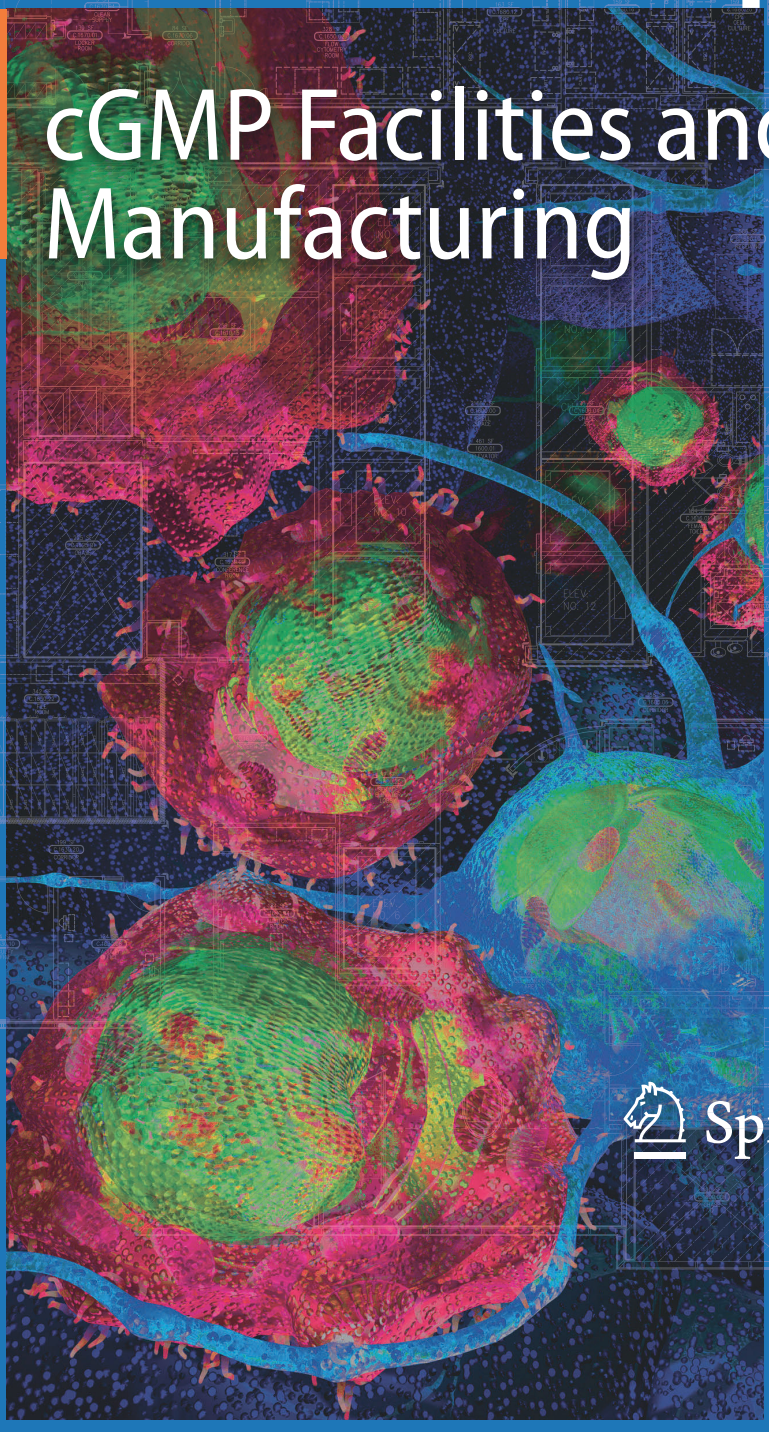
ADRIAN GEE

EDITOR

Cell Therapy

cGMP Facilities and Manufacturing



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To Gordon and Sally and to friends and colleagues whose lives have been touched by cancer.

Preface

The use of cell-based therapies is currently undergoing a rebirth, based upon the extraordinary ability of pluripotent stem cells to differentiate into every other type of cell. This opens up almost unlimited applications in tissue regeneration and repair. It is important to remember, however, that cellular therapies have a relatively long history, peppered with promises, some successes, and many disappointments. Over the years the interest has, as a result, waxed and waned, but there has been undoubted forward momentum, which has brought us to this important point. This progress has been made possible by work in many disciplines, including immunology, cell and molecular biology, hematology, and clinical medicine. A somewhat overlooked, but critical area has been the work of the cell processing or manufacturing technologists and researchers. These individuals are the true translational scientists. They have bridged that often quoted gulf between "bench and bedside." This was, and continues to be, pioneering work, since it required development of many of the tools and techniques that today we take for granted. Many of us have memories of times when the field seemed more like alchemy than science! It has been exciting and rewarding to see it grow and mature and to have the opportunity to work with and learn from colleagues with so many different perspectives. All of us have benefited from the experience of biologists and engineers, blood bankers and physicians, and even regulators and lawyers. If we are to succeed in this next important phase, that kind of interaction must be continued and strengthened.

An important change is occurring in the way we work. The area is now sufficiently mature that it is no longer acceptable to operate as an outgrowth of an academic research laboratory. We are now a stand-alone discipline with both expertise and responsibilities. This transition has occurred relatively rapidly and was necessitated by developments both in science and in regulation. We have the obligation to make possible these new therapies in the context of offering the recipient a safe and hopefully effective product.

There have been few resources to call upon to help us, apart from the support network that has grown between facilities and individuals. Initially this took the form of reassuring each other that we were operating in similar ways, now we need to build upon this foundation.

This book is an attempt to provide a written guide to how academic cell therapy product manufacturing facilities (usually referred to as Good Manufacturing

Practice (GMP) facilities) operate. The aim is to share the common experience of individuals who have worked in the field. It has its origins in the contract facilities of the original Production Assistance for Cellular Therapies (PACT) group – at Universities of Minnesota and Pittsburgh and Baylor College of Medicine. These centers worked under a contract from the U.S. National Heart, Lung, and Blood Institute (NHLBI) to provide cell product manufacturing services to clinical centers around the country. The contract also included administrative and coordinating services provided by the EMMES Corporation in Maryland. For this endeavor to succeed it was important to develop close communication between the centers, not only in relation to providing products, but also to achieve the additional goal of educational outreach to the community as a whole. These interactions resulted in collaborative studies, training courses, and webinars, and stimulated the development of this book. Through ongoing discussions, within and beyond PACT, it became clear that there were many common issues, questions, and concerns relating to operating an academic GMP facility. These ranged from what was the best design, how should they be cleaned and monitored, and what are the relevant regulations, to how do you train staff, order materials, and release products? While there is tremendous diversity in types of products, and where and how they are manufactured, we felt that it would be useful to catalog our experience within the PACT centers and to draw upon the expertise of colleagues to put together this book. Our hope is that it will be useful at many levels—both for those starting out and for those who are changing the way they currently operate. It should certainly not be viewed as the correct or only way of addressing a subject, but more as the collective wisdom of a small group who have wrestled with the problem!

In closing, I think it is important to remember the extraordinary courage and fortitude of the patients who consent to these still experimental therapies. We all owe them a debt of gratitude that we hope to repay by developing this field to its fullest potential.

Houston, Texas Adrian Gee

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Acronyms

Acronym	*Definition*
AABB	American Association of Blood Banks (Formerly)
AATB	American Association of Tissue Banks
ABM	Agence de Biomédecine
ACOG	American College of Obstetricians and Gynecologists
AFSSaPS	Agence Française de Sécurité Sanitaire des Produits de Santé
AHCTA	Alliance for Harmonisation of Cellular Therapy Accreditation
AHIPAA	American Health Insurance Portability and Accountability Act
ALG	Antilymphocyte Globulin
ANZTPA	Australia and New Zealand Therapeutic Products Authority
ASBMT	The American Society for Blood and Marrow Transplantation
ASFA	American Society for Apheresis
BLA	Biological License Application
BSC	Biological Safety Cabinet
CAGT	Center for Cell and Gene Therapy
CAP	College of American Pathologists
CBER	Center for Biologics Evaluation and Research
CC	Clinical Center (NIH)
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
cGTP	Current Good Tissue Practices
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical Laboratory Standards Institute
CMC	Chemistry, Manufacturing, and Controls
CMS	Centers for Medicare and Medicaid Services
COA, CoA, C of A	Certificate of Analysis
COI	Circular of Information

CPF	Cell Processing Facility
CPL/GTL	Cellular Products Laboratory/Gene Therapy Laboratory
CPS	Cell Processing Section
CT	Cellular Therapy
CTP	Cell Therapy Preparations
DLI	Donor Lymphocyte Infusion
DMF	Drug Master File
DMPQ	Division of Manufacturing and Product Quality
DQ	Design Qualification
EBMT	European Group for Blood and Marrow Transplantation
EFG	Etablissement Français des Greffes
EFS	Etablissement Français du Sang
EGBMT	The European Group for Blood and Marrow Transplantation
ELA	Establishment License Application
ESG	Electronic Submissions Gateway
EU	European Union
EUD	European Directives
FACT	Foundation for the Accreditation of Cellular Therapy
FACT-JACIE	Foundation for the Accreditation of Cellular Therapy & Joint Accreditation Committee of ISCT & EBMT
FAHCT	Foundation for the Accreditation of Hematopoietic Cell Therapy
FD&C Act	Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FIFO	First-in First-out
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practices
GTP	Good Tissue Practices
HCT	Hematopoietic Cell Transplantation
HCT/Ps	Human Cell, Tissue, and Cellular and Tissue-based Products
HEPA	High-Efficiency Particulate Air
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cells
HSC Lab	Hematopoietic Stem Cell Laboratory
HSCs	Hematopoietic Stem Cells
HVAC	Heating, Ventilation, and Air Conditioning
IATA	International Air Transport Association
ICCBBA	International Council for Commonality in Blood Bank Automation
IDE	Investigational Device Exemption
IgM	Immunoglobulin M
IMCPL	Immunological Monitoring and Cellular Products Laboratory
IML	The Immunologic Monitoring Laboratory

IND	Investigational New Drug
IQ	Installation Qualification
IRB	Institutional Review Board
ISBT	International Society for Blood Transfusion
ISCT	The International Society for Cellular Therapy
ISD	Instructional System Development
ISHAGE	International Society for Hematotherapy and Graft Engineering
ISO	International Standards Organization
ISSS	Information Society Standardization System
JACIE	Joint Accreditation Committee of ISCT and EBMT
LRA	Legal and Regulatory Affairs
MCT	Molecular and Cellular Therapeutics
MP	Medicinal Products
NDA	New Drug Application
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NK	Natural Killer
OCBQ	Office of Compliance and Biologics Quality
OCTGT	Office of Cellular, Tissue and Gene Therapy
OCP	Office of Combination Products
OOS	Out of Specification
OQ	Operational Qualification
PACT	Production Assistance for Cellular Therapies
PBR	Production Batch Record
PCR	Polymerase Chain Reaction
Pharm/Tox	Pharmacology/Toxicology
PHS Act	Public Health Service Act
PLA	Product License Application
PM	Preventative Maintenance
PQ	Performance (process) Qualification
PTA	Produits Thérapeutiques Annexes
QA	Quality Assurance
QC	Quality Control
QCU	Quality Control Unit
QM	Quality Management
QSEs	Quality System Essentials
R & D	Research and Development
RFD	Request for Designation
SOPs	Standard Operating Procedures
SPC	Standards Program Committee
SPU	Standards Program Unit
TCH	Texas Children's Hospital
TGA	Therapeutic Goods Administration
TJC	The Joint Commission

TPL	The Tissue Processing Laboratory
TRG	Tissue Reference Group
UCB	Umbilical Cord Blood
UPCI	University of Pittsburgh Cancer Institute
UPMC	University of Pittsburgh Medical Center
US	United States
VPF	Vector Production Facility
WMDA	World Marrow Donor Association

Part I
Regulatory

Chapter 1
Regulation of Cell Product Manufacturing and Delivery: A United States Perspective

R.W. Lindblad

Abstract Regulation of cellular therapy products in the United States is challenging and will continue to be so as long as advancements in the cell therapy field continue. As the field of cell therapy has advanced, and products are moving toward licensure, the regulation of these products has become increasingly complicated. The general principles involved in filing and maintaining an Investigational New Drug (IND) and interacting with the Food and Drug Administration (FDA) are described in addition to common reasons why INDs are put on hold. As the majority of cell therapy products are unique, the manufacturer must understand both the science behind the specific cell product and the regulations in order to successfully communicate with the FDA. Though the regulations are written in general terms to be applied to all cell therapy products, they can be tailored to an individual product with good communication and sound, data-driven scientific justification. Additionally, the components of Good Manufacturing Practice (GMP) will be discussed in detail as they relate to the interpretation of U.S regulations.

History of Cell Therapy Development

Effective cell therapy is a relatively recent phenomenon based on the advances in basic cell biology, the identification of cell markers and the relationship of these markers to the functional status of the cell, genetic mapping and protein production on a cellular level, and the ability to separate and grow individual cell types. Studies conducted over 100 years ago attempted to transplant cells or tissue homogenates in order to restore function [1]. These attempts failed, as there was limited understanding of immunology and the cell types that were used. In 1961, precursor cells were identified in the bone marrow and in 1969, the first bone marrow transplant for treatment of leukemia was performed [2,3]. Embryonic stem cells were isolated

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from animal blastocytes in 1981 [4,5]. Cell therapy clinical trials, using cells other than hematopoietic cells or lymphocytes, were initiated in 1986 using human pancreatic islet cells [6]. In 1997, the U.S. Food and Drug Administration (FDA) licensed autologous cultured chondrocytes for the treatment of cartilage defects in the knee [7]. This marketing approval stimulated the development of the current somatic cell regulations.

U.S. Food and Drug Administration (FDA)

The initial authority for the FDA comes from the Constitution and the federal government's right to regulate interstate commerce. Congressional acts provide the legal framework under which the FDA operates. These include authorities specified in the Public Health Service Act (PHS Act, initially used to regulate biological products) and the Food, Drug, and Cosmetic Act (FD&C Act, primarily for food and drugs, but also covering medical devices). Rules to interpret the laws and how they should be applied are written by executive departments and the responsible agencies of the government (e.g., the FDA), and published for public review and comment in the Federal Register. Permanent rules relating to FDA are adopted as regulations and organized under Title 21 of the Code of Federal Regulations (CFR). The legally binding regulations are supplemented by Guidance Documents written to provide the FDA's interpretation of the regulations. As such, Guidance Documents are not legally binding, but instead are provided to assist stakeholders in understanding the FDA's interpretation of the regulations, and to provide study sponsors and investigators with assistance when applying the regulations in specific cases. The interpretation of the regulations for any specific cell therapy product is a critical part of the regulatory pathway for any product being developed under FDA regulation.

The relevant FDA centers pertinent to cellular therapies include the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH). Within CBER is the Office for Cellular, Tissue and Gene Therapies (OCTGT) that directly regulates the cell therapy field. Combination cell and device products will fall between the two centers, with one center taking the lead in the review process and the other acting as a consultant. Typically for cellular therapy products, OCTGT will be the lead review team [8,9].

History of Regulation of Cell Therapies

The regulation of cell therapies is a recent addition to the FDA regulatory history. The agency over the years has gained authority primarily as a result of public and congressional reactions to widely publicized investigational medical treatment disasters [10]. As cell therapies have emerged, the agency has reacted by developing regulations and by defining cell products, now grouped under the term Human Cell, Tissue, and Cellular and Tissue-based Products (HCT/Ps) [9]. This is an ongoing

process as the field grows. The agency is looking for general rules and principles by which to regulate the field, and as such will try to group products and provide consistent regulations. This has inherent problems in an emerging field where the understanding of the biology is expanding faster than the regulations can address the issues. This will force all sides to interpret the regulations and come to agreements as to the specific issues for any particular cell therapy product.

As cell therapies emerged in the 1990s, the scientific community sought clarification regarding regulation of these products. In 1995, Genzyme Corporation began to market an autologous cartilage cell product in the United States called Carticel®, based on European study data. The FDA notified the company that the product would require a premarketing approval. Genzyme submitted a request for designation and in 1996, the FDA released a Guidance Document with advice to industry on applications for products comprised of living autologous cells manipulated *ex vivo* and intended for structural repair or reconstruction [11]. This began the FDA's formulation of policy and procedures to regulate somatic cell therapies.

The autologous cartilage cell product was approved in 1997 under an accelerated approval based on a review of European data and a commitment by Genzyme to conduct a U.S.-based controlled clinical trial. This approval required the agency to formulate a consistent regulatory policy regarding cell therapies and to tackle the definitions that are present in the current regulations – minimally manipulated and homologous use.

In 1998, the FDA published a request for proposed regulatory standards that focused on unrelated allogeneic peripheral and umbilical cord blood hematopoietic stem/progenitor cell products. The request included submitting product standards, manufacturing establishment and processing controls, supporting clinical and nonclinical laboratory data and any other relevant data supporting the safety or efficacy of the product. The FDA would determine the regulatory approach to licensure. The establishment registration and product listing regulation was proposed in 1998 and finalized in 2001. Donor eligibility requirements were proposed in 1999 and finalized in 2004. Current Good Tissue Practices (cGTPs) with inspection and enforcement authorities were proposed in 2001 and finalized as regulations in 2004. This is the current framework under which the FDA regulates cell and tissue products.

CBER

CBER currently regulates HCT/Ps under section 361 of the PHS Act [9,10]. There are products that require no pre-market approval and are defined in the tissue regulation 21 CFR 1270.10, [12] as minimally manipulated, homologous use, not a combination product, and either has no cellular or systemic effect, or, if it is active on a cellular or systemic basis, is used in an autologous setting, in an allogeneic setting in first- or second-degree blood relatives, or is for reproductive use. Additionally, CBER regulates HCT/Ps under section 351 of the PHS Act [8,10]. This includes products that require premarket approval, i.e., require data with clinical investigations to be collected for FDA review under an IND application, and do

not meet the definition of exempt products described above under 21 CFR 1270.10. More detailed explanations are provided in the section below.

CDRH

CDRH is the lead center for devices. This includes HCT/Ps that are classified as a device. Additionally, CDRH is involved in the regulation of cell products that are combined with a device such as a matrix or scaffold structure to enhance the activity or the growth of the cell product.

CDER

After the reorganization of the FDA in June 2003, the Center for Drug Evaluation and Research (CDER) became the lead center for the review of monoclonal antibodies, proteins for therapeutic work, immunomodulatory proteins and growth factors and cytokines intended to alter the function of cells *in vivo*.

Combination Products

As discussed above, many biologic products and specifically cell therapy products are combination products. These products may overlap all three centers of the FDA described previously. The lead center is designated based on the primary mode of action of the product. The difficulty with some of these products is determining the primary mode of action. When this is not clear, or if there is a dispute regarding the designation, the Tissue Reference Group (TRG) and the Office of Combination Products (OCP) will assist in making a determination. The TRG is comprised of three members from CBER, three from CDRH, a liaison from the office of general counsel, and a liaison from OCP. This group meets every 2 weeks and provides a response to applicants within 60 days. The TRG determines when a product meets criteria for regulation solely under section 361 of the PHS Act and is, therefore, regulated solely by CBER. If the product does not meet the criteria for regulation under section 361 of the PHS Act, the TRG would then make a recommendation as to which center would be the lead review center. If there is a dispute with the determination of the TRG, the product may be brought to the OCP. The OCP acts as an appeal organization for the TRG, though it may also act in the absence of a TRG recommendation, and will make a final designation regarding the applicable regulation (351 vs. 361) and the lead center for product review. The OCP group, created in 2002, is in the office of the commissioner at the FDA and prepares an annual report to Congress. The OCP operates using a Guidance Document jointly issued by CBER and the OCP. There is a formal application process based on a Request for Designation (RFD) and a required response time from the FDA within 60 days of

receipt of the request. The RFD decision is binding unless there is a change required to protect the public health. Disagreement with the initial ruling may be filed as a Request for Reconsideration within 15 days. The FDA response to the dispute will be received within 15 days. In some cases, the designation has changed based on this final dispute request.

The IND Process

Presented below is a summary of the basic procedures to file an IND with the FDA. The regulatory pathway to conduct a clinical trial using a cell therapy product will involve an IND the majority of the time. Some exceptions are made for homologous use and cells that are only minimally manipulated *ex vivo*.

Who Needs an IND?

Most cell therapy products will require an IND to conduct a clinical trial. Exceptions to this include products that qualify as being minimally manipulated for homologous use, not a combination product, and either having no cellular or systemic effect or, if it is active on a cellular or systemic basis, is used in an autologous setting, or allogeneically in first- or second-degree blood relatives, or is for reproductive use as defined in 21 CFR 1270.10. These products are regulated under section 361 of the PHS Act. They do not require premarket approval and are regulated by site registration and cGTP [13].

IND Sponsor/Investigator

The *Sponsor* of an IND trial is the individual or organization that takes responsibility for and initiates the clinical investigation. This may be an individual, an academic institution, the government (the National Institutes of Health – NIH), or a pharmaceutical company. In contrast, the *Investigator* is the individual who actually conducts the clinical trial and under whose direction the investigational product is administered. In many smaller cell therapy clinical trials, the sponsor may in fact also be the investigator, so that the trial is conducted under a single individual who is designated as a *Sponsor/Investigator* [13].

Requesting a Meeting

Product regulatory development almost always begins with meetings between the sponsor and the FDA. Even with the availability of various Guidance Documents, sponsors are rarely in a position to submit a successful IND application without direct FDA interactions in order to agree on submission details for their particular cellular product. The agency has designated meeting types to create a

consistent level of support for products under development. The most common meeting requests are for Type B meetings that involve the steps necessary in product development under IND. These are explained in more detail below.

Type A meetings are used to discuss products stalled in the development pathway and products that have been placed on clinical hold after a clinical trial is already under way. Type C meetings are any other meetings not covered under Type A or B [14,15].

Type B meetings include several specified time points in the development of a product. These include a pre-IND, end of Phase I, end of Phase II/pre-Phase III, pre-Biological License Application (BLA), Product License Application (PLA), Establishment License Application (ELA), and New Drug Application (NDA) meetings. Under the performance goals set for FDA, Type A meetings should occur within 30 calendar days from receiving the request, Type B meetings within 60 days, and Type C meetings within 75 days. Information should be submitted to the agency 14 days prior to the meeting for Type A meetings and 30 days prior to the meeting for Type B and C meetings [15].

Pre-IND Meeting

For cell therapy products, the most critical meeting is the pre-IND meeting. This meeting will set the stage for product development, including preclinical testing and cell product manufacturing and characterization that will carry through the entire product development life cycle. The general format of a pre-IND package will include a cover letter followed by a title page, a table of contents, and a brief summary of the pre-IND package under general information. This is followed by a list of questions that the sponsor would like the FDA to address specifically, the proposed clinical protocol and consent, preclinical information, any existing clinical information, a manufacturing section, and hard copies of pertinent references. Table 1.1 is an example of a table of contents for the pre-IND package [14]. Careful attention must be paid to the organization of the package so that the sections are complete and easy to review. These sections correspond to the main sections of an IND. The closer the pre-IND package parallels the content that will be submitted in the actual IND, the more likely a complete review can take place and key questions can be addressed prior to submitting the IND itself. Preclinical studies that have

Table 1.1 Sample table of contents for a pre-IND package

1. General information
2. List of attendees
3. List of questions
4. Draft clinical protocol and template informed consent
5. Summary of preclinical information
6. Summary of clinical information
7. Summary of chemistry, manufacturing, and control information
8. Complete list of references

been conducted (or are still under way) must be fully described and include detailed, rather than summary data for review by the FDA. Preclinical animal studies in general will be conducted in two species and should include at least one study using the same route of administration and the same cell manufacturing technique and product as will be proposed in the clinical study. Deviations from this ideal should be clearly explained and justified scientifically. The pre-IND package will also include the proposed clinical trial protocol. This should be preferably a fully developed protocol based on the preclinical and/or clinical studies conducted to date. It should also include the relevant inclusion and exclusion criteria and a detailed description of both the clinical assessments and related laboratory tests to be performed. Typically the initial studies will involve dose-ranging studies to develop early safety data and tolerability data.

In developing the pre-IND package, a list of questions that the sponsor wants the FDA to address should be submitted with the meeting materials. These questions are critical to focus the discussion in the areas that the sponsor has concerns or questions. The FDA will specifically address these questions during the meeting and provide a formal response as part of the meeting minutes. These questions should include issues related to the preclinical testing data, chemistry, manufacturing, and controls (CMC) information, and the clinical protocol. It is strongly recommended that a list of CMC-related questions be submitted for the agency to consider when reviewing the pre-IND submission package for any HCT/P. These questions will help build consensus regarding the manufacturing techniques and controls in addition to the appropriate characterization of the product relative to the stage of development. If the questions are well written, the IND submission will be tailored to address the concerns or issues raised in the pre-IND meeting, thereby avoiding the IND being placed on hold. The IND submission should include the pre-IND questions and the sponsor's response to the FDA comments.

The sponsor, the principal investigator, the individual responsible for the preclinical work, and the cell manufacturer should attend the pre-IND meeting. The FDA will be represented by reviewers to match these areas. After the pre-IND meeting, FDA reviewers in general make themselves available for further discussion and clarification, or review of a new manufacturing technique or preclinical study to ensure that the sponsor and the FDA are in agreement regarding the next steps. This is a collaborative process with the goal of moving the development into the clinical arena as quickly and as safely as possible.

IND Submission

The submission of the IND will follow the pre-IND meeting and will need to address the issues raised at the pre-IND meeting in order to move forward. Once the IND is submitted, the FDA has 30 days to respond. The IND may proceed unless the FDA reviewers provide comments, or place the IND on hold within that 30-day time limit. Typically the FDA will have comments and will contact the IND sponsor

prior to the 30-day deadline. The IND submission will be organized in a similar fashion to the pre-IND package noted above. Several key sections in the IND are the clinical protocol with appropriate endpoints, stopping rules and dosing justification, the CMC section, and the preclinical section [13].

Chemistry, Manufacturing, and Control (CMC) Section

The CMC section of the IND is crucial to the success of an IND submission [16]. This is especially true with cell therapy products [16]. The amount and content of the CMC section varies depending on the phase of study, the duration of treatments, and dosage form. The majority of cell therapy products are in early stages of development. Therefore, the controls on manufacturing and the initial assays used to characterize the cell product are critical to the success of the IND. From the regulations in 21 CFR 312.23 [17] sufficient information is required to assure the proper identification, safety, quality, and purity of the cell product. During pre-IND meetings, the CMC section is discussed in relation to the safety of the investigational product. The end of Phase II/pre-Phase III meeting allows both the sponsor, or sponsor/investigator, and the designated reviewing division to evaluate the data generated with respect to the cell product's development. Protocols are reviewed for their adherence to regulations and policies, and also to any applicable agency guidance. The CMC section is reviewed for its potential in generating meaningful data during Phase III.

Manufacturing control and characterization of the product is echoed throughout all phases of the IND process. The following information should be included in the CMC section of an IND (CFR 312. 23) [17]:

- Chemistry and Manufacturing Introduction
- Drug Substance
- Drug Product
- Brief description of composition, manufacturing, and control of any placebo used in a controlled clinical trial
- Labeling
- Environmental analysis requirements (not applicable to human biologics under 21 CFR 25.31)

Typical problems encountered with submission of CMC sections include:

- Poor organization and key elements missing from the submission

1. Following the suggested format helps to alleviate both of these issues. Careful organization using familiar section headings allows FDA reviewers to find the critical sections efficiently and focus the review on the scientific issues.

- Incomplete descriptions of materials and reagents used in the manufacturing process

2. A clear presentation of all substances used in manufacturing and their respective source is necessary for a complete review. Table listings including the manufacturer, concentrations, amounts used, supplier, clinical or nonclinical grade and certificates of analysis (C of A) for nonclinical grade reagents help to organize the information in a clear concise manner.

- Insufficient facility information

3. As mentioned below, a cross-reference to a facility Type V Master File will provide adequate information regarding the manufacturing facility. The facility Master File must be maintained by the facility with up-to-date information. Alternatively, the facility may have this information prepared to submit for each IND that uses a product from that cell manufacturing facility. In either case, the submission of the IND must be a collaboration between the sponsor of the IND and the manufacturer. INDs will consistently be put on hold when this collaboration does not exist.

- Insufficient details regarding release criteria and tests employed

4. Release testing for cell products must be well thought out, as the quantity of product and the timing of the product administration may be critical in shaping an appropriate set of release criteria. This is often product-specific with the underlying principles of providing an adequately characterized product free from infectious agents. A tabular format that characterizes the timing, the proposed acceptance criteria and the procedures or test methods used for sterility, endotoxin, identity of the product, viability, cell number, potency, and mycoplasma is generally expected.

- Standard Operating Procedures (SOPs)

5. SOPs are critical to understanding the manufacturing technique at a given facility and provide a basis from which to audit a facility to ensure that the manufacturing process is well controlled. A list of all relevant SOPs for the given manufacturing procedure should be provided in the IND. SOPs that describe the critical steps in the cell manufacturing procedure should be submitted in their entirety. Any SOP submitted to the IND must be maintained in a current form with updates submitted to the IND as they are made.

Chemistry and Manufacturing Introduction

A statement should be provided to indicate whether the drug substance or drug product (the HCT/P) has the potential for human risk. Any difference between the drug product in animal studies and the one proposed for clinical use must be documented.

Drug Substance

This section should focus on product type, derivation (starting material), procurement, process description, and test methods used to determine identity, strength, quality, and purity. If the FDA has already provided guidance for a similar cell product, pay special attention to the guidance and carefully note where your product or methods differ from the recommendations in the guidance. Preliminary product specifications are needed to support safety. Include information about infectious disease testing, cell processing, reagents (clinical grade, research), and any product stability data. In Phase I studies, the brief physical, chemical, and biological characteristics information is usually limited due to the early stage of development of the product. By Phase II, more specific data regarding the clinical product's characteristics should be provided. The manufacturing facility's name, address, and capabilities should be documented. A facility Type V Master File, if on file with the FDA, may be referenced in this section once written permission by the facility has been requested and given to the IND sponsor. A Type V Master File provides information on the facility design, operating procedures, an overview of production steps, deviation management, and personnel qualifications and training.

Drug Product

A summary of the product's composition, manufacturing methods and packaging, and stability data should be included. Components used in the manufacturing of the investigational new drug—active, inactive compendial, and noncompendial excipients—should be listed. If available, Certificates of Analysis for reagents not FDA approved should be submitted.

Placebo

A brief description of the composition, manufacturing, and controls of any placebo used in a controlled clinical trial must be included in the IND.

Labeling

Copies of the proposed label of the investigational product should be provided and indicate that its use is limited to investigational purposes. The specific cautionary

wording to be included on the label is given by regulation in 21 CFR 312.6 [18]. As many cellular products may be held at different stages during their production, the labels used on any intermediate containers should also be provided, as well as the final product label to be used in the investigational clinical setting. This ensures proper segregation from other products in inventory.

Pharmacology/Toxicology (Pharm/Tox) Section

The Pharm/Tox section must support the planned clinical trial. Pharmacology information should describe the pharmacologic effects and mechanism of action in the animal model and provide information on the absorption, distribution, metabolism, and excretion of the product. In cellular therapies much of this information is not readily measurable. An attempt to organize the preclinical data to address these areas should be made. If this information is not known, it should be stated. Toxicology studies, on the other hand, are critical to the initiation of clinical trials in humans.

Cross-Referencing

In submitting an IND, other information that is relevant to the IND may already exist at the FDA. In order to facilitate review and avoid duplicate information being submitted, the FDA permits one IND to cross-reference information that is already on file at the agency. This typically involves cross-referencing a previously filed IND or Investigational Device Exemption (IDE) that may have relevant clinical, device, or manufacturing information, or a Master File for the manufacturing facility. In cross-referencing an existing submission, those two files become linked and problems in one will affect the other. For example, if the manufacturing facility Master File is put on hold, other INDs cross-referencing that Master File may also be put on hold. Because IND content is proprietary, the FDA cannot provide details about one IND to the sponsor of another IND even if there is a cross-reference. Written authorization must be obtained from the sponsor of the submission that is being cross-referenced. Specific details including the submission and volume number, the heading, and page numbers should be provided to identify what material is being cross-referenced. This allows FDA reviewers to quickly locate the referenced materials, facilitating the review process.

Type V Master File

Master File submissions allow facilities to provide information in confidence to the FDA regarding facility design, manufacturing, processing, materials management, product release criteria, storage requirements, and personnel. Investigators or sponsors, through the permission of the manufacturing facility, may reference the facility's Master File in IND, BLA, and NDA submissions without the information being disclosed to the investigator. The FDA does not review a Master File until

it is referenced in an IND, IDE, BLA, or NDA. A Master File allows for facility information to be reviewed in one document thus facilitating the FDA's review of INDs, BLAs, and NDAs. However, there are potential drawbacks to submitting or referencing a Master File in a cell therapy IND submission. Once a Master File is submitted, any changes to the facility must be submitted to the FDA as an amendment to the Master File submission. The holder of the Master File is required to inform individuals authorized to reference their Master File in FDA submissions of such amendments. Additionally, if the Master File submission is put on hold for any reason, then all INDs that reference that Master File would be put on hold as well.

Filing an IND

Once the IND is filed, the FDA has 30 days to respond with comments prior to the IND automatically becoming active. The FDA can choose to not comment, which occurs rarely, or comment on items that can be addressed without putting the IND on hold, or place the IND on hold. The FDA prefers not to place INDs on hold and will negotiate issues with the sponsor so that the clinical trial can be initiated. This will often require a delay in starting the clinical trial to address the concerns, but is not an official hold. The FDA applies a clinical hold to stop the clinical investigation from proceeding until identified issues are adequately addressed [19]. For new INDs, this represents a failure of the pre-IND process. If the sponsor in the pre-IND meeting presents sufficient detail and asks appropriate questions, then potential hold issues will be addressed prior to the IND submission. The FDA will put a clinical trial on hold for predefined reasons that include:

- Exposure to unreasonable risk for significant illness or injury
- Clinical investigators are not qualified
- Investigator brochure is misleading, erroneous, or incomplete
- IND does not contain sufficient information to assess risk
- Gender exclusion for a condition that occurs in both men and women

In practice, a clinical hold on cell therapy INDs is applied for several reasons, which include:

- The clinical trial does not provide adequate safety protection, which includes appropriate dosing, based on the preliminary clinical or preclinical data, appropriate dose escalation, and appropriate stopping rules for the trial.
- The preclinical data does not support the clinical trial based on product manufacturing or route of delivery.
- The manufacturing section has inadequate characterization of the product, inadequate controls over manufacturing, and insufficient details.

These issues should all be addressed in the pre-IND process.

IND Maintenance

When an IND becomes active, future communication with the FDA outside of specific meeting requests occurs through the submission of IND amendments. Each submission is sequentially numbered and adds to the overall content of the IND. Amendments are submitted to the IND on a rolling basis and include protocol revisions, expedited safety reports, changes to the manufacturing technique or to the facility, key personnel changes, and any other significant changes to the clinical or manufacturing portions of the IND. Additionally, each IND sponsor is required to submit an annual report. In some cases, the FDA may require more frequent progress reports. Each annual progress report is an opportunity to submit other details regarding the IND that were not submitted during the year. The annual report is due within 60 days of the anniversary date of the IND becoming active.

The general sections of the IND annual report are shown in Table 1.2 and are described in 21 CFR 312.33 [20].

Table 1.2 The general sections of an IND annual report

Section 1: Individual study information for all studies conducted under the IND
Section 2: Summary information (Cumulative safety information, Changes to manufacturing procedures)
Section 3: Investigator brochure update
Section 4: Description of protocol modifications
Section 5: Summary of foreign market information
Section 6: Any outstanding FDA-related business
Section 7: Description of the general investigational plan for the upcoming year

The annual report is an opportunity for the IND sponsor to make the FDA aware of the general safety of the clinical protocol and manufacturing over the previous year and to update the IND with the most recent information regarding the clinical investigation and the manufacturing of the cell product. Section 2 will have summaries of all adverse events and serious adverse events in addition to changes in the manufacturing process. From a manufacturing perspective, the annual report is an opportunity to submit information to the FDA to keep the agency apprised of changes and improvements to the manufacturing techniques. Updates should include data regarding any failed manufacturing attempts, updated release criteria or new tests employed, updated facility information or key SOPs, and a summary of any stability testing results to date. A list of all other clinical products prepared in the facility should be provided. The manufacturing facility should review the submission for accuracy regarding the manufacturing sections and play an active role in monitoring these communications with the agency.

Current Good Manufacturing Practice (cGMP) and Cell Product Manufacturing

Current GMP is based on the Federal Food, Drug and Cosmetic Act (FD&C Act) which defines an adulterated substance in Section 501(a)(2)(B) [21] as a drug where

"the methods used in, or the facilities and controls used for, its manufacturing, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to *safety* and has the *identity* and *strength*, and meets *quality* and *purity* characteristics, which it purports or is represented to possess." This provides the framework of the minimum standards that must be met when producing a drug or biological product. These manufacturing requirements are described in the regulations in 21 CFR Parts 210 and 211 [22]. Quality Systems Regulations (QSR) refer to the minimum standards applicable to device manufacture and are based on similar language to the adulterated drug description in the FD&C Act. The regulations are in 21 CFR Part 820 [23]. As described in the beginning of the chapter, the authority to regulate drugs or devices comes from the FD&C Act and the primary authority to regulate biologics from the PHS Act. With the development of HCT/Ps, the FDA has actively pursued a regulatory strategy that addresses these products. The cGTP regulations have as their foundation the requirement to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (e.g., by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing). Communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents. cGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including, but not limited to, all steps in donor screening, donor testing, tissue recovery, processing, storage, labeling, packaging, and distribution. As stated earlier, this process is in active evolution as new products are developed and definitions of tissue products are further refined. An attempt has been made to harmonize the FD&C Act and the PHS Act under the regulations by differentiating between PHS 351 products which are considered similar to drug products and are regulated under the FD&C Act and applicable cGMP regulations, and PHS 361 products that meet strict definitions to be regulated only under the new tissue regulations found in 21 CFR 1271 [24]. In the event that a tissue regulation in part 1271 is in conflict with a requirement in the relevant cGMP regulations for drugs in parts 210, 211, or devices in part 820, the regulations more specifically applicable to the product in question will supersede the more general. Due to the broader scope of the tissue regulations, most of the cGMP regulations under parts 210 and 211 would be applicable for HCT/Ps that are not regulated solely under section 361 of the PHS Act and meet the definition of drugs in the FD&C Act and biologics in the PHS Act. Donor eligibility requirements are unique to the cGTPs and are applied to all HCT/Ps. This background provides the basis for the different regulatory pathways of the PHS Act for cell and tissue products regulated under section 351, and which fall under the regulations for IND submission and follow cGMP procedures. To be regulated under only PHS Act section 361 and the new tissue regulations, which require site registration, but do not require filing an IND, HCT/Ps must meet several criteria. Facilities that must register under the new tissue regulations in 21 CFR 1271 include:

- Labs that perform donor testing for communicable diseases
- Labs that perform microbiological testing of donor tissues
- Establishments that process store and/or distribute HCT/Ps (regulated under either PHS 351 or 361)

Transfusion facilities that store products for use in their facility do not need to register as an HCT/P facility.
To qualify as an HCT/P that is regulated only under the tissue regulations, four major criteria must be met. These include:

- Minimal manipulation
- Homologous use
- Not combined with another product or device
- No systemic effect and is not dependent on metabolic activity, OR has a systemic effect or is dependent on metabolic activity of living cells for its primary function, AND:
- Is for autologous use
- Is for allogeneic use in a first- or second-degree blood relative
- Is for reproductive use

The classification of a product as either minimally manipulated or homologous use has created a large debate in the cell processing community. The interpretation of these issues allows for the refinement of the regulations regarding specific cell therapies. Currently minimally manipulated includes tissues where processing does not alter the relevant characteristics of the tissue for reconstruction, repair, or replacement. For cells or nonstructural tissues, it includes processing that does not alter the relevant biological characteristics of the cell or tissue. Homologous use means the cell or tissue product performs the same basic function or functions in the recipient as the donor [25, 26].

The IND/GMP Continuum

Manufacturing under cGMP is a challenge for the cell therapy community. The regulations were established prior to the development of advanced cell manufacturing techniques and are structured to address issues in chemical manufacturing. As cell therapies have evolved, the application of full cGMP compliance in Phase I studies for cell products has been difficult. Safety is of paramount importance so that adequate release criteria and manufacturing controls to prevent transmission of communicable disease are critical at any stage of development. In biologic products in general and cell therapy products specifically, potency assays are problematic as the mechanism of action is rarely fully understood and multiple factors can affect the outcome including donor, manufacturing, and host factors. The goals of the agency in Phase I trials are to:

- Assure the safety and quality of the investigational product
- Maintain the ability to reproduce the manufacture of the product in a reliable manner
- Assure consistent quality of the manufactured product throughout the development phase.

This translates into well-written procedures, accurate data collection regarding the manufacturing process, and adequately controlled equipment. Perceived deviations from standard cGMP can be acceptable with scientific justification and an alternative approach proposed. The FDA will not direct the development of the product but will respond to the suggestions put forward in an IND application. As stated earlier, these discussions are in fact negotiations that should be held in the pre-IND phase of the process [25].

GMP Components

Regulatory compliance surrounding the overall function of a cell therapy laboratory is challenging. Facilities face obstacles when attempting to apply GMP regulations to several areas. These will be addressed in later chapters but briefly include:

Staff Training

21 CFR Part 211.25 [27]. Each person engaged in manufacturing or processing shall have education, training, and experience (or combination thereof) to perform assigned functions. This training is to be conducted by qualified individuals on a continuous basis and with sufficient frequency. Training programs should consist of basic GMP operations, which include a facility design overview, the development and implementation of standard operating procedures, the importance and function of worksheets and batch records, and laboratory safety. The laboratory is tasked with developing a comprehensive training program that will ensure competency and proficiency among its staff. Proof of staff capabilities resides in training record documentation.

SOP Development

The development of clearly written procedures helps ensure a consistently manufactured product. The format used for SOP writing should be consistent throughout all SOPs, if possible.

Processing Records

Batch records are critical to the traceability of a cell therapy product. They document each critical step in the manufacturing of the product and all of the materials,

reagents, and equipment used in the process. The information provided in the record should reflect what is required by the FDA's cGMP and cGTP standards.

Equipment Records, Calibration, and Cleaning

An equipment qualification plan is critical to validating equipment used in the manufacturing of cell therapy products. Once equipment validation has been performed it is essential that the equipment be monitored. Cleaning and calibration schedules help ensure that equipment is maintained and is functioning properly.

Facility Requirements

Facilities need to maintain a clean and sanitary environment. Clearly written procedures for cleaning must be validated and put in place. Frequency of the cleaning and environmental monitoring is determined by a number of factors including the types and number of products and changeover procedures.

Validation Procedures

The 1987 FDA's Guidance on General Principles of Process Validation states, "Process validation is establishing documented evidence, which provides a high degree of assurance that a specific process consistently produces a product meeting its predetermined specifications and quality attributes." A validation plan is critical to controlling processes. Installation, operational, and performance qualification are key elements to a validation plan. Qualification is part of the validation process.

Quality Assurance (QA)/Quality Control Program

A QA plan ultimately is implemented to determine whether or not a product can be released. It is designed to review the associated documentation in a manner that is consistent with GMP/GTP standards for the manufacturing, testing, and release of a quality product. A QA plan ensures that manufacturing processes and release testing are carried out according to laboratory SOPs. A quality control program helps to monitor several in-process control procedures such as performing testing of quarantined reagents prior to use, properly maintaining equipment, and that staff are adequately trained.

Management Systems

Management systems are implemented in the laboratory to facilitate many processes. A materials management system assists in receiving, tracking, and quarantining reagents and materials appropriately. Batch lot numbers can be cataloged

for easy retrieval and traceability purposes. Product/process deviation management procedures can generate metrics information on specific products and processes. A quality assurance team can review such data as trending of an in-process production issue. Information gathered from internal audits can help prepare the lab for inspections by the FDA or a sponsor performing vendor audits.

Controlled Labeling Operations

Labeling systems for both in-process reagents and end products need to be controlled to prevent sample misidentification and mix-ups. GMP and GTP regulations require that 351 and 361 products be labeled with specific information during their processing, storage, and administration. Special labeling exists for quarantine products and products from ineligible donors. Uniform product names exist in the GMP, GTP, and Foundation for the Accreditation of Cellular Therapy (FACT) standards. The integrity and legibility of the label needs to be considered with respect to the product's storage and shipping conditions.

Release Criteria Principles

General principles regarding the development of release criteria are described in the GMP sections of the regulations, 21 CFR 211. "For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to the final specifications for the drug product, including the identity and strength of each active ingredient, prior to release." The biologic section of the CFR, specifically 21 CFR 610 [28], describes specific issues relevant to cell products. Typical release criteria are both universal and product specific. Product release testing ensures that the manufactured product is not only safe for use, but that it meets its characterization requirements for a quality product. Depending on the phase of the study, not all product information with respect to identity, safety, purity, potency is fully characterized. Although full characterization is not required until Phase III, efforts should be made during Phase I and II to generate relevant data for use in determining the best approach to testing these parameters. Cell therapy products have their own set of unique regulatory concerns. The labile nature of many cell therapy products does not allow for all testing results, i.e., sterility in the form of multiday culture results, to be available prior to their release. A Gram stain result is typically applied as the surrogate for sterility at the time of release with follow-up cultures being obtained at the time of release and reported out after product administration. There are times when the volume required for testing impacts the overall volume required for administration. The FDA considers the use of in-process testing as a viable option in these situations; however, some level of end product testing is required.

A general outline of the type of testing that is typically required is provided in the table below. As previously described, cell therapy products may be limited in quantity and the timing for administration may not be conducive to all the testing

described. Specific rationale for proposing alternative testing must be provided with a goal to achieve the principles outlined in Table 1.3.

Table 1.3 Principles used to determine alternative testing

Test	Test method	Test timing	Specification
Sterility	Specified	Final product	Negative
Purity	Specified	Final product	Pass
Mycoplasma	Specified	Final product	Negative
Viability	Not specified[a]	Final product	Product specific[a]
Identity	Not specified[a]	Final product	Product specific[a]
Potency	Not specified[a]	Final product	Product specific[a]
Others (cell dose, etc.)	Not specified[a]	Final product	Product specific[a]

[a]Product specific and must be proposed by the manufacturer.

- *Sterility* – colorimetric, biochemical
- *Purity* – endotoxin, characterize all cell types, limit or eliminate the use of antibiotics, solvents, or animal products
- *Mycoplasma* – PCR testing may be done at the time of cell harvesting
- *Viability* – membrane integrity, O_2 consumption, ATP bioluminescence, ELISA
- *Identity* – product specific to identify the specific cell types that constitute the therapeutic population
- *Potency* – quantitative bioassay to measure biological function associated with the known *in vivo* mechanism of action. This type of testing is rarely possible so that alternative tests are proposed, scientifically justified, and refined as the development process for the cell product matures.
- *Other* – tests may be required to quantify the cell dose, other biologic activity beyond that measured for potency assays, phenotype characterization.

Unlike chemical manufacturers that may produce a massive lot to treat multiple individuals, cell therapies are usually a single lot to treat a single individual. Each lot produced must have the above-identified release criteria consistently performed. Careful record keeping and plans for notification of the treating investigator physician and the recipient in the case of a contaminated product should be established. The goal is to establish rapid, sensitive, and reliable test methods requiring minimal volume of the product. There can be flexibility regarding the timing of the testing, the tests performed, and when the results are obtained relative to the administration of the product with appropriate justification.

Delivery of Cellular Products

In addition to a product meeting the appropriate release criteria, the product administration process needs to be monitored. Patient baseline and postadministration

evaluations are conducted, adverse events are documented, and any deviations from the product administration procedures/processes are recorded. Such documentation can allow the cell-processing laboratory to evaluate common elements across different products as well as observe any product-specific trending.

Shipping is considered an extension of storage conditions. Selecting the right vendor is essential to shipping a stable product. The shipping containers purchased must be validated by the laboratory prior to their use. Transport documentation is a GTP requirement for traceability of donor to final product purposes [1271.290(e)] [29]. The U.S. Department of Transportation has guidance on classifying biological materials in accordance with 49 CFR 171 [30].

Depending on the type of product, certain postshipment release testing may be indicated prior to its use. Shipping validation procedures can be conducted to determine what tests are required for certain products. Establishing postshipment acceptance criteria is critical for the use of many cell therapy products.

Conclusion

Several elements must be taken into consideration when submitting an IND. Engaging the FDA early on in the IND submission process is recommended to facilitate the IND's overall success. The following chapters will address these items in more detail by practical application of the cell therapy regulations.

Special Considerations: Umbilical Cord Blood

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One cell therapy product, umbilical cord blood (UCB), an increasingly common source of hematopoietic stem cells (HSCs) for hematopoietic reconstitution [31–33], deserves special consideration. The Food and Drug Administration (FDA) Draft Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies was issued in late 2006 [34]. This document will serve to define the regulatory requirements for UCB and assist banks with the licensure application. Within the current draft is guidance on the applicable regulatory requirements, the license application procedure, the Chemistry, Manufacturing, and Controls (CMC) section, the establishment description, and the postmarketing activities. In addition to the FDA Guidance [34] there are standards from both AABB and the Foundation for the Accreditation of Cellular Therapy (FACT) that cover UCB collection, storage, and shipment for transplantation [35, 36]. Accreditation by both of these professional organizations is voluntary; however, given the complementary nature of the standards to the regulations, it is advisable to pursue accreditation to assure compliance.

Most UCB banks include a red cell depletion step prior to cryopreservation and storage [37]. UCB units are then typically stored in liquid nitrogen in the vapor

phase; both the FDA Guidance and standards indicate that units should be stored at < –150°C [34, 35]. Additional considerations for storage should include systems for monitoring and alarms and inventory management. Units may remain in storage for several years prior to shipment for transplantation. The FDA asks that banks establish expiration dates for cryopreserved units based on a stability program [34]. Units have been used successfully for transplantation after at least 12 years of storage (authors' experience). Cord blood banks are subject to FDA inspection [38].

The algorithm for identification of units for transplant is somewhat institution dependent; however, selection is generally based on level of HLA match and nucleated cell dose, and a UCB graft can be located in substantially less time as compared to marrow or mobilized peripheral blood [39]. Once identified, cryopreserved UCB units can be shipped to clinical transplantation centers throughout the world. As noted earlier, shipment is considered an extension of storage. Validated packaging and shipping procedures should demonstrate that acceptable temperatures and the overall integrity of the unit are maintained throughout shipment [36]. Shipping methods must be well-designed not only in order to preserve the quality and function of the UCB product but also to protect the safety of those involved in the shipping process [35]. The FDA, AABB, and FACT as well as the International Air Transport Association (IATA) and the U.S. Department of Transportation have established packaging and labeling requirements for shipping biologics [35, 36, 40, 41]. IATA requires that shipping containers withstand extreme external temperature variability and that the primary outer container be leakproof; additionally, containers must be constructed to resist breakage and durable enough to withstand pressure changes and trauma. An additional internal container with absorbent material to contain potential leaks/breaks must be included as well [35, 40].

The FDA Guidance and the AABB and FACT Standards provide more details of the requirements and recommendations for UCB banking, and the reader is encouraged to refer to these documents.

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Chapter 2
The Regulatory Situation for Academic Cell Therapy Facilities in Europe

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Abstract The European Legal and Regulatory Affairs (LRA) Committee of the International Society for Cellular Therapy (ISCT) has in its mission statement (see www.cellulartherapy.org) to serve those working in the field of cellular and gene therapy by being a source of information regarding compliance with European Union (EU) directives, local and professional regulations and by being a voice in the moderation of external regulation. One of our main goals is to keep ISCT members up to date on potential and actual changes in regulatory affairs and to respond to the authorities in open consultations on behalf of the membership.

In this chapter we outline the current issues with regard to the European Directives (EUD) and the proposal for Advanced Cell Therapies, which are of importance to cellular therapy facilities in Europe. We recognize that not all of the legislation is finalized, so we recommend readers visit our website for more information.

The European Union (EU) Directive on Quality and Safety of Tissue and Cells

Since cell therapy is a field which involves a worldwide exchange of products, an urgent need was felt within the European Community to have a unified regulatory framework ensuring high standards of quality and safety of tissues and cells.

The EU in collaboration with the Council of Europe, therefore, published the European Directive (EUD) 2004/23/EC entitled: "Setting standards on quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of tissues and cells" in the Official Journal of the European Union on April 7, 2004.

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The requirements set out in this Directive had to be translated into national law within the Member States before April 7, 2006.

Of importance for most cell therapy facilities is the fact that this EUD is applicable to all tissues including hematopoietic peripheral blood, umbilical-cord (blood) and bone marrow stem cells, reproductive cells (eggs, sperm), fetal tissues and cells, and adult and embryonic stem cells. It specifically excludes blood and blood products (other than hematopoietic progenitor cells), because these are regulated under 2002/98/EC and 2004/33/EC for blood and blood components. Also excluded are nonbanked organs, or parts of organs, and tissues and cells used as an autologous graft (removed and transplanted back within the same surgical procedure), or if the tissue is being used to provide the same biological function as it does in the human body. The EUD does not apply to research (animal studies) or to organs, tissues, and cells of animal origin.

The position of donor leukocytes for infusion after transplantation within the legal framework remained unclear for some time. Although the cells are harvested from the blood of healthy donors and fall within the description of "Blood Components," donor leukocytes are directed donations and collected from the original Hematopoietic Progenitor Cells (HPC) donor, usually at the original harvesting center. Donor leukocytes are not infused as a transfusion product, but are transplanted to enhance the graft-versus-leukemia/tumor effect. This distinguishes them from other blood components, and the decision was recently taken to include donor leukocytes under the EU Tissue and Cells Directive 2004/23/EC (Communicated at the Meeting of Competent Authorities, February 8, 2006).

In the 2004/23/EC Directive, the following items were addressed:

- Establishment of a register of entities operating in the field
- Designation of the competent authority (ies) in Member States
- Implementation of a quality system for tissue establishments (e.g., Standard Operating Procedures (SOPs), guidelines, training & reference manuals, reporting forms, donor records.)
- Introduction of a system of accreditation of tissue establishments by Member States and a system for notification of adverse events and reactions
- Organization of inspections and control measures within Member States
- Assurance of data protection and confidentiality
- Assurance of traceability of tissues and cells through laboratory identification procedures, record maintenance, and an appropriate labeling system
- Design of a single European coding system

However, there are two main issues that will probably need further regulation: the import and export of cells as described in Article 9 and the single European coding system.

In Article 9.4, it is stated that the competent authority "shall take all necessary measures to ensure that imports and exports of tissues and cells from/to third countries meet quality and safety standards equivalent to those laid down in this Directive." The World Marrow Donor Association (WMDA) has reported on the

international exchange of hematopoietic progenitor cells. In its 2004 annual report, the Association stated that currently 28.7% of all HPC imported to EU/EEA countries were from third countries, while 39.5% of exported products were sent to third countries.

To date, most of the collection sites for cellular products do not have a license to demonstrate that they fulfill the EUD criteria. Accreditation by organizations such as JACIE (Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Group for Blood and Marrow Transplantation (EBMT)) or FACT (Foundation for the Accreditation of Cellular Therapy) using their combined standards would ensure facility directors that accredited collection sites fulfill all EU requirements. Unfortunately, these organizations will not be able to inspect and accredit every collection site within the near future. Moreover, cell therapy facilities will not be able to individually inspect a collection center against the requirements of the EUD within the time frame of an allogeneic stem cell transplant. This has led to differing interpretations by the competent authorities within the Member States of the EU, ranging from the immediate cessation of importation of cells from third countries to no measures being introduced at all (e.g., in Belgium, and the Netherlands).

