

Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception

Guidance for Industry

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This guidance represents 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, the Center for Biologics Evaluation and Research (CBER)¹ at the FDA, are issuing this guidance to provide you, tissue establishments and healthcare professionals, with our current thinking on the scope of the exception set forth in Title 21 of the Code of Federal Regulations (CFR) Part 1271, specifically the exception set forth in 21 CFR 1271.15(b). This guidance does not address the other exceptions in 21 CFR 1271.15.

This guidance, presented in question and answer format, provides our current interpretation of this regulation and includes examples based on inquiries received by the Agency since the final rule, “Human Cells, Tissues, and Cellular and Tissue Based Products; Establishment Registration and Listing” (Establishment Registration and Listing final rule) was published on January 19, 2001 (66 FR 5447).

This guidance finalizes the draft guidance of the same title dated October 2014. This guidance also finalizes certain material related to adipose tissue that was included in the draft guidance entitled “Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry” dated December 2014 (Adipose Draft Guidance). These material, together with the material related to adipose tissue included in the final guidance entitled “Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff” dated November 2017, supersedes the Adipose Draft Guidance. Accordingly, we do not intend to finalize the Adipose Draft Guidance which is now withdrawn.

¹ This guidance has been prepared by CBER in cooperation with the Center for Devices and Radiological Health (CDRH), and the Office of Combination Products (OCP) at the Food and Drug Administration.

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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. BACKGROUND

HCT/Ps are defined in 21 CFR 1271.3(d) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.² Under the authority of section 361 of the Public Health Service (PHS) Act, FDA established regulations for HCT/Ps to prevent the introduction, transmission, and spread of communicable diseases. These regulations can be found in 21 CFR Part 1271 (Part 1271).

Under certain circumstances, an establishment may qualify for an exception from the requirements under Part 1271. These circumstances are set out in 21 CFR 1271.15, including the exception in 21 CFR 1271.15(b) that is the subject of this guidance. Section 1271.15(b) provides: "You are not required to comply with the requirements of this Part if you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure."

On February 28, 1997, we addressed this exception in the document entitled, "Proposed Approach to Regulation of Cellular and Tissue-Based Products."³ In explaining our proposed approach for regulating human cellular and tissue-based products, we stated that:

The agency would not assert any regulatory control over cells or tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure. The communicable disease risks, as well as the safety and

² Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following articles are not considered HCT/Ps: (1) Vascularized human organs for transplantation; (2) Whole Blood or blood components or blood derivative products subject to listing under 21 CFR Parts 607 and 207, respectively; (3) Secreted or extracted human products, such as milk, collagen, and cell factors, except that semen is considered an HCT/P; (4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); (5) Ancillary products used in the manufacture of HCT/P; (6) Cells, tissues, and organs derived from animals other than humans; (7) In vitro diagnostic products as defined in 21 CFR 809.3(a); and (8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2 that are intended for use in organ transplantation and labeled "For use in organ transplantation only." (21 CFR 1271.3(d)).

Please note, the regulatory status of products identified as not being HCT/Ps is beyond the scope of this guidance.

³ "Proposed Approach to Regulation of Cellular and Tissue-Based Products," (1997 Proposed Approach) dated February 28, 1997; (62 FR 9721; March 4, 1997) page 12.
<https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm062601.pdf>.

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effectiveness risks, would generally be no different than those typically associated with surgery.

Subsequently, in the *Federal Register* of May 14, 1998 (63 FR 26744), we published a proposed rule “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products” that proposed to require establishments that manufacture human cellular or tissue-based products that meet certain criteria to register and list with the Agency. In describing which establishments are required to register and list, we stated that:

“An establishment or person that removes human cellular or tissue-based products from an individual and then implants, transplants, infuses or transfers those cells or tissues into the same individual is not required to register or list with the agency, so long as the human cellular or tissue-based product is quarantined pending completion of the surgery.” (63 FR 26744 at 26748)

In the preamble to the Establishment Registration and Listing final rule, with respect to the exception in 21 CFR 1271.15(b), we reported that we had received one comment on the proposed exception. We also reported that the comment assumed that hospitals retaining autologous tissue, not used in a scheduled surgical procedure, to be used in a subsequent application on the same patient, are exempt from registration and listing because the two applications are essentially a single continuous procedure.

In response to that comment, we stated the following:

“We agree that, so long as the hospital does not engage in any other activity encompassed within [sic] the definition of “manufacture,” the hospital would not be required to register or comply with the other provisions to be codified in Part 1271. For example, if the hospital expanded the cells or tissues, it would not meet the terms of the exception. In reaching this conclusion, we note that hospitals that store autologous cells or tissues for subsequent application in the same patient must follow the guidelines of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO)⁴ for tissue storage, monitoring of storage devices, and tracking in order to obtain or maintain accreditation.” (66 FR 5447 at 5460)

In sum, FDA’s view is that autologous cells or tissues that are removed from an individual and implanted into the same individual without intervening processing steps beyond rinsing, cleansing, sizing, or shaping, raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery. FDA considers the same surgical procedure exception to be a narrow exception to regulation under Part 1271.

