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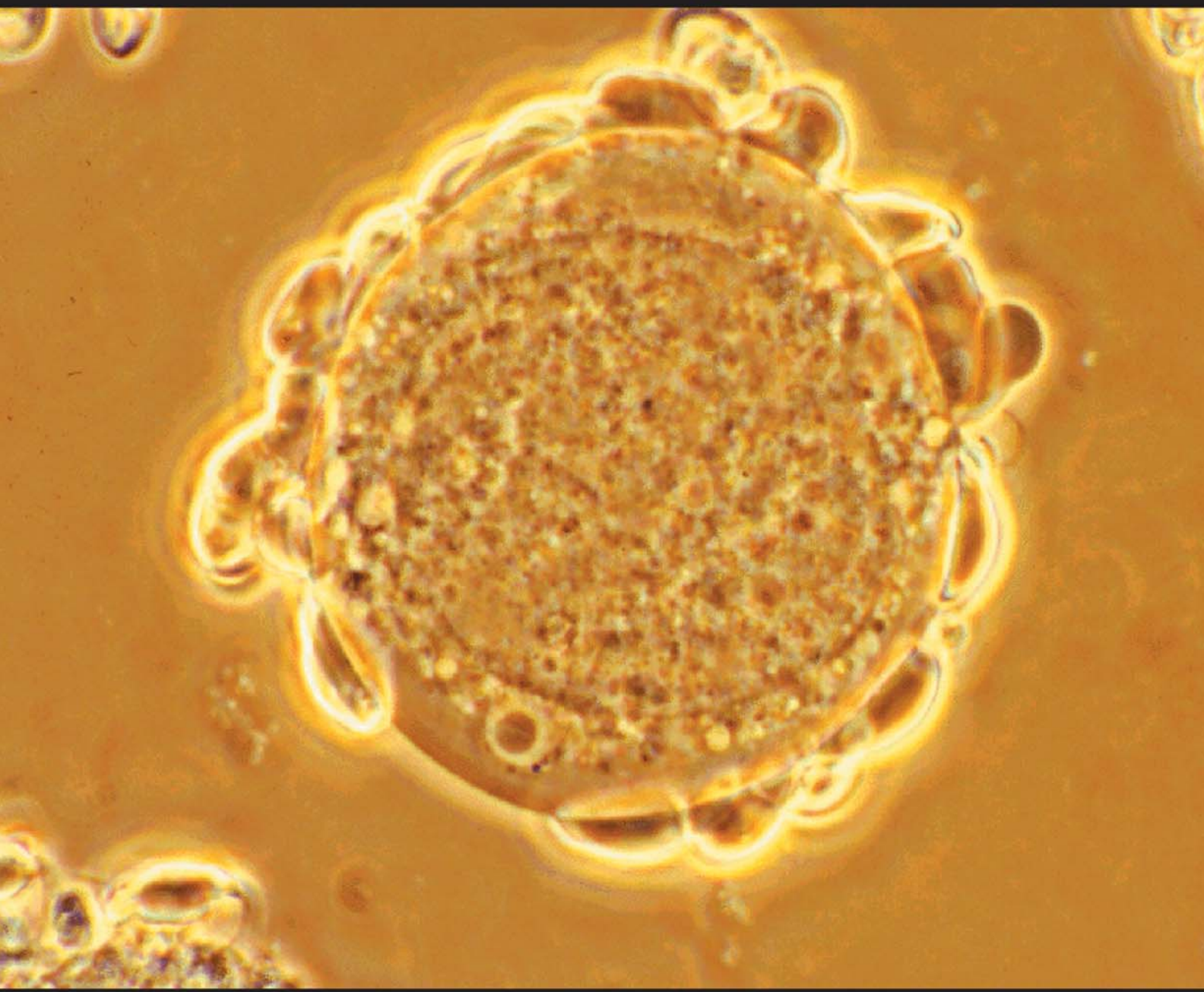

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Manufacturing Cellular Therapy Products in an Academic Facility

