

**Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC)
to the Center for Biologics Evaluation and Research (CBER),
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BRIEFING DOCUMENT

Response to OCTGT Office Site Visit Report

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Introduction

This document is a response to the report of the site visit committee that conducted an office-wide evaluation of the research programs of the Office of Cellular, Tissue and Gene Therapies (OCTGT) on September 29, 2005.

The site visit committee (roster included in Appendix 2) provided a detailed report that the CTGT Advisory Committee approved on February 10, 2006. OCTGT is grateful to the site visit committee for their time and effort, and for their insights and suggestions.

This response describes how OCTGT is implementing many of their suggestions, and notes changes in the OCTGT research management process. The site visit subcommittees for specific product areas (e.g., gene therapy, cell therapy) in some cases addressed similar or overlapping issues. To avoid redundancy, the organization of this response does not follow the exact format of the site visit committee report.

We appreciate the support of the committee for research in OCTGT, for example the following comments from the attached report:

... The fact is though that new treatment modalities like cell and gene therapy will never move from effective laboratory reagents to products for patients with disease unless the FDA maintains a strong cadre of researcher-reviewers who can participate in the development of paradigms for investigation and licensing of these novel therapeutics.....The Gene Therapy research program within the OCTGT is seen as a critical, productive, and innovative group of investigators.....The productivity of the current principal investigators is very strong, both in terms of scientific merit, and congruence with the overall mission of the FDA.....The science being conducted at OCTGT in the Cellular Therapy area (as it relates in broad terms and to stem cells) is of a high standard and is generally considered appropriate for the mission of the organization.

We also appreciate their critical insights and suggestions for change.

COMMENTS & RESPONSES

Comments quoted from the Site Visit Report are in italics, responses in regular type.

Research management

OCTGT priorities, horizon scanning, annual program reporting and assessment

Support formalizing the research project approval process within OCTGT. It is important that this process is designed and implemented in a manner that stimulates innovation and creative problem solving. It is recommended that the process include open communication of strategic goals including long term and short term priorities, a mechanism for annual review and alignment of projects against goals, a mechanism for review of the process itself to obtain feedback from all levels of scientists within the OCTGT regarding the effectiveness of the process and a mechanism for modifying the process to respond to and address the changing needs of researchers/regulators.

Response: We agree that research management within OCTGT should encourage innovation and creative problem solving. OCTGT is participating in development of research management practices for use throughout the Center for Biologics Evaluation and Research (CBER). The CBER Research Leadership Council has undertaken a number of initiatives to provide explicit goals and transparent procedures. In each Office, these initiatives included an initial analysis of the regulatory workload, horizon scanning for anticipated regulatory challenges, analysis of gaps in scientific expertise needed to handle the challenges, and announced Office priorities. Annual program evaluations are also included.

Periodic horizon scanning in OCTGT will continue to invite input from the staff, both researcher-reviewers and full-time regulatory scientists, who are also consulted regarding the research management procedures, priorities, goals, and research recruitments.

In 2007, an FDA-wide review by outside experts forming a subcommittee of the FDA Science Board provided additional valuable comments about the research programs and priorities. The Science Board subcommittee was provided with a great deal of information about CBER research programs as well as its regulatory responsibilities. Appendix F of the

FDA Science Board report discusses CBER specifically, and is attached here (see Attachment 3).

Given the inability to respond quickly to changes in the field, it is imperative that CBER develop a 2-year and 5-year approach outlining the most critical issues in the field and defining where they believe they can make a significant contribution.....One proposal that would allow significantly easier evaluation of each area of research within the OCTGT is to provide a short summary of how each laboratory and the specific projects in each laboratory fit with the 2-year and 5-year plan for CBER. It is difficult at present to understand how some of the programs do so.

The new research management process described above provides for an annual program evaluation, but once every four years a much more detailed and intensive evaluation is performed. This includes laboratory site visits by outside scientific experts as part of a Cell, Tissue and Gene Therapy Advisory subcommittee, providing more detailed discussion. Since the CBER and Office priorities will now be explicit and announced in advance, the site visit materials will include discussion of the relation between the research and the priorities. Office management will also review research program directions as part of the site visit process. In addition, CBER is initiating internal review of individual principal investigators (PIs) once every four years by the CBER peer review committee.

Funding sources

It will be important that this office work to improve the research environment, by promoting support for cores, by insuring sufficient funding for productive investigators, and by liaising with other agencies to enhance funding opportunities.

Response: In 2007, OCTGT PIs obtained funding from a variety of sources, including the Interagency Oncology Task Force program, an interagency agreement with National Institute for Allergy and Infectious Diseases (NIAID), a Department of Health and Human Services (DHHS) counter-terrorism program, Cooperative Research development Agreements (CRADAs), and royalties. Investigators also successfully competed for funding from supplementary sources within the FDA, including the Critical Path initiative and the pandemic influenza program.

OCTGT has also identified a potential future grant source for research related to cellular therapy for victims of radiation or burn-blast trauma, and is currently investigating the possibility of a new interagency agreement with National Heart Lung and Blood Institute (NHLBI).

CBER provides support for the animal care facility, as well as a core facility performing synthesis of oligonucleotides and peptides, amino acid analysis, DNA and amino acid sequence analysis, and mass spectrometry analysis. In addition, OCTGT supports a shared flow cytometry facility and equipment service contracts.

Amend current rules to provide a mechanism for obtaining NIH funding.

The Office of Vaccines Research and Review (OVR) has established an interagency agreement (IAG) with NIAID that provides a precedent for OCTGT. Expansion of such an

IAG to cover areas in which OCTGT interests overlap with those of OVRR and NIAID would support studies of tumor vaccines, cell substrates, adjuvants, and other biological products.

In addition, cellular products for treatment of acute radiation syndrome are of high interest to both OCTGT and NIAID. The goals of an IAG would be to enlist CBER scientific expertise and collaboration to develop improved methods for characterization and appropriate pharmacologic and toxicologic testing for cell therapy products. The initial focus would be therapies for acute radiation syndrome and other conditions that could be caused by terrorist attack.

Suggest formation of a committee to study and report on the ramifications of establishing an independent research foundation that would be established to provide an additional source of research funding to OCTGT.

As funding becomes limited, new ways should be found to allow OCTGT scientists to apply for extramural resources, without conflict of interest, including a FDA-based resource like the Henry M. Jackson Foundation for DOD.

Response: Title VI of the recently enacted Food and Drug Administration Amendments Act of 2007 created the Reagan-Udall Foundation, which is described on the FDA web site. This foundation will be a private, independent, nonprofit entity. It is too early to tell how its goals and procedures will evolve.

Recruitment and retention, mentoring, professional development

With respect to recruitment, retention and training of researchers, the agency seems to be doing a very good job, although it was noted that many of the recruits are from other agencies like the NIH.

Response: DCGT recruits the best scientific talent in response to changing research needs, regardless of affiliation. Specifically, when DCGT identifies a gap in its scientific expertise, it forms a search committee with the concurrence of CBER about the recruitment area, and advertises nationwide to identify candidates. As part of the competitive selection process the committee reviews a candidate's accomplishments, invites the candidate to present a public seminar and schedules interviews with CBER staff.

Since 2000, the fields of expertise covered by these recruitments included cell biology/development, adenovirus vectors, herpesvirus vectors, organ development, and proteomics. The investigators recruited to DCGT to establish independent programs have come from outside the government (American University, Johns Hopkins University, University of Chicago, the Jackson Laboratory, and the University of Kansas).

In light of tight budgets, OCTGT is challenged to develop and maintain the required expertise to be prepared for an expected rapid rate of growth in applications in this area over the next few years. Furthermore, this office represents technical areas that suffer from poorly developed regulatory criteria, making it even more critical that staff be competent to contribute scientific as well as regulatory insight. Recruitment from within FDA appears to

be a strategy....It is unclear how extensively the post doctoral programs are used to assist in recruitment; in principle this could be an important supply of high quality scientists.

Response: As described above, PIs are selected by a public, competitive recruitment process. CBER postdoctoral fellows who apply for PI positions are also evaluated along with other applicants. They can also compete for positions in the full-time review staff or the division and office management staff.

CBER must continue to balance the potentially conflicting nature of the research mission, specifically the scientific interests of the investigators, and the need for the agency to conduct mission-specific research. While CBER appears to have done an excellent job in recruiting investigators who can balance these potentially conflicting missions, this is an area that requires continuous monitoring. If the FDA begins to micro-manage research programs, it will likely impact the quality of work being performed and negatively impact retention.

Response: We appreciate this concern. OCTGT research-reviewers are performing mission-relevant research that satisfies scientific interests as well as providing information critical to our regulatory mission. We maintain this balance by identifying broad research priorities that are relevant to our regulatory mission, and then allowing PIs to develop their own approaches to address these priorities in their research. In order to assure that OCTGT addresses public health goals, maintains productive programs, and engages in successful advocacy for the research programs, a certain amount of research management is important, but we agree micromanagement is not necessary and would not be wise.

Mentoring is an area that may require additional attention. ... Junior investigators should receive mentoring about balancing the demands of research and regulatory workload. The mentoring committee should be distinct from the investigator's direct supervisor and should also function to provide the agency with feedback as to ways it can promote success of an individual investigator.

Response: CBER has instituted a Mentoring Program that is available to staff of all types regardless of seniority. Volunteer mentors and those who seek mentoring are paired based on experience and general area of expertise. This program is intended to address the types of needs the Committee noted: e.g., help with prioritizing research and review, multitasking, and dealing with supervisory problems, provided by someone who is not the supervisor of the staff member. During the program's first year, 15 mentor-mentee pairs set goals achievable within the year, though they could continue longer. In addition to this program, PIs supervising laboratory staff provide specialized research mentoring. OCTGT also encourages informal interactions and discussions about research, regulatory, and career issues.

Specifically, developing a curriculum for fellows that enhances their research experience should be a goal. For example, many academic institutions are providing fellows with training in ethics, grant and manuscript writing, and other professional development

workshops. These efforts can provide added value to the post-doctoral experience and can be used as a recruitment tool.

Response: We strongly agree, and currently support training and professional development for postdoctoral fellows and all other staff. Investigators try to provide post-doctoral fellows the opportunity to attend one professional society meeting/year, within the constraint that travel for post-doctoral fellows must be paid from laboratory research budgets. Fellows can also present their work at the annual National Institutes of Health (NIH) Research Festival, in seminar series of the various campus scientific Interest Groups, and in journal clubs and work-in-progress series at CBER.

The following opportunities are also available to our postdoctoral fellows locally:

- CBER training courses that include communication skills, scientific and technical writing, scientific writing for publication, making high-quality presentations, teamwork, managing time and priorities in the CBER environment, and negotiation skills.
- NIH training courses in scientific speaking, scientific writing, interview skills, and grant preparation.
- Courses in the FAES graduate school in a variety of subject areas.
- Representation at the NIH FelCom (campus fellows committee), which aims to enhance training opportunities and sponsors many training courses and seminars that NIH postdoctoral fellows are eligible to attend.
- Participation in an annual scientific job fair held as part of the NIH Research Festival
- Yearly NIH workshops on such subjects as résumé preparation and diverse career options (e.g., teaching, patent office, drug development, academia).