⁴ For the purposes of making a determination as to whether an establishment meets the exception in 21 CFR 1271.15(b), FDA does not take into account whether an establishment is accredited by a particular organization. Reference to the JCAHO (now The Joint Commission) was intended to serve as an example.

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III. QUESTIONS AND ANSWERS

Q1: What is the relationship between the exception in 21 CFR 1271.15(b) and the four criteria described in 21 CFR 1271.10(a)?

A1: The regulations in 21 CFR 1271.15, including 21 CFR 1271.15(b) provide exceptions from the requirements in Part 1271. The four criteria described in 21 CFR 1271.10(a) are assessed to determine whether an HCT/P that does not fall under any of the exceptions in 21 CFR 1271.15 is regulated solely under section 361 of the PHS Act and Part 1271.

The assessment of whether the exception in 21 CFR 1271.15(b) applies is independent from the determination of whether the HCT/P meets the criteria in 21 CFR 1271.10(a) (e.g., the criteria of minimal manipulation in 21 CFR 1271.10(a)(1) and homologous use in 21 CFR 1271.10(a)(2) are not considered when determining whether an HCT/P meets the exception in 21 CFR 1271.15(b)). Further, the assessment of whether the exception in 21 CFR 1271.15(b) applies is made before considering the four criteria in 21 CFR 1271.10(a). Thus, if an establishment meets the exception in 21 CFR 1271.15(b), the establishment is excepted from the requirements under Part 1271 and the establishment need not consider whether that HCT/P meets the four criteria in 21 CFR 1271.10(a).

Q2: When does the exception in 21 CFR 1271.15(b) apply?

A2: For the exception to apply, an establishment⁵ must:

- a. Remove and implant the HCT/Ps into the same individual from whom they were removed (autologous use);
- b. Implant the HCT/Ps within the same surgical procedure; and
- c. The HCT/Ps remain “such HCT/Ps;” they are in their original form.⁶

⁵ “Establishment” means a place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps (21 CFR 1271.3(b)). As stated in the “Guidance for Industry: Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Small Entity Compliance Guide,” one general physical location could be reasonably construed to include separate buildings within close proximity provided that the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and capable of being inspected at the same time. See: <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073366.htm>.

⁶ The communicable disease risks, as well as safety risks, generally would be no different from those typically associated with surgery.

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Q3: Section 1271.15(b) refers to implanting “such HCT/P.” What is meant by “such HCT/P”?

A3: An HCT/P remains “such HCT/P” when it is in its original form. Generally, the only processing steps that will allow an HCT/P to remain “such HCT/P” are rinsing, cleansing, sizing, and shaping.

Further, as described in the answer to Q1, the assessment of whether an HCT/P is “such HCT/P” under 21 CFR 1271.15(b) is different from the assessment of whether an HCT/P is minimally manipulated under 21 CFR 1271.10(a). Accordingly, even processing that may be considered minimal manipulation within 21 CFR 1271.10(a), will typically cause the HCT/P to no longer be “such HCT/P” under 21 CFR 1271.15(b), if the processing is not limited to rinsing, cleansing, sizing, or shaping.

Q4: What is autologous use?

A4: As defined in 21 CFR 1271.3(a), autologous use means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered. The exception in 21 CFR 1271.15(b) applies only when the HCT/P is removed from and implanted into the same individual.

Q5: Section 1271.15(b) refers to same surgical procedure. What types of procedures are considered the same surgical procedures?

A5: For the purposes of the exception in 21 CFR 1271.15(b), procedures that involve an incision or instrumentation during which an HCT/P is removed from and implanted into the same individual within a single operation performed at the same establishment, are generally considered to be the same surgical procedures. Examples include autologous skin grafting, and coronary artery bypass surgery involving autologous vein or artery grafting.

Q6: Are there any types of procedures consisting of more than a single operation that are considered same surgical procedure for purposes of the exception in 21 CFR 1271.15(b)?

A6: Generally, as discussed in the answer to Q5, procedures consisting of more than a single operation are not considered the same surgical procedure.

However, under limited circumstances, surgical removal and subsequent implantation of the autologous HCT/P may be considered same surgical procedure even though the removal and future implantation may be a number of days apart. During this time, the HCT/P may be rinsed or cleansed and

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temporarily stored after being labeled, pending implantation, and this would still be considered the same surgical procedure, provided no other processing steps and no other manufacturing steps beyond labeling and storage are performed.⁷

Establishments that perform the following procedures consisting of more than a single operation generally would qualify for the exception in 21 CFR 1271.15(b):

- a. Craniotomy or craniectomy with subsequent implantation of the bone flap to reverse the cranial defect.
- b. Parathyroidectomy with subsequent implantation of a portion of the tissue to preserve parathyroid function.

