February 10, 2006

SITE VISIT REPORT
REVIEW OF INTRAMURAL RESEARCH
OFFICE OF BLOOD RESEARCH AND REVIEW
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

1. Date of Site Visit: July 22, 2005

2. Office: Office of Blood Research and Review

3. On July 22, 2005, a team of independent reviewers conducted a review of intramural research programs within the Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA)

4. The members of the review group were:

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5. The FDA participants in the review included:

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6. This site visit was a periodic review of the progress and performance of the research program of the Office of Blood Research and Review. The review was intended to be an overarching summary of the research program's goals and support and not a focused review of individual investigators and their work.

7. The review included evaluation of background information about OBRR and its function within the mission of CBER; written research program descriptions; the Review of Research Programs at CBER report (dated October 21, 1998); investigators' curricula vitae; selected publications; and oral presentations followed by questions and discussion.

8. Summary of the 1998 report recommendations: The 1998 review committee strongly endorsed the fundamental need for basic science research at OBRR to support the regulatory mission of the Office and for adequate funding of that research program to assure its success and its ability to attract first-rate scientists. "The Committee recommends . . . that it is of greatest importance to provide the adequate support and expanded funding so that cutting-edge research and cutting-edge scientists continue to be attracted to work in an Agency that is so central to both the health and welfare of our economy." And: "Independent of the money for the review process, this Committee unanimously believes that it is critically important that the funding for basic research within the Center be expanded to facilitate and allow CBER scientists to carry our the evaluative part of their mission."

9. Summary of Review Findings:

Background

As one of three product offices within the FDA's CBER, the OBRR seeks to fulfill the Center's vision of "innovative technology advancing public health." To achieve this and to participate fully in the FDA's Critical Path research initiative, the OBRR maintains an active laboratory program with a focus on mission-related research to enhance the scientific regulation of blood-derived and analogous products; medical devices used to collect, process or store donated blood; and retroviral diagnostic tests. The core programs are oriented toward detection and control of infectious agents relevant to blood products and the characterization and standardization of blood components, plasma derivatives and related devices. Additionally OBRR engages in epidemiological studies in methods and development research to enhance product review and surveillance.

The OBRR research is primarily targeted at current FDA regulatory issues, but it attempts to maintain flexibility to respond to new regulatory concerns and safety issues. As is discussed below, these objectives create their own set of issues. The FDA concept of the researcher/regulatory scientist who both understands regulatory issues and has scientific expertise and research experience is unique, but absolutely essential for the continued successful implementation of the Critical Pathway model. The presentations and background material provided to the committee about the research programs in OBRR clearly demonstrate that both the Division of Emerging and Transfusion Transmitted Disease (DETTD) and the Division of Hematology (DH) have successfully managed to develop research programs with priorities that are directly relevant to the regulatory mission of the FDA. These research programs have made substantial and significant contributions supporting the Critical Pathway program.

Principal investigators and senior research staff at OBRR are expected to spend about half their time on research activities and half on regulatory activities. In actual fact, however, this balance is rarely achieved, and it does not account for other significant and time-consuming activities such as program management and administration. Nor does it account for regulatory time frames and priorities and similar issues that take precedence over research. Despite the fact that the senior scientists are clearly short staffed and under funded, their in total programs have typically published more than 50 articles per year, many in prestigious peer-reviewed scientific journals, and they have obtained favorable assessments on their periodic external laboratory site visits.

In addition to its regulatory and research responsibilities, OBRR has also sponsored a number of workshops in recent years, which provide a forum for broader discussion of new research and thought, contribute to the establishment of standards, and allow comparison of progress being made in numerous fields that relate to the OBRR mission.

General Findings

To respond to the questions posed by the CBER staff, the committee identified and discussed the challenges to further development of the OBRR research program. These include:

1. The breadth and focus of the research agenda reflecting the wide range of identified needs.
2. The need to remain in complete control of the agency's research agenda because of its unique mandate, and the limits this places on the potential for extramural collaboration.
3. The difficulty in attracting new researchers given a relatively low pay scale, competition from industry, the heavy workload and expected dual responsibilities in regulatory affairs and research, and the limited opportunities and defined pathways for advancement and academic promotion.
4. The limited laboratory resources, including fellows and technicians, space (an issue that may intensify in the coming years), equipment, and other supplies.
5. And a limited budget for research, either appropriated by Congress or from other acceptable sources.

