May 25 will mark the end of the beginning for FDA regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps). The last and, in some respects, most important of its panoply of regulations to govern the collection of the antecedent donor materials and the processing and distribution of the resulting products will be made effective as of that date.

This final piece of the regulatory framework first announced by the Agency in early 1997 was published in the Federal Register on November 24, 2004, as the “Current Good Tissue Practice for Human Cell, Tissue and Cellular and Tissue-based Product Establishments; Inspection and Enforcement; Final Rule” (referred to in this article as the “CGTP Rule”). Two earlier Final Rules, one providing for establishment registration (the “Registration Rule”) and the other establishing processes for donor screening (the “Donor Screening Rule”) had already set out significant portions of this framework.

The Registration Rule was made effective as of January 21, 2004; the regulations set forth in the CGTP Rule come into effect on the same day as the CGTP Rule. A conference, “FDA and the New Paradigm for Tissue Regulation,” which was held in Dallas on February 1, allowed for a dialogue between FDA and industry participants on the eve of the implementation of the completed regulatory plan for HCT/Ps.

The CGTP Rule represents the culmination of FDA’s efforts over several years to establish a comprehensive system for regulating human cell, tissue, and cellular and tissue-based products. Defined as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient, HCT/Ps include skin, musculoskeletal tissue (notably bone and ligaments), ocular tissue (especially corneas), heart valve allografts, dura mater, hematopoietic stem and progenitor cells derived from peripheral and cord blood, reproductive tissue, cellular therapies, and combination products consisting of tissue with a device and/or drug (such as cells on a natural or synthetic matrix).

The initial version of the CGTP Rule (issued as a proposed rule on January 8, 2001) had distinguished between “tissues intended for transplantation” and “human cellular and tissue-based products;” the CGTP Rule absorbs the former category into the all-encompassing class of HCT/Ps for donor materials collected after May 25, 2005.

In the late 1980s and early 1990s, the Agency recognized the need for regulatory oversight of these products. First, documented evidence of communicable disease transmission to recipients from infected donor tissue (such as Creutzfeldt-Jakob Disease) through dura mater and eye tissue, HIV and hepatitis virus through organ and tissue transplantation as well as bacterial and fungal infections presented a primary public health concern. Second, the rapid growth of the industry with the development of new applications and technologies for processing human cells and tissues, coupled with increased demand and international commerce, presented different issues. Finally, voluntary standards established by certain organizations had not been uniformly followed, as they are not legally enforceable.

All these factors, among others, together with public demand for safe products, compelled the Agency to adopt appropriate solutions.
Since many of the products were not easily categorized into a regulatory niche, FDA undertook a new risk-based approach to provide the framework for the appropriate oversight.

Novel Approach
The approach, announced in February 1997 through two documents, “Reinventing the Regulation of Human Tissue” and “Proposed Approach to the Regulation of Cellular and Tissue-based Products” (the “Proposed Approach”), indicated that the level and type of regulatory oversight would be based on the risk(s) posed by a product’s characteristics and the commensurate degree of oversight needed to protect the public health.

This framework was expected to complement, but not replace, existing regulations governing traditional medical products subject to pre-market review and post-market compliance requirements.

The primary concerns addressed through the Proposed Approach were prevention of communicable disease transmission; assurance of safe processing and handling; claims of safety and effectiveness; monitoring the industry; and promotional claims.

The Proposed Approach identified two regulatory tiers: products regulated solely under provisions of Section 361 of the U.S. Public Health Service Act (so called “§361 Products” in the Proposed Approach, but more accurately “§361 Products” going forward) and would not be required to undergo pre-market review.

All others to be subject to this framework would be regulated under existing drug, device, and biological product regulations, in addition to new regulations addressing the incorporation of living biological materials into the finished product.

The Public Health Service Act provides the legal authority for FDA to develop and enforce regulations necessary to prevent the introduction, transmission or spread of communicable diseases through the distribution of medical products.

