REDUCING RISK AND PROMOTING PATIENT SAFETY FOR NIH INTRAMURAL CLINICAL RESEARCH

DRAFT REPORT

April, 2016

The Clinical Center Working Group Report to the Advisory Committee to the Director, NIH

Charge to the Working Group

To make recommendations about ways to enhance the organization, financing, and management of the Clinical Center (CC) to improve the quality of patient care, and reduce the risk of clinical research and research-related activities. To inform its deliberations, the working group may examine the structural and cultural issues at the CC that may have contributed to the deficiencies identified in the Pharmacy and Pharmaceutical Development Service, and review other research activities at the CC that pose a potential risk to research participants.

The Working Group was constituted under the aegis of the National Institutes of Health (NIH) Advisory Committee to the Director (ACD) and, therefore, submits this report to that committee.

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Acknowledgements

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Executive Summary

When a U.S. Food and Drug Administration (FDA) inspection in May 2015 revealed significant deficiencies in the CC Pharmacy Department, the leadership of the NIH took action to determine the root causes of the failure. It became evident that the lapses in safety and compliance in the sterile manufacturing components of the pharmacy were likely symptomatic of more systemic issues in the structure and culture of the CC and NIH intramural clinical research. In response, NIH Director Francis Collins established the Clinical Center Working Group to provide a fully independent assessment and appropriate recommendations to strengthen intramural clinical research. The working group was given unfettered access to request documents and talk with NIH staff in pursuit of their charge. The working group approached its charge with a focus on the complementary aims of achieving the highest standards of safety for research participants and fostering an environment of cutting-edge clinical research. The sentinel event that led to the formation of the working group – the closure of the Pharmaceutical Development Section (PDS) sterile manufacturing function – served as a starting place for the committee's examination; however, the working group's charge, and their findings and recommendations, reflect a broader examination of the clinical operations conducted by the NIH Intramural Research Program (IRP), both within and outside the CC.

The working group recognizes that over the years the NIH IRP has made truly remarkable contributions to research to improve human health, and that clinical research has played a critical role in enabling many of these accomplishments. While there are certain risks inherent in leading-edge research conducted by the NIH, failing to take appropriate steps to minimize those risks is a disservice to both the patients and the quality of the research itself.

Overall, the NIH staff involved in inpatient and outpatient intramural clinical research was found to be highly dedicated in meeting what they viewed to be their responsibilities. Nevertheless, substantial operations issues were identified that represent important opportunities for improvement, including the following:

- Absence of a readily apparent and anonymous avenue to escalate concerns within NIH beyond immediate supervisors
- Failure of supervisors to appropriately address and escalate important deficiencies that were reported by staff
- Evolution of a culture and practice in which patient safety gradually, and unintentionally, became subservient to research demands
- Insufficient expertise in regulatory affairs, compounded by misunderstandings about how to comply with regulations for a federal research institution conducting clinical operations
- Fragmentation of authority and responsibility for clinical operations, driven by a unique decentralized structure, authority, and funding for intramural clinical research, resulting in accountability and quality assurance gaps that could compromise patient safety
- Inadequate independent oversight of safety and regulatory compliance within NIH
- Insufficient regular monitoring and metrics for identifying and tracking needed steps for improvement

In summary, investigation into specific concerns raised by the sentinel event led to an appreciation of broader organization deficiencies relating to priorities, quality, compliance, and accountability.

The working group offers recommendations in three major areas (descriptions of the relevant findings and recommendations for implementation are found in the main body of the report):

1. Fortify a culture and practice of safety and quality
2. Strengthen leadership for clinical care quality, oversight, and compliance
3. Address sterile processing of all injectables and the specifics of the sentinel event

The working group commends the prompt attention by NIH senior leadership to the issues with clinical operations once they became known and the NIH Director in seeking to use the sentinel event to strengthen the NIH clinical operations. The working group believes that, together with actions already underway, the implementation of the recommendations contained herein should greatly reduce risks and increase assurance of participant safety and research quality for NIH intramural clinical research.

