[Docket No. 95N-0200]

GUIDANCE ON APPLICATIONS FOR PRODUCTS COMPRISED OF LIVING AUTOLOGOUS CELLS MANIPULATED EX VIVO AND INTENDED FOR STRUCTURAL REPAIR OR RECONSTRUCTION

May 1996

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Center for Biologics Evaluation and Research

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I. PURPOSE

This document provides guidance for the clinical investigation and use of living autologous cells manipulated ex vivo and intended for structural repair or reconstruction (Hereinafter referred to as MAS cells or MAS cell products.)

II. SCOPE

Because the Food and Drug Administration (FDA) is in the process of revising 21 CFR 10.90(b), this document is not being issued under the authority of 21 CFR 10.90(b), and the document does not bind the agency and does not create or confer any rights, privileges, or benefits for or on any person. Sponsors may follow the guidance or may choose to use alternative procedures and study designs not provided in this guidance document. FDA may amend this guidance periodically as needed.

III. BACKGROUND

Federal oversight of therapeutic products comprised in whole or in part of living cellular material has evolved over the past several decades using authorities appropriate to address several issues related to the public health. The FDA began the regulation of blood as biological products during World War II under the Public Health Service Act (PHS Act) and the Food, Drug and Cosmetic Act (the Act) to help ensure the safety of the blood supply. FDA also regulates some human tissues, such as dura mater allografts and corneal lenticules, as devices under the Act. The Health Resources Services Administration (HRSA) oversees several programs for human organs and bone marrow under the National Organ Transplant Act (NOTA), and the National Marrow Donor Program (NMDP). These latter two programs are designed for fair and safe procurement and allocation of human organs, and information management to allow nationwide matching of compatible bone marrow donors.

The unmet demand for organs and tissues for transplantation began to stress the familiar organ donor procurement program, resulting in some facilities procuring cadavers and tissues without appropriate screening of donors. As a result of public health concerns raised by the use of organs and tissues for transplant procured in this manner, the FDA promulgated an interim rule for banked human tissue in the **Federal Register** of December 14, 1993 entitled "Human Tissue Intended for Transplantation" (58 FR 65514) under the authority of section 361 of the PHS Act. Banked human tissue products are defined in the interim final rule as any tissue derived from a human body which: (1) is intended for administration to another human for the diagnosis, cure, mitigation, treatment, or prevention of any condition or disease; (2) is recovered, processed, stored, or distributed by methods not intended to change tissue function or characteristics; (3) is not currently regulated as a human drug, biological product, or medical device; (4)

excludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ; and (5) excludes semen or other reproductive human tissues, human milk, and bone marrow. The interim rule does not apply to autologous tissue products.

The combined coordinated framework by the federal government creates a baseline "floor" of oversight and safeguards for human tissues and organs used for transplantation. These safeguards include, but are not limited to, prevention of exposure to infectious diseases, donor screening and testing, record keeping and inspection of facilities. Federal oversight also addresses fair distribution and access to scarce source materials such as human organs and allogeneic bone marrow.

Recognizing that sponsors developing tissue and cell based therapies would increasingly want to make these products commercially available, the FDA has been clarifying its approach to the regulation of these products. In response to the rapid growth of novel cell and gene based therapies, FDA issued a notice in the **Federal Register** of October 14, 1993 entitled "Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products" (58 FR 53248). The notice defined somatic cell therapy products as autologous (self), allogeneic (intra-species), or xenogeneic (inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. FDA defined "manipulation" as the ex vivo propagation, expansion, selection, or pharmacological treatment of cells, or other alteration of their biological characteristics.

