MD&DI
Medical Device & Diagnostic Industry

Federal and State Requirements for HCT/Ps: An Overview

With new regulations for tissue-based products coming into effect soon, it's important that manufacturers understand FDA's requirements.

Jeffrey K. Shapiro

Hogan & Hartson LLP

The Food and Drug Administration (FDA) is close to finalizing its program for the regulation of human cells, tissues, and cellular or tissue-based products (HCT/Ps). On May 25, 2005, the donor eligibility and current good tissue practice (CGTP) final rules take effect, putting into place the last major components of the new regulatory program for HCT/Ps. The CGTP regulation is somewhat more restricted in scope than originally proposed, but it still represents a substantial regulatory burden.

This article reviews the essential elements of FDA's requirements for HCT/Ps set forth in 21 CFR Part 1271. Also discussed are state law and other federal requirements that firms involved with HCT/Ps should keep in mind. Because of the breadth of Part 1271 and other federal and state tissue requirements, this review is limited to an outline of the basic regulatory landscape.

FDA Regulation

Avenues of HCT/P Regulation. FDA has several overlapping avenues of authority with regard to HCT/Ps. Section 361 of the Public Health Service Act (PHSA) authorizes FDA to issue regulations to prevent the introduction, transmission, or spread of communicable disease.[1] That is the basic authority FDA has relied upon for 21 CFR Part 1271. It is also the authority for 21 CFR Part 1270, which has been the basic regulation governing tissue products for more than a decade. The superseding Part 1271 requirements only apply to tissue procured on or after May 25, 2005. Part 1270 will be revoked when FDA is confident that no more tissue procured prior to May 25, 2005, is available for distribution.

As discussed more fully below, some HCT/Ps are eligible for regulation solely under Part 1271. These "361 HCT/Ps" are subject to Part 1271's requirements as to establishment registration and listing, donor eligibility, CGTPs, labeling, adverse-event reporting, and inspection and enforcement. Part 1271 does not have premarket review requirements. The Center for Biologics Evaluation and Research (CBER) is responsible for regulating 361 HCT/Ps.

Some HCT/Ps meet the definition of a biological product requiring licensure under Section 351 of PHSA.[2] These "351 HCT/Ps" may only be marketed upon approval of a biologic license application (BLA), and their manufacture must comply with current good manufacturing practices (CGMPs).[3] CBER is responsible for regulating 351 HCT/Ps.

Finally, still other HCT/Ps may meet the definition of a medical device or drug regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act). These device or drug HCT/Ps must receive 510(k) clearance, premarket approval (PMA), or new drug application (NDA) approval. Furthermore, their manufacture must comply with the quality system regulation (QSR) or CGMPs, as applicable.[3,4] The Center for Devices and Radiological Health (CDRH) is responsible for device HCT/Ps, and the Center for Drug Evaluation and Research (CDER) is responsible for drug HCT/Ps.

The Requirements of Part 1271. As noted, FDA's Part 1271 requirements are aimed at preventing the spread of communicable disease. Subpart A sets forth general provisions, including the definition of a 361 HCT/P eligible for regulation solely under Part 1271. Subpart B describes the procedures

for registration and listing for all HCT/Ps. Subpart C contains the eligibility requirements for donors applicable to all HCT/Ps. Subpart D imposes CGTP requirements applicable to all HCT/Ps. Subpart E sets out adverse-event reporting and labeling requirements for 361 HCT/Ps. Subpart F outlines FDA's inspectional and enforcement authority for 361 HCT/Ps.

It is worth emphasizing that for 351 HCT/Ps and drug or device HCT/Ps, the Part 1271 requirements include establishment registration and listing, donor eligibility, and CGTP (Subparts B, C, and D). This is in addition to all of the usual biologic, drug, and device regulatory requirements, which continue to apply to such HCT/Ps. For example, a device HCT/P is subject to both QSR and CGTP requirements. In FDA's view, the CGTP requirements supplement the QSR requirements. FDA has already amended the QSR and CGMP regulations to reference the donor eligibility and CGTP provisions in Part 1271. However, the reporting, labeling, inspection, and enforcement provisions in Part 1271 (Subparts E and F) apply solely to 361 HCT/Ps.

HCT/Ps Defined

FDA defines HCT/Ps in Part 1271 as "articles containing or consisting of human cells or tissue that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[5] Examples of such products include "bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem and progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue."[5]

The definition expressly excludes: vascularized human organs for transplantation; whole blood or blood components or derivative products already regulated as biologics under 21 CFR Parts 607 and 207; secreted or extracted human products except semen (e.g., milk, collagen, and cell factors); minimally manipulated bone marrow for homologous use (and not combined with another article except for water, crystalloids, or a sterilizing, preserving, or storage agent that does not raise new clinical safety concerns with respect to the HCT/P); ancillary products used in the manufacture of an HCT/P; cells, tissues, and organs derived from animals other than humans; and in vitro diagnostic products.[5]

When Is It a 361 HCT/P? A product regulated as a 361 HCT/P solely under Part 1271 does not require premarket clearance or approval, which is obviously a significant benefit. An HCT/P is eligible for such regulation if it meets these four criteria:[6]

- It is minimally manipulated.
- It is intended for homologous use as determined by labeling and advertising.
- Its manufacture does not involve combination with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent (not raising new clinical safety concerns for the HCT/P).
- It does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function or, if it has such an effect, it is intended for autologous use or allogeneic use in close relatives or for reproductive use. (FDA has postponed the application of most Part 1271 requirements with respect to reproductive tissue.)

