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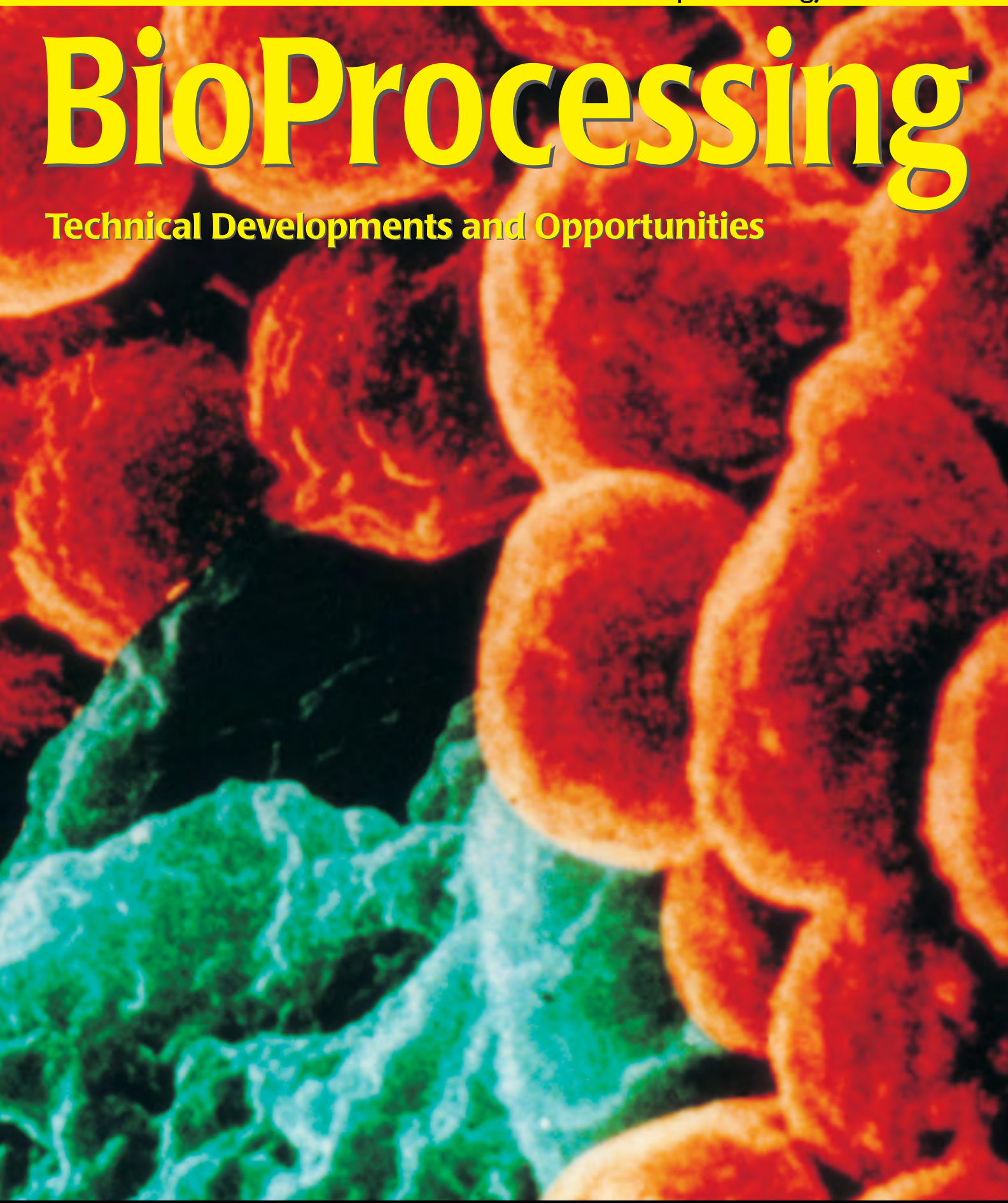

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Cellular Therapy

From the Research Laboratory to the Manufacturing Facility

BY LINDA LEMIEUX

As you stand on the brink of finalizing your first Investigational New Drug (IND) application for a cellular therapy product, there is always the question looming in the back of your mind, "What did we forget?" Hopefully, the answer is "Nothing." However, it is always good to undergo a review of the standard systems needed in order to transition from research to clinical manufacturing.

This article describes an overview of the basic regulatory guidelines and quality systems necessary to begin clinical trials under the regulations of the Food and Drug Administration. However, this should only be considered a guideline, as it does not necessarily address the standards of other regulatory agencies. The investigational product, the clinical indication, and the manufacturing materials used in the investigational product can also change the regulatory requirements needed to proceed with the initiation of clinical trials.

Code of Federal Regulations

FDA guidelines and industry standards for a cellular therapy product must be adhered to. The main regulation governing manufacturing is 21 Code of Federal Regulations (CFR) 211, Current Good Manufacturing Practices (cGMP) for Finished Pharmaceuticals. Even though this refers primarily to pharmaceutical products, the concepts are also applied to the manufacturing of cellular therapies.