It is critical for reviewers to have insight into emerging areas where they may need to recruit. The most efficient way to accomplish this goal is to insure that FDA scientists regularly attend [cell and] gene therapy conferences.

We agree that staff should attend conferences regularly, and we arrange for them to do so. In 2007 researcher-reviewers and regulatory scientists attended the American Society for Gene Therapy Conference, the WilBio Viral Vectors and Vaccines Conference, International Society for Cellular Therapy, International Society for Biological Therapy of Cancer, American Association of Immunologists, and other conferences. Many of them presented invited talks.

Resolving conflict of interest issues so investigators can attend small (usually commercially sponsored) meetings where unpublished data are likely to be presented is critical as is ensuring they can speak at or attend academic departmental seminars (which also may have commercial support).

Suggest introducing new mechanisms making it easier for researcher/reviewers to attend scientific, professional meetings and accept travel reimbursement from industry sponsored meetings provided the meetings are open. One idea is to have travel contributions go into a travel support pool so that specific source of meeting sponsorship is blinded.

Response: To adhere to conflict of interest rules yet permit investigators to give seminars or participate in conferences when they cannot accept the reimbursement offered with an invitation, our current approach is to address individual cases and use our intramural resources to support travel. A second approach applies under less frequent circumstances: the CRADA rules allow limited industry-supported travel that is included in a CRADA proposal. A third approach may be developed in the future involving the Reagan-Udall Foundation, if that organization is permitted to accept funds that an individual could not, and use them to create a pool of funds to support travel.

Sabbaticals and reverse sabbaticals:

Response: We recognize the benefits of sabbaticals for FDA staff, and the leadership considers them on a case-by-case basis. Some have taken place, but they are limited by the impact of staff absences on the workload of remaining staff. Another option for staff professional development is a government “detail” to permit a temporary assignment in another environment within CBER or other parts of FDA.

CBER also permits reverse sabbaticals, and has hosted outside researchers in the Center’s laboratories. For example, OCTGT has hosted scientists from Europe, Japan, and Korea who came to learn about FDA regulation, and, in some cases, to participate in laboratory work. Although visitors do not have access to confidential regulatory information, they can attend public meetings and learn about regulatory policies and procedures. In addition, the Interagency Oncology Task Force (IOTF) provides a form of reverse sabbaticals by accepting fellows who participate in both mission-related research and mentored review activities (see Tumor Vaccines section below).

The committee was asked to respond how to recruit, retain, and train scientists in the field. Clearly this is a dynamic field and investigators are moving in and out of it very quickly. To be able to attract high-quality scientists to the FDA, given the limitations of funding and time, it is important to provide several assurances. An important issue is autonomy. Investigators in this field are going to want to be able to move forward in novel and innovative ways. Defining a 2 and 5 yr CBER plan could facilitate this and provide a basic framework for investigators.

...Given limited time and resources, the ability to do high-quality science is going to have to be addressed. Providing post-doctoral fellows and high-quality staff scientists will facilitate this. It is important not to wait until the number of applications is overwhelming to provide scientific support to the investigators with regulatory responsibilities.....The ability to publish and attend scientific meetings must be ensured.

Response: We agree that these are important issues.

In order to address the issue of support for our investigators, we use forward funding of ORISE fellowships to the maximum extent possible. The FDA Critical Path initiative has helped recently with some of the resources deployed intramurally. In addition, investigators not only have the opportunity to publish and to speak at scientific conferences; such activities are expected and are criteria for promotion.

We also agree that preserving autonomy is important, and our approach to implementation of the new research management process is intended to allow that by setting priorities broadly.

The agency is developing a formal FDA-wide program to recruit fellows who wish to learn about FDA science and receive mentored review training. The Reagan-Udall Foundation mentioned above established policies for funding such training fellowships. That provision is intended to expand the opportunities in the future, but details are not yet available.

Communication and collaboration

Currently it is stated that research work-in-progress seminars occur “periodically” and that there are web-based searchable annual reports. These critical tools should be evaluated for their usefulness. Perhaps the internal reports should be searchable across the FDA to promote collaboration. Perhaps the work in progress seminar should occur more regularly to allow leadership to determine if given programs fit with the long-term goal of the organization.

Response: Brief research program descriptions and lists of publications are available on our external website. In a new FDA-wide initiative, research programs are listed in an FDA research database [REDACTED], in addition to being listed in our own more extensive and detailed CBER research database.

In response to the site visit comment, OCTGT increased the frequency of Office-wide work-in-progress seminars to once per month for a year. This year they are being held once every two months due to schedule conflicts with other meetings. However, it should be emphasized that work-in-progress talks within each of the three laboratory branches are held more often, and managers are welcome to attend.

It is clear that the CBER Research Program is highly collaborative. However, this collaboration primarily appears to be internal; the opportunity for external collaboration should be maximized both across the FDA as well as with NIH and other governmental organizations. This clearly provides an opportunity for synergy and to maximize outcome with the limited resources that exist.

Response: OCTGT researcher reviewers continue to explore opportunities for external collaborations. Listed below are major collaborations of PIs in each branch with outside organizations.

Cellular and Tissue Therapy Branch (CTTB) collaborations

NIH: National Institute of Child Health and Human Development (NICHD), National Cancer Institute (NCI), NHLBI, National Institute of Neurological Disorders and Stroke (NINDS) NIH Mouse imaging facility

Other: National Institute of Standards and Technology (NIST), Centers for Disease Control and Prevention (CDC), New Jersey Medical School, Georgetown University, Mayo Clinic, M.D. Anderson, University of California San Diego, Catholic University of Leuven, Belgium

Gene Therapy and Immunogenicity Branch (GTIB) collaborations

NIH: National Institute of Mental Health, NIAID, NHLBI, Vaccine Research Center; National Toxicology Program with National Institute of Environmental Health Sciences (also includes partnerships with University of Washington, Cincinnati Children's Research Hospital and Hamburg University)

Other: Scripps Institute, CDC, University of Georgia

Tumor Vaccines and Biotechnology Branch (TVBB) collaborations

NIH: NCI, NIAID, Molecular Carcinogenesis Unit in National Institute of Dental and Craniofacial Research

Other: University of Michigan, Naval Medical Center, University of Maryland, Mayo Clinic

Product and public health areas supported by the research programs

Gene therapy

OCTGT has recruited knowledgeable individuals in the area of Pharm/Tox who have also been important contributors to the Office's educational efforts. A challenge for the Office and Sponsors is the limitation of classic Pharm/Tox models in assessing the safety of biologic products. The OCTGT should consider adding an individual with a research interest in development of new Pharm/Tox models for cell and gene therapy products to their current review staff.

Response: We appreciate the committee's vision in this area. Identifying safety issues in our novel product areas is difficult yet critical.

In terms of current activities, the Pharm/Tox full-time review staff includes individuals interested in new approaches to testing cell and gene therapy products, including some staff with veterinary background or experience with animal models.

Although we lack classic pharm/tox research programs, our research programs currently include a preclinical model of adenoviral vectors that has been quite useful in identifying potential causes of clinically observed pulmonary adverse events.

Other projects relevant to pharm/tox in a broad sense include safety testing of cancer vaccines in murine models. In addition, OCTGT is collaborating with the National Toxicology Program (NTP) to answer questions regarding retroviral vector-mediated insertional mutagenesis.

Individual areas of expertise that are likely to be important going forward and that should be considered in new hires for the gene therapy group include:

Strong expertise in immunology, which will continue to be important for gene therapy product immunogenicity determinations.

Response: We agree that expertise in immunology is very important in the review of gene therapy products; and in fact, of all of our products. GTIB has several immunologists. Since the Office site visit in September 2005, we strengthened those programs with the addition of two staff fellows who do research and regulatory review. While there is research in GTIB on immune responses, we recognize that additional studies would be desirable. We are currently recruiting an immunologist due to the unexpected loss of one from our staff.

*Large scale studies, not being done by sponsors/investigators, could include:
Reproductive toxicology for a range of vectors. This will continue to be important as
gene therapy is developed for younger populations.*

Response: As mentioned above, OCTGT staff collaborates with NTP; and a long-term, large-scale study of plasmid DNA bio-distribution and germ-line alteration has been accepted as a priority project (not yet initiated) of the National Toxicology Program. CBER has requested that NTP gather information regarding PCR capabilities of their various contract testing labs, so the Center's scientists can verify that such studies would be done with high sensitivity and robust methods that minimally meet, but ideally exceed, our current recommendations for PCR-based vector bio-distribution studies.

In vivo tracing and imaging was mentioned by the committee in several places as expertise that would be important.

Response: We agree that *in vivo* tracing has become increasingly important as tracing agents are used more in the preclinical and clinical arenas. In the case of cellular therapies, products could be followed in the body during the migration and differentiation necessary for them to perform their functions.

Concurrent development of tracing and imaging techniques in animal and human studies could benefit CBER by providing increased knowledge with which to design clinical trials, and in predicting clinical distribution of various products.

To accommodate development of expertise in these new technologies, we are incorporating them into ongoing research programs. For example, investigators in CTTB and TVBB have recently begun performing *in vivo* tracking studies based on cell labeling using paramagnetic-, luminescence-, and fluorescence-based methods in rodent models. These studies use magnetic resonance imaging and charge-coupled device camera techniques (Luminex) available through the mouse imaging facility of NINDS, NIH. This expertise will contribute significantly to the regulatory process.

Cell therapy, combination product, and xenotransplantation

Note: in our responses, we have used the term *cell-based products* to include products containing living cells, whether or not they are given in combination with other components.

a)....a number of the programs are narrowly focused and not really relevant to developing the regulatory process in the areas of cellular therapies and most probably reflect the past research interests of staff recruited to the division.

Response: Priorities for the recruitments carried out in research areas related to cell therapy products were identified prospectively with concurrence of Division, Office, and Center management. The process used in those recruitments is the one described above (see page 4).

b) If cell signaling is going to remain a focus of research investigators, it would seem that signaling with regard to stem cell differentiation might be a more important use of resources.

Response: Work on signaling pathways controlling cell state and cell fate has important implications for regulation of cell therapy products, as it addresses the mechanisms controlling the behavior of cell-based products during manufacture and following administration to patients. Studies of the particular cell signaling pathways crucial for tissue development in a wide variety of animal models are needed to enable us to develop more sensitive assays than are currently available to predict cell behavior and outcomes. These general mechanisms apply to all cell-based products, including stem cells.

As the field of cell-therapy-based medical products continues to evolve, we will need to initiate studies in additional areas, as recommended by the site visit report. DCGT welcomes those suggestions for future work.

Toxicology studies. How do we design experiments to do toxicology studies in animals with cellular products from a different species? Specifically, traditional pre-clinical animal safety studies cannot be performed long term with human cells in most animal models because of rejection issues. Even with immunosuppression only short term studies can be performed.

