FDA Inspection Trends for Cellular Therapies

by Tom Pritchett

According to the late Norman Cousins, "Wisdom consists of the anticipation of consequences." When it comes to regulatory inspections, those consequences can be severe. However, the consequences of a problem anticipated can be prevented — given effective action to remediate the issue. In two previous articles (**1, 2**), I discussed the whys and hows of using the US Food and Drug Administration's (FDA's) notices of deficiency, FDA warning letters, and other information about inspection results to create an effective system to spot and rectify your own compliance issues before they become adverse inspectional outcomes. Here, I provide an analysis of more than 40 FDA warning letters to identify inspectional trends for cellular and tissue-based products.

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The Regulatory Landscape

The FDA's attempt to regulate human cells, tissues, and cellular and tissue-based products (HCT/Ps) emerged from its historic fragmentation in 1997 with the proposal of a new approach and an accompanying public meeting, first announced in the *Federal Register* (**3**). The agency stated

> The Food and Drug Administration (FDA) is announcing the availability of a document entitled, *Proposed Approach to Regulation of Cellular and Tissue-Based Products*. In addition, FDA is announcing a public meeting to solicit information and views from the interested public on the agency's proposed regulatory approach for such products. Those actions are taken in response to the administration's Reinventing Government initiative which seeks to streamline regulatory requirements to ease the burden on regulated industry, while providing adequate protection to the public health.

Subsequently, to implement this proposed new approach, the agency **published three final rules and two interim final rules.** The final rules were *Human Cells, Tissues, and Cellular and Tissue-Based Products: Establishment Registration and Listing* (2001), *Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products* (2004), and *Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments, Inspection and Enforcement* (2004) (**4–6**). The latter final rule, codified as 21 CFR 1271 (Title 21 of the *Code of Federal Regulations*, Part 1271) is known as the Current Good Tissue Practices (CGTPs). The interim final rules were 2004's *Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing* and 2005's *Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling*" (**7–8**). In August 2007, FDA further clarified regulatory expectations in an industry guidance document on HCT/P compliance (**9**). Underscoring the importance of the subject, that guidance was released "for immediate implementation," rather than being first released in draft form, as are the majority of guidance documents.

Table 1A: Synopsis of HCT/P warning letters (2000–2012) for cell and tissue (processing, banking and therapy) companies, GMP and QSR violations

Regulatory Citation	Typical Observation(s) of Noncompliance
21 CFR 211.22 Responsibilities of quality control unit	*Quality control unit does not have* • The responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products • The authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated • The responsibility for approving or rejecting all procedures or specifications that affect the identity, strength, quality, and purity of the product
21 CFR 211.42(c)(10) Design and construction features	• Failure to assure that an adequate control system for temperature and humidity is in place to prevent contamination during aseptic processing • Failure to assure that an air supply filtered through high-efficiency particulate air filters under positive pressure for aseptic processing operations is in place to prevent contamination during aseptic processing • Failure to assure that a system for monitoring environmental conditions is in place to prevent contamination during aseptic processing
21 CFR 211.68(a) Automatic, mechanical, and electronic equipment (calibration, Inspection, and checking performance)	Failure to assure that automatic, mechanical, and electronic equipment used in the manufacture, processing, packing, and holding of a drug product is routinely calibrated, inspected, or checked according to a written program designed to assure proper performance, and that written records of those calibration checks and inspections are maintained
21 CFR 211.80(a) General requirements (for written procedures that followed for receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures)	Failure to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures
21 CFR 211.84(a) Testing and approval or rejection of components, drug product containers, and closures (withholding from use until tested and released)	Failure to assure that each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit
21 CFR 211.100(a) Written procedures; deviations (requirement for written procedures)	Failure to establish and follow written production and process control procedures designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures are drafted, reviewed, and approved by the appropriate organizational units
21 CFR 211.113(b) Control of microbiological contamination (appropriate written procedures)	• Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. • Failure to validate all aseptic and sterilization processes
21 CFR 211.160(b) Laboratory Control (scientifically sound and appropriate specifications, standards, sampling plans, and test procedures)	Failure to maintain laboratory controls that include establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity
21 CFR 211.182 Equipment cleaning and use log	Failure to establish a written record of major equipment cleaning, maintenance and use to include in that record the date, time, product, and lot number of each batch processed
21 CFR 211.188(b) Batch production and control records	Failure to assure that batch production and control records are prepared for each batch of drug product produced and to document that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished
21 CFR 211.192 Production record review	• Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed • Failure to assure that all drug product production and control records, including those for packaging and labeling, are reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before the batch is released or distributed
21 CFR 211.196 Distribution records	Failure to assure that distribution records contain the name and strength of the product and the description of the dosage form, and the name and address of the consignee
21 CFR 211.198(a) Complaint files (requirement for written procedures)	Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product
21 CFR 820.20 (a) Management responsibility (quality policy) and 820.25 (b), personnel (training)	• Employee training files lack documented training on organization's quality policy. • Training in Quality System Regulations has not been administered to employees in critical management and production positions where knowledge of the such regulations is necessary to assure those employees perform their activities correctly