BY ADRIAN P. GEE

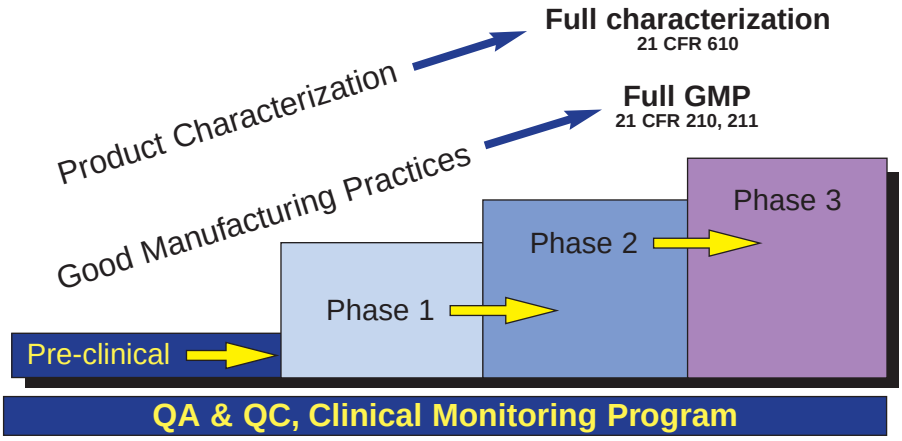

Figure 1. Stepwise Approach to Application of Regulatory Requirements in Cellular Therapy. Adapted from presentation made by CBER.

Cellular therapy is currently generating great interest in the treatment of a variety of diseases. In turn, this interest has stimulated the Center of Biologics Evaluation and Research of the Food and Drug Administration to examine its regulatory approach to the products used for these therapies. As a result, facilities preparing cell therapy products are now regarded as manufacturers, and are expected to comply with current Good Manufacturing Practices and/or the proposed current Good Tissue Practices. Compliance with these practices can be a culture shock to some academic centers whose background is firmly in research. The FDA has indicated that there is a sliding scale of compliance depending on the phase of the clinical study (Fig. 1). The difficulty for centers is deciding where they fall on the compliance scale, as well as determining what changes must be made to come into compliance. This article reviews some of the factors that must be considered when making these decisions.

Introduction

Recently, cellular therapies have received notable interest as new or alternative methods have been developed for treating cancer, diabetes, cardiac disease, and a variety of other conditions. Increased interest in cellular therapies is also the result of a better understanding of cellular and molecular biology, cell-to-cell interactions, and both purification and activation techniques. Combined with the ability to mark or modify cells using genetic manipulation, these methods provide an exciting approach to therapy. As with many new treatment modalities, it is clear that some practitioners have made errors in judgment, which have caught the attention of the regulatory authorities. In response, the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) has reviewed existing regulations and proposed new legislation to cover somatic cell and gene therapies. Reviewed elsewhere, the regulations are composed of four main components. These components are: registration of manufacturing establishments with the FDA; screening of cell and tissue donors for infectious disease; use and investigation of new drug applications and GMP manufacturing conditions for products that pose a higher risk to the donor and/or recipient (e.g. extensively manipulated cells or non-related donors; and use of GTP manufacturing conditions for other cells and tissues (except bone marrow). [1,2,3,4]

In reality, many aspects of GMP and GTP manufacturing are similar, and the regulations are intended to be complementary. [5,6,7] The primary emphasis for most facilities has been on GMP manufacturing, since the products are covered by IND and are intended for use in a clinical trials. The difficulty comes in determining what mode of GMP is required. There are GMP regulations covering production of pharmaceuticals, blood components, medicated feeds and articles; however, the underlying approach is similar in all cases. The intent of the regulations is to ensure use of a controlled and accountable process for manufacturing safe and effective products.

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In the case of cellular products, CBER has recognized that these regulations differ from finished pharmaceuticals, and that compliance with "full" GMP may not be possible or achievable prior to Phase Three of a clinical study (Fig. 1). Information such as stability testing and full characterization of the cellular product is often not available during early clinical studies, but it can be gathered as the trial progresses. The Agency has made it clear, however, that final GMP compliance will be expected to meet the regulations covering finished pharmaceuticals (Title 21, Code of Federal Regulations, Part 211). This "sliding scale" approach is somewhat of a mixed blessing for the manufacturer. It can be difficult to determine where a product falls on the scale at any particular time, and therefore, what "degree" of GMP is required. In the case of commercial facilities, the ultimate aim is to manufacture and sell a product. Therefore, it makes sense to conduct all studies under the highest level of GMP possible, perhaps even during Phase One trials.

An academic center may never intend, or may not have the resources, to bring a product to market independently, or even to go beyond a Phase One/early Phase Two study. The dilemma is to determine what aspects of GMP are required for compliance. The purpose of this article is to review the factors that should be considered when making this determination, and it is based upon our experience at the Center for Cell & Gene Therapy (CAGT) at Baylor College of Medicine (BCM) in Houston.

The Cost

Cost is always a primary consideration when considering a new venture. In the case of GMP manufacturing, cost is particularly important. The focus tends to be on building a facility, but the importance of facility issues tends to be over-emphasized. The heart of GMP is not the building but the systems that are used within that space. These systems are often labor-intensive and must be maintained, even when there is little manufacturing activity. There must be an investment in staff and the entire basic infrastructure required to maintain all systems. In the long term, the cost of operations will far outweigh the up-front building costs.

Having said that, it is still evident that facility structure is a primary consideration for the majority of academic centers. There appears to be a flurry of facility construction at the moment, which is accompanied by long and sometimes heated debates about what is actually required. Of course, the design will depend on what is to be manufactured and the intended use of the product. Centers that plan to go into Phase Three trials and/or produce licensed products should meet all requirements for a pharmaceutical manufacturer. Those centers that intend only to support Phase One and Two studies should consider whether they really need dedicated air handling systems, separate clean and dirty corridors, etc. The best advice is to consult CBER once a plan has been developed, and to ask for an informal review.

Cleanrooms

Air handling systems tend to excite much discussion since the installation and monitoring costs are high. Cleanroom systems appear to be appropriate when products are being manufactured in an open environment. This requirement is rarely the case for cellular products, which are routinely processed in Class 100 biological safety cabinets, and where the push has been to use closed cell handling systems wherever possible. Very few, if any, facilities would currently consider handling products in an open manner, even in a Class 10,000 environment (Fig. 2).

Cleanroom environments are favored in manufacturing of a "generic" type of cellular product that potentially could be administered to many patients, and where it is impractical to test each vial independently before release. As cellular therapies progress towards licensure, it is likely that this "generic" approach to manufacturing will become more common. Another example is one in which a facility is intended primarily to support internal Phase One or Two studies, but where excess capacity may be made available to commercial manufacturers on a contract basis. If either scenario is a possibility, it is advisable to plan a facility that meets pharmaceutical GMP requirements.

Special consideration should also be paid to the types of products that will be handled. If genetic modification of cells is part of the procedure, the facility should be designed to allow segregation of this activity and prevention of cross-contamination by vectors. Other important factors in the design include personnel traffic patterns, ease of cleaning, disposal of biohazardous material,

"Traditional" Manufacturing Cleanroom

- "Open" manufacturing process
- Room environment provides main protection
- Suitable for drugs & "generic" products
- Ideal for batch or campaign manufacturing
- Process approach to QA/QC

"Current" Cell Therapy Cleanroom

- Aim is to use closed systems
- Biological safety cabinet provides main protection
- Room provides secondary protection
- Production process may be long (months)
- Products intended for specified recipient
- Products tested individually

Figure 2. Differences between Traditional Pharmaceutical Cleanroom Manufacturing and Manufacturing of Cellular Therapy Products. Photograph of cleanroom courtesy Wyssen Systems (International), Zurich, Switzerland..

inventory management and storage, quarantine arrangements, released and non-released product storage, emergency power and alarm monitoring systems, and document storage areas.

The GMP Cell Processing Facility at the CAGT (Fig. 3) was intended to support internal Phase One and Two studies, act as a core facility for its establishing institutions (BCM, Texas Children's Hospital and The Methodist Hospital), as well as provide contract services for other member institutions at the Texas Medical Center and other external organizations. The Facility currently manufactures hematopoietic progenitor cells for conventional marrow and blood transplantation, virus-specific cytotoxic T-lymphocytes, alloreactive-depleted donor leukocyte infusions, genetically modified tumor vaccines, liver progenitor cells, pancreatic islets, plasmids, and monoclonal antibodies. There is a separate vector production facility, which adheres to pharmaceutical GMP regulations, and produces retroviral and adenoviral vectors as part of the National Gene Vector Laboratory system.

The footprint for the Cell Processing Facility already existed, and the decision was made to use a design that achieved GMP compliance appropriate for activities somewhere between traditional blood banking and pharmaceutical manufacturing. It was also decided that the entire facility would be rated at Class 10,000 to allow "open" manufacturing, if required at some future date, but that all cell manipulation would be within Class 100 biological safety cabinets. To meet budgetary constraints, air handlers would recirculate 40% of the air through central HEPA filters and supply and return registers would be at ceiling height. This arrangement has proved to be satisfactory, and the facility routinely operates well within Class 10,000 specifications. The described system requires that there must be ongoing documentation to show that it routinely operates within specifications. On a weekly basis, we perform routine static and dynamic particle, plus viable, counts in all rooms and common areas. With certain types of products, there is additional monitoring such as fallout plates inside hoods, RODAC plate sampling of surfaces, and personnel monitoring. The challenge is to develop a system that deals with the huge amount of data generated by environmental monitoring, and which also takes account of the fact that viable counts are received long after activities or productions have been completed.

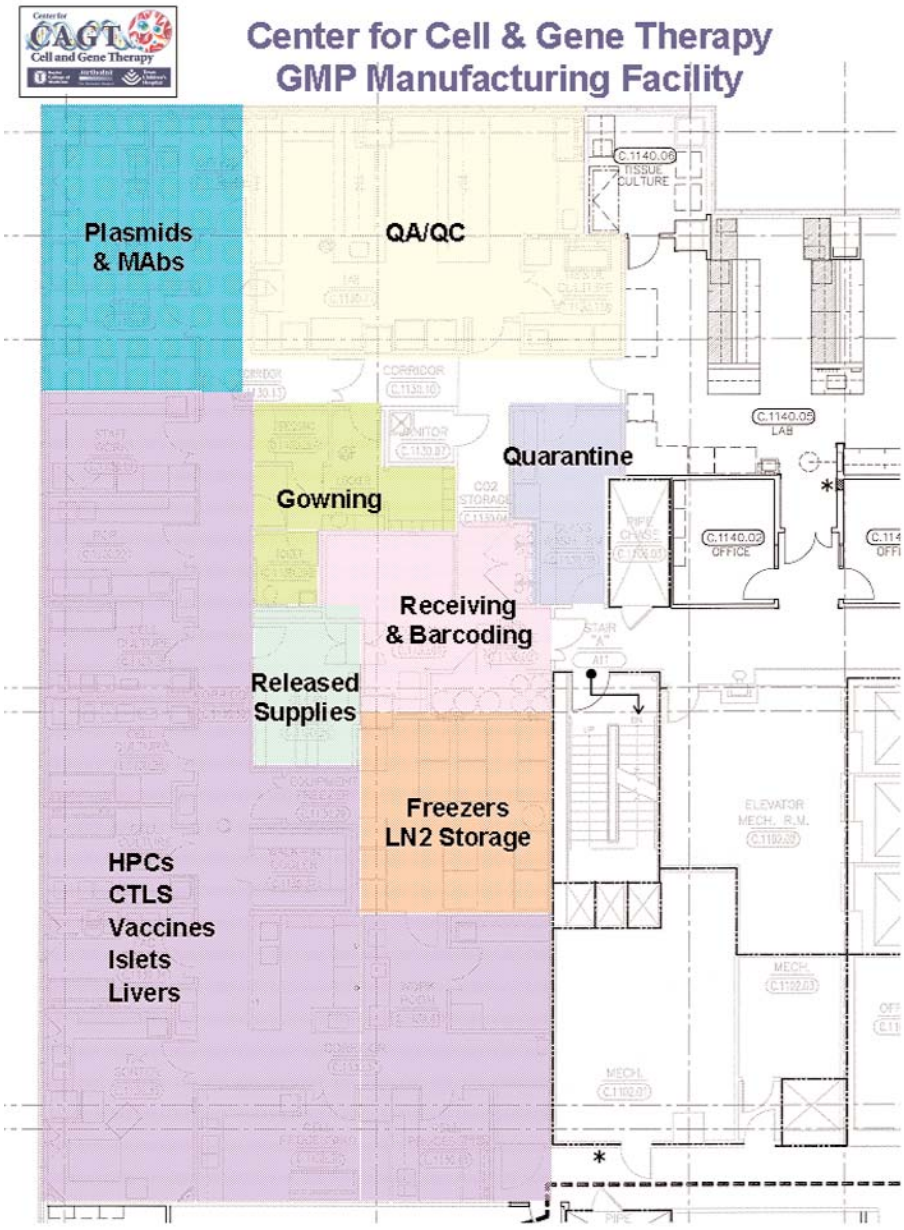

Figure 3. Floorplan of CAGT GMP Cell Processing Facility showing Relationship of Major Manufacturing Areas

Space limitations in the CAGT resulted in elimination of clean and dirty corridors, although waste can be removed from the facility through a separate exit. The facility does not use a batch or campaign manufacturing system due to the nature of the products prepared, of which many require prolonged culture periods during which other products may be manufactured in the same area. Development of strict cleaning, changeover, and labeling procedures to prevent mix-ups and contamination is necessary.

Manufacturing suites have some features of pharmaceutical facilities that facilitate cleaning, such as sealed work surfaces, seamless floors, raised cabinetry, epoxy coated walls, sloped tops of storage cabinets. Other features are not acceptable such as window ledges, sinks in the main corridors, or suspended ceilings with clamped, cleanroom-rated

tiles. These compromises appear to have worked well, since there have not been contamination or cross-contamination problems, operating specifications are routinely met, and the working environment is acceptable to staff that is used to working in a research environment.

Facility Features

Processing rooms within the facility were designed to be generic. Most contain a six-foot long biological safety cabinet, a tabletop centrifuge, an undercounter refrigerator, and between four and six incubators. Each room has a computer equipped with a barcode scanner that is connected to the hospital network system. Over time, some of the suites have been modified for specific projects. Equipment such as a tissue digestion apparatus, floor centrifuges, cell processors and concentrators, and an irradiator have been added. Initially, some larger pieces of equipment were centrally located, but they have been subsequently relocated to rooms used by the predominant user. The new equipment locations reduce traffic and resolve some gowning and gloving issues that are required for traveling between areas.

While difficult to anticipate, our experience suggests that growth in storage requirements cannot be overestimated. The number of different reagents and supplies in use seem to grow exponentially with time, and with the number of products. Culture systems frequently use bulky disposables that require spacious storage areas. In addition, cryostorage demands grow at a similar pace, and areas that seemed extravagant when the facility was planned can rapidly become exhausted.

An additional consideration for liquid nitrogen storage banks is whether the nitrogen supply manifold system can efficiently serve banks and controlled rate freezers that are located at increasing distances from the source. The choice of poured epoxy flooring in storage areas has proved to be a good one, with no signs of damage or wear after six years.

Equipment monitoring and alarm systems are vital, and several manufacturers market alarms that meet GMP validation requirements. When selecting a system, considerations include ease of changing, or moving, monitored equipment, remote monitoring, notification and response capability, controlled access and activation/deactivation of alarms, ease of calibration, validation services, data back-up systems, support and service from the supplier, and user friendliness when an alarm is sounded. Printouts from a properly validated and calibrated system can also be used for equipment quality assurance purposes.

Facility Systems

A major component in developing a GMP facility is the implementation of management and documentation systems. These systems provide the evidence that the facility operates in compliance with the relevant regulations. Unfortunately, there are few off-the-shelf systems or programs that aid in developing this infrastructure. Those that are available tend to be tailored to the needs of the developer and require modification to fit the end-user's needs.

Standard Operating Procedures

The first challenge for most new facilities is to develop Standard Operating Procedures (SOPs) for all aspects of facility operations and product manufacturing. This can be a daunting task, as completion of one SOP frequently reveals the need to write others. A useful tip is to consult other facilities and look at the Table of Contents for their SOP manual. The contents provide some indication of the scope of the undertaking. There is also an art to writing an SOP. Overly detailed SOPs are frequently too long and confusing for the reader, and they result in numerous variances. In contrast, brief and general SOPs are of little value for training, and they do not serve their intended purpose. The scope of an SOP is also critical. Use of procedures that cover every manufacturing aspect of an individual product, from accession of the sample to release for clinical use, will result in a complex and almost continual revision process. An easier approach is to provide an SOP for each component of a procedure (e.g. accessioning, cryopreservation, etc.) and then mix and match these to cover the complete manufacturing process.

The review and revision process is initially relatively simple when there are few SOPs. However, a large academic facility such as the CAGT now has several hundred SOPs, and this requires a different approach to document management. SOPs are written with a Microsoft Word template, and after approval by Quality Assurance who retains the Word version, the file is converted to PDF format and placed on the server. A software program (SOPTrak) provides the user with an easy-to-use interface with the SOP database. A list of SOPs is displayed on the startup screen. This list can be sorted by project group and searched by key word, or by a table of contents that can be displayed and printed. Highlighting an SOP on the screen opens a window that shows all the associated worksheets, equipment manuals, validations, and support information. Double clicking on any item opens the file in PDF format. Items may be printed, but they expire 24 hours afterwards to ensure that current versions are in use. The system is also used to provide direct access to relevant web pages (e.g.: CFR and FDA), and to institutional materials, such as MSDS sheets and safety manuals. Reports on SOP and procedure training that require review within a specified time frame also can be generated.