Response: The issue of appropriate animal models for human cell therapy products is an extremely important Critical Path challenge that is recognized widely within FDA, NIH, the Department of Defense (DOD) (relevant to counterterrorism and the animal rule for efficacy), and in the stakeholder community.

In many cases, advances will require new homologous mouse models of human conditions. While DCGT lacks the resources for a broad initiative in this area, we expect that many sectors of the scientific community will make important contributions in this area.

We are also exploring alternatives to traditional animal studies. OCTGT experts are seeking scientific collaboration with various organizations who wish to reduce animal testing through development of cellular, biomarker-based *in vitro* toxicity assays (the NTP Interagency Coordinating Committee on the Validation of Alternative Methods and the the Interagency Center for the Evaluation of Alternative Toxicological Methods).

Batch variability. Because cells are complex biological systems there is bound to be variability between different batches of the same cells. While there are many parameters that can be measured, how do we determine the correct parameters to measure to ensure safety?

Response: We agree that this is a critical challenge, and we are addressing this question through specific research projects, using, for example, genomics and proteomics technologies. OCTGT staff published a paper in 2005 on the identification of biomarkers to determine quality parameters for cell substrate; and they are now pursuing research projects in MRC5 cells. Plans also include studies of the proteomics and genomics of stem cell populations and differentiated cells.

OCTGT research priorities also include development of assays to predict the safety and efficacy of cellular products. For example, OCTGT is collaborating with NIST on a

project that uses computerized measurements of cell size to find correlations between the size of mesenchymal stem cells, their proliferation rates, and their ability to differentiate along appropriate pathways.

Another novel approach proposed to the Critical Path program uses high-throughput genomic screens to find key gene products that could be used as product-characterization biomarkers.

Combination Products. Many cell products will be combination products either with classical devices or encapsulation technologies or in other formats. How will the regulatory process deal with these combination products in the future?

Response: OCTGT research priorities that address the need for development of assays predictive of safety and efficacy of cellular products, including the cancer vaccines and immunotherapy discussed above, can be extended to combination products that have cellular components.

In addition, over the last five years the FDA has made significant strides in improving and clarifying the procedural and jurisdictional issues surrounding the regulation of combination products. These efforts are most prominent in the creation of the Office of Combination Products (OCP) in the Office of the Commissioner (<http://www.fda.gov/oc/combination/>).

OCTGT takes an active role in the development of regulatory policies for cell-based combination products, including cancer vaccines and immunotherapy products, whether they are cell-scaffold or encapsulated cellular products. This includes frequent and extensive consultation and collaboration with The Center for Devices and Radiological Health (CDRH) and The Center for Drug Evaluation and Research (CDER) concerning cellular, scaffold, and encapsulation materials, as well as cytotoxic drugs, antibodies and therapeutic protein combinations.

CDER, CDER, and CDRH have taken numerous steps over the last few years to facilitate timely and effective review of cell-scaffold products. These Centers have established collaborative tissue engineering and oncology product teams at both review and management levels. The teams devise joint solutions for scientific, regulatory review, review management, and policy issues as they arise; develop joint guidances that address both device and cellular components within a product area; hold continuing education seminars in particular areas of interest; maintain combined participation in outside standards organizations (such as the American Society for Testing and Materials, ASTM), and co-sponsor joint public workshops on issues pertinent to cell-scaffold products and to cancer vaccines and other agents.

Prudent regulation of these products necessitates regulation of many “classical” devices used in the collection, processing and delivery of human cell and tissue products (HCT/P).

In addition, the Committee felt that more emphasis should be placed on large-scale collaborative efforts in areas like biomarker identification, proteomics and bioinformatics. We recognize and acknowledge that efforts are being made in these areas but the Committee believes more emphasis needs to be brought to the forefront.

Response: In addition to the intramural research mentioned above, CBER physicians and scientists are active participants in the Biomarker Consortium, and its representatives serve on the metabolic, oncology, immunology and inflammation, and neuroscience subcommittees.

The Biomarker Consortium is a Critical Path Initiative of the FDA comprised of clinicians and scientists from FDA, NIH, and industry. The overall goal of the Consortium is to facilitate the identification, testing, and validation of biomarkers that can be used to characterize products or monitor clinical trials, thus accelerating the rate of development of new drugs and biologics. New research proposals are critically reviewed and, if successful, are recommended for funding. See also the bioinformatics section below.

It was thought that the agency ought to have procedures in place to be able to recognize and anticipate future directions in the development of the science behind cell-based products and therapies in order to be proactive rather than reactive to new developments.

Response: We agree that this strategy is important; and as noted above, OCTGT's horizon scanning process gathers staff input on where the science in our regulatory field is headed. Moreover, an Office-level leadership meeting held in November, 2007, provided a venue to discuss research priorities.

The Office Site Visit committee also provided valuable input concerning the directions anticipated to have a significant impact on this field. In response to site visit recommendations after a previous proteomics researcher-reviewer left CBER, DCGT recruited an expert in proteomics in 2006 to start a new program in TVBB.

Use of information from pre-submission inquiries to inform direction the field is taking is a very good way to identify emerging product areas.

Response: This strategy for identifying emerging product areas is underway, with considerable pre-pre-investigational new drug (IND) consultation and encouragement of pre-IND meetings in all OCTGT product areas. A recently established computerized tracking system in CBER will facilitate analysis of the number and distribution of pre-IND's by product type. However, pre-IND meetings do not always predict workload, since not all sponsors elect to have pre-INDs.

Another agency initiative is the invitation for Voluntary Genomic Data Submissions, encouraging interaction and discussion by sponsors and agency staff (see bioinformatics section below).

Cross-species (xenogeneic) comparison of stem cells and progenitor populations are likely to play an increasingly large role in the field. Understanding which stem cells must be used in preclinical studies, what markers are appropriate, and what characterizations are important, are areas where FDA research labs could have a major impact.... Defining FACS based markers for specific cell types or defining broad-based potency assays could likewise, have a major impact.

Understanding allogeneic and xenogeneic cell potentials for cardiac repair....is] also critical.

Response: We agree with the site visit committee about the importance of efforts in this area. DCGT scientists, in studying the immune response to differentiated progeny of human embryonic stem cells (hESC), have explored which markers may reliably identify cardiomyocytes, the differentiated progeny of the hESC. In addition, DCGT researchers' work with genetically altered mice aims to identify the cardiac progenitor cells arising from embryonic stem cells.

Counter-terrorism

As the agency becomes part of the Bioterrorism efforts, it should clearly state the capacity and time lines envisioned for potential responses. The staff is still limited in number and resources and others outside the agency should have a realistic understanding of the capacity within OCTGT.

Response: OCTGT preclinical, clinical, and product reviewers have participated in many scientific discussions with Defense Advanced Research Projects Agency (DARPA), DOD, and NIAID to give FDA insight and guidance regarding development of new products to counter the effects of bioterrorism. Such products would include new vaccines and treatment for infectious disease and cellular therapies for acute radiation syndrome.

Research programs in DCGT have received NIH, FDA, and DHHS intramural funding for counterterrorism projects relevant to influenza, filovirus, Venezuelan equine encephalitis virus, and cellular therapies for acute radiation syndrome. Regarding the regulatory process and requirements, OCTGT staff has had several discussions with DARPA, NIAID, and DOD regarding use of the animal rule for efficacy studies used to support efficient development of cell therapies for acute radiation syndrome. Responses to emergency events would of course take less time if products had already been reviewed.

Tissue bioengineering

Developing more of an expertise in bioengineering and biomaterials is likely to be important in cardiovascular repair as well.

... Specifically in the area of tissue engineering, collaborations are used to provide needed expertise in cell/scaffolding research. Specific areas of expansion include discovery and validation of biomarkers and assays for biomarkers.

Response: The DCGT and NIST collaboration on mesenchymal stem cell (MSC) metrology mentioned above includes characterization of MSC responses to several different extracellular matrix biomaterials. In addition, we will leverage research collaborations with interagency partners, such as CDRH's Office of Science and Engineering Laboratories; and NIST's Chemical Science and Technology Laboratory. This work is especially important since MSCs are currently used in cardiac repair clinical trials.

OCTGT has also been actively involved in the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group, organized under the auspices of the Subcommittee on Biotechnology, National Science and Technology Council (NSTC). In June, the NSTC released the MATES written report, "Advancing Tissue Science and Engineering: A Multi-Agency Strategic Plan," which outlines a strategic plan for the United

States government activities in the tissue engineering. The plan stresses the need for collaboration between regulatory and funding agencies. As an initial implementation step, FDA (OCTGT and CDRH) co-sponsored a public workshop with NIST to discuss the evaluation of cell/scaffold medical products in order to determine which test methods are currently available, and which new analytical procedures should be further researched. Participation in MATES benefits the FDA by encouraging other agencies to contribute to the development of technologies that will help improve product evaluation.

Tumor vaccines

The OCTGT has a commendable relationship with NCI that allows for shared information, training opportunities and interactive research programs. It needs to maintain and expand this relationship, particularly as the fields of high technology, such as genomics, proteomics, and bioinformatics converge, requiring costly investment both in personnel and equipment. Partnerships with other institutions such as NIAID are also good investments, in order to achieve rapid entry of new types of vaccines into clinical trials. Lastly, the OCTGT should maintain its leadership in Flow Cytometry for analysis of biomarkers in patients and regular capital investment for new updated cell analyzers and sorters is key for success.

Response: FDA routinely organizes workshops in collaboration with NCI (four in 2007) to bring together academic, corporate, and regulatory scientists and clinicians to discuss development of therapeutic cancer vaccines and immunotherapies. These workshops highlight and foster the collaborative efforts between innovators and regulators.

For example, on Feb. 8-9, 2007, FDA and NCI jointly sponsored a workshop entitled, "Bringing Therapeutic Cancer Vaccines and Immunotherapies Through Development to Licensure." This workshop attracted more than 350 attendees from academia, industry and government who are involved in product development and preparation for licensure. Several OCTGT scientists organized, presented and moderated sessions at this workshop. Individuals and companies gained important insights into the efficient development of cancer vaccines and immunotherapies, as well as strategies for avoiding roadblocks to product development.

This workshop enabled participants to provide feedback to regulatory agencies and strengthened the partnership between FDA and NCI. In addition, FDA gained critical insights for developing guidance documents to facilitate clinical development of these important products.

CBER played a key role with the National Cancer Institute, NIH and FDA in the establishment of an Interagency Oncology Task Force (IOTF) to train a cadre of scientists in research and research-related regulatory review so that they can develop skill sets for both processes. This program coordinates the NCI-FDA fellowships (<http://iotftraining.nci.nih.gov>), which focus on the development and regulation of new medical products (e.g. cellular therapy products and tumor vaccines) and provide cross-fertilization between the NCI and FDA. Many IOTF fellows have been recruited to various Centers of the FDA, and three are currently being trained in DCGT labs.

OCTGT has flow cytometry equipment for up to eight-color analysis and for cell sorting. In-house flow cytometry experts are routinely consulted on the issues related to regulatory files as well on research projects. Additional capabilities are needed, and proposals have been submitted for funding from the Critical Path initiative.