Under the Proposed Approach and subsequent rulemaking to implement the framework for regulating HCT/Ps, §361 Products are identified by: minimal manipulation of the source tissue through the processing stage; homologous use (i.e., the HCT/P performs the same function(s) in the recipient as the source tissue performed in the donor); freedom from combination with another article; absence of intended systemic effect; and absence of dependence upon the metabolic activity of living cells (except in cases of autologous use, use in first or second degree blood relatives, or reproductive use).

HCT/Ps not meeting these criteria would be regulated under the U.S. Food, Drug and Cosmetic Act (the “Act”) as devices, drugs, or biological products.

The Registration and Donor Screening Rules were subsequently published to implement aspects of the Proposed Approach. The Registration Rule has created a unified system for registering HCT/P establishments and listing their products.

Unified System
The Donor Screening Rule published on May 25, 2004, requires most cell and tissue donors to be tested and screened for relevant communicable diseases, with the type of testing and screening dependent on the type of tissue. The regulations promulgated under the Rule become effective on May 25. Testing and screening are not required for tissues obtained for autologous applications.

FDAs framework for establishing adherence to Current Good Tissue Practice (CGTP) was initiated approximately three years ago, with a proposed rule published on January 8, 2001. Significantly, the CGTP proposed rule stated that the Agency would require cells and tissues to be handled according to procedures designed to prevent contamination and to preserve tissue function and integrity.

The CGTPs incorporated in the proposed rule, included, among others, proper handling, processing, labeling, and recordkeeping procedures. The development and maintenance of a quality program by each establishment would be required to ensure compliance with CGTP.

In drafting the CGTP Rule, FDA re-evaluated each requirement of the proposed rule and considered the approximately 197 comments to the public docket, feedback from the industry and others through public meetings, and consultations with a number of different entities, to ensure that the requirements either directly prevent introduction, transmission, or spread of communicable disease or support such a requirement.

The Rule established certain “core” CGTP requirements. As a result, these requirements are viewed as the necessary minimum for assuring a safe manufacturing process and a safe product.

Important Changes
The CGTP Rule incorporates a number of important changes and additions to the requirements initially outlined in the proposed rule. Bowing to confusion and concern expressed in a number of public comments, the Agency struck from the CGTP Rule any reference to preservation of function. 

WEBLINKS FOR THIS ARTICLE
• www.fda.gov/cber/rules/gtp.htm
• www.fda.gov/cber/tiss.htm
In Silico Drug Discovery Using Molecular Fields

Cresset BioMolecular Discovery Sheds New Light on Hit and Lead Identification

Sue Pearson, Ph.D.

Traditionally, the pharmaceutical industry has used molecular structure data to determine how molecules will interact and, from this, generate drug-like molecules. However, one company, Cresset BioMolecular Discovery (Letchworth, U.K.), is building a business by challenging this perceived wisdom.

The firm, founded in 2001 with money from the Wellcome Trust’s Catalyst Biomedical fund, is offering a novel way of looking at molecules and their interactions.

Through 20 years of research at major pharmaceutical companies and the University of Cambridge, I have pursued the idea that molecular interaction is not really governed by the structure of the molecules,” explains Andy Vinter, Ph.D., CSO and founder of Cresset.

“It is the molecular fields around a compound that form an outer skin that are important, and this is why two structurally diverse drug molecules can have the same therapeutic effect. If these two compounds bind to the same region of a protein, their outer skins must be similar despite their structural differences.”

“We can now characterize the ‘skin’ precisely in a workable application. We called the company Cresset because a Cresset was a torch carried by medieval crusaders, and we like to think of ourselves as shedding new light on the problem of designing original, yet effective drug molecules.”

The firm originally provided its know-how to identify leads, hits, and pharmaco phores either as fee-for-service projects or collaborations with pharma and biotech companies.

“As well as building revenue, this is a great way to work with a large number of targets, which has meant we could really test our molecular field theory on a range of compounds. Fortunately for us it does work, and we have been able to help identify several interesting leads using it,” adds Dr. Vinter.