Introduction

The NIH IRP is the internal research program at NIH, comprising approximately 1,100 principal investigators and 3,500 postdoctoral fellows, across a wide range of basic and clinical biomedical disciplines. The IRP has numerous celebrated accomplishments that have significantly improved human health, including the development of cancer chemotherapy, discoveries leading to the development of the human papillomavirus (HPV) vaccine, and developing the first rotavirus vaccine. Representing approximately 11 percent of the overall NIH budget, the IRP includes both central infrastructure resources such as the Clinical Center (CC) and National Center for Biotechnology Information (within the National Library of Medicine), as well as the individual intramural research programs of the NIH Institutes and Centers (ICs).

In-patient and outpatient intramural clinical research conducted at the NIH CC and at other clinics has made remarkable contributions to biomedical science and public health, including, for example, the recent conduct of a Phase 1 trial for an Ebola vaccine. Eighteen of the 27 NIH ICs conduct research in the CC, making use of the hospital's centralized services and resources. Patients who visit the CC are enrolled in or being evaluated for research studies, including natural history studies that aim to understand the course of disease, managed by one or more of these 18 ICs. Additionally, intramural researchers conduct studies at a number of off campus hospitals and clinics.

Need for review identified

In May 2015, the FDA conducted a for-cause inspection of the NIH PDS and the Intravenous Admixture Unit (IVAU), which both conduct sterile and non-sterile drug processing in the CC Pharmacy Department. These services provide products for administration to research participants at the CC, either as batches produced for clinical trials (PDS) or in response to individual prescriptions (IVAU). The FDA identified that these services failed to meet regulatory standards and had extensive deficiencies with facilities, equipment, standard operating procedures (SOPs), and staff training[1]. In response, NIH immediately suspended sterile activities in the PDS, began remediation in the IVAU, retained a contractor to do a comprehensive inspection of the PDS and IVAU, and convened an internal task force to review the issues underlying these deficiencies[2]. Through its analysis, the above task force found that problems were pervasive and longstanding, and stemmed in part from cultural, compliance, oversight, and administrative issues related to the Pharmacy Department, the CC and the IRP. The task force reported its findings to the ACD in December 2015[3]. At that meeting, the NIH Director noted that issues were broader than the Pharmacy Department and called for the formation of the CC Working Group of the ACD to make recommendations to enhance the organization, financing, and management of intramural clinical research that would improve the safety and quality of patient care in clinical research and research-related activities.

While the working group reviewed issues underlying the deficiencies in the PDS and IVAU, it was charged with looking more broadly into clinical operations of the NIH IRP. This report therefore begins with findings and recommendations relating to a culture of safety and quality across intramural clinical

[1] http://www.nih.gov/news-events/news-releases/nih-suspends-operations-its-clinical-center-pharmaceutical-development-section

[2] http://www.nih.gov/news-events/news-releases/update-nih-provides-interim-corrective-action-plan-clinical-center-pharmaceutical-development-section

[3] http://acd.od.nih.gov/meetings.htm

research activities. The report then addresses findings and recommendations for the administration and leadership governing clinical operations. Finally, the report addresses the findings and recommendations related to sterile products.

Process for Deliberations

The working group held three in-person meetings over three months to review and discuss the operations, oversight and management, and patient safety and quality measures for intramural clinical research operations; to identify gaps and risks; and to develop the group's final recommendations. Additional communication between and among working group members took place between meetings. The working group's deliberations were based on information provided by NIH and CC leadership, IC staff (including institute directors, clinical program directors, and clinical investigators), facilities managers, and others involved in the oversight, management and use of the CC (see appendices). The working group considered extensive reports on the Pharmacy Department (including reports from the FDA and materials compiled during NIH's 2015 internal review of the PDS and IVAU) and clinical research operations. It also reviewed and discussed industry-wide best practices for hospital operations. Members of the working group toured relevant portions of the CC and the Frederick National Laboratory for Cancer Research.