The OCTGT is faced with a multitude of approaches for vaccine therapy of cancer patients.... Expertise for monitoring these vaccine approaches will need to be expanded, especially when more vectors become available with differing properties and are put into clinical trials. Safety issues will be paramount with each new type of vector. Scientists trained in relevant viral research should be sought to expand the base of researcher/reviewers. Attendance of gene therapy and vaccine meetings should be highly encouraged to anticipate the direction of new therapeutic modalities.

Response: OCTGT has limited staff studying various aspects of cancer vaccines and immunotherapy products. As cancer vaccines and related immunotherapy and gene therapy products for treatment of cancer make up a major fraction of the INDs in OCTGT, the committee's recommendation for additional expertise related to these approaches is quite appropriate. Recruitment for a new virology researcher is in progress.

OCTGT staff members regularly attend local and international cancer-related conferences/workshops e.g. International Society of Biological Therapy of Cancer, American Association for Cancer Research, American Society of Gene Therapy, and Cancer Vaccine Consortium, to the extent that the budget and the reimbursement rules permit.

OCTGT also organizes an annual US-Japan cellular and gene therapy conference that focuses on a different area of research each year. One year the focus was tumor vaccines. The goal of these meetings is to exchange ideas and cutting edge areas of biomedical research and to enhance opportunities for collaborations between scientists from the FDA, NIH, academic institutions in the US, and Japan.

Bioinformatics

Recommend opportunities for research expansion, redirection and/or new collaboration/leveraging.

OCTGT/CBER is uniquely positioned to aid in resolving some fundamental challenges facing industry. Strongly encourage leveraging this unique position to carry out meta analysis across data sets to identify gaps in knowledge that may be resolved by forming collaborations with multiple industry partners in a consortium approach with the goal of resolving well-defined issues slowing advancement of products for clinical application. Collaborations could be proposed in areas where data are needed to advance the field generally without divulging specific proprietary aspects of any one sponsor's data. The results of the collaboration would be shared among participating organizations and made public. This collaborative, consortium type approach would enable OCTGT to partner its own experts in bioinformatics, laboratory and clinical science with experts in public and private organizations. This approach has the potential to accomplish significant leaps forward for the entire field, puts OCTGT in a relationship-brokering role enabling selection of multiple partners, builds consensus and positions its own scientists to learn from and educate scientific peers outside of the agency.

Research management strategies for anticipating future biologics products and related scientific issues.

....

Use of information from pre-submission inquiries to inform direction the field is taking is a very good way to identify emerging product areas.

Response: Performing meta-analyses across data sets is a challenging proposition that is not currently carried out: it requires resources not currently allocated. There are also legal issues with respect to proprietary information that need to be addressed. As preliminary steps in that direction, FDA works with members of industry and academia to identify and address gaps in bioinformatics knowledge, for example, developing standards and appropriate statistical analysis methods for microarray data. Issues related to bioinformatics are discussed within FDA in a number of groups described below.

Our management strategy for using pre-submission information to identify emerging product areas also includes the work of these groups:

Microarray Quality Control Consortium (MAQC): Staff members participate in meetings with academia and industry to discuss issues and publish papers on quality issues. An issue of *Nature Biotechnology* was dedicated to publishing several articles resulting from this collaboration.

External RNA Control Consortium (ERCC): Staff participates in meetings with industry and academia on creating spike-in controls for microarrays.

Interdisciplinary Pharmacogenomic Review Group (IPRG): This group is headed by CDER, but CBER staff play an important role in the cross-center collaboration. This group has a unique ability to leverage FDA expertise in order to encourage innovation in the areas of safety and efficacy using genomics, proteomics, metabolomics, or other technology. The IPRG encourages industry to participate in the voluntary exploratory submission (VXDS) process. Industry submits bioinformatics data derived from pharmacogenomics and other biomarker studies, the group at FDA reanalyzes it, and then day-long face to face meetings are held. These voluntary exploratory submissions can alert CBER to upcoming products and potential new regulatory issues that will require new thinking on how to review the data. Thus, the process represents a learning opportunity for the sponsor, which gets advice from FDA, and for FDA, which keeps abreast of new developments in drug design and testing. A key potential benefit of this evolving use of bioinformatics data is the personalization of treatment based on specific biomarkers in each patient. The efforts of the group has resulted in a document entitled *Guidance for Industry: Pharmacogenomic Data Submissions* and a concept paper *Recommendations for the Generation and Submission of Genomic Data*.

OCTGT Biomarker Steering Committee: Newly formed in 2007, the group meets to discuss regulatory issues related to genomic and proteomic biomarkers, and how they can aid in biologics development.

CBER Genomics and Proteomics Coordination Group (CGPCG), chaired by OCTGT. This interdisciplinary group examines pre-submission information and discusses how these new technologies are used, and has the mission of integrating new -omics technologies into the regulatory review process.

New area: Human Tissue Safety

The 2005 office site visit materials and thus the report did not include any discussion of human tissue safety, because at that time OCTGT did not have a laboratory devoted to this subject. Tissue safety concerns were heightened by subsequent adverse clinical events. As with any product derived from a human source, tissue products have the potential to transmit infectious disease, although this risk is believed to be very low.

FDA first required the tissue industry to report adverse reactions involving relevant communicable diseases in May, 2005. In 2006 (the most recent calendar year for which data is complete), FDA received 147 reports of adverse reactions or product problems following tissue transplants, although in the majority of cases it could not be determined if the tissue itself caused the infection.

There have been several recent efforts to improve tissue safety. The Human Tissue Task Force (HTTF) was established in August, 2006, as part of the Agency's efforts to evaluate and, where needed, strengthen its regulatory approach. FDA's regulatory approach has become more encompassing in terms of the scope of cells and tissues covered and the requirements that must be met. These requirements include not only donor eligibility requirements, but also requirements for registration, control of manufacturing, adverse reaction reporting, and tracking. The HTTF has also recommended additional activities, including inspection and compliance activities, partnering, leveraging, education, and outreach activities, adverse reaction reporting and analysis, development of additional regulations and guidance, and development of a strong scientific program.

When the public health issues highlighted scientific gaps in this area, OCTGT proposed the creation of a laboratory program in this area within DCGT. This proposal, accepted by the Center Director, will establish a program that is expected to advance both the understanding of the microbiological issues and the development of measures to better assure the quality and safety of human tissues for transplantation. The goal of the program is to develop ways to prevent and detect tissue contamination and to develop approaches to pathogen inactivation. We are currently recruiting staff for a lab program. The investigator selected will serve as a key member of CBER's Tissue Safety Team, an interdisciplinary group responsible for coordinating ongoing tissue safety activities.

Conclusion

OCTGT is very grateful to the site visit committee for their valuable and insightful suggestions. We are implementing many of their ideas, and will continue to make changes and launch new initiatives, to the extent possible.

Attachment 1: Charge to the site visit committee

1. Please comment on the contributions OCTGT research makes to the Critical Path development of biologics product and their availability.
2. Please recommend opportunities for research expansion and redirection, and new collaborations or leveraging.
3. Suggest research management strategies for anticipating future biological products and related scientific and product issues.
4. Provide recommendations for attracting and retaining high quality scientific staff.

Attachment 2: Site Visit Report

on
**INTRAMURAL RESEARCH PROGRAM
OFFICE OF CELLULAR, TISSUE AND GENE THERAPIES
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION**

September 29, 2005
Holiday Inn Select, Bethesda, Maryland

Introduction

On September 29, 2005 the Research Review Subcommittee of the Cellular, Tissue and Gene Therapies Advisory Committee conducted a review of the intramural research program, Office of Cellular, Tissue and Gene Therapies (OCTGT), Center for Biologics Evaluation and Research (CBER). The members of the Subcommittee were:

Dr. Mahendra Rao, Chief, Stem Cell Biology Section, Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health,

Dr. James Mulé, Michael McGillicuddy Endowed Chair, Melanoma Research and Treatment, H. Lee Moffitt Cancer and Research Institute,

Dr. David Harlan, Chief, Islet and Autoimmunity Branch, National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health,

Dr. Hugh Auchincloss, Jr., Professor of Surgery, Department of Surgery, Harvard Medical School,

Dr. Kenneth Cornetta, Professor of Medicine, Microbiology and Immunology, Department of Medical and Molecular Genetics, Indiana University,

Dr. Julie Djeu, Professor and Program Leader, Immunology Program, H. Lee Moffitt Cancer and Research Institute,

Dr. Katherine High, William H. Bennett Professor of Pediatrics, Howard Hughes Medical Institute, Children's Hospital of Philadelphia,

Dr. Anne Plant, Research Chemist and Project Leader, Chemical Science and Technology Laboratory, National Institute of Standards and Technology,

Dr. Allan Robins, Senior Vice President and Chief Technical Officer, Novocell,

Dr. Doris Taylor, Medtronic Bakken Professor, Center for Cardiovascular Repair, University of Minnesota,

Dr. Janet Warrington, Vice President, Emerging Markets and Molecular Diagnostics, Research and Development, Affymetrix, Inc.

The Subcommittee reviewed research programs in the Division of Cellular and Gene Therapies (DGCT), OCTGT. Research programs reviewed included those broadly related to:

1. Gene Transfer Products:
Viral vector safety, biodistribution, detection and characterization and viral vector induced host immune responses;
porcine endogenous retrovirus detection.
2. Xenotransplantation:
Porcine endogenous retrovirus detection and species tropism and transplantation immunology/rejection.
3. Cellular Therapies:
Key signaling pathways determining cell fate, cell death and development of anatomic structures, cell-cell interactions controlling differentiation of cells derived from bone marrow precursors, and immune cell activation and immune responses to cellular therapy products.
4. Tissue Bioengineering:
Tissue anatomy and factors controlling joint development, molecular signals determining liver development.

The Subcommittee evaluated the management of OCTGT's research programs for their scientific quality, mission-relevance and scientific management and leadership. The review included the evaluation of written research program descriptions, selected publications and oral presentations. FDA asked the Subcommittee to comment and make recommendations on the following:

1. OCTGT contributions to the FDA Critical Pathway for biologics product development and availability.
2. Opportunities for research expansion, redirection and/or new collaboration/leveraging.
3. Research management strategies for anticipating future biologics products and related scientific issues.
4. Developing (attracting, retaining) high quality scientific staff in OCTGT.