Field Testing

Following on from this success, the company recently launched its first software product called Fieldscreen™. This allows users to search through their own in-house databases, as well as commercially available compound libraries, to select sets of molecules with diverse structures but the same biological effects.

According to Dr. Vinter what makes Fieldscreen unique is that hit selection is achieved by analyzing and displaying the electrostatic, ionic, and hydrophobic fields around molecules. From this information key-binding regions can be identified and the bound conformation of a ligand can be hypothesized.

“This type of virtual screening can be a laborious process for companies in early-stage drug development, but Fieldscreen can perform the task in a fraction of the time,” states Dr. Vinter.

The science behind the molecular field approach on which Fieldscreen is based was originally developed to improve the handling of π-π stacking in aromatic systems and has been used for predicting biological function in drug-like compounds for over ten years.

“Fieldscreen can even be used to identify leads for more GPCR targets where there is no x-ray structural data available. The lack of x-ray data usually limits standard computational methods that can be used effectively to find new hits. Since GPCRs makeup around 40% of current drug targets Fieldscreen could offer a major advantage to those screening this target class where they have little structural data.”

“We are turning computer chemistry on its head and this is why we have made Fieldscreen available, so that the pharma industry becomes more open to performing virtual screening in this way,” adds Sally Rose, Ph.D., director of business development.

“However, we feel justified in pursuing our molecular fields’ approach. Now it is beginning to show good results. For example, we have been able to help find novel hits from screening only a few hundred compounds rather than hundreds of thousands. In other successful collaborations, we have provided the information for companies to replace peptide with nonpeptide and steroidal based drugs, as well as find novel leads from existing drug-like molecules.”

“The pharma industry is now crying for tools that are able to analyzing the amount of data coming out of HTS and combinatorial projects, and this is where our new modeling method really scores. We are there are still many areas of it that even we don’t understand,” concludes Dr. Vinter.

AT-A-GLANCE

Cresset BioMolecular Discovery

LOCATION
Bridge Rd, Letchworth Herts, SG6 4ET U.K.

PHONE
+44 1462 476320

FAX
+44 1462 476329

WEBSITE
www.cresset-bmd.com

PRINCIPALS
Beatrice Leigh CSO
Andy Vinter, Ph.D. founder and CSO
Sally Rose, Ph.D. director of business development

NUMBER OF EMPLOYEES
7

FOCUS
Cresset BioMolecular Discovery is a drug discovery technology company that offers in silico applications for the analysis of molecular fields to identify leads and hits from compound libraries. The firm provides its technology to pharma and biotech companies as both project based services and a software product called Fieldscreen.

In summary, CGTP requirements cover all aspects of production, including: cell/tissue recovery; donor screening and testing; donor eligibility determinations; processing and process controls; supplies and reagents; equipment, facilities, and quality systems; donor eligibility requirements and will be minimized affected by the rule. Information published with the rule demonstrates the size of this undertaking of great importance.

Publication of the CGTP Rule completes the set of regulations proposed in 1997 and issued in proposed or interim form since 2001 to implement FDA’s framework for the regulation of HCT/Ps as tissue-like substances. As such, they are fundamental components of the health care delivery system and must be manufactured to help identify several interesting leads using it,” adds Dr. Vinter.

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Screening Continued from page 2

Serono is using the Array Scan II, a cell analyzer from Cellemics (www.cellemics.com), to look at multiple endpoints in parallel and is bene- fitting from the miniaturization of drug molecules and also at nuclear translocation of key proteins.

Dr. Horstmann's team is developing a technique called Frontal Affinity Chromatography (FAC), in which the target is trapped within a matrix, bypass- ing problems posed by chemical binding of the protein to the column. The mixture of compounds to be screened is infused onto the column, and the most weakly bound compound comes off first, and the mixture is analyzed on a mass spectrometer. This allows real-time analysis. FAC/M has shown promise with a mixture of 100 tripeptides binding onto a CHO cell membrane. The team has also looked at Factor Xa, a clotting pro- tein that is deactivated by conven- tional affinity chromatography.

