published numerous guidance documents related to IDEs, which can be found at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm162453.htm>.

Although a manufacturer or sponsor may submit any form of evidence to FDA in an attempt to substantiate the safety and effectiveness of a device, the Agency relies upon only valid scientific evidence<sup>17</sup> to determine whether there is reasonable assurance that the device is

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<sup>16</sup> See Section 520(g) of the FD&C Act (21 U.S.C. 360j) and 21 CFR 812.2.

<sup>17</sup> Valid scientific evidence is defined as “evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.” (21 C.F.R. 860.7(c)(2)).

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safe and effective. After considering the nature of the device and the rules in 21 CFR 860.7, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.<sup>18</sup>

#### **1. Premarket Notification (510(k))**

If FDA has previously cleared through a 510(k) or granted a De Novo request for another device of the same type (i.e., a legally-marketed predicate device),<sup>19</sup> as a new device, a 510(k) is typically the appropriate pathway for the new device.<sup>20</sup> Additional information on the 510(k) Program can be found in the guidance document entitled “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]; Guidance for Industry and Food and Drug Administration Staff,” dated July 2014, available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm284443.pdf>.

#### **2. De Novo Classification Request**

Devices of a new type that FDA has not previously classified based on the criteria at section 513(a)(1) of the FD&C Act are ‘automatically’ or ‘statutorily’ classified into Class III.<sup>21</sup> However, if the device appears, based on what is known about the device, to meet the statutory standards for classification into class I or II under section 513(a)(1) of the FD&C Act, (i.e., general controls or general and special controls would provide reasonable assurance of the safety and effectiveness of the device), the device may be eligible for De Novo classification.<sup>22</sup> If the requester demonstrates that the device meets the statutory standards for classification into class I or II under section 513(a)(1) of the FD&C Act, i.e., that general controls, or a combination of general controls and special controls, are sufficient to provide a reasonable assurance of safety and effectiveness, FDA will grant the De Novo request and issue a written order classifying the specific device and device type in Class I or Class II.

Additional information on the De Novo Program can be found in the guidance document entitled “De Novo Classification Process (Evaluation of Automatic Class III Designation); Guidance for Industry and Food and Drug Administration Staff,” dated October 30, 2017,

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<sup>18</sup> 21 C.F.R. 860.7(c)(1).

<sup>19</sup> Under 21 CFR 807.92(a)(3), a legally marketed predicate is a device that (i) was legally marketed in the United States prior to May 28, 1976 (preamendments device) and for which a PMA is not required; or (ii) has been reclassified from class III to II or I; or (iii) has been found substantially equivalent (SE) through the 510(k) process.

<sup>20</sup> See section 510(k) of the FD&C Act (21 U.S.C. 360(k)), and 21 CFR Part 807 Subpart E.

<sup>21</sup> Section 513(f)(1) of the FD&C Act (21 U.S.C. 360c(f)(1)).

<sup>22</sup> FDA may decline to undertake a De Novo request if the conditions set forth in section 513(f)(2)(A)(iv) of the FD&C Act (21 U.S.C. 360c(f)(2)(A)(iv)) are met.

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available at

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf>.

### 3. Premarket Approval Application

Premarket approval (PMA) is required before most Class III devices can be marketed.<sup>23</sup> A PMA application must demonstrate a “reasonable assurance of safety and effectiveness” by “weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,” among other relevant factors.<sup>24</sup> To aid in this process, PMA applicants submit valid scientific evidence, including one or more clinical investigations where appropriate, which FDA reviews to determine whether “the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device.”<sup>25</sup>

For information regarding PMAs, see FDA’s guidance entitled “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications,” dated August 2016. Available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm517504.pdf>. Additionally, the guidance entitled “Acceptance and Filing Reviews for Premarket Approval Applications (PMAs); Guidance for Industry and Food and Drug Administration Staff,” dated December 2003, may provide useful information to manufacturers when preparing PMAs. Available at <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313368.pdf>.

### 4. Humanitarian Device Exemption (HDE)

An HDE provides a regulatory path for devices that are intended to benefit patients with rare diseases or conditions. In order for a device to be eligible for an HDE, a sponsor must obtain designation as a Humanitarian Use Device (HUD).<sup>26</sup> Additional information on the HUD program and HDE applications can be found in the guidance document entitled “Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers,” dated July 2010. Available at

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm>.

FDA understands that applicants may have questions prior to submitting a premarket application. We have established a structured process for managing the various types of requests for feedback

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<sup>23</sup> See section 513(a)(1)(C) of the FD&C Act, 21 U.S.C. 360c(a)(1)(C).

<sup>24</sup> See sections 513(a)(2), 515(d)(1)(A) and 515(d)(2)(A)-(B) of the FD&C Act (21 U.S.C. 360c(a), 360e(d)(1)(A) and (d)(2)(A)-(B)); see also 21 CFR 860.7(b), (d), and (e).