Summary of Findings and Recommendations

Theme 1: Fortify a culture and practice of safety and quality

Major Findings

- **Failure to prioritize patient safety:** Research participant safety must be the number one priority for the intramural clinical research program. At the PDS and throughout the CC, patient safety was occasionally put at risk, perhaps as a result of a well-intended, single-minded focus on research with an unintended but concerning concomitant inattention to safety. In some instances, regulatory compliance and quality assurance was not viewed as a principal priority of the CC. NIH should ensure that the staff views the needs of research participants rather than researchers as their ultimate priority, and commensurately consider patient safety in all activities. Promotion of patient safety and adherence to the highest standards of practice must be viewed as an essential, non-negotiable mandate, not simply an exercise to satisfy internal and external regulators. NIH leadership should explicitly articulate the overriding values that govern NIH's responsibility through partnership with research participants, and document and demonstrate how these values are exemplified across the entire enterprise. Making patient safety paramount means that everyone is responsible for improving quality and reporting concerns and that management recognizes its responsibility to follow up stated concerns. There needs to be regular data collection, monitoring, and reporting of safety metrics. The working group strongly believes that research progress and patient safety reinforce one another.
- **Uniqueness of the CC patient population:** Because the CC is a research hospital, the patient population differs from typical patient care settings. It frequently represents the last and best hope for patients suffering from life-threatening disease and conditions. Overall, the patient volume is low and many patients receive highly specialized and individualized care. There are many patients with rare or intractable diseases, and there are relatively few patients with common conditions and diseases such as traumatic injuries or myocardial infarctions. This poses potential challenges for benchmarking to other hospitals, and must be considered when designing metrics.
- **Dearth of regulatory expertise:** The NIH IRP lacks definitive, comprehensive expertise on regulations that apply to research facilities, manufacturing facilities, or modern hospitals. There is no central source of information about the regulatory requirements that pertain to intramural clinical activities. The IRP does not have an office or a sufficient number of dedicated personnel with appropriate compliance and regulatory expertise. Because the CC is a federal facility, some formal requirements for oversight and regulation that are in place at typical research hospitals are not mandatory for the CC – and were not instituted. For example, the CC Pharmacy has not had regular comprehensive inspections, which are mandated at the state level. In addition, NIH staff occasionally erroneously generalizes from NIH's exclusion from HIPAA requirements that a number of other federal regulations do not apply to NIH. These limited regulatory differences, compounded by misunderstandings about which regulations do or do not apply have led some NIH staff and leaders to operate as though the CC does not need to comply with the standards of a more conventional hospital. Some researchers describe working in the intramural program at the CC as having the regulatory "flexibility" of the 1960s or 1970s. This is unacceptable. Intramural clinical research must match or exceed the highest quality and patient safety

standards for a highly specialized care facility engaged in research. NIH needs to adopt commonly accepted best practices and rules governing hospitals and clinical research programs. NIH leadership should ensure appropriate regulatory requirements are uniformly applied, meeting and exceeding minimum requirements for a federal research facility. The IRP should seek voluntary accreditation associated with quality and safety wherever possible, as it has done with accreditation of the intramural human subjects protections program. The NIH IRP should be an example of excellence and should meet the highest standards in safety, quality, and compliance.

- **Inadequate research and clinical support systems:** On a program-by-program or institute-by-institute basis, the NIH IRP depends on the dedication and influence of individuals who are uncompromising in their expectations for participant care and high quality research. However, despite these individual leaders and dedicated staff, there are insufficient systems in place (e.g. widely adopted SOPs, automated alerts, standardized monitoring, and systematic follow-up on identified deficiencies) to ensure that high standards are consistently met, regardless of who is in charge at any given time.
- **Variable standards:** The working group observed variable policies and resources for regulatory compliance across the different ICs. Some clinical research programs have exceptionally good training, protocol monitoring, and systems to ensure regulatory compliance and continual quality improvement. Efforts to standardize approaches should endeavor to bring all ICs up to the highest performance standards.
- **Failure to report or address concerns:** The events in the PDS brought to light serious failures in reporting and addressing known problems. Until the FDA intervened, CC and NIH leadership were not aware of issues in compliance, quality, and safety that spanned many years. NIH needs to foster a culture of ongoing improvement and open information sharing. Staff should feel safe reporting concerns, and information sharing, including near-misses, should not in itself be an indication for a need for reprimand or any negative consequences. Staff in the PDS raised concerns regularly, but these concerns apparently were never reported beyond the Pharmacy Department, and there was no formal mechanism at the CC for staff to report concerns outside their chain of authority. The CC does have an anonymous reporting system for concerns about patient care, but it is only available to clinical care staff and not to research staff who do not interact directly with patients. NIH needs to create more inclusive reporting systems and a culture that promotes information sharing without fear. The costs of not reporting—and following up—are real, as measured by negative impact on patient safety and research quality.

Recommendations

RECOMMENDATION 1: Adopt new CC mission and values statements that reflect the critical linkage and synergism of science and safety. Science and safety go hand in hand and should be the pillars of the CC's mission. The mission statement can help dispel the misconception that there are tradeoffs between innovation and compliance, acknowledging that scientific excellence depends on both. Explicitly stating the values underlying the mission statement will demonstrate the CC's commitment to science and safety and will also provide a foundation for developing policies and practices that support these values.

RECOMMENDATION 2: Establish a Research Support and Compliance Office. NIH should establish a central office that coordinates research quality and safety oversight activities across the IRP. This office must ensure that regulatory requirements are uniformly applied wherever appropriate, so that the

highest standards are met regardless of specific legal mandates for the CC and the IRP, and seek to meet or exceed all requirements (such as FDA regulations including cGMP and USP<797>)[4]. This office will require adequate funding and sufficient numbers of staff with appropriate expertise in regulatory requirements and compliance. The activities of the NIH Office of Human Subjects Research Protections (OHSRP) should be incorporated into this office, with additional support for fully dedicated staff with primary expertise in, and dedicated responsibility for, regulatory affairs and patient safety. The research support and compliance office should:

a. Serve in a coordinating role for existing compliance activities (including but not limited to human subjects protections, lab safety, and FDA compliance), and it should be equipped to efficiently respond to data calls about compliance;
b. Ensure that all institutes have sufficient compliance support, including training, auditing, and compliance tracking that feeds into a common, NIH-wide system;
c. Report directly to NIH senior leadership to ensure that there are no barriers to identifying or remediating compliance gaps;
d. Establish improved systems to reduce burden and increase research quality and safety, so that compliance creates better results for research participants and researchers;
e. Establish overarching systems, and serve as a repository for documentation of best practices and checklists that are robust and do not rely on the initiative of specific individuals;
f. Increase tracking and evaluation of both standard hospital metrics and metrics that are germane to a research hospital;
g. Evaluate institutional review board (IRB) activities and other human subjects protections activities and ensure consistent standards are met;
h. Be attentive to regulatory responsibilities for scientists, clinicians, and staff and seek mechanisms that promote standards, accountability, and performance without unduly increasing staff workload;
i. Improve training programs and implement a centralized learning management system to track training for regulatory compliance and patient safety, and share training resources across units.

RECOMMENDATION 3: Establish systems to monitor and enforce safety and quality standards.

RECOMMENDATION 3a: Implement strengthened reporting systems. Create improved mechanisms and new lines of reporting to ensure that concerns related to patient safety can be elevated appropriately. The CC should establish guidelines for the types of issues, including errors or near-misses, which need to be communicated to higher organizational levels. Staff at all levels and across functions should be trained and tested on detecting, reporting, and responding to errors and other system concerns. Training and systems should instill a sense of continual improvement, not of blame. Instances where potential hazards are raised should be

[4] FDA's Current Good Manufacturing Practice (cGMP) regulations contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have. USP <797> compounding standards "help compounding practitioners adhere to widely acknowledged, scientifically sound procedures and practices, and facilitate the delivery of consistent and good-quality prepared medicines to patients."

celebrated. The reporting system should allow reporting by anyone working in, or visiting, the CC and it should bypass the chain of command such that employees can internally and anonymously escalate serious problems that seem not to be receiving attention by the chain of command. There should also be a mechanism for patients and families to share comments with CC management. It should be clear how reported information is handled and what processes are in place to ensure anonymity if the reporting individual prefers. The CC should conduct regular surveys of staff perception of how safe it is to report problems. Actions taken in response to reports should be demonstrated and communicated to staff.

RECOMMENDATION 3b: Enhance accountability by establishing metrics for quality and safety measures. Common quality measures have not been collected or monitored centrally. Quality assurance officers across intramural clinical research need to provide regular reports on metrics to the compliance office. The CC should implement internal, unannounced audits to check the integrity of systems to ensure standards. A sense of pride should be instilled to ensure a highly reliable, safe organization. Mechanisms should be created to publicly discuss and understand gaps in performance – using these as a learning opportunity. It should be made clear that such practices cannot be punitive, but represent good organizational practices. Data from monitoring should be transparent, impact operations, and drive continual improvement. The CC should clearly demonstrate how measurement is connected to action and improvement. Individual position descriptions and annual performance evaluations should include patient safety elements that are consistent across all ICs to ensure that staff are meeting uniform hospital standards for patient care regardless of what IC sponsors their research.

Theme 2: Strengthen leadership for clinical care quality, oversight, and compliance

Major Findings

- **Fragmented governance, responsibility, authority, and accountability.** NIH is organized into 27 ICs with distinct areas of focus and independent budget authority. While, in general, this organization works well in achieving NIH's overall mission to improve human health through the advancement of scientific knowledge, the working group found that this fragmented authority presents unique problems for oversight of intramural clinical research. The majority of physicians and research personnel operating in the CC are IC employees, and report directly to the clinical directors or other leadership within their individual ICs. This makes central decision making and accountability nearly impossible, because the CC leadership has little authority over IC personnel or operations and no systematic way to monitor clinical practice across ICs. The working group also heard that this misalignment between responsibility and authority served as a contributor to inconsistencies in patient care, inefficiencies, and reporting of concerns. The fragmentation of authority from responsibility is a large part of the failure of the CC to operate like a modern research hospital.
- **Lack of funding transparency:** The CC infrastructure and clinical services are funded by a "school tax" system of mandatory contributions from each IC based upon the level of their overall IRP budget. In addition to the school tax, most ICs make certain additional contributions to the operations of the CC. For example, the ICs with research programs in the CC hire and oversee additional clinical staff. Some ICs provide consulting services (e.g. infectious disease, eye, or dental consulting services) and other central services (e.g. clinical pathology) for the benefit of all CC research programs. The Scientific Management Review Board's 2010 report examined other models for funding the CC, including "fee for service" and a single appropriations line item. The working group discussed those findings and concluded that funding alone was not the root cause of the issues identified in the CC; however, lack of transparency and accountability stemming from the current model may contribute to the fragmented authority described above. NIH should consider moving the underlying infrastructure costs of running the CC into its Management Fund to make this portion of the cost of doing research in the CC more transparent. These costs are separate from the direct costs of the research studies themselves, (borne by the individual ICs), and would thus be "charged" against the overall NIH budget, much like, say, the fire department or power plant facility. To support this approach, NIH will need to adopt a transparent and rigorous accounting of all CC expenditures to ensure that all NIH leadership has a clear understanding of why resources are being requested and how they are being applied.
- **Outdated facilities**: Outdated or inadequate facilities are a major concern for CC users, and facilities issues accounted for many of the deficiencies identified in the FDA inspection report of the pharmacy. The working group discussed facility needs, but recognizes that NIH has limited flexibility in spending appropriated funds for construction and renovation. As noted, some CC facilities do not satisfy well-established standards or meet regulatory compliance. However, the building is relatively new and aside from specific space issues there should not be major impediments to meeting quality and safety standards within the current building. Some critical hospital activities (surgery, radiology) are housed in the older parts of the CC and should eventually be moved to newer wings, which would require renovation. Other laboratory activities could continue to be well served in the older wings. The appendix contains the working

group's specific findings and recommendations regarding facilities and engineering in the Pharmacy Department and the CC.

- **Lack of adequate compliance expertise**. The lack of regulatory and compliance expertise observed at the staff level extended to clinical research and CC leadership. It is essential that those in leadership positions ensure that people with appropriate regulatory and compliance expertise are installed in advisory, oversight, and staff support positions.

Recommendations

RECOMMENDATION 4: Establish a hospital board. NIH should establish a hospital board that is ultimately responsible for the CC's clinical performance (see note below). The roles of a hospital board are to oversee management, finances, and quality; set requirements for hospital leadership and identify gaps in expertise; establish policies and organizational approaches that promote quality and patient safety; evaluate organizational approaches; and monitor implementation of policies and strategic plans. The board would receive regular reports on quality and safety measures, and additional measures upon request. This board would be made up of external advisors and replace the current NIH Advisory Board for Clinical Research.

RECOMMENDATION 5: Enhance clinical research leadership authority and responsibility.

RECOMMENDATION 5a: Centralize authority for intramural clinical research. NIH needs to assign a single individual to oversee all inpatient and outpatient intramural clinical research conducted at the CC and off-site facilities. The incumbent must have training, experience, and responsibilities equivalent to a conventional hospital administrator. This is primarily a management role and not a scientific role. Whether this is expanded authority and responsibility of the CC director or necessitates creation of a new position overseeing all clinical research is left to the NIH to determine. The hospital board should advise on the position requirements and selection of an incumbent.

RECOMMENDATION 5b: Clarify the responsibilities of CC leadership. The CC leadership team should have exceptional expertise in organization and management, with specific training in business administration, hospital administration, and regulatory requirements. Senior staff should include clinical, scientific, engineering, and administrative leaders and should reflect the expertise seen in leadership teams at other high-quality hospitals. With input from the hospital board, CC leadership should anticipate future patient safety needs given changing demands for services, structural assets and their functionality, and human resources, and their potential impact on patient safety.

RECOMMENDATION 5c: Integrate patient safety in individual performance plans. To overcome the current misalignment of accountability with responsibility in the CC, NIH should require that clinical care staff be responsible to and evaluated by the leadership of both CC and their individual IC regarding elements related to clinical performance, including adherence to safety standards; patient safety elements are added to performance plans for clinical staff; and CC supervisors are required to provide input on rating these elements.

RECOMMENDATION 6: Establish a Clinical Practice Committee (CPC). The CPC will be responsible and accountable for the leadership and management of clinical practice of intramural clinical research. This group will have significant authority and will require a substantial time commitment from members.

Committee members will need to have expertise in diagnostic practice, surgical and procedural activity, nursing care, patient experience, pharmaceutical formulary and administrative leadership (supply chain, capital equipment, etc.), ambulatory care policies and processes, patient safety and quality, cost, accreditation, and regulations. This committee is not intended to have "equal representation" from all ICs nor should it be populated by IC leadership. Rather, it is intended to comprise experts in clinical care and practice. The group should consist of six to eight people with staggered terms. While the details of implementation should be determined by the NIH, the working group suggests the following principles. The CPC will:

a) Set policies for all intramural clinical research (inpatient and outpatient settings at the CC and off-site clinics).
b) Work with the director of the NIH, deputy director for intramural research, CC director and institute directors to create a collaborative and collegial environment for the delivery of the highest quality and safest care.
c) Work with NIH leadership to develop standardized practices, core processes, and metrics to assure the highest quality and safest care.
d) Provide significant expertise and focus to standardize the delivery platform across the hospital and outpatient practices.
e) Oversee all aspects of clinical operations in these settings to assure patient-focused, high quality, and safe care delivered by teams of physicians/scientists, nursing personnel, and support staff.
f) Make decisions regarding personnel and capital equipment needs, maintenance of the pharmaceutical formulary, and all aspects of diagnostic, medical, surgical, and procedural care.
g) Establish goals and policies for aspects of patient and family communication, access of patients and their families to staff to share their concerns, health equity and inclusion, patient education, morbidity and mortality reviews, materials management and supply chain activities, drug diversion prevention, and the creation of an innovation platform.

RECOMMENDATION 7: Identify and eliminate potential gaps among clinical services. NIH should improve current systems to assure that patient care is coordinated and that there are no gaps in care when patients are served by staff from multiple ICs. A single enterprise electronic health record (EHR) is essential to routine care coordination. NIH needs to implement an explicit patient care hand-off system, including identification of the senior individual responsible for each patient at all times and across all services. There should never be a question who is in charge, and responsible, and that person should be accessible at all times. Service leadership positions with authority over clinical staff should be modeled after the newly established "Surgeon in Chief," who oversees all surgery regardless of IC.

Theme 3: Address sterile processing of all injectables and the specifics of the sentinel event

Introduction

Clinical research conducted as part of the NIH IRP relies on the availability of drugs, biologics, and other research products (e.g. products used to measure biomarkers) that are prepared under sterile conditions. The PDS, a component of the NIH CC Pharmacy Department, formulates sterile and non-sterile products used in CC research. The PDS does not manufacture active pharmaceutical ingredients (API), but packages drugs into customized doses and formulations for administration to research participants. As described above, the FDA conducted a for-cause inspection of the PDS in May 2015, and NIH responded to the serious deficiencies identified by suspending sterile operations in the PDS. Since that time, the Pharmacy Department and the NIH Office of Intramural Research (OIR) have assisted investigators in identifying alternative commercial sources and other alternatives to the PDS. The mid-term and long-term approach to remediating the PDS problems could include major reconstruction of a PDS facility, use of other NIH facilities, continued reliance on commercial sources, and/or other vetted external compounding facilities.

It is noteworthy that there are a number of other facilities at NIH CC that also produce sterile products for administration to research participants, including the National Cancer Institute's Biopharmaceutical Development Program (BDP). The BDP's primary focus is manufacturing APIs, in addition to formulating these products for administration to participants. Whereas the PDS processes over 100 sterile product requests each year, the BDP handles less than 10 requests per year, in large part, because the process of manufacturing APIs is much more time and resource intensive. Additionally, in order to maintain rigorous adherence to cGMP standards, care must be taken not to commit the facility beyond its capacity to do things correctly.

Major Findings

- **Compliance failures:** The FDA inspection reports, internal NIH review, and the contractor's report revealed numerous failures in basic regulatory compliance. The Pharmacy Department and the CC have been focused on remediation since the problems were identified, and NIH has been working closely with FDA throughout the remediation process. Renovation plans to make the IVAU compliant with the two principal governing regulations, USP <797> and USP <800>, are progressing. One of the most striking observations was the almost complete absence of formalized SOPs in the PDS. As continuing activities in the IVAU will be necessary for hospital functioning, well-developed programs and procedures developed and tested in other hospitals can be drawn upon. In addition, NIH needs to bring the physical condition of facilities into compliance with the most recent regulations and best practices, including providing adequate space for required activities. Facility and instrument function must be independently monitored in a systematic way, with appropriate redundancies, and the pharmacy must establish procedures to respond if instrument measurements fall outside the acceptable ranges described in SOPs as determined by regulatory standards. NIH should adopt well-characterized practices for similar facilities that have been deployed elsewhere by successful facilities. The regulatory platform on which the operation functions (21 CFR 211, USP<797>, etc.) should be viewed as the minimum acceptable standard. NIH must commit to being a national leader in compliance and standards setting as well as in the conduct of research.

