

Guidance for Industry

Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs)

DRAFT GUIDANCE

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For questions on the content of this guidance, contact Richard McFarland, Ph.D., M.D., at 301-827-5102.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The process of selecting peripheral blood stem cells (PBSCs) for autologous use is frequently performed shortly before re-implantation in the patient, at the laboratory in the health care facility, or, potentially, at the patient’s bedside. We, FDA, are issuing this guidance to provide advice to you, the industry, on when we consider the selection of autologous PBSCs that are minimally manipulated at the point of care by FDA regulated cell selection devices cleared or approved for this use to fall within the exception from the requirements in Title 21 Code of Federal Regulations (21 CFR) Part 1271 set out in 21 CFR 1271.15(b). We also provide recommendations on an approach for providing data intended to support approval of cell selection devices for this use, thereby facilitating the development of safe and effective autologous PBSCs for human medical use.

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. BACKGROUND

Devices are frequently used in the cell selection process. Some of these devices are quite sophisticated and are able to perform all of the steps in the processing of PBSCs, except collection. We have received a number of inquiries related to the regulation of such devices and the processed cells when used for specific clinical conditions, such as ischemic heart disease, peripheral vascular disease, and bone fracture.

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Cell selection devices that prepare autologous, minimally manipulated PBSCs at the point of care for direct re-administration meet the definition of a medical device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act). These devices are therefore subject to the Act and FDA medical device regulations (21 CFR Part 800 *et seq.*).

PBSCs used for these purposes meet the definition of human cells, tissues or cellular or tissue-based products (HCT/Ps) contained in 21 CFR 1271.3(d), which expressly include “hematopoietic stem/progenitor cells derived from peripheral blood.” Accordingly, the tissue regulatory scheme set out in 21 CFR Part 1271 applies to such PBSCs. However, 21 CFR 1271.15(b) provides the following exception to those requirements, “You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P’s from an individual and implants such HCT/P’s into the same individual during the same surgical procedure.” When the agency initially proposed this exception, FDA explained that the exception reflected FDA’s risk-based approach to regulating HCT/Ps “only to the extent necessary to protect public health.” (63 *Federal Register* 26744, 26745; May 14, 1998).

In this document, we explain when we consider PBSCs recovered from a patient and processed using a device that is approved or cleared for such purpose to fall within this exception. We note that when this exception does *not* apply, PBSCs for clinical use are subject to regulation under 21 CFR Part 1271, and may be subject to regulation as a biological product (21 CFR 1271.20), including requirements for investigation under the investigational new drug regulations (IND) (21 CFR Part 312) and biologics license requirements (42 U.S.C. 262(a), 21 CFR 601.2 *et seq.*).

III. DISCUSSION

A. Autologous PBSCs Recovered and Implanted in the Same Surgical Procedure

This guidance discusses certain cell selection devices that minimally manipulate autologous PBSCs at the point of care for specific clinical indications. As described in this document, FDA would consider the PBSCs to fall within the “same surgical procedure” exception to regulation under 21 CFR 1271.15(b) and therefore would not require compliance with 21 CFR Part 1271, or the submission of an IND and biologics license application (BLA) for the cellular product. FDA believes that, for autologous PBSCs processed at the clinical site, the presence of all of the following five factors supports the conclusion that the cells are removed and subsequently implanted in the “same surgical procedure” and are therefore subject to the exception:

- 1) The cells are autologous and are intended for use for a specific clinical indication;
- 2) The cells are minimally manipulated;
- 3) The device is solely responsible for the production of the autologous cells (i.e., no other manufacturing steps take place outside of the device other than the recovery of the source cells);
- 4) The cells are used within a short period of time (i.e., they are not stored or shipped); and

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- 5) The device and selected cells are only used at the point of care (i.e., cell processing is performed at and by the clinical site where cells are directly administered).

Under these circumstances, the cells are collected and selected as preliminary steps in the administration of those cells a short time later. The selection device is used in a location close enough to the patient that the recovery, processing, and direct administration of the cells will occur in a matter of hours (or less) and without the need for shipping. The processing should take place at and by the same clinical site in which the patient is receiving care, with the physical location of the cell processing proximate to the patient (i.e., within easy walking distance for those providing care to the patient). For example, investigational use of these cell selection devices and the resulting cells has commonly been conducted at a single clinical site, either in the operating suite or in a specialized cell processing laboratory that is located in close proximity to the patient.

