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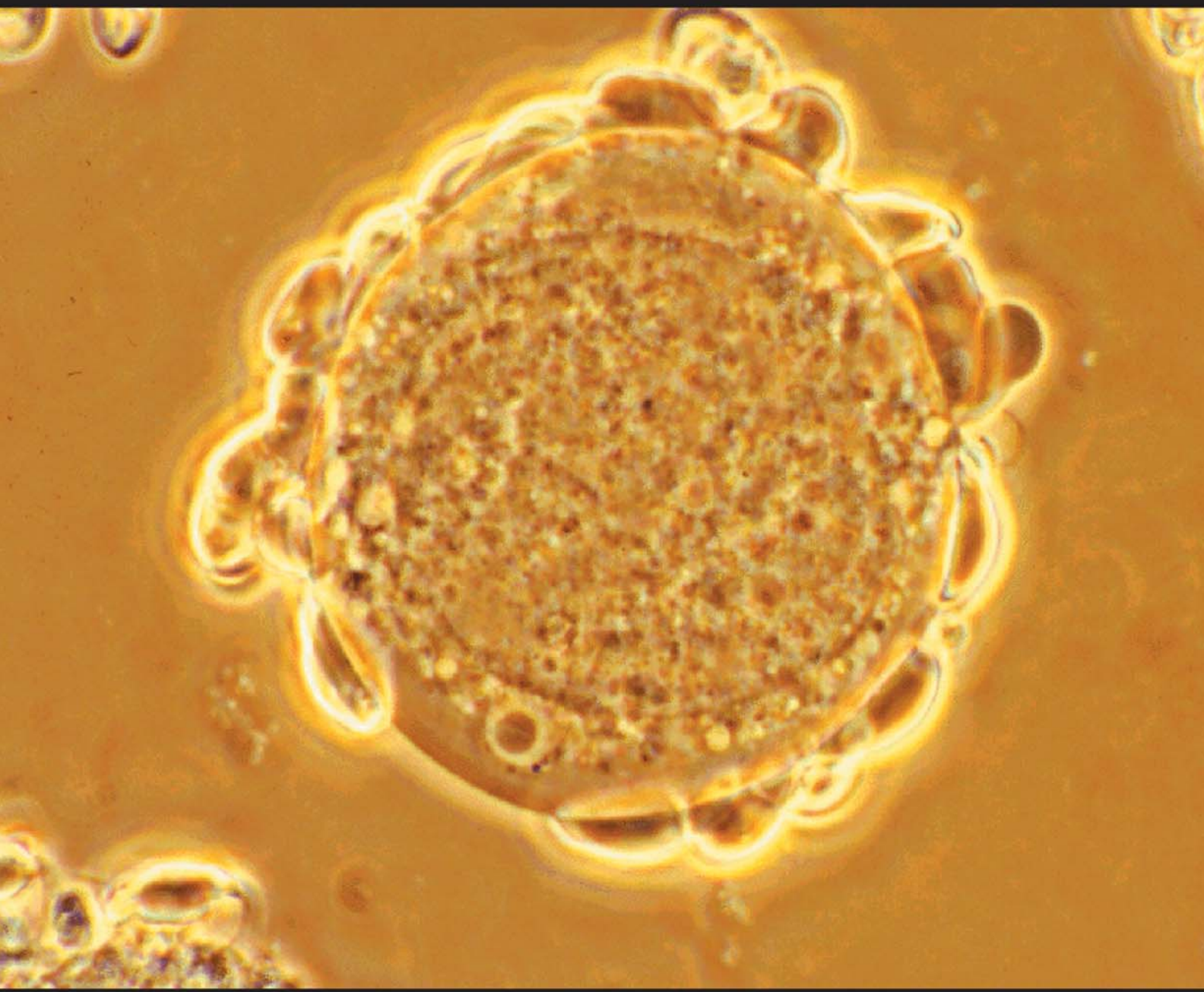

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FDA Perspectives on Characterization and Comparability of Cellular Therapy Products

BY KIMBERLY BENTON

Portions of this paper were presented at the 2002 Cell and Tissue BioProcessing Meeting held in Santa Barbara, CA.