Another new technique, with many potential screening applica- tions, is Respèreomic Screening Technology (RST) from Luxcel Biosciences (www.luxcel.com), which uses fluorescence quenching of a probe to give a measure of oxygen uptake by cells, organisms, oxygen-dependent enzymes, and metabolites.

"RST is amenable for the de- velopment of very sensitive cell-based assays," said Richard Fernandes, Ph.D., founder and CEO of Luxcel. Oxygen uptake is an important biomarker, giving a very direct beating myocytes (heart cells) and gives a readout like an ECG so that the importance of the QT interval on the QT interval can be assessed.

Martin Traebert, Ph.D., group head of in vitro safety pharmacology and in phloritoxic development at Novartis, said that hERG screening can be performed with the Fyscreen® 8500 patch clamp rig which creates whole cell systems. The system com- pares well with conventional approaches, as seen by experi- ments with E4031, a drug that is known to block hERG.

Novel Cell-Based Assays

There are other innovative approaches to cell-based screening. As discussed at the BioFocus Discovery Technology platform for screening and generation of human mono- clonal antibodies. They put the "bait" (a protein target) and an antibody together in a yeast cell and linked to a reporter gene.

The system can look at any type of protein target, including intracellular cellular proteins, secreted proteins, membrane proteins, and viral pro- teins. Work so far has involved screening antibodies to CXCR4, which is overexpressed in many metastatic cancers, and CCR5, a co-receptor for HIV.

Many of these screening approaches are being developed by companies such as cyclic AMP and inositol (IP3) triphosphate.

Split and Mix Techniques

Assays are being developed in order to tackle other challenging problems. Michael Orgeln, Ph.D., of the department of chemistry, York University, Toronto, pointed out that screening mixtures of compounds has posed difficulties in the past because of an aver- aging effect of assay results which makes it hard to single out those compounds with true potential.

"This has produced a tendency to shy away from mixtures," said Dr. Orgeln. Yet not rising to this chal- lenge may mean that companies are missing out on valuable combina- torial chemistry collections synthe- sized by "split and mix" techniques and other approaches.

Dr. Orgeln's team has been developing a technique called Genetastix (www.genetastix.com), which is another company develop- ing a range of assays for kinase inhibitors. They are also looking at another popular target class—G-protein coupled receptors (GPCR). Their approach to GPCR activation assays involves the measurement of second messengers such as cyclic AMP and inositol triphosphate.

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tissues and additional require- ments where necessary for product safety and effectiveness. Clear, enforceable requirements will protect the industry as well as the products and help ensure the continued availability of products deemed medically necessary. Predictable regulatory require- ments support innovation in techn- ology and the industry and mini- mize elements of uncertainty in the product-development process.

Finally, reducing the risks of communicable disease transmis- sion through HCT/Ps will result in improved product safety, improved outcomes for patients, and enhanced effectiveness when associated with treating complica- tions from use of contaminated products, all helping to maintain the public confidence.

However, certain challenges still lie ahead, as articulated at the February 1 1 D b a s e e n c h a n g e w i t h t h e staf f of the Office of Cellular, Tissue, and Gene Therapy at FDA's Center for Biologic Evaluation and Research.

Among others, reliance on existing statutory authority limits the Agency's ability to address tissue quality and functionality, and effi- cient methods of hospital-based treatments is a continuing prob- lem. In addition, the Agency has not yet finalized its proposed rules regarding reproductive tissues.

Next steps and priorities in mov- ing forward, as viewed by FDA, include, among others looking to rapidly detect, analyze and respond to communicable disease transmis- sion; providing outreach, training and guidance on implementation of the rule; defining license crite- ria for hematopoietic stem cells; and collaboration with the international community to enhance disease prevention and control.

Future guidance documents can be anticipated to help the industry apply the HCT/P regula- tions to specific product classes or applications.