The exception generally applies only to those establishments that both remove and implant the autologous HCT/P at the same establishment. An establishment that removes an HCT/P for implantation into the same individual, but intends the HCT/P to be implanted at a different establishment, would not qualify for the exception. Shipping the HCT/P to another establishment for implantation raises safety concerns, such as contamination and cross-contamination, beyond those typically associated with surgery. The establishment shipping the autologous HCT/P for use at another establishment is distributing the HCT/P⁸, which is a manufacturing⁹ step, and therefore the shipping establishment must register, submit an HCT/P list under Part 1271, Subpart B, and follow all other applicable regulations in Part 1271.¹⁰

For craniotomy, craniectomy, or parathyroidectomy procedures, FDA recognizes that under limited circumstances, in order to accommodate the medical needs of an individual patient, there may be a medical necessity for the establishment that removed the autologous cranial bone flap or portions of parathyroid tissue to send the HCT/Ps to a different establishment for reimplantation in the patient. In such cases, provided precautions will be taken to protect the HCT/P from contamination and cross-contamination, FDA does not intend to object to the recovering establishment sending the autologous cranial bone flap or portions of parathyroid tissue to a different establishment for reimplantation in the patient, without registering and listing with the FDA.

⁷ Temporary storage of a cranial bone flap or portion of parathyroid tissue may include steps to preserve those HCT/Ps in an appropriate condition for reimplantation, such as disinfecting or cryopreserving.

⁸ “Distribution” means any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet all release criteria, whether or not such conveyance or shipment is entirely intrastate (21 CFR 1271.3(bb)).

⁹ “Manufacture” means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor (21 CFR 1271.3(e)).

¹⁰ If you are an establishment that receives the autologous HCT/P only for the purpose of implantation in the individual within your facility, you are not required to comply with the requirements in Part 1271, including registration (21 CFR 1271.15(d)).

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Q7: Can an establishment that processes an autologous HCT/P after removal and prior to implantation still qualify for the exception in 21 CFR 1271.15(b)?

A7: Generally, an establishment that processes an autologous HCT/P prior to implantation would be required to comply with the requirements of Part 1271 and would not qualify for the exception. As a general matter, the establishment may qualify for the exception if the only processing steps taken are rinsing, cleansing, sizing, or shaping the tissue. Processing¹¹ of the autologous HCT/P raises safety concerns, such as contamination and cross-contamination, beyond those typically associated with surgery.¹²

In general, limited handling such as rinsing and cleansing, by centrifugation or filtration solely to remove debris (e.g., lipids, blood, bone particles) would allow the HCT/P to remain “such HCT/P.” Other processing steps, including by centrifugation or filtration, for cell isolation, cell expansion, cell activation, or enzymatic digestion generally would not allow the HCT/P to remain “such HCT/P” and the establishment would not qualify for the exception¹³.

Example 7-1: Adipose tissue is recovered by tumescent liposuction¹⁴. The lipoaspirate is centrifuged to facilitate removal of debris and extracellular fluid. No steps are taken to isolate stem cells (also commonly referred to as stromal vascular fraction) from the lipoaspirate. The adipose tissue remains “such HCT/P” because nothing else is added to the adipose tissue, only minor handling is performed, and the adipose tissue retains its original form as a connective tissue composed of clusters of adipocytes and other cells surrounded by a reticular fiber network and interspersed small blood vessels. It is then re-implanted into the same patient from whom it was removed in order to achieve the intended effect¹⁵. We generally would consider the establishment removing and implanting this HCT/P from adipose tissue to qualify for the exception under 21 CFR 1271.15(b).

¹¹ “Processing” means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage (21 CFR 1271.3(ff)).

¹² 1997 Proposed Approach page 12.

<https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm062601.pdf>. For example, “an infected product could cross-contaminate other cellular or tissue-based products...or could contaminate processing equipment, which, if not properly treated, could contaminate other tissue processed with that equipment. If contaminated tissue is not properly tested or labeled, health care workers as well as patients may be put at risk.”

¹³ Platelet rich plasma (PRP) and other blood products are not considered HCT/Ps, therefore the exception in 21 CFR 1271.15(b) is not applicable.

¹⁴ For additional regulatory considerations for adipose tissue, see the guidance entitled “Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff” dated November 2017.

¹⁵ In this situation, which may arise in some dermatologic or plastic surgery procedures where the autologous, cleansed adipose tissue is aliquoted, temporarily stored, and injected during a predetermined, limited number of subsequent operations to achieve the desired contouring effect, the establishment removing, temporarily storing, and reimplanting the autologous adipose tissue may still qualify for the exception in 21 CFR 1271.15(b).

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Example 7-2: Adipose tissue is recovered by tumescent liposuction and processed (e.g., enzymatic digestion, mechanical disruption) to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. Cell isolation would typically cause the adipose tissue to no longer be “such HCT/P” and the establishment would generally not be considered to qualify for the exception under 21 CFR 1271.15(b).

Examples of sizing and shaping that would generally allow the HCT/P to remain “such HCT/P” include dilatation to size a vascular graft in coronary artery bypass graft surgery, cutting parathyroid tissue into pieces appropriately sized for reimplantation, and meshing of skin grafts to facilitate shaping and sizing to cover cutaneous burn wounds.