IV. RECENT EVENTS

The FDA had recently become aware of the clinical use of autologous cell products for structural repair or reconstruction, such as chondrocytes expanded ex vivo, and implanted in focal cartilage defects (see notice published on July 18, 1995 in the **Federal Register** entitled "Public Hearing: Products Comprised of Living Autologous Cells Manipulated ex vivo and Intended for Implantation for Structural Repair or Reconstruction", 60 FR 36809 for additional information and references). When a commercial establishment began to provide these manipulated cells to surgeons within the United States in 1995, several issues arose:

1) It became clear that such a product class had not been explicitly considered by the FDA in drafting the somatic cell statement or the interim rule on tissues for transplantation, and advice to the industry by the agency was needed. Unlike autologous bone marrow for transplantation for which FDA had not required premarket approval, there has been very limited clinical experience with some MAS cell products, such as autologous cartilage cells. Additionally, the manipulation required for MAS cell products is more than that required for autologous bone marrow, where the source material is harvested, but otherwise undergoes minimal manipulation. MAS cells products are dissociated from human tissue, and expanded ex vivo in order to provide sufficient number of cells for implantation, and thus would fall within the definitions for

somatic

cell therapy products (58 FR 53248). However, unlike systemic cellular therapies to treat malignant and infectious disease, the chondrocytes were implanted within an enclosed space, and thus had similarities to some tissue and device products.

2) The commercialization and distribution of expanded cartilage cells to provide a potential solution to a relatively common medical injury suggested that numerous patients could be receiving these cells within a short period of time.

3) Orthopedic surgeons had been using a variety of autologous tissues such as rib cartilage for transplantation without federal oversight for some time. Thus, any regulatory program would need to strive to provide adequate patient safety and assurance of benefits to patients while avoiding unnecessary burdens to physicians.

In light of the potential public health significance of this new product class of MAS cell products, the growth of a commercial industry potentially affecting a large number of patients, and the need to decide which existing regulatory authorities (e.g. device versus biologics) would be appropriate to apply or whether a new regulatory framework was required, the agency held a Part 15 Public Hearing on November 16 and 17, 1995 (60 FR 36808). The intent of the meeting was to solicit information on the nature and diversity of these products, and to receive comments on the formulation and implementation of any new regulatory requirements. The Part 15 Public Hearing had 8 panels with 24 speakers, and there was general consensus that the establishment, the production process and the products produced should be of the highest quality. The speakers and attendees also agreed that MAS cell products should benefit the patient, but there was little consensus on the appropriate mechanism that should be used to show this benefit.

The agency also held a Commissioner’s Round Table on March 15, 1996 (Mar 7, 1996, 61 FR 9185), to discuss FDA’s thoughts on the regulatory approach to MAS cell products with respect to clinical and manufacturing issues, and to get input on the agency’s proposed approach. Many of the concepts presented were derived from ongoing FDA Reinventing Government (REGO) initiatives. In the same Federal Register notice, FDA also invited the submission of written comments concerning FDA' s plan for the regulation of MAS cells. Based on the discussions at the March 15 Roundtable public meeting and on a review of all comments to the docket, the FDA has decided that in light of the increased flexibility provided by REGO initiatives, FDA will apply the regulatory framework as detailed and for the reasons explained below. Comments on the framework may be directed to the open docket, 95N-0200.

V. REGULATORY PLAN FOR MAS CELLS.

A. Summary statement.

The Center for Biologics Evaluation and Research (CBER) is designated as the agency component with primary jurisdiction for the premarket review and regulation of MAS Cell products. The products are subject to licensure as biological products under section 351 of the

PHS Act (42 U.S.C. 262). Clinical investigation of MAS cell products should be performed in accordance with the requirements for investigational new drugs in

21 CFR 312 and the products are subject to licensure as biological products (21 CFR 601). The Current Good Manufacturing Practice (CGMP) regulations in 21 CFR 211 and 21 CFR 600, 601, and 610 will apply although FDA intends to consider on a case-by-case basis alternative approaches to specific regulations, consistent with 21 CFR 610.9, where the regulations may be impractical or unnecessary to assure the safety, purity and potency of the product.