Training

An associated task, that is frequently the focus of FDA audits, is documentation of training. This documentation requires a system that can keep track of initial training, annual retraining, and training on SOP revisions. We use two approaches for documenting initial training. In the case of staff who have been instrumental in developing the manufacturing process, retrospective documentation is used. This kind of documentation details experience, publications, etc., and is reviewed and signed by the supervisor and QA. Initial training of other staff is detailed in a worksheet that records the reading and discussion of the SOP, observation and

performance of the procedure under supervision, and where appropriate, completion of a quiz. Annual training, and training on revisions, is accomplished by sending out a revised procedure and a retraining worksheet that details any changes. The worksheet is completed by the staff member, and then signed by the supervisor and QA, before it is filed in the training file.

Developing a comprehensive system of SOPs takes considerable time and effort. Initially there may have to be frequent revisions, all of which require retraining. With time, the procedure becomes easier and can be considerably simplified by using on-line access to SOPs and limiting the number of hard copies in circulation.

Other Documentation

A similar approach can be used to deal with other types of documentation. We use internally developed software to order and track quality control testing, so that the staff can request tests, track progress, and print out results directly from a central database (QAQCTrak). Other software is used to issue unique identifiers for all donors, recipients, and components that are handled by the facility; and to track infectious disease testing of each donor. Product inventory is managed by CryoTrak, which is a system that configures a freezer or bank to order, based on the racking system, and then tracks and archives all entries and removals. Although all data is backed up, these systems are supported by a paper trail that serves as an additional safeguard and provides a hard copy for processing and batch records. Electronic systems that provide primary documentation need to be Part II compliant.

Production Records

Manufacturing documentation at CAGT takes several forms, depending on the product type. For directed autologous or allogeneic products, a system of worksheets is used. These sheets are either blank approved hard copies or on-line validated electronic versions. In the case of more generic products, such as cells that may be administered to any recipient of the appropriate HLA type, or viral vectors, a batch record system is used. Initially, a master batch record is generated by QA in association with the investigator. This record is approved and released. For each production run, a numbered production batch record is issued by QA to the manufacturing staff, who then complete the information as production proceeds. All production worksheets and batch records are accompanied by Activity Reports (see below) that provide details of the reagents, supplies, and equipment used in manufacturing, plus copies of all test results and any variances. Production records are reviewed by QA, who will release the product for use, usually with an accompanying Certificate of Analysis.

Barcoding

Managing reagent and supply inventories can also become a problem as the workload grows. The CAGT facility uses barcoding of all reagents, supplies and equipment. The barcodes are issued when the item is received, a certificate of analysis has been obtained from the manufacturer, and all release specifications are met. Encoded in the barcode are the lot number, manufacturer, expiration date, and date received. The barcode is scanned at the time of manufacturing, and an Activity Report is generated. This report details the nature of the procedure, the recipient and/or donor, the component, as well as all of the encoded information for each supply and piece of equipment used. Barcoding of products is a logical extension of this system; however, consideration must be given to the security of patient-related information.

Quality Systems

Regulatory agencies will request comprehensive details on the quality management systems that are in place during manufacturing. It is important to develop a quality plan that encompasses all aspects of GMP/GTP operations, from ordering raw materials, to clinical use of the final products, and follow-up on the patients. Particular attention needs to be paid to testing essential reagents that are not available in clinical grade form, or when they are derived from ruminants (e.g.: trypsin and fetal bovine serum). Other critical aspects of the quality plan include labeling, changeover procedures (when areas are used for manufacturing different products), contamination testing protocols, recall procedures for reagents and materials used in manufacturing; methods for notification of physicians, institutional review boards, and regulatory agencies when an infused product is found to be contaminated; plus cleaning and maintenance procedures. These items are generic to most IND applications, and a well thought-out and integrated quality system can smooth the regulatory approval process.

Conclusions

As I continue my work in cellular therapy, I am reminded of the old Chinese curse: "May you live in exciting times!" There is no doubt that GMP/GTP manufacturing is a challenge to most of us. The regulations for this field are new, or still under development, and we are struggling at all levels to understand, implement, maintain, and pay for what we think is being asked of us. I hope the suggestions offered here may provide an insight into how an academic facility can address some of these issues.

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