Recognizing that these problems cannot be overcome by any single professional organization, an alliance has been formed called Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA), in which JACIE, FACT, WMDA, ISCT-Europe and ISCT, EBMT, American Society for Blood and Marrow Transplantation (ASBMT), FACT-Netcord, and AABB (formerly the American Association of Blood Banks) are attempting to agree on a global set of standards. At the moment, AHCTA is in the process of defining minimal requirements, as a basis for self-evaluation of collection sites (see website www.AHCTA.org) in order to assist the Commission. The European Commission has decided that another Directive for the import and export to third countries will be necessary and is currently engaged in a consultation process.

The second issue to be further examined by the European Commission relates to the development of a single coding system for tissue and cell products. Difficulties arise because the import and export of cells does not only involve European countries; HPC and Donor Lymphocyte Infusion (DLI) are exchanged globally. Fortunately, there already exists an international coding and labeling system, called ISBT 128 (see www.iccbba.com). This coding system is used by blood banks and tissue banks primarily to code and label their products. A technical advisory group was established to look at cellular therapy products and define terminology, develop appropriate labels, and assist with the implementation in cellular therapy facilities [1,2]. The European Commission (DG Sanco) has established a working group to develop guidelines and to make specific recommendations. A European Committee for Standardization/Information Society Standardization System (CEN/ISSS) workshop was held in Brussels in April 2006 on coding of information and traceability of human tissues and cells, with the aim of developing specifications for a European coding system and its implementation. In November 2007, the Project Team published a workshop draft for open consultation, in which

they recommend the use of the ISBT 128 coding and labeling system, because of its proven utility in the face of the evolving demands. Plans are under way to implement the single European coding system according to the EUD.

Following the publication of the EUD 2004/23/EC (also called the mother directive) it took a great deal of time to publish the technical annexes, which describe the implementation of the EUD. These technical annexes were divided into two parts. The first part (EUD 2006/17) was published on February 8, 2006, and deals with the technical requirements for the donation, procurement, and testing of human tissues and cells, including the donor selection and evaluation criteria. Member States were instructed to bring into force laws, regulations, and administrative provisions necessary to comply with this Directive by November 1, 2006.

The main difficulty within this EUD for cell therapy facilities is the timing of the testing of donor leukocytes for infusion. Since the decision was made that these will fall under this directive, the timing of the infectious disease marker testing is clear (within 30 days prior to donation), but differs from the Food and Drug Administration (FDA) requirement that they should be tested within 7 days before the collection.

The second Technical annex (EUD 2006/86/EC) was published on October 25, 2006, and defines the traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for the coding, processing, preservation, storage, and distribution of human tissues and cells. Member States had to implement this Directive before September 1, 2007 and the single European coding system needed to be in place.

The major issue for cellular therapy facilities is the required air quality standard. It is stated that: "...where cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A as defined in the current European Guide to Good Manufacturing Practice (GMP), Annex 1 and Commission Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue/cell concerned, but at least equivalent to GMP Grade D in terms of particles and microbial counts." Results from laboratories processing cells in a laminar airflow (LAF) cabinet in a clean laboratory without pressure hierarchy, did not reveal significant microbiological contamination of their products (Mark Lowdell, abstract, EBMT 2007). Studies have been reported comparing microbiological contamination rates before and after the time at which operations were moved to cleanrooms. These showed no change in microbiological contamination of the products (E. Baudoux et al., abstract, ISCT 2006).

The EU Medicinal Products Directive

The EU Directive 2001/83/EC regulates products that are classified as medicinal products (MP). This includes somatic cell therapy MPs and gene therapy MPs.

The Directive defines a medicinal product as any substance or combination of substances presented for treating or preventing disease in human beings. Furthermore, it is stated that any substance or combination of substances, which

may be administered to human beings with a view to making medical diagnosis or for *restoring, correcting, or modifying physiological functions* in human beings, is likewise considered a medicinal product. Although it could be interpreted that hematopoietic progenitor cells and donor leukocytes for infusion fall under this description, they are in fact ruled out by the statement that this EUD shall not apply to blood cells of human origin. Furthermore, the definition section describes medicinal products derived from human blood or human plasma, as medicinal products based on blood constituents, which are *prepared industrially by public or private establishments*. The lack of description of "industrially prepared" has resulted in different interpretations within the Member States (MS) and has in turn generated a great diversity of approaches across Europe (see Fig. 2.1).

	Country	Austria	Belgium	Bulgaria	Cyprus	Finland	France	Germany	Ireland	Netherlands	Poland	Slovakia	Spain	Sweden	UK
framework	not at all			● ●	● ●				● ●	● ●	● ●	●			
	as medicinal product (MP)	● ●	● ●			● ●		● ●							
	as medical device (MD)														
	As MP or MD, decided on case- by-case basis												● ●	● ●	● ●
	specific national guidance						● ●								
	other regulations											●			● ●
authorisation	by product authorisation (PA)		●					●							
	by manufacturing authorisation (MA)	● ●						● ●							
	by accreditation…of the tissue establishment		● ●									●			
	by PA and MA						● ●	●					● ●		
import	from EU MS mandatory through accredited… tissue establishment in your country		● ●				● ●					●	● ●		
	from non-EU country mandatory through accredited… tissue establishment in your country		● ●				● ●					●	● ●		

● **autologous products** ● **allogeneic products**

Fig. 2.1 Differences in approach to cell therapy product regulation in Europe (Ref: Joint Research Centre, European Commission 2004)

Somatic cell therapy MPs must fulfill the criterion of being manipulated to achieve substantial alteration of their biological characteristics. These manipulations include culture, growth factor treatment, differentiation/dedifferentiation, or stimulation/activation. The consequences of this are that a GMP environment is required for the generation of a large number of cellular therapy products such as dendritic cells, mesenchymal stromal cells, or even stimulated DLI.

In some Member States a manufacturing authorization (GMP) is not needed, because a hospital exemption applies, or because the MP is manufactured and administered by an individual physician (for example, in Germany). Furthermore,

MP regulations do not apply to distribution of MPs by an individual physician in a single department/hospital (directed use).

To add to the confusion, recently the European Pharmacopoeia has published general methods of analysis for cellular products, including flow cytometry (2.7.24), microbiological control of cellular products, and a monograph on human hematopoietic stem cells (MG 2323). So far, there is no legal background for the document to classify HPC under medicinal products. Furthermore, the appropriateness of such a document can be challenged in the absence of alternative products for a specific patient.

Advanced Cell Therapies

On November 16, 2005, the EU and the Council of Europe launched a proposal for the regulation of advanced therapy MPs. The intention of this proposal is to unify the regulatory framework for medical devices, tissue engineering, and medicinal products, including cellular and gene therapy products. This initiative is required due to the regulatory gap for tissue-engineered products (see Fig. 2.2) as well as the rather broad spectrum of legal and regulatory implementation in the different Member States (see Fig. 2.1).

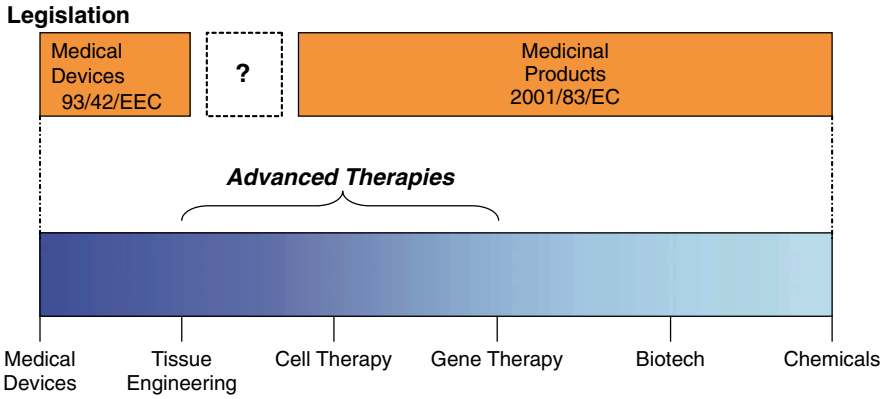

Fig. 2.2 The regulatory gap (Advanced cell therapies)

Basic elements of this regulation are: the marketing of these products will be subject to approval; there will be a new scientific committee established within EMEA; technical requirements for the quality, safety, and efficacy of the products will be defined and long-term traceability and risk management will be executed. The EUD 2004/23 is applicable for the donation, procurement, and testing of the tissues and cells contained in these products.

The definition of substantial versus nonsubstantial manipulation (centrifugation, cell separation, concentration or purification, and cryopreservation) again poses some difficulties. Article 5 of this Regulation states that the scope should be to

regulate advanced therapy MPs, which are intended to be placed on the market in Member States and either prepared industrially, or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC.

Advanced therapy MPs which are prepared in full in a hospital in a nonprofit manner, and on a one-off basis, according to a specific, nonstandardized and nonpatented process, and used in a hospital, in order to comply with an individual medical prescription for an individual patient under the exclusive professional responsibility of a medical practitioner or for clinical research, should be excluded from the scope of this Regulation. The report was adopted by the Environment, Public Health and Food Safety Committee of the European Parliament on January 30, 2007, and formally adopted by the Council on October 30, 2007. The Regulation on advanced therapy MPs (Regulation (EC) No. 1394/2007) was published in the Official Journal on October 11, 2007, and applies from December 30, 2008.

In summary, the individual interpretation of the EUD by the Member States has had a great impact on the legal requirements for all academic cell therapy facilities within Europe. In the last part of this chapter, the position of cell therapy facilities within France is described as an example of the current status.

An Example of European Regulatory Status – The Situation in France

French regulations consider therapeutic products prepared from human living cells and tissues either as drugs produced and marketed by pharmaceutical companies or biotechnology companies, and regulated as such, or as "cell therapy preparations" (CTP). The latter are mostly produced and distributed by cell therapy facilities that are operated either by the Public National Blood Bank Agency (Etablissement Français du Sang, EFS – approximately two-thirds of existing facilities), or by public university hospitals or private not-for-profit hospitals, including cancer research centers (approximately one-third of existing facilities). Only a few private companies operate in this field.

Since 1998 and the transformation of the Agence du Médicament (French Drug Agency) in the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) by the French government, the latter is in charge of regulation and authorization of cell therapy facilities. Authorizations are mandatory at three levels: facilities, CTPs, and biomedical research involving the use of CTPs as therapeutic agents. Laws that described and established the process to obtain these authorizations were published in February 2003. Existing facilities at that time filed applications with the agency by the deadline of July 2003. The process turned out to be lengthy and has still not fully been completed, although most operating facilities have now received an answer from AFSSaPS. Authorization or the failure of authorization results from a multistep process that includes validation of the application form, on-site inspection by AFSSaPS inspectors, file review by the "Agence de Biomédecine" (ABM – another public agency devoted, among other missions, to the facilitation and pro-

motion of organ, tissue, and cell transplantation in France (formerly "Etablissement Français des Greffes," EFG) and the "Commission de Thérapie Cellulaire et Génique" – a panel of public agency officials and of experts in the field of cell therapy), before the final decision is made by the AFSSaPS director. Authorization is valid for 5 years. Authorizations are granted based on evaluation of operations in the cell therapy facility, and compliance with regulations designed to ensure the safety and efficacy of CTPs. The most important regulation is the set of "GMPs" described in a law published in December 1998, and that are currently being revised at the time when the European Directive is being translated into national regulations. Current GMPs require strict separation of activities in the fields of cell processing and quality control, the need to establish a quality assurance policy, and distinction between three levels of complexity in cell processing (level 1 – minimally manipulated CTPs; level 2 – validated processes with CE-marked devices and reagents; and level 3 – experimental or nonvalidated processes, or processes involving one or several steps in open systems) with different requirements in terms of environmental controls: ISO 14644-1 class 8 (Class D) for levels 1 and 2; ISO 14644-1 class 7 (Class C) for level 3, personnel working under class II laminar-air flow microbiological safety cabinets in all situations. Compliance with general rules for cell or tissue procurement is also carefully scrutinized, and includes, at a minimum, donor information, consent and screening, as well as traceability of cells and tissues. Authorized facilities are currently filing with AFSSaPS to obtain authorization for CTP production; for example, for autologous hematopoietic stem and progenitor cells, allogeneic stem and progenitor cells, T-cell-depleted allogeneic hematopoietic stem and progenitor cells, autologous endothelial progenitor cells, etc. In addtion, tissue banks must also register and obtain an authorization from AFSSaPS to pursue their operations, and hospitals must obtain an authorization to collect marrow cells for transplantation. Finally, ancillary products ("Produits Thérapeutiques Annexes" or PTA) are the subject of recent and separate regulations to ensure their safety and efficacy.

As mentioned previously, the process is not fully completed, more than 9 years after the publication of the law creating AFSSaPS and defining its missions, and over 4 1/2 years after publication of the set of laws that describe the pathway to obtain authorization. Nevertheless, this had led many French academic cell therapy facilities to review and reorganize their operations, and to upgrade their cleanrooms. It is generally accepted that transcription of recently issued European directives into French regulations and other European publications, such as monographs from the European Pharmacopoeia Commission, will have little effect on routine operations over the next few years.

In addition to the described authorization processes, laboratories in charge of quality control must participate in a national quality control program for $CD34^+$ enumeration and microbiological assays for CTP, again coordinated and evaluated by AFSSaPS. In 2003, another law was issued that described the organization of "Bio-vigilance" in France; it aims at recording, notifying, investigating, and alerting the professional community about the occurrence of major or minor adverse reactions or events associated with cell, tissue, or organ transplantation, and completes the national organization of vigilance for other therapeutic products (e.g., drugs, blood products, biomedical devices, reagents, cosmetics). It requires that each

hospital or laboratory involved in collection, distribution, or transplantation of cells, tissues, or organs designate an individual responsible for the task of identifying, reporting, and investigating such adverse events. Coordination at the national level, evaluation, and design of corrective actions is under the responsibility of AFSSaPS and a panel of experts, government and agency officials, and patient representatives (Commission Nationale de Bio-vigilance). Activities in all aspects of transplantation (collection, processing, and transplantation) are annually reported by each French hospital or institution to the ABM, which publishes an annual report, and maintains a list of hospitals that are authorized for collection and transplantation of human cells.

Many cell therapy facilities and transplant programs have already exceeded the legal requirements, by obtaining an ISO 9001 certification or JACIE accreditation; as of August 2006, 12 French hematopoietic cell transplantation programs are JACIE accredited, out of a total of more than 50 centers. As a result of these efforts, French facilities have significantly improved their operations over the last few years; however, much remains to be done, especially for smaller facilities that have difficulty in securing the resources needed to comply with modern regulations and participation in the validation and establishment of innovative, complex, and sophisticated processes for the development of cell therapy in oncology or other medical fields.

Links

- International Society for Cellular Therapy: www.celltherapysociety.org
- Joint Accreditation Committee of ISCT and EBMT: www.jacie.org
- European Group for Blood and Marrow Transplantation: www.ebmt.org
- Alliance for Harmonisation of Cellular Therapy Accreditation: www.ahcta.org
- European Committee for Standardisation: CEN workshop on coding: www.cen.eu/isss
- ISBT 128 labeling: http://www.iccbba.org/cellulartherapy_home.html
- World Marrow Donor Association: www.worldmarrow.org
- Information on the tissue and cells directive: European Commission, DG Health and Consumer Protection: http://ec.europa.eu/health/ph_threats/human_substance/legal_tissues_cells_en.htm
- Advanced Therapies Tissue Engineering, Cell Therapy and Gene Therapy: http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm

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Chapter 3
A Regulatory System for Cell and Tissue Therapies: Proposed Approach in Australia

A. Farrugia

Abstract In Australia, the Therapeutic Goods Administration (TGA) is responsible for the regulation of therapeutic goods under the provisions of the Therapeutic Goods Act 1989. Health care policy in Australia is the collective responsibility of the governments of the Australian federation. In 2002, the federation directed the TGA to develop a suitable regulatory model for human cell, tissue, and emerging biological therapies. As the process for developing the model evolved, a parallel process was begun to establish a common regulatory agency for Australia and New Zealand through a joint Australia and New Zealand Therapeutic Products Authority (ANZTPA). The particular problems of regulating complex biological therapeutics, subject to intense governmental and public interest, within an agency structured and skilled based on the needs of the traditional pharmaceutical sector will be described in this chapter.

Introduction

Government regulation of the therapeutics industry remains a surprisingly established feature of public health care policy. In the face of the predominant deregulatory philosophy underpinning much of Western governmental agendas of the past 30 years, the oversight of the therapeutics sector has proven to be remarkably resilient. Even the occasional challenges resulting from review processes appear half-hearted and more questioning of detail rather than broad principles [1]. Why this should

Disclaimer: Any views expressed in this chapter are the author's, and are not necessarily reflective of any area of policy of the Australian Government

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be is beyond the scope of this review; it is likely due to a combination of various converging factors. The ever-present concerns of the "worried well" [2] regarding their health includes an interest in the medical products they consume avidly to preserve it. The unfortunate episodes of adverse events associated with such products justify the public's expectation that government serves to protect and assure them on issues of product safety. Although Western governments have been deregulatory in their approach in recent times, they have also not hesitated to employ the supposedly independent role of product regulators in managing other pressures, such as costs and industry protection. While in most instances regulatory agencies are by law separate from the policy and funding areas of government, the distinction between what constitutes "policy" and "regulation" generates a perpetual tension within government. Regulators are government officials, charged, like all their fellow bureaucrats, with the core task of implementing the policy of the government of the day and getting it reelected. Thus, the evidence-based decision making, which is supposedly the foundation of the regulator's responsibility to assure the safety, quality, and efficacy of therapeutic products, has of necessity been colored by the societal – and hence political – considerations which become evident when products of significant public interest are under review. The fact that this may occasionally lead to developments that draw public anger toward the regulator is generally ignored [3], and has now become accepted by regulatory agencies as an occupational hazard.

This complex nexus of processes and tensions has led to a system which, in most countries, works fairly uneventfully for mainstream medicines and medical devices. The established paradigm for assessing the safety, quality, and efficacy of medicines draws on a number of widely accepted concepts, such as Good Manufacturing Practices (GMP) during production, clinical trials to support claims, and preclinical assessments (such as toxicology and physicochemical characterization). The particular features of medical devices have required variations on the same themes, such as the system of conformity assessment now accepted in Europe and Australia [4].

Regulatory agencies are, in general, comfortable with these established product groups, and so are the regulated manufacturers. The regulatory profession itself, whether within government or industry, constitutes a sector in its own right, with substantial infrastructure and associated professional organizations and career paths. The level of comfort associated with "traditional" pharmaceuticals has not yet been achieved for the rapidly emerging biological therapies. These are frequently the result of innovations that have not necessarily come from the mainstream therapeutics industry. These therapies, exemplified by the areas of tissue engineering and cellular therapies, are not easily assimilated within the traditional medicines and devices frameworks, despite all being definable as medicines (physiological action) or devices (structural action). The level of public/political interest in these therapies is intense, and their potential use to treat conditions that cause significant morbidity and mortality further accentuates their difference from mainstream pharmaceutical development, which in recent years has focused on established agents – so-called "me too" drugs [5]. Regulators have, therefore, had to struggle with the need to

adapt, and in many instances, discard, known and loved ways of doing business with their traditional "clients".[1]

In many instances, new and not as easily accommodated clients have appeared. These include the academic sector, clinical investigators, and governments themselves, through their funding and oversight of institutions who are developing these therapies. The mainstream pharmaceutical sector has also engaged in this new area, contributing to the rich mix of players who form part of the novel environment requiring attention by regulators.

A Digression – The Regulation of Therapeutic Goods in Australia

The Australian Commonwealth is a federation of six States and two Territories.[2] The States and, to a somewhat lesser extent, the Territories are the governmental entities that deliver health care services in Australia's social market economy. Health care policy and delivery in Australia, therefore, involves the eight separate governments of these jurisdictions. The central government, based in the capital Canberra, provides overall coordination, global policy direction – and most of the funding.

As with most federations, the Australian jurisdictions jealously guard their individual systems and compete actively for central government funding while, somewhat perversely, maintaining a distant and suspicious attitude toward Canberra's control. Health care policy and decision making in Australia involve a complex and tortuous process of consultation and negotiation between the jurisdictions and the central government, with the ultimate aim of as wide a consensus as possible. Since this is rarely reached, some processes drag on for many years with substantial delays in the implementation of important policies.[3] The rapid turnover of both elected ministers and their bureaucratic advisors also contributes to the constant element of instability in the process.

In 1989, the central government, after negotiation with the other jurisdictions, introduced an Act of Parliament – the Therapeutic Goods Act – which became law in 1991. This created a national authority – the Therapeutic Goods Administration (TGA) – to regulate therapeutic products used across the country. Successive governments over the 1990s established for the TGA the principle of cost recovery from the regulated sector, a policy which currently enjoys partisan support across the Australian political divide.[4]

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[1] As governments, including that of Australia, have tended to introduce cost-recovery from the regulated sector as a way of paying for regulation, the concept of the public as the regulator's client has, perforce, had to take a modified role.

[2] The States of New South Wales, Victoria, Queensland, South Australia, Western Australia, and Tasmania, and the Northern Territory and the Australian Capital Territory.

[3] As an example, it is part of the Australian policy apocrypha that a decision to allow the importation of apples from New Zealand has been "maturing" for 80 years.

[4] Which consists currently of a center-left government opposed to a center-right opposition. The left-wing Green party opposes this policy, For a brief period during 2007-08, all the jurisdictions

The Therapeutic Goods Act imposes regulation on two classes of therapeutic goods – medicines and medical devices,[5] through a nexus of pre- and postmarket arrangements similar to those in Europe and North America. Premarket assessment involves review of scientific data and evidence of safety, quality, and efficacy, including evidence of GMP, alignment to product quality standards, and assessment of therapeutic claims. The ultimate product of this procedure, following review of the agency's evaluation by an independent committee, is approval to enter the Australian market by listing on the Australian Register for Therapeutic Goods. For the majority of approved goods, a separate and sequential process occurs to determine if approved products are to be given public subsidy in line with Australia's current policy of providing health care through government intervention and financing.

This system delivers effective outcomes for the majority of therapeutic goods which are conventional pharmaceuticals. The Australian States and Territories take little interest in the process as it regulates goods which ultimately are used by residents and patients in their individual jurisdictions, but for which they do not pay. When the TGA engages in areas that are more directly affected by individual jurisdictional policy, the States and Territories take a keen interest in the process. This has had a substantial effect on the regulation of biological therapies.

Current Regulation of Biological Therapies in Australia

In this chapter, "biological therapies" are defined as those therapeutic products derived from cells and tissues. These are currently regulated in a heterogeneous fashion across the TGA. This is due to a number of factors:

1. Since the Therapeutic Goods Act recognizes only medicines or medical devices, subtitle cell and tissue products are regulated as one or the other of these types of goods, depending on whether their action is pharmacological or structural. Since the regulatory system for medicines and devices is quite different (refer to Global Harmonization Task Force (GHTF) Global Device Regulatory Model – www.ghtf.org), this results in products which, while broadly similar in terms of safety concerns, go through different regulatory routes. As an extreme example, fibrin sealant which is applied topically is classified as a device, while the same agent applied internally is a medicine.
2. The difficulties inherent in the "pharmaceutical" classification of cells and tissues were judged to require an approach which did not include product premarket approval. This is an understandable position from regulatory authorities familiar with batch-based pharmaceuticals, and has been followed by similar agencies in North America.

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were governed by the centre-left Labour Party, a situation which did not enhance significantly the level of national consensus on health policy.

[5] Go to www.tga.gov.au for more information on the Australian regulatory system.

In the TGA it resulted in the use of facility licensure through oversight of GMP as the sole regulatory tool for banked unmanipulated cells and tissues. A similar approach was adopted for the fresh components of blood. The GMP framework was underpinned by a code of GMP for human blood and tissues. This was developed primarily with the requirements of the banked blood sector in mind. This led to a regulatory framework for cells and tissues that was fairly minimalist. The resulting absence of premarket assessment for safety and quality, not to mention efficacy, leads to a lack of appreciation of the particular features of these products, as will be discussed further.

3. Manipulated cells and tissues with a medicinal action are exempt from premarket review if they are autologous, unless they constitute gene therapies. They are still subject to GMP assessment, which is also aligned to the Human Blood and Tissues code. If they are non-autologous, they are subject to product assessment which, because of the way in which the TGA assesses medicines, is done on the basis of clinical indication. For example, a cell-based vaccine against melanoma will go down a different regulatory path from a hematopoietic progenitor cell for myocardial regeneration [6]. The clinical development of such products is clearly different. Manufacturing principles for experimental biological therapies would require a commonality which is best based on a common regulatory pathway.

A particular issue in the current arrangements centers on the exemption for autologous medicines. This is based on the concept of medicines as *extemporaneously compounded* [7] for specified individuals, thereby exempting autologous and directed therapies. The intent of this provision was to exempt the practice of preparation of pharmaceuticals in hospitals from the oversight of the national regulatory authority. It was considered that, in the Australian jurisdictional system, this was the responsibility of the State and Territory governments' regulations for hospital accreditation. Nevertheless, this wording is such that it exempts any therapies which are definable as autologous or directed medicines from the process of premarket approval. This exemption does not, however, extend to the process of manufacturing licensure, when manufacturing is not performed directly by a physician or pharmacist. This results in considerable and unnecessary regulatory uncertainty in facilities producing these therapies.

It should be noted that gene therapies are excluded from the exemption and, therefore, require full premarket approval as well as manufacturing licensure. As these therapies are classified as medicines, the current process for the assessment of safety, quality, and efficacy for medicines, including those for assessing the clinical development phase and the relevant code for GMP, apply to gene therapies [8]. Readers of this chapter will be sufficiently versed in the field to recognize the difficulties inherent in this approach. Further examples of the uncertainties generated by the current provisions are described by the TGA on http://www.tga.gov.au/consult/2004/hctpris.pdf.

In summary, the regulatory process that was developed with the needs of the mainstream pharmaceutical sector in mind presents several difficulties for the appropriate oversight of emerging experimental cell and tissue-based therapies.

Over the late 1990s, the TGA shared the experience of other regulatory agencies in recognizing and addressing this by development of a new regulatory framework for these therapies and including them in a broad new class of biological therapeutic goods.

Development of a Regulatory Framework for Cell and Tissue Therapies in Australia

As a result of a growing awareness of the limitations of current provisions outlined above, the TGA initiated a process that led in July 2002 to the primary body for setting health care policy – the Australian Health Ministers' Council – to request the agency to develop an appropriate regulatory framework for cell and tissue therapies. Following extensive public consultation a framework was developed which has been described by Farrugia [9] and Zheng et al. [10].

A global definition of cell and tissue therapies as:

> articles containing or consisting of, or derived from, human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient

resulted in a classification of *all* therapeutic goods covered by the definition (Fig. 3.1). The level of regulatory oversight associated with each class (Fig. 3.2) is intended to recognize the different risk:benefit ratios associated with the respective

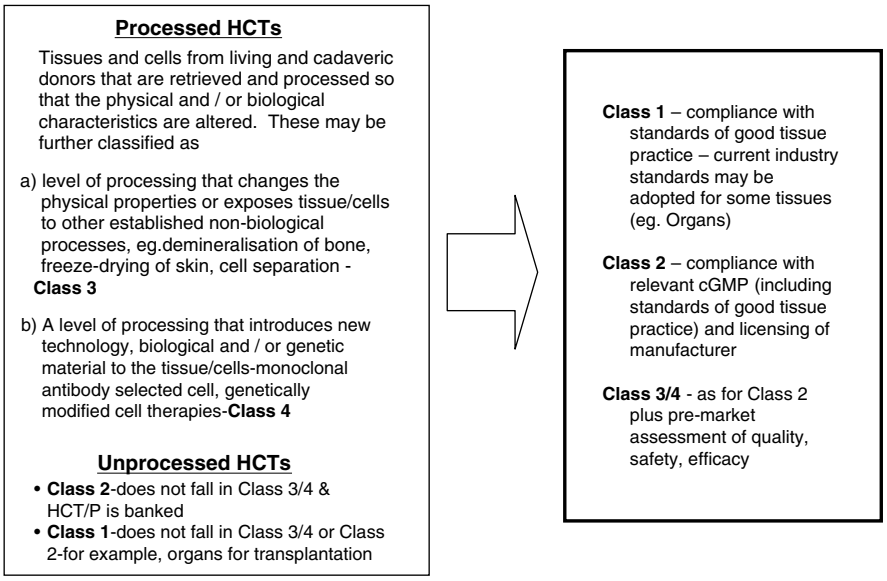


Fig. 3.1 Proposed classification and regulation of cell and tissue therapies in Australia

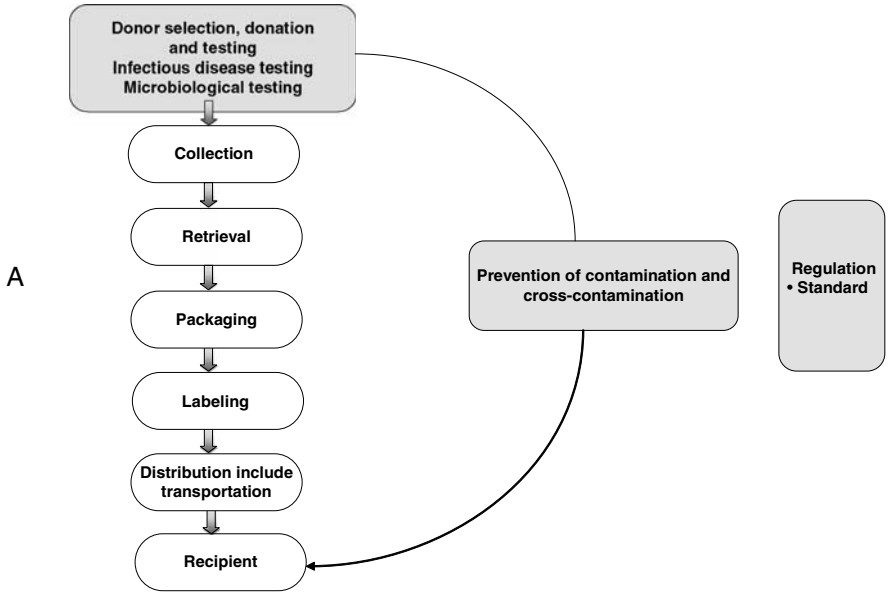


Fig. 3.2 Relationship of product class to regulatory measures. **a**. Class 1 products include minimally manipulated human cells and tissues for direct transplantation such as whole organs, bone marrow, and reproductive tissue. Currently, these human cells and tissues are not regulated by the government although they are products that are also the starting materials for regulated human cells and tissues. The basis of their regulation in the proposed approach is adherence to professional standards for compliance with practices that focus on the minimization of infectious disease risk. **b**. Class 2 products are processed and banked, but do not have their basic physical or pharmacological properties altered. They include the products of mainstream tissue banking such as bone, corneas, and skin. These are currently under the Therapeutic Goods Administration's oversight through alignment to a code of Good Manufacturing Practice. In the new system alignment to quality system principles, which will be overseen by the regulator, will be retained in addition to adhering to standards for product quality, which will be specific to the different products. Assurance of the product quality before its release to end-users will be through assessment by the regulator of data complied into a data dossier by the manufacturer. **c**. Class 3 products have been extensively processed to a stage that changes their physical properties or exposes them to other established nonbiological processes, but where this processing does not alter their genetic or pharmacological properties. Included in Class 3 are products such as dematerialized bone, lyophilized skin, and pancreatic islet preparations. This class will be regulated in the same way as Class 2, with an additional level of assessment of therapeutic claims. Such an assessment will not necessarily include formal clinical trials. **d**. In Class 4, the level of processing results in the introduction of biological or genetic material in the HCT/P and/or uses new technology. This class, therefore, is the highest level of manipulation and is regulated through the measures described for Class 3 with the addition of a higher level of scrutiny of claims of efficacy and therapeutic effect, which will be assessed by the regulator through formal clinical trials adapted for these products. QC = quality control

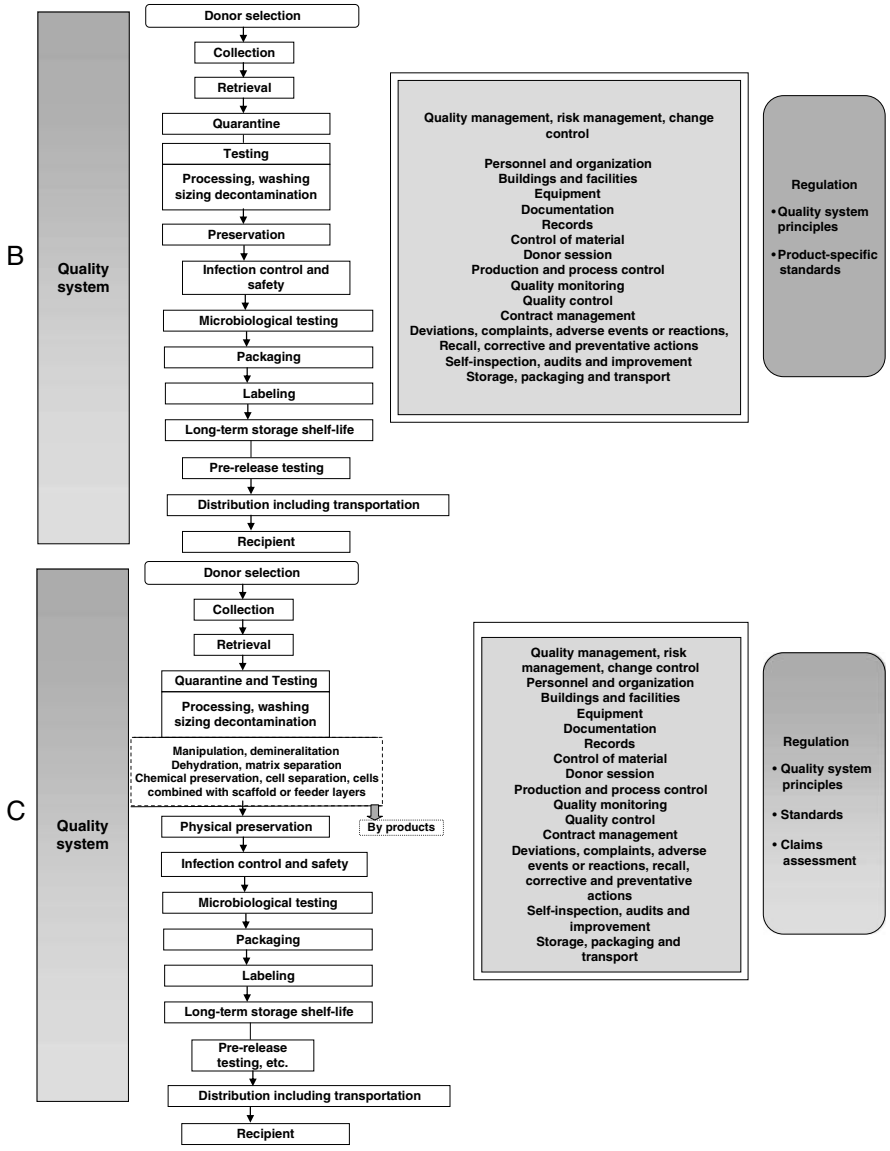
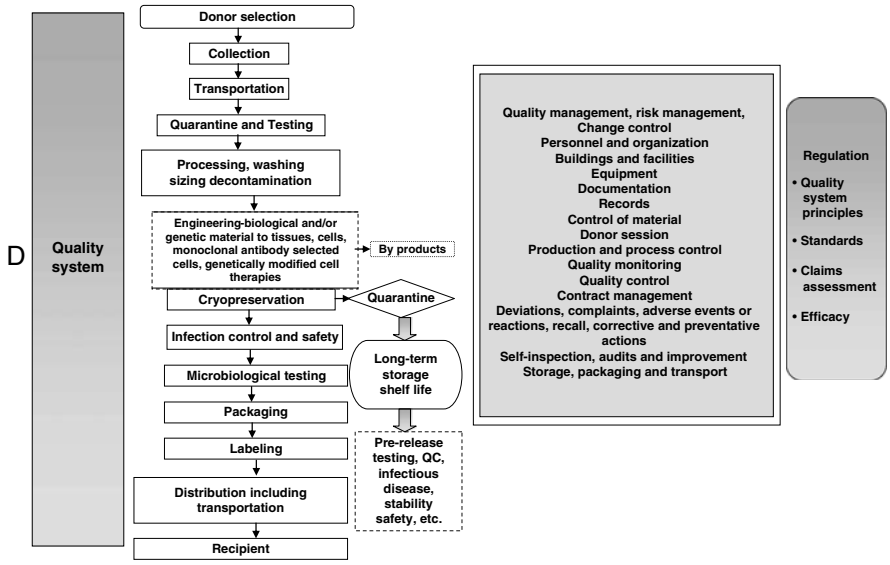


Fig. 3.2 (continued)

classes. For example, the scarcity of whole organs,[6] the general sensitivity toward considering reproductive tissue as a "therapeutic good" [11], leads to the oversight

[6]Regrettably, Australia is 12th out of a list of 14 OECD countries in terms of organ donation levels. See *MJA* 2006; 185(5): 250–254.



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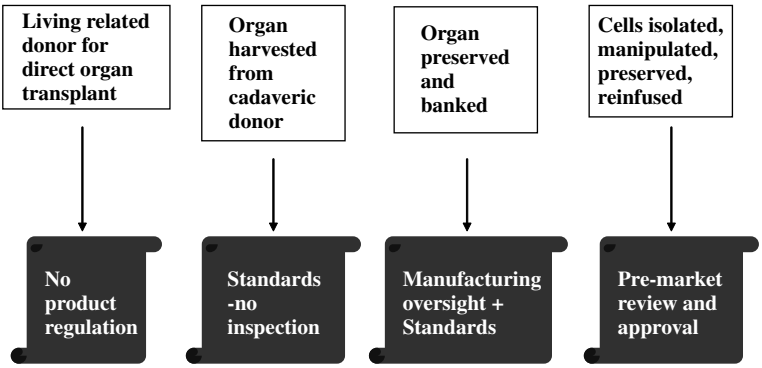

Fig. 3.3 Staged regulation of human cells and tissues

of these products being limited to ensuring the minimization of the risk transmission of infectious disease. As the cell/tissue products are subjected to a higher level processing and/or potential for exposure to increasing numbers of patients through banking, etc., a higher level of oversight is introduced, through assessment of the manufacturing process, premarket product review, and justification of therapeutic claims. A schematic representation of a progression through the regulatory scheme is shown in Fig. 3.3.

While readers are referred to other publications for more detail [9], [10], some issues arose during the consultation process, preceding the development of the framework, which are still under review with the relevant stakeholders. These will be discussed as they illustrate some of the problems associated with this complex area.

Assessment of the Manufacturing Process

As described above, the current code of GMP for Human Cells and Tissues was originally developed for the homologous banked blood and tissue sector. The manufacture of any products that were clearly definable as medicines was subject to the same GMP code as other medicinal products. This manufacturing assessment framework was unsuitable for cell and tissue-based therapeutics, although it included features of quality system management that were clearly desirable and, one might argue, attainable, by any producer of therapeutic goods for human use. The development of the new framework, therefore, provided an opportunity to devise new manufacturing principles more suited to cells and tissues. Specifically, requirements that are better aligned to product quality for premarket review purposes have been excerpted from the current codes to be incorporated into product standards. The proposed new manufacturing principles are thus limited to general principles of good practice that should be common for all cell and tissue facilities.

Oversight of Clinical Development

The conventional pathway for clinical development of a therapeutic [12] poses several challenges for cell and tissue-based therapies. Two particular aspects have engaged the Australian regulator in recent times. The phase of development at which GMP is required by the manufacturing facility has been conventionally considered at Phase II and above, with Phase I trials being exempt. With cellular therapies, where the transition between the phases has been at different time frames than those of traditional pharmaceuticals, this approach has been difficult to apply. The difficulties encountered by facilities in satisfying GMP when transitioning a trial from Phase I to II are undeniable.[7] The manufacture of therapeutic goods for human use requires good practices, and while regulators have recognized the need to align the manufacturing principles to the special features of the sector, the requirement for specialized facilities to manufacture these products from their earliest phase of development, has tended to concentrate trials into well-resourced and accredited facilities. This has resulted in the concept that regulation is "manipulating the market," which has provoked some resistance; however, it is difficult to justify conduct of trials by facilities that lack proper practices. The current practice of limiting oversight of many somatic cell therapy trials to that provided by hospital ethics committees is also under review. It is likely that all such trials will require regulatory approval.

The proposed regulatory infrastructure for cell and tissue therapies attempts to address the unique characteristics of these products through a suitably adjusted set of principles. In the end, regulation is somewhat analogous to pregnancy, in that

[7]Examples include facilities engaged in developing anti-cancer cell-based vaccines where the Phase I subjects are patients with the disease.

there is little room for ambiguity. Recognition of all the competing tensions posed by the needs for innovation, supply of essential therapeutics, small patient numbers, and the public/research origin of many of these therapies has strongly influenced the development of the TGA's proposed approach. It is hoped that a productive balance between the need to protect public health while enhancing access can be attained.

Conclusion

This chapter has attempted to draw out the dependence of regulatory progression on the political process. The policy described for cells and tissues has not been insulated from this, with an attempt to create a joint regulatory agency between Australia and New Zealand, now in abeyance, influencing progress. The ultimate manifestation of democracy – an Australian election resulting in a change of government – generated further delays. It is, therefore, satisfactory to end this work with the news of the new government's endorsement of the framework described herein for cells and banked tissues, communicated in June 2008. Other therapies such as whole organs and reproductive technologies will continue to be the subject of policy rumination, during which they will remain out of the regulator's purview. Still, to paraphrase Meatloaf, "Two out of three ain't bad."

Work is under way to establish a new part of the TGA that will address the needs for these products within an environment which includes other biologically derived therapeutics, such as blood, vaccines, etc. This should be analogous to the regulatory approach adopted in Europe and North America. All these developments will contribute, hopefully, to harmonization and the ability to facilitate access to these therapies on an international basis.

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Part II
GMP Facility Design

Chapter 4
University of Minnesota – Molecular and Cellular Therapeutics (MCT)

D.H. McKenna, Jr.

Abstract Facilities must maintain compliance with regulatory standards while maintaining flexibility to manufacture a variety of therapeutic cell types for clinical trials. Careful planning is required when designing a new or modifying an existing facility to maintain compliance with good manufacturing practice/good tissue practice (GMP/GTP) regulations. Likewise, considerable forethought is essential to meet current and anticipate future manufacturing requirements. If these goals are not clearly defined, any new construction or modifications may fail to meet demands. The choice to design a new facility or modify an existing one is often driven by the institutional constraints. There are unique issues associated with both approaches. This chapter focuses on the 36,000 ft^2 purpose-built stand-alone facility model in place at the University of Minnesota. This facility currently manufactures a wide range of cellular products that support 80 clinical studies.

Overview

Molecular and Cellular Therapeutics (MCT) of the University of Minnesota (Fig. 4.1) is a "stand-alone" biotherapeutics engineering facility that operates under current Good Manufacturing Practices (cGMP) [1]. It was established in 1992 to manufacture a single product, antilymphocyte globulin (ALG), a therapeutic antibody used in transplantation medicine. The facility was subsequently modified to become a multiproduct facility in 1996. The building is 36,000 ft^2 with approximately 12,000 ft^2 of production space. Approximately 1000 biologic products are manufactured annually to support approximately 80 clinical protocols, several of which are under investigational new drug (IND) status. Current products manufactured under IND include natural killer (NK) cells [CD3-depleted apheresis and

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Fig. 4.1 Molecular and Cellular Therapeutics (MCT), University of Minnesota, Saint Paul, MN

umbilical cord blood (UCB)] [2,3], allogeneic large multivalent immunogen tumor vaccine (melanoma and breast cancer) [4], UCB-derived T regulatory cells [5], marrow-derived mesenchymal stem cells, marrow-derived mononuclear cells for cardiac applications (post-myocardial infarction), and pancreatic islet cells (cadaveric and autologous) [6]. In addition to cellular therapies, an IgM (rHIgM22) for treatment of multiple sclerosis [7] is under development, and production of several small molecules for various therapeutic applications is being considered.

Facility Design

As noted above, after construction several modifications were made to the facility to accommodate the manufacture of multiple products. Walls were erected to improve the layout and to facilitate process flow. Figures 4.2 and 4.3 show the current floor plan. Recent construction on the upper level (see Fig. 4.2, lower left, rooms in orange) divided one impractically large production suite, initially used for large-volume antibody (ALG) production, into four separate suites ($\sim$300 ft^2 each).

The air handling system for MCT is provided for by seven separate air handlers (four serving production areas) consisting of supply and return fans, filters (including high-efficiency particulate air [HEPA] filters), dampers, heating coils, humidification ports, cooling coils, climate-control sensors, air velocity boxes, and exhaust fans. Specific air handlers work in tandem and operate at 50% capacity, increasing to full capacity when the "partner" air handler ceases to function properly. Production space is divided into five areas with regard to air handling. Two areas receive single-pass HEPA-filtered air, while the remaining areas are supplied with recirculated HEPA-filtered air. Additionally, one area was designed for containment, allowing

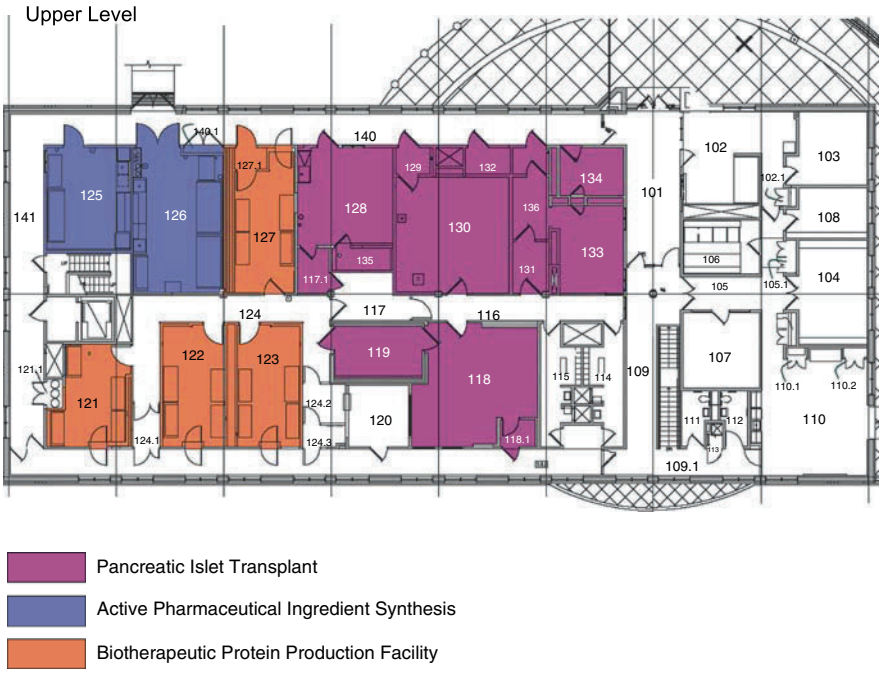

Fig. 4.2 Layout of the upper level of MCT. Three programs (Pancreatic Islet Transplant Program, the Biotherapeutic Protein Production Facility, or BPPF, and the Active Pharmaceutical Ingredient program, or API) currently occupy space on this level. Office space and lunchroom facilities occupy approximately one-third of this level

no air to enter the other areas of the facility. Terminal HEPA filters were added to each of the production suites after initial construction.

Flexibility with respect to manufacturing is optimal for an academic institution supporting several clinical trials using a variety of cell therapies. Modifications to design largely enabled this flexibility; however, establishment of logical work flow furthered this goal. An example of flow of staff, materials, product, and waste is shown in Fig. 4.4.

Aspects of Facility Design

There are advantages to having a "stand-alone" facility – the entire building is dedicated to production of biotherapeutics, and with that dedication comes a common understanding of requirements, goals, etc. This understanding fosters compliance with the various requirements for the facility, including Food and Drug Administration (FDA) regulations and accreditation standards of professional organizations. However, there will be situations where being a "stand-alone" facility brings added responsibilities or a need for special considerations, such as coordination with

Fig. 4.3 Layout of the lower level of MCT. A variety of activity takes place on this level. Standard hematopoietic stem cell processing takes place in the area indicated as Cell Processing Lab. Cancer Center space is primarily used for production of novel cell therapies. A centralized quality control laboratory is located on this level as well

institutional or outside services (e.g., cleaning/janitorial, courier, facility maintenance, and information technology). Overall our experience is that being a "stand-alone" facility is advantageous. Considering the breadth and complexity of activities, centralization of quality assurance alone has made being a "stand-alone" facility invaluable.

One enhancement to design would be the addition of pass-through windows at the exit as well as the entrance. Pass-through windows at the entrance may be used for supplies/reagents; those at the exit may be useful for sending quality control (QC) samples for in-process/lot release testing to a centralized QC testing laboratory, as well as for transfer of additional supplies and reagents. Currently we have windows located near the entrances to the cleanrooms, making sample testing and obtaining additional materials inefficient in areas where clean corridors are not located.

Inclusion of ample storage space is always strongly suggested when construction of a laboratory is under consideration. Growth of a facility can lead to inadequate space for product and document storage, as well as for accommodation of processing equipment. MCT employs both unidirectional flow in areas without clean corridors and bidirectional flow in areas with internal clean corridors. Both approaches are designed to minimize cross-contamination. When designing a facility, thought should be given to inclusion of a clean corridor around production suites. This

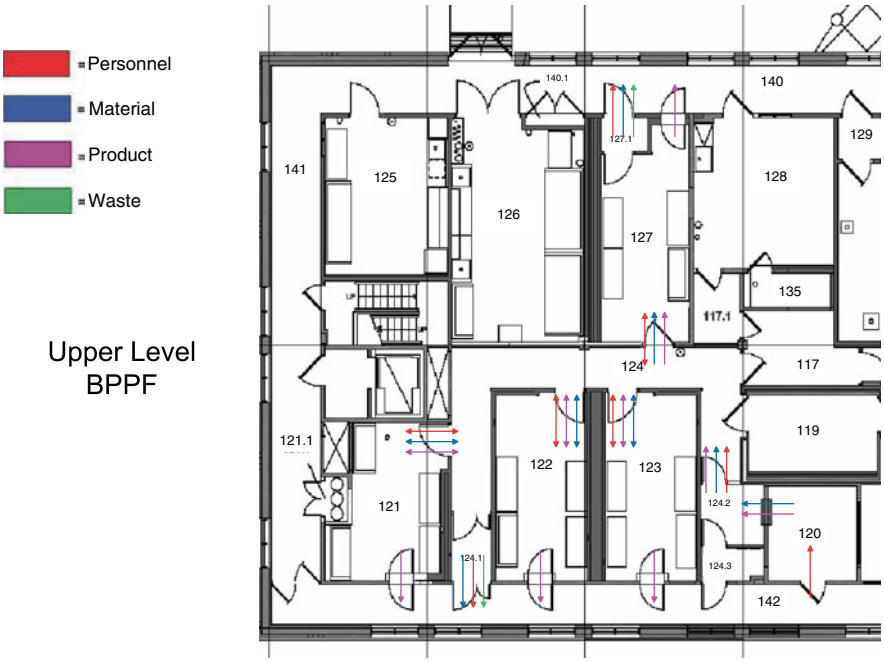

Fig. 4.4 An example of flow (personnel, material, product, and waste) in an area of the building with clean corridors

requires additional space; however, the advantage is additional "bio-burden" for the production area, as well as work-flow flexibility. Finally, addition of a "scale-up" room, a production area dedicated to the necessary process modifications prior to clinical production, is strongly recommended. Rarely, if ever, do processes arrive at the cGMP facility ready for clinical-scale production. Further, nonclinical practice runs do not require the cleanroom environment. We have such a space and find it critical to successful technology transfer and useful for research and development (as this often becomes the responsibility of our facility).

In summary, the MCT serves as one example of a "stand-alone" biotherapeutics engineering facility. A more detailed description of the MCT has been published elsewhere [1].

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Chapter 5
University of Pittsburgh Cancer Institute – Hematopoietic Stem Cell Laboratory (HSC Lab)/Immunological Monitoring and Cellular Products Laboratory (IMCPL)

D.L. Griffin, A.D. Donnenberg, and T.L. Whiteside

Abstract The Cancer Institute (UPCI) at the University of Pittsburgh Medical Center (UPMC) contains two cellular therapy laboratories: the Hematopoietic Stem Cell Laboratory (HSC Lab) and Cellular Products Laboratory/Gene Therapy Laboratory (CPL/GTL). These facilities are responsible for the final development and manufacturing of biological products required for University investigator-initiated research protocols, external partnerships, and contracts for cellular product manufacturing. This chapter describes the design features of these two laboratories.

Introduction

The 8000 ft^2 facility was constructed in 2002 as part of the new Hillman Cancer Center, to provide support for the development and production of advanced cell-, tissue-, and gene-based therapeutic products. The Cancer Institute (UPCI) Facilities provide technical expertise in translating research laboratory methodologies into biologic products acceptable for human therapy. They also provide regulatory structure and oversight to ensure that local and federal regulations, Food and Drug Administration (FDA) requirements, accrediting agency standards, and user expectations are met and satisfied.

The laboratories were designed in close consultation with John (Jay) Eltermann, Jr., FDA Office of Compliance and Biologics Quality (OCBQ)/Division of Manufacturing and Product Quality (DMPQ), with architectural features consistent with FDA recommendations for cleanrooms and controlled environment [1]. The overall design, air quality systems, and finishes meet regulatory requirements and are consistent with the need to integrate equipment and all utilities into the process of cell manufacture. Floors are seamless resin with rounded corners and integral

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cove base with a smooth transition between the flooring and wall panels. Casework and countertops are constructed from stainless steel. The ceilings in the cleanrooms and anterooms are solid. The building materials used withstand frequent cleaning and sanitization with approved sanitization agents. Walls and doors are smooth and cleanable and have minimal ledges and joints. Shelving units are either solid sheets of stainless steel or steel wire mobile shelving. Surfaces are nonshedding and nonporous. Doors incorporate interlock systems, and door operators are designed to overcome room air-pressure differentials. The cleanrooms have been designed to exceed class 10,000 requirements. They have ceiling-mounted HEPA filters and two have positive air pressure with respect to the outer lab, while one, the Gene Therapy Laboratory, has negative air pressure relative to the outer laboratory.

Products are cryopreserved using CryoMed controlled-rate freezers which are located in the facility a short distance from the cleanrooms. Frozen samples are stored in dedicated rooms within 50 feet of the laboratory. These rooms contain –70°C freezers, liquid nitrogen vessels, and vessels specially designed for vialed product aliquots. The vessels are under the control of a cryogenic control management and are linked to an SQR-1 fill sequencer system that supplies liquid nitrogen. When an individual liquid nitrogen vessel initiates a fill sequence, the entire bank of liquid nitrogen vessels is topped off automatically in sequence to ensure that liquid nitrogen wastage is minimized. Each laboratory possesses a redundant liquid nitrogen supply manifold to assure the proper functioning of the liquid nitrogen vessels. The manifold system has two banks of four liquid nitrogen supply cylinders that are monitored by a Pacer digital system remote alarm. When one bank is depleted, it alarms and the bank switching system automatically switches to the next bank. The empty tanks are then replaced twice a week with full tanks. Any failures of the system are also monitored by a Sensaphone® monitoring system that automatically contacts the user by phone. The freezer rooms are equipped with an oxygen alarm monitor for real-time measurement of the oxygen content in the room. Access to cleanrooms and testing areas is limited to authorized personnel.