B. Products Subject to the Regulatory Plan

MAS cells are defined as cells derived from a patient's tissues, which are manipulated ex vivo, and then implanted into the same patient with the intent of providing repair or reconstruction of a structure. The repair and reconstruction does not involve systemic action by the MAS cell product. Somatic cell therapy products (58 FR 53248) can include MAS cells. Typically, the manipulation involves dissociation of the human tissue into individual cells, which are then propagated and expanded into large numbers of cells using tissue culture methods. Examples include chondrocytes for repair of focal cartilage defects, autologous fat cells for cosmetic augmentation and autologous keratinocytes for dermal wound healing.

C. Registration and Inspection of Establishments

Establishments engaged in the manufacture of MAS cell products should register as a drug product manufacturer in accordance with section 510 of the Act and 21 CFR Part 207. Such registered establishments will be subject to inspection by FDA. Currently, FDA plans that a representative from CBER and an investigator from the FDA District Office closest to the establishment will participate in inspections on a biennial basis.

D. Clinical Studies of MAS Cell Products

1. Investigational Phase

MAS products that will undergo clinical study are subject to the regulations at 21 CFR 312 and 601.21, and sponsors should have an IND application. Guidance specific to IND requirements for MAS products is under development. In the meantime, early contact with CBER is welcomed. The timing of submission of an IND is given in part VI below.

2. Requirements for premarket approval

As should other experimental biological products, therapies using MAS cells should demonstrate safety and efficacy before marketing (October 14, 1993, 58 FR 53248). The Agency recognizes that a flexible approach for clinical investigations of MAS cell products may be feasible because of certain attributes of structural defects and MAS cell therapies. These include a) the likely persistence of many structural defects when left untreated; b) the possibility of short-term benefits together with the need to assess long term safety and efficacy; c) the frequent availability of imaging or biopsy evidence of structural repair with high likelihood of predicting clinical benefit; and d) the low probability of systemic toxicities.

The Agency intends to take the following approaches for marketing approval of MAS cell products. The use of short-term (ie., one year or less) endpoints directly measuring

clinical benefit may be sufficient evidence of efficacy to support approval, if a favorable risk-benefit evaluation has been established and long term safety concerns are low. In such cases, postmarketing studies or registry data may be used to assess long term safety and efficacy for expanded labeling. Evidence of normal or repaired structure may be accepted as evidence of efficacy where there is a high probability it will be associated with clinical benefit. Extensive screening by laboratory or physical examination of large numbers of patients for systemic toxicity generally will not be required in the premarketing phase for MAS cell products. Therapies using manipulated autologous cells for structural repair need not be demonstrated to be superior to other existing therapies.

MAS cell products intended for serious or life-threatening conditions may demonstrate efficacy under accelerated approval regulations using surrogate markers for clinical benefit (21 CFR 601 Subpart E). In these instances, more definitive proof of clinical benefit should be generated in post-marketing studies.

Prospective randomized controlled clinical studies traditionally have been the best way to demonstrate safety and efficacy. However, where studies of MAS cells without internal patient controls provide evidence of effective structural repair which substantially and clearly represents improvements in outcomes compared to patients in an appropriate historical database, this may be sufficient to demonstrate efficacy.

E. Cost Recovery for Investigational MAS Cell Products.

It is recognized that MAS cell products used as an individual patient therapy have inherent costs associated with production that can be substantially higher than normal product development costs. Consequently, as noted in the Mar 15, 1996, Commissioner's roundtable meeting (61 FR 9185), CBER will give full consideration to requests for cost recovery during the IND phase, consistent with 21 CFR 312.7(d).