The following critiques are provided by individual Subcommittee reviewers selected for his/her recognized expertise but reflect the unanimous consensus of all members:

Gene Transfer Products and Therapy

Overview: The Gene Therapy research program within the OCTGT is seen as a critical, productive, and innovative group of investigators. The American biomedical research establishment, over the past decade, has made tremendous investments in molecular and cell biology research. The public naturally has the expectation that these investments will lead to new treatments for disease. The fact is though that new treatment modalities like cell and gene therapy will never move from effective laboratory reagents to products for patients with disease unless the FDA maintains a strong cadre of researcher-reviewers who can participate in the development of paradigms for investigation and licensing of these novel therapeutics. The committee reviewed the previous recommendations outlined in prior reviews, concurred with these, and has the following additional comments:

Strengths:

- 1) The productivity of the current principal investigators is very strong, both in terms of scientific merit, and congruence with the overall mission of the FDA.
- 2) The researchers and regulatory individuals in this group are well recognized within the gene therapy community for their outreach efforts. These efforts include both education, participation in scientific meetings, and consensus building for guidance documents. This effort is highly valued by both academia and industry and is critical to moving gene therapy forward and understanding the key safety issues relevant to patients. The agency should continue to support these important efforts.
- 3) While the scope of gene therapy is broad and expertise in all aspects of this complex field is likely beyond the reach of a single program, the other research groups within the OCTGT provide complimentary expertise that enhances the gene therapy research group.
- 4) The current environment has led to retention of a number of highly productive, well-respected individuals. In addition, recruitment of new investigators indicates that the FDA gene therapy group has been able to select expertise highly relevant to gene therapy and foster a young investigator who has produced high quality research while at the Agency.
- 5) The Core Facilities at the FDA appear to be a valuable resource, and investigators also appear adept at establishing NIH collaborations that enhance the current program. An effort within the Office of Cellular, Tissue and Gene Therapies to establish a collaboration with the National Toxicology Program to study insertional mutagenesis is one example of outstanding networking to obtain funding for key research issues critical to gene therapy safety. Gene therapy technology is unique and

the agency will need to build on this strong foundation to meet the challenge of assessing the risk of gene therapy.

- 6) The description of a focused FDA initiative to oversee research throughout CBER is important. It will be important that this office work to improve the research environment, by promoting support for cores, by insuring sufficient funding for productive investigators, and by liaising with other agencies to enhance funding opportunities. If this office can work to provide the most productive research environment for FDA investigators, it will serve as a critical resource for an already strong program.

Concerns:

- 1) The major concern for the research program is the anticipated marked increase in the number of gene therapy IND applications, Phase III studies and licensed products in the next 10 years. The regulatory burden will be substantial and unless additional resources are identified the regulatory burden could overwhelm investigators resulting in their being unable to continue their research programs.
- 2) OCTGT has recruited knowledgeable individuals in the area of Pharm/Tox who have also been important contributors to the Office's educational efforts. A challenge for the Office and Sponsors is the limitation of classic Pharm/Tox models in assessing the safety of biologic products. The OCTGT should consider adding an individual with a research interest in development of new Pharm/Tox models for cell and gene therapy products to their current review staff.
- 3) CBER must continue to balance the potentially conflicting nature of the research mission, specifically the scientific interests of the investigators, and the need for the agency to conduct mission-specific research. While CBER appears to have done an excellent job in recruiting investigators who can balance these potentially conflicting missions, this is an area that requires continuous monitoring. If the FDA begins to micro-manage research programs, it will likely impact the quality of work being performed and negatively impact retention.
- 4) While retention was not seen as a significant problem by the OCTGT, it was also recognized that the office is relatively new. Therefore, a wider view of CBER should be taken. In particular, why the reasons that principal investigators have left the agency should be ascertained and an exit review process should be established.
- 5) Mentoring is an area that may require additional attention. Mentors for investigators should be successful scientists at the FDA, NIH or academia who can serve as a resource for the scientific program. Junior investigators should receive mentoring about balancing the demands of research and regulatory workload. The mentoring committee should be distinct from the investigator's direct supervisor and should also

function to provide the agency with feedback as to ways it can promote success of an individual investigator.

- 6) Access to quality post-doctoral fellows has been a concern identified by some investigators. Mentoring of post-doctoral fellows should be considered. Specifically, developing a curriculum for fellows that enhances their research experience should be a goal. For example, many academic institutions are providing fellows with training in ethics, grant and manuscript writing, and other professional development workshops. These efforts can provide added value to the post-doctoral experience and can be used as a recruitment tool.

In review, the FDA believes that the current structure allows for FDA investigators to quickly respond to potential adverse events. For those performing scientific work, the timeline is quick and the FDA performance is commendable. Nevertheless, non-scientists may see the timing differently. As the agency becomes part of the Bioterrorism efforts, it should clearly state the capacity and time lines envisioned for potential responses. The staff is still limited in number and resources and others outside the agency should have a realistic understanding of the capacity within OCTGT.

- 7) For future reviews, it would be helpful to present metrics in terms of research programs across the FDA. This would include: total funding by division, resources allocated by FDA vs. external funding, FTEs involved in research, regulatory workload, etc.
- 8) It is critical for reviewers to have insight into emerging areas where they may need to recruit. The most efficient way to accomplish this goal is to insure that FDA scientists regularly attend gene therapy conferences.

Additional recommendations:

1. Individual areas of expertise that are likely to be important going forward and that should be considered in new hires for the gene therapy group include:
 - a. Zinc finger nucleases, gene correction by homology-driven repair, double-strand break repair.
 - b. Promoters that can be regulated by small molecules, so-called "gene switches"
 - c. In vivo tracing, imaging, which could be developed in a Core.
 - d. Strong expertise in immunology, which will continue to be important for gene therapy product immunogenicity determinations.
2. Large scale studies, not being done by sponsors/investigators, could include:
 - a. Reproductive toxicology for a range of vectors. This will continue to be important as gene therapy is developed for younger populations.

Cellular Products and Therapies (as they relate in broad terms and to stem cells)

The science being conducted at OCTGT in the Cellular Therapy area (as it relates in broad terms and to stem cells) is of a high standard and is generally considered appropriate for the mission of the organization. The budgets of the division are very tight and the time constraints on senior investigators who are reviewing a substantial number of INDs means that progress in some areas is slower than would otherwise be anticipated.

However, a number of the programs are narrowly focused and not really relevant to developing the regulatory process in the areas of cellular therapies and most probably reflect the past research interests of staff recruited to the division. The cell therapy area is still in its infancy with few mature or licensed products. In general the current regulatory process is geared towards drugs and new insight and research is required when dealing with complex biologicals that comprise a cellular therapy. The Committee thought that OCTGT should be developing initiatives to deal with these issues. A number of examples are:

1. Toxicology studies. How do we design experiments to do toxicology studies in animals with cellular products from a different species? Specifically traditional pre-clinical animal safety studies cannot be performed long term with human cells in most animal models because of rejection issues. Even with immunosuppression only short term studies can be performed.
2. In Vivo Tracing. Cells can and do migrate in the body. Cellular therapies that implant living cells that are not physically restrained in some way may migrate. How do we track cells to study this migration and determine what is safe?
3. Batch variability. Because cells are complex biological systems there is bound to be variability between different batches of the same cells. While there are many parameters that can be measured, how do we determine the correct parameters to measure to ensure safety?
4. Combination Products. Many cell products will be combination products either with classical devices or encapsulation technologies or in other formats. How will the regulatory process deal with these combination products in the future?

In addition, the Committee felt that more emphasis should be placed on large-scale collaborative efforts in areas like, biomarker identification, proteomics and bioinformatics. We recognize and acknowledge that efforts are being made in these areas but the Committee believes more emphasis needs to be brought to the forefront.

It was thought that the agency ought to have procedures in place to be able to recognize and anticipate future directions in the development of the science behind cell-based products and therapies in order to be proactive rather than reactive to new developments.

With respect to recruitment, retention and training of researchers, the agency seems to be doing a very good job, although it was noted that many of the recruits are from other agencies like the NIH. With current budgetary restraints the suggestion of sabbaticals and reverse sabbaticals would add variety and exposure that will aid staff retention.

It was strongly recommended that the agency have proactive forward budgetary planning for the next 5 years in order to handle the greatly increased number of INDs in cell-based products and therapies that the Committee predicts will occur during that time. Without new resources the increase in INDs will greatly diminish the amount of research being conducted at the agency as most reviewer's time will be taken up with the review process. This predicted future lack of bandwidth poses the greatest threat to the agency being able to adapt and respond quickly to new treatment modalities as they develop and should be addressed in the near term.

Cellular Products and Therapies (as they relate to cardiac repair; xenotransplantation)

Research Impact:

Cardiac cell therapy is an actively growing field. To date, about 20 trials are underway overseas. Multiple cell types are being evaluated for cardiac repair; multiple animal models are being proposed; different cell administration paradigms are being presented. All of the aforementioned are relevant to FDA regulatory evaluations and could impact the need for research in the next few years. Obviously the FDA cannot provide in house research in each of these areas; however, several over-arching issues need to be addressed that will have impact on the entire field. These platform technologies are areas where the FDA should strongly consider intramural research. Those areas include:

- In vivo tracking of cells. Currently a major limitation in the field of cell-based cardiovascular repair is an inability to safely track cells after delivery. Development of such techniques would have a broad-based appeal and be useful in many areas.
- Cross-species (xenogeneic) comparison of stem cells and progenitor populations are likely to play an increasingly large role in the field. Understanding which stem cells must be used in preclinical studies, what markers are appropriate, and what characterizations are important, are areas where FDA research labs could have a major impact, especially given the large stem cell processing facilities and flow cytometry facilities that exist. Defining FACS based markers for specific cell types or defining broad-based potency assays could likewise, have a major impact.
- Developing more of an expertise in bioengineering and biomaterials is likely to be important in cardiovascular repair as well.
- Performing meta-analyses to the extent possible for some of the cardiovascular repair studies could also provide tremendous impetus to the field.
- Understanding allogeneic and xenogeneic cell potentials for cardiac repair are also critical.
- If cell signaling is going to remain a focus of research investigators, it would seem that signaling with regard to stem cell differentiation might be a more important use of resources.

Given the inability to respond quickly to changes in the field, it is imperative that CBER develop a 2-year and 5-year approach outlining the most critical issues in the field and defining where they believe they can make a significant contribution. The above list could provide a starting point. One proposal that would allow significantly easier evaluation of each area of research within the OCTGT is to provide a short summary of how each laboratory and the specific projects in each laboratory fit with the 2-year and 5-year plan for CBER. It is difficult at present to understand how some of the programs do so.

Currently it is stated that research work-in-progress seminars occur “periodically” and that there are internal web-based searchable annual reports. These critical tools should be evaluated for their usefulness. Perhaps the internal reports should be searchable across the FDA to promote collaboration. Perhaps the work in progress seminar should occur more regularly to allow leadership to determine if given programs fit with the long-term goal of the organization.

It is clear that the CBER Research Program is highly collaborative. However, this collaboration primarily appears to be internal; the opportunity for external collaboration should be maximized both across the FDA as well as with NIH and other governmental organizations. This clearly provides an opportunity for synergy and to maximize outcome with the limited resources that exist.

In this area, unlike many others, internationalization is quicker rather than slower. Cell studies are occurring abroad. Cardiovascular cell trials are occurring overseas. FDA scientists are going to have to develop bioinformatics approaches that allow them to integrate international data quickly as they come up to speed in CV repair. Finally, developing a strategy to create cell therapy guidance documents in a stream-lined manner would be of use to the field, especially as international studies emerge.

Looking at the critical path from basic research to FDA approval, clearly FDA-based internal research has the greatest opportunity to impact prototype design or discovery in preclinical development.

