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Making Medicine Out of Us

Harmonizing U.S. and EU rules on human-tissue products may help spark new therapies.

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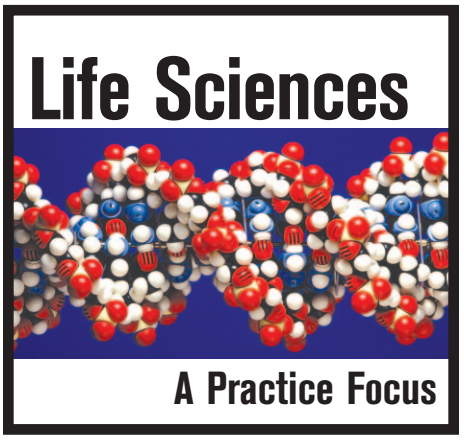
Not many people think of the human body as a source for components of medical products. Yet increasingly, medicines and medical devices are being developed from blood, skin, bone marrow, and other human tissues.

Just last month, the U.S. Food and Drug Administration implemented a comprehensive regulatory program for a wide range of tissues and cells—from basic human tissues, like bone and skin, to more-complex cells and cell components, such as umbilical-cord blood cells, pancreatic islets, and leukocytes. The regulations also cover novel therapeutics made possible by rapid advances in technological capability, such as using engineered cells to treat cancer, Parkinson's, and Alzheimer's.



Now that the FDA has finalized mechanisms to regulate these products, and the European Union has announced a key step in its analogous regulatory framework, the world's leading regulators are beginning to catch up with the leading biotechnology companies, which are beginning to commercialize their products.

But important issues remain unanswered. How can regulators protect public health and ensure ethical practices while leaving industry free to develop products that save lives and reduce suffering? Can a balance be struck without regulatory overkill? How will tissue regulations be harmonized among countries?

A New Framework

Until recently, the U.S. regulatory scheme for human cell, tissue, and cellular- and tissue-based products was largely limited to human blood and basic tissues—including bone, skin, ligaments, tendons, and corneas—intended for "homologous" use (that is, serving their normal function in the body). Examples include using bone fragments to treat orthopedic injuries and transplanting corneas to restore sight in blind patients.

The FDA strictly regulated blood and blood products for decades and transplanted tissue since the 1990s. What was lacking was an overall regulatory framework for commercial tissue products. Absent such uniform FDA regulation, some marketed tissue products were approved on a case-by-case basis.

In 1997, the Clinton administration began to develop a risk-based framework for tissues. Eight years later, this process nears fruition.

Effective May 25, 2005, the FDA finalized the last components of a comprehensive framework. Three sets of "tissue standards" were established: (1) registration of entities that remove, process, store, label, package, or distribute cell and tissue products, or that screen donors or donor samples for communicable diseases; (2) standards for donor screening and sample testing; and (3) good practices to ensure the proper handling and manufacturing of cell and tissue products.

To accommodate the various cell and tissue products, the FDA created a tiered regulatory structure, in which the degree of communicable-disease risk determines the degree of regulation. Where the risk of transmitting a communicable disease is minimal, cell and tissue products are exempt from regulation.

Tissues that pose more than a minimal risk of communicable disease and are "minimally manipulated" belong to an intermediate-risk category. Examples include stem cells removed from and then implanted back into the same donor or a close relative of the donor. While compliance with the new

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tissue standards is required, these cell and tissue products can be marketed without additionally obtaining pre-market approval from the FDA.

The most stringent requirements are reserved for cell and tissue products that are more than "minimally manipulated," combined with a drug or medical device, or implanted into unrelated patients. For these products, the FDA not only requires compliance with tissue standards, but also requires that the individual product receive pre-market approval as a drug, biological product, or medical device. Generally, pre-market approval will be granted when safety and effectiveness are demonstrated through human clinical studies.

Thus, as we move along the spectrum from basic tissue for homologous use to sophisticated, engineered cells intended for novel therapies, the FDA increases the level of regulation.

More Power to the FDA

This extensive federal control is based on the FDA's creative use of an old authority under the Public Health Service Act, 42 U.S.C. §264, which was aimed at preventing communicable-disease transmission. Previously, the FDA relied on this provision to regulate items moving through commerce, such as turtles and molluskan shellfish. But with the increase in viral infection transmission (such as HIV/AIDS and hepatitis C), the FDA has turned to this very general grant of authority to implement very specific and substantial new enforcement and inspection powers.

