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

---

Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.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*.

Additional copies of this guidance are available from the Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Avenue, Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002 or by calling 1-800-835-4709 or 240-402-7800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2014

Table of Contents

I. INTRODUCTION 1

II. BACKGROUND 1

III. QUESTIONS AND ANSWERS 3

Q1: When does the exception in § 1271.15(b) apply? 3
Q2: What is autologous use? 3
Q3: Section 1271.15(b) refers to same surgical procedure. What types of procedures are considered the same surgical procedures? 4
Q4: 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 § 1271.15(b)? If so, can an establishment still qualify for the exception if the establishment ships the autologous tissue to another establishment? 4
Q5: Can an establishment that processes an autologous HCT/P after removal and prior to implantation still qualify for the exception in § 1271.15(b)? 5

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

Draft Guidance for Industry

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA or Agency) current thinking on this topic.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 responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration, 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 criteria set forth in 21 CFR 1271.15(b) (21 CFR 1271.15(b)).

This guidance, presented in question and answer format, when finalized will provide 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).

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

Human cells, tissues or cellular or tissue-based products intended for implantation, transplantation, infusion or transfer into a human recipient are regulated as HCT/Ps.[1] Under the

[1] See definition in 21 CFR 1271.3(d).

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.

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 § 1271.15(b) that is the subject of this guidance. Section 1271.15(b) states: "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."

On February 28, 1997, we addressed this exception in the document entitled, "Proposed Approach to Regulation of Cellular and Tissue-Based Products."[2] 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 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 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 § 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,

[2] Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Docket. No. 97N-0068 (Feb. 28, 1997) at 12. http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm062601.pdf.

> We agree that, so long as the hospital does not engage in any other activity encompassed with in [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) 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, or sizing, or certain manufacturing steps, 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.

III. QUESTIONS AND ANSWERS

Q1: When does the exception in § 1271.15(b) apply?

A1: For the exception to apply, an establishment[3] must meet three (3) criteria:

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

Q2: What is autologous use?

A2: As defined in § 1271.3(a), autologous use means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom

[3] "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)).

[4] Note that the criteria of "minimal manipulation" expressed in 21 CFR 1271.10 (a) is not the standard for establishing whether an HCT/P is "such HCT/P" under § 1271.15. Accordingly, even manufacturing steps considered minimal manipulation within § 1271.10(a), will typically cause the HCT/P to no longer be "such HCT/P" under §1271.15(b), unless the HCT/P is only rinsed, cleaned, sized, or shaped.

the cells or tissue were recovered. The exception in § 1271.15(b) applies only when the HCT/P is removed from and implanted into the same individual.

Q3: Section 1271.15(b) refers to same surgical procedure. What types of procedures are considered the same surgical procedures?

A3: For the purposes of the exception in § 1271.15(b) and this guidance, procedures that involve an incision or instrumentation (e.g., incision or surgical technique) during which an HCT/P is removed from and implanted into the same patient within a single operation performed at the same establishment, are considered to be the same surgical procedures. Examples include autologous skin grafting and coronary artery bypass surgery involving autologous vein or artery grafting.

Q4: 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 § 1271.15(b)? If so, can an establishment still qualify for the exception if the establishment ships the autologous tissue to another establishment?

A4: Generally, as discussed in the answer to Q3, 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 temporarily stored after being labeled pending implantation, and still be considered same surgical procedure, provided no other processing steps, and no other manufacturing steps beyond being labeled and stored are performed.

Establishments that perform the following procedures consisting of more than a single operation may qualify for the exception in § 1271.15(b):

a. Craniotomy 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 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/P,[5] which is a manufacturing step,[6] and therefore the shipping establishment must register, submit an HCT/P list, and follow all other applicable regulations in Part 1271.[7]

Also, the establishment cannot qualify for the exception if the establishment ships the autologous HCT/P to another establishment for temporary storage prior to implantation. The establishment shipping the HCT/P to another establishment for temporary storage must register, submit an HCT/P list, and follow all other applicable regulations in 21 CFR Part 1271, such as predistribution shipment (§ 1271.265) and manufacturing arrangements (§ 1271.150(c)).

The establishment that receives the HCT/P, temporarily stores it, and ships it back when it is needed for implantation in the same individual, must also register, submit an HCT/P list, and follow all other applicable regulations in Part 1271.

Q5: Can an establishment that processes an autologous HCT/P after removal and prior to implantation still qualify for the exception in § 1271.15(b)?

A5: 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, or sizing the tissue. Processing[8] of the autologous HCT/P raises safety concerns, such as contamination and cross-contamination, beyond those typically associated with surgery.[9]

---

[5] "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)).

[6] "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)).

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

[8] "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)).

[9] Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Docket. No. 97N-0068 (Feb. 28, 1997) at 12. http://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." Id.