is in the distant future. However, commercial production of simple tissues has been accomplished.

15.2.2. Commercial Tissue Culture Processes

The two examples of commercial production of tissue-engineered products are for skin and cartilage.

15.2.2.1. Tissue-Engineered Skin Replacements. Skin replacements are needed for patients with burns, with pressure ulcers (usually due to diabetes), and with reconstructive surgery. Cadaver skin is undesirable because of potential disease transmission, possible immunological rejection, inflammation of the wound bed, limited availability, and high cost due to labor-intensive procurement. Animal products would be problematic due to immunological reactions. An "artificial" human skin replacement that can be taken out of the freezer and used by physicians is highly desirable. TransCyte™, a human fibroblast-derived temporary skin substitute, is such a product.

An artificial human skin is made from human neonatal foreskin fibroblasts which are obtained from routine circumcision discards. These fibroblast cells are easily available and not subject to rejection by the body; they are also capable of replication, and numbers can be expanded in a straightforward manner. Donor tissue is enzymatically digested and seeded onto a three-dimensional bioresorbable polymer scaffold. The cell-seeded scaffold is placed in a bioreactor that provides a physiologically similar environment to promote cell growth and secretion of proteins and extracellular matrix material. The cells and extracellular matrix material result in a three-dimensional tissue construct with metabolically active cells that is functionally similar to natural skin and promotes wound healing.

The manufacturing process is centered on a bioreactor system that mimics *in vivo* conditions through control of temperature, pH, oxygen level, nutrient supply, waste removal, and fluid hydrodynamics. It must produce thousands of individual products of uniform and reproducible quality. The manufacturing system requires a bioreactor for product growth that also serves as final packaging. The system is sealed after assembly and remains sealed to maintain sterility. Figure 15.1 is a schematic of the process. The bioreactor is made of plastic with inlet and outlet ports. It is flat and just large enough to hold a polymer mesh about 13 by 19 cm. Twelve individual bioreactors are manifolded together. Groups of twelve are then operated in parallel to provide the desired lot size. Once the system is sterilized, it is opened only for cell seeding and nutrient replenishment. About three weeks are required for growth. At the end of this growth period, cryopreservative is pumped into the bioreactor module. After sealing inlet and outlet tubes, the bioreactor is packaged, frozen, and then stored or shipped. The product is thawed and used by the physician.

This manufacturing process is similar to many we have discussed before, but differs in that the product is discrete and not in solution. The process must meet all of the FDA and GMP requirements discussed earlier.

15.2.2.2. Chondrocyte Culture for Cartilage Replacement. Articulate or hyaline cartilage is a thin layer of tissue found at the ends of bones. Damage to articulate cartilage in the knee is a common health problem. Cartilage consists of three primary