Heating, Ventilation, and Air Conditioning (HVAC) System

In all three cleanrooms, chilled (55–65°F) humidified (30%) air is provided from the house supply air system. The supply air is admixed with return air from the cleanroom in a ratio of approximately 25:75. The mixed air is prefiltered, and tempered with low-pressure steam (45–50% relative humidity) and a reheat coil as determined by the room humidistat and thermostat. Supply air grills in the cleanroom ceiling are equipped with HEPA filters for final filtration. Return air grills are located low on the cleanroom walls to maintain laminar flow. Return air is admixed with house supply air as described above. Airflow and pressures are designed to ensure a minimum air change rate (40 air changes per hour) and a minimum pressure differential between the cleanroom and waste vestibule (0.021 in. H_2O), and the cleanroom and anteroom (0.071 in. H_2O), and the anteroom and the testing laboratory (0.153 in. H_2O).

Exception reports are supplied by Facilities Management. The air particle count is tested according to ISO standard 14644-1, and operates at rest at class 6 (35,200 $\geq$ 0.5-μm particles/m^3 = 1000/ft^3). The cleanrooms and Class II Biological Safety Cabinets are certified annually, but undergo daily nonviable particle counting as part of the quality control of the facility.

Construction was completed on the Hillman Cancer Center Research Pavilion in late 2002 and the facilities began operations shortly thereafter. This facility has been designated by the National Heart, Lung, and Blood Institute (NHLBI) as one of the three Production Assistance for Cellular Therapies (PACT) centers [2].

Hematopoietic Stem Cell Laboratory (HSC Lab)

The HSC Lab provides production assistance for cellular therapies. The HSC Lab is directed by Albert D. Donnenberg, PhD; Joseph Kiss, MD, serves as the Medical Director. The Laboratory has been in continuous operation for more than 20 years. Its historical mission has been to support the Bone Marrow Transplant Program (now the Hematopoietic Stem Cell Transplant Program), but since 2002 the purview has expanded to serve as a production and reference laboratory for the manufacture of cellular products for additional clinical applications. Medical and technical staff of this laboratory perform product processing, testing, manufacture, and storage. In addition to processing and cryopreserving cellular products, the staff deliver the product to the bedside and assist with product administration. The HSC Lab also provides both expertise in current good manufacturing practice (cGMP) and assistance in translational development of novel stem cell products.

While production of conventional autologous and allogeneic hematopoietic progenitor cell products is the primary function of the HSC Lab, there are several Investigational New Drug (IND)-driven projects such as two-parameter immunomagnetic cell selection (positive selection for CD34, negative selection for CD3) for use in autoimmune diseases and haploidentical transplantation. Translational projects include GMP production of adipose-derived stem cells from the stromal/vascular fraction of lipoaspirates, and bone marrow-derived stem and progenitor cells from cadaveric vertebral bodies. The HSC Lab collaborates with several industrial partners involved in the development of clinical cell separation and testing to further advance the field. The HSC Lab tests more than 500 samples per year and processes more than 300 products.

Occupying approximately 1200 ft^2, the state-of-the-art laboratory was designed to facilitate cGMP-compliant processing of hematopoietic and somatic progenitor cells. The HSC Lab is equipped for cell processing, selection, testing, and cryopreservation. Processing equipment includes Baxter Oncology Isolex 300i clinical magnetic cell separator, COBE® 2991 cell washer, Beckman J-6 M centrifuges, a Heracell® incubator, and three biosafety cabinets. Testing equipment includes a Beckman-Coulter FC500 5-color cytometer, a Beckman-Coulter AcT-diff2™ hematology analyzer, and a fluorescence microscope. The Liquid Nitrogen Storage

Facility includes three controlled rate freezers, seven LN_2 product storage vessels with capacity of 500 cryopreserved components each, one LN_2 vessel for vial storage, automatic LN_2 filling system with redundant sources, continuous monitoring and autodial alarm system for all LN_2 vessels, and two dry shippers [3].

The HSC Lab is divided into two main work areas (Fig. 5.1). The Testing Lab and Cleanroom are designed for GMP workflow, are interlocked, and together occupy 800 ft^2. The laboratory is entered via a "locker room" that provides for a change of shoes and donning a lab coat to wear in the outer laboratory. The outer laboratory has a hard ceiling, a one-piece floor, and stainless steel casework like the cleanroom, but otherwise it is a typical BSL II environment. The outer lab is joined to the inner cleanroom via an interlocked gowning anteroom and there is a specimen pass-through from the outer lab to the cleanroom. There is a "waste out" room that connects to the corridor with an interlock, such that the door to the cleanroom and the door to the corridor cannot be opened simultaneously. Workflow patterns are identified to inform users of the laboratory of the proper movement of personnel, products/samples, and waste (Fig. 5.2). Personnel enter the HSC Lab through the locker room into the outer laboratory. Once staff enter the cleanroom, they must exit either through the anteroom or the waste-out room. Workflow through the anteroom is bidirectional, whereas movement through the waste-out room is unidirectional. Once personnel have entered the waste-out vestibule, reentry to the cleanroom is prohibited. Personnel must continue to exit to the hallway prior to reentry to the HSC Lab. Flow of supplies is unidirectional. Product flow is restricted to the clean

A. Vestibule for entrance into the lab
B. Office area where products and samples are accessioned
C. Outer laboratory space for WBC enumeration, Flow Cytometry, Preprocessing
D. Pass-through from outer lab to inner lab
E. Gowning area between outer and inner labs
F. Inner laboratory with Isolex and Cobe equipment
G. Waste vestibule

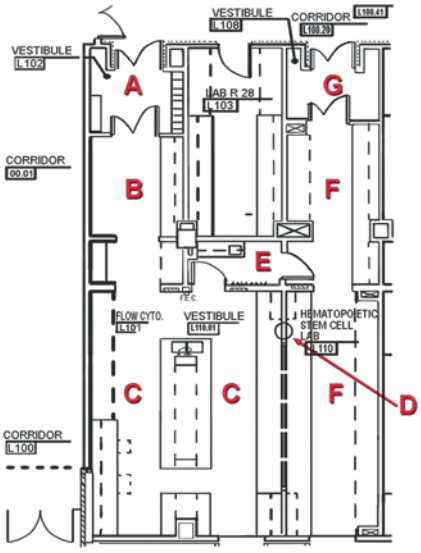

Fig. 5.1 Floor plan of the Hematopoietic Stem Cell Laboratory at the University of Pittsburgh Cancer Institute modified from architect's blueprint. Letters correspond to dedicated work areas of the laboratory. The laboratory occupies approximately 800 ft^2

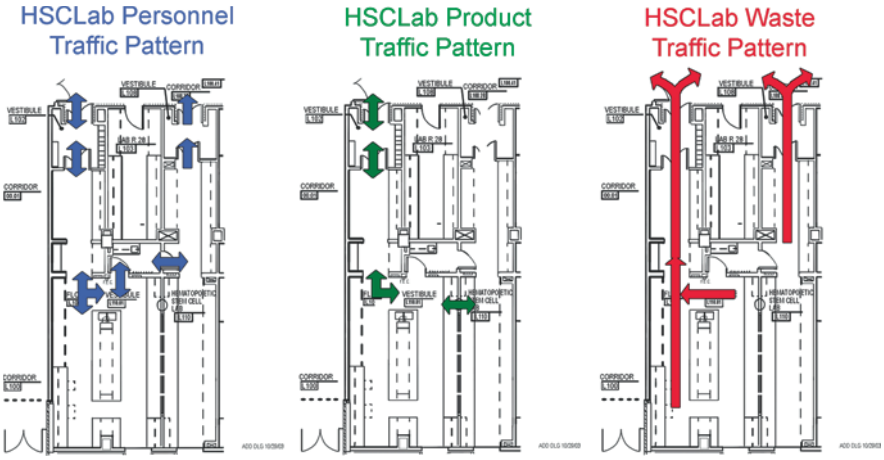

Fig. 5.2 Workflow patterns for Personnel, Products (encompassing products and samples), and Waste in the HSC Lab. This limits the exposure of the products to unnecessary environments, particularly where waste is deposited and transported

areas of the laboratory and products are not permitted in the waste-out vestibule. Supplies that enter the cleanroom are replenished as used, or discarded upon expiration. Waste flow is unidirectional to exit the facility and the main laboratory and the cleanroom does not commingle.

Immunological Monitoring and Cellular Products Laboratory (IMCPL)

As part of the IMCPL, the Cellular Products Laboratory/Gene Therapy Laboratory (CPL/GTL) is a cGMP facility which provides support for the development and production of advanced cell-, tissue-, and gene-based therapeutic products. The CPL/GTL facility provides technical expertise in translating research laboratory methodologies into a process for generation of therapeutic biologic products.

The CPL/GTL serves the following functions:

(i) The CPL/GTL is a cGMP facility, which processes somatic cells and, when needed, genetically modifies these cells in support of clinical and research protocols at the University of Pittsburgh Medical Center. The CPL processes apheresis products using the Gambro Elutra® System in the manufacture of dendritic cells. The CPL/GTL also provides expertise in scale-up technologies and transfer of cell-based research to clinical-scale applications [4, 5].

(ii) The Tissue Processing Laboratory (TPL) is operated as a Good Tissue Practice (GTP) facility for triaging, processing, testing, and cryopreserving of human tissues as needed for cellular product generation.

(iii) The Immunologic Monitoring Laboratory (IML) is a GTP facility located adjacent to the CPL/GTL which supports development and product characterization needed by the CPL/GTL. Phenotypic and functional characterization of cellular products is performed, and a wide range of assays is available [6].
(iv) The Research and Development (R&D) Laboratory, located in the Hillman Cancer Center, is responsible for translational research activities. It provides dedicated research space for laboratory activities in support of various projects that are in the preclinical phase of development.

The CPL/GTL is a manufacturing site for human cellular- and tissue-based products that require long-term tissue culture. Products include: lymphocytes (T cells/T-cell subsets, B cells, natural killer (NK) cells, and NK T cells), dendritic cells, hematopoietic cell lines, tumor cells/lines, tissue cells (fibroblasts, synoviocytes, and monocytes), and stem cells [7].

The IMCPL consists of several adjacent laboratories for accessioning, testing, and manufacturing of products, in addition to office space, meeting space, and storage areas. Areas H, I, and J in Fig. 5.3 correspond to the Gene Therapy Lab, Cellular Products Lab, and the Tissue Procurement Facility, respectively. Workflow patterns are identified to inform users of the laboratory of the proper movement of personnel, supplies, and waste (Figs. 5.4 and 5.5).

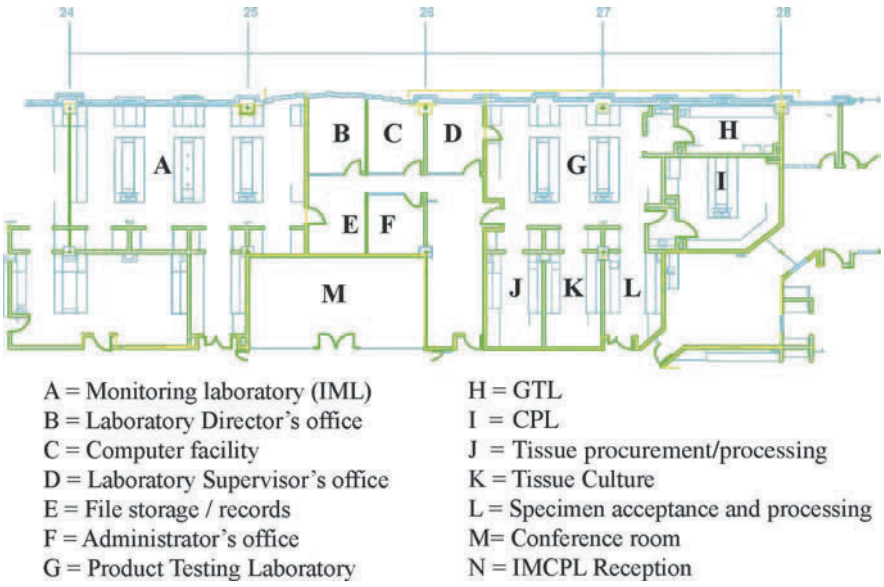

Fig. 5.3 Office, Laboratory, and Meeting Space of the IMCPL. Modified from the architect's blueprint. B-F are office areas, A and G-L are laboratory areas, while M is the conference room.

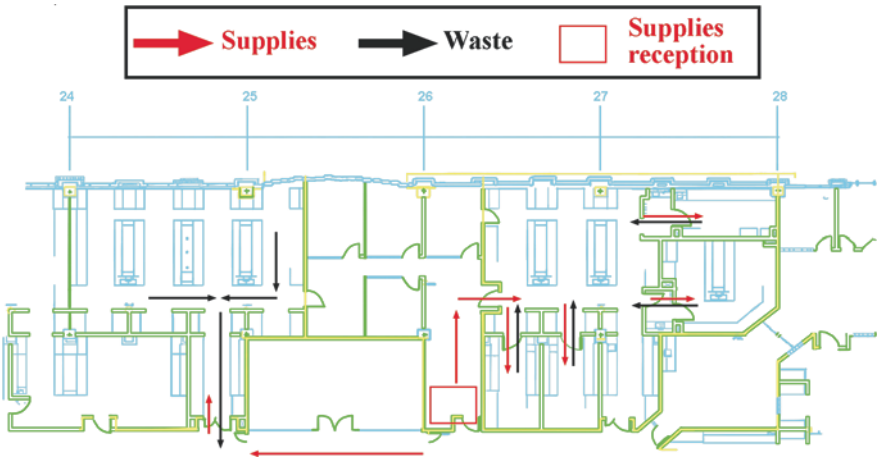

Fig. 5.4 Workflow patterns within the IMCPL. As in the HSC Lab, Supplies and Waste flow in a specific direction to minimize the contact between products and waste materials.

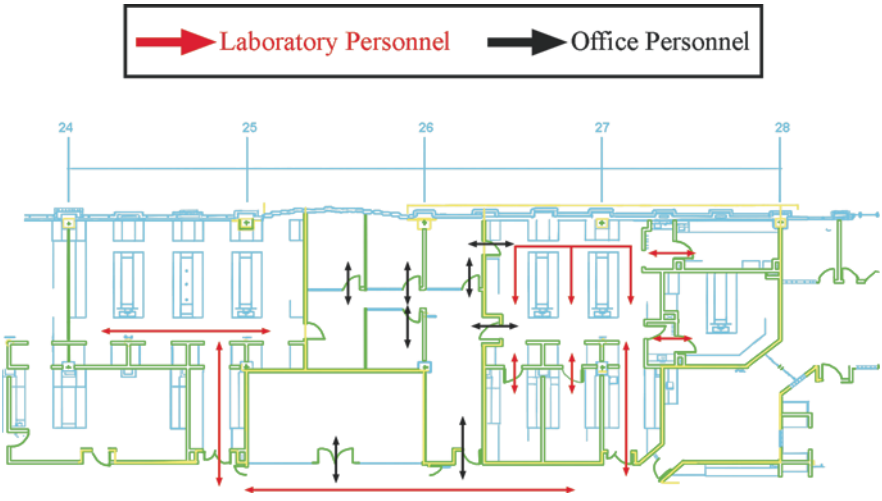

Fig. 5.5 Office personnel and Laboratory personnel have separate workflow patterns due to their work-related activities

Laboratory Features: What We Would Retain and What We Would Change

The redundant manifold system for LN_2 system provides a safety mechanism for the cryopreserved products while the filling algorithm minimizes the LN_2 that is wasted due to warming of the tubing in the automatic filling system. Liquid nitrogen levels

and temperatures are recorded electronically and captured for analysis and review. The only thing that we would change would be to use an external bulk LN_2 tank that can be filled by a tanker truck. This was considered during the design phase, but was not possible due to the physical location of the laboratory relative to the loading dock.

We have compensated for the fact that controlled rate freezing of products is performed in a noncontiguous laboratory space by installing a remote video camera and microphone for real-time monitoring of the freezing process. Additionally, the three CryoMed controlled rate freezers are interfaced to a single MS Windows XP computer such that all freezers can be monitored and controlled from the main laboratory using Windows Remote Desktop.

Efficient utilization of space was a primary design consideration. This inevitably led to compromises in work flow. In particular, the CPL cleanrooms are not efficient for multiple uses. Their size and shape do not allow for efficient processing. While only one technologist processes a single product at a time, according to our campaign Standard Operating Procedure (SOP), there are difficulties in logistics. With two or more technologists working in a confined space, the technologists must cross paths as they move from the biological safety cabinet to the incubator or other equipment. The anterooms are only large enough for one technologist to gown at a time. A more efficient model would provide for a number of small well-equipped cleanrooms connected to a corridor with a gowning anteroom. This would also allow for greater isolation of individual products and would allow processing to continue in the instance where a single room was deemed unsuitable for use (e.g., due to contamination or mechanical failure). As it currently stands, if the HSC Lab cleanroom were to be shut down due to an air-handling issue, all processing would cease until the issue was resolved.

Another serious compromise, again due to a lack of space, was the omission of a separate materials management area. All supplies and reagents are held within the laboratories. While newly acquired or received materials are stored in an area designated as quarantined and labeled appropriately, this does not allow efficient materials management. Other laboratories, such as the Center for Cell and Gene Therapy (CAGT) at the Baylor College of Medicine and Molecular and Cellular Therapeutics (MCT) at the University of Minnesota, have their own dedicated areas for supply management.

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Chapter 6
Baylor College of Medicine – Center for Cell and Gene Therapy (CAGT)

A. Gee

Abstract The Center for Cell and Gene Therapy at Baylor College of Medicine houses two cGMP facilities. The older of these, constructed in 1992 and renovated in 2008, prepares viral vectors for use in gene therapy. The second, purpose-built into existing space was opened in 1998 and manufactures cellular products for hematopoietic transplantation, immunotherapy and regenerative medicine. Together the facilities prepare approximately 3,000 products and intermediates annual and process and test about 12,000 samples. In 2009 both will be relocated to a new larger combined facility.

Introduction

The requirement to meet Good Tissue and/or Good Manufacturing Practices in the preparation of cellular therapy products has focused attention on the design of appropriate facilities. In reality, while purpose-built cell processing units may facilitate meeting requirements, the majority of existing establishments can comply with the regulations. It is a widespread misunderstanding that GTP and GMP regulations require manufacturing under cleanroom conditions. This necessitates installation, maintenance, and monitoring of specialized air handling systems at considerable expense. Centers that elect to install such equipment generally do so in anticipation of future, more stringent regulatory requirements, or because they believe that the cleanroom environment provides a higher degree of protection for the specific types of products that they will manufacture. The regulations do indicate that if a classified environment is employed, it must be monitored and adequately maintained.

There are a variety of cleanroom classifications, but those generally employed for this field are class 1000 and class 10,000 environments, with specifications of <1000 and <10,000 particles per cubic foot, respectively. These environments are

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really intended for open process manufacturing, rather than the approach used for the preparation of cellular therapy products, which are usually handled in class 100 biological safety cabinets using closed systems wherever possible. In such a situation placing the BSC in a class 10,000 environment mainly acts to provide an additional level of protection, without substantially contributing to the real safety of the products. Nonetheless, most new facilities have elected to include some classified space.

If the decision to include classified space is made, one of the next issues is to determine the traffic patterns that will be used. Traditional pharmaceutical cleanroom manufacturing practices employ single-pass patterns in which the manufacturing suites are situated between clean and dirty corridors. Staff, materials, and reagents move in a unidirectional pattern from the clean corridor, to the manufacturing areas and from there through the dirty corridor to de-gowning. Gowning may take place in up to three separate areas of increasing classification. The alternative is to select a single-corridor design in which there is multidirectional traffic, but air pressure relationships are set to protect the manufacturing areas from the corridors or general areas.

The unidirectional pattern provides the highest degree of stringency, but is expensive to maintain and requires the largest footprint due to the double-corridor design. Consequently, it may be difficult to design such a floor plan within an existing footprint. The unidirectional system also is best suited to a campaign style of manufacturing, in which a suite is cleaned, stocked, and monitored prior to the start of production. A specific product is then allocated to that suite and remains there throughout the manufacturing process. At the completion of production the suite is stripped of remaining materials and reagents and prepared for the next product. This approach works well for pharmaceuticals and certain types of biologicals, such as monoclonal antibodies, plasmids, and viral vectors. It may work for some cellular therapy products; however, as a facility becomes busier it is more and more difficult to use the campaign approach, since the manufacturing times vary from days to months, and it becomes impossible to dedicate a suite to each product. In fact, with time it may be necessary to prepare multiple products within a suite. To achieve this it is mandatory to develop detailed changeover procedures to prevent contamination and cross-contamination of products within a suite. This becomes a primary consideration if a multidirectional design is selected for a new facility.

The Center for Cell and Gene Therapy (CAGT) at Baylor College of Medicine was established with two GMP/GTP manufacturing facilities. The first is for the preparation of cellular therapy products (Cell Processing Facility, or CPF, Fig. 6.1) and the second for viral vectors (Vector Production Facility, or VPF, Fig. 6.2). As indicated previously, cell therapy products are manufactured in BSCs using closed systems wherever possible. The Center had a number of protocols that required the preparation of a variety of products with preparation times of days to months. These include hematopoietic progenitor cells from marrow and mobilized peripheral blood, donor leukocytes, gene-modified autologous and allogeneic tumor vaccines, virus-directed cytotoxic T cells, cells used in regenerative medicine protocols, and

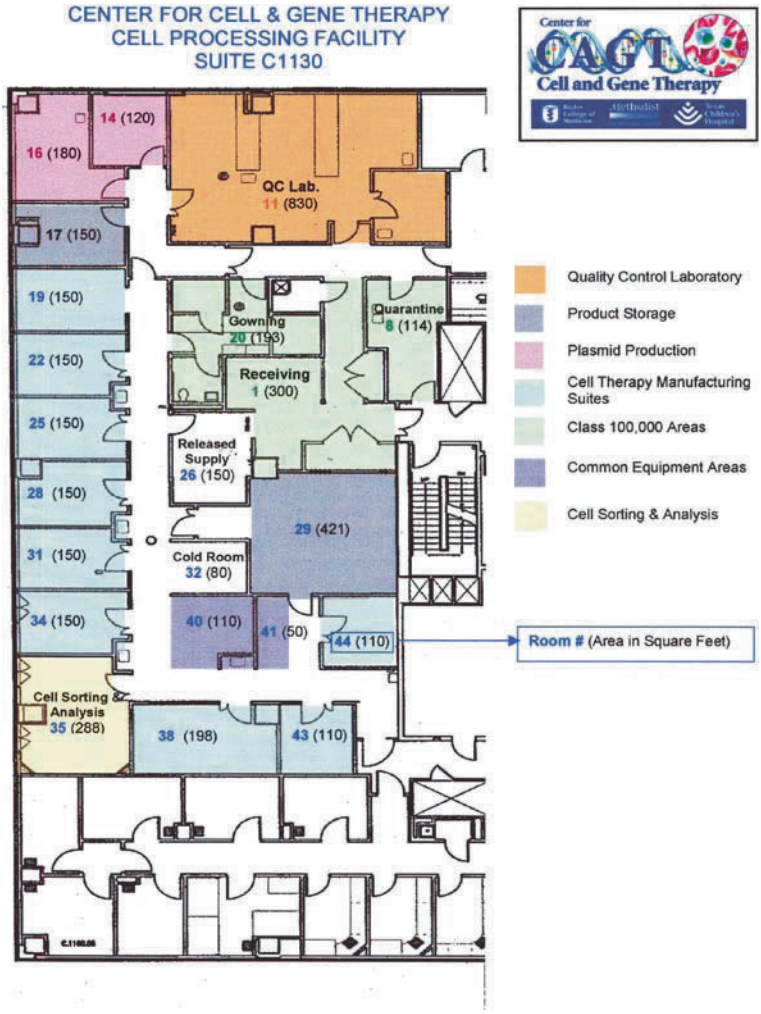

Fig. 6.1 Floorplan of the existing CAGT cell processing facility: single-corridor design

pancreatic islets. This would require multiple suites and a noncampaign manufacturing style. The facility also had to fit within a preallocated vacant footprint on the 11th floor of an occupied building. For this reason we selected a multidirectional single-corridor design and decided that all suites, the corridor, and cell storage areas would be rated at class 10,000. This was in anticipation of possible future regulations, particularly since some of the products were to be transduced with viral vectors.

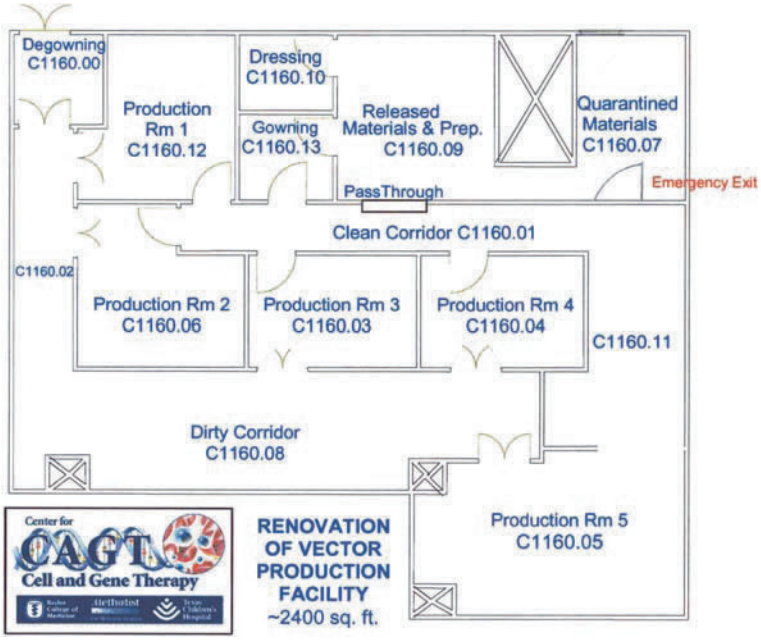

Fig. 6.2 Floorplan of the existing CAGT vector production facility: clean and dirty corridor design

Vector Production Facility (VPF)

The original CAGT VPF consisted of a research laboratory with two adjoining smaller production rooms on a separate air handling system. In 2003 the facility was renovated in response to meet increasing demand for vectors. At that time it was decided that a unidirectional design rated at class 10,000 would be chosen (Fig. 6.2). Although manufacturing activities were performed in BSCs, it was felt that vectors more closely resemble pharmaceuticals than cellular therapy products. They are made in relatively large batches and may be administered to many patients, either directly or as intermediates in the preparation of cellular therapeutics. In contrast, at the present time, most cell therapy products are designated for individual recipients, are prepared in small batches, and each is terminally tested to meet specific release criteria.

The renovated facility had to fit the expanded existing footprint. It was determined that five production rooms could be located between the clean and dirty corridors, whereas seven rooms could have been built if a single-corridor design was selected. The choice was made to increase the number of air changes per hour from 20 to 30 in the cell processing facility to 60 per hour. Additionally it was decided that the air would be single-pass rather than the 60% recirculation used in the CPF. This considerably increased the cost of the facility, since a new electrical chase had to be installed to meet the power demands. Operating costs were also increased as a

consequence. Two-phase gowning was selected to conserve space for manufacturing activities. Since campaign style manufacturing would be used, it was important to provide sufficient storage for clean supplies within each suite with additional storage in the clean corridor. The dirty corridor was designed to accommodate freezers, refrigerators, nitrogen banks and gas manifolds and other equipment that needed to be accessed without entering the classified space.

Cell Processing Facility (CPF)

The floor plan for the current CPF is shown in Fig. 6.1. The goods receiving area, the quality control laboratory, the quarantine room, and the liquid nitrogen and carbon dioxide manifold systems are located outside the classified space. Liquid nitrogen is handled by two separate manifolds both with primary and backup supplies. One serves the main storage banks and the second smaller manifold is used by the controlled rate freezers. The receiving area (Fig. 6.3) is linked to the classified space via a pass-through box. Supplies are delivered to the receiving area, where they are unpacked. Our policy is to set minimum specifications for receipt. These require that materials must have been shipped and received undamaged at the correct temperature and that they have a certificate of analysis (COA) on file at CAGT. After unpacking, the material is barcoded, wiped down with 70% ethanol, and transferred to the clean storage room inside the facility via the pass-through window or box. Materials for which a COA is not available are held in quarantine and clearly

Fig. 6.3 Cell processing facility – receiving area

marked to that effect. Quarantined materials are held in a separate storage room or in a refrigerator or freezer within the quality control laboratory. Once the COA is received, the quarantined material can be released and transferred to clean storage. A similar approach to quarantine is used for supplies that require additional testing by QC or the investigator prior to release. Depending on the amount of specification testing that is anticipated, facilities will need to allocate sufficient space to keep nonreleased supplies in quarantine during testing. Rapid release procedures, in which there is not extensive testing of materials or supplies before they can be used in manufacturing, reduce the requirement for quarantine space and for storage outside the classified areas. It is still easy, however, to underestimate the storage space required for incoming supplies, and high-density storage systems should be employed to make the best use of the space available.

Entry to the facility should be secured, and most use either a keypad or a badge reader to restrict access to authorized staff. The latter is generally more effective since it is easy to lose control of keypad codes once they have been in use for a while.

Depending on the nature of the manufacturing environment, different types of gowning practices will be used. These range from laboratory coats to full sterile gowning. When planning a facility it is important to provide sufficient space for gowning activities and for the storage of gowning materials. More complex gowning procedures may require changing rooms and a clear division between "clean" and "dirty" sides of the room as indicated by the positioning of a bench between the two areas.

The CAGT entry to the cell processing facility is by a combined locker and gowning room. Staff generally elect to wear scrubs, although Tyvek® suits may be worn over street clothes. Splash-proof disposable lab coats are worn over suits or scrubs. Booties, hats, and gloves are also worn. The design of the room does not allow designation of clean and dirty sides, but a permanent tacky mat is installed immediately in front of the door into the classified space. This door is interlocked with the entry door to the gowning area so that both cannot be opened at the same time.

The gowning room leads into the main central corridor (Fig. 6.4) along which are located the manufacturing suites (Fig. 6.5), the clean storage room, the cold storage facility, and two open areas for the location of shared equipment. There are two sinks in the corridor for the drainage of water baths and incubators. This was a conscious decision, although sinks are not normally located in cleanroom environments, due to their potential to become a source of contamination. In the new CAGT facility (see New Facilities chapter) sinks have been excluded.

In response to a demand to produce plasmids, one end of the corridor was segregated via a one-way door. This allows staff to enter a separate area in which there are three suites for plasmid manufacturing. The air balance is such that this area is at negative pressure with respect to the remainder of the facility and air is 100% exhausted from the plasmid facility. Pressure relationships provide a means of reducing the risk of contamination and cross-contamination. They can be established to protect the product that is being manufactured or to contain potential contaminants within a particular area. When planning a new facility it is important to meet with the HVAC engineers to discuss the flexibility of the air handling systems

Fig. 6.4 Cell processing facility – main corridor

Fig. 6.5 Cell processing facility – manufacturing suite

to provide positive and negative pressure areas, and how easy it would be to change the specifications. Air handling plans may also be submitted to the regulatory agency for feedback.

The dimensions of most of the main CPF suites (Figs. 6.4 and 6.5) are 11' × 15' which is probably the minimum to accommodate the required equipment and to provide a reasonable working space. The floors are sealed vinyl with coved edges to the walls. Walls are painted with epoxy paint and ceilings are clean-room tiles fixed to a suspension grid. These meet regulatory specifications and are considerably less expensive to install than solid ceilings. Care must be taken to ensure that the tiles remain fixed to the grid, particularly after access to above-ceiling utilities.

The suites are all equipped with a 6' BSC, tabletop centrifuge, one or two double-stacked incubators, inverted microscope, personal computer and barcode reader, and waterbath. The latter must be kept empty unless in use. Each room contains metal wall cabinets with sloped edges to facilitate cleaning. Benchtops are epoxy and there are metal under-counter cabinets. These cannot be removed for cleaning, but are clear of the floors. This design has generally worked well. For new facilities consideration should be given to using air-jacketed incubators (to eliminate water top-ups and changes) and to using removable stainless-steel tables and storage units.

Careful consideration should be given to the nature of the manufacturing processes that are to be used. In many cases it is very helpful to locate more than one BSC within a suite. This allows manufacturing to be ongoing while the second cabinet is used to set up testing or to prepare equipment and reagents for the next step in the procedure. Care must be taken to locate BSC so that the airflow pattern within the suite is not adversely disrupted. The CAGT CPF suites have ceiling air supply and return registers. This is not the usual design, in which the supplies are located in the ceiling and returns are at floor level, to maximize air circulation within the suite. In reality we have found that there has been excellent circulation with the rooms with ceiling supplies and returns, probably due to the increased airflow provided by the continuous operation of the BSCs. Although the official rating of the facility is class 10,000, it routinely operates at about class 1500–2000.

The CAGT facility includes shared open areas that house a cell counter, fax machine (used to receive STAT test results), barcode and label printers, an irradiator (new U.S. regulations now require that this should be located in a separate lockable area), and an over-wrapper used to double-wrap products for long-term storage. Dedicated larger equipment, e.g., magnetic and centrifugal cell separators, cell washers, etc., are located in the suites in which they are primarily used. In such cases, and where there is more than one BSC per suite, consideration should be given to the heat load that is generated by the equipment. In routine use, smaller rooms with multiple pieces of equipment in operation may become uncomfortably warm during the course of the day.

The cold storage room (Fig. 6.6) is located within classified space. This decision permits staff to freeze cells and retrieve frozen products without exiting the facility. The disadvantage is that the carts used to transfer frozen products to the bedside must be cleaned down when they return to the facility.

The external location of the nitrogen manifolds allows the supply tanks to remain outside the controlled areas. When planning a new facility it is easy to underestimate the amount of space that will be required for long-term frozen cell storage. There are

Fig. 6.6 Cell processing facility – nitrogen storage banks

now commercial entities that will store cells off site and provide the required transportation to and from the facility. The decision must therefore be made as to whether all products will be stored on site or whether such off-site storage services will be used. The most efficient and economic use of storage space is made by selecting larger storage banks. The predominant use of storage of products in vapor-phase nitrogen has reduced the weight of the banks considerably, but it is still important to discuss possible floor weight constraints with architects; this also applies to irradiators. Floors in areas where liquid nitrogen is handled should be constructed of either concrete or poured epoxy, both of which provide excellent resistance to spills. Oxygen monitors should also be in use, either as wall-mounted devices or as personal monitors worn by staff working in the area.

Non-campaign-style manufacturing requires restocking of suites on an ongoing basis. This is provided by the location of a clean supply room within the classified space. Again it is easy to underestimate the space required for storage. Tissue culture supplies are often bulky, and many different types may be required for manufacturing. Consideration should be given to the use of high-density storage systems, such as shelving systems on tracks. In addition. the manufacturing suites must be able to hold running supplies to reduce traffic to and from the suites. A cold room provides central storage for released temperature-sensitive media, etc. Under-counter refrigerators in the suites can be used for daily storage of supplemented media, but are generally not sufficiently temperature stable to be suitable for longer-term storage. If this is required, it is necessary to select larger refrigerators.

General considerations that are sometimes overlooked when designing a facility include ensuring that large or heavy equipment can be easily moved in and out of

the facility. Doors must be high and wide enough for passage, and corridors must provide sufficient turning width to turn equipment and move it around corners. The location of service elevators and access to them also become important issues. If the facility is on a higher floor, the liquid nitrogen supply tanks will be transported via the service elevator and must be wheeled from the elevator to the cryopreservation area. The route that they will take should be addressed as some facilities are located in areas where there is patient/public traffic and this is not an ideal mix.

Facilities must also be cleaned and waste removed. The traffic patterns for cleaning staff, locations of preparation areas for cleaning and disinfectant solutions, and for the disposal of waste are all important considerations. What water systems are to be used preparing disinfectants and should these be available for other purposes, e.g., reagent preparation? The simplest solution is to restrict water systems to use by cleaning staff and to purchase water that is to be used within the classified space. In a similar vein, thought must be given to sterilization systems. Again the simplest solution is to purchase sterile supplies and reagents rather than providing in-house sterilization services. These require ongoing qualification and maintenance. The use of hospital central sterile supply sterilization services is not always a viable alternative, since the procedures that they follow seldom meet FDA specifications. Similarly, if possible, it is easier to contract the disposal of biohazardous waste to a contract organization or to the institution in which the facility is located. This avoids the necessity of autoclaving waste before it leaves the facility and all of the issues associated with autoclave management.

Ongoing documentation of equipment performance is an important component of GTP and GMP. This can be achieved by the selection of a good facilitywide alarm and monitoring system. Traditionally these were hardwired to each piece of equipment and sounded a local alarm if monitored parameters went out of specification. The newer systems are much more sophisticated. The equipment probes connect wirelessly to the alarm control system, thereby allowing equipment to be moved easily without rewiring alarms. The systems interface with staff members' computers or can be Internet based allowing universal access. These systems record parameters on an ongoing basis and can provide required documentation of ongoing performance. Alarms are routed to specified individuals for each piece of equipment and remote response to alarms is now possible.

Other facilitywide systems that need to be considered include backup power for critical equipment and computer systems. This in turn relates to ensuring during the design phase that sufficient access is provided to regular and high-voltage outlets and to server connections in order both to meet future requirements and to allow relocation of equipment. Computer systems are now critical in the operation of a facility. It is important to determine the needs for the system in advance and to discuss how these may be impacted by institutional policies and procedures.

There is also increasing use of barcoding systems. These can be used for tracking reagents, materials, supplies, equipment, and products. Currently the International Council for Commonality in Blood Bank Automation (ICCBBA) is working to extend the ISBT 128 barcoding system for use with cellular therapy products, and it is hoped that this will be adopted as the standard for the field.

In the absence of a final standard, facilities should consider systems that are sufficiently flexible to read and generate a variety of barcode types, including two-dimensional barcodes.

The New CAGT Facilities

The CAGT will be relocating both GMP facilities to a newly built expansion of the Feigin Center in 2009. The new facilities are described in the New Facility chapter. This chapter discusses the changes that have been made and the elements that have been conserved from the old facilities.

General Comments

There are many considerations to take into account when planning or renovating a cellular therapy manufacturing facility. It is important to develop a clear understanding of the regulatory requirements. This provides the basis for setting the operational standard. The decision to adopt traditional pharmaceutical approaches will involve considerably higher construction and operating costs than adoption of manufacturing in nonclassified space. The FDA has indicated that expectations for GMP compliance change as products move from manufacturing for Phase I to III clinical studies. Often referred to as the sliding scale of GMP this gives facilities the opportunity to suggest the approaches they will employ to achieve regulatory compliance, including the facilities and methods used for manufacturing. Once a center has developed a facility plan and considered operational aspects, such as changeover procedures, they can consult with the FDA to obtain feedback prior to starting construction.

Budget is obviously a primary consideration for all centers. At the planning stage it is all too easy to focus solely on the construction costs; however, in the longer term this sum can be easily eclipsed by the running costs. These are higher for facilities with controlled environments. Building too large a facility will further inflate these costs, since monitoring activities and the basic infrastructure must be maintained whether or not the suites are in use. Centers must determine whether these costs may be covered by leasing excess capacity to other investigators or commercial entities.

As mentioned previously the configuration of the available space will have a major impact on the decision to go with a unidirectional or multidirectional design. This decision should be influenced by whether or not campaign style manufacturing will be used and by the type of products that are likely to be manufactured in the facility.

Chapter 7
Design of a New GMP Facility – Lessons Learned

A. Gee

Abstract The current Baylor College of Medicine GMP/GTP Cell Processing Facility is described in some detail in the chapter on Facility Design. During 2009–2010 the facility will be relocated from the 11th to the 16th floor of the Feigin Center at Texas Children's Hospital (TCH). This floor is a new addition to the building which is being expanded from 12 to 20 stories (Figs. 7.1a and b). This has given us the opportunity to redesign the space based on our experience working in the present facility. This chapter describes what changes have been made based on lessons learned from working in the previous facility for nearly 10 years.

Introduction

Space was much less of a constraint when designing the new Baylor GMP Facility, since an entire floor was available and could be subdivided according to our requirements. It was determined that the area would also have to accommodate the general offices for the Center for Cell and Gene Therapy, conference rooms, file storage, the quality control laboratory, and both the Cell Processing and Vector Production GMP facilities (Fig. 7.2). The overall total available space was, however, double our previous area, which allowed expansion of the QC laboratory and both GMP facilities.

The decision was made to retain the current approach of manufacturing both Type 351 and 361 products in a classified (class 10,000) environment. Our experience suggested that this simplified staff training and operations by employing a common manufacturing environment. We also decided to keep the basic design concept for each GMP facility, in that the VPF would function more as a pharmaceutical manufacturing area, with unidirectional flow of staff, material, and waste using clean

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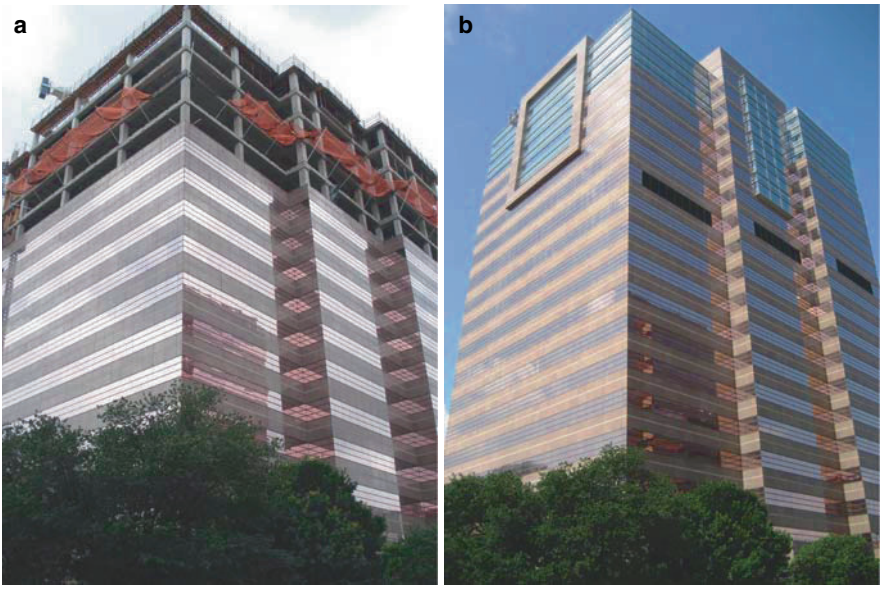

Fig. 7.1 **a** and **b** Construction of space that will house the new Baylor GMP facilities

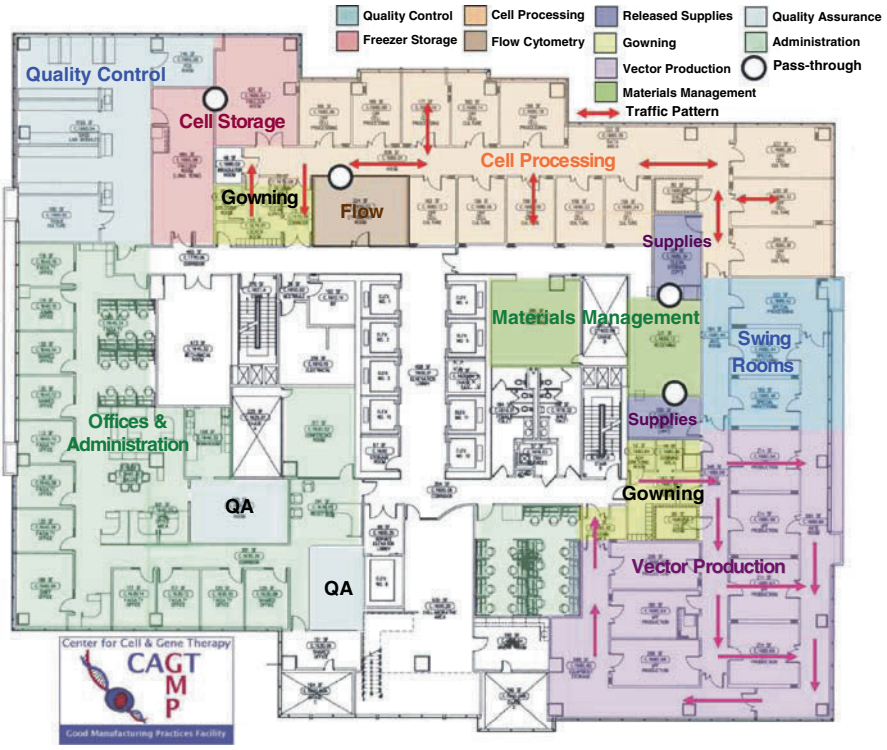

Fig. 7.2 Floorplan of the new Baylor GMP facilities

and dirty corridors. In contrast, the CPF would keep its single-corridor format in order to accommodate the maximum number of manufacturing suites within the designated footprint. Given the changing nature of the demand for vectors and cell therapy products, it was decided to include three "buffer" or "swing" production rooms between the VPF and CPF facilities. These could be operated as either part of the CPF or the VPF facility. Once allocated to a facility, the traffic patterns could be restricted to meet the respective requirements. These rooms would be on the VPF air handlers with 60 air changes per hour and 100% exhausted air. In contrast, in the CPF rooms a portion of the air would be recirculated through central and terminal HEPA filters. A sophisticated air handling system is to be installed in the remainder of the building. This monitors the air for noxious agents, such as solvents, and automatically increases air flow if these are detected. This will not be installed in the GMP areas where solvents and the like are rarely used and where an automatic increase in air flow may adversely disrupt pressure relationships. Although the air flow in the present facility has been adequate and the operating classification is nearer class 1000 than 10,000, we elected to move the return air registers from the ceiling to floor level, thereby providing a more traditional air flow pattern. This does limit the placement of equipment as it must not block return registers.

The minimum size of the processing suites has been increased from 165 to 200 ft^2 to provide a more spacious working environment. Wall space is more limited in some suites since the exterior walls of the building all have windows, and there are several corner rooms within each facility. This will necessitate blocking some of the window space with equipment. Several larger processing rooms have been included. These will house larger pieces of equipment and permit two biological safety cabinets to be located in a single room. This is of value for more complex types of processing where one cabinet can be prepared for the next processing procedure while the product is being handled in the other. Equipment not used directly for manufacturing, but required by several technologists (e.g., cell counters, barcode printers), are located outside of the manufacturing suites, on a long bench located in one of the corridors, but still within class 10,000 space.

Finishes in the rooms will also be changed from the current cleanroom ceiling tiles, to solid ceilings with access panels. All casework will be movable to facilitate cleaning and rearrangement. Work surfaces will be stainless steel rather than epoxy, although under-the-counter drawer units and cupboards will be topped with epoxy surfaces. Cabinets and shelf units will not be wall mounted, but will be directly attached to the base casework. The staff requested a larger number of cabinets than drawer units and asked that the doors be glazed. Where drawer units were required, the choice was for a smaller number of deep drawers capable of storing larger supplies or equipment. In addition to normal ceiling fluorescent lighting in sealed units, under-cabinet task lighting will be available in all rooms. Flooring will be seamless vinyl, although we have requested poured epoxy floor in the nitrogen bank and gowning areas where there is heavier wear. As is the case in the current facilities, all rooms will be equipped with networked computers and barcode readers. There is extensive emergency power in all suites and dual voltage supplies in the larger rooms.

The new facility will contain a substantial amount of new equipment in addition to that transferred from the existing suites. There will be very few changes to the type and source of the equipment. The majority of biological safety cabinets in the cell processing areas will not be vented. In rooms dedicated to vector handling and vector manufacturing, we chose cabinets that exhaust to the exterior of the building. There has also been discussion about the use of a high-temperature flash decontamination system to treat the exhausted air. For most suites we have selected 6-foot cabinets, as these provide the most flexible working environment. All new incubators for cellular therapy products will be air jacketed, to eliminate the task of refilling water jackets. The humidity in the chambers is controlled without the use of an internal water pan thereby reducing the risk of contamination and the task of checking and cleaning the pans regularly. The incubators have wider shelves to allow more cultures per shelf, which is important since we segregate patient products by shelf rather than by incubator. In the vector manufacturing area we will continue to use the copper-lined incubators with a self-decontaminating feature. We explored the use of alternatives to water baths but have been unable to find something that meets our needs, so we will continue to use traditional baths that are emptied and cleaned after each use. Ultralow-temperature freezers are designed for use in GMP facilities and have the appropriate data logging capabilities, although they will still be connected to a central monitoring system. They can also be connected to an external liquid nitrogen tank in the event of a complete power failure. The concept of a central major equipment area, which was a part of the design of the original facilities, was not employed in the new area. We have found that it is better to place the equipment in a particular suite and perform the manufacturing within the suite, rather than have multiple products enter a common equipment area. This helps reduce the possibility of contamination and cross-contamination. There will be one area that houses a cell counter, printers, fax machine, and desktop copier, all of which are used by multiple investigators.

A major concern has been to source a new central monitoring and alarm system. The existing facility originally had a wireless system that offered the convenience of being able to move equipment without rewiring the monitoring probes. After problems with technical support we switched to a wired system that allowed staff to access the data from their desktop computer. Over the years we experienced a number of problems with this system too, such that we did not feel that it was sufficiently reliable to be used in the new facility. We have found it difficult to find a system that addresses the problems that we have had with the previous systems, from a manufacturer who is able to provide the level of customer service that we expect. Only time will tell if we end up making the right choice.

The gowning areas have been redesigned to provide clear clean and dirty sides separated by a bench. In spite of the overall increase in space, these areas remain rather small, but should operate more efficiently than the current gowning rooms where such separation was not possible. The bathroom currently located in the gowning area has been relocated in the new facility to outside the classified space.

This is obviously less convenient for staff working in the CPF and VPF; however, numerous problems with plumbing in the old facility prompted us to make this change.

As a form of compensation, TCH has included on each floor a spacious break area equipped with armchairs, dining tables, and plasma televisions in addition to a well-equipped kitchen. This will certainly be welcomed by technologists working the extended hours common in cell processing facilities.

To meet current U.S. security requirements the gamma irradiator has to be enclosed in its own room with limited access. This is not required for X-ray sources which can be used as an alternative for irradiation. However, the cost of this equipment is substantial and we elected to keep the gamma source.

The flow cytometry laboratory will now be located outside the controlled space, so that flow technologists will not need to be completely gowned. It does, however, directly adjoin the main corridor of the CPF and is linked via a pass-through window for the transfer of samples.

Another change that was made when designing the new facility was to locate part of the nitrogen bank facility outside of the controlled area. This area would be linked to the storage facility in the controlled area via a pass-through window. This would allow transfer of products between the two areas. The advantage of this design is that staff would be able to store transport carts and collect products for administration without gowning up and entering the controlled areas. Cellular intermediates and frozen reagents used in the generation of certain types of cell therapy products could, in contrast, be stored inside the controlled area for ready access by gowned technologists.

Supply storage space is always at a premium and in the new facility an attempt has been made to maximize this by creating a larger common supply storage area that would be used to house materials for both the CPF and the VPF. As these are released, they can be transferred via pass-throughs to separate released supply storage areas. This avoids duplication of storage areas and allows the area to be staffed by one individual.

Other space that is in short supply in most facilities is filing space. The current facility has five high-density filing units in the office area and this will be increased to nine in the new area. In addition, all available wall space inside the office and general secure areas will be equipped with either filing cabinets or shelf space to provide maximum storage capacity for records. In spite of this expansion, it is likely that we will continue to use off-site storage for archived procedures and older records.

The new plan also includes a room for records review. The quantity of documentation that must be reviewed by quality assurance to release a product or to ensure ongoing compliance with regulations is such that it swamps a normal office. The review room will be a secure area in which records under review can be stored and examined. In addition to the storage space, it contains a long conference-style table and a networked computer and printer for access to electronic databases and for the generation of product certificates of analysis.

The quality control laboratory has been enlarged to accommodate the ever-increasing amount of equipment and associated computers required for testing. In addition to an en-suite tissue culture laboratory there will be an enclosed area for post-PCR amplification procedures. The space for refrigerators and freezers for the storage of test and archived samples inside the QC laboratory has also been increased.

Part III
Professional Cell Therapy Standards

Chapter 8
AABB Cell Therapy Standards

Z.M. Szczepiorkowski and E. Nunes

Abstract AABB standards have played a vital role in assisting blood bank centers and transfusion services to achieve regulatory compliance. These standards have subsequently expanded to cover the field of cellular therapies. This chapter will provide a brief history of blood banking and transfusion practices and the events leading up to the need to regulate these activities. It will also explore how the quality management system approach to regulatory compliance has been applied to the development of the AABB cell therapy standards and accreditation program.

AABB: History and Evolution

On November 17, 1947, an executive session of the Blood Bank Institute was convened in response to a request, signed by 67 attendees, that urged the Institute to consider the formation of an AABB (an American association of blood banks). The meeting in Texas resulted in the establishment of a committee, charged with oversight and organizational planning for the soon-to-be-formed association.

In the preceding years, the science and practice of transfusion medicine had advanced dramatically. During the Second World War, the U.S. military oversaw the creation of the largest chain of distribution for plasma and other blood components. Attacks on civilians in London placed new and unique strains on civilian blood banks. Serendipitously, these attacks helped physicians to appreciate the complexities of the vascular system and the limitations of transfusion, when patients expired, in spite of being repeatedly transfused.

In the immediate aftermath of the war, blood banking was developing as a medical specialty area. American blood banks that had sprung up during the war were seeking guidance and partnerships from senior professionals in the field. The Blood

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Bank Institute was the name given to the first meeting of blood banking professionals in 1947. The topics, even then, were familiar and prescient. They included techniques for antigen and antibody determinations and discussions on a nomenclature system for antigens. Administrative topics included public relations, hospital–transfusion service relationships, and personnel training.

Another event lending poignancy to the formation of AABB was the Texas City freighter explosion of 1947, an event that at an early time underscored the critical role that a robust health care system can play during a calamity [1].

Development and Evolution of Standards

In 1958, the *Standards for a Blood Transfusion Service* were published, and an independent accreditation program was developed. In 1960, the establishment of the AABB Committee on Inspection and Accreditation represented the official separation between the committees responsible for standards-setting and for inspection program overview. This delineation still exists within AABB.

While initially geared toward education, the standards and accreditation programs evolved continuously, a reflection of the growing challenges and complexities of modern health care. By keeping pace with these new challenges, AABB developed a history of helping regulated facilities meet federal, state, and local requirements.

During the late 1980s, the U.S. Food and Drug Administration's (FDA) application of current Good Manufacturing Practice (cGMP) regulations to blood banks, together with the enactment of CLIA 1988 (Clinical Laboratory Improvement Amendments) requirements in the early 1990s, increased the extent of regulatory oversight of blood banks, and resulted in increased cost pressures associated with bank operations. In 1991, AABB's standards-setting philosophy moved toward universal quality management principles based on internationally accepted standards for quality systems. The idea of applying quality management systems business models to the clinical setting was unique at the time, and predated by many years the widespread application of the philosophy of quality management to health care – a model subsequently embraced by many regulatory and accrediting bodies [2].

The original program originally designed for blood centers and hospital-based blood banks and transfusion services grew to encompass standards in five different disciplines, including cellular therapy product services. Since 1997, a discipline-specific Standards Program Unit (SPU), acting under an interdisciplinary umbrella committee, called the Standards Program Committee (SPC), has developed each set of Standards. The SPC also includes expertise of a Quality Management Subcommittee, the group responsible for ensuring consistency in quality management concepts across different disciplines. All individuals serving on these committees are volunteers who are active within their fields.

Every set of *Standards* is revised on a defined cycle, which varies from 18 to 24 months, according to the priorities of each field. The *Standards for Cellular Therapy Product Services* is published on an 18-month cycle.