FDA defines *minimal manipulation* for structural tissue as "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement."[7] For cells or nonstructural tissue, it is "processing that does not alter the relevant biological characteristics."[8] While these definitions are fairly subjective, FDA has said specifically that cutting, grinding, shaping, soaking in antibiotic solution, sterilization by gamma irradiation, lyophilization, freezing, and demineralization of bone are all examples of minimal manipulation.

For cells, FDA believes that density-gradient separation, cell selection, centrifugation, and cryopreservation constitute minimal manipulation. Furthermore, FDA has found that cell expansion in culture and human skin processed into human collagen are examples of more than minimal manipulation.

FDA defines HCT/Ps in Part 1271 as "articles containing or consisting of human cells or tissue that are intended for implantation, transplantation, infusion, or transfer into a human recipient."

FDA defines *homologous use* as the "replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor."[9] FDA agrees that homologous use does not imply that tissue must be used in its native location or even a homologous location.[10] According to FDA, the homologous-use requirement guards against "promotion of an HCT/P for an unproven therapeutic use, such as curing cancer."[11] FDA has stated that it intends to "interpret 'nonhomologous' narrowly."[11] As examples of nonhomologous uses, FDA has given: using dermis as a replacement for dura mater (which encapsulates the brain); the use of amniotic membrane in the eye; and use of cartilage in the bladder.

Registration and Listing. Registration and listing data must be submitted on Form FDA 3356. Registration is required within five days of beginning HCT/P manufacturing operations and must be updated annually and amended within five days of a change of ownership or location. The product listing must be updated at the time of a change or each June or December, whichever month occurs first after the change.

Donor Eligibility. The donor eligibility provisions of Part 1271 apply to tissue collected on or after the May 25, 2005, effective date. There are two basic requirements for all HCT/Ps:

- Donor screening by reviewing medical records for freedom from risk factors and clinical evidence of infection with communicable disease.
- Donor testing that is negative or nonreactive.

The regulations prohibit the use of HCT/Ps unless the donor has been determined eligible.

Although Part 1271 specifies testing for HIV types 1 and 2, hepatitis B and C virus, and *Treponema pallidum*, other implementation details are in a published draft guidance that FDA expects to finalize and update as scientific knowledge develops, new tests are introduced, and additional disease agents emerge. Ancillary requirements in the regulation relate to the following appropriate procedures: recordkeeping, quarantine until the eligibility determination is complete, and the storage of ineligible HCT/Ps.

Interestingly, in certain situations FDA allows the use of HCT/Ps prior to a donor eligibility determination or in cases when the donor is ineligible based upon screening or test results. For example, such HCT/Ps can be used based on a documented urgent medical need, if labeled with required warnings.

Current Good Tissue Practice. The CGTP provision in Part 1271 applies to all HCT/Ps. It is somewhat narrower than the proposed version. For instance, the proposed rule had requirements intended to help ensure HCT/P function and integrity. In response to comments from the public suggesting that these requirements were only tenuously related to FDA's statutory authority to prevent the spread of disease in Section 361 of the PHSA, all such requirements were removed from the final rule.

The basic requirement of the CGTP provision is that firms must recover, process, store, label, package, and distribute HCT/Ps (and screen and test donors) in a way that prevents the introduction, transmission, or spread of communicable disease (including contamination introduced during HCT/P processing).

There are specific provisions relating to the following:

- Quality program.
- Personnel.
- Procedures.
- Facilities.
- Environmental control/monitoring.
- Equipment.
- Supplies and reagents.
- Recovery.
- Processing and process controls.
- Process changes.
- Process validation.
- Labeling.
- Storage.
- Receipt.
- Predistribution shipment/distribution.
- Records.
- Tracking.
- Complaints.

Reporting. The manufacturer of a 361 HCT/P must investigate any adverse reaction involving a communicable disease related to an HCT/P that is available for distribution. An *adverse reaction* is defined as a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response. The adverse reaction must be reported if it is fatal, life threatening, results in permanent impairment of a body function or permanent damage to body structure, or necessitates medical or surgical intervention, including hospitalization. The reports must be submitted on Form FDA 3500A within 15 calendar days of initial receipt of the information.

The manufacturer of a 361 HCT/P must investigate any adverse reaction involving a communicable disease.