This Part refers to many aspects of the manufacturing process including the function of the Quality Department, personnel, facilities, equipment, raw materials, in-process materials, final product, testing, labels, and documentation. Products manufactured and administered to humans must be compliant with cGMP requirements.

It is also necessary to become familiar with the regulations as outlined in 21 CFR 610-General Biological Products Standards; 21 CFR 820-Quality Systems Regulations for Devices; 21 CFR 1270-Human Tissue Intended for Transplantation; 21 CFR 11-Electronic Records, Electronic Signatures; 21 CFR 606-Current Good Manufacturing Practice for Blood and Blood Components; and 21 CFR 640-Additional Standards for Human Blood and Blood Products (as applicable).

Other standards that must be followed include United States Pharmacopeia (USP) Monographs, USP General Tests and Assays Chapters (such as Chapter 71 on Sterility Testing), USP General Information Chapters, as well as relevant FDA "Points to Consider" or "Guidance for Industry" regulations. If that is not enough, there are also industry standards that should be considered. If one company does it better, quicker, and/or smarter, we all need to strive to achieve that level of expertise. Refer to Table 1 for a listing of regulations and standards.

Quality Systems

Generally, the main aspects of Quality Systems needed to manufacture product for clinical trials include personnel, documentation, facility, materials, product, and quality. Table 2 provides an overview of the necessary quality programs.

Personnel. A company that is planning to file an IND should ensure that the essential personnel are in place with expertise in Regulatory Affairs, Quality Control, Quality Assurance, and Manufacturing/Production. Ancillary staff is also needed such as shipping/receiving, cleaning, and administrative assistants.

Note that Part 21 CFR 211, specifically states that a Quality Department is absolutely necessary to ensure that the proper systems are set up and the proper authority is in place over all aspects of the manufacturing process, testing, and materials to be compliant with cGMP requirements.

Documentation. Proper documentation is essential for any clinical development program. Throughout the CFR, documentation plays a lead role in all aspects: from raw material warehousing to final clinical use. Documentation is provided in the form of Controlled Documents. Controlled Documents are standard operating procedure (SOPs), forms, or batch records in which the document is: assigned a tracking number, approved by management and Quality Assurance personnel, and officially copied and distributed. Controlled Documents ensure that all operators are following the most recent and approved version. This reduces variability within procedures, and ensures that procedures are compliant with management directives, regulatory submissions, and regulatory guidelines.

Documents can exist in paper or electronic format. All computer-generated documents must comply with regulations outlined in 21 CFR 11. Following operator training and procedure implementation, the procedures must be followed and forms must be correctly completed, since "if it was not documented, it was not done." One must document his/her own work at the time of performance using indelible ink. Errors should never be obliterated, but rather should be crossed-out with a single line, and then initialed and dated.

Facility. The facility is a key aspect for any clinical trial. Generally, all cellular therapy products are manufactured in a clean environment. A clean environment is referred to as a cleanroom or biological safety cabinet (BSC). There are different classes of clean rooms, as dictated by the Federal Standard 209E. This document lists the different classes with the required testing and qualification work. A Class 10,000 clean room is a room in which the concentration of airborne particles is controlled through HEPA filters to contain a maximum of 10,000 particles (0.5µm and larger) per cubic foot. Table 3 provides a classification chart from the Federal Standard 209E.

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The product's intended use may influence the necessary classification of the cleanroom. For example, an injectable cellular product will have different requirements than a topical product. Also, the classification should be determined based on the work being performed in that area. Most cellular therapy products are produced in Class 100 BSCs that are used in Class 10,000 clean rooms. This approach is taken since the product is not typically terminally sterilized, and end product testing time is limited, unless the product is cryopreserved.

The high expense of manufacturing cellular therapies and the usually limited initial starting material also play a critical role in the need for a clean, sterile area throughout the manufacturing process. The highest level of product protection in a clean environment is essential for manufacturing processes in which the starting material is either rare or unique.

Once the classification of the cleanroom is determined, other programs must be put in place to maintain the cleanroom environment. These programs include those for environmental monitoring (USP <1116>), personnel and gowning, and facility cleaning. The environmental monitoring program must include static and dynamic monitoring to ensure all other systems (air filters, cleaning, gowning, traffic flow, personnel) are robust enough to ensure reduced bioburden levels within the clean environment. All systems must be validated prior to the end of Phase 3 clinical trials, yet not necessarily prior to initiation of the Phase 1 study.

Materials. Requirements regarding materials used in manufacturing processes are also covered in 21 CFR 211.80. A raw material program is critical to ensure consistent, potent, and safe materials are used to produce the final product. All materials become part of the raw material program including liquids, chemicals, plastics, etc. A raw material program consists of materials

Table 1. Listing of Regulations and Standards References

21 CFR 11	Electronic Records, Electronic Signatures
21 CFR 211	Current Good Manufacturing Practices for Finished Pharmaceuticals
21 CFR 610	General Biological Products Standards
21 CFR 820	Quality Systems Regulations for Devices
21 CFR 1270	Human Tissue Intended for Transplantation
USP <71>	Sterility Tests
USP <85>	Bacterial Endotoxins Test
USP <111>	Design and Analysis of Biological Assays
USP <1041>	Biologics
USP <1116>	Microbial Evaluations of Cleanrooms and Other Controlled Environments
USP <1225>	Validation of Compendial Methods
Federal Standard 209E	Federal Standard Airborne Particulate Cleanliness Classes In Cleanroom and Clean Zones
FDA Guidance for Industry	Guidance for Human Somatic Cell Therapy and Gene Therapy (March 1998)

Table 2. Areas for Quality Programs

Product packaging	Validations
Metrology	Auditing
Documentation System	Nonconformances
Raw Materials	Environmental Testing
Formulated Intermediates	In-Process Testing
Computer Systems	Final Product Testing
Training	Product Shipping

being tracked according to internal part numbers. The part number is a unique, sequential number used to track ordering, product, and testing information on the material, and it is usually linked to a material specification that details this information.

Upon receipt of a material, it is placed in quarantine. Quarantined materials are distinctively numbered, labeled, and then tested according to the material specification. Tests should include assessment of potency, sterility, endotoxin, identification, and performance. Special assessments should include adventitious viral testing for animal or human derived materials. Testing requirements can change depending on the phase of clinical trials. Once the material passes all required testing, it is re-labeled as "released for use." If a material does not pass the testing specifications, it will be labeled as rejected, and disposed of. The status of the material must be clearly marked at all times.

Quality. Quality must be built into the manufacturing process, and cannot be tested for only at the final product stage. This is especially true for many cellular therapies that are administered to the patient prior to receiving all final testing results. The product must be manufactured to consistently be safe and effective. To ensure uniformity and integrity, in-process and final product testing must be performed.

Tests to ensure purity and potency include sterility, pyrogen, viral, performance, potency, and product based contaminants. These tests are outlined in the USP and other FDA regulations. Many product-testing regimens are outlined in specific guidance documents, such as for antibodies or blood products.

Container and labeling. An important, yet sometimes overlooked, aspect of the final product is the container/closure system and labeling. The product, the application, container construction, and seal integrity are all key aspects in determining the best final product container.

Another important aspect related to the final product is labeling. Labeling is dictated in Part 21 CFR 211.122. Labels must contain the business name and address, product description, and expiration date (as determined by stability testing). The label or product insert also must contain storage information, warnings, and instructions for use. For investigational products, the statement "Caution: New Drug- Limited by Federal (United States) Law to Investigation Use" must also be printed on the label (21 CFR 312.6). Final product labels must be reconciled after use. Reconciliation of labels is performed to ensure that product tampering by way of mislabeling or fraud cannot occur.

Conclusion

In summary, quality needs to be built into all aspect of the product. Key Quality Systems for any product include metrology, documentation system, raw materials, formulated intermediates, computer systems, training, validations, auditing, nonconformances, and testing (environment, in-process, and final product). Constant reviewing of guidance documents, keeping current on new or changing regulations, and continued learning through seminars and conferences is necessary to ensuring compliance with the relatively new and exciting world of cellular therapy.

Table 3. Federal Standard 209E: Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones, (Table 1 in 209E)

Class Name**		Class Limits									
		0.1 µm		0.2 µm		0.3 µm		0.5 µm		5 µm	
		Volume Units		Volume Units		Volume Units		Volume Units		Volume Units	
SI	English***	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)
M 1		350	9.91	75.7	2.14	30.9	0.875	10.0	0.283	--	--
M 1.5	1	1240	35.0	265	7.50	106	3.00	35.3	1.00	--	--
M 2		3500	99.1	757	21.4	309	8.75	100	2.83	--	--
M 2.5	10	12400	350	2650	75.0	1060	30.0	353	10.0	--	--
M 3		35000	991	7570	214	3090	87.5	1000	28.3	--	--
M 3.5	100	--	--	26500	750	10600	300	3530	100	--	--
M 4		--	--	75700	2140	30900	875	10000	283	--	--
M 4.5	1000	--	--	--	--	--	--	35300	1000	247	7.00
M 5		--	--	--	--	--	--	100000	2830	618	17.5
M 5.5	10000	--	--	--	--	--	--	353000	10000	2470	70.0
M 6		--	--	--	--	--	--	1000000	28300	6180	175
M 6.5	100000	--	--	--	--	--	--	3350000	100000	24700	700
M 7		--	--	--	--	--	--	10000000	283000	61800	1750

* Class limits are given for each class name. The limits designate specific concentrations (particles per unit volume) of airborne particles with sizes equal to and larger than the particle sizes shown. The class limits defined in Table 1 are defined for classification purposes only and do not necessarily represent the size distribution to be found in any particular situation.

** Concentration limits for intermediate classes can be calculated, approximately, from the following equations:

particles / m^3 = $10M\ (0.5/d)^{2.2}$ where M is the numerical designation of the class based on SI units, and d is the particle size in micrometers, or

particles / ft^3 = $N_c\ (0.5/d)^{2.2}$ where N_c is the numerical designation of the class based on English (U.S. customary) units, and d is the particle size in micrometers.

*** For naming and describing the classes, SI names and units are preferred; however, English (U.S. customary) units may be used.