Recruitment/Retention:

The committee was asked to respond how to recruit, retain, and train scientists in the field. Clearly this is a dynamic field and investigators are moving in and out of it very quickly. To be able to attract high-quality scientists to the FDA, given the limitations of funding and time, it is important to provide several assurances. An important issue is autonomy. Investigators in this field are going to want to be able to move forward in novel and innovative ways. Defining a 2 and 5 yr CBER plan could facilitate this and provide a basic framework for investigators.

Given limited time and resources, the ability to do high-quality science is going to have to be addressed. Providing post-doctoral fellows and high-quality staff scientists will facilitate this. It is important not to wait until the number of applications is overwhelming to provide scientific support to the investigators with regulatory responsibilities.

The ability to publish and attend scientific meetings must be ensured. Resolving conflict of interest issues so investigators can attend small (usually commercially sponsored) meetings where unpublished data are likely to be presented is critical as is ensuring they can speak at or attend academic departmental seminars (which also may have commercial support).

Funding:

The funding issue is also raised. In cardiovascular repair, the majority of funding currently either comes from commercial sources or the NIH. It is imperative that the FDA have access to funding in this area through intramural funding, and through collaborations with investigators at NHLBI as well as investigators at other institutions or through other sources. Again, funding sabbaticals for investigators in the laboratories of individuals who are actively working in the field and developing a federal foundation to allow extramural and other research dollars be funneled in to these areas is critical.

Tissue Bioengineering

Overall, the program is very strong technically, and is well aligned with mission needs.

The following focuses on the area of tissue bioengineering in the context of:

- The contributions of OCTGT research to the Critical Pathway objectives.
- Recommendations for research expansion, redirection, collaboration or leverage.
- Research management strategies for anticipating future biologics products and related science issues.
- Recommendations for attracting and retaining high quality scientific staff.

1. The contributions of OCTGT research to the Critical Pathway objectives.

DCGT is strongly focused on developing the needed risk-based regulatory framework, developing guidance documents, and evaluating technologies. Many of the DCGT research priorities cut across specific applications.

2. Recommendations for research expansion, redirection, collaboration or leverage.

Cells, tissues, and gene therapies, while the subjects of a rapid rate of product development, are difficult to benchmark and to quantitate, and therefore it is difficult to predict outcomes. The scientific understanding of these areas is at a critical and incomplete stage. Investment in evaluation tools is needed, both for assisting development of applications, as well as for providing the required underpinning of technologies that could be used in unambiguous evaluation of potential therapeutic products. Thus, a healthy research program is essential, and mechanisms for developing more financial support for these activities are needed. Given the state of this field, where a large increase in numbers of applications is anticipated, procuring more resources in this area is advised.

Because of scarce resources and the magnitude of the responsibilities, collaboration is an important mechanism for leveraging resources. There are some impediments, such as conflict of interest rules, that can limit collaborations. In general, it appears that interagency agreements work well. Specifically in the area of tissue engineering, collaborations are used to provide needed expertise in cell/scaffolding research. Specific areas of expansion include discovery and validation of biomarkers and assays for biomarkers. Interaction with the interagency NSTC group in tissue engineering (MATES) has the potential to lead to great benefit to the FDA by encouraging other agencies to contribute to technology development that can lead to better methods for product evaluation.

Even outreach and collaboration requires resources, and the limitations of resources (particularly personnel) limit the extent of collaboration and outreach relative to potential opportunities.

3. Research management strategies.

A direct effort is being placed on formalizing the decision-making process for research program development. There appears to be close connectivity between the scientific activities and program planning and implementation, including mentoring of science investigators to help redirect projects to better address mission needs.

Participation in forums involving companies and industrial organizations is used to develop consensus on technical issues. In addition, Project Summaries are being developed for each project to describe the public health issue and how the project is addressing the issue, as well as expected outcomes and impact. These summaries will provide for better communication within the office. Sabbatical and 'reverse' sabbaticals are also potential mechanisms for expanding expertise both within FDA and through collaborators.

4. Recommendations for attracting and retaining high quality scientific staff.

In light of tight budgets, OCTGT is challenged to develop and maintain the required expertise to be prepared for an expected rapid rate of growth in applications in this area over the next few years. Furthermore, this office represents technical areas that suffer from poorly developed regulatory criteria, making it even more critical that staff be competent to contribute scientific as well as regulatory insight. Recruitment from within FDA appears to be a strategy. It is unclear how extensively the post doctoral programs are used to assist in recruitment; in principle this could be an important supply of high quality scientists.

Oncology and Tumor Vaccines

The Subcommittee was asked to address 4 areas at the Site Visit. This report focuses on evaluating these areas pertaining to research and regulatory issues on Oncology and Tumor Vaccines.

1. Discuss contributions of the OCTGT's research to the Critical Pathway of biologics product development and availability.

The Critical Pathway has been successfully followed in the pursuit of the development of tumor vaccines. It is clear that the researcher/reviewers are highly motivated and committed to bringing safe and efficacious products to clinical trials in a timely manner. Research performed in-house spans from basic immune mechanistic studies to identification of signal pathways and molecules in tumor cells, and assessment of their potential as tools to monitor effectiveness of vaccine or immunotherapy. High quality expertise in tumor immunology is evident, both from peer-reviewed publications and from invited talks at prestigious national and international meetings. The group has also been effective in reaching out to NCI, academic institutions, European regulatory agencies, and private industry by co-sponsoring conferences and working groups. They have brought awareness of the need for early product characterization as well as the need for identification of meaningful biological/immunological endpoints. The high quality of research on the Critical Pathway for vaccine development and the high visibility of the program should be encouraged and fostered to continue to bring respect and prestige to CBER.

2. Recommend opportunities for research expansion, redirection, and/or new collaboration/leveraging.

The OCTGT has a commendable relationship with NCI that allows for shared information, training opportunities and interactive research programs. It needs to

maintain and expand this relationship, particularly as the fields of high technology, such as genomics, proteomics, and bioinformatics converge, requiring costly investment both in personnel and equipment. Partnerships with other institutions such as NIAID are also good investments, in order to achieve rapid entry of new types of vaccines into clinical trials. Lastly, the OCTGT should maintain its leadership in Flow Cytometry for analysis of biomarkers in patients and regular capital investment for new updated cell analyzers and sorters is key for success.

3. Identify research management strategies for anticipating future biologics products and related scientific issues.

The OCTGT is faced with a multitude of approaches for vaccine therapy of cancer patients. They include cellular products which can be modified by pulsing with mRNA/peptides or by gene modification to express a protein of relevance for immune recognition and activation. Non-cellular products are also in clinical trials that include isolated tumor antigens, peptides and fusion proteins, as well as plasmids or viral vectors carrying tumor antigen and/or immune modulator genes. Expertise for monitoring these vaccine approaches will need to be expanded, especially when more vectors become available with differing properties and are put into clinical trials. Safety issues will be paramount with each new type of vector. Scientists trained in relevant viral research should be sought to expand the base of researcher/reviewers. Attendance of gene therapy and vaccine meetings should be highly encouraged to anticipate the direction of new therapeutic modalities. The practice of pre-IND meetings also is a good strategy to predict the workload.

4. Provide recommendations for developing (attracting, retaining) high quality scientific staff in OCTGT.

In order to attract high quality scientific staff to OCTGT, the scientific environment is critically important, which means that peers of high quality must already be in place. To maintain quality staff, a well-balanced workload consisting of independent research and regulatory work must be accompanied by sufficient funds for laboratory staff and supplies. As funding becomes limited, new ways should be found to allow OCTGT scientists to apply for extramural resources, without conflict of interest, including a FDA-based resource like the Henry M. Jackson Foundation for DOD.

The sabbatical and reverse sabbatical systems should be encouraged to either send OCTGT scientists for training in specifically-needed areas or bring experts into CBER to upgrade the scientific expertise. Collaborative research programs within the campus with top NIH scientists are also encouraged to bring familiarity of these scientists to OCTGT and to allow them to spread awareness through their contacts and networks.

Bioinformatics

General Observations:

1. Strongly recommend maintaining and expanding the research component of the OCTGT program at CBER. Research activity within the agency maintains the necessary expertise required for effectively carrying out regulatory activity,

accelerates product development across industry contributing to the efficient advancement of safe products to market. The research function of OCTGT is consistent with the goals of the national Critical Path initiative.

2. Support formalizing the research project approval process within OCTGT. It is important that this process is designed and implemented in a manner that stimulates innovation and creative problem solving. It is recommended that the process include; open communication of strategic goals including long term and short term priorities, a mechanism for annual review and alignment of projects against goals, a mechanism for review of the process itself to obtain feedback from all levels of scientists within the OCTGT regarding the effectiveness of the process and a mechanism for modifying the process to respond to and address the changing needs of researchers/regulators.
3. Suggest formation of a committee to study and report on the ramifications of establishing an independent research foundation that would be established to provide an additional source of research funding to OCTGT. With the realization that the establishment of such a foundation would require a significant amount of work including an Act of Congress, it would be prudent to understand the potential impact, positive and negative, on the current workload, efficiency and goals of the OCTGT and CBER

Specifically:

1. Recommendations for attracting, developing and retaining high quality scientific staff.
 - a. Retention. The scientific expertise and demonstrated versatility within this program is impressive. Retention of expert, high quality, dedicated and productive personnel is a challenge in both private and public research environments. The opportunity to participate in contributing to the very important goals of the FDA is appealing to many scientists but this alone will not sustain top quality scientists long-term. Realistic expectations with respect to workload, productivity and research support are necessary to attract and retain top quality people. Involving scientists in strategic discussions regarding agency goals, providing forums for brainstorming and maintaining an open-door culture contributes to job satisfaction. Resources for continued professional development including succession planning and leadership training supporting clearly articulated paths for career advancement aid in retention of top quality talent. Support for travel to scientific meetings and hosting workshops for the research community advances scientific interaction and acknowledges the professional expertise and contributions of the scientists in the OCTGT.
 - b. Recruitment. Outreach through participation in (bioinformatics) professional meetings, collaborations with academia and industry to provide young scientists with information by example of how data

analysis, statistics and bioinformatics are applied within CBER to advance research/regulatory goals. Perhaps consider chairing an education panel at a bioinformatics professional society meeting with panelists from the FDA describing how research/bioinformatics is conducted at the FDA (e.g. ASHG 2004 there was an education panel featuring geneticists from the pharmaceutical industry describing what geneticists actually do at pharmaceutical companies featuring every part of the drug discovery and development pipeline, identifying aspects that are similar and different from an academic environment. More than 1000 people attended this session.)