Table 8.1 From 1991 to 2008: history of AABB involvement in cellular therapy through standards-setting

Year	Event
1991	*Standards for Blood Banks and Transfusion Services,* 14th edition addresses bone marrow and peripheral blood progenitor cells in dedicated chapter. Chapter includes definition, donor selection, preparation/processing, sterility, and storage
1994	AABB convenes North American Task Force for the Development of Standards for Hematopoietic Progenitor Cell Transplantation, an interorganizational task force
1995	Stand-alone Standards for Bone Marrow and Peripheral Blood Progenitor Cells published (excerpted from 16th edition of *Standards for Blood Banks and Transfusion Services*)
1996	*Standards for Hematopoietic Progenitor Cells* published (includes section on quality management)
1997	AABB Quality System Essentials published and implemented by accredited facilities
March 2000	2nd edition of *Standards for Hematopoietic Progenitor Cell Services* becomes effective
October 2001	1st edition of *Standards for Cord Blood Services* becomes effective
May 2002	3rd edition of *Standards for Hematopoietic Progenitor Cell and Cellular Product Services* becomes effective
May 2005	1st edition of newly consolidated *Standards for Cellular Therapy Product Services* becomes effective. The publication encompasses cord blood products, HPCs, and other somatic cells procured from living and cadaveric donors
March 2007	2nd edition of *Standards for Cellular Therapy Product Services* becomes effective
October 2008	3rd edition of *Standards for Cellular Therapy Product Services* becomes effective

Quality Systems Approach to Cellular Therapies

The AABB approach to the field of cellular therapies has aimed to balance flexibility in an outcome-based approach with the need for rigorous evidence-based standards. This approach was formalized in the second edition of *Standards for Hematopoietic Progenitor Cell Services* (2000) by the use of a quality template. The template, originally designed for consistency with International Standards Organization (ISO) 9000:1994, was also used in the third edition of the *Standards for Hematopoietic Progenitor Cell Services* (2002) and in the first edition of *Standards for Cord Blood Services* (2001).

In 2002, the AABB Board of Directors approved a proposal to consolidate Hematopoietic Progenitor Cells (HPC) and cord blood requirements into a single publication, alongside new requirements for somatic cells such as pancreatic islets and donor lymphocytes. The Cellular Therapy (CT) SPU sought to streamline the formatting of the document, to ensure that product-specific content could be

appropriately stratified in an intuitive way. The CT SPU recognized that other AABB SPUs relied on the ten-chapter template instead of the twenty chapters that formed the basis for the *HPC* and *Cord Blood Standards,* and elected to revise the format accordingly. The ten chapter headings are based on the AABB Quality System Essentials (QSEs), published in 1997 as AABB Association Bulletin No. 97-4. The 10 QSEs correlate directly with ISO.

Under a quality management system approach, each chapter progresses from general policies to specific procedures. For example, the "Process Control" chapter encompasses most of the work associated with collecting, processing, storing, and releasing the cellular therapy product. It opens with broad statements requiring that a facility has policies, processes, and procedures to control the work performed. The chapter then addresses several aspects of process control that apply throughout the chain of work, such as change control and process validation, sterility and operational controls, in-process and final inspection of products, and identification and traceability of materials and products. The technical standards then follow a *cascading* pattern, according to the type of donor or type of product collected. For example, Standard 5.0 addresses general process control requirements. Standard 5.7 follows the general process control requirements and begins the "workflow" section by addressing the determination of donor eligibility. It includes general requirements that apply to all products and all donors, such as confidentiality of the process and the approval for medical exceptions. These general donor eligibility standards are followed by more detailed requirements specific to the type of human cells, tissues, or cellular or tissue-based products (HCT/P) donated. Other activities that are covered include packaging and labeling, testing of HCT/Ps and donors, and abnormal results on screening and testing. Finally, Standard 5.7 and its sub-standards further require that donor qualification be performed and completed in accordance with specific "reference standards." These appear at the end of Chapter 5, and are numbered in a way that links the reader back to the body of Chapter 5. In the example given, since the reference standards are cited in Standard 5.7.1, they appear as Reference Standards 5.7.1A and 5.7.1B. These Reference Standards contain the most detailed requirements for the qualification of maternal cord blood donors, including the health history risk screening, risk factors for relevant communicable diseases, and screening for a family history of genetic disorders that might affect the therapeutic value of the product [3].

Transparency in Standards-Setting

The CT SPU deliberates over every requirement in the *Standards for Cellular Therapy Product Services.* This process is summarized in Fig. 8.1.

This deliberative process occurs before a draft is made available to the public for a 60-day comment period. The CT SPU then reconvenes to discuss the comments submitted, and to determine whether additional changes are required, or whether

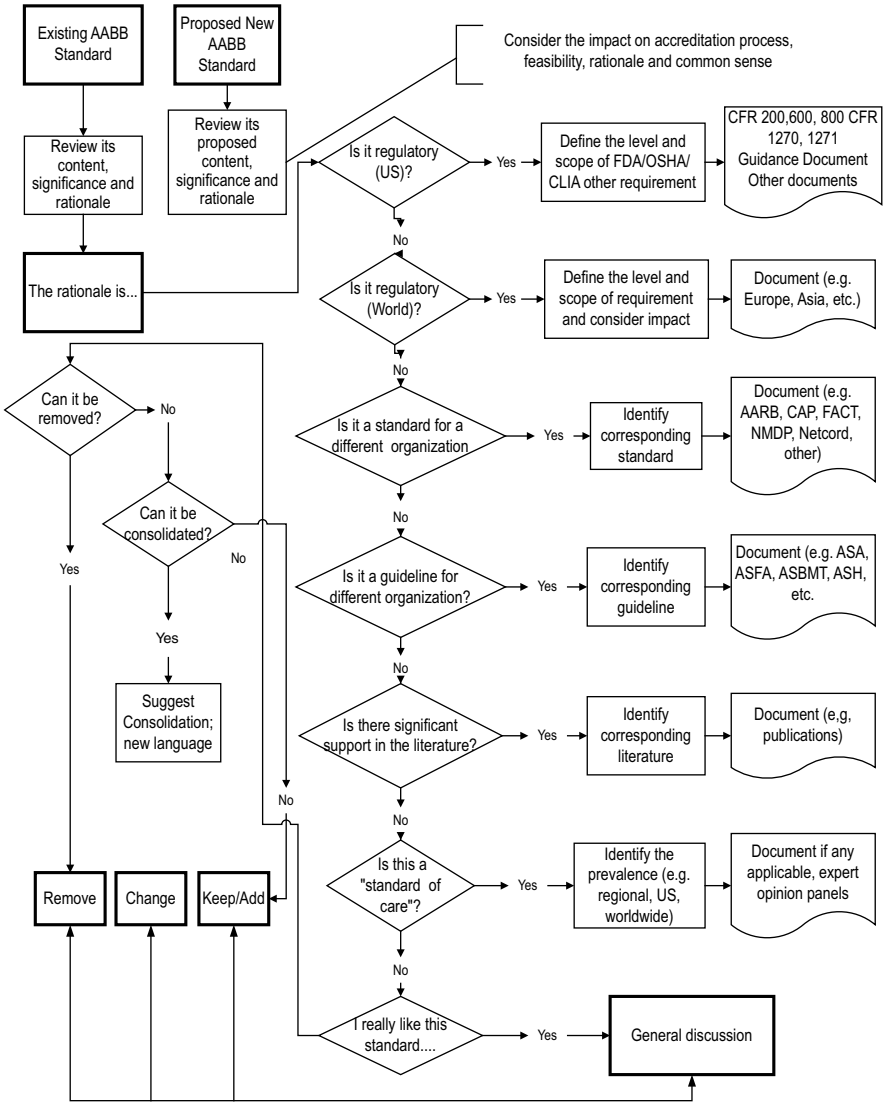

Fig. 8.1 The process of review, change, and approval of technical standards within the standards

proposed changes should be rescinded. The comment period is an integral part of the process, as it affords the CT SPU the opportunity to obtain external feedback in an effort to identify logistical challenges that the CT SPU may not have foreseen. It is a vital part of the dialogue between the accreditor and the accreditee, and helps to promote transparency in standards-setting. Figure 8.2 provides an example of how a standard can be developed as a result of public comments.

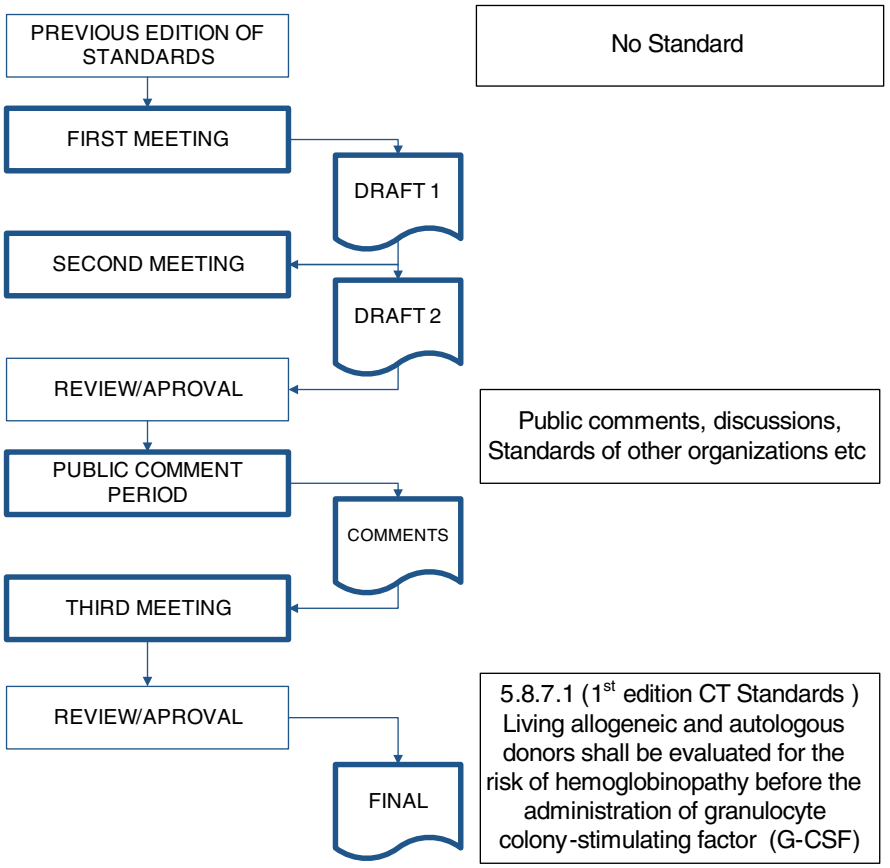

Fig. 8.2 An example from the 1st edition of *Standards for Cellular Therapy Product Services* of standard evolution based on the available data and public comments

The process used for developing AABB Standards is designed to ensure compliance with antitrust laws. In addition, representatives from external organizations (such as other standards-setting bodies and the FDA) promote consistency with laws and voluntary requirements. External feedback may also include requests for clarification of a standard, requests for variance from a standard, and reports from the accreditation program on frequent nonconformance from existing standards. The CT SPU relies on these reports to identify areas that may need revision.

In addition to external feedback and reviews, AABB Standards are also reviewed internally for technical accuracy, as well as for legal and regulatory compliance.

A description of the makeup of the CT SPU, who worked on the third edition of *CT Standards,* is presented in Table 8.2.

Table 8.2 Organizations and expertise represented on the cellular therapy standards program unit that participated in writing the 3rd edition of the standards

- Members with expertise in the field of cellular therapy (e.g., donor evaluation, collection, processing, transplantation)
- Public member (ethicist)
- FDA liaison(s)
- Liaisons from other AABB committees (CT Program Accreditation Unit, Information Systems Committee, Quality Management Subcommittee)
- Liaisons from other organizations (e.g., AATB, ACOG, ASFA, ASH, FACT, ISCT, NMDP, State of California)
- AABB BOD representative
- Consultants (as deemed necessary)

AABB provides representatives to the Alliance for the Harmonization of Cellular Therapy Accreditation (AHCTA) (www.ahcta.org)

Assessing Conformance to Standards

The AABB Accreditation program has evolved in tandem with the standards. While education has always been a component of the accreditation process, the ultimate goal of the program is to ensure that AABB-accredited facilities conform to AABB Standards, which, in turn, are developed with the goal of promoting optimal donor care, product handling, and patient treatment.

In the late 1990s, the AABB Standards and Accreditation programs underwent considerable change. The primary goal was to ensure that standards would focus on endpoints and objectives and contain only requirements. Guidance, or recommendations, on how to achieve those objectives, would be published separately. The purpose of the delineation was to ensure that accredited facilities and AABB assessors have a clear understanding of what constitutes a requirement, as opposed to what is a recommended method for meeting that requirement. To date, the strict criteria are maintained, and only the requirements published in *Standards* are used as the basis for accreditation decisions.

Accreditation

All policies, processes, procedures, and forms associated with AABB accreditation activities are documented in the *Accreditation Program Policy Manual* and on the AABB website (http://www.aabb.org/Content/Members_Area/Members_Area_Accreditation/accreditation.htm). AABB membership is required for accessing this information on the website.

AABB believes that it serves the best interests of patients and donors to extend the requirements of accreditation to as many facilities as possible. Consequently, the staff work very closely with facilities to help them achieve and maintain their accreditation. Accreditation is granted for a 2-year period. There are a number of

events that could trigger a loss of accreditation or a mandatory reassessment of the facility. These are defined in the Accreditation Program Policy Manual, a detailed information tool facilities can use to clarify administrative issues related to their accreditation.

Assessment of facilities seeking accreditation for cellular therapy is conducted by a lead AABB staff assessor and a team of volunteers. These "on staff" individuals are full-time assessors, who provide a high level of detail and consistency across assessments. Administrative checks and balances ensure that an assessor does not visit the same facility twice in a row, and that the findings of previous assessments are shared with incoming assessors in order to determine whether the root cause(s) of previous nonconformance(s) has/have been eliminated. In some cases, AABB may request proof of implementation before approving a corrective action plan. The recurrence of a previous nonconformance is an immediate decision trigger, and results in a facility's status changing from "accredited" to "conditional." Facilities in conditional status are considered to be nonaccredited. The facility is promptly removed from the list of accredited facilities on the AABB website. The list of facilities accredited for cord blood, HPCs, and other cellular therapies can be viewed at http://www.aabb.org/Content/Accreditation/accreditation.htm.

Starting in 2007, AABB assessments became unannounced. This policy ensures that facilities are always ready for an on-site assessment and decreases the perception that facilities may prepare for an assessment by rapidly bringing systems into compliance shortly before the on-site visit. The AABB team makes an unannounced visit to the facility within a 3-month window for the assessment. Implementation of this practice is designed to increase public confidence in the quality of products and services offered by AABB-accredited facilities.

Validation of Assessments

The accreditation program undergoes rigorous and continuous validation, as AABB participates in both internal and external review. Externally, AABB findings are validated by the Centers for Medicare and Medicaid Services (CMS), as a result of AABB's deemed status for CLIA. As of the spring of 2007, CMS has found no discrepancies between AABB findings and those performed by CMS inspectors.

Internal validation of assessments is performed by AABB as part of the Accreditation Program's quality system. Each year a representative sample of assessments is reassessed by a second, different team. These practices help to both ensure process control and promote continuous improvement.

Technical Highlights of the Third Edition

The third edition of the *CT Standards* has a number of new, and more detailed, technical requirements. In accordance with the AABB standards-setting process, the committee benefited from reviewing all comments submitted. Many of these helped to improve the final product.

The majority of technical standards can be found in Chapter 5, Process Control. This chapter combines standards related to very general concepts (e.g., process control, clinical outcomes, and design control) with standards following the workflow from procurement of the cellular therapy product to administration. The titles of the subsections define the critical steps in this workflow: verification of donor eligibility; medical management and emergency care of donors; procurement; procurement endpoints; packaging; distribution and transportation; inspection and testing; processing; storage and preservation; final cellular therapy product release; and administration.

There are a number of reference standards associated with this chapter. As discussed above, reference standards contain the most detailed requirements, addressing donor eligibility (including clinical evaluation and laboratory testing); requirements for notification of abnormal results; labeling of products; and processing tests for different cellular therapy products.

The overarching principle of the standards-setting process is to create a framework for provision of the highest quality product, within a well-controlled environment, while minimizing the influence of chance. However, creating the requirements for such an infrastructure must not obscure the most critical test of all – clinical outcome. For this reason, rigorous tracking, trending, and monitoring of patient outcomes is an integral part of the *CT Standards.* The quality of a cellular therapy product is only one of several variables affecting clinical outcome; nevertheless, it is the one variable over which the laboratory has the most control. Accordingly, accreditation of a cellular therapy program by AABB signifies that the facility has successfully implemented the systems which result in the highest quality products and, consequently, to the best possible clinical outcome [4].

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Chapter 9
Professional Standards for Cellular Therapies: Foundation for the Accreditation of Cellular Therapy (FACT)

P.I. Warkentin

Abstract The Foundation for the Accreditation of Cellular Therapy (FACT) was founded in 1995 to promote quality patient care and laboratory practice in hematopoietic cell transplantation (HCT) through its program of professional standards and voluntary accreditation for the procurement, processing, and transplantation of hematopoietic cell products. This chapter describes the FACT Standards and Inspection and Accreditation Program.

Historical Background

The Foundation for the Accreditation of Cellular Therapy (FACT) was initially founded as the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT). The name was changed in December 2001 to encompass, in addition to hematopoietic cell products and therapies, the new and exciting therapies using mesenchymal stem cells, dendritic cells, targeted lymphocytes, genetically modified cells, pancreatic islets, and others. This change followed the lead of the parent organization, the International Society for Hematotherapy and Graft Engineering (ISHAGE), which changed its name in 2001 to the International Society for Cellular Therapy (ISCT).

FACT is the accreditation arm of two professional societies dedicated to improvement and progress in cellular therapy. ISCT was formed in 1992 as a professional society of scientists and physicians working in hematopoietic cell manipulation. Its membership includes most of the major hematopoietic cell transplant (HCT) programs worldwide. The Regulatory Affairs Committee of ISCT developed the first draft of Standards for Hematopoietic Cell Collection and Processing in 1994. The other parent society of FACT is the American Society for Blood and Marrow

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Transplantation (ASBMT), formed in 1993 as a professional society of physicians and investigators involved in the clinical conduct of HCT. The ASBMT Clinical Affairs Committee developed the first Clinical Standards for Hematopoietic Cell Transplantation. Believing that quality care can only be achieved if both clinical and laboratory issues are addressed, the ISHAGE laboratory standards and the ASBMT clinical standards were merged into a single document in December 1994, forming the foundation for the first edition of FAHCT *Standards for Hematopoietic Progenitor Cell Collection, Processing & Transplantation*, published in 1996 [1].

FACT Standards apply to hematopoietic progenitor cells, defined as self-renewing and/or multipotent stem cells capable of maturation into any of the hematopoietic lineages; lineage-restricted pluripotent progenitor cells; and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source). These Standards also include Therapeutic Cells, defined as nucleated cells from any tissue source (marrow, peripheral blood, and umbilical cord blood) collected for therapeutic use other than as hematopoietic progenitor cells. FACT Standards apply to all phases of collection, processing, storage, and administration of these cells that have been derived from marrow or peripheral blood, including various manipulations such as removal or enrichment of various cell populations, expansion of hematopoietic cell populations, and cryopreservation.

The Standards apply to all phases of collection, processing, storage, and administration of these cells that have been derived from marrow or peripheral blood, including manipulations such as removal or enrichment of various cell populations, expansion of hematopoietic cell populations, and cryopreservation.

FACT Standards also apply to the administration of hematopoietic progenitor cells derived from cord blood; however, additional standards are required for the complexities of cord blood collection and banking. In collaboration with members of NetCord, an international organization of independent cord blood banks, these additional standards were promulgated. The first edition of *NetCord-FACT International Standards for Cord Blood Processing, Testing, Banking, Selection and Release* was developed by consensus of international experts in the field, initially published in June 2000, and revised in 2002 [2]. Now in its third edition, these international standards require all cord blood banks to maintain a comprehensive Quality Management Program, to document training of all collection and processing staff, to utilize validated methods, supplies, reagents, and equipment, to maintain product tracking, and to document and maintain details of clinical outcome. These Standards form the basis for the voluntary accreditation of cord blood banks worldwide. Fifteen cord blood banks from the United States, Europe, and the United Kingdom have achieved FACT-NetCord accreditation [3].

FACT representatives have also worked with colleagues from the European Group for Blood and Marrow Transplantation (EBMT) and ISCT-Europe, to establish the Joint Accreditation Committee of ISCT-Europe and EBMT (JACIE) [4]. The primary aim of JACIE is to improve the quality of hematopoietic cell transplantation in Europe, through its accreditation and education programs, and to work toward international harmonization of standards and regulations. There are

over 160 active FACT inspectors who have attended one or more of the 22 cellular therapy inspector training courses since 1996. JACIE adopted the first edition of FAHCT Standards in 1999 [5]. The second edition of Standards was jointly reviewed by FACT and JACIE. Most recently, the fourth edition of Standards, published in 2008, was jointly developed and entitled *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration* [6]. FACT and JACIE collaborated in three training workshops in Barcelona, Spain (January 2000, March 2001, and May 2002) to share accreditation tools and experience, and to initiate the European accreditation program. Following a pilot project in Spain between 2000 and 2003, during which FACT inspectors performed the first on-site survey, the JACIE accreditation program was fully implemented in January 2004 with support from the European Union under the Public Health Programme (2003–2008). The JACIE accreditation process is similar but not identical to the FACT process described below. Since 2004, 90 facilities in 15 countries in Europe have been accredited by JACIE. During this process, JACIE inspectors and staff found that almost all centers were functioning at a high level of excellence, with the majority having only minor deficiencies noted at the on-site inspection. When formally surveyed, these centers reported that implementation of JACIE accreditation required a significant investment of time and resources; however, all believed that the result was demonstrable improvement in the accredited program [7]. Additional information and documents are available on the JACIE website: www.jacie.org.

FACT is now an established nonprofit organization with a central office and staff in Omaha, Nebraska. The core of FACT is its active Board of Directors, comprised of an equal number of representatives from ISCT and ASBMT, the Presidents-elect of these two parent organizations, the FACT Medical Director, and the Chairperson of the Standards Committee, who represents ASBMT, ISCT, or both. Standing Committees of the Board oversee the activities of the Foundation. The FACT Board of Directors approves all publications and sets the agenda for the Foundation. The infrastructure of the organization includes a Director of Standards and Training, a Quality Assurance Director, and Accreditation Coordinators.

FACT Standards

All FACT Standards are developed by consensus of experts active in the field. Wherever possible, standards are based on established evidence from the literature. Standards are also reviewed by legal counsel and internally for technical accuracy, consistency, and regulatory compliance. Draft standards are published for comment by members of ASBMT, EBMT, ISCT, NetCord, other practitioners in cellular therapy, and the general public. Each comment is discussed and carefully considered by the Standards Committee, and incorporated as appropriate. All Standards require compliance with applicable law, but as appropriate, requirements of Standards may exceed the minimum regulatory requirements.

The Standards are developed by the Standards Subcommittees and oversight Committees. A Standards Committee Chairperson is appointed by the FACT Board of Directors for a term of 3 years to encompass the development of an edition of each set of standards, cellular therapy and cord blood banking. FACT-JACIE Standards are developed by three subcommittees: Clinical, Collection, and Laboratory Processing. Each subcommittee has a FACT representative and a JACIE representative as a co-chair. An oversight committee ensures consistency among the sections. NetCord-FACT Standards for Cord Blood Banking are developed by separate subcommittees for Collection, Laboratory, and Quality Management and Banking. NetCord and FACT representatives co-chair the subcommittees, which also include additional experts in cord blood banking.

FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration

These Cellular Therapy Standards are designed to provide minimum guidelines for facilities and individuals performing hematopoietic cell transplantation and related cellular therapies. FACT Standards require that all clinical, collection, and processing facilities develop and maintain a comprehensive Quality Management Plan that includes at least the following components:

- Defined organizational structure
- Personnel requirements
- Process development
- Agreements
- Outcome analysis
- Audits
- Management of errors, accidents, and adverse events
- Document control; product tracking; and where appropriate, validation and qualification

The current edition also includes many of the regulatory requirements from the U.S. Food and Drug Administration (FDA) and the Directives of the European Union, including donor eligibility and product labeling. The cellular therapy product proper names as defined in Standards are consistent with the names and definitions proposed for inclusion in the official terminology of *ISBT 128.*

Standards for each of the services or facilities participating in the cellular therapy program describe facility requirements, standard operating procedures, and personnel requirements for the area, including minimum education, training, experience, and competencies for each position. In addition, all services participating in a cellular therapy program are expected to maintain active and clear communications with one another. Clinical standards define a blood and marrow transplant program; enumerate support staff; cover donor evaluation, selection, eligibility, and consents;

provide minimal guidelines for administration of cellular product therapy, including the preparative regimen of high-dose therapy (where appropriate); describe the appropriate management of clinical research and IRB-approved protocols; and require the maintenance of complete and accurate records. Standards for cell collection define elements common to both bone marrow and apheresis-derived peripheral blood progenitor cells, as well as detail those requirements unique to each cell source, such as administration of mobilizing growth factor, potential need for a central venous catheter, or general anesthesia for marrow harvest. Comprehensive laboratory standards detail requirements for personnel, process controls, inventory management, validation and qualification of facilities, supplies, reagents, and equipment, labels and labeling, storage, transport, and records. Laboratory and collection personnel are expected to follow clinical outcome as one measure of product safety and efficacy.

FACT-JACIE Standards and the accompanying accreditation guidance manual are available on-line at the FACT website: www.factwebsite.org.

NetCord-FACT International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection, and Release

These Standards are intended for the field of cord blood banking, in which a cord blood bank is defined as an integrated team responsible for the collection, processing, testing, banking, selection, and release of cord blood units. It is important to note that the Standards begin with the processes of maternal donor recruitment, consent, and screening and the process of collection, rather than only covering those processes occurring in the laboratory. The Standards apply to both the banks responsible for cord blood units collected, stored, and reserved for use by a designated individual or family ("private" banking) as well as to those banks responsible for units collected, stored, and donated for use by unrelated recipients. There are some differences between standards for family units and those for unrelated donor units. Most Standards are similar; however, the methodologies employed to meet these Standards may be somewhat different in the two situations. The nature of the collection sites and the relationships among the bank, the cord blood unit collector, the donor, and the collection facility are among the prominent differences in the Standards for related and unrelated units.

Similar to the Cellular Therapy Product Standards, these standards require that each Cord Blood Bank establish and maintain a comprehensive quality management program that covers all aspects of the operation and includes at least the following: organizational structure; personnel requirements, qualifications, training, and competency; systems for document creation, review, control, and maintenance; quality assessments and audits; detection, investigation, reporting, corrective action, and follow-up of errors, accidents, biological product deviations, adverse events, and complaints; validation, qualification, calibration, and maintenance of

equipment, supplies, reagents, and materials; inventory control for reagents and products; process controls; systems for product identification, labeling, and tracking; outcome analysis; facilities and safety management; donor suitability determination; vendor qualification, and agreements with third parties. The bank staff is required to follow clinical outcomes from each unit released for transplant in sufficient detail to ensure that the procedures in use continuously provide a safe and effective product. There are standards for unique issues that may face a bank, such as inventory transfer or interruption of operations at established collection or laboratory sites. Comprehensive processing, storage, and labeling standards are consistent with *ISBT 128* terminology and labeling requirements.

Accreditation

The goal of the FACT Accreditation Program is to raise the quality of performances for all cellular therapy programs and services in the expectation that such improvements will lead to better patient outcomes [8]. The process is intended to be educational rather than punitive to allow capable and committed personnel to achieve accreditation. In addition, FACT conducts periodic training programs designed to assist the applicant program in preparation for an on-site inspection. The accreditation processes for hematopoietic stem cell transplant programs and for cord blood banks are parallel, but separate.

FACT Accreditation is voluntary and based on documented compliance with the current edition of Standards through submission of written documents and an on-site inspection. Facilities eligible to apply for accreditation are clinical transplant programs, Hematopoietic Progenitor Cells (HPC) collection facilities, and/or HPC processing laboratories. If applying separately, a clinical transplant program must utilize both a collection facility and a cell processing laboratory that meet FACT-JACIE Standards and that have a clearly defined contractual or reporting relationship. A collection service may provide services for clinical transplant programs that are or are not FACT accredited, but must use a processing laboratory that meets FACT-JACIE Standards. Accreditation may be for allogeneic transplantation, autologous transplantation, or both. Accredited programs are reinspected every 3 years, or in response to complaints or information that a facility may be noncompliant with the Standards, or as determined by the FACT Board of Directors.

The inspection process utilizes an inspection checklist corresponding to each Standard. This checklist is initially completed by the applicant facility personnel as part of the application process, and subsequently utilized by the inspectors to record observations at the on-site inspection. This methodology is effective in focusing the content of the inspection on the Standards, and in promoting thoroughness and consistency among inspectors and inspections.

The on-site inspection is the responsibility of a team of volunteer inspectors who are active and expert in the field of hematopoietic cell therapy and meet the minimum qualifications of education and training as defined in Table 9.1. For each inspection, inspectors are chosen to ensure that the team has the depth and breadth

Table 9.1 Inspector qualifications

FACT hematopoietic progenitor cell inspector
• Meet all educational and experience requirements for position
• Individual member of ISCT, ASBMT, ASFA, or NetCord
• Affiliated with FACT-accredited or applicant facility or cord blood bank
• Has attended a FACT or FACT-NetCord training course, passed a written exam, and completed successfully a relevant inspection as a trainee
• Has submitted formal application, confidentiality and other required agreements
Clinical program inspector
• Is a licensed physician
• Has a minimum of 2 years' experience in HPC transplantation
Apheresis inspector
• Has a relevant doctoral, nursing, or biological science degree
• Has completed formal training in apheresis or has at least 1 year's experience in peripheral blood progenitor cell collection by apheresis as a director, physician, or supervisor or associate supervisor
Cell processing facility inspector
• Has a relevant doctoral or biological science degree
• Has at least 2 years' experience as director, medical director, or supervisor of a cellular therapy processing facility
Cord blood bank inspector
• Individual member of organizations above, plus ISCT-Europe, EBMT, or JACIE
Cord blood bank collection inspector
• Has a relevant doctoral, nursing, or biological science degree
• Has at least 1 year's experience as a collection supervisor in a cord blood bank; or an active FACT or JACIE clinical or collection inspector
Cord blood bank laboratory inspector
• Has relevant doctoral or biological science degree
• Has at least 1 year's experience as director, medical director, or supervisor of a cord blood bank laboratory or hematopoietic progenitor cell processing laboratory

of expertise and experience to adequately survey the applicant program. There are over 160 active FACT inspectors who have attended one or more of the 22 cellular therapy inspector training courses held since 1996.

Inspectors compile observations from the on-site inspection and from review of the submitted documents into a comprehensive report that is reviewed first by trained and experienced accreditation specialists in the FACT office and subsequently by an Accreditation Committee, comprised of persons in leadership roles in the field of hematopoietic cell therapy. Citations that Standards have not been met and professional recommendations intended as suggestions for program improvement are each reviewed to maintain consistency throughout the process. Facilities with deficiencies at the end of this review are given the opportunity to document correction of each deficiency and to achieve accreditation. Documentation that deficient processes have been corrected to meet Standards always requires a written response,

and may require review by the Accreditation Committee. In the event of serious and systemic deficiencies, a repeat on-site inspection may be required following the written submissions to adequately document correction of problems noted at the initial visit. The Board of Directors retains accountability for the accreditation, and acts to resolve discrepancies or disagreements, to deliberate and determine the outcome of any appeal, and to make precedent-setting decisions, particularly as these decisions involve interpretation of a Standard.

Accredited programs are listed in the newsletters of ISCT, ASBMT, and FACT, and are posted on the FACT website at www.factwebsite.org. The first blood and marrow transplant programs in North America were FACT-accredited in March 1998. Currently, there are 173 accredited programs in North America, representing an estimated 90% of eligible programs.

The common deficiencies observed at FACT inspections were published [9]. Similar to the results observed by JACIE in its accreditation process, the results of recent on-site FACT inspections demonstrate that most programs are functioning at a high level of quality and have addressed at least most of the Standards. Deficiencies observed generally represent failure to completely address a Standard. The most commonly observed deficiencies based on inspections related to the third edition of FACT Standards are listed in Table 9.2. Quality Management and Policy and Procedure deficiencies were the most commonly cited in all three areas, clinical, collection, and laboratory. Specifically, the deficiencies that were observed in all areas included missing policies and procedures for customer-reported product failures, concern, or complaints, lack of procedures and/or approval for planned or unplanned deviations, and absence of documentation of corrective action and/or evaluation of its effectiveness. Management of products with positive microbial cultures was frequently cited; however, most programs addressed some but not all of the specific points required by Standards. Audits were also commonly cited in Collection and Processing Facilities. Frequently audits were not used effectively as a means for identifying problems and improving operations, were not reviewed to identify trends or opportunities for improvement, or were conducted either by unqualified personnel or by personnel directly responsible for the work being audited. Also across

Table 9.2 Most commonly cited standards

Most commonly cited standards (Relevant Sections of Standards are shown in parentheses)		
Clinical program	Collection facility	Processing facility
• Quality management (B4)	• Quality management (C4)	• Quality management (D4)
• Policies and procedures (B5)	• Policies and procedures (C5)	• Policies and procedures (D5)
• Donor selection, evaluation, and management (B6)	• Labels (C7)	• Labels (D7)
• Therapy administration (B7)	• Donor selection, evaluation, and management (C6)	• Storage (D9)
• Personnel (B3)/data management (B9)	• Cellular therapy product collection procedure (C8)	• Process controls (D6)

all sections, policies and procedures were commonly cited for lack of specific documents or specific processes, such as annual review or documentation of training prior to implementation. Donor consents were commonly cited for failure to document each of the required elements.

Accreditation of cord blood banks by FACT-NetCord follows a separate but similar process to that described above for cellular therapy products. Minimum requirements for inspectors are detailed in Table 9.1. There are currently over 40 active cord blood inspectors who have each attended at least one of the eight cord blood bank inspector training workshops. The process also includes a checklist specific to these Standards. Experienced inspectors spend 2 days at each cord blood bank, and assess both laboratory and collection sites. There is no separate accreditation for the laboratory processing and storage only without some control over the collection process. All fixed collection sites up to five and a percentage of additional sites are inspected. Collection sites to be visited are chosen to be representative of each variable in the collection process, including collection method (ex utero or in utero); type of collector (midwife, physician, bank employee, hospital employee); distance from the laboratory, bank, and/or intermediate storage facility if applicable; and the type of transport (staff delivery, courier, express delivery). The accreditation process allows for various processes to be used to meet the Standards; however, there must be a process in place to address each standard. The report of the inspection team is reviewed by an accreditation specialist and a separate Cord Blood Bank Accreditation Committee. Potential outcomes are the same as described for cellular therapy programs, where banks are given the opportunity to correct noted deficiencies and to achieve accreditation by documentation of corrections, either in writing only, or by an on-site reinspection of all or a portion of the Cord Blood Bank. Nineteen Cord Blood Banks in nine countries have achieved accreditation. Accredited banks are also published and listed at www.factwebsite.org.

FACT Standards for cellular therapy products and for cord blood banking are both developed by international consensus, and have gained international acceptance. FACT-JACIE cellular therapy standards have been adopted in Australia for cell collection and processing. In the United States, cooperative clinical trials groups, several states, and many insurance companies require or recommend FACT accreditation for participation. NetCord-FACT Cord Blood Standards have been adopted by the Therapeutic Goods Administration in Australia, by the World Marrow Donor Association, and AsiaCord. In this era of rapid advances in cellular therapies, both regulations and voluntary standards coexist and hopefully, contribute to the safety and efficacy of such therapies. Clinical outcomes remain the highest standard of quality care.

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Part IV
Facility Operations

Chapter 10
Standard Operating Procedures

C.G. Lindgren

Abstract Good Manufacturing Practices (GMPs) and Good Tissue Practices (GTPs) are based on the recognition that quality cannot be determined by examining or testing a finished product. Rather, the quality, safety, and efficacy of a product must be established throughout the manufacturing process. Another major tenet of GMP/GTP is "if an activity was not documented, it was not done." Both quality oversight and documentation are largely facilitated by use of Standard Operating Procedures (SOPs). This chapter reviews the structure and development of SOPs.

Introduction

The use of Standard Operating Procedures (SOPs) ensures that all manufacturing processes are controlled and codified, thereby increasing the likelihood of consistent finished products that will be acceptable for clinical use. In addition, it prevents the expansion of "tribal" knowledge, where operators may perform erroneous procedures based on unreliable information passed down orally from person to person.

The use of SOPs and a Document Control System are required by the Food and Drug Administration (FDA) for both Good Manufacturing Practices (GMPs) and Good Tissue Practices (GTPs) as described in Title 21: Code of Federal Regulations (21CFR 211.100, 211.188 and 1271.180, respectively). Additionally, accrediting agencies, such as FACT-JACIE [1], FACT-NetCord [2], and AABB [3], also require the use of SOPs. While each agency describes baseline requirements and expectations of an SOP system, they do not provide instructions on how to actually write SOPs or set up a document control program. For the novice, the task of developing and implementing a full SOP program can be overwhelming. However, armed with a little knowledge, the establishment of such a system is relatively simple. The

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goal of this chapter is to provide useful information and helpful hints in order to make the process of developing an SOP infrastructure for cell-based therapy a little less daunting.

Types of SOPs

An SOP should be written for each and every procedure that could have an impact on the quality of the product, operator safety, and the safety of the facility and environment. When planning an SOP system, it is often very helpful to review an SOP Table of Contents from another institution or facility that performs similar procedures to your own. Many of the SOPs used by one facility will be applicable to another, although there will almost certainly be some degree of difference, based on the structural design of the facility and the nature of products being manufactured.

Another extremely helpful method for deciding what procedures should be governed by an SOP is to begin with a walkthrough of all of the events that take place during manufacturing of a cell product. An example is shown in Fig. 10.1.

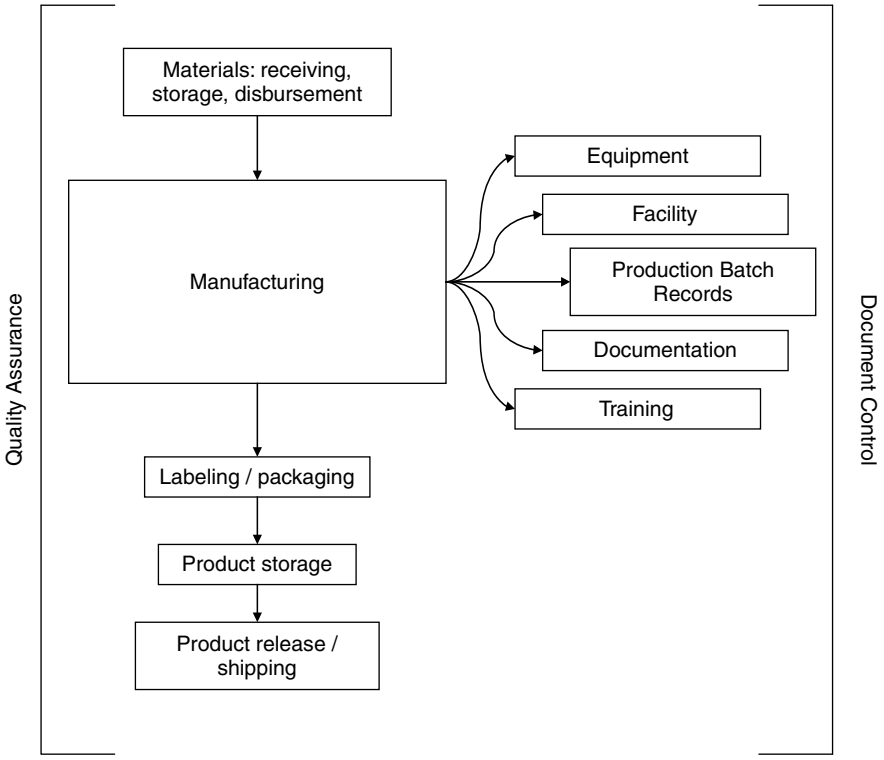

Fig. 10.1 Flowchart for activities performed in a cellular therapy manufacturing facility

When using such a flow sheet, each square can be further divided into additional SOPs. For example, subdivisions of the training square shown in Fig. 10.1 include the employee training program, gowning procedures, aseptic technique, employee laboratory exclusion policies, and so on. This is a helpful exercise to undertake to determine if your SOP program is comprehensive, as well as to prevent redundancy or overlapping of procedures.

SOPs describe procedures, policies, and processes that support manufacturing of multiple lots of a given product, such as an environmental monitoring plan, facility cleaning, record retention policy, aseptic technique, and the like. An SOP which describes and records procedures for a single lot of processed or manufactured cell product is called a Production Batch Record (PBR). PBRs contain space for manufacturing personnel to document all steps in the manufacturing process, including lot numbers of manufacturing supplies and reagents, equipment used, calculations performed during manufacturing, signatures of operators and verifiers, cell counts, and so on. PBRs will be described more fully in the Product Manufacturing chapter.

Document Control

Document control is a multicomponent system that provides a process for document approval, revision, and archiving, as well as protecting documents from accidental or unauthorized use and/or modification. Document control provides the infrastructure for management of large numbers of SOPs. The responsibility for document control can lie with groups as diverse as a small department within a large facility, Quality Assurance, Quality Control, the Laboratory Manager, or another assigned person within a smaller facility. For the purpose of this chapter, the party responsible for performing document control duties will be referred to as DC. The required elements for document control consist of the following:

- Standardized numbering system
- Standardized format and content for SOPs
- Procedure for approval of document submissions and/or revisions
- Distribution (and subsequent return) of SOPs to staff
- Training documentation
- Archiving of retired or obsolete documents
- Annual review of policies, processes, and procedures

Numbering Systems for SOPs

Development of a system for assigning unique identification numbers to SOPs is essential for efficient and effective SOP use. A numbering system allows for easy

organization, tracking, and document control of an SOP system. Numbering can be accomplished in many different ways. The University of Washington Gene and Cell Therapy Laboratory has employed a five-character alphanumeric system in which the first two characters are letters denoting the document category and the remaining characters within each document category are a sequentially assigned three-digit number beginning with 001. A description of those document categories and their corresponding two-letter characters is provided below:

DC Document Control Policies and Procedures
EQ Equipment-related Policies and Procedures (e.g., operation, maintenance, calibration)
FA Facility/Utility System-related Policies and Procedures (e.g., operation, maintenance, calibration)
GN General/Administrative Policies and Procedures (SOPs applicable to more than one department)
PR Production/Process-related Policies and Procedures (lot numbering systems, aseptic techniques)
QA Quality Assurance/Quality Control Policies and Procedures
SP Specifications for materials, components, or product
TM Test Methods/Analytical Procedures
PH Apheresis Program Procedures
BR Production Batch Records

Formatting and Content of SOPs

The appearance of SOPs can vary greatly from one manufacturing facility to another, depending on personal preferences; however, a standardized format should be developed and implemented within a facility. One of the first SOPs written should be "SOP Formatting" and should include specifics regarding:

- Font style and size
- Use of bolding and italics
- Contents of headers and/or footers
- Description for numbering sections using Roman numerals, alphanumeric or numeric outlining

Each SOP must include approval signatures from personnel with oversight over that particular procedure. Generally, these signatures include Quality Control, facility management, and/or research study principal investigator. Signatures are located at either the beginning or the end of the document. Additionally, the following information must appear on each page of an SOP:

- Title and number
- Revision level
- Effective date
- Page numbers

The following sections make up the body of an SOP:

Purpose: Provides a brief description of the intended function of the SOP.
Scope: Provides a statement that describes the applicability of the SOP, including identification of those area(s), operation(s), and/or facilities affected by the SOP.
Definitions: Defines any acronyms, abbreviations, and scientific terminology required to understand the SOP.
References: Lists applicable references such as regulations, manuals, investigator protocols, and other SOPs that relate to the SOP. If other SOPs are referenced, include the document number only and not the revision level.
Health and safety: Describes any health and safety concerns or precautions associated with the SOP.
Equipment and materials: Lists materials and/or equipment required for use in the SOP.
Procedure: Provides a step-by-step set of instructions for the activities required to perform a specified task or function.
Expected endpoints: Includes any result reporting, test results, acceptable endpoints, or objectives.
Attachments: List attachments, forms, and data report sheets included as part of the SOP.

Writing SOPs

Once formatting and numbering issues have been decided, the work of writing the SOPs begins. SOPs should describe in concise and easily understood language the details of all the steps involved in a process or procedure in a chronological manner. They should describe checks and controls that allow for assessment that the procedure meets the desired endpoint requirements, and they should not conflict with other SOPs. Basically, say what you are going to do and then do what you say.

The language used in an SOP should be unambiguous, avoiding words like *appropriate* and *adequate*, unless definitions of those words are also included. While it is vitally important not to be ambiguous, on the other hand, it is equally important not to "write yourself into a corner" by setting extremely stringent requirements for procedures in which some flexibility could be allowed. When possible and appropriate, it is best to include a window within which an operation can be performed, such as "every 7–10 days," rather than the more limited "every 7 days."

Language which would seem extremely clear in day-to-day use can be ambiguous in the context of an SOP. As an example, envision a procedure which is described as "performed monthly" in an SOP. Does monthly mean once every 4 weeks? Does monthly mean once every 30 days? What about once every calendar month, in which case the 60-day window between June 1 and July 31 would be within the range and, therefore, compliant? It can be helpful to define what terms like *monthly* mean in your facility.

It is also important to keep in mind that when writing an SOP, sometimes less specific language is wiser than very specific language. An example of this might be a procedure in which 5 ml of a liquid is to be pipetted into a 15-ml test tube. You might be inclined to state in your SOP, "Using a sterile 5-ml pipet, transfer 5 ml of liquid A into a 15-ml test tube." However, when operators perform this task, they might instead elect to use a 10-ml pipet to transfer the 5 ml of liquid. While the gradations on a 10-ml pipet are perfectly adequate to do so accurately, and the procedure has clearly been performed appropriately, you are now in deviation of the SOP because the 5-ml pipet was not used. Therefore, if it is not critical to the product, in this case it might be more prudent to say, "Using a sterile pipet, transfer 5 ml of liquid A into a 15-ml test tube."

Whenever possible, have the personnel who are to perform the procedures draft the SOP. Document control should allow for easy accessibility of an SOP template and staff should be encouraged to draft SOPs for procedures that fall within their job description. At the University of Washington's Gene and Cell Therapy Laboratory, drafts of SOPs are written by the laboratory staff and circulated among themselves for editing, before reaching outside review and Quality Assurance for approval.

New employees can be excellent reviewers of SOPs. The best way to find out if an SOP is clear and comprehensive is to have someone new try to follow it. They will almost always find the parts that are unclear and difficult to understand, and can provide valuable feedback into the clarification of such sections.

Lastly, it can be of enormous value to obtain SOPs from another institution or facility. Use the shared SOP as a starting point, because, as mentioned before, no two facilities are exactly alike, and modifications are likely to be required. For example, the size of your production suites, whether you have a classified cleanroom facility, and the number and type of products are being manufactured within your establishment will drive how often you need to clean your facility.

Validation Plans

Quite often the procedures described in an SOP are based on data generated within the same facility. The process of approving a procedure based on controlled experimental data is called *validation*. A validation protocol is written prior to initiation of the testing process, and provides a detailed description of how the process will proceed and what the acceptance criteria will be. The validation protocol requires

approval signatures prior to initiation and again following execution for acceptance of the validation test results. Validation studies are an integral part of the SOP draft process.

Document Approval

New SOPs

SOPs need to be approved before their first use. However, SOPs in draft form can be used during practice and qualification runs, and in fact it is usually helpful to "test drive" an SOP in draft form to work out any problems and unclear sections prior to final approval. Document Control (DC) typically receives the SOP drafts along with a document change request form. An example of the Document Change Request Form used at the University of Washington's Gene and Cell Therapy Laboratory is shown in Fig. 10.2.

DC will normally assign the document number to each new draft document received, enter the assigned document number into the header or footer of the document, and verify the correct formatting of the draft document prior to initiating the routing for review cycle.

DC sends copies of the draft to all parties that need to review the document. This can be done either in hard copy or electronically. Reviewers examine the document for accuracy and completeness, including verification of any formulas or calculations contained in the document. Reviewers may annotate the document with any comments or modifications that the originator must address prior to final document approval. Once all changes have been collected, reviewed, and completed by the originator, a final version is drafted. A hard copy is generated by DC and routed for approval signatures. DC will assign a date on which the SOP will go into effect. Typically, the effective date will be 5 days or more from the date of obtaining the last approval signature on the document. This delayed effective date is used to allow adequate time for document distribution and staff notification and training for the new SOP.

Revised SOPs

Individuals who possess a working familiarity with the subject matter usually initiate SOP revision requests. The person initiating the revision will submit a document change request form and request a copy of the effective, current SOP from DC. DC will provide either an electronic or hard copy to the requester, who will either "redline" the changes to be made on the hard copy, or use the "track changes" feature of a word processing application when working with an electronic copy. Again, it is helpful to have other staff familiar with the subject matter look at the revision request and provide input before it is returned to DC for routing for review. Any

UNIVERSITY OF WASHINGTON
GENE AND CELL THERAPY CORE LABORATORY **SOP No: GN-001**
STANDARD OPERATING PROCEDURE Revision No: 01
Effective date: 12/25/05
Supersedes: 00
Page no: 4 of 6
Title: Drafting, Approval, and Revision of Standard Operating Procedures, Specifications and Master Batch Records

Document Change Request Form

Document Type: [ ] SOP [ ] Specification [ ] MBR

Status: [ ] New Document [ ] Revision [ ] Retire

Document Title: _____

Document No.: _____ Revision No. _____

Originator/Author: Department:

Describe the proposed change(s) and reason(s) for the revision/retirement (attach additional pages if necessary):

[ ] Check if supporting data/justification is attached and indicate number of pages: _____

Reviewer	Accepted (A)/Accepted with Comments (AC)/Rejected (R)	Date/Initials	Number of Copies
Originating Department			
Quality Control			
Principal Investigator			
Originator			

To be completed by QC

[ ] Impacts other documents, list:

_____

[ ] Impacts validation status [ ] Impacts regulatory commitments

Comments (include date and initials of individual commenting):

Fig. 10.2 Document change request form

supporting data or documentation justifying the requested changes should also be provided. Documentation of the reason for requesting document revision and providing the supporting data is extremely important as revision of a document may impact regulatory commitments, other SOPs and documents, process, facility, or analytical method validation status, and so on. If a proposed change impacts other SOPs, they must also be reviewed as appropriate. Once again, DC will assign the revision number and provide the final hard copy for approval signatures.

Retired SOPs

On occasion, a facility may decide that a particular SOP is no longer needed. The same procedure used for new and revised SOPs of request, review, and approval, is carried out, culminating with the retirement of the SOP from active use. It is important to note that any other SOPs that reference the SOP being retired will also need to be revised to remove such references.

Document Distribution and Availability

As previously mentioned, one of the key roles of DC is to safeguard documents from accidental and/or unauthorized use. Therefore, it is imperative that originals of all SOPs are kept in a secure location and manufacturing staff only have access to the most recent revision of an SOP. This is accomplished by a DC distribution system. DC keeps a master list of all SOPs which include the SOP number and title, revision number, effective date, and the location of all copies of the SOP. The master list can be generated in a simple Excel spreadsheet, or in a larger and more involved database program such as Microsoft Access.

Once final approval of a new or revised SOP is completed, it is the responsibility of DC to distribute copies to the appropriate persons and/or departments. For hard copies, copies are typically made and stamped "COPY" on each page. Your manufacturing facility may also want to have some or all of your SOPs available for viewing electronically by staff. DC can write protect the SOP, watermark it for read-only, or use another indicator that will allow the document to be viewed but not altered.

DC is responsible for collecting and destroying all of the old copies of SOPs in circulation. That can be done by physically collecting the old copies for destruction or by documentation of the destruction of the old copies by persons within or outside of DC. DC will always keep the original revised copy for archive.

Production Batch Records (PBR)

The use of PBR SOPs represents another key area for document distribution. Although it is a regulatory requirement that distribution of PBRs is controlled, the methodology used to achieve that goal is not prescribed by the regulatory agencies. Some facilities have a very formal process whereby only the designated DC person/s can issue a PBR for use. Other smaller facilities may elect to have a laboratory manager sign out PBRs, or even utilize a policy in which the production staff sign out documents for their own use as needed. When choosing which method to employ, it is important that PBRs are available at all times for use by staff. A too-stringent document sign-out policy could lead to a situation in which the laboratory staff need a PBR for processing a product in the evening, and are unable to get it as

the authorized distribution person is gone for the day. Whatever system your facility sets up needs to control and document the distribution of the PBRs, but be flexible enough to allow the manufacturing personnel to perform their tasks in a timely fashion and deal with any unexpected situations that might arise.

Training Documentation

Often the first area that a regulatory agency will inspect during an audit is the employee training records. They want to be sure that personnel performing the work are adequately trained to perform all procedures they are tasked to do. Therefore, a system needs to be in place that documents that personnel training has been completed on new and revised SOPs. A documentation system for training may be easy in theory to design and to initially implement, but it can be one of the most difficult systems to maintain on an ongoing basis.

Some facilities file training documentation records by employee. Every time personnel train on a new or revised SOP, documentation is placed in the employee's file. Another method used by some facilities is to have the training records tied with the SOP. Essentially, all personnel are trained on a new or revised SOP, at which point the personnel sign and date a document that tracks with the master records for that SOP.

These records may be kept through electronic documentation or in hard-copy.

Archival of SOPs

When an SOP is retired, or undergoes revision and is superseded by a new version, the old versions are destroyed within the manufacturing facility to prevent their continued use. However, DC must retain and archive the original version of the revised or retired SOP indefinitely. These documents should be labeled as retired on each page to prevent them from being issued by mistake in the future. Retention of revised or retired documents is important, because during an audit some procedures may have been performed using the previous, now-revised SOP and, therefore, may be requested by an auditor. Additionally, retention of old revisions of SOPs can provide a good window from which to view how a process or procedure has evolved over time.

Annual Review

It is a GMP/GTP requirement that all policies, processes, and procedures must be reviewed annually. Annual procedural review is performed to assess the suitability of existing policies and procedures that support clinical product manufacture, and is used as an aid in determining the need for changes to or further evaluation

CENTER FOR CELL & GENE THERAPY
GMP FACILITY, 11TH FLOOR, FEIGIN CENTER
1102 BATES STREET, HOUSTON, TEXAS 77030

SOP: A01.05.8 GMP-GTP FACILITIES QUALITY MANAGEMENT PLAN

If using a printed copy, insert print date here:_____(on first page only)

16 Review and Revisions

Written by: *Adrian Gee*
Director, Quality Assurance

Reviewed by: *Jeannette Bloom*
Manager, Cell & Tissue Processing Lab

Malcolm Brenner
Laboratory Medical Director

Carlos Lee
Manager, Quality Assurance

Date issued: 01/15/08 Replaces: SOP # A01.05.7

In SOPTrak ☐ Training Forms Issued ☐ Hard copy filed & old version archived ☐

Annual Review:

2009

	Reviewed without changes	Changed and this version archived
Reviewed by:	_____	_____
QA/QC by:	_____	_____
Date:	_____	_____

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2010

	Reviewed without changes	Changed and this version archived
Reviewed by:	_____	_____
QA/QC by:	_____	_____
Date:	_____	_____

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2011

	Reviewed without changes	Changed and this version archived
Reviewed by:	_____	_____
QA/QC by:	_____	_____
Date:	_____	_____

In SOPTrak ☐ Training Forms Issued ☐ Hard copy filed & old version archived ☐

Fig. 10.3 Example of an SOP sign-off page

of manufacturing processes or SOPs. Typically, Quality Assurance is responsible for the compilation, evaluation, and documentation of annual procedural review with input and assistance from manufacturing personnel. In addition to reviewing SOPs, review of trends in deviations, rejections of materials, repetitive environmental action levels, and other supporting data are also used to ascertain whether changes in manufacturing procedures and SOPs are needed.