Overall, the committee concurred that the OBRR research program merits high grades for the depth and quality of the research, especially considering that each investigator is simultaneously responsible for a huge regulatory workload as well as working within the other limitations mentioned. The DETTD and DH have productive and diversified research agendas. Both divisions presented excellent examples of the current and future application of their work to the Critical Pathway of biologics product development and availability. They are to be commended on their productivity in this regard in spite of the lack of resources both in terms of staffing and money to conduct research.

Committee members who have been familiar with the research programs at OBRR over a period of years note that there has been a striking improvement over time in the following areas:

1. Focus and relevance. Previously, the program was relatively unfocused and much of the research, though interesting, was not relevant to the critical mission of CBER. The research presented for this review had direct relevance to the Critical Pathway of biologics product development and availability.
2. Quality. In addition to mission relevance, the quality of the research has also improved; many of the ongoing studies are equal in quality to those in the intramural program at the National Institutes of Health (NIH) and of sufficient caliber to compete for RO1 and other NIH grants.

3. Diversity of funding sources. In times of appropriated budget restrictions at the FDA, the investigators have been innovative in finding alternate funding sources and in establishing collaborations that expand their capabilities without increasing costs.

OBRR leadership is commended for their success at maintaining a stable, productive research and regulatory organization, including key staff at multiple levels that are bright, motivated, collegial and engaged. The challenge of maintaining a productive program while balancing allocations of research principal investigators, other fixed staff positions, and the very limited temporary fellowship slots and dwindling equipment and reagent dollars is daunting. In general, OBRR appears to have successfully maintained a strong interface between the research interests and activities and the areas of regulatory oversight, resulting in capable investigators who both contribute to the advancement of their fields of expertise and who are knowledgeable and thoughtful regulators able to engage scientists in for-profit and not-for-profit industry on an equal footing. This balance should be continued with the goal being to enhance and assure this transparent but nurturing research/regulatory interface.

One specific point that bears mention is that many of the OBRR scientists have developed ongoing collaborations with laboratories outside of the FDA that help support the research program. They should be commended for taking this initiative and the committee encourages them to continue to initiate such collaborations whenever possible. The collaboration between FDA and NIH laboratories provides an excellent example of how government agencies with different missions can collaborate in ways that both support and enhance their respective missions. Such collaborations further the OBRR research program by providing access to equipment and facilities that cannot be acquired at the current level of funding. The close proximity of the OBRR offices and laboratories to the NIH on a single campus is extremely important for this successful collaboration, and the committee strongly recommended that this be maintained in order to encourage further research interactions between FDA and NIH.

Research Program Concerns

Despite the review committee's affirmation of the quality and integrity of the OBRR research program, a number of issues and concerns were raised during the discussion.

The committee discussed the challenges to the further development of the OBRR research program. These include

1. The breadth of OBRR's research agenda reflecting the wide range of identified needs.
2. The need to remain in complete control of the office's research agenda because of its federal mandate; this, in turn, limits the potential for extramural collaboration.

3. The difficulty in attracting highly qualified new research scientists given a low pay scale (and competition from industry), the expected dual role of regulatory affairs and research, and the poorly defined pathways for advancement and academic promotion.
4. The limited laboratory personnel resources (fellows/technicians) and space (an issue that is likely to intensify in the coming years).
5. The extraordinarily limited budget for research as appropriated by Congress (which is not likely to increase in the near future).

BREADTH OF OBRR RESPONSIBILITIES VERSUS NEED TO FOCUS RESEARCH EFFORTS

With the limited financial and personnel resources available to it, a major conundrum facing the OBRR research program is to define and adhere to the focus and mission of the research program. From a needs perspective, OBRR scientists should be engaging in all types of research:

1. Cutting-edge basic science research that seeks answers to the theoretical questions and that anticipates future developments and products and novel experimental therapies but that may not have any practical application in the immediate future.
2. Applied research to assess the safety, potency, and efficacy of candidate products and therapies that are currently under development or in clinical investigation or to address questions and issues that arise during or after the licensure process of a product.
3. Directly applicable research to develop methods and techniques to enhance regulatory oversight, quality control and standard laboratory assessments to ensure the safety, potency and efficacy of currently licensed products.