When these five factors are present, and consistent with FDA's risk-based approach to regulating HCT/Ps, FDA would not require an individual clinical site using a cell selection device that is approved for this use, to register and list as a tissue establishment, or otherwise to comply with the tissue regulations (21 CFR Part 1271). FDA would not require the submission of an IND and BLA for the cellular product. The cells processed by the device would be covered under the surgical procedure exception in 21 CFR 1271.15(b).

PBSCs that are recovered and implanted under different circumstances are not covered under this guidance, and the determination of whether the "same surgical procedure" exception applies would require a different analysis. For example, the same surgical procedure exception applies only for autologous HCT/Ps. Consistent with FDA's risk-based approach to regulation of HCT/Ps, allogeneic cellular products do not fall within the 21 CFR 1271.15(b) exception. Allogeneic cellular products raise additional safety concerns due to the potential effects of histocompatibility antigen mismatch, other immunologically-mediated toxicities, and infectious disease transmission, which are not present with autologous PBSCs.

Another circumstance that may present additional risks and accordingly preclude application of the 21 CFR 1271.15(b) exception involves shipment of the HCT/Ps between recovery and implantation. Such shipments may introduce additional risks and warrant validation of shipping and storage containers and procedures.

Finally, the same surgical procedure exception is available only when "such HCT/P's" are implanted in the donor. More than minimal manipulation of the cells may alter them extensively, changing their essential character. Moreover, such manipulation introduces significant risks into the manufacturing process. Under FDA's risk-based approach, more than minimal manipulation typically involves the use of drugs, biologics and/or additional devices that warrants regulation of the manufacturing process and the resulting

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cells as biological products. Alternatively, significant processing introduces other risks (including contamination) that may so significantly change the cells that we are no longer able to conclude that they are “such HCT/P’s”.

B. Devices Used to Minimally Manipulate Autologous PBSCs

The data we would expect to be submitted in applications for the devices discussed in this guidance will likely vary based on multiple factors including device technology, and clinical indication; therefore we suggest that sponsors considering using this approach seek pre-submission advice from us. Although detailed recommendations are beyond the scope of this guidance, we provide some general advice regarding device submissions using this approach below.

The cell selection devices covered by this guidance are subject to all applicable premarketing and postmarketing regulatory controls in the device provisions of the Act (see e.g., section 515 (21 U.S.C. 360e)), as well as all applicable FDA regulations governing medical devices, including the premarket approval device regulations (21 CFR Part 814), and the quality system regulations relating to the design, manufacture, and testing of a device (21 CFR Part 820). Marketing application submissions for cell selection devices to process cells under the five conditions outlined in this guidance must include data demonstrating that the device is safe and effective under the prescribed conditions of use (section 515(c)(1) of the Act) (21 U.S.C. 360e(c)(1)). Demonstration of the safety and effectiveness of the device must include data on the device design, manufacturing, and performance characteristics (21 CFR 814.20).

In order to establish the performance characteristics of a device covered by this guidance, the manufacturer should provide data demonstrating that the device is capable of reliably producing the intended cells under routine use conditions (see 21 CFR 814.20). The specifics of the data expectations for the non-clinical studies (e.g., bench and/or animal studies) should reflect the design and performance specifics of each individual device for each cell type and clinical indication under consideration. To demonstrate the clinical performance of the device, the sponsor should conduct appropriate clinical studies to demonstrate that the device, including the device output, is safe and effective. Clinical studies must be conducted under the investigational device exemption regulations (21 CFR Part 812). We expect that the trials would be adequately designed and powered to demonstrate that the device produces clinically effective cells for each specific clinical indication under consideration. Our recommendations for clinical trial design features may vary depending on the specifics of the device and the clinical indication for which approval is being sought. Prior to the submission of a marketing application for a cell selection device covered in this guidance, we recommend that sponsors consult FDA for specific guidance relevant to the clinical indication intended.

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In addition to providing data demonstrating the reliability of device performance, we also recommend that the manufacturer provide instructions for use and a training program for operators of the device as marketed, in order to facilitate appropriate use of the device. The manufacturer may also be required to monitor device performance in the postmarketing period (see 21 CFR Part 822).