<sup>25</sup> Section 513(a)(3)(A) of the FD&C Act, 21 U.S.C. 360c(a)(3)(A).

<sup>26</sup> 21 CFR 814.102(a).

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prior to a premarket submission, referred to as “Q-Submissions.” FDA has issued guidance that provides an overview of the mechanisms available to applicants through which they can request feedback from FDA regarding potential or planned medical device IDE applications or other premarket submissions, such as PMA applications, HDE applications, De Novo requests, 510(k)s, and BLAs.<sup>27</sup>

### IV. COMBINATION PRODUCTS

Consistent with the Agency’s approach to simplify and streamline the regulatory approaches for combination products in general, RMAT-based combination products are generally reviewed under a single application. Devices intended for use with a specific RMAT may, together with the RMAT, be considered to comprise a combination product and be evaluated for marketing under a BLA in the Center for Biologics Evaluation and Research (CBER).

Some devices that can be used with approved RMATs may be evaluated independently as stand-alone devices using premarket submissions pathways identified in section III.B. Examples include general use devices used in recovery (e.g., surgical tools, syringes, apheresis collection devices), or delivery (e.g., syringe, catheter). When a separate premarket application for a device to be used with an RMAT is appropriate, FDA will apply the least burdensome provisions of the FD&C Act as noted above to determine the “minimum required information” necessary for marketing authorization of that device.

In some instances, the RMAT and its specified delivery device may be separately packaged but labeled for use together. The two products may comprise a combination product. Regardless, separate marketing applications for each product may be appropriate, particularly if the delivery device may ultimately be labeled for use with multiple RMATs that have similar characteristics and administration requirements. In instances where there are separate applications for the RMAT and delivery device, fulfillment of regulatory requirements may be simplified or streamlined by reducing redundancy in data requirements, e.g., using clinical data generated in association with the RMAT IND studies to support the approval or clearance of the device application as well as the BLA and/or cross-referencing existing device nonclinical performance data in the BLA when available and such reliance is permissible. If a separate device application is appropriate for a dedicated delivery device constituent part of a combination product, the least burdensome provisions of the FD&C Act<sup>28</sup> will be applied to determine the data and information necessary to provide reasonable assurance that the delivery device is safe and effective for its intended use.

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<sup>27</sup> See Guidance for Industry and Food and Drug Administration Staff: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff, dated February 2014. Available at:

<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>.

<sup>28</sup> See footnote 11.

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### 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**

RMAT designation is granted for a specific therapeutic product and specific intended uses. RMATs may represent a highly diverse group of products with distinct biological and physical characteristics. These characteristics, along with other factors such as target patient population (e.g., adult vs pediatric), intended use and conditions for use must be considered when determining which device, or devices, may be suitable for use with a specified RMAT. These same factors will influence when a device may be limited to a specific intended use with only one particular type of cell-based RMAT.

RMATs are likely to differ with regard to characteristics that can impact the way the RMAT interacts with different device materials and affect the RMAT's safety and effectiveness. In the case of cellular products that are RMATs, the interaction between cells and a delivery device can have an impact on critical characteristics, such as cell viability, differentiation potential, activation state and ability to respond to stimuli after administration. Further, differences in physical characteristics such as cell size and sensitivity to shearing forces can directly impact the potential utility of a given delivery device with a specific RMAT. For example, it may not be possible to use a small bore catheter or pen/jet injector to deliver an RMAT that contains a large delicate cell type because the shearing forces may negatively impact cell viability. In contrast, an RMAT that contains a smaller, more robust cell type may require the use of a small bore catheter to facilitate delivery to a specific tissue site, but have special requirements to prevent the cells from adsorbing to the interior catheter surface or to each other, resulting in occlusion of the tip. Such factors along with the demonstrated performance will influence whether the device can obtain marketing authorization for a broader use, or should be limited to use with a specific RMAT(s).

Because cellular products can possess extremely variable sensitivities to physical and chemical stimuli, it may be necessary to repeat testing to assess interactions of each new device-RMAT combination. To leverage compatibility data which uses a different device-RMAT combination, a detailed and specific scientific rationale for the applicability of this data would be needed. Sufficient compatibility data should be provided to the Agency prior to initiation of clinical trials.

If, during development, a given RMAT, including one that is a cell-based RMAT, is determined to have characteristics and use requirements that would allow it to be administered with a general class of devices (e.g., conventional syringe or catheter), or specific subset of delivery device(s) with defined characteristics, without compromising the safety and efficacy of the RMAT, the RMAT may be approved on its own with appropriate labeling for use with such devices. Experience gained over time with a specific RMAT or class of RMATs in different use settings may allow for identification of delivery device characteristics that could support approval of more general labeling rather than specifying use with a particular device.