To do this effectively given the broad mandate of the OBRR's areas of responsibility and the need to react immediately to new situations or crises (such as the discovery that the West Nile virus could be transmitted from asymptomatic donors through transfused blood components) would require far more staff, funding, and laboratory resources than are currently available. Another issue is the extent to which limited research resources should be directed to working with and understanding new technologies that are not being regulated directly (eg, microarrays, nanotechnology), and how should priorities be established for these decisions and to avoid overlap among OBRR programs.

The committee wrestled with these issues but did not reach consensus. While some members of the committee believed that the OBRR has achieved a reasonable balance of its research and regulatory efforts, others felt that the limits imposed on staff by budget and other resource restrictions required a more highly focused approach to determine which research should be given priority. From this perspective, OBRR needs to decide whether it should try to maintain research expertise in the wide range of areas that it regulates or whether it should focus on a smaller number of topics so as to perform more in-depth research and have greater expertise and critical mass with existing staff. This

latter approach would require more dependence on outside sources for scientific expertise, although the ability for OBRR to do this effectively given its regulatory mission and responsibilities was not discussed with the committee.

A related issue is that the internal OBRR mechanism for selection of research to be performed should be carefully considered. The formal mechanism at OBRR for choosing the nature, direction, and priority of research to be carried out was not discussed with the committee. Given the limitation of research resources at OBRR, pertinent questions include: Is a given research topic, and the derived results, the most relevant information that OBRR needs in order to perform its regulatory function? What are the areas of investigation that are not addressed by industry, academic and research institutions that should be addressed by CBER in order to fully support its regulatory mission? For example, rare disorders, orphan diseases, or new and emerging diseases and special problems that are unlikely to be studied by industry or academia perhaps should be considered a research priority for the FDA.

These interrelated decisions will be difficult, and the best course is neither easy nor obvious. Each option requires compromise that will need to be balanced against mission goals and available resources.

BUDGET AND PERSONNEL RESTRICTIONS

As noted above, the committee is extremely concerned about dwindling congressional appropriations of funds for research at the OBRR. The current funding allocation for laboratory reagents, supplies and equipment is less than half that in academic research settings, and there is an impending crisis in equipment maintenance and replacement. The issue for FDA scientists is not only the inadequate appropriations but also that they are precluded from applying for extramural funding from the NIH or of seeking research support from regulated industries. To their credit, the OBRR research scientists have been resourceful at seeking acceptable funding mechanisms to support their research.

On a longer-term basis, the paucity of research funding support also has a clear impact on the ability of OBRR to be competitive in hiring and retaining well-trained and promising young investigators who are also willing to learn the regulatory process.

The committee finds this situation unacceptable and emphasizes that it has the potential to seriously hamper productivity, makes it difficult for investigators to maintain their scientific expertise, and undermines morale and personnel retention. Creative mechanisms need to be considered to enhance this funding.

POTENTIAL RESEARCH BIAS AND THE REGULATORY ENVIRONMENT

The committee also raises concerns about the potential for research findings by OBRR scientists to inadvertently bias regulatory decisions. Several committee members raised the concern that the dividing line between research results from FDA scientists and official FDA positions may not be easily drawn in many circumstances. Given this fact, there is a

significant potential for research conducted by CBER to condition the design of pre-clinical studies, clinical trials, and product or industry regulatory decisions. This potential needs to be constantly considered, monitored, and addressed. Given the inherent tendency of scientists to promote and believe in their own work, OBRR needs to be attentive to such potential or perceived bias. One mechanism to address this concern is to continue to assure that primary product reviewers not report through scientific investigators who may be conducting research that could impact regulatory decisions.