As product development proceeds in the field of cellular therapies, adequate product characterization remains a challenge for both IND Sponsors and FDA/CBER. Cellular therapy products are not considered to be well-defined products, and therefore the control and characterization of each stage of the production process helps to ensure product safety and consistency. Product characterization of cellular products includes demonstration of safety, plus the determination of identity, purity, potency, and product stability. Development of appropriate specifications for each of these parameters is necessary for lot release, and also provides an important database of knowledge for addressing regulatory issues, such as lot-to-lot consistency and potential issues with product comparability, should the manufacturing process, or other aspects of product development, change over time.

Elements of Cellular Product Characterization

Product safety is the primary concern during investigational clinical trials, as well as post licensure. To ensure safety, each unique product and associated manufacturing scheme must be assessed to determine appropriate testing. Because any biological, viral, or chemical agents to which the cells are exposed have the potential to remain associated with the final cellular product, the quality of all starting materials and reagents should be evaluated and demonstrated to be sterile and free from adventitious agents. Reagents purified from cell lines or ascites, such as recombinant proteins or monoclonal antibodies, should undergo appropriate adventitious agent testing, depending on the species of origin of the cell line and/or ascites fluid.[1,2]

The FDA recommends testing the donor of the cellular product, whether the donor is allogeneic or autologous. Testing of allogeneic donors must be performed to prevent inadvertent transmission of adventitious agents to the patient, and autologous donor testing is recommended due to potential for expansion of adventitious agents during manufacturing. For specific guidance, please refer to the "Suitability Determination for Donors of Human Cellular and Tissue-Based Products, Proposed Rule."[3] Any cell bank system used should be qualified with appropriate testing.[1,4]

Product safety includes testing the product for sterility, mycoplasma, pyrogenicity or endotoxin, and the presence of adventitious agents. Such testing should be built into the quality control of the manufacturing process and must be performed on each lot of the final product. In-process testing and testing as part of component qualification might also be needed, depending on the specific product. Cellular therapy products are exempt from the requirement for general safety testing (21 CFR 610.11(g)).

Product purity may be analyzed by a number of parameters that may vary depending on the product. Analysis of product purity extends beyond testing for pyrogenic substances, and may include cell viability, phenotype, and quantitation of phenotypic subpopulations. Cellular products are rarely comprised of a single, pure population of cells. A mixture of cell types may be key to efficacy, but supporting data must be collected and analyzed. Freedom from extraneous materials such as media components, or activation and chemical agents is another parameter of purity. These characteristics are also important as in-process controls. It is not only important to establish a measurement of purity for lot release, but also to monitor the changes in purity that may occur with manufacturing changes. Additional product characterization could include identifying and quantitating at least two activation markers, such as the level of expression of a differentiation molecule. If properly validated, analysis of these characteristics could potentially be used as a surrogate to a potency assay.

Cell therapies generally exert their effect through a biological activity. When possible, the measured biological activity should reflect the relevant function of the product. This activity measurement might include analysis of the cytolytic activity, induction of cytokine release, or antigen presentation.

***Kimberly Benton, Ph.D.**, is a chemistry, manufacturing, and controls reviewer in the Division of Cellular and Gene Therapies, Office of Cellular, Tissue, and Gene Therapies, CBER/FDA; bentonk@cber.fda.gov.*

Flexibility may be needed for assays that take several days to complete. In such cases, it may be appropriate to attempt a correlation between the biological activity of the product and a physical characteristic. However, without proper characterization of the product, this type of analysis cannot be performed and the correlation cannot be validated.

Importance of Product Characterization in Demonstrating Comparability

The need for product characterization becomes increasingly clear when one attempts to evaluate the effects of a manufacturing change on a cellular product. If the process defines the product, how does one predict and assess the possible changes in the product that may result from a change in the process?

Changes are often necessary to improve the product or manufacturing efficiency. Potential manufacturing changes could include changes in reagents, culture vessels, length of total culture time or specific steps, addition or subtraction of growth factors, and reformulation of the final product. There may be a change in manufacturing site, as when moving to a new site or adding additional sites. Without comprehensive product characterization data, it will be difficult to demonstrate that the new process or new site produces a comparable product. Meeting lot release criteria will not likely be sufficient for demonstrating product comparability. Demonstration of comparability is not always required during early phases of product development, but will be required when manufacturing changes are implemented just prior to, or during, pivotal trials and post-licensure.

Definition of Comparability and Concepts from the 1996 Guidance Document[5]

What is comparability? In 1996, the Agency published a guidance document discussing principles of comparability, from which the following definition was taken: "FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency."[5] This document was intended to discuss post-approval changes for therapeutic biotechnology products, such as those specified in 21 CFR 601.2(a) and with which the Agency has years of experience.