Manufacturers of 361 HCT/Ps must report HCT/P deviations relating to distributed HCT/Ps and involving core CGTP requirements (a listed subset of CGTP requirements). An HCT/P deviation is defined as a departure from applicable standards or specifications that relate to preventing the spread of communicable disease or HCT/P contamination, or that is an unexpected or unforeseeable event that may relate to the spread of disease or HCT/P contamination. Each deviation must be investigated and those related to core CGTP requirements must be reported on Form FDA 3486 within 45 days of discovery.

Labeling. Under Part 1271, a 361 HCT/P must be labeled clearly and accurately. It must have a distinct identification code, description of the type of HCT/P, and an expiration date, if any, and include applicable warnings (for example, the warnings for an HCT/P not yet determined to be donor eligible that will be used under an exception for urgent medical need). In addition, the following information must either appear on the label or accompany the product:

- Name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution.
- Storage temperature.
- Other warnings, when appropriate.
- Instructions for use related to preventing the spread of communicable disease.

Inspection and Enforcement. Finally, Part 1271 has provisions allowing FDA to inspect facilities engaged in manufacturing 361 HCT/Ps and authorizing orders of retention, recall, destruction, and cessation of manufacturing if FDA has reasonable grounds to believe that an HCT/P is violative. There are also requirements relating to the import of HCT/Ps to allow FDA to make an appropriate admissibility decision.

State Regulation of Tissue Banking

At least nine U.S. states have some form of tissue-banking regulation. The largest and most active are California, Florida, New York, and Maryland. A

second tier includes the District of Columbia, Georgia, and Oklahoma. Delaware and Illinois require only registration.

Any firm that processes tissue in a state or ships tissue into it must consider whether that state has an applicable regulatory scheme. Depending upon state law, even if the firm is engaged only in storage and distribution in a particular state, or if it merely ships from out of state directly to in-state customers, there still may be significant regulatory requirements.

A company with a central headquarters must determine whether distribution facilities in various states require individual licenses or may be brought under the umbrella of a single corporate license. The answer to this question varies depending on the precise corporate structure of the company and the specifics of state law.

FDA's regulatory treatment of a tissue product is not always consistent with state regulation of the same product. For example, FDA classified Dermagraft TC, a human fibroblast–derived temporary skin substitute for burn wounds, as a Class III medical device requiring premarket approval. Nonetheless, after approval was obtained, the State of New York insisted that the company obtain state tissue-banking licensure in order to ship product into New York. Although federal preemption of such state requirements is a theoretical possibility, in practice it is very difficult to obtain.

National Organ Transplant Act of 1984

Under federal law, it is unlawful "for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation."[12] The term *human organ* is defined as "human (including fetal) kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, and skin or any subpart thereof."[13] The term *valuable consideration* excludes "reasonable payments associated with the removal, transportation, implantation, processing, preservation, quality control, and storage of a human organ."[13]

There has been virtually no criminal enforcement activity with respect to the National Organ Transplant Act (NOTA) in the 20 years since it was enacted. There is one reported criminal case involving an alleged conspiracy to sell the organs of executed Chinese prisoners for use in human implants in the United States, in violation of NOTA.[14] While this history is no guarantee against future enforcement, it suggests that such criminal proceedings would be likely to arise from egregious circumstances.

Still, given that NOTA is a criminal statute, firms that transfer tissue should be careful about how their contracts are drafted. For instance, to minimize the risk of criminal liability, the contract should be drafted as reasonable payment for processing and handling services and not for the sale of tissue itself. Nothing in the statute seems to prevent a firm from making a profit as part of its reasonable payment.

Firms should also be aware of the risk that a court could refuse to enforce their contracts. In one civil case, the court found that a contract violated NOTA and, therefore, refused to enforce it.[15] This case points to the need to draft contracts carefully to minimize the risk that the other party can raise a NOTA violation defense in a breach of contract action.

FDA's regulatory treatment of a tissue product is not always consistent with state regulation of the same product.

Conclusion

FDA's heightened regulatory requirements for HCT/Ps are intended to increase safety, but they also impose substantial new burdens on industry. It will be interesting to see how quickly FDA moves to enforce the new requirements, how well trained their inspectors are, and whether the inspectors are reasonably consistent in their approach. One thing is certain: a new era of heightened regulatory scrutiny for HCT/Ps has only just begun.

References

1. *U.S. Code*, 42 USC Section 264.
2. 42 USC Section 262.
3. *Code of Federal Regulations*, 21 CFR Parts 210 and 211.
4. 21 CFR Part 820.
5. 21 CFR Section 1271.3(d).
6. 21 CFR Section 1271.10(a).
7. 21 CFR Section 1271.3(f)(1).
8. 21 CFR Section 1271.3(f)(2).
9. 21 CFR Section 1271.3(c).
10. *Federal Register*, 66 *FR*:5447, 5478 (January 19, 2001).
11. 66 *FR*:5458.
12. 42 USC Section 274e(a).
13. 42 USC Section 274e(c).
14. *U.S.* v. *Wang*, 1998 W.L. 556160 (S.D.N.Y.).
15. *Wilson* v. *Adkins*, 57 Ark. App. 43, 941 S.W. 2d 440 (1997). ■