An alternative to a yearly review of SOPs used by some facilities is a rolling review process. The total number of SOPs are divided into sections and reviewed at different time intervals with all SOPs being reviewed once every year. Whichever method employed, documentation of the review process is required. This can be achieved using a spreadsheet such as Excel, a simple word processing document, or even showing the review process on the SOP itself. An example of the latter is shown in Fig. 10.3 from the Baylor College of Medicine.

With the development of an efficient and effective document control system and use of SOPs, a quality infrastructure is formed which provides a critical base on which assurance of quality, safety, and reproducibility of products is built.

Useful Literature

1. FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration. 4th edition, October 2008.
2. NETCORD-FACT *International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release.* 3rd edition. FACT-NetCord, Omaha, NE. 2006.
3. AABB, *Standards for Cellular Therapy Product Services.* 3rd edition. AABB, Bethesda, MD. 2008.

Chapter 11
Staffing, Training, and Competency

D.M. Kadidlo

Abstract The complex nature of cell therapy manufacturing requires well-trained, competent professionals. Training is essential to ensuring the quality of the products and services provided by biologic manufacturing facilities. Mandated by the U.S. Food and Drug Administration (FDA) in Good Manufacturing Practices (GMPs) and Good Tissue Practices (GTPs) regulations, training is as much a requirement as it is the right of passage to becoming a productive and skilled employee. This chapter describes the development and implementation of a training program for cell therapy product manufacturing staff.

Introduction

Extensive on-the-job training is generally the norm in cell therapy manufacturing, as most new employees bring with them little to no relevant Good Manufacturing Practice (GMP)/Good Tissue Practice (GTP) manufacturing experience [1, 2]. Training programs must be effective and all-encompassing, focusing not only on developing technical skills, but also scientific knowledge, experience in quality system essentials, and understanding biologic regulations, in order to develop independence and critical thinking skills.

Selection of the right employee can be just as challenging as creating a meaningful training program. As the baby-boomer generation rapidly approaches retirement age there is increased competition for qualified workers, forcing companies to put more of their resources into attracting and retaining the right people for their job needs. According to the Baldrige National Quality Program core values developed by the National Institute of Standards and Technology, companies that center their attention on the employee through personal learning see improved employee retention, personal satisfaction, and versatility [3]. Investing in the employee's personal

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career development and well-being through job optimization, training, mentoring, and career enrichment is just as important as the effort that the company puts into the products and services it provides. Integrating the needs of the company, the employee, and the applicable regulatory requirements into the design of a training program is key to development of a meaningful training program. These programs are most effective when there is an evolution in the progression of employee learning from knowledge acquisition, through skill mastery, to application, critical thinking, and dynamic problem solving.

One approach to developing an effective training program is to use the instructional system development (ISD) method [4]. This is a stepwise approach for creating a standardized training program. It consists of five phases: analysis, design, development, implementation, and evaluation. Through each step of the ISD model informational outputs and controlled process decisions are generated and incorporated into the next phase. The model begins with an assessment of training needs through the evaluation of the job task, regulatory requirements, the organization's needs, and the level of education and experience of the employee. Based on the training needs assessment, instructional objectives, training tools, and lesson plans are constructed. Once the preparative work has been completed the actual training can be performed. The final phase of the ISD model is an evaluation of the trainee and the training process via feedback mechanisms, in order to identify what went well and where process improvements can be made.

Analysis

The analysis phase of the ISD model consists of an evaluation of the training needs, whether training is truly needed, analysis of job duties and learning requirements, and development of performance objectives [4]. The first question concerns whether training is truly needed. If an employee does not know how to perform a task expected of their job, then it obvious that training is warranted. However, if an employee does not know the job expectations, or lacks resources to do his or her job, then training alone may not be the solution. In the analysis phase information regarding training needs is gathered from employees, subject experts, and the management and quality assurance unit, through interviews, observations, and questionnaires. The subject matter expert can assist in identifying essential job tasks, the key processes to be mastered, and competency measures. Management can provide input on the organization's mandatory training requirements, such as safety, disaster plans, and American Health Insurance Portability and Accountability Act (HIPAA) training. The Quality Assurance unit can assist in defining the types of training needed to comply with regulatory requirements.

Job Description

Included in the analysis phase is an evaluation of the job duties and responsibilities specific for each job class. Every employee should have a written job description

Clinical Manufacturing Scientist	
Core Competencies	**Knowledge, Skills and Abilities Needed**
Performs a wide variety of complex biologic processing and quality control testing • Functions independently in performing a wide variety of complex biologic manufacturing and testing • Performs biologic manufacturing procedures including: positive and negative cell selection, mononuclear cell separation, cell depletion or purification, cryopreservation, cell culture, vaccine preparation, cell activation, expansion and retroviral transduction. • Operates laboratory instrumentation and information systems	Knowledge of cell biology. Demonstrates aseptic techniques Problem solving skills Working knowledge of instrumentation and ability to take corrective action.
Recognizes problems and takes appropriate measures to resolve them. • Acts as a resource for problem solving, corrective action and troubleshooting for procedures and unexpected events • Initiates proper safety or emergency responses. • Consults with management if unable to resolve issues. • Exercises critical thinking to maintain and improve department productivity and efficiencies	Knowledge of safety protocols, ergonomics and body mechanics. Knowledge of infection control principles and practices. Knowledge of emergency and other relevant policies and procedures.
Evaluates testing results and processes for accuracy and appropriate intervention. • Determine if test results or process fall within normal parameters and reporting protocols. • Correlates data based on clinical knowledge, technical expertise and other conditions affecting test results or process outcome. • Takes appropriate action to recheck abnormal, discrepant, or unexpected results. • Directly communicates abnormal and critical results to appropriate parties	Critical Thinking Knowledge of laboratory testing and significance in human physiology. Knowledge of relevant factors which can influence testing results.
Demonstrates understanding of and commitment to Quality Assurance, Performance Improvement and Compliance Programs • Documents deviations and action taken. • Recognizes and communicates values and trends that exceed the QC decision levels. Takes action to resolve and consults with supervisor as needed. • Documents compliance with regulations of governmental or voluntary regulatory agencies • Collaborates with the customers to promote customer satisfaction.	Knowledge of policies and procedures that are based on FDA, AABB, FACT, CAP standards, as appropriate to the work setting. Knowledge of quality assurance principles and practices.

Fig. 11.1 Job description: clinical production scientist

that defines the job functions and outlines the physical, technical, educational, and training requirements to perform that role. Job descriptions should include a description of the job responsibilities and a detailed listing of the assigned functions needed to fulfill the expectations of the job (Fig. 11.1). Job descriptions should be used to define the training specifications.

Training Regulations

Ensuring that your training program complies with all applicable regulatory requirements is essential for biologic manufacturing. The Food and Drug Administration (FDA) requires training of all personnel in GMP and GTP regulations [1, 2]. *Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination there of, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including cGMP regulations in this chapter and written procedure required by these regulations) as they relate to the employee's functions* [1]. The FDA goes on to state that ongoing GMP training must be conducted by "qualified individuals" [1]. The specifications for that qualified individual are up to each institution and should be clearly defined in writing. Professional accrediting organizations such as AABB and the Foundation for the Accreditation of Cellular Therapy (FACT) have also defined requirements for initial and ongoing training, competency, continuing education, and trainer qualifications for all laboratory, medical, and collection staff [5, 6].

Based on the technical, organizational, and regulatory training needs assessment the next step is to compile a master list of training tasks. Table 11.1 is an example of a GMP/GTP master training schedule.

From this master list instructional objectives are created that describe what the trainee should be able to perform, under what conditions they will be able to perform the task, and the criteria for evaluation of the trainee. These objectives support the goals of the training program and aid in development of instructional tools and the establishment of standard performance measures. The following is an example of performance objective for aseptic technique.

Performance:	To be able to demonstrate aseptic technique by transferring medium from the primary container to twenty 2-ml vials according to current standard operating procedure in a manner that maintains sterility.
Condition:	The trainee will be able to perform this procedure independently.
Criteria:	The trainee will be evaluated for adherence to the SOP and acceptable microbiological test results.

The final step of the analysis phase is to prepare a document that summarizes the findings and defines the training program. The analysis document should include the training needs, goals and objectives that have been identified, the target audience to be trained, what performance measurements will be used, the financial impact that training will have on the company, and potential obstacles that could impact success. Training takes resources, both financial and human. The development of training tools and documents and performing the actual training takes time, incurs costs,

Table 11.1 Master training list

GMP/GTP manufacturing training needs
1. Orientation
a. HIPAA
b. Infection control
2. Safety
a. Chemical hygiene
b. Fire
c. Disaster plan
d. Hazardous waste
3. Technical processes
4. GMP/GTP
a. Aseptic processing
b. Facility design
c. Equipment management
d. Environmental monitoring
e. Supplies and containers
f. Quality assurance unit
g. Process controls
h. Labeling
i. Product packaging
j. Document control
k. Product testing and release
l. Storage
m. Deviations
n. Recordkeeping
o. Complaints
p. Adverse events
q. Distribution

and impacts productivity. Training budgets should be constructed to cover all initial and ongoing staff training costs and this information should be shared with management, so that sufficient resources are allocated. The analysis documents should also identify potential obstacles that could impede the development of a successful training program, such as insufficient staffing to perform training, or lack of funding to purchase training tools. A thorough needs assessment is the foundation of a training program and will be the guiding document for the next phases of ISD model.

Design of Training Program

The decisions and outputs from the analysis phase should lead to the creation of a training policy or plan. A training plan is the policy document that defines the organization's expectations, processes, and responsibilities for employee training. Similar to a Quality Plan it serves as the governing document that details the essential elements of the training program and the organization's intent to comply with applicable regulations. The training plan is the foundation from which training

procedures, tools, and records are devised [4]. For GMP/GTP manufacturing environments a training policy document may include the following elements [7]:

1. Scope
2. Types of Training
3. Responsibilities for Training
4. Personnel Training
5. Timeframe for Training
6. Role and Responsibility of Quality Unit
7. Learning Plans and Development Process
8. Qualification of Instructors
9. Documentation and Record Retention
10. Learning Assessments
11. Program Evaluation
12. Reports to Management

Scope: Includes the personnel and/or departments that are included in the training plan.

Type of training: Describes the type of training covered by the training plan: technical, GMP and GTP regulations, safety, employee orientation, initial, and ongoing training and competency.

Responsibilities for training: Defines who in the organization is responsible for the training program, training design, auditing the training program, and training execution.

Personnel training: Identifies the personnel to be trained. Technical, administrative, janitorial, and management should all be trained in GMP regulations.

Timeframe of training: Defines the timeframe for conducting training including initial and ongoing training.

Role and responsibility of quality assurance unit: Defines the role and responsibilities of the Quality Assurance (QA) unit. The QA unit should play an integral role in the training process. While QA staff may not be experts on technical procedures their role should be to review and approve of training procedures, especially GMP training, for relevancy and usefulness. QA should audit training records for completeness and ensure that instructors are qualified.

Learning plans and development process: This details the curriculum used for training and the approach used for developing training materials, such as the ISD method.

Qualification of instructors: Describes the process for qualifying training instructors.

Documentation and record retention: Defines what constitutes training documentation, such as attendance sheets, test completions, and/or instructional/training forms. Defines how long training records are maintained.

Learning assessments: Defines measures used for assessing the training, participation in ongoing competency assessments, and the corrective plan for when an employee fails training and/or competency assessment.

Program evaluation: Describes how the training process is evaluated, for example via feedback and/or surveys, and how the data are analyzed and distributed.

Reports to management: Describes the method by which management is made aware of the activities of the training program, such as number of training courses, length of time to complete training, and training feedback.

The value of establishing a policy or procedure that describes the overall training cannot be overstated. It demonstrates the organization's intent to incorporate quality elements and a standardized approach to training, and serves as the foundation on which training strategies, performance measures, supporting procedures, and training modules are developed. From the master list of training requirements the next step is to establish a standardized approach to training. This should include identifying training delivery strategies and the creation of a lesson plan template. Effective delivery strategies focus on the learning needs of the target audience, in this case the adult learner.

The Adult Learner

Since the 1920s much has been written about adult learners and what motivates them to learn [8]. Unlike children, who prefer a teacher-directed style of learning motivated by rewards, adults tend to want to be more involved in the learning process and prefer to be guided in their training [4]. This arises from the adults' fundamental need to be self-sufficient and in control of their learning [4]. Along with this core principle, there are several basic assumptions about most adult learners:

1. Adult learners are intrinsically motivated to learn.
2. Adult learners are self-directed.
3. Adult learners have a need for self-esteem, broadened responsibilities, and achievements.
4. Adults come to the job place with valuable worldly experiences that make them eager to demonstrate their abilities.
5. Adults need the value of what they are being taught [4].

These needs fuel the adult learner to know what is expected of them, so that they can be successful in their job. Training programs should not only be designed to fulfill technical training requirements, but should also incorporate the needs of the adult learner into their instructional strategies. Involving the adult learner in establishing his or her training plan, formulating and executing objectives, and assessing his or her own learning goals, will lay the foundation for developing a productive and engaged employee.

With adult learner concepts in mind, a standardized instructional format or lesson plan that demonstrates a logical progression to the mastery of learning objectives and skill acquisition can be created [9]. Use of a lesson plan template ensures that all of the critical elements are covered. A typical lesson format has an introduction, a middle in which core concepts are taught, and a conclusion that summarizes, reinforces, and evaluates the information presented.

The introduction is an overview of the lesson and provides the adult learner with the rationale for learning, performance expectations, measures of success, concepts to be covered, review of the past information, and a training timeline. The core section of the lesson plan includes presentation, demonstration, and application of technical information, feedback, and skill refinement or improvement. The last portion of the lesson reorients the learner through the reconstruction of main ideas, integration of the lesson with past lessons, review of objectives and benefit of the lesson and assessment of performance [10].

Included in the design phase is the decision on how the material is to be presented. Various methods are available including: instructor lectures, on-the-job skill development, technology enhanced (e-tools, computer simulations, Internet-based or assisted courses), self-study, cooperative learning, and inquiry-based, in the form of cases, projects, and problems [11]. In the cell therapy manufacturing setting the most common approach is instructor-based, one-on-one training of technical staff. The instructor is typically responsible for gathering and prioritizing key lesson information in a logical order and for ensuring equipment and training space are available. The instructor may use discussion, questioning, role-playing, and/or lecturing and other tools for presenting the information [12].

e-Learning

An increasingly popular approach to training, learning, or education is Internet-based learning [13]. The convenience and flexibility of using electronic or e-learning allows training and education to occur at home or work, at any hour, making training schedule easier to manage. Web-based audioconferences are an excellent means of fulfilling continuing education requirements with the most current information. A quick search on the Internet will reveal a huge variety of web-based training modules, such as mandatory training (HIPAA, safety, and GMP training), some of which are free of charge. With e-learning there is consistency and standardization in the material that is presented, and web-based training material can be updated readily, in contrast to textbooks, CDs, or videos. The upfront costs of purchasing interactive software, audio conferences, and the like, can be offset by a reduction in the "nonproductive" time that the employee instructor requires to prepare training materials. e-Learning reduces the need to travel to attend external workshops and conferences. Lastly, e-learning satisfies the needs of the adult learner by providing a self-paced approach [13].

Development

Once the lesson plan has been defined, the next step is development of instructional tools and materials. It is during this phase training that information and materials are gathered, organized, and presented to the trainee in a clear, concise, and logical progression to facilitate effective learning and skill mastery. Using the objectives for the lesson as a guide, key information that the trainee needs to know to master the task should be identified. Training information can be assembled from the standard operating procedures, scientific journals, textbooks, and applicable regulations. Many regulatory and federal agencies' websites (FDA, National Institutes of Health, Centers for Disease Control and Prevention) offer a plethora of cell therapy-related information and presentations that can be easily downloaded and used as instructional materials. Instructional tools, such as videos, interactive software, and pictures of procedures, can all be used to facilitate training. Biologic product simulations or "mock products" are an excellent means of providing hands-on training and for demonstrating aseptic technique. These products allow the instructor to correct deficiencies without stress or potential risk to a clinical product.

Information should be organized in a logical sequence, so that each step builds on the last. With the information and tools compiled and organized, the final step in development is to prepare a training document.

The training document is the evidence of record and should indicate the type of training performed, the names of the trainee and the instructor, dates of training, the critical training elements, and whether the training was successful. For each training element, acceptable measures of performance should be developed, such as: observation, reading assigned material, ability to perform the task independently, a passing test score, and so on, as shown in Fig. 11.2. For complex technical training, checklists are useful tools for ensuring all critical steps are taught.

Objective	Date Completed	Performance Acceptable Yes/No	Instructor
1. Review of SOP-519, *General Laboratory Policies*, with instructor.			
2. Review of SOP -461, *Biological Safety Cabinets*, with instructor.			
4. Review of SOP -595, *Laboratory Safety Plan* with instructor.			
5. Review of SOP -623, *Laboratory Disaster Plan* with instructor.			
6. Review of SOP -630, *Segregation of Products and Prevention of Cross-contamination* with instructor.			
7. Review of general safety/waste disposal policies (SP-001)			
9. Describe policies for disposal of biohazardous & chemical waste. Review list of chemicals used and MSDS manual.			
10. Locate the following safety equipment: handwashing sinks (2), fire pull alarms(3), eyewashes (4), fire extinguishers (3) & safety showers			
11. Describe liquid nitrogen safety precautions.			

Training Objectives Met and Competency Questions Completed Successfully YES / NO

Reviewer _____ Date_____

Fig. 11.2 Training

Implementation

The execution of the training lesson is the output from lesson planning and training preparation. During the training process objectives are demonstrated, reinforced, and evaluated. It is no surprise that an important key to successful training is the role played by the instructor. Charged with ensuring that materials are presented accurately, learned, and practiced, the instructor is also responsible for monitoring, correcting, and providing positive reinforcement to the trainee [9]. The instructor also facilitates the progression of learning by creating a supportive environment. Acknowledging achievements and efforts, and developing mutual trust by actively listening and judging the action, and not the behavior, are teaching styles that should be required of all instructors. Effective trainers use techniques such as asking questions of the trainee and presenting problem-solving scenarios that will reinforce training concepts and foster confidence and analytical thinking skills [11]. Not all employees make effective trainers. It is management's role to define the qualifications for instructors based on criteria such as experience, demonstration of competency, and/or additional training. Instructor qualifications should be defined in the training SOPs.

Evaluation

Evaluation is the final phase of the ISD model. This includes not only evaluation of the trainee and his or her ability to meet established objectives, but also an assessment of the overall effectiveness and value of the training program. Whether through exams, written assessments, or observations there must be documented objective evidence that the trainee is competent to perform the specific job functions. Periodic review of the effectiveness of the training program identifies strengths and areas for improvement. Feedback can be obtained from the trainee using surveys and interviews and by asking questions about the adequacy of training, the effectiveness of the trainer, the usefulness of the instruction tools, and for suggestions for improvement [14].

Competence

Evaluation of competence prior to the completion of independent performance of a job function and ongoing on an annual basis is a requirement of laboratory accrediting agencies, including College of American Pathologists (CAP), AABB, and FACT [15, 5, 6]. AABB and CAP have instituted additional requirements for repeat competency assessments for new employees within the first 6 months of employment [5, 15]. There are many approaches to assessing competence [16–18]. These provide the opportunity to spot errors and introduce improvements to preserve the quality of the product and/or service provided. One strategy for the design of a competency program is to model it on the U.S. federal regulations for clinical diagnostic or testing laboratories. In 1988, the government passed an amendment to the Clinical

Laboratory Improvement Act (CLIA'88) that detailed requirements for training and ongoing assessment of competency for laboratory personnel [19, 20]. While it is arguable whether the requirements of CLIA'88 apply to GMP/GTP manufacturing, the requirements are nonetheless useful. Using the CLIA'88 regulations as a model, the essential components of a competency assessment program are as follows [19]:

1. Direct observation of performance
2. Monitoring the recording and reporting of results
3. Review of intermediate test results, Quality Control (QC) records, proficiency testing results, deviations, and preventive maintenance records
4. Assessment of technical performance via clinical or simulated products or test samples, internal blind testing samples, or external proficiency testing samples
5. Assessment of critical knowledge and problem-solving skills

Direct observation is a means of assessing adherence to SOPs, technical skills, accurate interpretation and notification of test results, and appropriate completion of QC processes. Figure 11.3 is an example of competency assessment. Review

Employee:			**Title:**		
Competency Assessor:			**Competency ☐ Annual ☐ Initial**		
Process Assessed: **Receipt and processing of an allogeneic peripheral blood stem cell product**					
	Competency Measurement **A = Procedure Reviewed** **B = Direct Observation** **C = Unknown specimen**		**Level of Competency** **1. Competent and can perform independently** **2. Competent and can perform independently, able to assess the competency of others** **3. Failed competency measurement**		
Date	**Measurement**	**Assessor Initials**	**Competencies**	**SOP #**	**Level of Competency**
	B		Product receipt and inspection.	P-22	
	B		Donor eligibility determination	P-23	
	B		Operation of equipment	P-18, P-09, P-26	
	C		Performs all QC testing	P-55	
	B		Demonstrates aseptic technique	P-02	
	B		Completes documentation	P-01	
	B		Product release	P-12	
	A		Adverse Event Reporting	P-33	
☐ The employee has demonstrated competency in performance all applicable processes associated with the above procedure ☐ The employee requires retraining for the following:_____					
Supervisor Review_____ Date_____					

Fig. 11.3 Competency assessment

of intermediate test results, QC records, proficiency testing results, product deviations, and preventive maintenance records can also serve as evidence of competency and understanding quality control and quality assurance. Assessment of technical proficiency can be achieved through use of clinical or simulated products or test samples, internal blind testing samples, or external proficiency testing. CAP offers proficiency surveys for human somatic cells and associated QC testing methods including hematology, flow cytometry, and microbiology. StemCell Technologies™, a commercial supplier of clonogenic assay kits, offers proficiency testing to its customers. Critical knowledge and problem-solving skills can be assessed by asking the employee questions (oral or written) on technical or procedural problems, and testing their knowledge of GMP/GTP and other regulations. Another approach to demonstrate critical thinking abilities is to ask the employee to document real examples of problem solving that they have encountered within the past year [20].

Competency requirements should be specific to the job description. Emphasis should be placed on assessing areas that are at a high risk or most critical to product safety, problematic, or prone to error [20]. The qualifications of the competency assessor and the role of QA in the review of competency should be described in the appropriate SOP.

Remediation

The intent of competency assessment is to evaluate employee performance, to pinpoint potential problems, and to address issues before product quality or patient care is impacted. Correction or remediation of the problem is an important element of the competency process. Unless the employee is deliberately remiss in his or her performance, remediation should not be punitive, but an educational and improvement process that focuses on the performance and not the behavior [20]. Remediation should include identification of the problem, root cause analysis of the failure, and a corrective action plan. If it is determined that an employee has failed a competency assessment, the first step is to review the event to evaluate the adequacy of the competency process to ensure that procedures and objectives were clear and concise, and not confusing or ambiguous. If the competency process was acceptable, the employee should be evaluated to ascertain the cause of the failure (knowledge issue, technical error, or documentation error). Based on these findings a corrective action plan can be formulated. This may include rereading the procedure and discussion with supervisor and retraining, followed by reassessment, either by observation or by exam. As a last resort, the employee may need to be reassigned to another area. During the review process the employee should not be allowed to perform that particular task until remedial action has been completed and they are deemed competent.

Recordkeeping

Records of training and competency must be kept on file, together with documentation of the employee's signature, initials, and inclusive dates of employment. FACT standards require that records be maintained in a confidential manner and as required by governmental laws and regulations [6]. Personnel records should include:

- Job descriptions for all job classes
- Resumés, curriculum vitae
- Relevant degrees as required by job description
- Training records: initial, ongoing
- Institution-required training (e.g., Safety, HIPAA, infection control)
- Continuing education
- Annual competency
- Annual GMP training

Conclusion

An effective training and competency assessment program is the foundation for developing skilled and productive employees. It is integral to ensuring the safety of the products and services provided by GMP/GTP facilities, and its value cannot be overstated. By remembering that training is as much about personal satisfaction as it is a technical requirement, we can better design training programs that will be mutually satisfying to the institution and the employee.

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Chapter 12
Cleaning Procedures

A. Gee and D.L. Lyon

Abstract Professional standards and governmental regulations all require that the facility and equipment be maintained in a clean condition. This in turn requires the development and implementation appropriate and effective methods for cleaning, procedures to monitor if these methods are indeed effective, and documentation of cleaning procedures on an ongoing basis. This chapter discusses various approaches that can be used to fulfill these requirements in different types of cell processing facilities.

Choices and Getting Started

One of the major choices when planning or renovating a facility is whether you will classify your space as Class 10,000 by the use of High-Efficiency Particulate Air (HEPA) filtration and dedicated air handlers. If this is the case, in addition to normal cleaning requirements, you will need to develop a program of environmental monitoring that provides assurance that the facility is consistently meeting its classification. This is discussed separately in another chapter. It is mentioned here only as a reminder that the cleaning staff in classified facilities must understand gowning procedures, and staff and waste traffic patterns, to assure that the classification is not compromised. Otherwise the steps in developing a cleaning plan are generally similar for both classified and unclassified space.

A good general recommendation is to start by monitoring your space for the types of organisms that are present inherently. This is ideally done when the construction of a new facility is completed, the equipment is in place, and the area has undergone a routine cleaning using regular cleaners and disinfectants that are used elsewhere in the institution. At this stage avoid cleaning any equipment. The surfaces in the facility can then be sampled using touch plates, taking care to record the locations at

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which the samples were taken. The organisms that are detected should be speciated by a local microbiology or hospital laboratory. Most academic cell processing facilities are located in close proximity to the hospital laboratories and infection control units. These provide an excellent resource for your facility. It is advisable to take the results of your first survey to infection control and discuss with them whether these are typical skin flora, or if there are particular organisms of concern. They will generally also be able to recommend cleaning and disinfecting agents with broad specificity to use for routine cleaning. It is a good idea to follow their advice if possible to avoid the risk of developing resistant organisms that could pose a threat if they spread to the hospital environment. It is important to select at least two and preferably three "approved" cleaning agents that can be rotated on a regular basis to reduce the risk of the appearance of resistant organisms. It is also advisable to avoid choosing a mixture of phenolic and nonphenolic disinfectants as their residues on cleaned surfaces can interact to produce a sticky residue.

Once you have a list of potential cleaning agents, pull the product sheets from the manufacturers and check how they are to be prepared and used; have they documented activity against the organisms detected in your facility, what is the required contact time with the surface to be cleaned, are they compatible with the material on which you intend to use them, e.g., can they corrode certain surfaces; are there specific precautions that should be taken when using the agent? Also pull the appropriate material data safety sheets to check any exposure risks.

The remaining component in preparing the cleaning agents is the water. You should have the tap water in your facility tested if you intend to use this. Determine the hardness and the microbial content, prepare a dilution of the disinfectant, and test the dilution for the presence of any resistant organisms that would be spread during cleaning. Ensure that the tap water is suitable for diluting each cleaner, e.g., does it meet any water hardness specifications? Usually, the city or local water department can provide you with this information. If there are any critical specifications that the water must meet, a testing schedule should be implemented to ensure that these are being met routinely. It is also possible for water supplies to become contaminated with microorganisms at low persistent levels. In such cases, it is a good idea to introduce a terminal UV sterilizer (Fig. 12.1) to rectify such problems – naturally this will also require some form of monitoring to assess ongoing efficacy. For cleaning critical areas some facilities have elected to install a dedicated clean water system, or to use bottled water, and again these should be monitored.

The next step is to draft a Standard Operating Procedure (SOP) for facility cleaning. Remember that in many cases this will be read and used by staff who are not scientists, and whose first language may not be English. Clarity and simplicity rule here, so keep instructions and associated documentation simple and easy to understand. There are general principles that apply to all facilities, including starting cleaning at the greatest distance from the door and working back toward the door, using disposable mop heads, not reentering fully cleaned rooms, and so forth. You may also want to consider various degrees of cleaning; for example, a routine cleaning in which the floor and benches are cleaned, versus a complete clean which would also include walls, windows, and ceilings (Fig. 12.2). Also give some thought

Fig. 12.1 Automatic disinfectant dilution system attached to a UV sterilizer on a water system

to videotaping an experienced cleaner cleaning a room as this may get the message over more clearly than reading pages of text. It is also important to emphasize that it is understood that mistakes may happen and these must be reported and not concealed.

The cleaning staff must then be identified and trained. Very few academic facilities use contract cleaning services due to the expense. The alternatives are to have the manufacturing staff or the institutional cleaning staff perform cleaning. Both are acceptable and have their own advantages and disadvantages; however, whichever is selected, there must be documented training of cleaning procedures. There should be detailed clear instructions on which cleaning agents are to be used, how they are to be prepared and used, which areas are to be cleaned, and how the cleaning procedure is to be documented. Institutional cleaning staff needs to be informed as to the critical importance of cleaning these areas and of following instructions to the letter. One way to facilitate this is to ask the institution to dedicate a specific cleaning team, so that turnover and retraining can hopefully be reduced. Whoever does the cleaning, it is a good idea to audit them regularly to ensure that practices have not drifted over time. Audits should also be performed if monitoring indicates a downward trend.

Fig. 12.2 Complete cleaning of a production suite

Schedules and Practices

Once the reagents have been selected, the SOP written, and the staff trained, the next stage is to perform a test clean of the facility using all of the above. This procedure starts by monitoring the areas to be cleaned using touch plates. The cleaning is then performed and the areas are remonitored. The results should be examined carefully, usually with the involvement of quality assurance and the facility director. In the absence of a formal validation study (discussed later), there should be a substantial reduction in the colonies counted postcleaning. Ideally, such a test should be performed for each of the cleaning agents that you intend to use.

If the results of these tests are satisfactory, the cleaning schedule can be developed (Fig. 12.3). This will specify which cleaning agents are to be used that day, which areas are to be cleaned and by whom (if you have multiple cleaners), and the type of cleaning that should be performed, e.g., routine or complete, together with any special instructions. There should be accompanying documentation (including initials or signatures) to record who prepared the cleaning agents and who cleaned each area.

These schedules should be closely related to the environmental monitoring program. This allows identification of problem areas and adjustment of the cleaning schedule and practices to address these specifically. The monitoring program can

WORKSHEET AW03.2.3B: CLEANING OF GMP CONTROLLED ENVIRONMENT

SCHEDULE FROM: TO:

CLEANER TO USE	VESPHENE II ( ) LpHst ( ) Use 5% BLEACH ( )				
	Lot Number of Selected Disinfectant:			QS for week: Yes No Initials:	
DAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
Clean Floors and	C 1130.41	C 1130.25	C 1130.40	C 1130.32	C 1130.44
Wipe down Equipment	C 1130.43	C 1130.28	C 1130.19	C 1130.14	
		Gowning Areas	Gowning Areas	Gowning Areas	
		Corridors*	Corridors*	Corridors*	
COMPLETE CLEANING					
Clean Floors, Walls	C 1130.38	Gowning Area	C 1130.31	C 1130.16	Gowning Areas
and Ceilings	C 1130.22	Corridors*	C 1130.34	C 1130.17	Corridors*
of Room Number		C 1130.35			C 1130.26
		C 1130.19			C 1130.29

Special Instructions

* Corridors consist of C1130.23, C1130.37, C1130.13
Wipe down ALL of the door handles with 3MQuat before leaving for the day.
Bleach must be used only on the floor and 3M Quat must be used for wiping down the equipment.

CLEANED BY:					
CLEANED BY:					

REVIEWED BY DATE:

This SOP and/or worksheet is being provided for informational purposes and therefore requires validation

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Fig. 12.3 Example of a cleaning schedule

also help identify the emergence of resistant organisms or particular seasonal problems, such as mold. There is unfortunately a time disconnect between collecting monitoring data and receiving the results. For this reason, it is a good idea to read contact plates at early (2 day) and late (7 day) time points, to try to reduce the lag between identifying a problem and being able to address it.

The schedule chosen for cleaning is dependent on both the size and workload of the facility and its work habits. Some facilities operate a campaign style of manufacturing in which rooms are stripped of supplies and reagents, thoroughly cleaned, restocked, monitored, and released for manufacturing of a specific product. Routine cleaning is then performed at the end of each production activity and is usually restricted to benches and equipment. At the end of manufacturing, the room then undergoes a complete changeover (see Changeover Procedures section of this chapter for discussion). In the case of most cellular therapy products this style of manufacturing is not typical. Manufacturing times may range from less than a day to many months. In the latter instance, it is often the case that other products may commence or cease manufacturing in the same room over an extended period of time, thus making true campaign manufacturing impossible. Under these circumstances, a schedule of routine and complete cleaning can usually be developed by examining the production schedule for the room and tailoring the cleaning schedule accordingly.

There are a number of factors that can impact on the efficacy of a cleaning program. For example, standing water and drains can be a potent source of microorganisms. Many facilities ban the use of water baths and others allow them, but mandate that sterile water is used, and that they are drained and cleaned immediately after use. Classified facilities will usually not contain sinks and will use air-jacketed, rather than water-jacketed, incubators. Seasonal variation will also impact the type of contaminants that are detected. In warm humid weather, fungus and mold can become a major problem. This may be controlled in classified facilities by reducing the humidity; however, achieving a good balance between temperature and humidity can pose a challenge to some air handlers. A hidden source of mold can be slow leaks above suspended ceilings. These need not be severe enough to penetrate the ceiling but simply keep the inner surface of the tiles damp. This provides a breeding ground for mold and fungus, which are then spread by air movement. Addition of bleach as a supplement to regular disinfectants may help, although we have found it variable in efficacy. If using bleach, it is important to specify the concentration (usually 5% v/v) and to restrict its use to walls and floors as it can cause corrosion and pitting if applied to painted or metal surfaces. There are some disinfectants with higher activity toward fungus and mold and these can be used effectively to spot-treat affected areas.

Validation of Cleaning

The preceding sections have described the selection and simple testing of cleaning reagents. Many regulations indicate that, as products proceed toward regulatory

approval, validated procedures should be used. Many facilities have struggled with how to validate cleaning procedures. Our approach has been simplistic. Having performed the initial monitoring procedures described above, we identified our potential contaminants as predominantly skin flora. To validate cleaning efficacy, we then seeded the test surface with skin contaminants by having a staff member cover it with handprints. The surface was then sampled using RODAC™ plates and cleaned using the disinfectants and procedures specified in the cleaning SOPs. It was then resampled. The colony counts were plotted pre- and postcleaning and resistant colonies were speciated. Prior to validation, specifications were set as to the fold reduction in colonies that must be achieved after cleaning. This straightforward approach generated sufficient data to demonstrate the efficacy of our cleaning procedures.

If viruses are to be included in the validation, the study design is somewhat more complicated. Replication-competent virus should be used and this should be handled in an area outside the manufacturing facility. A transport medium must also be selected that will maintain the viability of the virus between sampling and setting up the detection assays. Your hospital or university virology department can be of great assistance in selecting the appropriate virus for these studies and in performing the detection assays that will be required. For manufacturing of Phase I/II products it is a good idea to consult with your regulatory authority to determine whether this type of validation will be acceptable.

Equipment Cleaning

Equipment cleaning should be performed by the user(s) of the equipment. This avoids potential damage by cleaners who are not familiar with the specific device. It also minimizes the time that elapses between use and cleaning of the equipment. Obviously any spills that occur during use must be cleaned up immediately, and this section deals predominantly with routine cleaning procedures.

Instructions for cleaning are found in the equipment manual, and time should be spent reviewing the manual and excerpting the sections that deal with cleaning and maintenance. Most manuals will recommend the type of cleaners that should be used and the schedule for cleaning. For example, it may be acceptable to clean the walls and tray of a biological safety cabinet after each use and to clean under the removable tray on a weekly schedule. Read the maintenance section of the manual carefully to ensure that cleaning of all components of the equipment is addressed, and whether these should be performed by the manufacturer or by laboratory staff. In most cases the disinfectants and cleaners used to clean the facility may also be suitable for cleaning equipment, but check carefully and take care to exclude any that may cause corrosion or pitting of metal or painted surfaces. Also staff need to be reminded that these reagents require a minimum contact time to do their job, and may be completely ineffective if sprayed on and immediately wiped off. In some cases it may be necessary to “rinse” the cleaned surface by spraying with 70% isopropanol.

As stated previously, documentation is required for cleaning procedures. This includes cleaning SOPs, staff training records, and cleaning logs. These can be structured in a number of ways. Some facilities choose to have a single SOP that deals with cleaning of all major pieces of equipment. Others elect to have an SOP that covers the cleaning and operation for a specific piece of equipment. Cleaning records should indicate, at a minimum, when the equipment was cleaned and by whom. Since many regulations also require that it is possible to track which products were handled using each piece of equipment, the cleaning log can also be used as this record. This is accomplished by recording the component that was handled and the cleaning of the equipment subsequently performed on the same document.

Policies also need to be developed as to how and when equipment is to be cleaned when it is not in use. Some equipment may not be in service for a complete recording cycle, e.g., an incubator. Is the policy to continue to clean the device, or to turn it off, take it out of service, and completely clean before reuse? This needs to be determined and documented. At the other end of the spectrum there may be incubators that are in very heavy use, and how are these to be cleaned without risking potential contamination of products? Is it acceptable to delay cleaning and to transition the products to a different incubator over time to facilitate cleaning? Again a uniform policy should be developed. Equipment monitoring for contamination should be a component of the cleaning process. In most cases this can be restricted to biological safety cabinets and incubators which are potentially the most susceptible to contamination. Sampling of surfaces can be conducted on a predetermined schedule using RODAC^{TM} plates. As described earlier, checking the plates at 2 days may hasten the detection of contaminants and allow earlier intervention in the form of recleaning and remonitoring. Evidence of persistent contamination should trigger removal of the equipment from use until the source is identified and cleared. Persistent contaminations may be prolonged due to the design of the equipment. Incubators with complex internal architecture (particularly around the HEPA filters) can be difficult to clean properly. Incubators with copper interiors and with self-decontaminating heat cycles provide a method for dealing with persistent contaminants and should be considered. Maintenance of adequate humidity in the incubator is often achieved by the use of water pans. These are a potent source for contamination and this can be reduced by regular cleaning of the pans, addition of antimicrobial agents to the water (take care to select those which do not generate a potentially harmful atmosphere within the incubator), and by the use of sterile water in the pans.

For understandable reasons, liquid-nitrogen storage banks are often not included on the cleaning schedule. It is usually felt that the risks posed by disturbing products during cleaning outweigh the benefits achieved by cleaning. In addition, most facilities now use vapor-phase storage where the products are not in contact with liquid nitrogen and any contaminants that it may contain. If liquid storage is used, consideration should be given either to changing to vapor-phase storage, or to implementing a cleaning procedure in which products would be transferred to a different bank, and the original storage container would be drained and cleaned.

Changeover Procedures

Changeover procedures are designed to ensure that when multiple products are handled in a facility the risk of contamination and cross-contamination is minimized. This can be achieved in a number of ways; however, in every case a formal procedure must be developed, implemented, and its use documented.

The type of changeover procedure is largely determined by the type of manufacturing that is being used. Mention of campaign production was made earlier. Under this system a product is handled in a dedicated space from start to completion of manufacturing. Prior to manufacturing the room is stripped of reagents and supplies, the room and all equipment thoroughly cleaned, restocked, and monitored. The documentation of the changeover is usually reviewed by quality assurance and they release the room for manufacture of the specified product.

Where there is sufficient space to dedicate manufacture of a product to a single room, such an approach is feasible. In most cases, however, it is necessary to use a room for the preparation of multiple products. Where possible, these should be products of the same type prepared under the same protocols. Under these circumstances it is necessary to implement a different type of changeover procedure. This will generally consist of cleaning equipment and surfaces used during the previous activity, documenting this cleaning, and removing all worksheets associated with the preceding product. All products must be labeled with the appropriate information (such as that specified by the Foundation for the Accreditation of Cellular Therapy; FACT) and segregated in such a way as to prevent mix-ups. In some cases this can be achieved by dedicating one incubator per product, but in large volume facilities this may not be possible, and segregation by incubator shelf may be necessary. Whatever system is used, it should be audited to ensure that it is being followed rigorously. When starting to work a new product, it is advisable to have a second staff member double-check the product label and the product information on the worksheets that are to be used. It is also a good idea to dedicate specific bottles of supplemented media to the manufacture of a particular product. This reduces the risk of contamination and cross-contamination of products.

A further check on identity that is possible for certain products is to compare the HLA type of the original donor to that of the finished product.

Summary

Effective cleaning procedures are vital for the prevention of contamination. The components of a cleaning program should include demonstration that the selected cleaning/disinfection products are effective against microbes that are found in the manufacturing facility. This requires the development of an environmental monitoring program that will be used to identify these microbes and to monitor the efficacy of the cleaning program (see elsewhere in this volume). Staff must be carefully trained in cleaning practices and should be audited to ensure that the practices are

being maintained. Training must also include aseptic technique, which is fundamental to the preparation of uncontaminated products. Evidence of cleaning relies on documentation and this should include preparation of the cleaning agents, documentation of room cleaning, documentation of equipment cleaning after use, and a record of what products were being manufactured using that equipment.

Prevention of cross-contamination between products relies on good changeover procedures. These should ensure that all traces of a product are removed from a manufacturing site before a different product is introduced. Again careful documentation of each step in the procedure should be maintained. This can be coupled with release testing of the final product to demonstrate that there has been no introduction of other materials during manufacturing, including microbes or cells from a different product.

Useful Literature

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Chapter 13
Environmental Monitoring

A. Gee and D.L. Lyon

Abstract Cell processing facilities should implement and maintain a program of environmental monitoring regardless of whether product manufacturing occurs in an unclassified laboratory space or in a Class 10,000 cleanroom. Classification of space will, however, necessitate that there is documentation to verify that the specific classification is maintained on an ongoing basis. In facilities that are unclassified, the aim of the environmental monitoring program is primarily to demonstrate that conditions are appropriate for operations, and that the risk of possible contamination and cross-contamination is eliminated or minimized. This chapter discusses the development and implementation of an environmental monitoring program.

Regulations

The language used in this section is predominantly taken from Title 21 of the U.S. Code of Federal Regulations (21 CFR). The terminology and grammar used are characteristic of governmental publications, and may be difficult for the first-time reader. It is a good idea to become familiar with "regulatory-speak" since it is carefully crafted to mean exactly what it says and no more! In later sections of this chapter more user-friendly language will be used.

Good Tissue Practices (GTP)

U.S. GTP regulations do not mandate that products must be manufactured in a classified or cleanroom environment, although many centers elect to do so. The regulations (21CFR Part 1271.195) state that in the case where environmental conditions could reasonably be expected to cause contamination or cross-contamination of

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human cells, tissues, and cellular and tissue-based products (HCT/Ps), or equipment, or accidental exposure of HCT/Ps to communicable disease agents, the environment must be adequately controlled; and there must be provision of proper conditions for operations. The regulations indicate that, as appropriate, the following must be controlled: temperature and humidity, ventilation and air filtration, cleaning and disinfecting of room and equipment to ensure aseptic processing, and maintenance of equipment to control conditions for aseptic processing operations.

In order to verify that the environmental control systems (including necessary equipment) are adequate and functioning properly there must be periodic inspections. In the case where environmental conditions may reasonably be expected to cause contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents the conditions must be monitored; and, where appropriate, there must be monitoring for microorganisms. Records of environmental controls and monitoring activities must be maintained (21CFR Part 1271.195).

Good Manufacturing Practices (GMP)

GMP regulations are more detailed in comparison to the GTPs as they relate to buildings and facilities (21CFR Part 211, Subpart C). The GMPs emphasize facility design and construction to facilitate cleaning, maintenance, and proper operations. While there are specific requirements for the construction of buildings regarding lighting, plumbing, and sanitization, the requirements for operations are relatively generic in nature, e.g., operations must be performed within specifically defined areas of adequate space. The GMPs prescribe that there must be systems in place for the cleaning and disinfecting the rooms and equipment, for monitoring environmental conditions, and for maintaining the equipment used to control aseptic conditions.

Air handling systems used for GMP manufacturing are to be designed to provide adequate ventilation, air filtration, air heating, and cooling (21CFR Part 211.46). The GMPs state that equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product. Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If the air is recirculated to production areas, there must be measures to control dust recirculation. The key words here are “when appropriate”; this creates a dilemma for many cell therapy laboratories in trying to determine to what extent these regulations must be applied.

“Academic” GMP and GTP

In response to the GMP regulations many academic institutions manufacturing Type 351 products for Phase I/II Investigational New Drug (IND) studies elected to install cleanroom manufacturing areas, usually rated at Class 10,000 (i.e., maintaining

less than 10,000 particles of greater than 0.5 μm per cubic foot of air). This usually involves the installation of specialized dedicated air handlers equipped with in-line and/or terminal high-efficiency particulate air (HEPA) filters. This is expensive in terms of both the installation and the maintenance costs, and mandates a more complex monitoring program to ensure that this environment is maintained.

Given that Part 211 regulations were implemented primarily to cover manufacturing of traditional pharmaceuticals, it is reasonable to ask how relevant these are for the preparation of cellular therapy products.

The traditional approach for the manufacturing of Type 361 (GTP) products is within nonclassified space using Class 100 biological safety cabinets (BSCs). Typically, BSCs are used for "open" processes while functionally "closed" procedures are performed outside the BSC. This is in marked contrast to many pharmaceutical manufacturing operations, where the room environment provides the main protection for the product. Locating BSCs in a Class 10,000 area may provide some additional level of protection, but does it warrant the expense and labor associated with the maintenance of that Class 10,000 environment? Even with the added expense and resources, some facilities have elected to consolidate preparation of both Type 361 and 351 products into a cleanroom environment as a means to unify operations. The decision as to whether to perform manufacturing in a cleanroom or in unclassified space is critical and often difficult to make. Consultation with the Food and Drug Administration (FDA) is strongly advised. The proposed European requirements appear to be more detailed and stringent.

As stated in FDA regulations, where a specific cleanroom classification has been established it must be monitored. The 2008 U.S. Pharmacopeia chapter on "Microbiological Evaluation of Cleanrooms and Other Controlled Environments" provides an excellent review of cleanroom classifications, monitoring practices, choices of sampling sites, surface sampling, and the like, and can be used as the foundation on which to build an environmental monitoring plan for a cleanroom environment. For academic cell processing facilities that are manufacturing either GTP or Phase I/II GMP products, the FDA has not provided clear guidance on what is expected in an environmental monitoring plan. Some very basic information is available in a Guidance document "CGMP for Phase 1 Investigational Drugs" published by the FDA in 2008. Most facilities will develop an approach based on traditional pharmaceutical practices, seek feedback from the regulatory agency, or wait until they are audited!

From our own experience we have found the agency flexible as to the components of the plan, as long as there are adequate data to support the specific classification of the areas. Particulars, such as the frequency of monitoring, the establishment of alert levels for particulate counts, and so forth, appeared not to be "set in stone," but the facility is asked to explain the reasoning on which these were chosen. The same is undoubtedly true for monitoring plans for non-cleanroom environments. As a consequence, this chapter provides some of the basic elements of monitoring plans, rather than providing a model template.

Elements of Environmental Monitoring

For the vast majority of cellular therapy product manufacturing, a Class 100 biological safety cabinet provides the primary protection from contamination of the product by the environment. It is, therefore, essential to have documentation to show that BSCs are functioning within specifications. This can be achieved in a number of ways. The first, and most important is to ensure that BSCs are maintained and calibrated regularly (at least yearly, or preferably more frequently). In some facilities this is regarded as sufficient, while others record pressures from the Magnahelic® gauges at each use, or perform particle and/or viable counts within the BSC during use. Care must be taken that placement of counting equipment inside the cabinet does not disrupt the air flow. As an alternative, fallout plates may be used. Airborne organisms settle on these plates which are then incubated to promote colony formation. The normal exposure period is no more than 4 hours for one plate. Personnel monitoring may be performed by sampling staff members' gloves and coats and cabinet surfaces using touch plates before, during, and after production activities.

Provision of a controlled environment is intimately related to the selection and proper use of cleaners and disinfectants, and is addressed elsewhere in this volume. Facilities should validate these reagents to ensure that they are effective against microbes that have been detected in the manufacturing environment. It is essential to link the environmental monitoring and cleaning schedules so that out-of-specification results can be addressed promptly by recleaning and remonitoring contaminated areas.

Air Handling

Even in a non-cleanroom environment it is a good idea to have a diagram of the heating, ventilation, and air conditioning (HVAC) system of the facility that includes details about the air handling unit(s). This will provide some indication of the type of air entering the facility, the likelihood of potential contamination or cross-contamination of this air, whether the air handler supplies other areas, the recirculation patterns, and the exhaust arrangements. A log should be kept of maintenance on air handlers, filter changes, and checks on pressure relationships where appropriate. This is even more critical in cleanroom environments, where detailed records on air handler maintenance, checks on pressure relationships, air changes per hour, and recirculation patterns are mandatory. In both types of environments it is important to understand the pressure relationships between manufacturing rooms and adjacent spaces. Depending on the nature of the product being prepared, pressures should be consistently positive or negative to prevent contaminants entering the room, or to prevent biohazardous agents from escaping from the manufacturing area, respectively. In cleanroom environments it is normal to have inbuilt pressure monitors, with displays or linked to alarm systems. In other facilities smoke guns can be used to detect the direction of air flow.

Fig. 13.1 Electronic counters. *Left*: Viable counter with agar strip shown at the base. This strip is inserted into the drum-shaped chamber at the top of the counter and viable organisms are deposited onto the strip during monitoring. *Right*: Particle counter

The environment outside the BSC should also be monitored regularly. If the room is classified, it will be necessary to perform regular sampling of the air for particulates and for viable organisms. Electronic counters are available for both types of sampling (Fig. 13.1). The sampling sites should be chosen to be in proximity to areas where critical operations are occurring, e.g., at benchtop level. Care should be taken not to place counters next to refrigerator compressors or running centrifuges as these can elevate particulate counts. The sampling location should be recorded together with the temperature and humidity during sampling (most electronic counters automatically provide this information) (Fig. 13.2). The counters are set to draw in a predetermined volume of air in which particles of different sizes are enumerated or viable organisms are trapped on an agar strip that can be removed from the counter and placed in an incubator, or held at ambient temperature depending on the type of organism that is being detected.

Each facility should develop an action limit for counts. This will trigger a predetermined remedial response. In Class 10,000 facilities, an action limit of > 8000

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WORKSHEET: BW03.01.8C ENVIRONMENTAL MONITORING WORKSHEET

Analyst :____________________ Date:________________

THIS FORM IS DOUBLE-SIDED – REMEDIAL ACTIONS RECORDED ON REVERSE

	NON-VIABLE PARTICLE COUNTS Alert = 8,001 – 9,999 particles per ft³ Alarm ≥ 10,000 particles per ft³			VIABLE PARTICLE COUNTS Alert Limit = 0.4 CFU per ft³ Alarm Limit ≥ 0.5 CFU per ft³					
Room#	Laboratory Operation	Monitoring Site	Particle Counts	°C	% RH	Viable 2 – 4 day	Viable 7 day	¹CFU per ft³ 7 day	QAQC#
		☐ DYNAMIC ☐ STATIC	☐ PASS ☐ FAIL					☐ PASS ☐ FAIL	
		☐ DYNAMIC ☐ STATIC	☐ PASS ☐ FAIL					☐ PASS ☐ FAIL	
		☐ DYNAMIC ☐ STATIC	☐ PASS ☐ FAIL					☐ PASS ☐ FAIL	
		☐ DYNAMIC ☐ STATIC	☐ PASS ☐ FAIL					☐ PASS ☐ FAIL	
		☐ DYNAMIC ☐ STATIC	☐ PASS ☐ FAIL					☐ PASS ☐ FAIL	
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		☐ DYNAMIC ☐ STATIC	☐ PASS ☐ FAIL					☐ PASS ☐ FAIL	
		☐ DYNAMIC ☐ STATIC	☐ PASS ☐ FAIL					☐ PASS ☐ FAIL	

2-4 day CFU Count: Analyst:__________________ Date:__________ *CFU/ft³ = [CFU₇ day per 1000 liters] divided by 35.3*

7 day CFU Count: Analyst:__________________ Date:__________ Production Reports Attached: ☐

This SOP and/or worksheet is being provided for informational purposes and therefore requires validation Reviewed by:

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Fig. 13.2 Recording sheet for environmental monitoring

particles per cubic foot may indicate an emerging problem that requires checking of air handlers and HEPA filters. High viable counts may suggest ineffective cleaning procedures, hidden colonies of fungus, or other causes. Alert or alarm limits are generally set at the classification standard, e.g., 10,000 particles per cubic foot in a Class 10,000 facility. An alert should trigger closure of the manufacturing area, in-process testing of the product under manufacture at the time of the alert, documented remedial action, and remonitoring prior to releasing the area for use.

Monitoring Frequency

Frequency of sampling will depend on the nature of the ongoing activity and how critical it is in the manufacturing process. The U.S. Pharmacopeia provides guidelines that suggest that Class 100 and 10,000 areas should be monitored during each work shift. Most academic facilities are not in continuous operation, and it is up to

each facility to develop a monitoring plan that reflects the manufacturing environmental conditions over a specified period. Important information can be obtained by documenting what was happening in the room during monitoring. For example, were staff present, was there high traffic, was equipment in use? For some products the decision may be made to perform monitoring during every step of manufacturing, whereas with others it may be sufficient to conduct random monitoring over the months that it may take to prepare the product.

In addition to air sampling, monitoring procedures can include surface and personnel sampling using touch plates. This can be used to detect types of resident microbes that populate the manufacturing areas and the efficiency of their removal by the cleaning and disinfection procedures. Surface monitoring also alerts staff to the emergence of new organisms in the suite and to seasonal changes that may occur that would necessitate a change of disinfectants.

Changeover Procedures

Cross-contamination of products is a particular concern in GTP regulations (21CFR Part 1271.145). This can be addressed by the establishment of written changeover procedures that are implemented following the completion of a manufacturing step on one product, and prior to starting work on a different product in the same area. The basic elements of a changeover procedure should include documentation that the first product has been removed from the area and that all associated paperwork, reagents, and materials have also been put away. There must be additional documentation that all the equipment that was used has been cleaned following the approved procedures. The second product can then be introduced into the area. For some products and facilities a more comprehensive changeover may be used (Fig. 13.3). This would include removal of all unused supplies and reagents from the area, complete cleaning of the room followed by restocking, full environmental monitoring, and review of the changeover procedure and formal release of the area by the quality unit prior to starting manufacture on the next product. Again it is up to each facility to determine what best meets their needs and to discuss this with the appropriate regulatory agency.