2. Recommend opportunities for research expansion, redirection and/or new collaboration/leveraging.
 - a. OCTGT/CBER is uniquely positioned to aid in resolving some fundamental challenges facing industry. Strongly encourage leveraging this unique position to carry out meta analysis across data sets to identify gaps in knowledge that may be resolved by forming collaborations with multiple industry partners in a consortium approach with the goal of resolving well-defined issues slowing advancement of products for clinical application. Collaborations could be proposed in areas where data are needed to advance the field generally without divulging specific proprietary aspects of any one sponsor's data. The results of the collaboration would be shared among participating organizations and made public. This collaborative, consortium type approach would enable OCTGT to partner its own experts in bioinformatics, laboratory and clinical science with experts in public and private organizations. This approach has the potential to accomplish significant leaps forward for the entire field, puts OCTGT in a relationship-brokering role enabling selection of multiple partners, builds consensus and positions its own scientists to learn from and educate scientific peers outside of the agency.
 - b. Strongly encourage continued development of adequate infrastructure, equipment and dedicated bioinformatics and computing expertise to enable CBER/OCTGT to constructively take advantage of the vast amounts of biochemical, cellular and molecular data generated by existing and new technologies. Adequate database and bioinformatics infrastructure support will enable CBER to effectively compete for external funding and partnerships. It seems highly likely that this tool will enhance the knowledge base supporting expert regulatory review and ultimately will be required to maintain the expert knowledge base necessary to effectively carry out the regulatory role of the agency. An integrated, well-designed database has the potential for becoming an electronic collective memory for CBER.

- c. Support sabbaticals and reverse sabbaticals to increase interaction with scientists in specific relevant areas of the research community.
3. Research management strategies for anticipating future biologics products and related scientific issues.
 - a. Use of information from pre-submission inquiries to inform direction the field is taking is a very good way to identify emerging product areas.
 - b. Suggest introducing new mechanisms making it easier for researcher/reviewers to attend scientific, professional meetings and accept travel reimbursement from industry sponsored meetings provided the meetings are open. One idea is to have travel contributions go into a travel support pool so that specific source of meeting sponsorship is blinded.
 - c. Amend current rules to provide a mechanism for obtaining NIH funding.
4. Comment on existing program, scientific contributions.
 - a. OCTGT has demonstrated research excellence. The workload demands on the researcher/reviewer staff are considerable and there appears to be no redundancy or excess of researcher/reviewer staff. A serious challenge will be maintaining the current level of productivity as the number of submissions increase. Managing this risk will be challenging and requires continued efforts at communicating clearly defined goals, transparent goal alignment procedures and disciplined prioritization of research projects and resources. Optimally, additional funding will be made available to enable expansion of the program as the regulatory burden increases. Some additional administrative support to key personnel would allow them to focus more of their experience and talents on the areas requiring highly skilled people, e.g. hiring one dedicated lower level FTE for reviewing funding opportunities and bringing these opportunities to the attention of reviewer/researchers, help in preparation of grants and budget administration/tracking of externally funded projects relieves researcher/reviewers from a task that can be handled by well-trained junior staff.

Closing Comments

On September 29, 2005 the Research Review Subcommittee of the Cellular, Tissue, and Gene Therapies Advisory Committee conducted a site visit of the FDA's Office of Cellular, Tissue, and Gene Therapies in Bethesda, Maryland. In preparation for that review, the Subcommittee members read the final report, dated October 21, 1998, of the Review of Research Programs for the Center for Biologics Evaluation and Research program, and current Subcommittee members endorsed that previous report. Most important from that earlier report was the conclusion that CBER performs an invaluable function to promote biomedical science and industry, all toward the goal of improving the health of U.S. citizens.

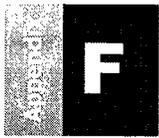
Further, that an active research component within the FDA is essential for reviewers to remain up-to-date with current scientific thinking and techniques so as to advance the science, and as important, insure fair and complete regulatory oversight functions. Further, that budget constraints within the FDA threaten the intramural research efforts.

For the recent review, the Subcommittee made several other suggestions.

1. The Subcommittee learned of some intermittent intramural retreats to discuss future research priorities, and suggested that such efforts be strongly encouraged. Further, that these retreats take place on a regularly scheduled basis. And last, that when considering future research needs, the FDA continue to reach out to the extramural community, and to industry, to plan for future research needs. In words Dr. Carbone (Associate Director for Research, CBER/FDA) quoted for Subcommittee members (and she was paraphrasing Dr. Ruffolo from Wyeth), "...you can't manage [product development] science. But it needs to be."
2. In an effort to facilitate additional funding opportunities for FDA investigators, Subcommittee members suggested consideration of a Congressionally mandated organization like the Henry M. Jackson Foundation (HMJF) for the Advancement of Military Medicine be created for the FDA. The HMJF facilitates DOD investigators' research by making it possible to apply for federal grants and to raise charitable contributions in support of DOD research. An HMJF-like organization could also help support FDA to instigate meetings to discuss research relevant to the FDA.
3. A program should be supported to allow FDA investigators to take periodic sabbaticals to extramural laboratories and/or to industrial laboratories to gain first hand experience with emerging techniques and scientific disciplines. Such opportunities will allow more rapid development of in-house scientific expertise.

The subcommittee endorsed a "reverse sabbatical" program inviting investigators from academia and/or industry to spend time with the FDA (with all due controls over conflict of interest) such that those individuals could learn through active participation in the regulatory process.

Appendix F of the FDA Science Board Report, 2007, follows. It is entitled "Center for Biologics Evaluation and Research (CBER)," and is an appendix to the report, "FDA Science and Mission at Risk. Report of the Subcommittee on Science and Technology," prepared for the FDA Science Board, November, 2007.



Center for Biologics Evaluation and Research (CBER)

1. *CBER's Mission and Vision*

CBER's mission is to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through its mission, CBER also helps to defend the public against the threats of emerging infectious diseases and bioterrorism. CBER's vision is to use sound science and regulatory expertise to protect and improve public and individual health in the United States and, where feasible globally; facilitate the development, approval of and access to safe and effective products and promising new technologies; and strengthen CBER as a preeminent regulatory organization for the biologic products that fall under its regulatory authority, i.e., whole blood, blood derivatives and blood components, vaccines, somatic cell and gene therapy, allergenic extracts, xenotransplantation and tissue therapies.

As with the other Centers of the US FDA, CBER develops, maintains and supports a high-quality and diverse workforce; ensures compliance with laws and regulations through review, education, surveillance and enforcement; but is preeminent within FDA in conducting research as an essential element of science-based decision making.

A. Background

In preparing this analysis, members of the Subcommittee met with CBER senior staff on three occasions, two of those at CBER, read written reports of past advisory committees and other expert committee reviews, reviewed the extensive documentation provided by each of the five CBER offices (blood research and review; vaccine research and review; cellular, tissue, and gene therapies; biostatistics and epidemiology; compliance and biologics quality), analyzed the responses provided to the Subcommittee's questions and interviewed representatives of organizations knowledgeable of CBER programs. The latter group included: Dr. Jesse Goodman (Center Director), Dr. Karen Midthun (Medical Deputy Director), Dr. Kathryn Carbone (Associate Director for Research), Dr. Celia Witten (Director, Office of Cell, Tissue, and Gene Therapy-OCTGT), Dr. Suzanne Epstein (Associate Director for Research, OCTGT), Dr. Norman Baylor (Director, Office of Vaccines Research and Review-OVRR), Dr. Michael Brennan (Associate Director for Research, OVRR), Dr. Jay Epstein (Director, Office of Blood Research and Review-OBRR), Dr. Chintamani Atreya (Associate

Director for Research, OBRR), and Dr. Mary Malarkey (Director, Office of Compliance and Biological Quality-OCBQ).

The Subcommittee probed the organizational aspects of CBER and particularly paid attention to CBER research successes and potential forces that could limit such successes in the future.

The guiding principle of CBER research is that it be of high quality, efficient, and directed and managed to provide outcomes that address scientific and regulatory challenges in product development, safety, efficacy and quality that cannot or are not being met by the regulated industry. The CBER research program is highly collaborative and includes laboratory, epidemiological, statistical and clinical sciences and its scope encompasses the scientific basis of pre-clinical and clinical studies, manufacturing, regulatory submissions, inspections, post-marketing surveillance and Guidances. For fiscal year 2006 CBER had 979 FTEs, of which 772 were in the Center, and 207 in the field, with a total program support of \$197.7 million. Of the Center staff 334 (43 percent) held doctoral degrees (216 PhDs, 71 MDs, 17 MD/PhDs, 16 Doctorate of Nursing, three PharmDs, nine JD and two DVM).

In fiscal year 2004, a total of 216 FTEs were transferred from CBER to CDER; 84 of those FTEs were PDUFA fee paid positions and 128 were Salaries and Expenses FTEs. A total of \$27.6 million was transferred from CBER to CDER. This includes payroll and operating dollars, of which \$9.3 million was from PDUFA fees and the remaining \$18.3 million was from salaries and expenses. CDER reimburses CBER for four to eight FTEs a year depending on the level of support provided for animal care, IT, Resource Information Management (RIMS) and facilities. Approximately \$1 million is transferred back to CBER from CDER for these activities.

Approximately, 10–15 percent of CBER staff are “Researcher–Reviewers” who devote substantial time to research. All of the staff who do research (i.e., those termed Researcher–Reviewers) do both review and research with their time spent divided approximately 50 percent to research and 50 percent time devoted to review activities. Research–Reviewers are generally considered the CBER “product” experts whose research is focused on their product expertise area (e.g., childhood vaccines, blood products, gene therapies, etc.). The distribution of these Research–Reviewers within the various Offices show that about 50 percent are in vaccines, 30 percent in blood and 20 percent in cell, tissue and gene therapy.

In response to the Subcommittee’s question the Center identified 42 areas of Researcher–Reviewer expertise falling under the categories: virology; bacteriology; parasitic and unconventional agents; cell-tissue and plasma biology; manufacturing and emerging medical technologies.

B. Summary of Findings

The CBER review Subcommittee was impressed with the quality of science, the focused approach to regulatory science within CBER, the stability of the scientific staff within the Center, the strong commitment to priority setting and management processes, and the anticipation of the Center in moving forward in areas that likely will require expertise in the future. However, we are concerned with the lack of funding, the limited ability to provide professional development within such a resource restrained Agency and the potential for an issue of a changing environment when CBER moves to the White Oak facility.

2. Science Infrastructure

A. Scientific Expertise

As stated above, 42 different areas of scientific expertise for Research-Reviewers were identified for the Subcommittee. All areas of need and anticipated need appear to be included, but due to continuing budgetary restrictions, the number of individuals within each area of expertise is very limited, often with only one scientist identified. For example, nanotechnology and genomics were identified by CBER as areas of priority needs in the coming years, but only one and three Research-Reviewers PI scientists, respectively, can be presently identified with adequate expertise. The Subcommittee was concerned, for example, that only four PI scientists within CBER were identified with immunology expertise when this is a critical area of product evaluation within the area of Cell, Gene, Tissue and Plasma Biology. If 10-15 percent of the staff are research reviewers (RRs), and there are 42 different areas of scientific expertise, then there are only approx. 120 available RRs, only 2.9 RRs per science area. Thus the situation for nano and genomics is reduplicated throughout the Agency. Furthermore, in addition to the "cutting-edge" areas listed above, the areas of cell and tissue therapies are also expanding areas of science. There is certain to be increased applications for approvals in this area adding to the rather striking deficiencies in manpower and expertise posed by CBER's functioning at the cutting-edge of human therapies.

