Guidance for Industry

Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit written comments on this guidance at anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. You should identify all comments with the title of this guidance.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Office of Compliance and Biologics Quality, at (301) 827-6190.

U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

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I. INTRODUCTION

We, FDA, are issuing this guidance to emphasize to you, establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps), your responsibility to comply with Title 21 Code of Federal Regulations 1271.150(c)(1) (21 CFR 1271.150(c)(1)), if you enter into a contract, agreement, or other arrangement with another establishment to perform for you any step in manufacture. (Ref. 1). If you engage another establishment to perform for you any step in manufacture, that establishment must comply with requirements applicable to that manufacturing step (21 CFR 1271.150(c)(1)(i) and (ii)). The intent of this guidance is to highlight your responsibilities in ensuring that establishments that engage in any step in manufacture for you are in compliance with the current good tissue practice (CGTP) requirements of the HCT/P regulations in 21 CFR Part 1271.

FDA evaluates compliance with CGTP and, where needed, takes compliance actions to stop recovery or other practices which do not meet applicable requirements. We also evaluate during an FDA investigation an establishment's actions to ensure that contracting establishments comply with applicable CGTP requirements if they perform one or more manufacturing steps for the establishment. Your activities to ensure that contracting establishments comply with applicable CGTP requirements can help identify and prevent problems such as those observed during recent FDA investigations. Your actions help prevent undue risks to product quality and patient safety.

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

FDA's recently implemented HCT/P regulations addressing CGTP, including those in 21 CFR 1271.150(c)(1), are effective for HCT/Ps recovered on or after May 25, 2005. Ongoing FDA investigations of some recovery establishments under contract, agreement, or other arrangement with processing establishments have identified significant violations of CGTP requirements, which may put some tissue recipients at potentially increased risk of communicable disease transmission. These violations relate to donor screening and record keeping practices relevant to risk factors for, or clinical evidence of, relevant communicable disease agents and diseases. Title 21 CFR 1271.150(c)(1) is designed to help ensure that these and other violative practices do not occur.

III. DISCUSSION

A. Am I Responsible for Ensuring that Establishments that I Have Manufacturing Arrangements with are in Compliance with CGTP Requirements?

Yes. If you engage another establishment to perform for you any step in manufacture, that establishment must comply with requirements applicable to that manufacturing step (21 CFR 1271.150(c)(1)(i) and (ii)). Under 21 CFR 1271.150(c)(1)(iii), before entering into a contract, agreement, or other arrangement with another establishment to perform for you any step in manufacture, you must ensure that the establishment complies with applicable CGTP requirements. If, during the course of this contract, agreement, or other arrangement, you become aware of information suggesting that the establishment may no longer be in compliance with such requirements, you must take reasonable steps to ensure the establishment complies with those requirements. If you determine that the establishment is not in compliance with those requirements, you must terminate your contract, agreement, or other arrangement with the establishment.

B. What Additional Information would be Helpful to Me in Understanding My Responsibilities for Manufacturing Arrangements?

In the preamble to 21 CFR Part 1271, the final rule for CGTPs (Ref. 1), at comments 28 through 30,[1] we discuss several approaches that might be helpful to you if you engage another establishment to perform for you manufacturing steps. As we discussed in the preamble, those include the following:

- You should choose carefully establishments with whom you have manufacturing arrangements;

[1] 69 *Federal Register* 68612 at 68622-3.

- You do not have to validate the processes of an outside establishment that you engage to perform for you a manufacturing step (e.g., a firm that performs terminal sterilization such as irradiation on HCT/Ps for a processor). That establishment is itself subject to the regulations in 21 CFR Part 1271. However, you are required to enter into and maintain such arrangements only with establishments that comply with applicable CGTP requirements;

- We note that there are many ways of performing the due diligence necessary when entering into a manufacturing arrangement with another establishment. An initial audit is one method. Other ways of learning about another establishment before you enter into an arrangement with that establishment might include reviewing test kit package inserts and a testing laboratory's standard operating procedures, and reviewing the establishment's compliance history. If you enter into an arrangement with an establishment that does not have a compliance history, review of that establishment's standard operating procedures might assist you in ascertaining that entity's compliance status; and

- Although we recognize the usefulness of an initial audit before entering into an arrangement with another establishment, we note that an initial audit would not satisfy this requirement throughout the term of a continuing relationship. Under 21 CFR 1271.150(c)(1)(iii), you may not ignore information that indicates that a company that performs work for you is not in compliance with applicable CGTP requirements. For example, if you have reason to suspect that an establishment performing work for you is not in compliance with those requirements, you would need to take appropriate action and determine whether the establishment is still in compliance with CGTP.

IV. SUMMARY

As described above, this guidance is intended to ensure that you, an establishment that manufactures HCT/Ps, fully comply with 21 CFR 1271.150(c)(1) if you enter into a contract, agreement, or other arrangement with a contracting establishment to perform for you any step in manufacture (Ref. 1). Your activities to ensure that contracting establishments comply with applicable CGTP requirements can help identify and prevent problems such as those noted during recent FDA investigations. Your actions will help prevent undue risks to patient safety.

V. REFERENCES

1. Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement - Final Rule (69 *Federal Register* 68612, November 24, 2004).