Interpretation of Data

The volume of data generated by environmental monitoring, and the actions that should be taken in response to an out-of-specification result, pose a tremendous challenge to facilities. At the present time, most cell therapy products are prepared in relatively small batches that are all terminally tested for sterility and purity. In the case of a positive test result from a product, environmental monitoring data may facilitate detection of where and when contamination may have occurred. In contrast, an out-of-specification result during environmental monitoring invariably does

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WORKSHEET: HW03.21.2A MANUFACTURING SUITE CHANGEOVER

MANUFACTURING SUITE #:
LAST PRODUCT PREPARED IN THIS SUITE:
DATE MANUFACTURING OF THIS PRODUCT WAS COMPLETED:
DATE OF START OF CHANGEOVER PROCEDURE

DATE	ACTIVITY (Should be performed in sequence indicated)	PERFORMED BY
	INITIAL PREPARATION	
	All opened & unopened packages removed from suite	
	All opened packages discarded	
	All unopened packages removed from VPF	
	Items removed from cabinets	
	Cabinet interiors wiped down	
	CLEANING OF EQUIPMENT	
	Centrifuge as per SOP A04.14	
	Biological Safety Cabinet as per SOP A04.07	
	Refrigerator as per SOP A04.13	
	Water Bath as per SOP A04.12	
	Microscope as per SOP A04.08	
	Incubators as per SOP A04.39 for air-jacketed ☐ as per SOP A04.10 for water-jacketed ☐	
	Pipettors – surfaces cleaned with 70% ethanol	
	CLEANING OF SMALL EQUIPMENT	
	Equipment type: How cleaned:	
	Equipment type: How cleaned:	
	Equipment type: How cleaned:	
	Equipment type: How cleaned:	
	Equipment type: How cleaned:	
	ROOM CLEANING, RESTOCKING & RELEASE	
	Complete cleaning of room performed	QC to sign:
	Room restocked	Tech to sign:
	Environmental monitoring performed (attach copy of results)	QC to sign:
	Room released for production	QA to sign:
	New product to be manufactured in this suite (if known)	QA to sign:

Items to be attached:

Environmental monitoring results ☐ Signed for QC by:_____

Cleaning schedule showing date of last complete clean ☐ Signed for QC by:_____

Disposition of Forms

Place a copy of this form at the start of the Batch Record for the new product ☐ Performed by:_____

Place the original of this form in the Changeover Records Binder ☐ Performed by:_____

Page 1 of 1

Fig. 13.3 Worksheet for room changeover

not result in contamination of the product under manufacture. This is particularly true in the case of monitoring conditions within the room in which manufacturing is being performed in a BSC. It is unlikely that an increase in particle count in the room will have a negative impact on the environment within the BSC. Changes in

the room environment would primarily be of importance when open manufacturing procedures were being performed outside the BSC.

Another difficulty arises when trying to deal with changes in viable counts. An out-of-specification viable count will be first detected anywhere from 2 to 7 days after monitoring has been performed. It may or may not be associated with an out-of-specification total particle count. The question is what to do with this information. As stated previously, changes in parameters in the room are unlikely to affect products being handled in the BSC, and does an increase in the room viable count warrant additional in-process sterility testing on the product? It is up to the facility to develop policies to deal with these issues. Our practice has been to remonitor rooms with high particle counts immediately, to determine whether the reading is transient or more serious. If it is thought to indicate a problem with the air handlers, the production activities in the BSC would be completed and the room then closed until an investigation can be initiated and remedial action taken. High *viable* counts within the room detected *after* the completion of a manufacturing step, would not automatically trigger in-process sterility testing of the product that was being manufactured at the time of monitoring. It would, however, prompt a complete clean and remonitoring of the room before the next production activity.

In contrast, high particle counts in a BSC would immediately result in that cabinet being taken out of service until the cause was found and remedied. High fallout or viable counts would result in in-process testing of the product that was under manufacture at the time, and in the absence of an increase in the particle counts in the hood, would trigger complete cleaning of the cabinet and remonitoring.

Over the course of 8 years of environmental monitoring we have been unable to establish any link between product contamination and environmental conditions in the manufacturing suite. Contaminations were extremely rare and generally were the result of the receipt of a contaminated starting sample due to an infection in the donor, or to a contaminated catheter.

A standard policy should be to speciate all product contaminants, to investigate the likely source and take appropriate remedial action. Unless there are extraordinary circumstances, contaminated products should be destroyed. In the case that a contaminated product may be required due to urgent medical need, the antibiotic sensitivities of the contaminating organism should be determined and this information provided immediately to the intended recipient's physician.

The use of antibiotics during manufacturing should be avoided as these can mask poor aseptic technique and chronic low-level contaminations. Clinical use of products containing antibiotics may cause allergic or adverse reactions in recipients if not removed from the product before administration.

Databases

As stated previously, data management is a challenge when developing an environmental monitoring program. Even small programs will generate large amounts of information. There is a need to link monitoring data with cleaning information. It is

also important to be able to track results from a sampling site over time. The easiest way to do this is to develop some form of electronic database. This should detail the test site, date, type of monitoring performed, the results obtained, and the actions taken in response. Follow-up actions consisting of remonitoring, cleaning, speciation of contaminants, and determination of sensitivities should also be captured. It is vital to develop this database as early as possible in the monitoring program, and preferably before the program starts. Retrospective data entry is extraordinarily difficult and is likely to reveal problems that were not properly addressed at the time!

The database is an essential quality improvement tool (Fig. 13.4). It can be used to detect important trends in environmental parameters that may be indicative of emerging problems with air handlers, aseptic technique, cleaning practices, resistant organisms, and so on. It also provides the facility with a background picture of their normal working environment that can be used to modify working practices including changes to the monitoring program over time.

Monitoring programs can be complex, expensive, difficult to maintain, and are often not used effectively to assure the best possible manufacturing environment. For academic cell processing facilities the major challenge is to develop a program that meets regulatory requirements, but is not overly burdensome. Most guidelines relate to the manufacture of pharmaceutical agents by commercial entities and it is difficult to determine which components are relevant to cell therapy manufacturing. At present, most regulatory agencies have issued rather generic regulations that are of limited help in developing a monitoring program. Under these circumstances, perhaps the best approach is to read the regulations and to structure a program that best meets how your facility operates. Take advantage of the opportunity to submit your plan to the regulators before implementation, or for the brave of heart, wait to get their reactions when the facility is audited. In either case, you should be able to explain the rationale behind the structure of the plan, and wherever possible, to present supporting data for the decisions that were made.

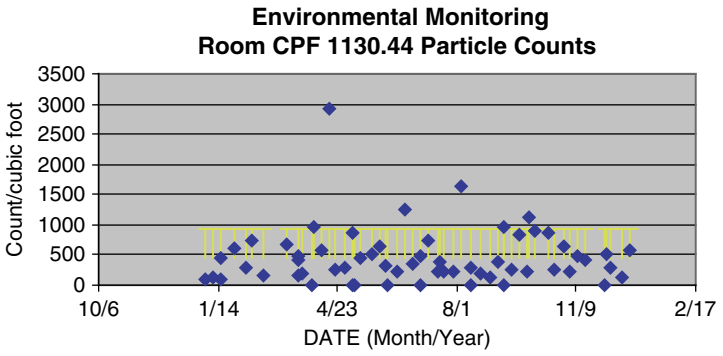

Fig. 13.4 Trending of environmental monitoring data

Summary

Monitoring programs can provide important information on the quality of the manufacturing environment. This in turn helps ensure the purity and safety of the products. Currently cellular therapy products are in many ways different from traditional pharmaceuticals, as most are prepared in small lots in Class 100 BSCs. Each lot is tested before release, and is usually assigned to a specific recipient. The trend toward operating in a cleanroom environment with all of the associated expense and workload of monitoring this "secondary" environment monitoring should be weighed against the small potential benefit to the safety of the product.

Acknowledgments The authors are grateful to the staff of the CAGT for their help in the preparation of this article, and especially to Carlos Lee and Crystal Silva-Lentz for their suggestions and the photographs.

Useful Literature

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Chapter 14
Supply Management

A. Gee and C.M. Rooney

Abstract Both Good Manufacturing Practice (GMP) and Good Tissue Practice (GTP) regulations address the management of supplies used in the manufacture of drugs and cellular therapy products. In addition, a controlled and auditable procedure for the management of supplies and reagents is essential to provide traceability, and to ensure that products are manufactured using safe and appropriate components. This chapter describes procedures for developing and implementing a supply management system.

Regulatory Requirements

This section covers the regulations that address supply management in the United States. These are published in Title 21 of the Code of Federal Regulations (CFR). This summary uses the official terminology and grammar of the CFR, which can be somewhat tortuous for the beginner. In subsequent sections covering methods for compliance the regulations are described in simpler terms. Definitions of the types of products covered by the two sets of regulations are provided elsewhere in this volume.

Good Tissue Practice (GTP) Regulations

The GTP regulations (21 CFR Part 1271.210) state that supplies and reagents should not be used until they have been verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases.

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In this context, verification can be performed either by the facility that uses the supply or reagent, or by the manufacturer. Most facilities rely on the manufacturer for verification, and the most usual mechanism is to ask the manufacturer to provide a Certificate of Analysis (CoA) with each lot of the supply or reagent. CoAs must be kept on file if they are used as the primary means of reagent/supply verification. At a very minimum, the CoA must state that reagents used in processing and cryopreservation of human cells, tissues, and cellular and tissue-based products (HCT/Ps) must be sterile. Under GTP regulations, if a reagent is manufactured in-house, the process used for production must be verified or validated, and these records must be maintained.

The GTP regulations also require that a record be kept of the receipt of each supply or reagent, and that these must include the type, quantity, manufacturer, lot number, date of receipt, and expiration date for each reagent or supply. When the material is used for the preparation of HCT/Ps, the lot of supply or reagent must also be documented.

Good Manufacturing Practice (GMP) Regulations

The applicable GMP regulations pertaining to supplies (21 CFR Part 211, Subpart E) were originally written for pharmaceuticals and, as a result, are more detailed.

These specify that there must be written procedures that describe the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures, and that these procedures must be followed. Components (and containers and closures) must be handled and stored in a manner that prevents contamination. Storage must be off the floor and the spacing must allow cleaning and inspection. Each of the containers or groups of containers of drug or drug component must be identified with a distinctive code for each lot in each shipment. This code is used to record the disposition of each lot. The code should also allow the reagent to be identified as quarantined, approved, or rejected.

The GMP regulations covering the receipt of reagents state that incoming materials must be examined visually for appropriate labeling, container damage or broken seals and contamination. Incoming supplies must be stored under quarantine until they have been tested, or examined and released. In 21CFR Part 211.84 there is extensive information on the testing and approval or rejection of components, containers, and closures. In brief, these state that reagents and materials must not be used until the lot has been tested or examined, and released for use by the quality control unit. The samples used for testing must be representative of the lot, based on some form of algorithm. There are detailed instructions on how samples are to be taken and more generic regulations on the type of testing that should be performed, e.g., each lot of component that is liable to microbiological contamination shall be subjected to microbiological tests before use.

Materials that meet written specifications relating to identity, strength, quality, and purity and related tests may be approved and released for use. Materials that do

not meet these specifications must be rejected. Rejection requires that the materials be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations.

Management of released supplies must use a first-in first-out (FIFO) system, so that the oldest approved lots are used first. The regulations do allow deviations from this approach if the deviation is temporary and appropriate. Materials that have been stored for long periods, or have been exposed to conditions that might adversely affect them, must be retested or reexamined as appropriate.

Other sections of Part 211 describe in extensive detail the types of procedures that must be followed when handling, sampling, and testing components. These are more specifically designed for pharmaceutical manufacturing. They address, for example, the position at which samples must be taken from containers and mandatory testing to verify the identity of each component of a drug component. This can be difficult for manufacturers of Phase I/II cellular therapy products to interpret. In practical terms, many of these issues will be addressed when an Investigational New Drug (IND) for the manufacture of a specific cell therapy product is submitted to the Food and Drug Administration (FDA) or other regulatory agency.

Compliance with GMP manufacturing regulations has been recognized by the FDA as being on a continuum. Products prepared for early phase clinical trials are not required to comply fully with all GMP requirements; however, as the studies progress toward manufacturing the product for Phase III studies, full compliance must be achieved, e.g., a fully validated manufacturing process should be in place. In 2008, the agency published a new guidance and a final rule regarding GMP compliance for Phase I investigational drugs. Under the final rule (Federal Register 73, 40453, 2008) these are exempt from the requirements of 21 CFR Part 211; however, the FDA retains authority over these agents under the IND and Food, Drugs and Cosmetics Act regulations. Investigators and facilities are strongly advised to read the guidance "INDs – cGMP for Phase I Investigational Drugs." This covers somatic cell therapy and gene therapy products and describes what is expected in terms of staff, quality control, facility and equipment, control of components, production and documentation, laboratory controls, and the like.

Establishing a System

Compliance with both GMP and GTP supply management regulations can usually be achieved in an academic cell therapy manufacturing facility by adopting a single procedure that meets the required elements of both sets of regulations. The following is a suggested approach that is provided for guidance.

In this section, "reagents" would be analogous to the FDA components, in that these are biologicals, chemicals, and pharmaceuticals used for manufacturing. "Materials" are other things such as culture flasks, pipettes that are used during the product preparation. The term "supplies" is used more generically to cover both materials and reagents.

The first step is to write the formal procedures that will be used to source, order, release, and manage supplies. These should describe the process in sufficient detail to meet the regulatory requirements described previously. At a minimum, they should cover how supplies are received and what documentation is generated, quarantining of reagents and materials, generation of release specifications, release procedures, management of inventory, documentation of use during manufacturing, and management of recalls. As a general rule, it is useful to include a flowchart illustrating the passage of supplies from receipt through use in manufacturing (Fig. 14.1).

Approved Supplies

The safest approach when sourcing supplies for cell therapy product manufacturing is to select reagents and materials that are already approved for human use. There are many reagents that meet this classification and these are widely used in hospitals and stocked by the hospital pharmacy or supply room. It is worthwhile taking the time to meet with a pharmacist or blood banker when developing a manufacturing procedure to determine what approved reagents and materials are available. Consideration should always be given to changing to an approved reagent whenever it is available, provided that its performance will meet the specifications required. Some reagents may be approved for indications other than for use in manufacturing cellular therapy products, and these should also be considered, since they will usually meet more stringent specifications than any research-grade supply.

Supply Release Specifications

Even if approved reagents and/or materials are used, it is important to keep CoAs on file and to determine whether additional testing may be required to ensure that the supply functions properly for the intended use. This is usually done in the context of establishing a formal supply release specification worksheet (Fig. 14.2). This describes the reagent or material and the intended source or vendor. It then lists the specifications that must be met before that supply can be released for use in manufacturing. Some of these specifications may be met by the information that is included on the CoA, while others may necessitate further testing, e.g., ability to support cell growth. The supply is held in quarantine until the results of all tests are available. These are then reviewed by the quality group and they determine whether the supply should be approved for release or rejected. In many cases, all of the information required for release may be available on the manufacturer's CoA and the release procedure would essentially consist of logging in the supply details on receipt, documentation that it arrived in satisfactory condition (undamaged, at correct temperature, and so on), and ensuring that the CoA for that lot is on file. Sample CoAs should be reviewed by the quality unit prior to sourcing the supply to ensure that the appropriate information, e.g., on sterility, is contained within the document.

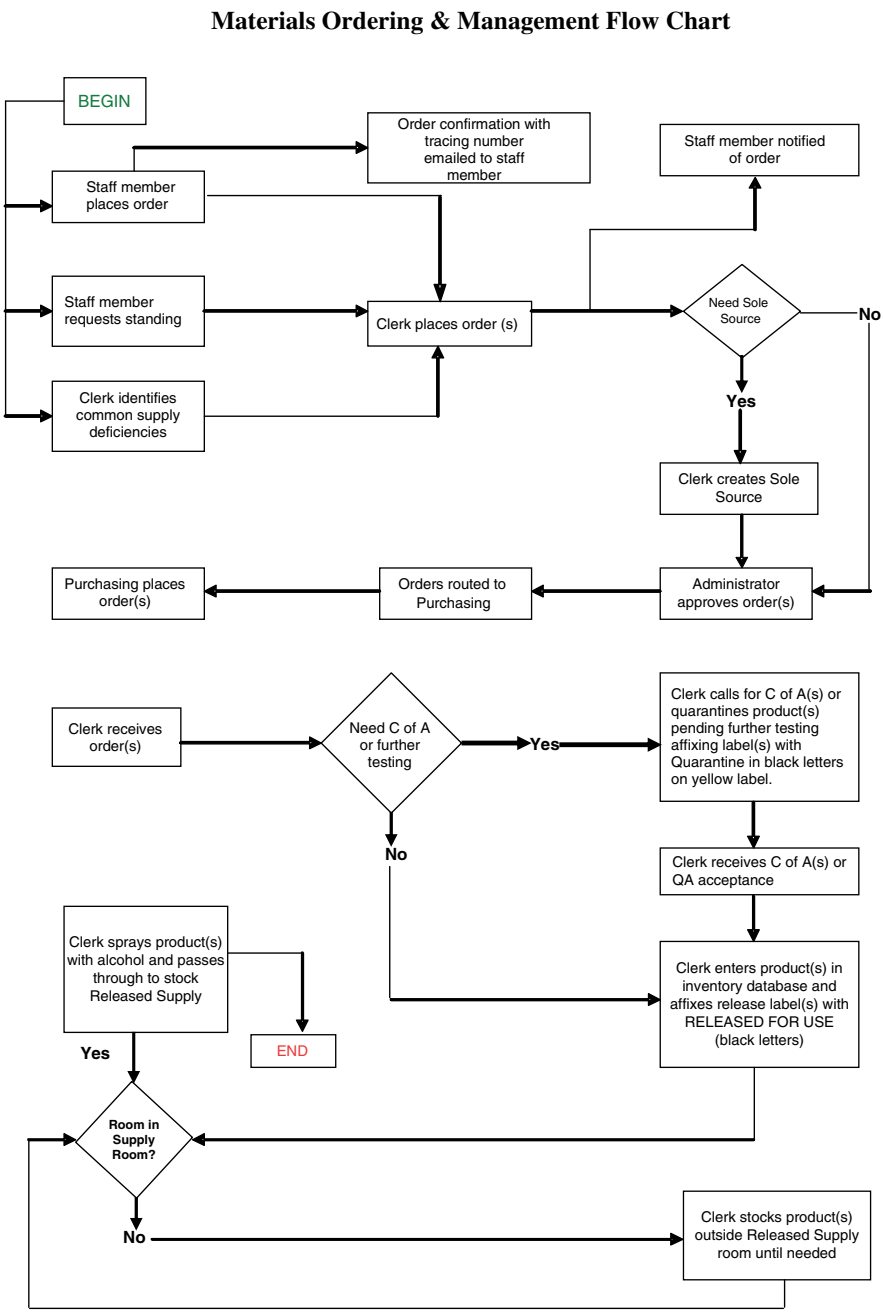

Fig. 14.1 Materials ordering and management flowchart

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WORKSHEET AW03.12.1: SUPPLY SPECIFICATION WORKSHEET

Supply Name Manufacturer

Lot Number: _____ Amount Received: _____

Date received Store at

Place a copy of the bar code label in the box below:

Place Bar Code Label Here

QUARANTINE UNTIL ALL SPECIFICATIONS ARE MET

General Acceptance Criteria *(usually completed by receiving clerk)*

Criterion	Specification	Results Pass / Fail
Manufacturer		☐ Pass ☐ Fail
Appearance		☐ Pass ☐ Fail
Volume		☐ Pass ☐ Fail
C of A		☐ Pass ☐ Fail
		☐ Pass ☐ Fail

Sample given to QC for Testing by on

QC Testing Criteria

Criterion	Specification	Results Pass / Fail
Endotoxin by LAL	<5.0 EU/ml	☐ Pass ☐ Fail
Sterility by CFR assay	Negative	☐ Pass ☐ Fail

Reviewed and approved by investigator: _____ Date_____

Reviewed and Released by QA : _____ Date_____

Fig. 14.2 Sample supply release specification worksheet

For most routine manufacturing of GTP products, approved reagents are available and there have been several publications describing the change from unapproved to approved processing reagents without compromise to product safety or quality. There has been a general move away from tissue culture media and animal sera to buffered salt solutions and plasma components, for example. Additional information on approved alternatives may be obtained from the regulatory agencies, and professional organizations such as the Foundation for the Accreditation of Cellular Therapy (FACT) and the AABB.

Sourcing components for manufacturing cellular therapy products covered under IND are often more difficult, due to the more complex nature of the manufacturing process. By definition, these products may have been transduced or transfected with vectors, cultured ex vivo or activated in culture. These manufacturing procedures

have their origins in the research laboratory where reagents and materials are not of clinical grade. In many cases there is no equivalent supply that has been approved for human use. Under such circumstances, the normal procedure is to source the highest available grade of material or reagent that meets performance specifications. The CoA for this supply is then submitted to the FDA, or equivalent regulatory agency, as part of the IND application. During the review process the FDA will examine the CoA and determine whether it is acceptable to use that specific reagent, or whether an alternative or additional testing will be required. In the latter case, a supply release specification should be generated that includes these additional testing requirements.

Parts Lists

Many facilities will establish a parts list. This contains a listing of approved supplies that can be used for manufacturing. For example, specifications are established for a particular culture medium and CoAs from several manufacturers of this medium are examined to determine whether each meets specifications. Upon review by the quality unit it may be determined that there are several approved sources for the media and that these may be used interchangeably, provided that the CoA for each lot number that is received is kept on file. The medium is then assigned a unique part number that is linked to the approved suppliers.

Vendors of critical materials and reagents should undergo some form of audit to verify that their manufacturing and quality control procedures are adequate. Most academic facilities do not have the resources to conduct on-site audits of manufacturers. Opportunities may arise if a staff member is attending a meeting in the same area as a manufacturer. An alternative is to send out a questionnaire yearly to each vendor. This can ask, for example, if the manufacturer has been recently audited by the relevant regulatory agency and whether there were any deficiencies, and if these have been corrected.

Records should also be kept of any product recalls and how these were handled by the cell processing facility to ensure that the affected material was removed from inventory. There must also be a mechanism to trace products that may have been manufactured using the recalled materials and documentation that the appropriate individuals have been informed.

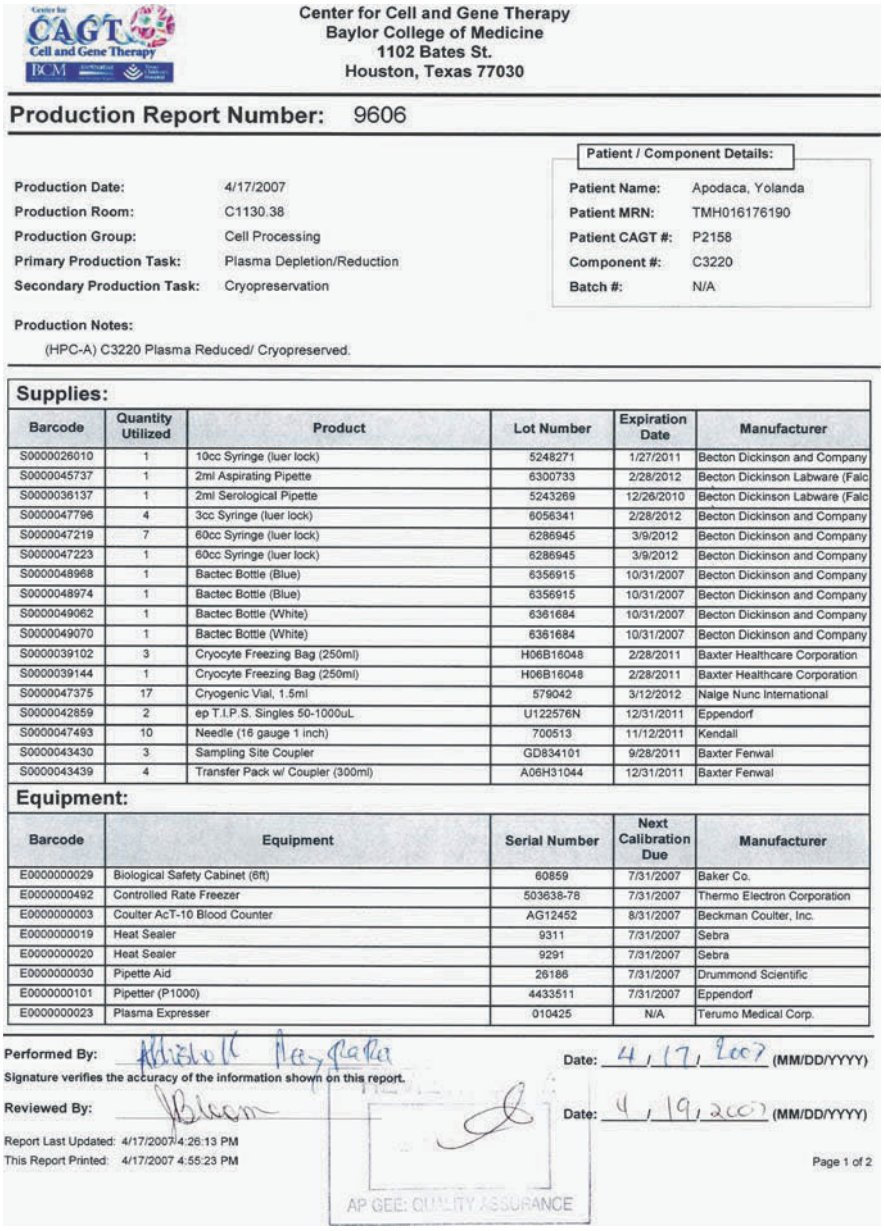
Receipt of Supplies

Ordering mechanisms are usually unique to individual facilities. In general, the CoA should be requested at the time of placing the order, although some manufacturers may prefer to supply them by fax or e-mail after shipment. These should be reviewed on receipt of the material to ensure that the appropriate specifications have been met for that particular lot. Every supply or reagent must be examined on arrival to ensure

that it is received intact and without damage, that it has been shipped at the required temperature, and that there is no evidence of contamination or cross-contamination. This review should be documented. A log must be kept of incoming supplies. This should detail the supply type, quantity, manufacturer, lot number, date of receipt, and expiration date for each reagent and material.

GMP regulations require coding of each shipment to allow tracking of its use and for determination of its release status. This can be achieved in numerous ways. The simplest, although not the cheapest, is to use a barcode label to identify each incoming shipment and to use the associated software to determine its status and use. At Baylor College of Medicine all incoming supplies are barcoded (Fig. 14.3) using a system that encodes all of the required information, issues a unique identifier to the supply, and is used to determine whether the supply has been released. During manufacturing the barcode is read whenever the supply is used and at the end of each manufacturing step a report (Fig. 14.4) can be printed that details all of the supplies used, their manufacturer, lot number, expiration date, and so forth. Expired supplies will not scan and the system also tracks inventory to assist in reordering.

Fig. 14.3 Barcode and release sticker



Center for Cell and Gene Therapy
Baylor College of Medicine
1102 Bates St.
Houston, Texas 77030

Production Report Number: 9606

Patient / Component Details:

Production Date:	4/17/2007	**Patient Name:**	Apodaca, Yolanda
Production Room:	C1130.38	**Patient MRN:**	TMH016176190
Production Group:	Cell Processing	**Patient CAGT #:**	P2158
Primary Production Task:	Plasma Depletion/Reduction	**Component #:**	C3220
Secondary Production Task:	Cryopreservation	**Batch #:**	N/A

Production Notes:

(HPC-A) C3220 Plasma Reduced/ Cryopreserved.

Supplies:

Barcode	Quantity Utilized	Product	Lot Number	Expiration Date	Manufacturer
S0000026010	1	10cc Syringe (luer lock)	5248271	1/27/2011	Becton Dickinson and Company
S0000045737	1	2ml Aspirating Pipette	6300733	2/28/2012	Becton Dickinson Labware (Falc
S0000036137	1	2ml Serological Pipette	5243269	12/26/2010	Becton Dickinson Labware (Falc
S0000047796	4	3cc Syringe (luer lock)	6056341	2/28/2012	Becton Dickinson and Company
S0000047219	7	60cc Syringe (luer lock)	6286945	3/9/2012	Becton Dickinson and Company
S0000047223	1	60cc Syringe (luer lock)	6286945	3/9/2012	Becton Dickinson and Company
S0000048968	1	Bactec Bottle (Blue)	6356915	10/31/2007	Becton Dickinson and Company
S0000048974	1	Bactec Bottle (Blue)	6356915	10/31/2007	Becton Dickinson and Company
S0000049062	1	Bactec Bottle (White)	6361684	10/31/2007	Becton Dickinson and Company
S0000049070	1	Bactec Bottle (White)	6361684	10/31/2007	Becton Dickinson and Company
S0000039102	3	Cryocyte Freezing Bag (250ml)	H06B16048	2/28/2011	Baxter Healthcare Corporation
S0000039144	1	Cryocyte Freezing Bag (250ml)	H06B16048	2/28/2011	Baxter Healthcare Corporation
S0000047375	17	Cryogenic Vial, 1.5ml	579042	3/12/2012	Nalge Nunc International
S0000042859	2	ep T.I.P.S. Singles 50-1000uL	U122576N	12/31/2011	Eppendorf
S0000047493	10	Needle (16 gauge 1 inch)	700513	11/12/2011	Kendall
S0000043430	3	Sampling Site Coupler	GD834101	9/28/2011	Baxter Fenwal
S0000043439	4	Transfer Pack w/ Coupler (300ml)	A06H31044	12/31/2011	Baxter Fenwal

Equipment:

Barcode	Equipment	Serial Number	Next Calibration Due	Manufacturer
E0000000029	Biological Safety Cabinet (6ft)	60859	7/31/2007	Baker Co.
E0000000492	Controlled Rate Freezer	503638-78	7/31/2007	Thermo Electron Corporation
E0000000003	Coulter AcT-10 Blood Counter	AG12452	8/31/2007	Beckman Coulter, Inc.
E0000000019	Heat Sealer	9311	7/31/2007	Sebra
E0000000020	Heat Sealer	9291	7/31/2007	Sebra
E0000000030	Pipette Aid	26186	7/31/2007	Drummond Scientific
E0000000101	Pipetter (P1000)	4433511	7/31/2007	Eppendorf
E0000000023	Plasma Expresser	010425	N/A	Terumo Medical Corp.

Performed By: Mitchell Reyna Date: 4/17/2007 (MM/DD/YYYY)

Signature verifies the accuracy of the information shown on this report.

Reviewed By: Bleam Date: 4/19/2007 (MM/DD/YYYY)

Report Last Updated: 4/17/2007 4:26:13 PM
This Report Printed: 4/17/2007 4:55:23 PM

AP GEE: QUALITY ASSURANCE

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Fig. 14.4 Production report

Supply Release

When coupled to the receipt of an acceptable CoA a supply may be released provided that no other testing is required. Until release, the supply must be held in quarantine. This is usually accomplished by clearly marking the supply as being "In Quarantine" and storing it in a specified location that separates it clearly from released materials. The normal method of release is to move the item from quarantine to the released supplies storage area and to re-mark it as "Released for Use," and indicate the date on which this happened (Fig. 14.3).

Storage

Storage areas must be clearly identified and kept in a clean, orderly, and sanitary condition. If manufacturing is performed in a cleanroom environment, it is normal to unpack the supplies and discard all cardboard before taking materials into the facility. In addition, where possible, the supply packaging may be wiped down with disinfectant before transfer. Supplies should not be stored directly in contact with the floor, and, in most areas, fire codes require that there must be at least 18 in. between the ceiling and top of the stored items. There are a number of high-density storage systems that maximize usable space. These usually consist of shelving units on tracks mounted to the floor and/or ceiling (Fig. 14.5). This allows the shelves to be kept in very close proximity when not in use, and access is obtained by pulling out the required shelf from the stack.

Items requiring controlled temperature storage or protection from light must be maintained under conditions where it can be demonstrated on an ongoing basis that these conditions were maintained. These would include the use of temperature recorders on fridges or freezers, and ensuring that light-sensitive materials are allocated to lightproof refrigerators.

Released Supply Management

When an item is released it should be placed behind any remaining released supplies of the same item, so that the oldest materials are used first (FIFO). It is important for the quality unit to audit supply areas and procedures regularly, since supplies are usually accessible to multiple individuals with the associated risk of mix-ups. In the same vein, it is also important to secure supply areas from access by unauthorized individuals to ensure that control of inventory is maintained.

Although released supplies have met the required specifications, it is a good idea to implement a random sampling audit. Samples of critical reagents and materials should be taken at random and tested to ensure that they meet the specifications on

Fig. 14.5 High-density storage for supplies

the CoA, e.g., sterility and endotoxin levels. This provides a quality check on the vendor and provides assurance as to the accuracy of the information supplied with the specific lot.

Use of supplies must be documented during manufacturing. A list must be kept detailing the material used, the quantity, the lot number, manufacturer, and expiration date. Most facilities will document the amount used in a worksheet or batch record and then include the remaining information in a list of materials used during a manufacturing step. There are a number of ways in which this can be done. Some facilities prepare a listing of all materials and reagents currently in use and attach this to the worksheet. Although this may reduce the amount of writing required, it runs the risk that the listing is not accurate on a particular day because a new lot of a supply has been started without modifying the list. It is important to document that such a system is audited frequently and shown to be accurate.

A more labor-intensive approach is to write down all of the information required for each supply on a worksheet each time that it is used. This should improve

accuracy; however, it is susceptible to clerical errors, especially when recording long or complex supply names and lot numbers. The fastest method is to use a barcoding system, such as that described previously. The technologist then swipes the barcode as the item is used and the software stores the record. This system can be expanded to barcode the identity of the product being manufactured and the equipment that is used during the manufacturing procedure. Equipment barcodes may encode serial numbers, calibration dates, and so forth, thereby providing additional documentation that is required under GMP and GTP regulations. As with other recording systems, it is important to validate that barcoding is generating accurate information. This can be done initially by showing that the software system generates identical data to that obtained using a manual system. This should be supplemented by an auditing process to document that barcodes are being generated with accurately encoded information, that the barcodes remain readable over the lifetime of the supply or material under the required storage conditions, and that technologists are remembering to swipe all supplies used during a manufacturing step. An advantage of barcoding is that it also facilitates tracking products that may have been manufactured using recalled components. With a manual system this may be extremely tedious, but most barcoding software can readily recall this information and provide a listing of all products prepared using a specific recalled material or reagent. With the move toward barcoding of cellular therapy products using the ISBT 128 system, consideration should be given to using a compatible barcoding system to track supplies and equipment used during manufacturing.

There is some debate as to the level of documentation that is required when recording the use of materials and reagents. In some facilities every supply is barcoded and recorded. This would, for example, include alcohol wipes, syringe needles, sample tubes, etc. If a manual recording system is in use, this presents a formidable challenge, and a safe rule of thumb would be to record, at a minimum, information on all supplies and reagents with which the product has direct contact, and which could potentially introduce contaminants into the product.

Formulations

It is important to remember that various reagents may be used in combination after being released to inventory. For example, culture media may be supplemented with sera and glutamine. This process requires some form of control. Such a procedure may increase the risk of contamination, and the quality control group should establish release specifications for formulated reagents such as these. Each facility should determine whether such a formulated supply requires testing for sterility prior to use. This will substantially delay the time at which items such as supplemented media can be used, but will also eliminate the risk of contaminating a product by the use of potentially contaminated media. In addition, a new expiration date will need to be established for the formulated reagent. This is normally based on practical experience of working with the specific reagent, or

more commonly by setting the expiration date as that of the first component to outdate.

Reagents Prepared In-House

In contrast to the supplementation of media, some facilities may elect to prepare reagents from base components, e.g., salt solutions, density gradients. GMP and GTP regulations detail the kind of documentation that is required on the preparation and testing of in-house reagents. The level of testing that is required when preparing such materials for a Phase I/II IND study should be discussed with the regulatory agency prior to submission of the application for review. For example, in some cases the identity of each component may have to be confirmed chemically before it is used for compounding.

Expired Materials

Use of expired supplies is generally not acceptable to regulatory agencies. There are circumstances; however, when a particular reagent either has no expiration date established by the manufacturer, or where stability testing information is limited, and a very short expiration date is assigned. In such cases, it is important to contact the manufacturer directly to determine whether they have additional information on product stability that would support use after the date indicated on the CoA. In addition, a study should be conducted to demonstrate that the expired reagent performs as expected, and over what time period beyond the stated expiration. This information should be presented to the regulatory agency to support the use of outdated components or reagents and approval should be obtained before using such materials.

Updates

As cellular therapy becomes more widespread and integrated into traditional medicine, it is likely that the supply of approved reagents and materials will increase. The transition to full use of approved supplies will be welcomed by regulatory agencies and should not require exhaustive documentation to justify the change. Facilities should, therefore, maintain close contact with manufacturers, regulatory agencies, and colleagues to keep updated on the availability of newly approved supplies, and to institute their routine use whenever possible. In the interim, organizations such as FACT, AABB, and Production Assistance for Cellular Therapies (PACT) provide an invaluable resource for learning more about nonapproved reagents that have been widely used in clinical product manufacturing.

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Useful Literature

1. cGMP in manufacturing, processing, packing, or holding of drugs and finished pharmaceuticals. Title 21 Code of Federal Regulations, Parts 210 and 211.
2. Human cells, tissues and cellular and tissue-based products. Title 21 Code of Federal Regulations, Part 1271.
3. Current good manufacturing practice and investigational new drugs intended for use in clinical trials. Final rule. Federal Register 73, 40453, 2008.
4. Guidance for Industry – CGMP for Phase 1 Investigational Drugs, Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Office of Regulatory Affairs, July 2008.

Chapter 15
Facility Equipment

D.L. Griffin

Abstract Control of laboratory equipment is critical in a cGMP facility. Equipment management ensures compliance with all regulations and standards and documents the lifecycle of the equipment, encompassing product selection, installation, validation, maintenance and disposal.

Introduction

It is essential to manage laboratory equipment to ensure the highest quality of cellular therapy product. Good equipment management ensures control over that aspect of manufacturing and facilitates easier detection of failures that may result in process deviations. Properly managed equipment is less likely to fail, as preventative maintenance should rectify problems before they compromise processing of products. This chapter reviews the elements of equipment selection and management [1].

Equipment Selection

Design Qualification (DQ)

DQ is part of the equipment selection and qualification process (Fig. 15.1) and refers to the specifications for the instrument with regard to its function and operation. It happens prior to the purchase of a piece of equipment and should document the decision-making process. These decisions should always involve the intended user. In fact, the College of American Pathologists (CAP) specifically queries whether the Laboratory Director has significant input into the decision-making process [2]. Justification for the equipment should include an evaluation of the current situation or problem, (e.g., obsolete equipment, increased production volumes, future needs,

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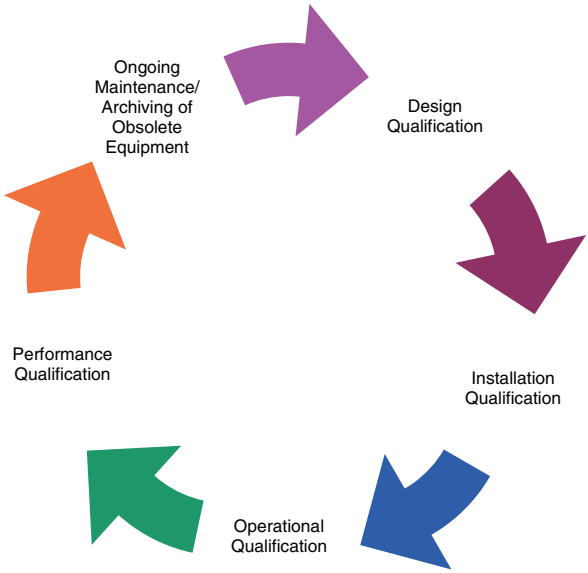

Fig. 15.1 The equipment qualification cycle

the intended function of the equipment), the location of installation (e.g., cleanroom environment or nonclassified space), the various instruments that were considered, an objective comparison, the rejected instrumentation and reasons for rejection, and the accepted/preferred instrumentation. The DQ may consist of only a few simple sentences, or may comprise a large document, depending on the complexity of the equipment. It may be useful to develop a generic DQ template document. This serves to standardize the information that must be gathered.

Purchasing departments should not be permitted to dictate which equipment make/model is purchased. They will sometimes withhold ordering of critical equipment in order to force a manufacturer or distributor to offer a relatively insignificant discount. The purchasing process should be closely monitored to ensure that decisions are made promptly, and to allow for intervention if necessary. Ideally, every facility will have all of the required equipment, with backup for critical items. For example, there should be two centrifuges capable of spinning blood bags. Alternatively, there should be another device somewhere in the hospital or institution that can serve the same function.

Choosing Equipment

The choice of equipment can be overwhelming. All manufacturers claim that their product is the best on the market. The appropriate equipment is the product that best suits the needs of the laboratory, not the requirements perceived by the manufacturer, or their sales associates. In general terms, the right equipment is cost effective, meets high standards for accuracy and precision and the specific needs of the facility. The manufacturer must be responsive to customer needs both before and after

the sale. The selected equipment must be capable of reliably producing a consistent product. It is always worth locating other users, independently of the manufacturer, and reviewing their experience.

Capital Budgeting

In an academic setting, the capital budget request is an annual process where a laboratory may justify to the financial department its future needs. The staff must determine which pieces of equipment need to be replaced and what additional items may be needed. The first step is to draw up a wish list of pieces of equipment that the ideal cell processing facility should contain. What equipment could substantially decrease processing time, or would allow multiple products to be processed simultaneously? For example, a laboratory may be required to process three products. Food and Drug Administration (FDA) regulations were designed in part to prevent product mix-ups [3, 4]. This means that only one product should be handled in a biological safety cabinet at a time, regardless of the number of technologists available. If there is only one biological safety cabinet, then the products must be processed sequentially, which may not be cost effective. Requests for two additional stations may not appear reasonable on initial review, but the longer term savings in staff overtime, potential for program growth, and so forth, should be presented to the administration as justification for the request. Growth projections must be supported by data, such as numbers of new products required for upcoming protocols, closure of a competing program in the hospital's service area, addition of physicians to the existing program, or an impending accreditation visit that may result in citations for inadequate equipment.

Capital budgets typically require identification of the equipment, the manufacturer and price, for a new piece of equipment or a replacement; the ongoing cost for service contracts or other maintenance agreements, and a justification of the purchase. The critical need for certain equipment must be emphasized as this may not be fully appreciated by purchasing departments. The criticality may be related to the function of the equipment, the choice of a particular model or supplier, or the requirement for compatibility with existing equipment. Since many institutions require that bids be tendered for items above a certain cost, it is important to communicate to them when this approach is not acceptable. This information is usually provided in the form of a written sole source justification, and can be derived from the DQ documentation. Sometimes it may be necessary to justify the need for multiple pieces of equipment, for example, primary and backup controlled rate freezers.

Just like biological organisms, equipment has a finite lifespan. Recordkeeping starts with the decision to purchase equipment and should continue until it is retired. Documentation has traditionally only covered maintenance procedures and use of the instrument for manufacturing. Records should allow two-way tracking, so that there is a list of all products prepared using that piece of equipment, and conversely, each product record lists all of the equipment used for its preparation. The critical events of equipment "birth" and "death" have frequently not been adequately documented. Current FDA regulations, however, require documentation of equipment receipt/installation, qualification, and retirement.

Warranties and Service Contracts

The warranty is one of the most overlooked documents provided by the manufacturer. It is just as critical to review this document as it is the operating manual. If a service contract is offered at the time of purchase, it may be redundant to the coverage already provided by the warranty. Warranties are typically in place for one year from delivery date of the instrument, but this can vary based on time or usage. The warranty should cover, at a minimum, service calls, labor, and parts. If it is a small piece of equipment that can be packaged and shipped, such as a small particle monitor, ensure that shipping costs are included in the warranty if there is no onsite repair service. For an additional fee, the company may provide a replacement unit while the damaged unit is returned for repair. Warranties typically do not cover consumables unless specified within the purchasing contract. If equipment is supplied under a "Reagent Rental" agreement, then the user is expected to purchase a certain volume of supplies in order to retain the instrument. Warranties do not cover misuse, including use for purposes other than those specified by the manufacturer. In fact, use of this type may invalidate the warranty. Abuse, alteration of the equipment, neglect or damage caused by unauthorized repairs, or inappropriate or lack of cleaning may also void the warranty. Usually there will also be language in the warranty that states any damage or personal injury from use of the instrument is not covered.

If a delay occurs between receipt and installation of the instrument, the company providing the warranty should be contacted to request a delay in the start date of the warranty. This should be followed up by a written confirmation of the modification of the warranty.

Make sure that the date of expiration of the warranty is known in advance. This can be scheduled using an online calendar or database, so that a reminder is triggered several months in advance. At this time it should be determined whether the manufacturer's coverage is to be continued or if an alternative will be explored. In-house resources should be investigated; in the hospital setting the Clinical Engineering department may be able to perform minor or major repairs. This may allow a lower level of coverage by the manufacturer; however, once the warranty has expired, repairs made by unauthorized personnel may invalidate future service contracts or warranty extensions. Another alternative may be to enroll in an "insurance plan" rather than the manufacturer's service contract. These are generally a little less expensive; however, service contracts may be negotiable. Larger customers may be able to obtain a higher level of service, at lower cost or with longer coverage. These options should be examined critically. Service contracts frequently involve considerable up-front expenditure, but there are few to no out-of-pocket expenses. In contrast, insurance plans may cover only a single repair or service visit, with additional travel, parts, and labor charges for any further work. At the end of the coverage period these may exceed the initial savings achieved by selecting the plan over the service contract.

Some service contracts expire while some self-renew. If a piece of equipment is retired during the coverage period, the service contract company should be contacted to discontinue the contract. It may be advisable to avoid long-term service

contracts in a rapidly changing field, such as cell therapy product manufacturing, where instruments may become obsolete relatively quickly.

Decisions also need to be made on the level of coverage. Should every piece be covered or only critical items? Does there need to be a priority list?

Qualification

It is a basic requirement of laboratory testing that the supplies and instruments be suitable for the job they perform. Documentation of all of the steps from the decision to purchase to actual use of the machine is critical.

Qualification Versus Validation

A qualification plan is necessary for a new piece of equipment. Unlike a validation plan, which generally covers processes and procedures in the laboratory, a qualification plan covers the critical functions of the equipment that must be reviewed prior to acceptance for use in the facility. A basic qualification plan is generally intended to show that the equipment functions as described by the manufacturer, rather than demonstrating its functionality in a specific process or procedure. A qualification plan is composed of several phases (Fig. 15.1). Design qualification, described above, is used to select the right equipment. The next phase is Installation Qualification (IQ), which details the arrival, set up, and basic testing of the instrument. This is followed by Operational Qualification (OQ) that demonstrates that the equipment works as per the manufacturer's description. Performance (process) qualification (PQ) documents that the instrument meets expected performance criteria. Depending on the design of the PQ this evaluation may overlap with validation of the instrument.

The qualification plan as a whole should be developed before the instrument is received. It should describe what is to be done during each phase, what information is to be obtained and recorded, and what criteria will be used to determine that the qualification procedure was successful. The format is up to each facility, but useful sections include:

- Goal of the qualification
- Reagents and supplies to be used
- Procedure to be followed
- Manufacturer's test data supplied
- Tests to be performed by the facility
- Target values/acceptance standards
- Results obtained
- Quality Control procedures
- References and appendices

The plan should be reviewed and approved by the Quality Assurance unit and the facility technical director before implementation.

Installation Qualification (IQ)

It is critical to document the initial delivery of the equipment. The first check should be made at the shipping and receiving area to confirm that the equipment delivered is exactly what was ordered, that it was not obviously damaged during shipment, and that all items were received as expected.

Installation management documents initial placement of the equipment in the facility. Often this will take place concurrently with the IQ. It records that all necessary inspections have been made and that the appropriate department has been contacted to manage asset inventory and electrical testing (if appropriate). Documentation should include:

- Date of receipt and initials of accepting tech entered into ordering log book or other inventory system
- Inspection of packaging
- Unpacking of equipment
- Evidence of any visible physical damage
- Assistance of manufacturer's representative for major equipment
- Check of items against the packing list and original order

The equipment is then positioned in the intended area. This should have been preselected based on manufacturer's specifications and facility needs. Considerations generally include adequate space for instrument and users, proper ventilation and power supply (e.g., dedicated circuits, emergency power or special voltage where necessary), adequate lighting, and so forth. Equipment must be installed according to the manufacturer's instructions in order to avoid damage or voiding the warranty.

Completion of the IQ will involve turning the equipment on and ensuring that it powers up as expected. If there is an built-in self-test procedure, this should be performed and the results documented.

Operational Qualification (OQ)

The OQ phase involves documenting that the equipment operates as described by the manufacturer. For example, do the controls function as expected, does the equipment reach the required operating speeds or temperatures, does it run without problems for the desired times? This is generally preceded by careful reading of the operator's manual, development of a Standard Operating Procedure (SOP), and training of staff who will ultimately use the equipment.

The SOP should cover the most salient points of the use of the equipment. Although it is acceptable to refer to the operator's manual for troubleshooting and rarely used procedures, it is necessary to develop a step-by-step procedure for the

daily use and routine care and quality control of the equipment. The scope of the SOP depends on facility policy. Some prefer to cover basic and specific uses, maintenance, and Quality Control (QC) in a single procedure, while others prefer to separate operation from care and maintenance. Many manufacturers now provide manuals on line or via e-mail. This makes it easier to incorporate their information directly into the facility SOP, and can facilitate development of procedures prior to the arrival of the equipment. It is usually possible to start on the process of creating documentation prior to the arrival of the equipment. This can assist in only needed refinement of the SOP once the equipment is installed. Having a standardized template for the documentation is a great help, although the initial creation of the template may involve a significant time investment. See the appendices A–E for examples of Installation Plans, SOP templates, QC forms, and Maintenance Schedules.

Process/Performance Qualification (PQ)

Any processing that is to be performed using the equipment must be validated prior to implementation. Up to this point, the equipment has only been qualified for general use. When a particular protocol calls for use of a particular piece of equipment, then that piece of equipment must be validated for the process required by that protocol. For example, although a centrifuge has been qualified for general use, its use in cord blood or peripheral blood progenitor cell processing must be validated prior to use in processing of those materials for patient use. Cord blood centrifugation may require using the centrifuge at a different speed than for peripheral blood progenitor cells. The diluent, the type of bag, and the properties of the cells may all affect the outcome, and this needs to be evaluated and documented. A validation plan is written up much like a qualification plan, listing the goals, procedure, and acceptable outcomes prior to initiation of testing. The plan must be developed and formalized prior to performing any tests and should include the following elements:

- Principle
- Goal
- Reagents and supplies
- Procedure
- Data to be collected
- Target values/acceptance standards
- Result reporting
- Statistical analysis of results
- Quality Control
- References and appendices

The results should be reviewed by a member of the quality team to determine whether the specifications were met and the equipment can be released for manufacturing applications. The validation plan and final report should be maintained

as templates and modified for each individual circumstance. For consistency, each test in the laboratory should be documented identically, whether it refers to instrument qualification, process validation, quality control, or patient product processing/testing.

Operator Qualification

There should be an individual who is identified as being primarily responsible for the equipment. Ideally the same person should be involved in the DQ/IQ/OQ/PQ. In this manner, it is possible to track responsibility and authority from the beginning of the equipment selection process to the retirement phase. If possible, this person should have experience with, or an interest in, biomechanical engineering. Often hospitals will have a department that covers this area, but it may not be possible for them to do much more than basic inventorying and yearly preventative maintenance or tachometer readings. This equipment *superuser*, if not a dedicated staff member or manager, should be able to research equipment, perform IQ/PQ/OQ, manage documentation, and perform minor repairs.

Equipment Prioritization and Backup

An inventory of all laboratory equipment is essential to adequately control the instrumentation in the laboratory. In some cases a Clinical Engineering Department will maintain an inventory of the facility's biomedical equipment; however, this list is often restricted to electrical equipment and does not include equipment such as pipets, timers, and thermometers. In any inventory it is important to determine whether equipment is critical to operations (Table 15.1). A critical piece of equipment is one where the failure of that piece of equipment could result in a potential problem situation. This would include items such as a hematology analyzer, flow cytometer, cell selector, centrifuge, or incubator. Naturally, this is also determined by the availability of backup equipment. If there are two flow cytometers, the temporary loss of one may have limited impact, only requiring a triage of samples to effectively analyze the most critical samples first. However, if the failure of a cytometer results in having to use an instrument that was not intended for clinical applications (i.e., an instrument used primarily for research), an SOP should be developed proactively for use of that machine, in which acceptable backup instruments are identified. Validation of the instrument prior to its final acceptance as a suitable backup is essential. An SOP must be available for these instruments, and this should describe QC procedures, directions for use, the conditions under which the instrument is to be used, documentation of use, and notification of the owners of the instrument.

While the research instrument may have a minimum of QC performed if it is in a core facility, the same may not be true of an instrument in another area. Ensure that regular checks are performed on the equipment, including calibration, preventative

Table 15.1 Sample prioritization of equipment table

Priority	Equipment
A	Cytometer
A	Hematology analyzer
A	Scientific balance
A	Biological safety cabinets
A	Floor model centrifuge
A	Cell washer
A	LN_2 Transport container
A	LN_2 Vial vessel
A	Cryogenic control management & fill system
A	LN_2 vessels (1 -> 5)
A	Cell separator
A	Control rate freezers
A	Heat sealer
A	Active blood bank refrigerator
A	Sterile connecting device
A	Transplant water baths
A	Particle monitor
A	Centrifuge inserts for CBUs
B	Serofuge
B	Dry shipper
B	Flourescence microscope
B	Brightfield microscope
B	Pipettors
B	Quarantine blood bank refrigerator
B	Vial coolers
C	CO_2 incubator
C	–70 freezer
C	Cleanroom fridge
C	Cleanroom freezer
C	Stopwatches and timers
C	Thermometers

A - High priority, C - Low priority

maintenance, and so on. Immediately prior to use, the routine clinical laboratory QC tests should be run to set up the backup equipment in exactly the same way as the routinely used equipment. Settings should be double-checked before running samples as these may have been inadvertently altered by previous users.

Quality Control (QC) and Documentation

Daily QC or Use QC must be documented at the time of QC testing or monitoring. The FDA's requirement for Good Manufacturing Practice (GMP) management of equipment and their recommended testing, testing frequency, and calibration frequency are outlined in 21 CFR 606.60 [5]. This refers to the highest level of equipment control, and if this level of compliance is achieved, then most other

requirements of regulations and standards will be met. If the equipment is used for clinical testing, the CAP standards will need to be reviewed [6]. Even if CAP accreditation is not maintained by a laboratory, the CAP standards can serve as a good reference point for equipment maintenance, covering items such as thermometers, centrifuges, refrigerators/freezers in the Laboratory General Section and more specialized pieces of equipment in the Hematology, Flow Cytometry, Transfusion Medicine, and Immunology sections. As the equipment SOPs are being created, a schedule should be created for the routine maintenance and quality. This should be incorporated into a master schedule that covers all of the equipment in the facility. This will list all chronologically of the maintenance, calibration, and checks that must be performed on equipment during the year.

Organization of the documentation should start prior to purchase. A binder should be created for each type of equipment using a standardized format for the contents, for example:

1. Design Qualification
2. Ordering and Receipt
3. Qualification
4. QC Procedures
5. QC Results
6. Preventative Maintenance (PM) Documentation
7. Deviation Management (failures, malfunctions, accidents, service calls)
8. Validations (qualifications, method validations, and manufacturer's manuals)
9. Archiving and Disposal

If an electronic documentation system is used, the Manufacturer's Operating Manual can often be downloaded. This may come on a CD for more recently purchased equipment. A virtual folder can then be created for the equipment, and documents, such as SOPs, forms, and scanned images of preventive maintenance and repair reports, can be included or linked.