Table 1B: Synopsis of HCT/P warning letters (2000–2012) for cell and tissue (processing, banking and therapy) companies, 21 CFR Part 1270 (human tissue intended for transplantation) violations

Regulatory Citations (in numerical order)	Typical Observation(s) of Noncompliance
21 CFR 1270.21 Determination of donor suitability for human tissue intended for transplantation	Failure to make an adequate determination of donor suitability for human tissue intended for transplantation
21 CFR 1270.21(a) Determination of donor suitability for human tissue intended for transplantation (donor specimen testing)	Failure to ensure that donor specimens are tested using an FDA-licensed donor-screening accordance with manufacturer's instructions
21 CFR 1270.21(d) Determination of donor suitability for human tissue intended for transplantation (records of specific licensed screening tests)	Failure to accurately document the results and interpretation of all required infectious disease tests of cornea donors before distribution and transplantation
21 CFR 1270.21(e) Determination of donor suitability for human tissue intended for transplantation (summary of records and determination of suitability for use)	Company shipped human skin tissue intended for transplantation without a summary of records or copies of the original records of the donor's relevant medical records
21 CFR 1270.21 (f) Determination of donor suitability for human tissue intended for transplantation (determination by a responsible person)	Failure to make a determination by a responsible person that a donor of human tissue intended for transplantation is suitable, including ascertainment of donor's identity
21 CFR 1270.21 (h) Determination of donor suitability for human tissue intended for transplantation (human tissue shall be determined to be not suitable for transplantation)	Failure to develop adequate written procedures for all significant steps used in determining the suitability of banked human tissue in accordance with manufacturers' instructions
21 CFR 1270.31(a) Determination of donor suitability for human tissue intended for transplantation (Written procedures for all significant steps in the infectious disease testing process; these procedures shall be readily available to personnel in area where the procedures performed unless impractical. Any deviation from the written procedures shall be recorded and justified.)	Failure to have written procedures for all significant steps in infectious disease testing
21 CFR 1270.31(b) Written procedures (written procedures for all significant steps for obtaining, reviewing, and assessing the relevant medical records of the donor)	Failure to have and to follow written procedures for all significant steps associated with obtaining, reviewing and assessing relevant medical records of donors of human tissue intended for transplantation
21 CFR 1270.31(c) Written procedures (written procedures for designating and identifying quarantined tissue)	Company routinely shipped quarantined tissue without records to indicate that the tissue had not been determined to be suitable for transplantation
21 CFR 1270.31(d) Written procedures (written procedures prepared/validated/followed for prevention of infectious disease contamination or cross-contamination by tissue during processing.)	Failure to prepare, validate, and follow written procedures for prevention of infectious disease contamination or cross-contamination by tissue during processing
21 CFR 1270.33(a) Records, general requirements (accurate, indelible, and legible records maintained concurrently with performance of each significant step required of infectious disease screening and testing of donors of human tissue).	Company failed to maintain accurate records that identify the person performing the work, the dates of the various entries, and providing a complete history of the work performed as the records relate to the particular tissues involved
21 CFR 1270.33(b)(2) Records general requirements (quarantining until donor screening completed)	Failure to quarantine human tissues until donor screening has been completed, reviewed by a responsible person, and determined to assure freedom from risk factors for and clinical evidence of HIV infection, hepatitis B, and hepatitis C
21 CFR 1270.33(d) Records, general requirements (summary of infectious disease testing and screening records reviewed by the responsible person, and found to be negative, and that tissue has been determined suitable for transplantation.)	Failure to maintain records documenting that human tissue intended for transplantation has undergone appropriate infectious disease testing and screening, and that the records have been reviewed by the person responsible for such reviews, and that the tissues have been determined to be suitable for transplantation
21 CFR 1270.35 Specific records	Failure to adequately document the receipt, distribution and destruction or other disposition of human tissues
21 CFR 1270.35(c) Specific records (documentation of the receipt and/or distribution of human tissue)	Failure to accurately document quarantine of corneas coded as being suitable for surgical transplantation prior to and during distribution
21 CFR 1270.35(d) Specific records (documentation of the destruction or other disposition of human tissue)	Company failed to maintain records documenting the destruction or other disposition of human tissue, as required by 21 CFR 1270.35(d), in that the tissue destruction log was incomplete and/or inaccurate.