B. Professional Development

This was an area of great concern to the Subcommittee. In response to questions about professional development it was emphasized that limited staff and limited budget prevented CBER scientists from engaging in professional development at the levels that the management and the scientists themselves would need. Furthermore, because of the limited scientific staff in any particular area of expertise, CBER product specialists were further restrained from participating in professional development activities when product submissions were received and PDUFA goals had to be met. Yet the

Subcommittee was impressed with the stability of scientists within the Center and the obvious *esprit de corps* that was evident in the presentations and scientific interactions with the Subcommittee.

C. Priority Setting

The Subcommittee was provided with an extensive list of research goals center-wide and in each of the Offices. The Subcommittee was provided with the fiscal year 2007 planning document for the fiscal year 2008 budget. Here by mid-year it is expected that Offices will update regulatory workload, public health portfolio analysis and scientific gap analysis and then provide the Center Director with updated Office research priorities. This then is translated in the office of the Center Director to an updated list of Center research priorities with each Office then providing individual research program reports that include achievements over the past year and the proposed research plan for the next year. The Center budget targets are then distributed by the office of the Center Director in late summer, revised with interactions through the various Offices with a final draft completed by the end of September. This draft of research priorities and budget is then presented for Advisory Committee input on the Office research plans.

The Subcommittee requested CBER to provide a detailed explication of how the malaria program was made a priority activity, the CBER response to this prioritization and how this prioritization affects other programs within CBER.

D. Resources and Technology

The Subcommittee was presented with an extensive list of CBER infrastructure needs categorized under the headings: General; Science and Science Innovation; Scientific, Technical and Medical Staff Development; Outreach, Communication, Partnerships and Leverage; Physical Plant needs; Computing and Information Technology needs.

As an example, one of the seven bullets under the heading Science and Science Innovation related to "improving capacity for safety and efficacy evaluations/monitoring of candidate and license products and to modernize current regulatory pathways and develop new regulatory pathways where there are currently none, through additional scientific expert staff, administrative support, space, research support and equipment to:

- Develop a Human Tissue Safety Testing Branch with a focus on tissue microbial safety
- Develop a multidisciplinary Vaccine Safety Team with a focus on candidate and licensed vaccines from initial development through clinical testing, licensure and post-licensure

- Develop a multidisciplinary Tissue Engineering team to work collaboratively with CDRH
- Develop a multidisciplinary CBER Personalized Medicine Team to develop/evaluate/validate/standards development for complex biological products, such as cell therapies, blood components (e.g., clotting factors), tumor vaccines, prophylactic vaccines.”

One of the seven bullets under Physical Plant needs states “adequate and appropriately designed and resourced laboratory space for research efforts, including BSL3+ laboratories.”

The Subcommittee was generally supportive of these infrastructure needs. CBER provided documentation of successes in a number of instances, some of which are described subsequently, where the science would not have been carried out except for CBER’s initiative. During one of its visits the Subcommittee was presented a case study related to work in the Agency on the safety and efficacy of hemoglobin-based oxygen carriers (HBOCs). It was recognized by CBER that preclinical safety and efficacy testing methods for HBOCs were limited and outdated, and that product failures were occurring during clinical testing phases. CBER developed better preclinical tests of oxidative chemistry, NMR and mass spectroscopy to predict safety and efficacy performance in clinical trials, thereby facilitating development of a technically challenging yet high potential public health value product. Draft guidance for industry detailing the criteria for safety and efficacy of HBOCs was prepared and presented to the Blood Products Advisory Committee. The public health impact of this work provided a clearer pathway to support more efficient development of safer, second generation HBOCs.

Currently, CBER has approximately 400,000 square feet of space in four research buildings. Two laboratory facilities have been completed at White Oak providing a current total of 167,470sf at White Oak. Total useable laboratory square footage at NIH and NLRC is 175,678.

E. Collaborating/Leveraging

CBER scientists continue to markedly interact with their colleagues who were transferred to CDER in fiscal year 2004. Strong interactions occur with CDER and CDRH due to the requirement of combination of products and devices used with CBER regulated products. Details of the budgetary interaction with CDER were presented above. CBER has extensive interactive relationships with NIH and CDC. The Subcommittee was told that approximately 70 percent of the non-FTE research personnel, research supplies and equipment money for research projects within CBER came from outside sources, mostly NIH.

3. Critical Path Approach

CBER provides leadership in the Critical Path research initiative. CBER's intramural, multidisciplinary disease and product oriented research programs are focused on challenges of unique priority to the FDA mission. CBER's intramural research regulators work collaboratively with government, academic and industry scientists with critical areas of expertise. And CBER takes advantage of extramural science and scientific efforts. All of these sources are used to contribute to Guidances, standards and regulatory decision making to support product development, safety efficacy assessment and review, as well as consistent manufacturing processes.

4. Management Structure/Processes

In 2002, CBER experienced a change in both Center and Research leadership. Over the past four years CBER completed external scientific Site Visit reviews of the CBER Laboratory Research Programs at the laboratory/researcher-reviewer and at the Office levels. Site visits are conducted through appropriate CBER Advisory Committees for each product office. Each Research-Reviewer PI receives a site visit every four years within a laboratory unit consisting of several PI research programs within a laboratory of the product offices. The subgroup evaluations are co-chaired by two Advisory Committee members and the evaluation is supplemented with appropriate outside scientific experts. Each PI prepares and submits site visit documents detailing achievements during the past four years and proposals for future research during the next four years, which is presented to the Advisory Site Visit Review Team. The Advisory Site Visit Review Team then holds individual interviews with each PI. The draft report is developed and finalized with presentation to and discussion by a full Advisory Committee vote. Formal responses to the comments within Site Visit reports are prepared and will be presented to Advisory Committees in the next year.

CBER scientific expertise and scientific contributions are critical to ensure the safety, effectiveness and availability of licensed biologic products, and play an important Critical Path role in facilitating biological product development and evaluation. Thus CBER initiated a Research Management Initiative to set a responsible, value driven course for the research, ensuring that research priorities and programs at CBER maintain the needed flexibility, infrastructure and collaborative scientific links to resolve regulatory challenges and emerging natural and man-made public health threats. In 2006 under the Research Management Initiative, CBER formed the CBER Research Leadership Council (RLC), composed of Research-Regulator and Regulatory Scientist leaders and managers from across the Center to develop and manage a formal research prioritization, planning and evaluation process within CBER. That process was described earlier in this report.

5. Examples of CBER Regulatory Sciences Successes

The following list documents only briefly a subset of regulatory science accomplishments that support the CBER model of science within the FDA. In general, CBER is in a unique position to: identify a cross-cutting issue; resolve scientific questions critical to regulation; to enhance the scientific quality of products reviewed; to maintain the capacity to investigate product failures; and to coordinate efforts across a spectrum of issues and companies involved in manufacturing biological products related to product characterization, safety and efficacy determinations and supply impacts. Some of these successes include:

- The lack of a blood donor test for West Nile Virus (WNV) – CBER laboratories developed and tested WNV standards and performed *in vitro* tests that supported policy making and guidance writing to safeguard the nation's blood supply.
- Donor testing for Chagas disease – CBER-led intensive interactions with industry that facilitated the development, testing and licensure of an ELISA test to detect T.Cruzi antibodies in donors. This work was done in collaboration with WHO/PAHO, the American Association of Blood Banks and CDC.
- Transmission of transmissible spongiform encephalopathies (TSEs or "Prion diseases") to humans from materials of human or bovine origin indicated a serious potential risk to recipients of biological products. An FDA Guidance in this area and many public meetings/workshops were initiated working together with NIAID/NIH, WHO, PAHO, academia, the American Red Cross and the NIBSC of the UK.
- Lack of standardized measurements for doses of adenovirus vectors led to difficulties in comparing different clinical trials in terms of dosing related adverse events and efficacy concerns. CBER led the partnership with industry and academia to develop an Adenovirus Reference Material (ARM) that is now available worldwide.
- CBER had been regulating musculoskeletal, skin and ocular tissues since 1993 but the focus was narrow. To ensure that the safety of newer cell therapies, such as reproductive cells and tissues and hematopoietic stem/progenitor cells, CBER needed to develop regulatory pathways for these products and advance the tissue rules. CBER proposed and finalized three rules that became effective in May 2005. In addition, CBER has published numerous Guidances for industry to help the tissue industry implement these rules.
- Safety of xenotransplantation and animal-sourced blood factors. Because of CBER's scientists' expertise in development of

important product quality tests, all xenotransplantation products are now rigorously tested for expression of infectious retroviruses.

- Home-Use HIV Test Kits – CBER virologists, epidemiologists and statisticians working together with CDC and NIH developed a set of acceptable standards for performance of these test kits and worked to insure that clinical testing could be performed efficiently and rapidly.
- Mumps – CBER testing and collaboration with NIBSC confirmed that current non-human primate neurotoxicity tests for mumps vaccine was not statistically predictive of human risk for vaccine-induced meningitis. A prototype pre-clinical neurovirulence safety test using rodents predictive of human risk for vaccine-induced neurotoxicity was developed by CBER and is being validated through a joint collaboration with WHO.
- Safety and efficacy of hemoglobin-based oxygen carriers (HBOCs). CBER developed better preclinical tests of oxidative chemistry, NMR and mass spectroscopy to predict safety and efficacy performance in clinical trials of HBOC products.
- Statistics innovations: simultaneous tests for non-inferiority and superiority – CBER statistical scientists developed and proved statistical methods for determining that clinical trial outcomes reflect product benefit and will better ensure product performance after licensure.

6. CBER Challenges in the Next Five Years

In the wake of huge increases in support for medical product discovery science, similar support is needed for FDA to maintain an advanced scientific expertise and to develop the new product evaluations science to efficiently review and support these new candidate complex biological products and facilitate their progress to marketed products. Infrastructure needs at CBER just to bring scientific capacity up to a realistic level of support are significant and overwhelming following years of funding challenges. However, the prioritizations formula now being utilized by CBER should identify the most critical needs and approaches. Yet the scientific infrastructure needs to advance and grow to prepare for current and future products. Support for adequate office and laboratory facilities at White Oak will be important. CBER products bring unique capacity to White Oak, but also challenges and resource needs. CBER scientists require BLS3+ labs and animal facilities for vaccines and blood product issues; NMR flow cytometry core and other unique equipment; quality assurance laboratories and the co-localization of research-regulatory and regulatory science staff. The CBER Subcommittee is concerned that the move from the NIH may be detrimental to the morale of CBER scientists who will then find themselves distantly located from their research collaborators on the NIH campus and from the many seminars and scientific expertise

available within the NIH. We anticipate that a significant management effort must be undertaken to address this potential problem.

CBER scientists have identified nanotechnology, genomics and advances in vaccine development as five year needs for increased resources. CBER does obtain funding for lot release, but insufficient for several initiatives needed for lot release. The ability for CBER to continue to fund its research programs through collaborations with NIH and CDC are critical five-year issues.