QC data documentation is an essential part of the equipment record and has several components. Daily QC data may be captured as paper or electronic records. This documentation should be located close to the actual piece of equipment. Periodic QC must be performed and documented as specified. These records usually include documentation of routine cleaning of the equipment. Calibration should be performed as per the manufacturer's instructions and documented within the equipment management filing system.

Documentation of preventive maintenance is required. In many healthcare facilities this is the responsibility of the Clinical Engineering Department. This department usually maintains an inventory of laboratory biomedical equipment and performs at least basic yearly preventive maintenance. The laboratory should keep a master list of all equipment and update it monthly. It should include all of the equipment that has ever been used in the facility and its disposition, whether discarded, archived in the warehouse, or in current use. When the services of a Clinical Engineering Department are used, they should be contacted prior to

plugging the equipment into the main or emergency electrical circuit in order to review the wiring and grounding needs, to ensure compatibility with the electrical system. They may also be able to perform additional qualification, such as tachometer readings on centrifuges, temperature readings, etc.

Repairs to equipment and any associated requalification must also be documented and maintained as an integral part of the equipment records.

Retiring Equipment

When an instrument has reached the end of its lifespan in the laboratory, assessment of its future should occur. Is this piece of equipment obsolete? Has it been replaced by newer technology? If your facility no longer has a need for it, consider donating it to a basic research or clinical laboratory in your institution. It may also be placed into storage if future use is likely. Surplus equipment may be sold online at sites such as www.surplusequipment.com and www.labx.com; or donated to bodies such as Direct Relief International (www.directrelief.org) and International Organization of Medical Physics (www.iomp.org). Alternatively, used equipment, in good working condition, may be donated, via the Used Equipment Program, to developing countries. The receiver of the donation pays for handling and shipment.

If equipment is to be discarded or put into surplus, the equipment binder should be retained and the following documented:

- Name of equipment, model number, manufacturer and serial number, local inventory asset number (if applicable)
- Reason for discard: obsolete, replaced, beyond repair, no longer needed
- Proposed method of discard: trash, donate to research lab, local storage, sell for surplus, donate to charity
- Value of equipment (to determine this, the manufacturer should be able to provide the trade-in value, or research comparable items by searching the secondary market)
- Authorization for discard: Laboratory Director and/or Laboratory Administrator. The institutional financial department may also require review and/or approval of disposal
- Date of discard, technologist(s)/personnel responsible for discard, cleaning/disinfection performed if applicable/required
- Personnel removing discarded equipment
- Final disposition of the equipment
- Review of discard by Laboratory Director and signature/date

The Equipment Binder should now provide a record of the entire lifecycle of the equipment. If the equipment is destined for another laboratory or institution, a copy should be made of the binder and shipped with the equipment. Prior to release of the documentation, ensure that no patient names or identifiers are located within the documentation. This sometimes occurs in deviation records, where equipment

performance affected a specific product. It is important that the recipient of the equipment be made aware of all occurrences with the machine. The original binder should be identified as archived equipment and retained by the laboratory. While some of the regulations state an expiration date of recordkeeping, if there are cryopreserved products that are maintained indefinitely, the relevant equipment records must also be maintained indefinitely. In the case of closure of a facility, arrangements should be made with the institution to maintain the records in a secure location.

Regulations and Standards

In the United States there are regulations pertaining to laboratory operations of most types. These include the following:

- *Good Laboratory Practice Regulations* Title 21 Code of Federal Regulations, Part 58 Subpart D covers equipment design and maintenance and calibration of equipment. Written standard operating procedures and records are required for equipment used in the testing of nonclinical laboratory studies (Table 15.2)

Table 15.2 Equipment section from Title 21 Code of Federal Regulations Part 58 Subpart D (good laboratory practice)

58.61	**Equipment design**. Automatic, mechanical, or electronic equipment used in the generation, measurement or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning and maintenance
58.63	**Maintenance and calibration of equipment**
(a)	Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized
(b)	The written standard operating procedures required under Sec. 58.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation and copies of the standard operating procedures shall be made available to laboratory personnel
(c)	Written records shall be maintained of all inspection, maintenance, testing, calibrating, and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the standard written operating procedures. Written records shall be kept of non-routine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect

Table 15.3 Equipment checks from Title 21 Code of Federal Regulations Part 606

Equipment	Performance check	Frequency	Frequency of calibration
Temperature recorder	Compare against thermometer	Daily	As necessary
Refrigerated centrifuge	Observe speed and temperature	Each day of use	Do
Hematocrit centrifuge			Standardize before initial use, after repairs or adjustments, and annually. Timer every 3 mo
General lab centrifuge			Tachometer every 6 mo
Automated blood-typing machine	Observe controls for correct results	Each day of use	
Hemoglobinometer	Standardize against cyanmethemoglobin standard	.....Do	
Refractometer	Standardize against distilled water	.....Do	
Blood container scale	Standardize against container of known weight	.....Do	As necessary
Water bath	Observe temperature	.....Do	Do
Rh view box	.....Do	.....Do	Do
Autoclave	.....Do	Each time of use	Do
Serologic rotators	Observe controls for correct results	Each day of use	Speed as necessary
Laboratory thermometers			Before initial use
Electronic thermometers			Monthly
Vacuum blood agitator	Observe weight of the first container of blood filled for correct results	Each day of use	Standardize with container of known mass or volume before initial use, and after repairs or adjustments

- *Good Manufacturing Practices for Blood and Blood Components* Title 21 Code of Federal Regulations, Part 606 (Table 15.3)
- *Good Tissue Practice Regulations* Title 21 Code of Federal Regulations, Part 1271 (Table 15.4)
- *Current Good Manufacturing Practices for Pharmaceuticals* Title 21 Code of Federal Regulations, Part 210/211 (Table 15.5)

These may be supplemented by local regulations in several U.S. states, such as California, Florida, and New York. Professional organizations, including the CAP, provide inspection and accreditation of a variety of laboratories; while the

Table 15.4 Equipment section from Title 21 Code of Federal Regulations Part 1271.200 (good tissue practices)

1271.200(a) General. To prevent the introduction, transmission, or spread of communicable diseases, equipment used in the manufacture of HCT/Ps must be of appropriate design for its use and must be suitably located and installed to facilitate operations including cleaning and maintenance. Any automated mechanical, electronic, or other equipment used for inspection,measuring or testing in accordance with this part must be capable of producing valid results. You must clean, sanitize, and maintain equipment according to established schedules.
1271.200(b) Procedures and schedules. You must 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.
1271.200(c) Calibration of equipment. Where appropriate, you must routinely calibrate according to established procedures and schedules all automated, mechanical, electronic, or other equipment used for inspection, measuring, and testing in accordance with this part.
1271.200(d) Inspections. You must routinely inspect equipment for cleanliness, sanitation, and calibration, and to ensure adherence to applicable equipment maintenance schedules.
1271.200(e) Records. You must document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with this section. You must display records of recent maintenance, cleaning, sanitizing, calibration, and other activities on or near each piece of equipment, or make readily available to the individuals responsible for performing these activities and to the personnel using the equipment. You must maintain records of the use of each piece of equipment, including the identification of each HCT/P manufactured with that equipment.

Table 15.5 Equipment section Title 21 Code of Federal Regulations Part 211.63 (good manufacturing practices – pharmaceuticals)

Sec. 211.63 Equipment design, size, and location.
Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance
Sec. 211.65 Equipment construction.
(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements
(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements

Table 15.5 (continued)

Sec. 211.67 Equipment cleaning and maintenance.

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

  (1) Assignment of responsibility for cleaning and maintaining equipment;
  (2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
  (3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
  (4) Removal or obliteration of previous batch identification;
  (5) Protection of clean equipment from contamination prior to use;
  (6) Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in 211.180 and 211.182.

Sec. 211.68 Automatic, mechanical, and electronic equipment.

(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained

Foundation for the Accreditation of Cellular Therapy (FACT) (in Europe: JACIE – Joint Accreditation Committee of ISCT and EBMT) [7] and AABB [8] provide specialized accreditation for manufacturers of cellular therapy products.

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Chapter 16
Quality

J.W. Atkins

Abstract Functional quality systems are essential to a successful cellular therapy program. A major driver to implementation of a quality management system in the United States is the federal law outlined in the Code of Federal Regulations (CFR) Title 21 parts 211 and 1271. Almost every accrediting agency now requires the implementation of a quality program including the AABB, Centers for Medicare and Medicaid Services (CMS), The Joint Commission (TJC), the College of American Pathologists (CAP), the Foundation for the Accreditation of Cellular Therapy (FACT), the International Standards Organization (ISO), the American Association of Tissue Banks (AATB), and the Clinical Laboratory Standards Institute (CLSI).

Introduction

The Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) regulations in 21CFR 1271 require that the facility designate a responsible party to ensure that the core requirements have been met. These requirements are very similar to those found in the 21CFR 211 pharmaceutical current good manufacturing practices (cGMPs), but the language is more specific [2]. They are the foundation for the AABB [3] and the FACT [4] Standards.

The FDA Quality Unit regulations and industry standards require a comprehensive quality program that is:

- Designed to ensure quality outcomes through:
  - Qualified and trained staff at all levels and positions
  - Clearly written Policies, Procedures, and Processes

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  - Validated facilities and equipment
  - Use of qualified materials for human use
- Monitored for Quality Assurance (QA) compliance through:
  - Product manufacturing record and labeling specification review for compliance prior to distribution
  - Audits
  - Quality Indicator Monitoring
  - Complaint Files
- Improved based on findings from any of the monitoring systems

Designing a Quality Management Program

For products not solely regulated under 21CFR 1271, sometimes referred to as cGMP products or 351 products, the cellular therapy manufacturing facility must also adhere to the requirements in 21CFR 211.28-208. The foundation for a quality management system is outlined in 211.22 and calls for the creation of a "quality control unit" (QCU). The fundamental requirement is for empowerment of a nonbiased group with responsibility to ensure that all components and elements from raw material to final, labeled finished pharmaceutical have been manufactured without error. This unit must have the authority, independent of operations, to halt production and distribution if quality specifications have not been met. The quality unit must fully investigate and this group is charged with approving or rejecting all production batches prior to final release [5]. The QCU must also ensure that all personnel are qualified by training and experience to perform tasks and functions for which they are responsible and that impact the quality of the product. There must be a program of continued education and competency assessment that ensures the right people are doing the right job to ensure consistent product that meets customer expectations.

The QCU must have a process to ensure that all policies, processes, and procedures are written to comply with both regulations and industry standards and are medically sound, so as to not pose potential harm to a patient.

Quality Program fundamentals may be accomplished using cross-trained staff if the volume and types of products will permit adequate attention to achieve both manufacturing and quality assurance processes. The workload, the number of products manufactured, and/or the complexity of the processing steps may all increase the resources needed to manage the quality program and overwhelm the number of available staff. Many cellular therapy programs are beginning to use staff dedicated solely to the management of the quality assurance program.

U.S. federal regulations and peer accrediting association standards are very clear in their expectations for a fully implemented, functional, and effective quality system. There is an expectation that quality systems will be continuously managed and

assessed for effectiveness on a regular basis. A surrogate discipline is developing around the specific elements of designing, implementing, managing, and assessing the effectiveness of quality systems. Collectively this may be referred to as "Quality Systems Management."

In order to develop quality systems we have to define quality. What is quality and how do we know it when we get it? Quality has been defined as the features and characteristics that determine the extent to which outputs satisfy the customer's needs [6]. In other words, are we providing what the customer wants or even exceeding their expectations? Implementation of a quality system and its management begin with a soundly formulated and written quality policy. This states the "overall intentions and directions of an organization related to quality as formally expressed by top management" [7]. The policy should be broad in concept and express corporate core values and beliefs. It should be approved and adopted by senior staff as the organization's commitment to quality [8, 9]. This action step will create a true investment in the success of quality initiatives and should ensure that senior management understands the role of the quality management (QM) personnel. QM staff are charged with ensuring that there is documented evidence that the quality policy is being fulfilled.

The quality policy should also define the quality objectives [10]. These are directly related to the quality policy and must be stated in clear and measurable terms. They should provide a specific direction for the organization with regard to quality. Product and service quality will differentiate organizations and those that succeed in exceeding their customer's expectations will thrive. An example of a measurable objective may be: "We will deliver novel, high-quality, cellular therapy products within 18 months of Institutional Review Board (IRB) approval." Definition of the objective facilitates the development of two measurable outputs: quality and timeliness. The quality component can be measured by evaluation and summary of validation data; as well as by ongoing product characterization and quality control data from production runs. Timely delivery can easily be measured by tracking the number of months for product development. The key is to understand your production and development processes, so that you can write both obtainable and measurable promises to your customers.

Monitoring Quality Systems

Senior management must develop and implement the policy and objectives in a manner that provides clear direction to all staff. The staff must be able to understand the intent of the quality objectives and their own role in accomplishing them. Eventually the Quality Management System will be evaluated for success by determining if the objectives have been or are continuously being met or exceeded.

The Quality Policy and the Quality Objectives form the structure for a Quality Assurance Plan. QA includes the planned, formalized activities intended to provide confidence that the output will meet the required quality levels [11].

Although the quality policy statement does not have to specifically address every aspect that ensures quality, developing each policy and procedure with the quality policy plan in mind will drive the organization toward a quality mindset and create an environment where quality is first. The wording of procedures should be developed in a manner that will allow the desired outcome to be measured. The QA plan should specifically acknowledge the factors that determine quality, including organizational structure, resource selection, equipment, suppliers, process control, documents and records, error management, assessments, process improvement, and safety. There should be a written policy statement that addresses these crucial factors. The goals of these specific policies, along with the overarching Quality Policy and its measurable objectives, are the foundation of a Quality Plan that can be monitored by the quality management staff.

Assessments of compliance with policies and procedures should be conducted periodically and reported to senior management. If there are shortcomings, then corrections must be made. Just like technical processes and procedures, the quality management processes and procedures must be monitored for effectiveness. To understand how well you are doing at meeting your goals and objectives there must be a way to measure them [12]. It is important that the management goals be written so that they can be measured. These objective measures are often referred to as monitors or indicators and can be process or outcome based. Processes should be measured in a manner that demonstrates that there is consistency or reproducibility. Outcomes should measure if the desired effect has occurred [1, 13].

The indicators should also take into account whether the goal or threshold is obtainable, economically feasible, organizationally valuable, and straightforward [14]. This is often very difficult to accomplish effectively. It will tax the skills of even the sharpest staff to develop indicators that meet all four elements, but it can be done. The individuals who develop these indicators must fully understand the capabilities and the limitations of the organization.

Setting an obtainable goal sounds simple, but it is human nature to wish for absolute perfection and to be overly optimistic. It is not realistic to expect one hundred percent perfection in human-based systems, so reasonable thresholds should be developed that meet the customer's and management's expectations. Often an indicator is included because it is guaranteed to produce favorable results. Avoid this trap. If it is possible to achieve the goal routinely, then a different indicator should be selected. It is not effective time and resource management to monitor items that cannot be improved. Often, in order to set achievable thresholds, the objective must be measured over a period of time to determine performance. It is acceptable to monitor an objective and collect data before setting a realistic but obtainable threshold. When it is appropriate, the threshold may be changed in order to see if corrective actions have improved a process. For example: An indicator was established for a cellular therapy lab to determine if adequate orders for product manipulation were being received, so that processing could start without delays resulting from changes to the original order. The initial threshold was set at 10% per month. After 3 months of data collection, the indicator was always outside the threshold, at around 20% of errors in the initial order. After looking more closely at the data, it was noted that

monitoring by percentage was too variable, because of the difference in the number of orders received per month. The threshold was, therefore, changed to three events per month to see if training on placing orders with enough specific processing information was effective. This change to the metric for the indicator was a better method to determine if the corrective actions were effective.

When selecting indicators the cost of monitoring them must be considered. There are many elaborate and expensive measurements that can be made to characterize or define the quality of cellular therapy products. If the measure indicates process stability, and is not a required release assay, then it may be permissible to test some of the products and not all of them. A random sample can be used if the process has been validated and determined to be reproducible. If the sampling shows a trend that is outside the acceptable limits, more samples may have to be tested to determine the extent and cause of the problem. For example, you might wish to perform an extensive flow cytometry panel on every product, but that may be prohibitively expensive. A compromise could be to perform a basic flow panel on all products and then randomly select additional products for more extensive analysis.

Selection of an indicator that has real meaning to the organization will also help to maintain buy-in from staff at all levels. If everyone values the desired outcome, then there is increased drive to achieve the goal. Success is measured by output, so there should be less resistance to measuring the indicator to see if the goal is being achieved. Successful indicators are often associated with the core values of the organization. The indicator should also be straightforward, so that the outcome can be measured in a way that clearly demonstrates that the goal has been met. There may have to be several steps or calculations to determine whether the goal has been achieved, but the final result should be clear to everyone who is familiar with the process.

Audits

Once the policies, procedures, processes, and monitoring systems are in place, a system of checks or audits can be developed. These create expectations for performance. Auditing is the action of inspecting or examining a process or quality system to ensure compliance with requirements. An audit is an assessment performed by a qualified person to determine if the steps described in procedures and policies are being performed. It is often impossible to inspect every quality expectation for a cellular therapy product. One hundred percent inspection of parts or widgets may be possible in some industries, but this is not the case in cellular therapy product manufacturing. For example, it is not possible to perform a laboratory test that will detect whether the donor was asked all of the questions required to determine eligibility and suitability. When dealing with lot sizes of one individual product for each patient, random sampling cannot be used to determine compliance. Each product must be developed with quality built in and we should not rely on a test for quality. Recordkeeping practices provide the documentation that policies and procedures designed to ensure quality have been followed. An audit of these records

for their accuracy and completeness can serve as a surrogate to demonstrate that the required actions were taken and, therefore, that quality expectations were met. The audit process in turn provides formal evidence that required actions were completed and documented. If the audit finds a lack of compliance, then corrective action can be taken to prevent an undesirable outcome. An audit of a problem-prone procedure may identify areas of particular weakness where problems may originate. This allows preventive action to be taken before an error occurs.

There should be a written document to describe the audit process and its elements. While the quality plan addresses the management's requirement for audits, an audit plan should be written so that everyone in the organization can understand the process. The plan should cover the elements of auditing: types of audits, what will be audited, who will perform the audit, the audit schedule, how and to whom audit findings will be reported, and what will be done with the findings.

As with all other procedures, there should be a written document to explain the audit process and its component elements. While the quality plan addresses the requirement for audits, a specific audit plan should be developed so that everyone in the organization can understand the process. The plan should cover the elements of auditing: types of audits, what aspects will be audited, who will audit, the audit schedule, how audit findings will be reported, to whom findings will be reported, and what will be done with the findings.

There are first-, second-, and third-party audits. Each type has specific uses and outcomes. First-party audits are internal audits authorized by the management and conducted by employees of the same organization. These are probably the most thorough, because the auditor is very familiar with internal processes, procedures, policies, and the employees. Second-party audits are external audits conducted by an agent outside the organization, but are also requested by the management. The value of these audits is that the operation is evaluated by someone with a different perspective. These auditors are usually paid consultants who may be recognized as experts in their field. The value of the external viewpoint may be offset by the time it takes for the auditor to understand fully the operation that is being audited. Whereas the first two types of auditors work on behalf of, or at the request of, management, third-party audits are conducted by an outside agent to determine compliance with regulations or standards for accreditation.

For first- and second-party audits, the scope of the audit plan can be devised and agreed on by management. This describes the elements, processes, and records that will be reviewed. These internal audits may, therefore, be focused or process or system based.

Focused audits usually look at a specific step, procedure, or record to determine compliance with written directions to staff. Examples of focused audits include review of temperature monitoring records or donor eligibility and suitability records for completeness, and review of critical calculations for accuracy. As the name suggests, these audits focus on a single, measurable element, and are usually the most straightforward and least controversial.

Process audits look at the results of putting several independent steps or procedures together to achieve a desired outcome. Process audits evaluate the consistency

in achieving the expected result. Often these audits cover many independent areas within the organization and review how well the process is controlled when more than one staff member is responsible for the final result. An example of a process audit may be a review of the effectiveness of finding suitable, eligible, and compatible donors, collection of sufficient cells to provide a therapeutic dose, and processing of those cells in a manner that allows viable cells to engraft in a timely manner.

System audits are even more comprehensive and complex. A system is composed of all the elements needed to ensure that processes and procedures have been adequately and consistently established and maintained to achieve success. Many systems are usually required to ensure outcome quality. The system audit should evaluate if written policies and procedures are in place that direct what must be done to ensure quality. The auditor then should look for objective evidence of compliance with these policies and procedures. For example, a system audit might examine how vendors of critical supplies and services are evaluated to determine if they have established and implemented systems to ensure the quality of elements over which you do not have direct control. A systems audit may also be performed to determine if credentials and references for each new hire are reviewed prior to employment. These types of audits are intended to ensure that quality is being brought into the system and that it is maintained at a level that meets or exceeds the customer's expectations.

Development of a schedule is essential to the success of the audit program. The schedule allows managers, supervisors, employees, and auditors to be prepared for the process. Unannounced audits should only be conducted unless everyone has agreed in advance to the practice. A schedule also allows all parties to manage their workload and responsibilities. The auditor will need to allow time to review policies and procedures, develop an audit tool, conduct the audit, write a report of findings, and deliver this report to senior management. The auditor may also be responsible to verify that appropriate follow-up has been completed. The staff being audited need to ensure that critical processes are not interrupted by the process, leading to irreversible errors. A published audit schedule also provides a tool to assess the compliance of the quality unit with their own policies and procedures.

Careful selection of internal auditors is critical. The auditor must not only understand the organization, policies, processes, and procedures but also have a firm foundation in the principles of auditing. He or she must be fair, unbiased, and not involved in the management of the operation being reviewed [15]. Involvement in the process or responsibility for corrective action on the part of the auditor may lead to bias when reporting findings. The auditor must also have strong written and verbal communication skills, and the ability to put people at ease so that open-ended questions can be readily answered. He or she must also be prepared for the pressure of delivering unfavorable findings. Meetings may become contentious and the auditor will have future interactions with their fellow employees. Professionalism and tact are key to surviving as an internal auditor.

Interactions between the auditor and staff are critical in the success of the program. The audit must not distract from the work process and much of an audit can

usually be performed away from the workspace. For example, procedures, policies, and records can be reviewed before observations or interviews.

After the auditor has gained an understanding of the work process and final product, an audit tool or checklist of the critical steps should be made so that the audit can stay on track. A list of open-ended questions should be developed. Written interview questions ensure that the same questions will be asked of multiple staff members. After the tools have been developed, then direct observation can be performed to determine if the procedures and policies are being followed consistently by staff. These observations should be performed from a location that allows a clear view, but does not impede, distract, or intimidate the employee performing the function. After observations have been completed, then staff interviews can be conducted. Once again it is important that interviews take place away from the work process so that the potential for error is not increased by the audit. It is also important to the integrity and confidentiality of the interviews and findings, so that the auditor maintains the respect of the client and becomes a trusted part of the process.

The report of findings is central to the audit process. This must be written and fact-based. Good auditors will verbally report likely findings at the time of detection and many will allow the individual who was audited to review a draft of the report before providing it to management. This may alleviate any tension that has been created. Initial findings must always be corroborated before they are reported. This confirmation may be from another staff member who provides the same answer to a question, or multiple examples of the same deficiency.

Audit findings must be based on facts and not opinions. The most effective written audit reports specifically cite the regulation, standard, or internal policy or procedure that has not been met.

Improving Cellular Therapy Services

The purpose of internal audits should be to find areas for improvement. After the report has been delivered it is the responsibility of the process owner to develop a response. Information may be submitted to clarify or refute a finding, but more often a corrective action or prevention plan will have to be written, so that the nonconformance can be corrected.

Another important component of the Quality Assurance Plan is an Error Management System. Even with properly written Standard Operating Procedures (SOPs) and effective training programs there will be times when errors occur. How these are to be handled is dealt with in an Error Management system. There must be written procedures and policies that describe actions to be taken when an error occurs. When the error is detected it should be reported to management as soon as possible. Errors should be carefully investigated to determine the real cause of the problem. This investigation is referred to as a root cause analysis. Error reports should be collated and trended over time to look for patterns. These may reveal trends related, for example, to the time of day that errors occur, who is involved,

at what step they happen in the process, if they happen on certain shifts or days, or only on certain protocols. Looking for these patterns can help in discovering and eliminating the cause. Once an error is fully understood, corrective action can be taken. An effective corrective action will fix the root cause. Once the action has been determined, staff should be made aware of the error and trained on changes that need to be made. Even after corrective actions have been taken, the issue should continue to be monitored to ensure that the actions are effective and sustainable, and that the change has not disrupted another part of the process that was working.

There may be occurrences when an error has potentially impacted the purity, potency, or efficacy of a product. If this is the case, there must be policies and procedures on action to be taken on affected products that are still in inventory or that have been distributed. If the cellular therapy product is still available, then a decision must be made as to disposition. If there is an acceptable alternative in inventory, then disposal should be strongly considered. If no equivalent or suitable product is available, then clinicians and the manufacturing facility's medical director should discuss risk versus benefits and determine if the patient should receive the product. These discussions and decisions should be meticulously documented. If an FDA-licensed product has been distributed, then Agency notification may be required. If the product was not licensed, then the incident may have to be reported to the IRB or Ethics Committee and documented in the Investigational New Drug (IND) annual report.

A fundamental element of quality management is to learn from errors. The analysis of errors, resolution of patient safety issues, and application of corrective actions are crucial in quality improvement.

By definition, quality is pleasing the customer. In order to do so, there must be a mechanism to evaluate customer satisfaction. For regulated cellular therapy products, these issues should be documented in a complaints file. This should be reserved for issues concerning patient safety and the purity, potency, or efficacy of the product. Unexpected disease transmission or failure to engraft within expected time frames are examples of incidents that should be included in complaint files. These should be treated in the same manner as errors. There should be a complete investigation to determine the root cause, and if possible, corrective action should be implemented as soon as possible. If the complaint is potentially a threat to public health, then consideration must be given to ceasing manufacturing until the issue is resolved to the satisfaction of all involved parties. As with all other systems, there must be a plan of action determined by senior management.

Quality Improvement

When policies and procedures are in place that define the Quality System, the quality section personnel can focus on continuous improvement. Quality Improvement projects demonstrate management's intent to achieve the quality goals. There needs to a written policy and procedure to address how to select, develop, track progress,

and document improvement projects. Such projects can be very resource intensive in terms of both time and budget.

Careful attention to the performance for quality indicator data, findings from audits, and complaint file entries are all sources to identify opportunities for improvement. It is easy to try to turn every incident into an improvement project. Some events will be addressed by a specific corrective or preventive action. Quality Improvement projects should be reserved for multiple stakeholder problems.

Understanding the root cause of a problem-prone process will allow the development of a project plan. Each stakeholder needs to be represented during the problem-solving and decision-making sessions so that all aspects of the issue will be considered. Once the required changes have been identified, an action plan should be created. This helps to coordinate the efforts of the staff charged with making the changes. Quality Management employees or a project leader should plan periodic meetings to track progress and maintain the momentum.

There are several reasons to document the success of a project improvement team. These include showing commitment to success, and many accrediting organizations require documentation of quality improvement activities to achieve accreditation. Improvement can be documented in a narrative or pictorial format. A narrative would include a written summary report that includes the baseline data that identified the problem, the actions of the team, and the data summary that demonstrates improvement. The pictorial format, sometimes referred to as a story board, shows the same results but using visual presentations, such as graphs or charts, to demonstrate improvement.

Conclusions

Quality Management is the practice of ensuring that processes to identify error-prone issues are identified, their cause determined, changes made to eliminate the problem, and corrective or preventive actions successfully implemented. Many cellular therapy programs are finding that, no matter the size of the program, there should be dedicated personnel to focus on just these activities. Quality issues and solutions can be complex and time-consuming but are critical to the sustained success of any cellular therapy program.

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Chapter 17
Product Manufacturing

A. Gee

Abstract Once a manufacturing process has been validated, it moves into routine production. It is important to ensure that this transition goes as smoothly as possible. Many of the basic elements should already have been anticipated during the validation phase. These would include generation of the standard operating procedures and batch records or worksheets, training of staff, and decisions on appropriate testing of the product. The next phase is to use these materials as the basis for starting routine manufacturing. This chapter deals with these preparations in a little more detail.

Design of the Manufacturing Procedure

Although validation is discussed in more detail elsewhere in this volume, it is important to reiterate some important features that will assist in the design of a routine product manufacturing procedure. Validation is primarily intended to provide evidence that the product can be made by a reproducible process that ensures that it routinely meets release specifications. It is important to read the relevant Good Manufacturing Practice/Good Tissue Practice (GMP/GTP) or European regulations prior to designing the procedure and associated documentation [1–3]. In the United States the Food and Drug Administration (FDA) has published useful guidances for reviewers of somatic cell [4] and gene therapy products [5] that provide very valuable insight into what they look for when reviewing the chemistry, manufacturing, and control sections of Investigational New Drug (IND) and Investigational Device Exemption (IDE) applications.

It is preferable to use disposable closed systems whenever possible [4]. In their absence, semiclosed systems, fabricated from transfer packs, lines, and connectors joined using sterile connect devices, are a good alternative. The number of

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transfers and manipulations should always be kept to a minimum to reduce risk of cell damage, contamination, and loss. Nonspecific cell loss can be minimized by handling cells in containers of the appropriate size, such that residual volumes in the container after emptying represent only a tiny fraction of the product, and can be recovered if necessary by small-volume washes.

Prior to starting validation, a draft standard operating procedure (SOP) will have been prepared, together with data recording worksheets and written product release criteria. These form the basis for the documentation that will be used during subsequent routine manufacturing. The draft SOP should be finalized in a form that provides sufficient detail for the staff to perform the procedure, but also allows for inherent biological variability in the starting material and its handling characteristics. With experience, it may become necessary to amend the procedure, but it is advisable to make changes only when these truly reflect what has become standard practice. Interim changes can be recorded as deviations or planned variances until a new version of the SOP is issued.

Worksheets and batch records can also be developed from the data recording forms developed for the validation studies (Fig. 17.1). These documents provide the primary manufacturing data and must be sufficiently detailed to allow all phases of production and testing to be tracked. Regulatory agencies generally like the records to mirror closely the consecutive steps described in the SOP. This facilitates review and allows easier detection of variances. In many cases the worksheets will contain more specific detail, so that the exact conditions can be recorded, rather than the use of the range of acceptable conditions described in the SOP. It is important to include the raw data used to perform calculations. Calculations can be presented in a "fill in the blanks" format, rather than expecting the technologist to remember how a particular calculation is performed. All calculations should be checked and verified in real time by a second individual for accuracy, and space must be provided to document this check. In the same way, major steps in the procedure should be initialed and dated for identification purposes by the technologist responsible. Since it is impractical to have a technologist who is working at a biological safety cabinet continually stop and sign and date records, it is better either to have a second individual document the steps and have the technologist sign at appropriate stopping points, or to break the manufacturing into a series of activities which are then reviewed and signed appropriately. Careful design of worksheets up-front pays dividends subsequently. A form that is easy to use and logically organized will reduce the frustration of the technologist, reviewer, and auditor. Simple devices such as checkboxes, preprinting of repetitive information, and incorporation of clear instructions at decision points in the process add to the ease of use (Fig. 17.2). Judicious use of color print can aid in following the process; however, this will be lost on photocopied versions. Spaces should be left to affix copies of labels that are used during manufacturing, and to record storage locations of the final and intermediate products. Where appropriate, worksheets can also be used to record man-hours, environmental monitoring performed, and samples submitted for testing.

Worksheets may be handwritten in blue or black ink, or may be preprinted on on-line forms. For on-line documentation there must be a system in place to ensure the

Written By / Date:		Issued By / Date:
Jeffrey Wilson 5/31/2006	GMP Cell and Tissue Processing Facility 11th Floor, Feigin Center, 1102 Bates Street, Houston, Texas 77030	
Approved By / Date: Adrian Gee 5/31/2006		

CW03.32.6: MANUAL DENSITY GRADIENT SEPARATION FOR THE ISOLATION OF AUTOLOGOUS MONONUCLEAR MARROW CELLS FOR CARDIAC PATIENTS

3.0 Product Receipt

3.1 Receive Product and Verify Information		Performed By	Verified By
3.1.1 Record date and time of product receipt into the GMP facility	Date and Time:		
3.1.2 Verify product labeling against the prescription for processing	Labelling Agrees with Rx: ☐ Yes ☐ No		
3.1.3 Confirm Initial Product Container Integrity	Container Intgrity Check: ☐ Good ☐ Bad		
Comments:			

3.2 Pre-Processing Sampling			Performed By	Verified By
3.2.1 If the initial product is received in more than one container, select an appropriately sized transfer pack and pool aliquots into a single vessel.	Number of Containers Rcvd:			
3.2.2 Filter product through a 170um blood filter.				
3.2.3 Measure the volume of the "Initial Product".	Product Volume:			
3.2.4 Thoroughly mix the product. Aseptically remove a 2.1ml sample and aliquot as follows:				
	Volume	**Test**	**Performed By**	**Verified By**
	0.5ml	Bacterial Sterility		
	0.5ml	Fungal Sterility		
	1.1ml	Unlabelled cryovial for dilution, cell count, and flow cytometric analysis		
3.2.5 Complete the QA/QC Test Request form, place the samples in a small biohazard bag, and notify QA/QC.				
3.2.6 Transfer 1.0ml of the 1.1ml aliquot from step 3.2.4 into the previously prepared 1:5 dilution tube and mix thoroughly. Aliquot as follows:				
	Volume	**Test**	**Performed By**	**Verified By**
	1.0ml	Cell Count and Immunophenotyping		
	1.0ml	Confirmatory Blood Type		
	3 x 0.5ml	Initial Specimen Reference Vials		
3.2.7 Label the Confirmatory Blood Type sample appropriately and contact QA/QC to take the sample to Blood Bank. Record the results of the Confirmatory Blood Type and the name of the technician reporting the result.	ABO/Rh:	Reported By:		
3.2.8 Perform cell count. Calculate cell concentration, total nucleated cell count (TNC), and Packed RBC content of the product to be processed.				
		Value	**Performed By**	**Verified By**
	Product Volume *(Initial Product Volume [Step 3.2.3] - Initial Sampling [Step 3.2.4])*			
	Cell Concentration			
	Total Nucleated Cells *(Cell Concentration x Volume to be Processed)*			
	Hematocrit			
	Volume of Packed RBCs *(Hematocrit x Volume to be Processed)*			

Fig. 17.1 Example page from a cellular therapy product manufacturing worksheet showing some suggested design elements

veracity and security of the forms and for validation of any embedded calculations, for example. There should also be a validated electronic signature system in use to record the identity of the technologist performing the procedure. It is also advisable to print out each page of an electronic form as it is completed.

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BATCH RECORD: HBR03.23.11 PURIFICATION OF ADENOVIRUS

For the Production of: **Date:** **Room:**

Dialysis of Adenoviral Vector - Continued

Dispense thedialyzed vector into a sterile labeled Container
Labeling must follow vector nomenclature (SOP H01.02)
Record the volume _____ml Initials & Date:_____

If not proceeding directly to vialing, submit a sample to QC for STAT viral particle concentration assay [SOP B03.13]
Attach a copy of the Sample Submission form to the Batch Record Initials & Date:_____

Attach a copy of the test results to the Batch Record Initials & Date_____

Dilute the vector to ~$5x10^{12}$VP/ML

#ml vector at 5 x10^{12} = **Titer of vector in vp/ml X # ml vector / 5 X 10^{12}**

_____X_____= _____ml
5 X 10^{12}

Volume of dialysis buffer to add = # ml vector @ 5 X 10^{12} vp/ml Current Vector Volume
= _____ - _____= _____ml

This volume of dialysis buffer was added to the vector

Measure & record the total volume: _____ml Initials & Date_____

Attach a copy of the label used for the container(s) in the space provided

Example
Ad5-hRTVP VM408
Master Virus Bank
5 x10 e12vp/ml
11/11/2004

ATTACH A COPY OF THE LABEL IN THIS SPACE

Initials & Date_____

Transfer the vector to a -80°C freezer.
Record the location below

Freezer #_____ Shelf_____ Rack_____ Box_____ Slot_____

Initials & Date_____

Generate & attach Production Report

Initials & Date_____

Reviewed by: Date:

Fig. 17.2 Example page from a complex vector product batch record indicating spaces for sample calculations and attachment of labels

Error correction must follow GMP/GTP or European regulatory practices, in that the error must not be obliterated by crossing out or by using correction fluids or tape. Instead, a single line should be drawn through the mistake, the correct information entered nearby, and the change initialed and dated. If appropriate, a short explanation for the change should also be provided. Major changes must also be recorded as planned or unplanned deviations, and this documentation must become part of the manufacturing record.

Batch records must also record the reagents and equipment that are used during manufacturing. In smaller facilities this is often addressed by preprinting a list of the materials currently in use, together with the lot number, expiration date, and manufacturer. The technologist then signs and dates that this list is accurate for the product under manufacture. While this reduces documentation, great care must be taken to ensure that the list is both current and accurate. Many larger facilities are introducing barcoding systems to capture these data and these can alert the technologists to expired items and to equipment that might be out of calibration.

Even though a process has undergone validation, it is often desirable to include supplementary in-process testing during the early phase of routine manufacturing. This is particularly true for cellular therapy products for which sterility is primarily guaranteed by the use of aseptic manufacturing techniques [6]. Validation processes frequently may be rudimentary and involve the preparation of only three lots that meet the release criteria. Subsequently it may be advisable to identify a number of additional critical control points during manufacturing at which in-process tests will be performed. These can include sterility tests, cell yields, and purities after each of the major steps in manufacturing [6]. These provide important information to characterize the process in more depth. With time and experience this in-process testing can be reduced.

Production Monitoring

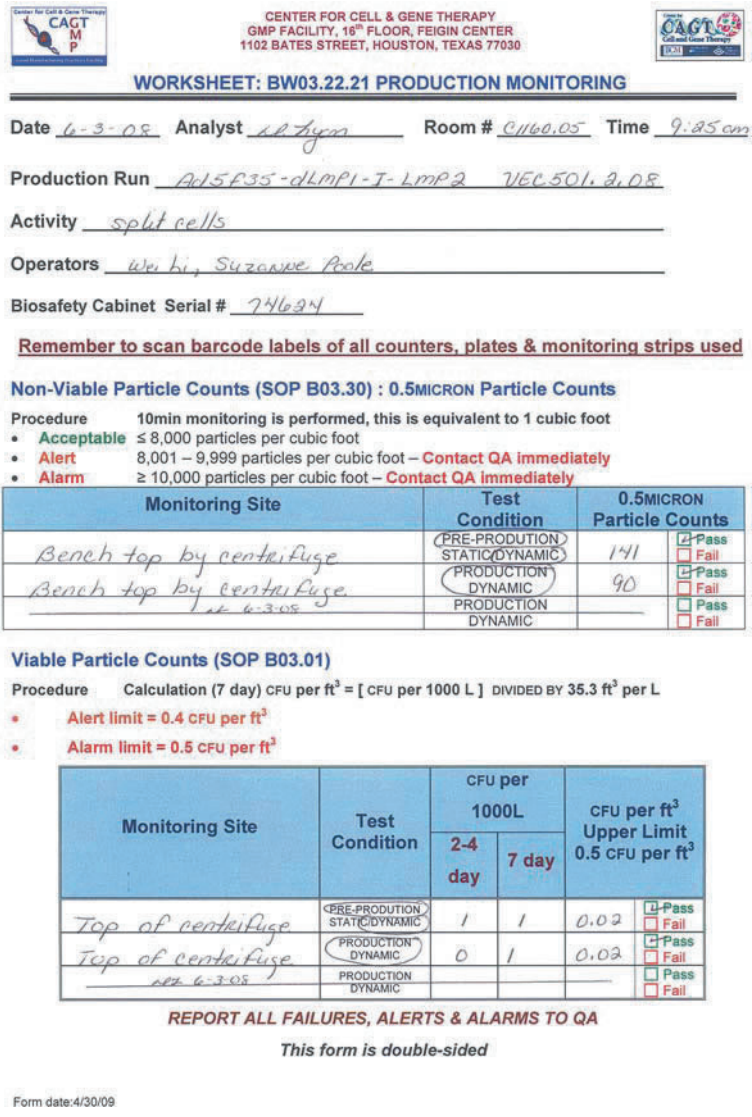
A decision should be made as to the nature and extent of environmental monitoring that is to be performed during product manufacturing. It is probably true that most centers have not performed any form of monitoring during the preparation of Type 361 products. These have traditionally been manufactured using a certified biological safety cabinet and/or using closed or functionally closed systems. A variety of techniques are used for preparing Type 351 products and the Regulatory Agencies should be consulted during the IND preparation to determine what monitoring needs to be performed. For procedures that involve extensive manipulation of cells in a biological safety cabinet in a classified room we generally perform the following production monitoring (Fig. 17.3)

- Particle counts in the room and biological safety cabinet prior to starting production
- Viable particle counts in the room prior to starting production
- Fallout plates (changed every 4 hours) in the biological safety cabinet during production
- RODAC^{TM} contact plates in the biological safety cabinet at the end of production

The results of particle counts can be used to determine whether production should start. Since viable count and fallout plate results are not available until manufacturing has been completed, if they indicate out-of-specification results, then additional sterility testing of the product should be performed.

Review

Secondary review of worksheets should be prompt, to ensure that error detection and corrective action is possible. For this reason, interim review of each step of a complex manufacturing procedure may be more efficiently performed by a qualified technologist prior to "official" review and release of the final product by Quality Assurance (QA). The reviewer must have sufficient understanding of the procedure



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WORKSHEET: BW03.22.21 PRODUCTION MONITORING

Date 6-3-08 Analyst LR Tyn Room # C1160.05 Time 9:25 am

Production Run Ad5F35-dLMP1-I-LMP2 VEC.501.2.08

Activity split cells

Operators Wei Li, Suzanne Poole

Biosafety Cabinet Serial # 74634

Remember to scan barcode labels of all counters, plates & monitoring strips used

Non-Viable Particle Counts (SOP B03.30) : 0.5MICRON Particle Counts

Procedure 10min monitoring is performed, this is equivalent to 1 cubic foot

- Acceptable ≤ 8,000 particles per cubic foot
- Alert 8,001 – 9,999 particles per cubic foot – Contact QA immediately
- Alarm ≥ 10,000 particles per cubic foot – Contact QA immediately

Monitoring Site	Test Condition	0.5MICRON Particle Counts	
Bench top by centrifuge	PRE-PRODUTION STATIC/DYNAMIC	141	☑ Pass ☐ Fail
Bench top by centrifuge	PRODUCTION DYNAMIC	90	☑ Pass ☐ Fail
LR 6-3-08	PRODUCTION DYNAMIC		☐ Pass ☐ Fail

Viable Particle Counts (SOP B03.01)

Procedure Calculation (7 day) CFU per ft³ = [CFU per 1000 L] DIVIDED BY 35.3 ft³ per L

- Alert limit = 0.4 CFU per ft³
- Alarm limit = 0.5 CFU per ft³

Monitoring Site	Test Condition	CFU per 1000L		CFU per ft³ Upper Limit 0.5 CFU per ft³	
		2-4 day	7 day		
Top of centrifuge	PRE-PRODUTION STATIC/DYNAMIC	1	1	0.02	☑ Pass ☐ Fail
Top of centrifuge	PRODUCTION DYNAMIC	0	1	0.02	☑ Pass ☐ Fail
LR 6-3-08	PRODUCTION DYNAMIC				☐ Pass ☐ Fail

REPORT ALL FAILURES, ALERTS & ALARMS TO QA

This form is double-sided

Form date:4/30/09

Fig. 17.3 Sample of production monitoring worksheet

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WORKSHEET: BW03.22.21 PRODUCTION MONITORING

Remember to scan barcode labels of all counters, plates & monitoring strips used

Fallout Plates (SOP B03.21)

‡ If Activity Time is greater than 4 hours, replace with fresh plate

Results

Plate #	Initials	Monitoring Site	‡Activity Time		CFU Per plate	
			Start Time	End Time	Day 2-4	Day 7
1	WL	BSC - left back corner	9:45 am	10:30 am	0	0

RODAC Plates (SOP 03.18.)

Sample #	Monitoring Site	Initials of Sampler	Time of Sampling	Sampling	Colony Count Per Plate		
					Day 2-4	Day 7	Evaluation
1	BSC - left	SP	10:32	☑ PRE-CLEAN ☐ POST-CLEAN	0	0	☑ 0-5 GOOD ☐ 6-15 FAIR ☐ >16 POOR
2	BSC - right	SP	10:32	☑ PRE-CLEAN ☐ POST-CLEAN	0	0	☑ 0-5 GOOD ☐ 6-15 FAIR ☐ >16 POOR
3	BSC - left	SP	10:50	☐ PRE-CLEAN ☑ POST-CLEAN	0	0	☑ 0-5 GOOD ☐ 6-15 FAIR ☐ >16 POOR
4	BSC - right	SP	10:50	☐ PRE-CLEAN ☑ POST-CLEAN	0	0	☑ 0-5 GOOD ☐ 6-15 FAIR ☐ >16 POOR

REPORT ALL FAILURES ALERTS & ALARMS TO QA

Remember to scan barcode label of the incubator used Temperature 30-35 °C

Date & Time Plates *into* Incubator on 6-3-08 at 11:05 am

Date & Time Plates *out of* Incubator on 6-10-08 at 13:00 pm Total Incubation Time 7 days

Results 2-4 day Evaluation Read by [illegible] Date: 6-10-08

7 day Evaluation Read by [illegible] Date: 6-10-08

Actions taken / Comments

[illegible] 6/10/08

Form date:4/30/09

Fig. 17.3 (continued)

to be able to detect problems and deviations that could have an impact on product quality. This review should cover reagents and equipment that were used, variance documentation, calculations, and test results. It may be advisable to pull and include record copies of critical certificates of analysis for reagents such as fetal bovine serum and trypsin, so that they are readily available if the record is subsequently audited. In addition, a flowchart (Fig. 17.4) showing the manufacturing process diagrammatically and indicating the critical control points and associated tests is useful to both the reviewer and the auditor.

It is also important that both the interim and the final reviewer have an understanding of the regulatory status of the product [1–5]. Specific regulations apply to GMP and GTP cellular therapy products [1, 2, 4, 5], and these determine, for

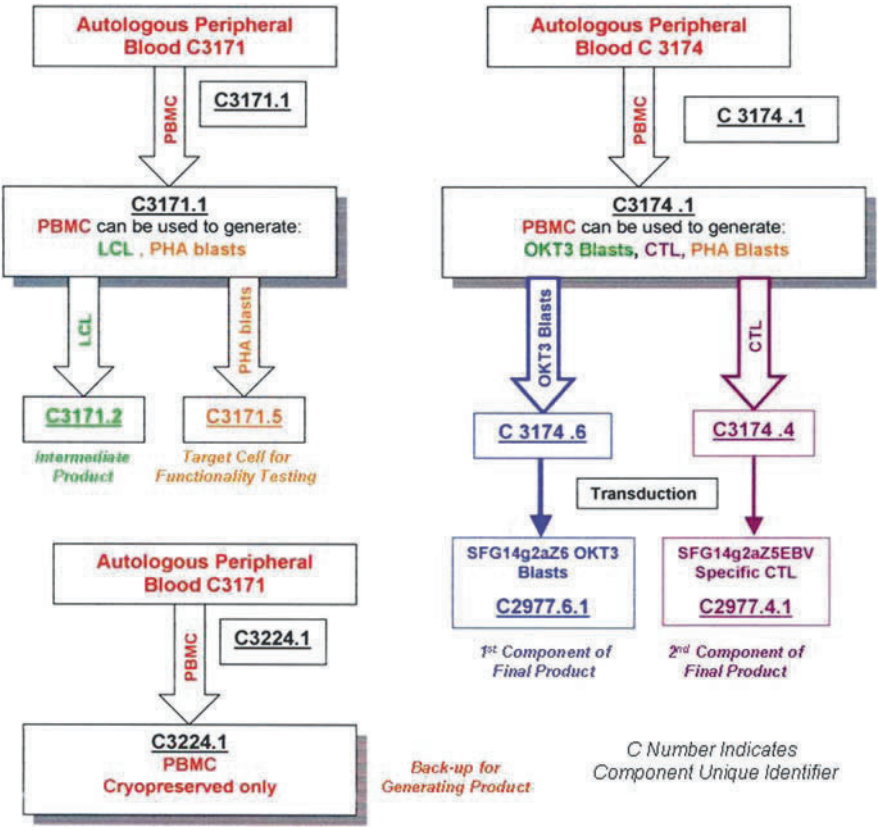

Fig. 17.4 Flowchart of components used and processing of cellular therapy product. C indicates Component Number; PBMC = Peripheral Blood Mononuclear Cells; CTL = Cytotoxic Lymphocytes; SFG14g2AZ6 and Z5 are Retroviral Vectors; EBV = Epstein–Barr Virus

example, the type of labeling to be used, release testing to be performed, documentation practices, and so on. Type 351 [1] products usually require specific labeling, including a designated product name. In contrast, Type 361 product labels may use more generic standard product terminology (such as that designated in Foundation for the Accreditation of Cellular Therapy (FACT) and AABB standards), but also require specific label elements and language [2].

Release Testing

All products will undergo some form of release testing prior to issue for clinical use. This is discussed in more detail elsewhere in this volume. This section is designed to provide a more concise overview as release testing is an important component of manufacturing.

The choice of tests is based on FDA requirements for purity, identity, and potency evaluation [7]. Similar requirements are in place for products manufactured in the European Union [8]. Potency assays are generally still somewhat rudimentary for cellular therapy products and are not strictly required for Phase I/II clinical trials. A formal characterization of the product, together with appropriate potency testing will be required by Phase III studies. In general, however, most manufacturers will develop some form of surrogate potency test, even for early clinical trials, to demonstrate that the product has some type of functional activity *in vitro*. These may include cytotoxicity or cytokine release assays, for example. Purity and identity assays are required for all products regardless of the phase of the clinical trial. Sterility testing is always required, and the general expectation from the FDA is that it should follow the 21 CFR 610.12 regulations [9]. These test protocols are generally regarded by the field as out of date and many manufacturers use automated methods developed for sterility testing of blood products, e.g., Bactec™ and BacT/ALERT® that can detect aerobic, anaerobic, and fungal contaminants [10, 11]. There has been some confusion as to whether these assays are acceptable to the FDA for Phase I/II studies and for GTP products, and investigators are advised to contact the FDA for advice on this subject. Although the general consensus is that the automated assays are both more sensitive and accurate, particularly if the incubation times are extended from the routine 4 days to 14–28 days, the FDA may require formal validation of these techniques to show their equivalence or superiority to the approved test methods [11, 12]. There have been a number of publications to demonstrate equivalence [10, 11], but to date automated methods have not been formally acceptable by the FDA as validated for widespread use. In the case that a cell therapy product must be given before the results of standard sterility tests can be obtained, the normal procedure is to perform a stat Gram stain on the fresh cells. This test is notoriously insensitive and unreliable, but it is the only available rapid release method. When it is used for release testing, the normal requirement is to perform the routine method in parallel, and to have in place a procedure for dealing with any positive results that may be obtained from these methods after the product has been administered to the recipient.

Endotoxin testing is also a standard requirement for release of cell therapy products [13, 14]; even for certain traditionally Type 361 products that have not been cultured *ex vivo*, but are now being used as Type 351 products for nonhomologous use, e.g., marrow mononuclear cells used for tissue regeneration applications. There are a number of commercially available testing methods that meet regulatory requirements. These include gel clot and Limulus amebocyte lysate-based methods. These assays usually take several hours, and samples may fall out of specifications due to presence of hemoglobin or high serum protein concentrations, for example, in the test sample. This requires treatment of the sample and repetition of the assay. For "fresh" cell therapy products this further delays administration to the patient. Recently a handheld device, the Endosafe® PTS™ system [15] (Fig. 17.5), has been developed that permits testing within 20 minutes using an automated LAL assay. While this is ideal for testing fresh products, it currently performs a single test and is, therefore, unsuitable if a large number of assays need to be run. The normal release specification for endotoxin tests is <5.0 EU/kg/dose.

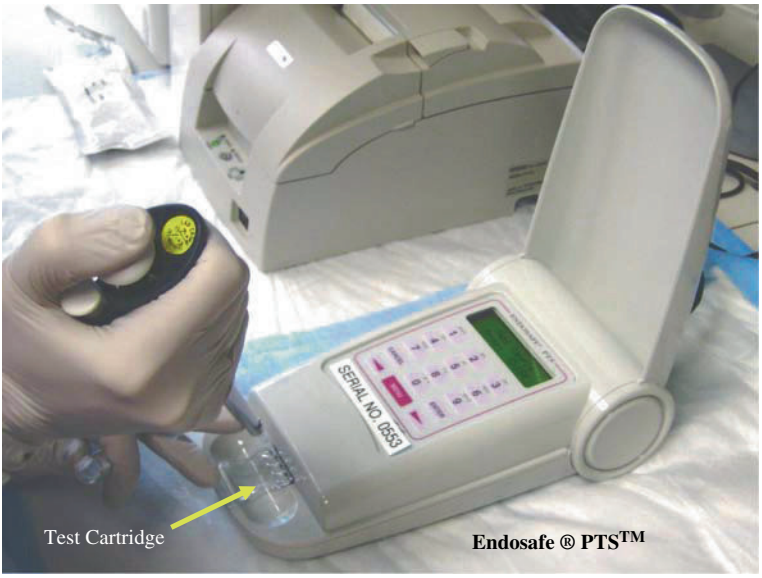

Fig. 17.5 Endosafe® PTS™ endotoxin testing device manufactured by Charles River

Mycoplasma testing is usually required for products that have been cultured *ex vivo* (Type 351 products). The approved testing method detects both agar cultivable and noncultivable products. It is available from a number of commercial testing laboratories; however, it is expensive and the turnaround time is usually several weeks. PCR-based assays (Fig. 17.6) are commercially available and these can detect > 90% of the most common mycoplasma species. The turnaround time is ~48 hours and the cost is about $300. Again, since this is not the approved testing method, its use should be discussed with Regulatory Agencies on a case-by-case basis. There is a rapid laboratory test system, MycoAlert®, that is being evaluated for release testing applications, but this is still at a relatively early stage.

For most cellular therapy products, testing for adventitious viruses has not been requested, although this is routinely required for cell banks and vectors.

The type of identity assay will depend on the nature of the cell therapy product. The most widely used test is flow cytometric analysis, where the phenotypes of the effector cells, or the potential contaminating cells, are known and can be used to establish basic release specifications. These are usually developed in collaboration with the Regulatory Agency and may set acceptable minimum purity levels for the effector cells, or maximum acceptable levels of contaminating cells with the product, or a combination of the two.

In some cases, such as for lymphocyte products, HLA typing may be used to ensure that the final product is HLA-identical to the original cells from the donor.