F. Marketing Application for MAS Cell Products.

Sponsors submitting premarket applications for MAS cell products may use either the ELA/PLA dual application process as described in 21 CFR 601.2, or, on a voluntary basis a single Biologics License Application. A draft BLA form may be obtained from CBER (address above); it may also be obtained by FAX by calling the CBER Voice Information System at 1-800-835-4709. Currently, for MAS cell products both an establishment license and a product license will be issued whether an ELA/PLA or a single BLA is submitted and approved. Sponsors voluntarily using a BLA will not need to file a separate application to receive an establishment license. FDA intends at a later date to propose that only one license covering both the product and establishment will be issued.

G. Chemistry, Manufacturing and Controls Section of BLA.

The FDA is preparing a guidance document entitled "Guidance for Preparation of the Chemistry, Manufacturing, and Controls Section of a Biologics License Application for Manipulated Autologous Cells for Structural Repair or Reconstruction" for later announcement

in the **Federal Register**. Sponsors are encouraged to contact CBER for advice in the interim.

H. Inter-Center Working Group.

MAS cell products may have properties of both biological products and medical devices. Therefore, to help ensure consistency with agency review standards and practices, and to use the best available expertise, CBER and the Center for Devices and Radiological Health (CDRH) have formed an Autologous Cell Product Working Group that will meet on a periodic and regular basis to discuss issues related to autologous cell products and therapies.

I. Contracting of Manufacture of MAS Cell Products.

In the **Federal Register** of May 14, 1996, a final rule entitled "Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products" (61 FR 24227), was issued. In addition to eliminating the requirement for an establishment license for certain specified biological products, the rule amended the definition of "manufacturer" in 21 CFR 600.3(t) to include an applicant for a license.This amendment permits the contracting out of all or part of the manufacturing process without requiring separate licensure of each contract manufacturer engaged in significant manufacturing. The applicant would assume responsibility for the safety, purity, and potency of the final product but would not have to be personally engaged in significant manufacturing steps. Thus, an applicant or manufacturer may be granted a license for a MAS cell product even if not personally engaged in the product's manufacture.

J. Lot Release.

Consistent with 21 CFR 610.2 (a), the Director, CBER generally does not believe that submission of samples and lot release protocols to CBER for official release is needed to ensure the safety, purity, or potency of MAS cell products. Accordingly, lot release by CBER will not be required, unless the Director of CBER finds otherwise for a particular MAS cell product and notifies the manufacturer.

K. Applicability of CGMP Requirements.

The CGMP regulations in 21 CFR 210 and 211 and the applicable regulations in 21 CFR 600, 601, and 610 will apply to MAS cell products. FDA recognizes, however, that it may be difficult or impossible to comply with certain regulatory standards when testing MAS cell products. The general safety, sterility, and mycoplasma tests prescribed in 21 CFR 610.11-12 and 610.30 may be inappropriate due to changes which may occur to the product during the period required for cell testing. However, the manufacturer **must** still **employ** appropriate controls to provide assurance of safety, purity and potency of MAS cell products. Equivalent methods of demonstrating a product’s safety and sterility can be requested in accordance with 21 CFR 610.9. This may include modified test procedures, conducting assays during the cell processing, and testing product samples obtained at the time of administration. If appropriate, FDA intends to permit alternatives to these and, as necessary, other regulations as part of the approval process of these products.

VI. REGISTRATION AND APPLICATION SUBMISSION

The agency acknowledges that manufacturers will need time to prepare applications. Firms manufacturing MAS cell products should register within 6 months of the date of this notice. All clinical uses of MAS cell products should be under an active IND or an approved BLA within 18 months of the date of this notice. Sponsors are encouraged to discuss the timing of submission of applications with CBER in order to minimize disruption of clinical development and use of MAS cell products.

VII. SUBMISSION OF COMMENTS

FDA recognizes that the clinical use of MAS cell products constitutes a new and evolving scientific area. FDA will review and consider written comments on the guidance set forth in this notice to determine whether revisions are appropriate. Comments may be submitted at any time; however, submission of comments should be as timely as possible when guidance is revised or updated. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments received and other information on which FDA has relied in developing this regulatory approach are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday