Improving the basis for FDA CBER identification of adverse effects of blood products and vaccines

A report of the Science Board to the FDA

20 May 2014

Chair: Lynn R. Goldman, M.D., M.P.H.
Dean and Professor, George Washington School of Public Health and Health Services

Russ B. Altman, M.D., Ph.D.
Professor and Chair of Bioengineering, Computer Sciences, Stanford University

Michael C. Gibbons, M.D., M.P.H.
Assistant Professor and Associate Chair, Johns Hopkins Urban Health Institute

Lawrence T. Goodnough, M.D.
Professor of Pathology and Medicine, Stanford University

Saad Omer, M.B.B.S., M.P.H., Ph.D.
Associate Professor, Global Health, Epidemiology and Pediatrics, Emory University

Patrick Ryan, Ph.D.
Head, Epidemiology Analytics, Janssen Research and Development

1. Executive Summary

In February of 2013, FDA charged a subcommittee of the FDA Science Board with the task of conducting a scientific review of the CBER Post-Marketing Safety Practices for blood products and vaccines, a function located in its Office of Biostatistics and Epidemiology (OBE). The committee carried out its work through teleconferences, review of background data, a self-study by FDA CBER's OBE and a site visit on December 17, 2013. In response to the charge, the subcommittee specifically focused on three dimensions of the work: "issues" – population surveillance, spontaneous reports, and genomics; "regulatory" – blood products and vaccines; and "big picture" – science resource management and public confidence. During the time of the review CBER underwent a major transition with the departure of the former OBE Director, Robert Ball, and management by an interim team. Of note is that Dr. Ball was listed a principal investigator for a number of OBE's science efforts in this area, and has had a prominent role in the authorship of publications. It is hoped that OBE will be able to recruit a strong science and public health leader to take his place. Despite this transition the review went smoothly and the Subcommittee was pleased with CBER's responsiveness to our requests for data, and found the site visit to be informative as well.

To summarize our recommendations, which are given in full in the sections below:

- General: CBER needs to more effectively communicate its activities in OBE. It needs an anticipatory process to adapt its approaches to changes in the healthcare delivery system. It needs to consider how to improve its capture of adverse effects on subpopulation groups like minorities and women.

- Science and Resource Management: This issue was flagged in the self study. Budgets for FTE and other resources need to be more clearly articulated, stable and predictable. Staff vacancies need to be filled more quickly. At the same time OBE needs to more vigorously engage the scientific community in its work, while at the same time, OBE scientists need to have a stronger presence publishing and presenting their work publicly.

- Population Surveillance: CBER should consider establishing Data Safety Monitoring Board – like processes as a way of obtaining more robust external scientific review. Science workshops would also provide enhanced external input. We support the focus on pregnancy related outcomes. We recommend expanding and strengthening international collaborations particularly for rare but clinically important outcomes.

- Spontaneous Reporting: We would recommend that CBER expand the requirements for manufacturers to include events occurring outside the US and to be more proactive in exchanging safety information with other national regulatory authorities. Blood product adverse event reporting needs to be extended to serious events other than those resulting in mortality. We support CBER's exploration of social media approaches.

- Genomics: We support CBER's effort to recruit scientists with expertise in genomics and informatics related to genomics data but would recommend, in the short term, that CBER consider collaborating across FDA centers and with academics to more quickly increase its pool of expertise. As noted above, there is a need to expand the range of scientific input being made available to CBER and specifically in this area to make use of external peer reviewers in the development and evaluation of projects to assure that the portfolio of projects is more at the state-of-the-art. CBER, and FDA generally, need a stronger computational infrastructure and scientific staffing to support the analysis of genomics data.

2. Introduction

The FDA Science Board has been charged with conducting a review of the scientific basis for CBER's current and planned post-market safety effort for licensed vaccines and blood-derived products. This function is housed within CBER's Office of Biostatistics and Epidemiology (OBE) and is one aspect of the Office's public health mission to ensure the safety of CBER regulated biologics within the FDA regulatory framework. In addition to vaccine and blood products, CBER regulates allergenics, cell and gene therapies, tissues, xenotransplantation products, and related devices (including certain in vitro diagnostics). Vaccines comprise 20% of CBER regulated products. OBE's involvement is across the lifecycle of a product and involves its three Divisions: Epidemiology (DE), Biostatistics (DB) and Risk Assessment. In the pre-licensure phase, OBE participates in multidisciplinary review teams that evaluate the product licensure submissions. By law FDA evaluates the benefits of a biologic product in relation to its risks, reviews product characteristics and manufacturing processes, and assesses the integrity of underlying data. DE reviewers evaluate sponsors' proposed pharmacovigilance plans; identify risks, potential risks, and missing information; recommend risk mitigation strategies, e.g., labeling modifications; and whether any further studies are needed. DB informs the assessment of safety and efficacy from clinical trial data. OBE Risk Assessment staff conduct and review risk assessments where needed. Thus, by the time that post-market activities are underway, OBE already has been quite engaged with a given product.

FUNCTIONS OF THE OFFICE OF BIOSTATISTICS AND EPIDEMIOLOGY

Division of Biostatistics

- Review of clinical study and bioassay data and statistical analyses
- Methods Development

Division of Epidemiology

- Review adverse event reports, pharmacovigilance plans, study protocols
- Conducts surveillance and epidemiological studies

Risk Assessment Staff

- Conducts quantitative benefit risk assessments & modeling
- Simulation modeling and quantitative analyses

Research Team

- Genomics Evaluation Team for Safety
- Epidemiology Team
- Biostatistics Team

Administrative staff

Special support for contracting, visiting academic faculty and research fellows

Post-licensure, DE monitors a number of data sources. They monitor industry case reports, periodic reports and any required postmarketing studies. They routinely scan the medical literature for case reports, studies, and other publications relevant to the safety of their assigned product portfolios, as well as staying abreast of any product safety signals that are emerging in other countries. They manually

review all expedited individual spontaneous reports in the FDA Adverse Event Reporting System (FAERS) and all serious reports in the Vaccine Adverse Event Reporting System (VAERS) databases. They also develop and review aggregate FAERS and VAERS information.

In recent years, the demands on OBE have been challenging. First, scientific advances have enabled OBE to develop more sophisticated approaches to postmarking safety surveillance. Over the years, spontaneous reporting systems have been a mainstay for all FDA postmarketing safety surveillance efforts, including those at CBER. These pharmacovigilance systems are in essence observational and passive in nature. According to OBE, they are still the best source of unexpected safety signals, which can be rapidly communicated from the point of care to the FDA for evaluation. The DE has developed methods to identify which such signals require follow-up, and has utilized observational epidemiologic studies to validate these signals. More recently, DE is taking advantage of powerful microcomputers and large healthcare databases to develop population-based surveillance projects like their collaborative effort with the Centers for Medicaid and Medicare Services (CMS) to evaluate safety of pneumococcal and influenza vaccines among the elderly (>=65 years old) and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system (vaccines) and the Blood Safety Continuous Active Surveillance Network (Blood-SCAN). In theory, availability of genomics data may further enhance DE's ability to identify safety signals. CBER hopes to better understand gene-biologic interactions that are involved with safety issues, not only to improve pharmacovigilance but also to enhance regulatory decision-making.

A second challenge is rising congressional expectations of CBER that were transmitted through the FDA Amendments of 2007. This has resulted in significant growth of OBE, from 47 FTEs and 5 post docs in 2008 to 81 FTEs and around 20 fellows and science support contractors in 2012.

3. Subcommittee Charge and Objectives

At the May 2, 2012 Science Board meeting, the FDA Science Board supported the formation of a subcommittee to review the CBER Post-Marketing Safety Practices. Initially broader in scope, the charge was narrowed to include just two categories of products regulated by CBER: blood products and vaccines. According to the final charge (as revised 2/19/2013):

The FDA Science Board is charged with conducting a review of research to improve CBER's current and planned post-marketing safety practices for vaccines, blood and blood-derived products. Review objectives include research to improve:

- *Processes and analysis tools FDA/CBER uses for identifying safety signals for CBER regulated vaccines, blood, and blood-derived products in FDA spontaneous reporting systems, especially the Vaccine Adverse Event Reporting System (VAERS) and the Adverse Event Reporting System (AERS).*
- *Approaches FDA/CBER is taking to use population-based healthcare databases for both safety surveillance and hypothesis testing studies of vaccines, blood, and blood-derived products including the FDA/CBER's Mini-Sentinel projects, PRISM and BloodScan; collaborative activities with other government agencies including CMS and CDC; and special studies with private health care providers.*
- *Efforts to use genomic data from the post-marketing period to improve the safety of CBER regulated vaccines.*
- *Efforts to develop and evaluate novel methodological approaches in the post-marketing safety areas outlined above.*

Major areas for Review

1. Spontaneous Reporting System – Development of methods to improve efficiency and validity of inference

   a. *Statistical data mining*
   b. *Artificial intelligence approaches, especially text mining*
   c. *Incorporation of external information about intrinsic properties of vaccines through collaboration with Georgetown University's Center of Excellence in Regulatory Science and Innovation project.*

2. *Population-based surveillance systems - Developing New Vaccine, Blood and Blood-derived Product Safety Surveillance Infrastructure and Capabilities*
   a. *Mini-Sentinel Initiative - Post-licensure Rapid Immunization Safety Monitoring (PRISM) and active surveillance (including coordination with Vaccine Safety Datalink (managed by CDC) and Blood Safety Continuous Active-surveillance Network (Blood-SCAN) to create an inpatient surveillance system for blood safety*
   b. *Centers for Medicaid & Medicare Services (CMS) – SafeVax and SafeBlood*
   c. *Other government data systems including Department of Defense, Department of Veterans Affairs, and Indian Health Service*
   d. *Private data holders*
   e. *International collaborations – research project on 2009 H1N1 influenza vaccine and Guillain-Barré Syndrome*

3. Genomics – Strategy for applying personalized medicine approaches to vaccination

   a. *Epidemiological studies of potential genetic risk factors for vaccine adverse effects and establishment of vaccine adverse effects registry*

4. Process of Review

a. Subcommittee formation and expertise; assignments

FDA appointed the Subcommittee on December 1, 2012. Members of the Subcommittee include three members of the Science Board (Altman, Gibbons and Goldman) and three other experts (Goodnough, Omer and Ryan). Goldman was asked to chair the Subcommittee.

The subcommittee had telephone conference meetings with CBER leadership on the following dates: 1/15/2013, 2/11/2013, 3/14/2013, 4/4/2013, 9/20/2013, and 12/13/2013, a site visit on 12/18/2013 and a post site visit call among Subcommittee members only on 12/20/2013.

In approaching its work the Subcommittee set about to specifically review:

- Processes and analysis tools FDA/CBER uses for identifying safety signals for CBER regulated vaccines, blood, and blood-derived products in FDA spontaneous reporting systems, especially the Vaccine Adverse Event Reporting System (VAERS) and the Adverse Event Reporting System (AERS);
- Approaches FDA/CBER is taking to use population-based healthcare databases for both safety surveillance and hypothesis testing studies of vaccines, blood, and blood-derived products including the FDA/CBER's Mini-Sentinel projects, PRISM and BloodScan; collaborative activities with other government agencies including CMS and CDC; and special studies with private health care providers;
- Efforts to use genomic data from the post-marketing period to improve the safety of CBER regulated vaccines; and
- Efforts to develop and evaluate novel methodological approaches in the post-marketing safety areas outlined above.

The Subcommittee requested that FDA CBER conduct a self-study to evaluate the strengths, weaknesses and opportunities to enhance its science efforts in post market surveillance of vaccine and blood products. Specifically the Subcommittee requested that CBER provide case studies for both vaccine and blood products. The Subcommittee also requested that CBER provide a number of background materials in advance of the site visit. These included:

- Research strategy
- Full listing of CBER-funded research projects related to post market surveillance of blood and vaccine products, perhaps over the last five years
- Biosketches of CBER researchers in this area
- Organization chart indicating the location of CBER researchers in this area
- Listing of CBER-funded extramural grants and contracts related to research in this area
- Budgetary resources for research in this area, including FTE, extramural and intramural funds
- Non-budgetary resources for research in this area, e.g., laboratories, libraries, computing resources, support contracts, pre-doctoral and postdoctoral fellows, etc.

Additionally during the site visit the Subcommittee requested additional information about budgetary resources, as well as a copy of a McKinsey evaluation that had been commissioned by CBER.

b. CBER preparations for review

1. Data and information provided to subcommittee (Appendices)

In advance of the site visit, CBER provided the following information to the Subcommittee:

An Overview of FDA Science Board Review of the CBER OBE Post-Market Safety Monitoring Programs for the FDA Science Board Review, dated August 28, 2013. This document in essence responded to the request for background materials. This document Includes:

- Appendix A, "List of Project Overviews"
- Appendix B, "Spontaneous Reporting Systems"
- Appendix C, "Population-Based Surveillance Systems – Developing New Biologic Product Safety Surveillance Infrastructure and Capabilities"
- Appendix D, "Genomics – Strategies for Applying Personalized Medicine Approaches to Biologics, Especially Vaccines"
- Appendix E, "Bibliography"
- Appendix F, "Biosketches"

CBER OBE Postmarket Safety Monitoring Programs for the FDA Science Board Review: Two Case Examples, dated September 19, 2013. (These are the case studies requested by the Subcommittee; CBER used Fluzone and febrile seizures and Octagam and thromboembolic events as cases.)

A Self-Assessment of the CBER OBE Postmarket Safety Monitoring Programs for the FDA Science Board Review, dated September 23, 2013.

After the site visit, in response to the Subcommittee request for a copy of the "McKinsey Report" that was referenced in the above document, CBER provided the following:

CBER OBE Project: Deliverable for the Center for Biologics Evaluation and Research (CBER) U.S. Food and Drug Administration (FDA), dated February 11, 2013. (No author is listed; this is a management review of OBE focused on the significant changes that had occurred since the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and a desire by CBER leadership to assess OBE's processes and organization and to identify potential opportunities to further improve OBE's performance. This assessment took place between October 2012 and December 2012.

2. CBER Self study conclusions

CBER summarized the conclusions of their self study as follows:

"OBE has expanded its regulatory mission and scientific capabilities since enhanced postmarketing safety authorities were granted to FDA in 2007. The public health effectiveness of the U.S. vaccine and blood supply depends upon public confidence, and CBER receives and must be prepared to address multiple "false positive" signals from external stakeholders on a regular basis. Thus, OBE has and will continue to invest the majority of its resources in population-based systems to refine and evaluate signals. However, OBE remains engaged in developments that might enhance signal detection from spontaneous reporting systems. In addition OBE has explored the impact of genetic polymorphisms on adverse event response. To some extent, the marketplace and FDA level initiatives will likely dictate the pace of OBE's engagement with genomic research. While some OBE initiatives undertaken in the last few years will not lead to operational tools, the majority of the signal refinement and evaluation methods have been operationalized. Thus, the primary risk to the progress made to date is not feasibility. Instead, the primary risk is a decrease in funding or available human resources." (CBER Self Study, p. 15)

3. CBER Conclusions

Spontaneous reporting systems

The Self-Study identified advantages and disadvantages of individual spontaneous reporting projects. The Self-Study noted that "the public health effectiveness of the U.S. vaccine and blood supply depends upon public confidence, and CBER receives and addresses multiple "false positive" signals from external stakeholders on a regular basis. Thus, OBE has and will continue to invest the majority of its resources in population-based systems to refine and evaluate signals." In terms of the individual projects:

Data Mining:

Advantages:

- *"Bayesian data mining has an advantage over other methods in its limitation of false-positive signals due to 'shrinkage' towards the null with low observed or expected counts. "*
- *"In addition to serving as a triage tool, the data mining application aggregates the intellectual efforts of different reviewers over time since analyses span the history of the databases and since permanent records will be accessible. "*

Disadvantages:

- *"The primary weakness of statistical data mining methods is that they deal with confounding, multiple comparisons, and sparseness of data rather than the inherent limitations of spontaneous reporting systems. "*
- *" In addition, our current statistical data mining methods are also limited in their ability to identify potential product-adverse event patterns that involve interactions between more than two products. "*

Network Analysis:

Advantages:

- *"Network analysis enables both visual and quantitative identification of patterns among the vaccines and AEs that might otherwise go unnoticed. "*

Disadvantages:

- *" The primary disadvantage of network analysis is the substantial resources necessary for validation and the possibility that the expected marginal benefit for pattern recognition might not materialize. "*

Text Mining:

Advantages:

• *"Currently, CBER would experience a small absolute time-savings and would experience some loss of fidelity to the original report content. If adverse event reporting were to increase then the resulting increase absolute time-savings might become significant enough to justify expansion of the system. "*

Disadvantages:

• *"More advanced uses of the system for automated case classification will require substantial validation effort."*

Population based surveillance projects

Key Points

Continued, Adequate Funding

"CBER has integrated surveillance into its annual budgeting processes and provides funding for core biologic safety surveillance activities. Budgetary uncertainties could hamper the commitment and curtail surveillance systems that already have a proven track record of positively impacting public health."

Staffing and Professional Development

"The second most significant challenge facing population based surveillance projects is the need to foster the development of a larger cadre of qualified physician scientists and epidemiologists both internally and at the Mini-Sentinel Operations Center. At times, this goal is hindered by the reality that skilled reviewers can return to clinical practice and are ideal candidates for higher paying positions in the pharmaceutical industry. Thus, retention is a constant challenge. DE staff determine the underlying medical rationale for the studies and heavily influence study design. In many instances, the collaborating academic pharmacoepidemiologists may have the ability to travel to meetings to present findings while government travel may be restricted because of reductions in travel budgets across government agencies. Finally, CBER could consider providing additional graduate training to skilled reviewers in biostatistics, informatics, and epidemiology from institutions with strong postmarketing safety programs in exchange for obligated terms of service to the agency. Pathways for such training might open under the auspices of the Reagan Udall Foundation, which is an independent 501(c)(3) not-for-profit organization created by Congress to advance the mission of the FDA by advancing regulatory science and research."

Integration of Safety Surveillance into the Regulatory Process

"Another challenge is the integration of population based surveillance projects into regulatory decision making. Norms have been informally developed, but formal standard operating procedures should be developed and approved by the Center. Routine use of these population-based systems require shared decision making between product offices and OBE on a level and frequency not previously encountered. In addition, OBE's regulatory project management support needs have increased as the volume of studies increases."

Genomics

Key Points

• *"The initial goal of OBE genomics activities was to advance research in identifying biomarkers of vaccine safety. Because of the complexities of the human immune response and the human genome this goal may be difficult to achieve."*

• *"OBE has several relatively large genomics research projects underway but is awaiting the outcomes before determining next steps."*

• *"GETS is leveraging the research efforts of NIH, other government agencies and stakeholders and the team is collaborating on regulatory research and review efforts within FDA."*

• *"OBE is planning organizational and programmatic changes that will dissolve the GETS and integrate its functions into the larger Associate Director for Research Group where it currently resides."*

c. Site visit

1. Process

The Subcommittee scheduled a site visit, which was originally intended to occur on October 8, 2013, but was rescheduled for December 17, 2013 due to a lapse in government appropriations. The Subcommittee assigned members to take responsibility to serve as principal reviewers in specific areas. All subcommittee members read all materials but members were prepared to lead off discussions in specific areas, and to be responsibility for completing first drafts in those areas. Assignments were:

Issue focus:

Population Surveillance: Saad Omer and Patrick Ryan

Spontaneous Reports: Tim Goodnough and Patrick Ryan (with assistance from Russ Altman)

Genomics: Lynn Goldman and Russ Altman

Regulatory focus (and case studies):

Blood Products: Tim Goodnough

Vaccines: Saad Omer

Big Picture:

Science Resource Management: Chris Gibbons and Russ Altman

Public Confidence: Tim Goodnough and Chris Gibbons

2. Agenda

Agenda for Site Visit
Tuesday December 17, 2013
FDA Science Board Review:
CBER OBE Postmarket Safety Monitoring Programs
Woodmont Office Complex 2 (WOC2) Rm 31011451
Rockville Pike, HFM-210
Rockville, MD 20852-1448

8:30am: FDA Deputy Center Director Dr. Peter Marks will provide initial overview of her vision for Division of Epidemiology PM Surveillance, role of surveillance and how these efforts fit with CBER's mission and other CBER activities.
9:00am: Overview from Steve Anderson of structure and function of CBER's surveillance groups, impacts of Dr. Ball's departure, how science direction and management are provided to the group.
Overviews from David Martin (DE) and Rich Forshee (Research Staff) of their vision and leadership of reviewed programs.

9:30am: Population based surveillance
· 15 minute Overview presentation by FDA tailored to Questions/Issues raised by Committee reviewers **(Presenter: Dr. Michael Nguyen)**
· 15 minutes by primary reviewers
· Questions and discussion by entire subcommittee of possible findings and recommendations.
10:15am: Spontaneous reporting
· 15 minute Overview presentation by FDA tailored to Questions/Issues raised by Committee reviewers **(Presenter: Dr. Craig Zinderman)**
· 15 minutes by primary reviewers
· Questions and discussion by entire subcommittee of possible findings and recommendations.
11:00am: Genomics
· 15 minute Overview presentation by FDA tailored to Questions/Issues raised by Committee reviewers **(Presenter: Richard Forshee)**
· 15 minutes by primary reviewers
· Questions and discussion by entire subcommittee of possible findings and recommendations.

11:45am: LUNCH Subcommittee has closed discussion about observations over lunch.

OBE staff would join Committee members for the following sessions
12:30: Goodnough leads off discussion on **blood products** and other possible findings
1:00: Omer, leads off discussion on **vaccines** and other possible findings
1:30: Gibbons and Ryan leads off discussion on **resource management** and other possible findings
2:00: Goodnough and Gibbons leads off discussion on **public confidence** and other possible findings

Committee members would be alone for the following session
2:30-3:30: Subcommittee meets *in camera/telecon* to discuss findings and recommendations to propose to the Science Board and process for finalizing our report

OBE Managers would join Committee members for the following session
3:30-4:00: Summary session to answer any final questions, additional discussion, decide next steps.
4:00pm: Adjourn

5. Findings

a. General

Our review found that CBER/OBE has a long history in post-market safety evaluation of biologic products. CBER/OBE's current vision, which was developed after the expansion of their mission in 2007, is for a system that will automatically generate safety signals from a range of data sources and seamlessly integrate the evaluation of those signals with methods to allow rigorous inference in support of regulatory decision making. In the view of the review committee this mission is the right mission to drive the work of CBER and to enable it to respond effectively to the current and emerging challenges facing the agency. Since 2007 CBER has significantly increased its staff particularly in the Office of Biostatistics and Epidemiology as well as the Division of Epidemiology. This is also seen in the addition of the Genomics program in 2010. The committee found the new staff of young scientists and physicians to be of high quality, hard workers who are committed to the work of CBER and achieving the mission. In addition the committee finds, though, little evidence that the general public is aware of the fine work of these civil servants despite all their efforts.

In the view of the review committee, CBER has made significant strides in an effort to be responsive and proactive about maintaining an organization that employs not only the best scientists and staff, but also is using the newest technologies and evidence based scientific methodologies to conduct its work. This is primarily, though not only evident in the addition of the Genomics program in 2010. The review committee finds that in addition to Genomics, CBER needs to consider the possible impacts of emerging issues that are occurring in healthcare that could have significant implications for CBER, the Agency and the public. These include, but are not limited to a) changes in point-of-care, b) changes in health laws and coverage (Affordable Care Act), and electronic health records. Specifically, changes in point-of-care refers to the reality that while historically the vast majority of healthcare occurred within the context of a recognized clinical setting, increasingly healthcare services are being provided by an array of mid-level providers and other caregivers in nontraditional and non-clinical settings that include grocery stores, shopping malls, pharmacies, community centers and even the homes of patients.

In addition, the Affordable Care Act likely provides many opportunities, and potentially several new challenges, that may be important for CBER to consider. At a minimum, the emerging role of Electronic Health Records and Health Information Exchange as mandated by the law, may represent new opportunities for data collection or enable mechanisms to enhance ongoing surveillance and reporting efforts.

Another emerging area of likely significant importance for CBER is the potentially differential impacts and outcomes associated with specific populations. Specifically a significant and growing literature documents the often differential susceptibilities, excess morbidity and mortality associated with special populations including racial and ethnic minorities, those with less access to care, pregnant women, and immunocompromised individuals. As our nation and our healthcare system work to ensure optimal outcomes for every citizen, it is clear that the role of the FDA and in particular CBER in helping to accomplish this goal cannot be overstated.

Recommendations

Recommendation a.1. In the future OBE should work to more effectively communicate its activities at the Center and at the product-specific level to the general public. Presentations at scientific and industry related meetings and scientific research publication, while important, should not be seen as adequately communicating OBE accomplishments to the general public. CBER should consider the value of using traditional as well as current and emerging media to communicate its message more effectively to the general public.

Recommendation a.2. OBE should consider undertaking (or commissioning) an environmental scan to identify how the changes underway in healthcare affect the administration of and reporting of adverse consequences due to these biologic products (vaccines and blood products) and to consider what (if any) research or other activities are warranted to adapt to these changes

Recommendation a.3. OBE should consider undertaking (or commissioning) an analysis of the degree to which current procedures capture adverse effects on members of specific subpopulation groups, e.g., federally recognized minorities, those with less access to care, pregnant women, and immunocompromised individuals.

b. Science and Resource Management

The committee greatly appreciated the efforts of CBER staff to help prepare us for the site visit by providing useful and organized documentation of their mission, activities, and projects. CBER leadership also helped explain the process of budgeting and finances at the Center to the committee during the site visit, and we recognize that this is a critical topic, which underlies all the activities it supports, and which deserves careful attention.

We note that the scientific evaluation of CBER itself was disrupted by the federal government shutdown in October of 2013, and this is symptomatic in many ways of the stresses felt by all parts of the FDA, including CBER, as they try to plan for the financial realities of working for the government. It was very clear that CBER leadership has a full understanding of the different challenges in hiring and funding CBER scientists, and were generous in sharing these insights with the committee. It is also apparent, however, that there are substantial challenges to CBER in the area of funding that, if addressed, could markedly improve their ability to focus on their mission.

To be blunt, it seems to the committee that CBER lacks adequate financial resource to support its mission. OBE resources are a combination of FTEs from their ongoing budget and additional funds from internal and external grants, contracts, cooperative agreements that provide additional funds for additional activities. The committee was surprised to see that OBE is challenged in both areas. In the area of FTEs, OBE seems to be chronically running below its FTE ceiling with several open positions that are not filled. At a time when financial resources are tight, and many units have likely been squeezed by the normal budget pressures, it seems like a lost opportunity to not at least have all approved positions filled. According to OBE, in early 2013, several Medical Officers left OBE to pursue other

opportunities leaving several vacancies. As OBE noted during our review, "it is extremely difficult to recruit medical officers with the requisite skills to perform the postmarket safety work. To compound the challenges, due to the uncertainties around the budget and to buffer us against the sequester, CBER had put in place a temporary hiring pause, in order to maximize FTE underburn and provide a financial buffer against the unknown impact of the sequester. FTEs that were not filled (underburn) were essentially turned into operating dollars at the Center level. It wasn't until late FY13 that the pause was lifted. We have successfully begun to rebuild our staff numbers in OBE and expect to be nearly fully staffed by mid-2014." The committee noted these challenges, but nonetheless concluded that the gap between available and filled positions should generally be much smaller. We agree that appropriately skilled Medical Officers are difficult to recruit, more the reason to recruit aggressively when positions are vacated, as well as to seek to understand and rectify any conditions that may be adversely impacting job satisfaction in OBE. In the area of grant and other "soft" support, the committee was surprised to see very large fluctuations in the amount of funded work, varying from $12M to $6M or less even over the last few years. This creates a very difficult situation with respect to scientific project planning, continuity, and staff attention. Taken together, these two sources of funding conspire to make funding of CBER's mission much more stochastic than is best for the safety of the American public in the context of vaccines and biologics.

As a result of both the chronic under-staffing and the swings in available project dollars, it is not surprising that it is difficult for OBE to conduct regular and impactful assessments of the scientific progress of both the FTE staff and the staff hired on these external shorter-term projects. The Committee noted that several projects seem to lack external review from scientists outside of the FDA, who are un-conflicted and not currently collaborating with FDA or funded by FDA in some other manner. The Committee believes that scientific peer review is critical for quality control and for decision making under limited resources, and so in addition to firming up the basis for funding by making it predictable and more "smooth", the committee believes it is critical for CBER to employ critical and timely review of projects both at their inception and during their course, in order to identify both wins and losses and adjust the allocation of resources accordingly.

<u>Recommendations</u>

As a result of our discussions with CBER leadership during the site visit and review of the material provided, the committee makes the following recommendations.

Recommendation b.1. CBER needs to have a better articulation of staffing and budget resources associated with all its activities, currently and over time. The committee understands that the sources of funding for CBER are varied and consist of both predictable and less predictable sources. Nonetheless, it is critical that the CBER leadership have a consolidated budget, at fairly fine granularity that shows how each of its projects/efforts is being funded and also looks out at least 3 years in order to be useful as tool for rebudgeting and reprioritization. This data will not only be useful as an internal tool for decision making and resource allocation, but also as a tool for negotiating its budgets and choosing its externally funded projects with the outside. It was our impression that because the FTE budget is relatively fixed (although under-staffed), the leadership focused mainly on the external budget, and this

produced an impression of wild fluctuations that are probably less dramatic because the total budget is significantly larger.

Recommendation b.2. OBE needs a stable and predictable source of support for its activities, and its percent dependence on stochastic funding sources external to FDA should be no more than 10-20%, and most activities should be funded by hard money from FDA and other stakeholders, who commit user-fee dollars to these activities. The safety of vaccines and blood products is of critical strategic importance for the public health, with a very different profile required compared to drugs. These require a portfolio of research and review that is predictable, regular and does not fluctuate wildly as different scientific programs and opportunities arise. The "feast and famine" of funding associated with unreliable external grants should have only a minimal affect on general operations of CBER, and it is critical that FDA leadership ensure more stability in funding—while also ensuring that approved positions and projects are fully staffed and productive on agreed timelines.

Recommendation b.3. It almost goes without saying that the committee feels that OBE must make a concerted effort to fill all vacant scientific (and staff) positions, working with FDA leadership to identify creative ways to attract skilled scientific talent in areas that are in great demand (genomics, informatics, e.g.).

Recommendation b.4. As OBE gains a more level approach to funding and staffing, the committee believes that further quality and stability would be afforded by the increased engagement of external scientific community in development and review of scientific initiatives. Such advisory groups should be separate from existing scientific collaborators, and should enter these review activities with no pre-existing personal interest in the proposed or reviewed projects. OBE scientists should expect regular peer review (as do all scientists in industry and academia) and should recognize that projects that do not perform well could have resources removed or be ended. In choosing external scientific advisors, CBER should look broadly nationally and internationally with no biases in favor of local, convenient institutions.

Recommendation b.5. The committee noted that in some areas there is robust and diverse publication by many scientists in OBE. In other areas, a few individuals dominate the bibliography. This reflects, in part, the uneven distribution of expertise and staffing in different areas, and we expect that filling all vacant positions will partially help this situation. However, the committee feels that scientific publishing should be an expectation for all scientists in OBE—with emphasis on publications relevant to the CBER dual mission of science and review. As part of this, CBER (and all of the FDA) must re-emphasize the importance of professional development, particularly in the context of travel to key national and international meetings. These meetings are absolutely critical for both bringing the mission and perspective of CBER/FDA scientists to these groups, and to ensure that CBER/FDA scientists maintain state-of-the-art scientific knowledge as they approach their work. Again, the focus of these efforts should be professional development activities at the best national and international meetings, with no biases in favor of local, convenient places.

Recommendation b.6. The committee was generally very excited about the institution of population surveillance efforts at CBER (and the FDA more generally), and thinks that these are very exciting developments. However, they do raise issues in the area of resource management that deserve special attention. It is vital that there be robust procedures in place to evaluate the ongoing work in population surveillance. This is a new area, only enabled recently with the introduction of ubiquitous computational capture of information. At the same time, it may be fraught with difficulties as best practices emerge from the scientific community about all aspects of how to do this well (measurement, analysis, removal of bias, etc.). Thus, the best external advice will be absolutely critical both at project conception and ongoing evaluation. More than other areas, this may be a "wild west" for innovation and learning, and so CBER must be plugged into the best sources of wisdom. In the same vein, even the growth of spontaneous reporting methods will require external scientific advice, as the rate of new methods increases and powerful analytics become available. After a period of relatively slow change in epidemiology, the committee expects the fusion of informatics, population monitoring, epidemiology, genomics, and spontaneous reporting to create fantastic opportunities. In order for CBER to manage these effectively, they will not only need stable funding plans and full staffing, but also the best external advice to help them make decisions about resource allocation

c. Population Surveillance

Surveillance of healthcare data, such as administrative claims and electronic health records, offers tremendous opportunities to support the identification and evaluation of the effects of medical products, and CBER is commended for making substantial investments in exploring and developing in this area. Further focus in this area is likely to yield important improvements in the capacity and reliability of surveillance-based data analyses to support CBER's safety operations.

In recent years, CBER/FDA has made substantial investments in population surveillance. The areas of emphasis for investments – improvements in methods and data and the development of new population surveillance efforts – have been appropriate and forward looking. The investments, if sustained, are likely to continue to provide dividends in the coming years. Overall, the subcommittee was pleased by CBER's efforts in the area of population-based surveillance of vaccines and blood products. However, the subcommittee identified several areas for improvement.

The Mini-Sentinel pilot project initially established a distributed network of administrative claims from large private payers across the US. A fundamental limitation of this data network is that private payers often under-represent certain subpopulations, such as children receiving immunizations through state Medicaid programs and elderly who receive flu vaccines and other services through Medicare benefits. Data from individual inpatient encounters inadequately capture more detailed information; for example, for blood and blood derivative products, specific product-identifiers as well as information about surgical procedures and inpatient treatments. Recognizing these limitations, CBER staff have looked to augment the capabilities afforded by Mini-Sentinel by incorporating additional data sources through the initiation of a partnership with Hospital Corporation of America as part of its BloodSCAN pilot, as well as through analyses through the Federal Partners Consortium including CMS and its Medicare claims data.

CBER's efforts for population surveillance have primarily focused on signal refinement and evaluation, whereby potential safety issues are identified from other sources (such as clinical trials, spontaneous adverse event reporting, or scientific literature) and a post-marketing study is conducted in response via modular programs or through the design and execution of a protocol-based assessment. This work has resulted in generating product-specific information, such as intussusception risk in rotavirus vaccination, as well as in enhancing center-wide capabilities for future analyses. One concern raised was the viability of expanding the current capabilities to meet the needs of all safety priorities across the CBER product portfolio; within Mini-Sentinel, each protocol-based assessment costs between $250,000 and $2,000,000, with as much as half of those resources dedicated to source record verification to assess outcome misclassification error.

As described within the Food and Drug Administration Amendment Act, FDA was to develop 'active postmarket risk identification and analysis methods.' As of yet, the data network established within the Mini-Sentinel pilot project has not been used for signal detection to identify risks of medical products, but instead has focused on the evaluation of risks identified from other sources. CBER staff highlighted its intent to eventually use these data for population-level data mining, and has pilot work ongoing to test one analytical approach but has not released this capability. Further research is required to develop and evaluate multiple alternative methods for risk identification and to establish the empirical evidence base necessary to enable CBER to execute large-scale analyses across its product portfolio for all health outcomes of public health interest.

The results from analyses of surveillance data are rightfully positioned as only one piece of information, used in conjunction with all other evidence, to support regulatory decision-making. The relative contribution of population surveillance to regulatory decision-making has not yet been established, in part due to lack of empirical evidence about the reliability of the observational analyses themselves. Of potential concern is that observational analyses can yield 'false negative' findings which are equally disruptive to the public confidence in the safety surveillance infrastructure.

Any robust safety surveillance system requires continuous generation of relevant hypotheses. Often these hypotheses are generated as a result of developments in fields not directly related to safety surveillance (e.g. immunology, cell biology, and clinical disciplines such as neurology and cardiology). Under the current system, most CBER safety studies are initiated by CBER staff and are conducted either in house or in collaboration with external contractors. Moreover, the primary mechanism for external input into new and ongoing protocols is through posting these protocols online and providing external stakeholders the opportunity to comment on them. While sharing the protocols is an excellent mechanism for ensuring transparency, it is not necessarily the most proactive and sufficient approach for seeking scientific input –particularly from non-industry stakeholders. Given the structure of research funding in the United States in which specific projects rather than labs/research groups are funded, vaccine company employees are more likely to have the compensated time available for commenting on online CBER protocols. Other related fields have evolved mechanisms for ensuring ongoing independent input. For example, Data and Safety Monitoring Boards (DSMBs) can ensure that a variety of stakeholders can provide input into clinical trials. Additionally, topic-specific workshops – such as those

organized by the NIH – can bring together individuals from a variety of backgrounds to generate relevant scientific questions.

Moreover, CBER does not routinely monitor administrative errors in products as they are used in medical practice. CBER needs to monitor administrative errors as well as product specific issues in fulfillment of its broader mission to prevent adverse health consequences of blood products and vaccines.

Pregnancy is a major gap in the premarket approval process. In this context, CBER's post-marketing surveillance activities are particularly important as they have the potential for filling this gap. CBER's PRISM program has initiated several protocols with a focus on pregnancy and birth outcomes.

FDA is considered a global leader in safety science and has a history of collaborating with international partners. Given that several important, but thankfully rare, outcomes require large denominators such international collaborations are particularly important. Pooled and meta-analyses of data from a variety of surveillance systems focusing on rare but clinically important outcomes provide an opportunity to evaluate these outcomes. One relevant example within the U.S. is the recent meta-analysis of Guillain-Barré Syndrome after influenza vaccination using data from several U.S. based surveillance systems. Collaborating with international partners on such analyses is likely to further strengthen population based safety surveillance.

BloodScan is in the developmental phase as a tool for continuous active surveillance. While the Mini-Sentinel PRISM pilot program has had some success with vaccines and BloodScan is now being developed for surveillance of blood and blood products, with an initial study focused on transfusion-related acute lung injury (TRALI). . Needed are large inpatient populations that include those that are heavily transfused and also may be candidates for other biologic therapeutics: patients undergoing stem cell or solid organ transplants; open heart surgical procedures; sickle cell patients; and patients with end stage renal disease undergoing hemodialysis.

Recommendations

Recommendation c.1. CBER should continue to have a diversified portfolio of collaborations across multiple disparate data sources for population surveillance. To minimize its risk of over-reliance on private-payer claims data, CBER should consider researching the use of electronic health records from both inpatient and outpatient settings, as well as actively engaging in international collaborations that are bringing together claims and EHR data across multiple countries to monitor product safety. A broader diversity in data will better support the products under surveillance and the diverse populations exposed to these products.

Recommendation c.2. Projecting from the prior year's annual budget, CBER's resources likely constrain them to perform fewer than 6-8 protocol-based assessments a year, insufficient when multiple safety issues of public health importance arise in close proximity. Further research and development is required to improve the efficiency of observational analyses, to reduce time and resource requirements. The newly-developed PROMPT tools may ultimately figure into an improved process, but require

substantial evaluation before they can be put into widespread use. Additionally, the relative merits and cost-effectiveness of source record verification should be assessed so that CBER can direct its limited resources where most appropriate. Finally it is likely that CBER requires more resources for this activity.

Recommendation c.3. Surveillance data about product exposure often are analyzed only at the population level. However, there are opportunities to systematically perform subgroup analyses to assess product effects within vulnerable populations of public health interest, such as children, elderly, pregnant women, and minorities. Such data are useful for risk management, not only on a population level, but also to support patient-level assessment of risk of an adverse effect.

Recommendation c.4. Methodological research is necessary to provide objective assessments about the empirical performance of analysis methods when applied to the observational data available for the study of vaccines and blood products and their risks of specific health outcomes of interest. Method operating characteristics- such as predictive accuracy, bias, and coverage probability- are needed to assess the appropriateness of the system and to allow calibration of effect estimates if the system is put in use. Such research likely requires both retrospective assessment of method performance of known product-outcome associations to quantify observational study concordance with the pre-defined ground truth, as well as prospective monitoring of signals generated to assess how observational results contribute to future regulatory decision-making. While collaborative work with CDER in this area is encouraged and should be fully supported, the unique nature of the products under surveillance within CBER necessitates independent assessment of method performance for CBER's specific use cases rather than generalizing from findings of method performance for safety assessment of prescription pharmaceuticals. Empirical assessment of the operating characteristics of the surveillance methods in use is necessary to provide objective criteria for interpreting study results and proper synthesis of observational evidence with other sources throughout the continuum of signal detection, refinement, and evaluation.

Recommendation c.5. CBER could benefit from a "DSMB"-type process to generate external review by disinterested parties and to generally improve the ongoing population surveillance process. Moreover, external input for identifying emerging hypothesis could be sought through workshops organized by the FDA, with multi-disciplinary participants, around specific product classes (e.g. influenza vaccines) and/or special populations (e.g. pregnant women).

Recommendation c.6. CBER could monitor administrative errors, e.g., ABO incompatibility-related deaths – in the context of existing efforts, for example, with CMS.

Recommendation c.7. Given new recommendations for use of a robust number of vaccines in pregnant women (influenza and Tdap vaccines) and vaccines on the horizon with likely pregnancy indication (e.g. RSV, Group B Streptococcus), CBER should continue a robust focus on pregnancy-related outcomes.

Recommendation c.8. FDA/CBER should continue and expand its international collaborations with special focus on the logistics (e.g. common data standards) for facilitating pooled analyses of data to evaluate rare but clinically important outcomes.

Recommendation c.9. CBER's newer initiatives in the area of active surveillance are valuable, but they requires an adequate and stable base of resources (funding, staffing), as well as stronger integration into the regulatory process, similar to currently-existing passive surveillance processes.

d. Spontaneous Reporting

Spontaneous adverse event reporting remains a cornerstone of pharmacovigilance activities within the FDA. The committee commended CBER's commitment to the timely review of expedited or serious adverse event reports for all products under its jurisdiction, and encourage greater public communication around these efforts as it is likely poorly understood and could improve public perception and confidence in the safety surveillance process to know CBER's level of attention given to the safety of marketed products.

In general, the areas of emphasis for investments – improvements in methods and data – have been appropriate. In particular the areas identified for methods development generally are logical and seem to be higher priority areas. It is also appropriate to begin to explore the utility of data mining of social media as a way of capturing reports. The effort underway seems appropriate.

Post licensure procedures for evaluation of safety for Biologic Products, reside in several different arenas:

- Passive surveillance: FDA's adverse event reporting system (FAERS): Here there is flow of information from the manufacturers via quarterly reports for the first three years post approval, then yearly thereafter. Manufacturers report expedited adverse events (serious and unlabeled) within 15 days of receipt of the information. Serious labeled events, and non-serious events are reported quarterly or annually as described. The Division of Epidemiology cross-checks these reports against their own surveillance studies, along with monitoring foreign regulators. Case study example 2 (Octagam and thromboembolic events) illustrates how this procedure can be of value. The review of each individual, expedited AE report (i.e., serious events that are unlabeled) by medical officers in OBE/DE, while labor-intense, is regarded as an important and reassuring oversight to ensure safety. The Vaccine adverse event reporting system (VAERS) has a similar flow of information for vaccines from vaccine manufacturers to the VAERS database. VAERS and FAERS are separate databases. As with FAERS, VAERS reports are submitted within 15 days if serious and unlabeled. Both FAERS and VAERS are able to collect reports directly from consumers or providers via an on-line website or faxing or mailing the forms. eVAERS is an initiative to enable vaccine manufacturers to submit adverse event reports electronically to VAERS, as is done currently for many drug and biologic manufacturers submitting reports to FAERS.

- Manufacturers are required to submit expedited adverse event reports within 15 days of receipt of the information about the event, regardless of the country where the event occurred (so long as the product is also licensed in the U.S. Further, Periodic Reports of Adverse Events submitted to quarterly for the first three years and annually thereafter, often contain summary information about reports received worldwide.
- CBER's Data Mining effort consists of empirical Bayesian data mining via private contractors to identify safety signals. One disadvantage noted by CBER's self-assessment, is the sparseness of the data and inability to identify adverse event patterns between products. Case example 1 (Fluzone and febrile seizures) illustrates how this approach can provide valuable information.
- CBER's Network Analysis approach is developed and used retrospectively to analyze known safety signals.

Beyond review and adjudication of individual case series, CBER employs disproportionality analysis methods to identify product-outcome associations warranting further exploration. The processes for spontaneous reporting analysis are more mature than those for population surveillance. CBER has focused much of its current research effort on population surveillance, under the principle that projects that improve the speed and quality of signal refinement and evaluation are primary priorities relative to projects that improve signal detection capabilities. However, CBER also is concerned about the percentage of false positives that are generated from current signal detection methods for analyzing spontaneous reporting data; more research in this area is warranted to evaluate the performance of data analysis methods and to develop alternative strategies with more desirable operating characteristics. Moreover, most of the research in spontaneous data mining methods has been based on assessments of pharmaceutical products, and it is unclear the extent to which these results are generalizable to vaccines and blood products.

CBER rightfully has not prioritized research to further develop disproportionality methods, however, it is worth noting that recent research has highlighted opportunities to systematically extract additional information from spontaneous data by considering different aspects of the reports beyond the disproportionality of product-outcome co-occurrence. While disproportionality analysis is an important approach to include within the pharmacovigilance process, other approaches for analyzing these spontaneous data may be considered to supplement current practice. For example, the WHO Uppsala Monitoring Centre has recently introduced the notion of drug association predictive modeling from spontaneous data, whereby they construct features of spontaneous reports and feed into a logistical model to determine which attributes predict true associations and discriminate from false findings, and how well the overall system functions. Some of the novel features the team had devised include report completeness (how many of the fields in a spontaneous report are actually populated);narrative length (how many words were included in the text provided by the reporter); geographic diversity (how many different countries contributed reports); and temporal diversity (how many different years did reports come in). Alongside the actual case count and disproportionality metric, they found that product-outcome associations having more complete reports with longer narratives, increased geographic diversity, and more temporal spread were more likely to be true effects. The performance of the system substantially outperformed the predictive accuracy from using disproportionality analysis alone. This

work highlights the opportunity to continue to research novel approaches to learning from spontaneous data but also serves as a general model for any novel data source whereby an evaluation framework can be systematically applied so that FDA can understand the reliability of the available evidence in allowing the timely and accurate identification of potential safety effects.

CBER should continue to stay abreast of developments in this space, and consider integrating these new ideas into their practice where appropriate. CBER and CDER have worked collaboratively to develop, validate and implement new approaches for evaluating adverse event reports.

Recommendations

Recommendation d.1. For passive surveillance, CBER should consider expanding the requirements for manufacturers to include events occurring outside the US and to be more proactive in exchanging safety information with other national regulatory authorities. For example, CBER could have access to the primary source information as it occurs (e.g., quarterly), to be added to the surveillance US database. We see no reason why CBER needs to wait to be contacted by foreign regulators regarding potential safety signals within reporting data outside the US, or to rely on annual summaries.

Recommendation d.2. Reporting of possible blood product-related adverse effects needs to be expanded beyond deaths to include other sentinel events. There is no scientific justification for using mortality as the only indicator of a serious adverse effect, given that there can be large variability in patient outcomes due to variability in medical care, and that a number of nonfatal events are of significant public health consequence.

Recommendation d.3. Additional sources of patient-generated information, such as social media and web search logs, present new opportunities to infer medical product safety events and warrant exploration. These new data sources should be evaluated within the same framework as existing data sources, such that CBER can have a comprehensive assessment of how all evidence can and should contribute to its safety review activities. The social media approach, while high risk, is worth exploring. It needs to be pursued in a manner that will not create privacy concerns among members of the general public.

Recommendation d.4. Most disproportionality analyses is carried out with the premise that all medical products and all adverse effects are treated equally, with a consistent signaling threshold applied based on the co-occurrence of the product-outcome among the database of reports. However, it could be the case that different signaling thresholds are required for different product types, and that the spontaneous data for these products may have different utility across the collection of health outcomes of interest. It would valuable for CBER to establish an evaluation framework upon which the performance of spontaneous data analysis methods can be empirically assessed to provide a benchmark for expected behavior and a context for interpreting new analysis results. Methodological research of spontaneous data mining and population surveillance should be complementary, and may offer opportunities to learn the circumstances in which one source should be considered more reliable than the other.

e. Genomics

CBER/OBE is charged, among other things, with implementing post-marketing safety assessment for biologics and blood products. They have created methods for combining spontaneous reports, prelicensure safety data, medical literature and other data sources to detect and then refine signals. They also describe (as reviewed elsewhere in this report) their plans to implement prospective surveillance of populations through mechanisms such as Sentinel/Mini-Sentinel and others. An important emerging source of information related to safety is Genomics. Genomics offers the possibility of evaluating both host factors and pathogen factors (in the case of infectious disease) to identify variables that may be important in predicting or explaining adverse events associated with products within CBER's portfolio.

The committee was pleased to see that CBER has identified Genomics as an important area for development, and that resources had been allocated for some pilot projects. In addition, CBER was proactive in creating the GETS (Genomics Evaluation Team for Safety) to concentrate and coordinate its efforts in these areas. In the briefing materials, CBER summarized several interesting projects related to Genomics. The genome appendix listed 5 publications, 2 poster presentations, and 20 oral presentations in the area of genomics. The details are provided in Appendix D of their information for the committee, but the scientific research projects can be summarized briefly here:

1. A case-control genome-wide association study (using exome sequencing) to seek associations between single nucleotide polymorphisms and the occurrence of febrile seizure following MMR or MMRV vaccination;

2. An exome-sequencing project to identify candidate genes associated with the onset of ITP following MMR vaccination;

3. A computational simulation of genome data to understand the power of genome sequencing to predict rare adverse events following vaccination;

4. A database of autoimmune disease genes from the published literature;

5. Assessment of a potential association of Lyme disease with HLA status;

6. Test for association of IVIG treatment response in Kawasaki disease and CNV copy numbers for several candidate genes; and

7. Multi "omics" collaboration with Vanderbilt University for studying the safety and tolerability of H5N1 vaccine using RNA-seq, proteomic data and pathway analysis.

In addition to the written materials in the briefings, the committee also discussed the genomics activity during its deliberations and with CBER scientists during the site visit. The findings of the committee were:

1. Investing in genomics is appropriate. This is a rapidly changing and emerging area, and it is appropriate that CBER develop and maintain domain-expertise in this field. At the same time, there are multiple genomics-related efforts going on at FDA in many centers, and there is a genomics working group that CBER should continue to interact with. As the briefing documents point out, the GETS is a good idea in principle, but there were insufficient numbers of genomics experts at CBER to support it. The new plan is to incorporate genomics work into the newly formed and larger Associate Director for Research (ADR) group within the Immediate Office of the Director (IOD) of OBE focusing on risk assessment and analytics. This is a reasonable strategy.

2. CBER should consider redirecting some of its specific investments in genomics to other genomics areas. The committee found that some of the current genomics projects are too narrow, and may inappropriately focus resources on scientific projects that have not been sufficiently peer-reviewed or vetted for likely success. CBER has succeeded in asking reasonable questions, almost always appropriately related to its mission (vaccine safety, for example) but the mechanisms by which projects are selected and reviewed, and progress is monitored, are not clear to the committee. It seemed that some projects were not state-of-the-art and did not seem to take into account progress and best-practices within genomics and/or informatics analytics fields. Given that genomics projects can be very expensive because of the numbers of the samples required, the cost of sequencing, and the cost of storing and analyzing the data, it is critical that these resources be deployed very selectively and with high standards for review to ensure useful information and experience is gained in the efforts. CBER, based on ongoing annual rigorous review, including science consultants who are not involved with existing genomics efforts, could end projects that are not likely to be successful, and divert the resources to genomics projects that have a higher likelihood of meeting CBER's objectives.

<u>Recommendations</u>

The committee recognizes the potential importance of genomics in CBER's mission, but also notes the difficulty of recruiting and retaining a critical mass of CBER scientists with expertise in genomics and informatics analysis of genomics data. This is a common problem globally, and means that CBER may have to join forces with other centers to build up access to this expertise. The plan to include genomics internally within risk assessment and analytics is a good start, but will probably not yield enough internal knowledge in genomics to allow projects to proceed in the future. Thus, new ways will be needed to bring genomics expertise and collaborations into CBER and to ensure that they are the highest level of scientific quality. Therefore, the committee makes the following recommendations.

Recommendation e.1. CBER should continue to recruit for scientists with expertise in genomics and informatics analysis of genomics data. At the same time, we recognize that this is difficult, and so backup strategies should be pursued, including joining forces with other centers at FDA to either "borrow" the time of their genomics experts, or recruit jointly so that recruits could be presented with a larger portfolio of exciting project ideas. Along these lines, CBER may find academic collaborators with an ability to work in collaboration on genomics-related projects central to the CBER mission. In so doing, CBER should reach out broadly to the academic community.

Recommendation e.2. CBER should create a broader range of scientific input on the selection and monitoring of projects in its genomics portfolio. Genomics is sufficiently new to many scientists that it is easy to get enthusiastic about it without a deep understanding of what has been done already by others, and the likelihood of success for new projects. In the selection of genome-wide association studies, careful consideration must be given to the evidence for heritability for a trait, the expected effect size, penetrance, and power calculations on the target population. In the selection of informatics projects, the landscape of existing algorithms and databases should be carefully evaluated and projects should be selected that specifically take advantage of existing resources built externally, and should focus only on those elements of the infrastructure that are unique to CBER and its mission. Thus, the committee believes that CBER should take more advantage of ad hoc peer review of all internal and external collaborations. CBER should seek collaborators internationally from among the very best scientists with the strongest track record of productivity and contribution. This will allow it to strategically invest its limited resources in people and projects that are optimized to provide useful information and experience to CBER scientists/reviewers in the field of genomics.

3. The computational demands of genomics are great. This impacts two different but related groups at FDA. First, there must be adequate IT facilities for capturing, storing, annotating and retrieving genomics data (which can be very large). This is an FDA-wide requirement and CBER should be at the table with other Centers as an institution-wide infrastructure is designed and deployed. According to OBE: "Over the past several years OBE and CBER staff have been working with others within the agency to build the infrastructure needed to analyze and store large amounts of data. FDA has a cluster or 'hive' of computers with approximately 1000 cores of computing power. There is also supercomputer and a cloud for storage of ~2 pedabytes. OBE staff use the supercomputer and hive for some analyses."

Second, there must be adequate scientific computation people and tools. This is not about IT, but about the scientific analysis of genomic data. Scientists with these skills are rare and expensive at this time, and this is the area in which CBER might want to consider joining forces with other centers that have genomics within their sights, in order to identify and retain the strongest genomics scientists at FDA and keep them excited about their work by offering a diverse set of scientific projects/capabilities. For both these activities, there are external advisors who would likely be happy to advise FDA on the best practices for genomics IT and the scientific quality control on genomics science projects. These efforts can build on existing efforts related to recruiting additional staff to CBER; participating in the FDA Genomics Working Group; and collaborating with the genomics group at the FDA's National Center for Toxicological Research (NCTR).