Viability assessment of cells is also a routine requirement. This can be done by a variety of methods, including vital dye exclusion or by 7-AAD staining and flow cytometric analysis. For stored products this is normally performed prior to

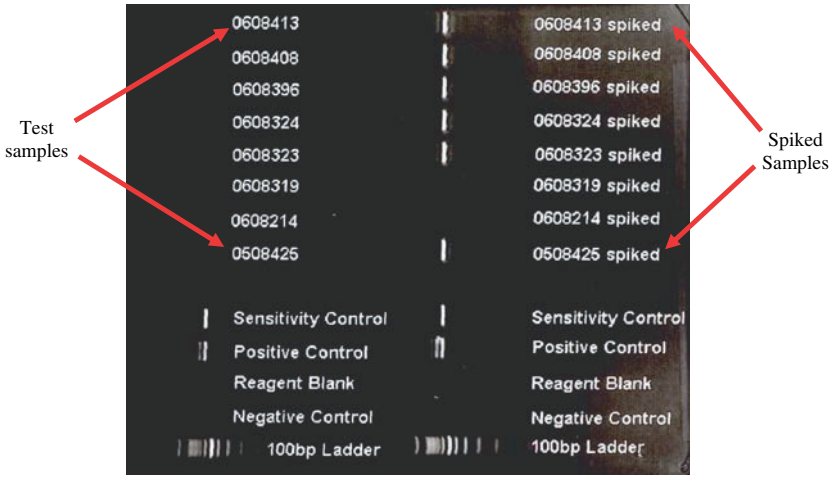

Fig. 17.6 PCR reaction for mycoplasma testing. Test samples were treated with proteinase K and, following deactivation of the enzyme, a PCR reaction was performed using TaKaRa primers as part of the PanVera Mycoplasma Testing Kit. Controls are provided in the kit for use as the positive control and for spiking the test samples

cryopreservation for storage and the release specification is usually >70% viability. The Regulatory Agencies are increasingly asking for post-thaw viabilities and also for information on the stability of the thawed product, to determine the timeframe within which it should be administered to the recipient.

Consideration must also be given to the source of test samples. In an ideal situation, all tests would be performed on samples of the final product. In reality, however, this may be of small volume and contain very few cells in excess of those required for therapy. In such circumstances, alternative samples may be used. For example, supernatants from the final cell wash, and samples of nontarget cells remaining after CD34-positive selections can be used for sterility testing. In the case of endotoxin and mycoplasma testing, samples taken prior to washing the cells are more likely to provide accurate results than those obtained from the final product. These alternatives should be discussed with the Regulatory Agencies to determine their acceptability. Additional release testing may be required that is specific for particular products, and, as always, early and ongoing discussions with the Regulatory Agency are critical.

Type 361 products have historically not been released using a formal Certificate of Analysis system, and the battery of tests used for release has been much smaller. In most cases, the only testing performed has been standard blood culture-based sterility testing even on "fresh" products. Again it is important to have a system in place for notification of the recipient's physician if a positive result is obtained after product infusion. Most centers have not performed Gram stains, endotoxin, or mycoplasma testing on these products. Identity testing is, however, frequently performed, with CD34 analysis being the most commonly used test. There are

rarely specific release criteria based on CD34 content, although a prescription may request a particular dose. The standard-setting organizations are now requiring viability assessment, CD34 analysis if applicable, nucleated cell counts, and, where appropriate, assays for particular cell subpopulations that may have been depleted or enriched *ex vivo*. Most facilities still have not implemented a certificate of analysis system for the release of Type 361 products, in part because it is impractical to generate such a document when products arrive at all times of the day or night.

Whatever test systems are used, there should be access to SOPs for performing the assays, even if a commercial testing company is used. Most companies will provide these on request. Where external contractors are used. they should have undergone some form of vendor audit. Ideally this will consist of a visit to their facility. This may not be financially feasible for smaller cell processing facilities, and in these cases audits can be performed by questionnaire.

Ancillary Records

While the main emphasis is on documentation of the actual manufacturing process, there are a number of ancillary records that must be available for review and audit. These include certificates of analysis for the reagents and materials used during processing. It is usually impractical to include all of these in the batch records, but they must be available if required and should have undergone review to ensure that specifications have been met. Records of equipment calibration and cleaning must be accessible, as must documentation of cleaning of the rooms in which manufacturing was performed. Environmental monitoring of some type should be carried out during manufacturing. In controlled environments the specifications are set by the classification of the facility, e.g., Class 10,000 or specific International Standards Organization (ISO) Classification. In nonclassified space some form of monitoring should have been performed to determine potential contaminants within the area. This may consist of contact or fallout plates, and personnel monitoring.

Records of staff training must also be available. These should cover not only training on the specific manufacturing protocols, but also education on aseptic technique and on GMP and GTP regulations. Where appropriate, and available, there should be records on proficiency and competency testing of the staff.

Product Storage and Release

If products require formal release testing, they should be held in controlled storage until that process is completed. This is to prevent accidental clinical use of nonreleased products. Review of records for product release should be by an individual who was not directly involved with manufacturing. In larger facilities, this is usually a member of the QA group. In smaller facilities this may be difficult, and review can be assigned either to a second technologist, or to an individual out-

side the manufacturing group, but who has been educated on the manufacturing process. In extreme circumstances review may be performed by the manufacturing technologist, but only after a suitable time has elapsed. In many cases an IND holder may wish to review the manufacturing records, but it is important to exclude this individual from the release process, since he or she has a potential conflict of interest. If the reviewer decides that the product fails to meet the release criteria, but the IND holder feels that is required for urgent medical use, the Regulatory Agency should be contacted and permission sought to use the product. This process should be documented and this documentation included in the batch record. If products are released using a certificate of analysis (C of A) system, the C of A should describe the testing performed, together with a brief description of the method used, e.g., endotoxin by LAL method using Endosafe® assay; the identity of the facility performing the assay, the specification for acceptability of the result, e.g., <5.0 EU/kg/dose, and the actual result obtained. Additional information, such as the sensitivity of the assay, the date performed, and the version number of the testing SOP, may also be of value. The certificate should indicate who reviewed and issued the C of A. This will usually include the individual from quality assurance, the technical director of the manufacturing facility and any others designated in the release procedure SOP. Proposed certificates of analysis for IND products are usually submitted to the Regulatory Agency as part of the IND application process.

Upon issue of a C of A the product can be transferred to a released product storage area. This must still be controlled, usually by Quality Assurance/Quality Control (QA/QC). Release of material from this area for any reason must have appropriate documentation on file. This includes material that is provided for patient care, research, stability, or other supplementary testing. It is important to be able to account for all of the material that was manufactured and released. Product provided for clinical use must undergo appropriate identification, usually by two individuals, when released from storage and immediately prior to clinical use. Any surplus material must also be accounted for, even if it is discarded. These records should be readily available to Regulatory Agencies on request. Similar accountability and documentation is required for material that may be shipped to another center for any purpose.

It is also the responsibility of the manufacturer to determine the best storage conditions for the product. For cellular therapy products long-term storage is usually in liquid nitrogen banks in vapor phase. Consideration should be given to temperature fluctuations during storage, caused either by product transfers or by opening and closing the bank. Continuous temperature recording is generally required for products stored in vapor phase, together with appropriate monitoring of liquid nitrogen levels and temperatures. Alarm systems should be in place to alert the facility staff if storage conditions do not meet specifications, and these should be set to allow timely transfer of the product in the event of an emergency. Regulatory agencies are also asking manufacturers to give expiration dates for products although these have not yet been formally established for cellular products. In their absence, most manufacturers will set a very long expiration date and couple this to a stability testing program, in which samples of the product, or different lots of similar

products, are thawed at regular intervals and tested against the original release criteria. For this reason, most manufacturers, where possible, will freeze down reference aliquots of a product at the time of manufacturing to provide material for stability testing. These aliquots should be stored under identical conditions to those for the bulk product. As discussed previously, the stability testing program should also incorporate testing the stability of products after thawing, to determine whether a delay in administration is likely to affect product integrity adversely.

Records of the shipment of products, including temperature monitoring where appropriate, should become part of the batch record. If the material is provided for clinical use, the recipient facility must be informed of the methods used by the manufacturer to track the product and of their responsibility to provide the appropriate follow-up data. Any complaints regarding the products must be addressed and documented by the manufacturer and appropriate steps taken to quarantine and recall affected material if necessary.

The manufacturer is also responsible for registering annually with the FDA in the United States and providing a list of activities performed and types of product manufactured. For products covered by INDs the manufacturer will generally also assist the IND holder with an annual report that includes a listing of all products prepared by the facility, including those that were manufactured but not used.

Conclusion

Product manufacturing may be thought of encompassing all of the procedures that start with procedure validation and end with follow-up of the product recipient. This chapter attempts to provide advice on some of the more important components of this continuum. Many issues are discussed in more detail in other chapters of this volume. The new regulatory environment in which these products are prepared presents the manufacturer with an almost overwhelming amount of information to digest and implement. At the same time many regulatory documents provide valuable advice and tips on compliance. The challenge for us all is to allow development of this extraordinary new field of medicine while manufacturing products that are safe and beneficial.

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Chapter 18
Product Review, Release, and Administration

N.H. Collins

Abstract Once a cell or tissue product has been manufactured, a controlled process must be in place for review and release *before* distribution of the product. The procedure and documentation surrounding product review and release is both a microcosm of the Quality Assurance/Quality Control (QA/QC) structure and an encapsulation of the scientific data generated during manufacturing. Review and release attest that the entire system from accession of product into the laboratory, through removal of final samples for testing, to labeling and transportation of the finished product, has functioned as intended. This chapter describes the processes involved in the review of production and testing records and for product release.

Understanding Product Review and Release

The review and release procedure serves to confirm that cell therapy products have been manufactured following appropriate procedures under the prescribed conditions and have met all of the testing specifications required for clinical therapeutic use. If all aspects of production and testing are not as dictated by Standard Operating Procedures (SOPs) and policies, then a process must exist for exceptional release of the product. The exceptional release procedure summarizes how and why a product did not meet criteria, and the justification for its release. Cell therapy products also face the complication that the results of certain tests may not be available prior to product administration. The release procedure must, therefore, also include a mechanism to deal with results obtained after release and administration. In addition, since the only true measure of the product's function is restoration of some biological activity in the recipient, surrogate *in vitro* measures of the product's intended function *in vivo* must often be used for release.

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The adage that quality cannot be tested into a product is particularly true for cellular products. It is expected that as a product transitions from one developmental phase to the next (preclinical, Investigational New Drug (IND) phase, through licensure) the control of the manufacturing and testing process will become more stringent [1]. Likewise, the release process must become more robust.

A well-constructed review and release procedure has two components. The first component is record review. This demonstrates that appropriate documentation and associated control procedures are in place during all aspects of manufacturing. The second component is final product testing. This must show that the product meets predetermined specifications. As discussed above, the major challenge in release testing of cell therapy products is the frequent need for issue and administration before test results are finalized. As a result, final documentation of product characteristics is often delayed until after administration. Parameters that measure product function in the recipient, such as engraftment of hematopoietic cells (measured by rising absolute neutrophil count or hemoglobin) or functioning of pancreatic islet cells (measured by restoration of insulin production), may be the ultimate indicator of the success of processing and of functionality of the product, but these cannot be used as components of the formal review and release procedure.

Regulatory Issues

Cellular products in the United States can be either essentially unregulated or regulated as drugs, biologics, or devices, depending on tissue source of the cells, the degree of manipulation *ex vivo*, and the intended use of the product [2]. The level of regulation in turn dictates the rigor of review or oversight needed for product release, the type of release testing, and the person or entity responsible for ensuring that all criteria have been met. The degree of oversight is based largely on the perceived degree of risk (see Chapter 1 in this book). Less complex review and release criteria are required for Type 361 cellular products manufactured in facilities operating under Good Tissue Practice (GTP) regulations as described in Title 21, Part 1271 of the U.S. Code of Federal Regulations [3]. These are designed to ensure that the manufacturing process is controlled, and that products are handled in a manner that prevents contamination, cross-contamination, and introduction of transmissible disease agents.

A more stringent regulatory approach is in place for products manufactured under new drug and/or new device regulations (IND or Investigational Device Exemption (IDE)). In this case, manufacturing must be under Good Manufacturing Practices (GMP) as outlined in Section 351 of the Public Health Services Act ("Type 351 products") [4]. GMP regulations provide the framework for manufacturing of pharmaceuticals, blood components and blood products, and contain detailed sections covering product release. In addition, state and/or local laws may mandate supplementary requirements for release [5].

Products that fall outside the federal or state regulatory framework (e.g., bone marrow intended for autologous homologous applications) may be processed and issued without adherence to the full range of procedures described in this chapter.

However, it is clear that in the United States, manufacture of all products used clinically, even "unregulated" Type 361 products, and/or those not intended to proceed toward final licensure, should conform to the spirit of these regulations. Since most cellular processing facilities adopt the stricter interpretation of the regulations to ensure maximal safety for their patients, and to provide consistency in operations, this "regulatory creep" has resulted in a higher degree of control over all products. Facilities have recognized that use of standardized release procedures for all products generally increases laboratory efficiency. However, this universal approach also imposes an additional cost for documentation and labor in the review, and release of products which do not have to meet the stricter regulations.

Although it is essential that staff responsible for all aspects of manufacturing and testing clearly understand review and release procedures, the ultimate responsibility for determining whether the product has met predetermined specifications usually depends on where the product falls in the regulatory continuum. As products progress toward licensure, release becomes the responsibility of fully mature Quality Assurance (QA) units. In the academic environment, the laboratory medical or technical director is usually responsible for all aspects of manufacturing; however, in practice, release is often handled by the manufacturing staff, especially during the early developmental phases or when processing is finished outside of regular working hours. Some professional standards, e.g., those of the Foundation for the Accreditation of Cellular Therapy (FACT) [6], only require that at least two "trained" personnel inspect the product and label, and leave the level of that training open to interpretation. However, even in early phase studies, it is recommended that manufacturing staff should be distinct from those with Quality Assurance/Quality Control (QA/QC) responsibilities (see Chapter 16 in this book). Use of the phrase "or designee" in product review and release SOPs allows the director to identify specific staff to review records and authorize off-hour product release.

In facilities with small numbers of staff, manufacturing, final review of records and labels, and release of the product may potentially involve the same individuals. If this cannot be avoided, there should be a separation in time and space between these activities.

As products move toward licensure this approach changes, since the complexity of release testing increases, and the differentiation between manufacturing and quality assurance activities becomes more rigorous [7, 8].

Institutional Review Boards (IRB) or Ethical Committees may also influence the type and timing of testing during all phases of product development. Most regulations and professional standards agree on the basic release test criteria for products in the earliest phases of clinical trials. These include assays for product identity, viability, and sterility. During later stages of clinical evaluation, additional assays, including potency testing, are required.

Product Review and Documentation

The dictum that unless an action is documented it has not happened is particularly important in product release. The pharmaceutical model of batch records for each

production cycle has been applied to cellular products; however, these currently differ from traditional pharmaceuticals, as they are patient specific and manufactured in very small lots. In addition, unlike a traditional drug, a cellular product that does not meet specifications may have to be used if medically necessary. There are, however, certain common elements in the documentation for any cell therapy product. These are listed in Table 18.1 [6, 9, 10].

Deviations that occur during manufacturing must be carefully reviewed by the quality program staff (QA). They must be managed in accordance with SOPs and their potential impact on product quality must be carefully assessed. There must also be a mechanism to report notifiable deviations to governmental agencies when required [5, 11].

Product release is often handled through a certificate of analysis (C of A) system (Table 18.1). The C of A summarizes the characteristics of the product, and the tests performed (Fig. 18.1), whether or not the results are available at the time of distribution. For this reason, a procedure for the addition of post-release test results and associated rereview of all documentation should be developed, as well as a mechanism to deal with postrelease test results that do not meet specifications.

The C of A details release specifications and results of each test, with the method used for testing and the assay sensitivity or acceptable range of results. Release specifications for test results are generally derived from the regulations, the IND or IDE, and the literature. As products move toward licensure, these specifications may be refined or become more stringent. Additional product information, such as details on vialing or packaging, storage conditions, and expiration date, may also be documented in the C of A. The certificate should be signed by the individual(s) responsible for its generation and review, and a copy is usually released with the product, while the original is retained by QA or in the patient chart as dictated by laboratory SOPs.

Review of the infectious disease status of the cell or tissue donor is an important component of the release process. In the United States, Part C of 21 CFR Part 1271 [12] requires that, with specific exemptions, donors must be classified as eligible or ineligible, as determined by infectious disease testing, assessment of risk behaviors, and clinical examination and history. Ineligible donors may be used under defined circumstances and with appropriate handling and labeling of the product, and notification of the intended recipient. Most U.S. centers have now developed systems to document that the patient is aware of the possibility of transmission of disease from a product obtained from a donor who has tested positive, has pending test results, or where the donor has known risk factors.

Product Testing for Release

Practical and scientifically defendable release tests must be chosen [13]. There are few *in vitro* assays for functionality that reliably reflect likely cellular activity *in vivo*. Tests for the release of Type 361 products have not been specified and those

Table 18.1 Most common elements for review as part of product release

- Physician order for cell or tissue collection
- Informed consent for collection
- Informed consent for participation in study
- Donor eligibility assessment and supporting documentation
  - Donor risk questionnaire
  - Infectious disease test results with interpretation
    - Appropriate test kits and samples used
- Clinical history/examination
- Manufacturing records to ensure that proper procedures have been followed
  - Flowchart of manufacturing and testing process
  - Properly completed worksheets or batch records
  - Planned or unplanned deviation documentation
  - Listing of material, reagents, supplies, and equipment used
    - Copies of certificates of analysis for "critical" reagents, e.g., sera, enzymes, and growth factors
  - Cleaning and environmental monitoring records
  - In-process testing performed and results
  - Availability of appropriate staff training records
  - Information on in-process and final storage locations and conditions
  - Release testing performed and results
  - Label copy and label approval documentation
  - Review of tracking records to ensure that there has been no product mix-ups
  - Complete inventory of available product
- Certificate of analysis
  - Proper name of product
  - Identity of donor and/or intended recipient as appropriate
  - Required regulatory language, e.g. For Autologous Use Only
  - Expiration Date
  - Required storage conditions
  - Cautionary statements, e.g., Do not thaw and refreeze
  - Packaging information
  - Listing of all required testing
  - Method used for testing
  - Sensitivity (and specificity) of test method
  - Specification to be met for product release
  - Identity of test laboratory
  - Test result obtained
  - Appropriate "Reviewed by" and "Released by" authorization
- Physician order to issue product
- *Urgent medical need authorization* or regulatory approval documentation for use of nonconforming products if appropriate
- *Documentation of cross-checking of product identity* at time of removal from storage and transfer for administration
- Transfer/shipping documentation
  - Establishment and notification to all parties involved of requirement for product tracking
  - Removal from inventory with cross-check of product identity and integrity
  - Transportation records
    - How and when transported
    - Validated procedure used for transportation
    - Documentation of transportation container/equipment and labeling
    - Inclusion of instructions for receiving staff
    - Receipt documentation
    - Transportation temperature records
    - If shipped from external organization, procedure in place for reporting outcome of procedure

Not all elements are applicable to every type of cell therapy products.

CERTIFICATE OF ANALYSIS
GMP Cell Processing Facility
University of Anytown, Anytown, USA
Caution: New Drug-Limited by Federal Law to Investigational Use
Properly identify intended recipient and component
For Autologous Use Only

Non-Transduced Autologous EBV-specific Cytotoxic T Lymphocytes

Patient Name: **SAMPLE, Patient**
Medical Record Number# **P9999**
Hospital #: **12345678 Regional Medical Center**
Component Identification # **C2999.9**

TEST	LABORATORY	SPECIFICATION	RESULT
Lot # P9999C2999.9 Frozen: July 15, 2008 **1x10^7 T cells/ml/bag 10ml/bag in Plasmalyte** ***Store below -150°C Do not thaw & refreeze Expiration: July 24, 2013***			
Viability (Cell Product pre-cryopreservation) by dye exclusion	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	>70% viable	98% viable *(July 15,2008)*
Endotoxin (Cell Product) by Limulus Amebocyte Lysate Assay (K-QCL method)	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	<5.0 EU/ml	<2.0EU/ml ***<2.6EU/kg @ 70kg recipient weight*** *(July15,2008)*
Mycoplasma (Cell Product & Supernatant medium) By Points to Consider 1993 Assay	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	Negative	Negative *(August 15,2008)*
Sterility (Cell Product & Supernatant) by 21 CFR 610.12 assay	Quality Control Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	Negative	Negative *(August 15,2008)*
Immunophenotyping (Cell Product) by Flow Cytometry	Flow Cytometry Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	<2% CD19$^+$ Cells	0.1% CD19$^+$cells *(August 15,2008)*
HLA Typing (Donor and Cell product) by High resolution typing	Donor and Final Cell product must match **Donor** Deutsche Herzzentrum Berlin Transplanationsambulanz II Augustenburger Platz 1 Germany **Cell Product** Histocompatibility Laboratory Department of Laboratories, Univ. of Anytown, Anytown USA	**Donor** A*0301,1101 B*1510,5101 Cw*0304,1502 DRB1*1001,1501 DQB1*0501,0602 DRB3*Neg DRB4*Neg DRB5*0101 *(January 3, 2008)*	**Cell Product** A*0301,1101 B*1510,5101 Cw*0304,1502 DRB1*1001,1501 DQB1*0501,0602 DRB3*Neg DRB4*Neg DRB5*0101 *(July 30, 2008)*

Approved for Release for Autologous use ONLY by:

My signature Date: 29th August 2008
Quality Assurance, Anytown University Quality Assurance Department, Anytown, USA

Fig. 18.1 Example of certificate of analysis

used are basic, e.g., sterility. Type 351 products must meet a higher standard for product release. Listed in the CFR, these tests include sterility, mycoplasma contamination, purity, identity, potency, and others developed by the product manufacturer [14]. The test methods are specified for sterility, mycoplasma, and purity (pyrogenicity), but not for identity and potency.

The short shelf life of many cellular products poses a challenge when selecting release tests. Certain products may be cryopreserved providing the time in which to perform tests which require longer turnaround times for results; however, some products require release immediately after preparation, and prolonged testing cannot

be performed. In this situation, rapid tests must be used [15] if available. This is of particular importance if cells are required for intra operative procedures.

Sterility Testing

Sterility is a fundamental test requirement for cellular products. Since cellular therapeutics and some cell-derived products (e.g., lysates, semipurified extracts) cannot be filter-sterilized they must be handled aseptically throughout the manufacturing process. When manufacturing procedures are short, they do not allow sufficient time to obtain results from traditional tests for bacterial and fungal contamination. In these cases extra controls involving in-process testing during manufacturing are often set in place, and must be reviewed before product release [16]. Since the standard sterility test described in 21CFR 610.12 [17] uses a 14-day incubation, other tests for microbial contamination, such as microscopic examination following Gram staining (or other bacterial and fungal stains), should be used at release. While a Gram stain is rapid and easily performed, it suffers from the problems of insensitivity, sampling error, and operator variation.

Recent investigations have cultured cellular products using automated blood culture systems to shorten the incubation time [18]. While these results are promising, there is no consensus on which is the most reliable assay, and the Food and Drug Administration (FDA) often has asked that the 21CFR 610.12 method be used for IND or IDE studies; or that the rapid method must be formally validated locally against the CFR technique.

The small volume/cell number of some cellular products also hampers sterility testing, due to the inability to sacrifice a large enough sample for testing, or the problem of obtaining a sample that is representative of entire product. Under these circumstances supernatants from washes of the cell product may be used for testing, but the acceptability of supernatants has not been universally established for all types of cellular products. Another issue is that recipients of cellular therapy products are frequently immunosuppressed and, therefore, on broad-spectrum antibiotic coverage. The low rate of complications associated with infusion of contaminated products [19] suggests that this coverage may permit the use of products carrying a microbial burden. This approach should, however, be considered more as a "safety net" rather than as an acceptable practice.

Mycoplasma Testing

Mycoplasma testing is used for products that have been cultured *ex vivo* [20]. FDA-approved tests for this intracellular parasite are listed in 21 CFR 610.30, but the recommended "Points to Consider" method cannot provide rapid results.

There are several commercially available kits that can be used to detect mycoplasma by PCR within 24–48 hours [21, 22]. These, like the automated blood culture tests listed above, have not been approved by the FDA. Validation of

alternative test methods is essential since inconclusive or unreliable results necessitate repeating the test while cells deteriorate, or the intended recipient is kept waiting. Since few of these tests have received regulatory approval, proposals to use them in place of the approved method must be discussed with the regulatory agencies.

Purity

Purity is interpreted as meaning lack of contamination with endotoxin or other potential harmful materials added during manufacturing. Endotoxin, a component of the gram-negative bacterial cell wall, is both a cause of adverse reactions on infusion and an indicator of possible contamination with other bacteria. This highly stable material can be found not only in the lysed bacteria, but also as a residual contaminant of supplies and reagents used in manufacturing. Many tests for endotoxin have been developed; however, mainly the older and longer assays have been approved by regulatory agencies. Some rapid release assays that can be performed on site are now available [23], but many manufacturers still choose to send samples to commercial testing laboratories that use the more traditional testing methods. This can be costly in both time and money.

Viability

Cellular properties such as viability can be measured immediately by microscopic evaluation of cells stained with vital dyes such as Trypan blue, or by using flow cytometry and stains such as 7-AAD. In some products the cells required to exert the therapeutic effect may be a subpopulation remaining after destruction of other subpopulations. Under such circumstances it is important to determine the viability of only the effector population. This can be achieved most effectively by flow cytometry. The commonly accepted release specification for viability is >70%. For cryopreserved products the timing of viability assessment should be discussed with the regulatory agency. Most manufacturers measure viability pre-cryopreservation; however, increasingly there is a requirement for assessment at the time of thawing for administration.

Identity Testing

The identity of the cells in the product is frequently established by flow cytometric analysis for either surface phenotype, or identification of intracellular components. In certain circumstances testing of functional capacity (such as cytokine secretion) may also be used. Molecular techniques, such as PCR, can also provide extremely precise information on the genetic identity of cells present in the product. In many cases, the investigator responsible for the development of the product may be initially required to suggest the most appropriate assays for product release to

the laboratory manufacturing the clinical product. As the product moves along the regulatory pathway the responsibility for testing, test validation, and development of potency assays will fall to the quality unit (Table 18.2).

Table 18.2 Analytical tests for cell and gene therapy biological products

		Gene therapy products	
Test	Cell therapy products	Viral	Nonviral and antisense-oligonucleotide
Identity of biological substance	Surface marker determination	Restriction enzyme map	Restriction enzyme map
	Species	PCR	PCR
	Morphology	Immunoassay for expressed gene	Immunoassay for expressed gene
	Bioassay	Sequencing	Sequencing
	Biochemical marker		
Dose	Viable cell number	Particle number	Plasmid-DNA weight
	Enumeration of specific cell population	Transducing units (DNA hybridization assay)	Formulated-complex weight HPLC or capillary electrophoresis is assay using authenticated reference standard
	Total DNA	Total protein	
	Total protein	HPLC assay using authenticated reference standard	
Potency	Viable cell number (cells intended for structural repair)	Function of expressed gene (induction of secondary effect and other bioassays)	Function of expressed gene (induction of secondary effect and other bioassays)
	Bioassays: Colony-formation assay Function of expressed gene Induction of secondary effect (e.g., human leukocyte antigen (HLA) induction, secretion of cytokines, and up-regulation of surface marker)		
Purity	Percentage of viable cells	Residual host-cell DNA	Percentage of specific physical form (e.g., percentage supercoiled)

Table 18.2 (continued)

Test	Cell therapy products	Gene therapy products: Viral	Gene therapy products: Nonviral and antisense-oligonucleotide
	Percentage of transduced cells	Process contaminants (e.g., serum and cesium chloride)	Residual host-cell DNA
	Percentage of cells with specific surface marker	Residual helper virus	Residual RNA
	Process contaminants (e.g., serum)	Optical density ratio	Residual host-cell proteins
		Residual host-cell proteins	Residual solvents
		Viral protein profile (HPLC assay for defective or immature particles)	Optical density ratio
		Residual RNA	Process contaminants (e.g., cesium chloride and synthetic oligonucleotide by-products)
Safety	Mycoplasma	General safety	
	Sterility	Mycoplasma	Mycoplasma
	Pyrogen and endotoxins	Sterility	Sterility
	Adventitious viruses	Pyrogen and endotoxins	Pyrogen and endotoxins
	Residual virus (for transfected cells)	Adventitious viruses	
	Replication-competent vector virus (transfected cells)	RCV	

From United States Pharmacopeia USP 31-NF26 1046 Table 6.

Out-of-Specification (OOS) Results

The critical nature of some cell therapy products (e.g., hematopoietic cell grafts) are such that they may be required to sustain life in the intended recipient and alternative products may not be available. Under such circumstances it may be medically necessary to use products that do not meet release specifications (out of specification – OOS). This is usually described as release to meet urgent medical need. The use of such products requires medical justification and may additionally need approval from regulatory agencies and the informed consent from the intended recipient. Professional standards again give more operational guidance. FACT requires that a medical director authorize exceptional release for "nonconforming" product and that the patient's physician be informed and consent obtained to use of the prod-

uct. AABB standards additionally require identification of lot release tests, ranges of acceptable values, and actual product values. These provide the physician with appreciation as to where the particular product falls within the established ranges. This information is often provided by the C of A; however, AABB lists the review of specific items (e.g., red cell and HLA compatibility) required for release, and requires that the physician discuss risks of the use of nonconforming product (as do GTP regulations in their labeling requirements). All standards and regulations require special handling and careful documentation of the use on nonconforming products.

Product Release, Transportation, and Shipment

Administration of products may consist of a number of phases that should be described in standard operating procedures. These should cover the removal of the product from manufacture and inventory or storage, transportation within and/or shipping between facilities, instructions for and documentation of administration, possible adverse reactions, possible return to inventory, complaints and recalls, handling of positive test results received following administration, and communication of outcome results to the collection/production facility in the case of shipped products. Many of these are addressed by governmental regulations and professional standards and will be product-dependent. In most cases the key element is to develop a system of documentation that clearly records not only everything that happens to the product during manufacturing, but also all events after the completion of manufacturing and testing to final disposition. This system must be able to account for all of the material that was manufactured and to deal with potential complications, such as adverse reactions to administration, recalls, and complaints.

The administration of a product requires a formal documented request (prescription) from the intended recipient's physician. This specifies precisely the product to be administered, the dose to be given, and the date and time of the administration. Additionally it may request some supplementary manipulation of the product, such as thawing, washing, and so on. Under such circumstances it may also be necessary to perform additional release testing following the manipulation.

Products will generally require transport or shipping to the site of administration under conditions that have been validated to maintain cellular viability and functional integrity. Movement of product may be done under the custody of trained couriers, or by commercial shipping companies. Regardless of whether trained couriers accompany products, some formal demonstration that appropriate temperature range has been maintained during transit should exist. The temperature will be specific to the type of product, ranging from ambient to <–150°C (attained by the use of liquid nitrogen "dry" shippers). The use of recording thermometers during transportation has become the norm and these are now available for most widely

used temperature ranges. Professional standards from FACT and AABB address transportation and describe the labeling to be used and precautions to be followed to ensure safe and timely shipment between and within facilities. In the United States, federal regulations address the nature of the accompanying records and establishment of tracking and tracing capability between all parties involved in the manufacture, testing, release, and administration of the product. Instructions should be provided that describe handling of the product on arrival, contact information in case of delay or delivery problems, transfer to on-site storage, preparation for administration, and follow-up (e.g., adverse events and engraftment). Additional national and international standards and regulations address the use and labeling of appropriate shipping containers and provision of customs declarations when appropriate. This information is usually readily available from commercial shipping and courier companies.

Administration

Product administration should be clearly described and include instructions on procedures to be followed in case of problems (e.g., the rupture of a product container during thawing). The staff performing the administration should also have access to a document (often referred to as the Circular of Information or Instructions for Administration) that describes the indication and contraindications for product use, product format, and possible adverse reactions. In the United States a Circular of Information (COI) for cell therapy products has been jointly developed by a number of professional organizations [24]. The COI is intended to be generic, so is often supplemented by product and institution-specific information. Adverse reactions to administration should be anticipated and potential remedial actions described. In some cases these are expected, as is the case when products containing dimethylsulfoxide are infused. Under such circumstances the acceptable range for these reactions can be described to reduce unnecessary documentation and follow-up. Governmental regulations usually mandate reporting of serious adverse reactions to regulatory agencies within a specified timeframe and require some form of attribution. In the United States the regulations for products under IND and IDE (Type 351 products) are detailed and specific. For Type 361 products the FDA requires reporting of specific biological product deviations on products that have been administered [11].

Conclusions

Product release is one of the most critical components of cell therapy product manufacturing. As was stated earlier, quality cannot be tested into a product postmanufacturing, but is the result of a properly engineered production process. The release procedure, however, provides the final opportunity to ensure that the product was

manufactured as specified using a controlled and auditable procedure and is safe for administration. The variety of cellular products and potential applications is already enormous and our ability to test them in a predictive manner is still limited. Their manufacturing processes and testing procedures still differ radically from those used for pharmaceuticals. This makes it all the more important to ensure that these potentially very promising medicines are released using a process that ensures, at very least, their safety. As the field progresses, we must continue to work with the regulatory agencies to develop faster assays that better predict clinical outcome.

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Chapter 19
Use of a Facility Master File to Facilitate Regulatory Submissions for Cell Therapy Products

E.J. Read and H.M. Khuu

Abstract Investigational new drug applications (INDs) for novel cell therapy products require written documentation not only of the proposed clinical protocol and specific product manufacturing process, but also of information on items that may be generic for all products manufactured within a given facility. For facilities supporting multiple IND-related protocols, this generic information can be organized into a Drug Master File (DMF). This chapter will discuss the rationale, design, maintenance, and use of a DMF, either as an official submission to the U.S. Food and Drug Administration, or as an internal reference document that compiles information for subsequent extraction and incorporation into IND submissions.

Definition and Types of Master Files

The definition of a Drug Master File (DMF) by the Food and Drug Administration (FDA) is a submission of information that may be used to provide detailed confidential information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs and biological products [1]. The FDA has accepted DMFs for many years in support of applications and supplements for Investigational New Drugs (INDs), biologics license applications (BLAs), and new drug applications (NDAs). DMFs are typically used to allow a sponsor of an IND, BLA, or NDA to cross-reference material in a DMF. This process allows the FDA to review a DMF without disclosing the specific contents of the DMF to the

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sponsor who is cross-referencing the DMF. The FDA reviews information in a DMF only when a sponsor or applicant cross-references the material in the DMF; in other words, the FDA does not "approve" a DMF, but reviews and comments, if necessary, on specific items in the DMF in the context of reviewing an IND, BLA, or NDA.

The types of DMFs are listed in Table 19.1. Before January 12, 2000, Type I DMFs had been used to document details of the manufacturing site, facilities, operating procedures, and personnel. However, the final rule "New Drug Applications: Drug Master Files," published on January 12, 2000, with an effective date of July 10, 2000, amended the regulations in 21 CFR 314.420. This removed the provision for Type I DMFs and recategorized the Type I DMFs that included facilities-related information for Phase I and II clinical trials, as Type V DMFs [2]. A guidance published in August 2001, "Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research (CBER)," detailed the specific information that may be submitted in a Type V DMF without submitting a letter of intent, for (a) facilities producing gene or cell-based therapies for Phase I and II clinical trials and (b) contract manufacturing facilities in support of BLAs or BLA supplements [1]. In that guidance, the FDA stated that "DMFs are generally not appropriate for product-specific information."

Table 19.1 Types of master files

File type	Description
Type I[a]	Manufacturing site, facilities, operating procedures, and personnel
Type II	Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
Type III	Packaging materials
Type IV	Excipient, colorant, flavor, essence, or materials used in their preparation
Type V	FDA-accepted reference information, which may include items previously included in Type I DMF

[a]Type I DMFs that include facilities-related information for phase 1 and 2 clinical trials were categorized as Type V DMFs, effective July 10, 2000.

Use and Content of the Cell Therapy Facility Master File

A DMF may be particularly useful for academic or commercial contract facilities handling cell therapy products of multiple types and/or for multiple INDs. For example, the Cell Processing Section (CPS) at the National Institutes of Health (NIH) Clinical Center supports a wide range of early phase clinical trials of hematopoietic transplantation, pancreatic islet transplantation, immunotherapies, and cellular gene therapies, most of which require IND submission. For each IND, the NIH physician-investigator serves as the IND sponsor and CPS serves as the product manufacturer. In 2002, following a series of FDA requests for documentation of facility policies and practices, CPS decided to streamline the process of responding to these requests and to facilitate future submissions and communications by writing a DMF.

The contents of a given cell therapy facility's DMF should reflect actual policies and practices that address specific requirements. Therefore, before writing the DMF, it is useful to list and review specific regulatory documents that apply to a given facility's operation. The NIH/CPS DMF was designed primarily to be responsive to the FDA's guidances for somatic cell therapy and gene therapy CMCs (Chemistry, Manufacturing, and Controls), the current Good Manufacturing Practice (cGMP) regulations, the current Good Tissue Practice (cGTP) regulations, the Human Cell, Tissue, and Cellular and Tissue-based Products (HCT/P) Donor Eligibility Rule and the related Donor Eligibility Guidance [3–8]. FDA regulatory and other documents that contain requirements applicable to most cell therapy facilities are listed in Table 19.2 [9–16]. Although the facility DMF should primarily address items required for IND submission, it may be useful to also incorporate responses to requirements of standard-setting and accreditation organizations such as the Foundation for the Accreditation of Cellular Therapy (FACT) and the AABB [13–16]. In addition, inclusion of specific state or local requirements should be considered, especially if they contain items that are not addressed, or are discrepant for items, in federal regulations. The list of documents should be updated as new regulations, guidances, and standards are published.

Table 19.2 FDA regulations and regulatory guidance, and standards most relevant to development of a cell therapy facility master file

Document common name	Reference(s)
FDA regulations	
cGMP regulations (21 CFR 211)	[5]
General biologics regulations (21 CFR 610)	[9]
HCT/P donor eligibility final rule	[7]
HCT/P cGTP regulations	[6]
IND regulations (21 CFR 312)	[11]
Drug master file final rule	[2]
FDA regulatory guidance	
Somatic cell therapy CMC guidance	[3]
Gene therapy CMC guidance	[4]
HCT/P donor eligibility guidance	[8]
Aseptic processing guidance	[10]
Type V drug master file guidance	[1]
Phase I cGMP guidance	[12]
Standards	
AABB standards	[13]
FACT standards	[14]
USP general chapters <1046> and <1043>	[15, 16]

Table 19.3 shows the table of contents for the NIH/CPS DMF, designed to be a logical order of elements compiled from the relevant regulatory and standards documents. The DMF audience consists primarily of FDA reviewers who know the regulations, but need to determine if a given facility is actually following the requirements; the DMF should be written to facilitate that process. The overall

Table 19.3 Table of contents and attachments for the NIH cell processing section's cell therapy facility master file

1. Contact information and authority to change master file
2. Introduction
3. Quality program
4. Physical plant
5. Environmental control and monitoring
6. Operational control systems and aseptic processing
7. Equipment, supplies, and reagents
8. Donor selection and eligibility
9. Manufacturing systems and process controls
10. Product evaluation and lot release
11. Storage
12. Product labeling, label controls, and tracking
13. Product receipt and distribution
14. Final product preparation, issue, and administration
15. Attachments
    - (1) Organizational chart
    - (2) Relationship between institute investigators and Clinical Center regarding protocol design, implementation, and quality assurance
    - (3) Listing of products manufactured and handled in CPS (clinical and nonclinical)
    - (4) Quality control schedule
    - (5) CPS facility floorplans
        - 5-A Basic floorplan
        - 5-B Personnel flow within CPS facility
        - 5-C Product and materials flow within CPS facility
        - 5-D Waste flow within CPS facility
        - 5-E Air pressure differentials and flow within CPS facility
    - (6) Donor selection and eligibility tables
        - 6-A Living autologous donors
        - 6-B Living allogeneic family-related donors for products other than cord blood
        - 6-C Cord blood donors (autologous or allogeneic family-related)
        - 6-D Cadaveric donors
    - (7) Assay/testing tables
        - 7-A Donor transmissible disease testing
        - 7-B Sterility testing (bacterial and fungal culture)
        - 7-C Mycoplasma PCR testing
        - 7-D Endotoxin testing
        - 7-E Automated cell counting
        - 7-F Trypan blue viability testing
        - 7-G Flow cytometric 7-AAD viability testing
        - 7-H Flow cytometric phenotyping of cells
        - 7-I Hematopoietic colony assays
        - 7-J Testing for ABO group, Rh type, & unexpected RBC antibodies
        - 7-K HLA antibody screening

requirements for an IND application are presented in the IND regulations [12], and the recommended contents and format for the CMC section of the IND are presented in the CMC guidances [3, 4]. The generic information in the DMF can then be referenced within the text of the CMC.

Writing the Cell Therapy Facility Master File

The process of writing a DMF is challenging and time-consuming, but provides staff the opportunity to review existing internal policies and procedures and identify gaps that need to be addressed. The writing task is best tackled as a collaborative effort between technical, medical, and quality/regulatory staff, to ensure that what is presented reflects real practices, and not just what one believes should be practiced. The process is likely to improve communication among responsible parties within the facility and lead to design and implementation of new systems, policies, and practices.

The facility DMF should be written in straightforward, concise, descriptive language that responds to specific requirements. Tables and diagrams can be used to summarize complex information. For example, floor plans, including those that show location of major equipment, air pressure differentials, and flow of products, materials, personnel, and waste, can be accompanied by brief text descriptions with reference to diagrams. Donor testing procedures are particularly suited to tabular display, because most test methods are defined in regulations or by manufacturer's requirements for a given test kit. The NIH/CPS donor testing tables include information on what samples are tested, what tests are performed, the test kit manufacturer, and the name and location of the lab performing the testing, i.e., by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory within the NIH Clinical Center.

Sufficient detail should be given for the reviewer to gain an understanding of whether the facility is complying with regulations and guidance, but without the level of detail typically provided in standard operating procedures (SOPs). For most topics, it is sufficient to state that the facility has an SOP that addresses a particular technical or quality system requirement, with a reference to the SOP and a brief summary of the key points of that SOP. For example, the general procedure for cryopreservation of cell therapy products can be summarized in terms of the reagent/media names, final reagent concentrations, acceptable range of cell concentrations, container types, use of overwrap bags, and the use of a controlled rate device and target temperatures during the controlled rate process, with reference to the full SOP. This allows the FDA reviewer the option of requesting a copy of the current version of the SOP, without creating the need for continuously updating SOPs that have been submitted as part of the DMF.

A number of quality and technical issues demand both generic and specific information for IND submission. One example is product labeling. The DMF is an appropriate place to describe the general product labeling process and control of that process, while the CMC section of the IND may be the appropriate place to include a copy of the actual product label. Another example is the use of ancillary reagents: the DMF can describe the general process for selecting, qualifying, storing, and tracking ancillary reagents, while information about specific reagents used in the manufacture of a specific product should be included in the CMC.

The focus placed by FDA product reviewers on particular quality or technical issues depends on feedback from FDA field inspections and current guidance.

Therefore, any comments from the FDA that are not specific to the product, but are related to general operational or quality issues, and especially product issues that relate to safety, are likely to recur when future INDs are reviewed. It is worth addressing these generic issues in a careful manner with language that can be incorporated into the DMF and used for future IND submissions. Examples include validation of microbial testing methods, description of action plans in case of abnormal test results (e.g., for microbial contamination or endotoxin), use of ancillary reagents from bovine sources, procedures for preventing cross contamination and mix-ups, and documentation of environmental monitoring during product manufacturing.

Options for Use of Master File as a Formal FDA Submission Versus an Internal Document

There is no absolute FDA requirement for a cell therapy facility to submit a DMF, but the information that would logically go into the DMF would otherwise need to be submitted at the time of each IND submission. Therefore, cell therapy facilities compiling a DMF can decide to submit it formally to the FDA and reference appropriate DMF sections in the CMC, or alternatively to use the DMF as an internal reference document from which material can be cut and pasted into the CMC.

If formally submitted to the FDA, the DMF must adhere to the FDA's specifications [1, 2, 17]. Each DMF submission (original or amendment) should include, along with the specific DMF contents:

1. A transmittal letter, identifying the submission as original or amendment, the Type of DMF (e.g., Type V), the subject of the submission, identification of the applications, if known, that the DMF is intended to support (including name and address of sponsor/applicant/holder and relevant document numbers), and the name and signature of the DMF holder or authorized representative; and
2. Administrative information, including the DMF holder, location of corporate headquarters and/or manufacturing/processing facility, contact for FDA correspondence, Agents (if any), the specific responsibilities of key persons listed on the organizational chart (including those authorized to make changes to the DMF), and a signed statement of commitment certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

In addition to the general submission requirements, amendments must describe the purpose of submission (e.g., update, revised process) in the transmittal letter, note the affected section and/or page numbers, and provide the name and address of each sponsor/holder (with number of each IND, DMF, etc.) who relies on the subject of the amendment for support, and particular items within the IND, DMF, etc., that are affected.

Additional guidelines for document format and assembly apply to standard (non-electronic) DMF submissions [17]. These include specifications for standard paper

dimensions, margin widths, location of punch holes, and document size. An original and duplicate must be submitted for all DMF submissions (original and amendments), with both copies collated, fully assembled, and individually jacketed. Additional instructions for submitting DMFs and other applications are available in CBER's SOPP 8110 [18]. DMF submissions to CBER should be addressed to: FDA, Center for Biologics Evaluation and Research; Document Control Center, HFM-99, Suite 200 N; 1401 Rockville Pike; Rockville, MD 20852-1448. More recently, the FDA has published guidance and working instructions for electronic regulatory submissions, and has announced the availability of the FDA Electronic Submissions Gateway (ESG), for the receipt and processing of electronic documents [19, 20].

DMFs formally submitted to the FDA must be maintained for accuracy and completeness. This is typically done by submitting an annual report containing all pertinent changes to the last version of the document. Significant changes resulting from implementation of new regulatory requirements and/or those that may have impact on products require an amendment before the anniversary date. In addition, if review of the facility DMF triggered by submission of a given IND application results in identification by the FDA of deficiencies that need to be addressed, the facility must communicate this to sponsors of all INDs that have cross-referenced the DMF. This can result in other INDs being put on hold until the issue is resolved, leading to additional paperwork. While this event is relatively unlikely to occur with a well-written and well-maintained DMF, the potential for an additional burden of written communications raises the question of whether the DMF should be simply maintained as an internal facility document, i.e., one from which pertinent information can be extracted and submitted with each new IND application. Use of the DMF as an internal document does not obviate the need for staff to keep up with current regulatory requirements and to update policies and procedures accordingly. However, it may reduce the administrative requirements of maintaining the DMF as a separate submission to the FDA.

Summary

A cell therapy facility DMF containing technical, quality, and operational information that is generic for all products manufactured within that facility, can be useful for streamlining communications with the FDA. Information should be presented in a manner that demonstrates compliance with current FDA regulations and guidance. Questions to be considered by parties contemplating development of a facility DMF include:

1. Does the number of products and INDs supported by the facility warrant the time and effort of writing the DMF?
2. What standards and regulations need to be addressed in the DMF?

3. What product information that would normally go into the CMC section of each IND will be considered (a) generic, and therefore appropriate for inclusion in, or (b) product-specific, and therefore excluded from, the DMF?
4. What staff will be responsible for (a) writing the DMF and (b) maintaining the DMF?
5. Would the facility's interests be met better by (a) formal submission of the DMF or (b) use of the DMF as an internal reference document?

References

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20. 71 Federal Register 152 (August 8, 2006). "Food and Drug Administration Electronic Submissions Gateway": Notice.

Appendix A Template Form referred to in Chapter 15 - Facility Equipment

Form A

Your name and address here

EQUIPMENT RECEIPT AND INSTALLATION

Type of Equipment:_____

Equipment	Manufacturer	Model number	Vendor

Date ordered_____ Tech:_____ *Attach Purchase Req

Receipt

Date of Receipt:_____ Time of Receipt:_____ Carrier:_____

Inspection of Packaging ☐Acceptable ☐Unacceptable Tech:_____

Entered into Inventory Log Book ☐ Tech:_____

Installation

Unpacking performed by:_____Date:_____

Factory Vendor/Service Rep present: ☐ No ☐Yes, Name_____

1. Serial Number_____

Inspection of Equipment ☐Acceptable ☐Unacceptable Tech:_____

Inspection of Accessories ☐Acceptable ☐Unacceptable Tech:_____

Clinical Engineering

Clinical Engineering contacted: Date:_____Time:_____Tech:_____

Electrical and Safety Assessment ☐Acceptable ☐Unacceptable Tech:_____

Asset Management Inventory Number _____ PM Due _____

Signature of Tech Completing Form:_____Date: _____

Director Analysis: Initial Installation ☐Acceptable ☐Unacceptable

Director Comments: _____

_____

Laboratory or Medical Director Signature:_____Date:_____

Laboratory Supervisor Signature:_____Date:_____

Quality Assurance Signature:_____Date:_____

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Appendix B Template Form referred to in Chapter 15 - Facility Equipment

Form B – Equipment Discard

Your name and address here

EQUIPMENT DISCARD

Type of Equipment:_____

Equipment	Manufacturer	Model number	Vendor

Reason for Discard

☐ Obsolete Comments: _____

☐ Replaced _____

☐ No longer in use _____

☐ Beyond repair _____

☐ No longer needed Tech:_____ Date:_____

Information in Equipment Log Book Tech:_____ Date:_____

Proposed Method of Discard

☐ Trash Comments: _____

☐ Donate to research lab _____

☐ Local storage _____

☐ Sell as surplus _____

☐ Donate to charity Tech:_____ Date:_____

Value of Equipment:_____Determined by:_____

Equipment Records copied for recipient, checked for personal identifiers ☐Yes ☐N/A

Clinical Engineering

Clinical Engineering contacted: Date:_____Time:_____Tech:_____

_____

Asset Management Inventory Number _____ last PM Due _____

Removed from Clinical Engineering Inventory ☐Yes ☐No, reason_____

Form B Con't

Authorization for Discard

Director Authorization ☐Acceptable for Discard ☐Unacceptable for Discard, reason below

Comments: _____

_____

Laboratory Director Signature:_____Date:_____

Laboratory Administrator:_____Date:_____

Discard

Tech(s)/personnel responsible for discard_____ Date of discard_____

Cleaning/disinfection required? ☐Yes ☐No

Cleaning/disinfection performed if required? ☐Yes ☐No ☐Not Applicable

Personnel removing discarded equipment_____

Final disposition of the equipment_____

Review of Discard

Discard according to plan? ☐Yes ☐No, reason below

Comments: _____

_____

Laboratory Director Signature:_____Date:_____

Appendix C Template Form referred to in Chapter 15 - Facility Equipment

Form C – Quality Control of Laboratory Scales

Quality Control of Laboratory Scales											
		Standard weight									
Date	**Scale**	**500 g**	**100 g**	**50 g**	**20 g**	**5 g**	**2 g**	**1 g**	**Tech**	**Reviewed by:**	

Supervisor Review: Date:
QA Review: Date:
Tolerance limits: Denver and Ohaus scales +/–5%, Mettler Analytical balance 10-50 ug +/- 5%, 51-1000 ug +/- 3%.
If scales are out of range, adjust and retest. If still out of range fill out Deviation Management Form and call for maintenance.

Appendix D Template Form referred to in Chapter 15 - Facility Equipment

From D – Sample Policy New Equipment Qualification

Your facility information here

General Policy for Qualification of New Equipment

The lab selects and purchases equipment for processing, storage, and testing of specimens and their derivatives. The selection of the equipment is based upon prior experience with the equipment and/or performance features that are required for the tasks to be performed. Once selection is approved and equipment is received the following sequence of events occurs:

1. Upon receipt, all equipment is inspected for obvious and visible, physical damage.
2. The equipment is uncrated/unpacked with assistance of the factory or vendor representative, if needed; and further inspected for damage. In addition confirmation that the shipment is complete and that the correct equipment (model and features) was received along with any and all accessories.
3. Equipment should be positioned so that it can be plugged into dedicated circuits and/or emergency back up power outlets as deemed necessary for the particular piece of equipment.
4. The equipment is installed according to the manufacturer's recommendations.
5. The equipment is turned on and run to assure proper start up and general operation.
6. Training of technical staff on general maintenance, routine operation and quality control is provided. For some equipment, the manufacturer provides the initial training at the time of installation.
7. The equipment is tested prior to authorizing its routine use in order to assure performance. This will depend on the specific piece of equipment. In some cases, the telemetry unit must verify certain functions. In other cases, the lab may be sufficiently skilled and equipped to check and verify proper functioning.
8. Special consideration is given to all critical pieces of testing equipment such as plate reader and counters. Where possible, the same tubes or assay plates are run on the other qualified equipment in the lab (when additional units are obtained) or in other certified laboratories (when the equipment is new to the laboratory).
9. This testing is performed prior to release of the equipment for use in routine processing/testing in the lab. The procedure and parameters are specified and reviewed with the final testing results. If all specifications are met, the equipment is designated as qualified and routine use is implemented. A report is prepared, reviewed, and signed off on by the Laboratory Director, Laboratory Supervisor and/or Quality Assurance. If the equipment is to be used prior to final preparation and sign off of the report, an interim report is drafted and signed specifying that the instrument is qualified for use and that the final signed report is pending.
10. The final report and all testing source documents are filed in the appropriate Equipment Binder.

Prepared by:

_____ Date:_____

REVIEW AND APPROVAL:

_____ Date:_____

Laboratory Director

_____ Date:_____

Quality Assurance

Appendix E Template Form referred to in Chapter 15 - Facility Equipment

From E – Sample QC SOP Quality Control Procedure for Scale

Your facility information here

QUALITY CONTROL PROCEDURE FOR SCALES

10. Principle

To ensure accurate calculations and measurements in the processing of human progenitor cells, scales must represent an accurate determination of weight. Quality control of the scales will be performed twice annually.

Specimen or Product Requirement

NA

Reagents and Supplies

NA

Instrumentation

Equipment	Manufacturer	Model Number
Scale	O'Haus	
Scale	Denver Instrument Company	
Analytical Balance	Mettler	PM1200
	Sartorius	B4100
Double Beam Balance	Fisher Scientific	Model 821
Standardized weights	O'Haus	

Procedure

***=Key points in procedure**

Cautionary Notes

*Allow 5 – 10 minutes for electronic scales to warm up.

Detailed Methods

O'Haus and Denver Instrument Company Scales

1. *Tare scale.
2. Place the standardized weight on the scale.
3. *Record the standard weight and the digital readout on the F27 Quality Control of Laboratory Scales Form.
4. Repeat with two more weights.

Mettler Analytical Balance

1. Press signal control bar (All display segments light up for several seconds).
2. *Tare Scale
   a. Open glass door and place container on the weighing pan.
   b. Close door and press control bar briefly.
   c. The display should change to zero.
3. To weigh
   a. Place standardized weight in the center of the container.
   b. Close glass door.
   c. *Record digital display on the Quality Control of Laboratory Scales Form.
   d. Repeat with two more weights.

Form E Con't

Sartorius Scale

1. Press control panel to turn on scale.
2. Calibrate as per manufacturing instructions.
3. To weigh
    a. Place standardized weight in center of platform.
    b. Record weight from the digital display using 1g, 100g and 1000g weights.

Double Beam Balance

1. Center balance indicator needle using thumbscrew counterweight as needed

Result Reporting

If a scale does not meet the standard, adjustments can be made. If the scale is adjusted or repaired, it must be retested by this same procedure. Follow the manufacturer's directions to adjust scale. If adjustments do not correct the problem, the scale must be repaired by an authorized repair center. Complete Deviation Management form and arrange for repairs.

Quality Control

Tolerance Limits:

O'Haus and Denver Scales: +/–5%

Mettler Analytical Balance:

10 – 50 µg	+/–5%
51 – 250 µg	+/–3%
251 – 1000 µg	+/–3%

Sartorius:

1g	+/–10%
100g	+/–10%
1000g	+/–10%

References

This procedure developed by the Hematopoietic Stem Cell Laboratory.

Appendices

Form: Quality Control of Laboratory Scales Form

Index

Note: The letters '*f*' and '*t*' following the locators refer to figures and tables respectively.