Table 1c: Synopsis of HCT/P warning letters (2000–2012) for cell and tissue (processing, banking and therapy) companies, GTP (Part 1271 — human cellular and tissue-based products) violations

Regulatory Citation	Typical Observation(s) of Noncompliance
21 CFR 1271.3(s) How does the FDA define important terms in this part? (relevant medical records)	Medical records, which were available, were not obtained and reviewed as part of donor screening and donor eligibility determination.
21 CFR 1271.21(a) When do I register, submit an HCT/P list, and submit updates?	Failure to register this establishment and to submit a list of all human cells, tissues, and cellular and tissue-based products that this establishment manufactures with the FDA
21 CFR 1271.55(d)(4) What records must accompany an HCT/P after the donor-eligibility determination is complete; and what records must I retain? (record retention requirements)	Failure to retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest
21 CFR 1271.75(a) How do I screen a donor? (all donors)	Failure to screen a donor of cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases
21 CFR 1271.80(c) What are the general requirements for donor testing? (tests)	Failure to test using appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases
21 CFR 1271.145 Prevention of the introduction, transmission, or spread of communicable diseases	Failure to develop adequate written procedures for all significant steps used in determining the suitability of banked human tissue in accordance with manufacturers' instructions
21 CFR 1271.160 Establishment and maintenance of a quality program	Failure to establish and maintain a quality program intended to prevent the introduction, transmission, or spread of communicable diseases through the manufacture and use of HCT/Ps
21 CFR 1271.160(b)(5) Establishment and maintenance of a quality program, (functions)	Failure of the quality program to establish and maintain appropriate monitoring systems as necessary to comply with regulation
21 CFR 1271.180(a) Procedures (general)	Failure to establish and maintain procedures appropriate to meet core current good tissue practice (CGTP) requirements for all steps performed in the manufacture of HCT/Ps.
21 CFR 1271.190(b) Facilities (cleaning and sanitation)	Failure to prepare, validate, and follow written procedures for prevention of infectious disease contamination or cross-contamination by tissue during processing
21 CFR 1271.195(c) Environmental control and monitoring (environmental monitoring)	Failure to monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents
21 CFR 1271.200(b) Equipment (procedures and schedules)	Failure to establish and maintain procedures for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination, accidental exposure of HCT/Ps to communicable disease agents, and other events that could reasonably be expected to result in the introduction, transmission, or spread of communicable diseases
21 CFR 1271.200(e) Equipment (records)	Failure to document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed
21 CFR 1271.230(a) Process validation (general)	Failure to validate and approve a process according to established procedures; the validation activities and results must be documented, including the date and signature of the individual(s) approving the validation.
21 CFR 1271.265(c)(2) Receipt, predistribution shipment, and distribution of an HCT/P (availability for distribution)	Must not make available for distribution a HCT/P that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible or for whom a donor eligibility determination has not been completed or that otherwise does not meet release criteria designed to prevent communicable disease transmission
21 CFR 1271.270(a) Records (general)	Failure to maintain records concurrently with the performance of each step required in subpart C and subpart D
21 CFR 1271.270(b) Records (record management system)	Failure to properly establish procedures for all steps performed in the manufacture of HCT/Ps
21 CFR 1271.290(e) Tracking (tracking from donor to consignee or final disposition)	Failure to establish and maintain a method for documenting the disposition of each of HCT/Ps, to enable tracking from the donor to the consignee or final disposition
21 CFR 1271.370	Failure to label each HCT/P in accordance with the requirements in 21 CFR 1271.370