For instance, all entities handling cellular and tissue products are now required to track their movement from the donor to the person responsible for implanting the tissue. This often involves multiple players—hospitals, testing facilities, processing labs, and manufacturers.

The FDA also granted itself broad authority to (1) inspect locations that remove, process, store, label, package, test, or distribute cellular and tissue products; (2) require notification about certain imported products; and (3) order entities to recall, retain, destroy, or stop the manufacture or distribution of products that the FDA believes may pose a communicable-disease risk.

The enforcement powers the FDA granted itself were significantly more far-reaching enforcement powers than was previously imagined. How and to what extent they will be implemented is still up in the air.

European Vision

Meanwhile, the European Union has also been moving to regulate tissue products. By April 2006, all EU member countries must enact laws implementing a 2004 directive on human tissues and cells. And last month the European Commission proposed the establishment of a uniform regulatory framework for "advanced therapies"—gene therapy, somatic cell therapy, and human-tissue-engineered products.

This proposal would give the European Medicines Agency, the EU organization that regulates drugs**,** jurisdiction over human-tissue-engineered products as "medicinal products." It would create a "single, integrated, and tailored" framework for all advanced therapies. The use of the European Medicines Agency, which relies on committees composed of representatives from EU member states, sends a clear signal that EU authorities think human-tissue-engineered products need centralized handling and stringent regulation.

The assignment of human-tissue-engineered products to the European Medicines Agency was disappointing to the medical device industry, which had hoped that the European Union might choose a regulatory approach like that covering medical devices. EU medical device assessments are carried out not by regulators, but by various accredited bodies generally in the private sector.

The European Commission argues that treating human-tissue-engineered products as medicines bridges a regulatory gap, creates legal certainty, and thus fosters innovation. The European Medicines Agency already evaluates 70 percent of new medicines entering the EU marketplace, and it has gained respect for sound decisions through a centralized system that relies on member states' expert resources. Also, under this new system, intellectual property rights unique to pharmaceuticals (for example, certain exclusivity periods) would be available to tissue-product innovators.

Manufacturers of tissue-based therapies that entered the EU market as medical devices would have three years to obtain authorizations from the European Medicines Agency. One piece of good news is that such products would be exempt from that agency's user fees. But manufacturers that have already jumped through the medical-devices hoop would have a good case for an exemption from this authorization process, or at least more time to win approval from the European Medicines Agency.

Getting Together

With the globalization of the biotech industry, harmonization of regulatory requirements will encourage the development of innovative medical therapies. U.S. and EU regulators could provide the leadership to push for a harmonized global approach to regulation of human-tissue products. But first they must achieve this harmonized approach bilaterally.

In both the United States and the European Union, cellular and tissue products that are removed from and then implanted into the same person during the same surgical procedure are treated as low risk and are exempted from regulation. At the opposite end of the spectrum, U.S. and EU regulators agree that products posing a high risk of communicable-disease transmission must comply with tissue safety standards, as well as meet costly and time-consuming testing and approval requirements.

In the middle are moderate-risk products that, in the United States, are subject to the new tissue standards but not to FDA pre-market approval. The European Union proposal has no corresponding middle category, and thus apparently would require the submission of individual pre-market applications for these products too. Convergence between the U.S. and EU approaches on moderate-risk products is important.

EU lawmakers should give the European Medicines Agency clear authority to regulate products in this category through stringent class regulations, but without individual product applications, in a manner similar to that of the FDA. Such a sensible, risk-based approach would avoid overregulation and advance harmonization. As interested persons were given until June 20 to provide comments to the European Commission, a proposal along these lines might have been suggested.

International collaboration and harmonization of regulatory frameworks will be needed precisely because bioengineered

tissue products present so many unanswered questions. For instance, can data from animal tissue predict the safety of human-tissue products? What analytical testing methods are suited for tissue products? What does "effectiveness" mean in the context of autologous therapies, where patient-specific tissues and cells are used, as opposed to the traditional context of common drug formulations for all patients?

As biotech companies seek to answer these questions, complementary regulations in the United States and the European Union can help ensure that beneficial tissue therapies are commercialized in a safe and timely manner. Regulators need to fine-tune their requirements based on the real risks so that human-tissue therapies will fulfill their tremendous potential to save lives.

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