VISIBILITY OF OBRR RESEARCH ACTIVITIES

Several committee members during conversations with industry representatives at the site visit learned that these representatives did not previously have a comprehensive view of the breadth and scope of OBRR research. Instead, they commented on the relative invisibility of the OBRR research program despite the fact that many of the research papers are published in select peer-reviewed journals and OBRR scientists present abstracts and papers at national meetings. This relative invisibility of the OBRR research program needs to be carefully considered and addressed. Doing so will enhance credibility and support for the OBRR research programs and might be an important aspect of educating Congress about the need for adequate funding of the research sites.

10. **Summary Conclusions and Recommendations**

Following its review of the OBRR research program, the committee offers the following recommendations:

1. The OBRR Intramural Research Site Review Committee strongly supports the FDA's continued emphasis on the importance of having a strong intramural research program to support its Critical Pathway program for effective and efficient regulatory activities. Having experienced and active research scientists involved both in the regulatory process and in the development and evaluation of scientific knowledge critical to the support of the regulatory activities is both sound and an essential component of the regulatory process that facilitates approval of biological products and protects the health and safety of the American public.

2. The OBRR senior management and the research scientists are highly commended for the depth and quality of the research program that was presented at this review, especially considering that each investigator is simultaneously responsible for a huge regulatory workload. Both DETTD and DH have developed productive and diversified research agendas that have increased in value over the years despite both budget and personnel restrictions, and both divisions have contributed to the Critical Pathway program.

3. The issue of sufficient time and qualified personnel to conduct the research remains important. The environment must be competitive to be able to attract outstanding young scientists and to retain more senior scientists as principal investigators and regulators. These issues are critical to the continuation of an effective and productive research program that supports the regulatory mission.

4. Among the most critical issues facing the OBRR research program is funding to support the basic activities, including reagents, supplies, and adequate equipment. The meager budget available to OBRR through congressional appropriations to support research directly is totally inadequate to conduct even a significant part of the wide range of important program priorities for which the Office is responsible.

5. Other options to increase the research budget through sources outside the FDA, although difficult and time-consuming for OBRR staff, are essential. Opportunities for collaboration and to seek acceptable funding sources must be pursued, although this must be done within the confines of the research priorities established by OBRR.

6. Adequate laboratory space and equipment are clearly essential components of a strong and productive research program, and the inability to assure these in the future could have a definite impact on future research activities. These issues need to be addressed as funding is sought to support the research program.

7. As was noted during the presentations and discussions, it is imperative that OBRR have the flexibility, capacity and resources to address new scientific and regulatory issues that become apparent at any point in time, perhaps as a crisis. Planning for these is difficult, especially when OBRR is also being faced with decisions about trying to develop a more focused research program. These issues must be factored into the decisions, however.

8. Given the current realities of the research funding limits, the committee recommends that OBRR must decide whether it should try to maintain a broader array of research activities that attempt to address the responsibilities within its mandate or whether it should focus on a smaller number of research topics and priorities, allowing staff to develop greater expertise and critical mass in fewer areas. If this model is adopted, OBRR could define a research matrix based on the potential for collaborating effectively with academia or industry through contracts and other mechanisms. The committee recognizes that this approach also requires funds and other resources that may not be included in the budget.

9. A related issue is the need for OBRR to define the best mechanism for identifying research priorities to be pursued, either through intramural research or outsourcing. A good mechanism may already be in place, but it was not discussed with the committee.

10. OBRR needs to be attentive to the potential or perception of bias introduced into the regulatory process by intramural research findings that are portrayed as FDA policy positions.

11. The visibility of the OBRR research program is an important aspect of its broader acceptance and support. Despite the meritorious work that is accomplished, there seems to be little appreciation outside the FDA for the extent and quality and importance of the work that is being accomplished. It is important for OBRR to define and exploit opportunities to expand their visibility. Certainly information available through the new website may be one opportunity, as are workshops, scientific presentations and publications, and other venues. Every opportunity should be taken to provide strong links between the research program activities and the regulatory capabilities that this research supports.

12. To directly enhance funding to support research activities, OBRR should work with FDA and Department leaders to identify creative funding mechanisms. Establishing a research endowment fund, for example, that could be funded by major philanthropic organizations, private donors, and regulated industry might be one example (see, for example, the CDC Foundation).