Despite the dogs of controversy barking about FDA's jurisdiction over stem cell therapies and the precise meaning of "minimally manipulated" (**10**), the regulatory caravan moves on. This includes, among other things, regulatory inspections of HCT/P companies for compliance with current good manufacturing practice (CGMP) as contained in 21 CFR Parts 211 and 820 (the device GMPs called QSRs — quality system regulations), the human tissue intended for transplantation regulations contained in 21 CFR Part 1270, and current good tissue practice (CGTP) in 21 CFR Part 1271. Additional detail about the HCT/P regulatory environment are provided elsewhere (**11, 12**), and inspections and 21 CFR regulations are listed on www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm.

Inspection Results and Inspection Trends

To look for trends in inspections related to the production of cellular and tissue-based products, I analyzed **41 FDA warning letters** sent to HCT/P companies after adverse inspections. Those letters spanned the years 2000 through 2013. Represented companies in the warning letters include those in cell and tissue processing, banking, and therapy as well as those for human reproductive cells and tissues. The latter often have the purpose of in-vitro fertilization (IVF).

Inspection teams often know that a deficiency at one company will often be found at others, so they tend to look for what teams have found in previous inspections. A numerical analysis of past inspections results in the discovery of inspection trends for future inspections (Tables 1 A–C and 2). Although only warning letters are analyzed herein, HCT/P 483s are discussed in other sources (**13, 14**).

The warning letters over this 14-year period were split almost evenly among companies that could be classified as cell/tissue processing/banking/therapy companies and those whose primary purpose is restricted to IVF, with 21 letters going to the former and 20 going to the latter. A signal difference, however, is that only 21 CFR Part 1271 (CGTPs) was named in the warning letters to the human reproductive cell/tissue (IVF) companies, whereas warning letters to other cell/tissue processing/banking/therapy companies cited a variety of regulations. Those regulations include not only CGTPs, but also 21 CFR Part 1270 (human rissue intended for rransplantation), 21 CFR Part 211 (CGMPs), and even a citation from 21 CFR 820 (medical device QSRs).

The warning letters were not spread out evenly over those years, as might be expected by growth of both the number of new companies and HCT/P-related activities at existing companies. A little more than one-third (15, 37%) of the letters were issued in the seven-year period from 2000–2006, and almost two-thirds (26, 63%) were issued during the seven-year period 2007–2013. The peak thus far came in 2012, with seven warning letters issued, but 2013 saw a decline, with four letters sent. In all, over 60 regulations (counting subparts) were cited in those letters, with 22% coming from the CGMPs (including the one QSR citation), 55% coming from the CGTPs, and the remaining 23% coming from 21 CFR Part 1270.

Overall, **the most cited regulation** was 21 CFR 1271.85 (15% of all citations). It deals with donor screening, as do 1271.75 (11% of all citations) and 1271.80 and 1270.31 (each 10%). 21 CFR 1271.47, which also regulates donor screening, made up 6% of all citations. The fifth most cited regulations (each 5% of total), were 21 CFR 1270.21 and 1271.55, whose subjects are, respectively, donor screening and donor eligibility records.

In all, donor screening and documentation issues made up slightly over 60% of all warning letter citations when categorized by 21 CFR part/subpart number. Other important issues were 21 CFR 1270.33, general documentation and records requirements (4%); 1270.35, documentation of receipt, quarantine, distribution, and destruction/disposition of tissues (3%); and 1271.150, general requirements of CGTP (3%). The tables list other, less-cited regulations.

Considering the topics and subjects most cited — rather than citations by 21 CFR part number — donor screening/testing/documentation issues accounted for almost half (49%) of the citations when they were analyzed in this way. The next most frequent topic cited was the ever-present documentation/recordkeeping (other than for donors) at 21%, followed by issues with a deficient quality unit (9%), quarantine/withholding from use issues (4%), deficient processing operations (also 4%), and inadequate process validation (3%). Labeling issues, inadequate environmental monitoring, and deficient equipment calibration/maintenance/performance checking each accounted for 2% of the adverse inspections results, and deficient facilities design/construction, failure/deviation/discrepancy investigations, training inadequacies, cleaning and sanitation deficiencies, and contract service provider issues each accounted for 1% of the citations. Other issues, undoubtedly important but accounting for less than 1% each of the citations were deficient product testing, inadequate handling of complaints, and failure to register the establishment.

Taking Precautions

The analysis here clearly shows that much compliance attention should be paid to the systems in place for donor screening and documentation of that screening because they were the overwhelmingly most-cited issues in regenerative medicine warning letters so far. In addition, documentation and recordkeeping issues other than those having to do with donors loom large as does having an adequate quality unit and quality systems. I hope this analysis will help your company be ready when the next inspection team comes knocking. Readers may be able to tease still more knowledge from the data I have given. Happy mining!

References

1 Pritchett T. A 483 Primer. *BioProcess Int.* 9(3) 2011: 12–16.

2 Pritchett T. Spotting, Tracking, and Predicting Inspection Trends. *BioProcess Int.* 10(6) 2012: 16–21.

Table 2: Synopsis of HCT/P warning letters (2006–2013) for reproductive HCT/P establishments, GTP violations

Regulatory Citations (in numerical order)	Typical Observation(s) of Noncompliance
21 CFR 1271.47(a): What procedures must I establish and maintain? (general)	Failure to establish and maintain procedures for all steps that you perform in testing, screening, determining donor eligibility
21 CFR 1271.50(a): How do I determine whether a donor is eligible? (determination based on screening and testing)	Failure to determine whether an HCT/P donor is eligible based on the results of donor screening
21 CFR 1271.55(a): What records must accompany an HCT/P after the donor-eligibility determination is complete; and what records must I retain?	Failure to provide or affix a distinct identification code to accompany the HCT/P at all times, that relates the HCT/P to the donor and to all records pertaining to the HCT/P
21 CFR 1271.55(b)(2): What records must accompany an HCT/P after the donor-eligibility determination is complete; and what records must I retain? (Summary of records)	Failure to provide a summary of records to accompany an HCT/P, that contains a listing and interpretation of the results of all communicable disease tests performed
21 CFR 1271.55(d): What records must accompany an HCT/P after the donor-eligibility determination is complete; and what records must I retain? (Record retention requirements)	Donor eligibility records are not accurate, indelible, and legible
21 CFR 1271.60(a): What quarantine and other requirements apply before the donor-eligibility determination is complete? (quarantine)	Failure to keep an HCT/P in quarantine until completion of the donor-eligibility determination
Sec. 1271.65(b): How do I store an HCT/P from a donor determined to be ineligible, and what uses of the HCT/P are not prohibited? (limited uses of HCT/P from ineligible donor)	Failure to prominently label an HCT/P, made available for limited use from an ineligible donor, with the biohazard legend and the statement "WARNING: Advise patient of communicable disease risks," and in the case of reactive test results, "WARNING: Reactive test results for (name of disease or disease agent).
21 CFR 1271.75 (a): How do I screen a donor? (all donors)	Failure to screen an anonymous or directed reproductive donor of cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases
21 CFR 1271.75(d): How do I screen a donor? (ineligible donors)	Failure to determine as ineligible a donor who has risk factors for, or clinical evidence of, relevant communicable disease agents or diseases
21 CFR 1271.75(e): How do I screen a donor (abbreviated procedure for repeat donors)	Failure to screen an anonymous or directed reproductive donor of cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases
21 CFR 1271.80(b): What are the general requirements for donor testing? (timing of specimen collection.)	Failure to collect a donor specimen for testing for relevant communicable diseases at the time of recovery of cells from a semen donor; or up to 7 days before or after recovery
21 CFR 1271.80(c): What are the general requirements for donor testing? (tests)	Failure to test using appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases
21 CFR 1271.80(d): What are the general requirements for donor testing? (ineligible donors)	Failure to determine as ineligible, a donor whose specimen tested reactive on a screening test for a communicable disease agent
21 CFR 1271.85(a): What donor testing is required for different types of cells and tissues?	Failure to test a specimen from an anonymous or directed reproductive donor of cells or tissue for evidence of infection due to relevant communicable disease agents
21 CFR 1271.85(b): What donor testing is required for different types of cells and tissues? (donors of viable, leukocyte-rich cells or tissue)	Failure to test a specimen from an anonymous or directed reproductive donor of viable, leukocyte-rich cells or tissue to adequately and appropriately reduce the risk of transmission of relevant cell- associated communicable diseases including Human T-lymphotropic virus, types I and II (HTLV-I/II) and/or cytomegalovirus (CMV)
21 CFR 1271.85(c): What donor testing is required for different types of cells and tissues? (donors of reproductive cells or tissue)	Failure to test a specimen from an anonymous or directed reproductive donor of cells or tissue to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents of the genitourinary tract
21 CFR 1271.90(b): Are there exceptions from the requirement of determining donor eligibility, and what labeling requirements apply? (required labeling)	Failure to prominently label an HCT IP, for which a donor eligibility determination was not performed, with the appropriate warning statements Failure to prominently label an HCT/P with "NOT EVALUATED FOR INFECTIOUS SUBSTANCES," unless you have performed all otherwise applicable screening and testing under 21 CFR Parts 1271.75, 1271.80, and 1271.85
21 CFR 1271.150(a): Current good tissue practice requirement (general)	Failure of a responsible person to determine and document the eligibility of an anonymous or directed donor of reproductive cells or tissue
21 CFR 1271.150(c): Current good tissue practice requirement (compliance with applicable requirements)	Failure to ensure that an establishment that performs any step in manufacture for you (by contract, agreement or other arrangement) complies with applicable CGTP requirements

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Continued from page 13

The primary benefits come during the first two steps: project setup and technology transfer. Those are routine operations for a contract manufacturer that has gathered related expertise by executing a number of other projects. For small/virtual companies, however, such efforts can present major challenges because they need to create facilities and processes, hire and train staff, and establish routine procedures. Larger, more-established companies may already have such experience in-house upon which they can capitalize. Table 2 compares costs and timeline efficiencies for this case study with an experienced contract manufacturer against performing the same services in-house.

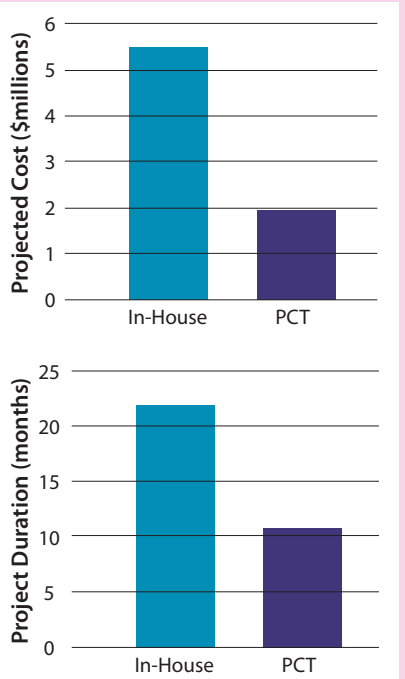
Aside from benefits realized during program implementation, engaging a CMO can be an efficient way to mitigate the resource strain that arises from unpredictable clinical trial patient accruals. The cost of maintaining "idle" capacity remains one of the most significant and common cost drivers related to cell-therapy manufacturing. The deeper and more sophisticated is the capacity, the higher will be its cost burden to the program. Expertise and capacity at a CMO can be used on a pay-per-use or minimum-retainer basis to reflect changes in accrual levels; in-house manufacturing must be maintained at a constant baseline even during low-accrual periods. Tables 3 and 4 illustrate how, in several accrual scenarios, the flexibility of engaging a CMO can dramatically reduce the costs of manufacturing resources and infrastructure.

Thus, cost and timeline efficiencies for this case study are significantly greater when using an experienced contract manufacturer than when performing services in-house (Figure 6).

A Path to Success

As the cell therapy industry grows and matures, many companies seek the most efficient model by which to develop their products. Speed to market, operational efficiency, and reduction of risk are three main drivers for business model choices. If companies choose to outsource development work to a CMO, "strategic fit" will be a main factor in how they make their selection among the pool of available partners. Our case study represents how one sample company benefited specifically in speed to market and operational efficiency by outsourcing their development and manufacturing.

Figure 6: Cost and timeline efficiencies



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Further Reading

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