Cellular products are generally difficult to characterize, and due to their extremely complex nature, will remain relatively poorly defined. They do not meet the definition of specified products, and thus the same standards of comparability will be extremely difficult to attain. However, many of the concepts from the 1996 guidance document can serve as a guide for determining the types of studies that may be needed to demonstrate comparability of cellular products.[5]

Comparability studies may include the following categories of testing: i) analytical testing with chemical and physical assays; ii) bioassays or functional tests to assess biological activity and/or potency; iii) pre-clinical animal studies; and iv) clinical studies. In vitro analytical tests and bioassays may analyze parameters of product characterization such as viability, phenotype, protein expression, and biological activity.

The assays used in comparability studies may differ from those used for lot release. For example, for a cellular product that is not cryopreserved, bioassays requiring several days to complete are not used for lot release, but may be part of comparability studies. When feasible, side-by-side analysis should be conducted with product manufactured by the previous system or site and material from the new process or site. When available, fully characterized reference standards should be included. Pre-clinical tests in relevant animal models may be needed to address pharmacokinetics, pharmacodynamics, immunogenicity, and toxicity. If in vitro laboratory analyses and pre-clinical studies cannot clearly demonstrate product comparability, then human clinical studies may be necessary, and may include pharmacology, immunogenicity, and bridging efficacy studies.

Several factors may affect the extent of comparability testing needed to assess whether the change will result in significant changes in clinical safety or efficacy. These factors include the complexity of the product and manufacturing process, the stage of product development, the type of change, the ability of test methods to detect product differences, and the sensitivity of the biological/functional assays. Although comparability testing may be considered to increase in complexity from in vitro analytical assays to pre-clinical studies to clinical studies, these categories of testing are complementary rather than purely hierarchical.

The greater the extent of product characterization using qualified assays, the greater the likelihood of demonstrating comparability by analytical and pre-clinical testing alone, without additional clinical efficacy studies. All components of the product, such as the cell populations and any residual impurities, should be characterized and quantitated. Assays for lot release testing and additional product characterization should be developed and validated. The limitations of the assays should be defined and the capacity of the assays to measure change in product should be demonstrated. Multiple tests for a single characteristic, such as measuring potency by both biologic activity and expression of multiple surface markers, may be useful. Data collected throughout product development, especially in early clinical trials when many manufacturing changes are more likely to occur, may provide important information for predicting the potential effects of certain types of manufacturing changes on the safety and efficacy of the product.

Discussion at the 2002 Cell and Tissue BioProcessing Meeting

At the Cell and Tissue BioProcessing Meeting held in Santa Barbara in 2002, a panel discussed the issues of product characterization and comparability for cellular therapies. It was noted that many assays might be used to demonstrate changes in cellular products. Newer technologies such as microarray and proteomics may be useful, but sup-

porting basic science is needed to interpret the data. For patient-specific cellular products, small lot size limits the samples available for testing; but with planning and creativity, sufficient product samples may be obtained to conduct assay development and product characterization studies.

It was noted that in order to demonstrate comparability prior to or soon after licensure, it may be necessary to characterize the product, validate assays, and comply with GMP standards earlier in product development. While validation of assays is not expected until late in product development, the variability in the manufacturing process and test methods should be analyzed and reduced as much as possible. It is important to consider individual products and manufacturing processes, and not create artificial categories and criteria. The panel discussion illustrated the need for additional consideration of this issue by CBER and the cell therapy community, so that the issues of product characterization and comparability do not hinder the continued development of the field and the progress of products toward licensure.

Conclusions

Currently, CBER has received limited scientific data to evaluate the potential impact of manufacturing changes on cellular products. Until sufficient experience is gained with these products, evaluation of comparability will be performed and reviewed on a case-by-case basis, following the principles of the 1996 guidance document.[5] Prior to the implementation of a manufacturing change, sponsors should discuss the proposed change and the need for comparability testing with CBER prior to implementing the change.

An internal CBER working group has been formed on Comparability for Cellular Therapies, and the majority of its members are from the Office of Cellular, Tissues, and Gene Therapies. The working group is considering ways to obtain additional input on this issue, such as participating in sessions and panels at various meetings, or by sponsoring a public meeting dedicated to the topic of comparability. We encourage your suggestions and data submissions, which can be directed to the author at bentonk@cber.fda.gov.

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