- **Failure to certify facilities:** There was no final certification of the IVAU and PDS facilities before they opened. A "Validation Master Plan" was adopted, but it was never implemented. The only documentation that the facility was ready for use was a certificate of occupancy, but there was no certification that the facilities met standards prevailing at the time for current Good Manufacturing Practice (cGMP) requirements.
- **Reporting failures:** A subset of PDS staff periodically reported quality and safety concerns, but these concerns were not ameliorated. Moreover, the established reporting lines, in which the quality assurance staff reported only to the head of the PDS and pharmacy, may have contributed to these concerns escaping the attention of the CC and NIH leadership. Such reporting structures are inappropriate and not in keeping with standard practice for cGMP facilities.
- **Inadequate attention to capacity and prioritization:** There is little scientific prioritization across ICs, and this becomes particularly problematic in the case of shared resources such as the CC. There is discordance between the largest ICs that have greater resources and ICs with more modest resources. The PDS was operating well beyond both its physical and personnel capacity. Responsiveness to investigator requests gradually became *de facto* prioritized above patient safety. Additionally, there is no system for prioritizing PDS services across NIH ICs. As described above, in response to the suspension of PDS sterile processing, NIH established an internal committee to assist in identifying alternative sources, and this group has been generally successful at assisting researchers seeking specific products. The OIR must develop a system to establish priorities across ICs if any shared resource (potentially including the BDP) is to be needed by more than one IC.
- **Potential to expand use of BDP:** The BDP facilities located in the Advanced Technology Research Facility (ATRF) in Frederick, MD, are state of the art and appear to adhere to high standards. The BDP staff has significant industry experience and expertise in compliance with cGMP and other regulations governing sterile production. Unlike the PDS, the majority of the BDP products are used in extramural research projects conducted outside of the NIH campus. The BDP has a full complement of SOPs and training programs, and is often used as a training facility for other federal employees including FDA employees. In addition, the ATRF has significant excess capacity that can be leveraged. The NIH has recently established an agreement to continue some of the former PDS activities at this facility. CC employees who formerly worked in the PDS are being retrained at the BDP and will work on non-NCI products in space adjacent to BDP labs. The volume and prioritization of non-NCI products should be established by the OIR. The ATRF is severely underutilized; however, because of restrictions in the original building use plans, there are limitations on the availability of the facility for expanded federal use.

Recommendations

RECOMMENDATION 8: Do not rebuild the PDS in the CC. Because of physical limitations, the former activities of the PDS cannot be brought into current regulatory compliance in its current location. Rebuilding a similar facility in the CC is estimated to cost in the range of $50 million and would take multiple years to complete. Because many of the PDS products can be obtained from commercial sources, and because the costs of rebuilding the PDS are high, we do not recommend rebuilding the PDS. Commercial sources should be the first line solution for sterile products, followed by vetted outsourcing facilities or production by the BDP if commercial sources are not an option. The working

group did not explore the non-sterile production systems within the PDS and would encourage NIH to carefully consider whether that function should continue, based on research needs, availability of alternative sources, and costs of remediation.

RECOMMENDATION 9: Create a prioritization and governance system for sterile products. NIH needs to establish a formal process to evaluate and prioritize sterile products to avoid the overburdening of shared resources with limited capacity. In response to the PDS suspension, the OIR formed a committee to assist researchers in identifying alternative product sources; this committee's scope should be expanded to include evaluation and prioritization of potential projects if access to shared resources is requested. A possible model for the structure and charge of a governance group is the Shared Resources Subcommittee of the NIH Board of Scientific Directors, which evaluates and makes recommendations for the allocation of intramural resources funded by all ICs. Patient safety should be an explicit and driving component of the prioritization process.

> **RECOMMENDATION 9a: Analyze future product needs.** Based on past, current, and planned research product needs, evaluate the potential future needs for products over the next five to 10 years to determine whether the current capacity of the BDP and other planned alternative sources is sufficient.
>
> **RECOMMENDATION 9b: Enhance resource sharing across ICs.** OIR should create a more comprehensive inventory of research facilities and resources across NIH (such as the BDP) and require sharing of resources to reduce redundancy and increase efficient use of available funds. This process should make it clear to all ICs that support for and use of shared services is essential to efficiency and stewardship. There should be clear governance and project prioritization for shared resources, including the CC.

RECOMMENDATION 10: Ensure that the IVAU and non-sterile PDS are fully remediated. NIH should continue to work with FDA until the facilities are fully compliant for IVAU and any continuing non-sterile PDS activities. This includes facility and equipment remediation, as well as SOPs and training. As required by regulation, the Pharmacy Department must formally adopt clear, written SOPs that detail processes for training, production, system monitoring and maintenance, and quality control and assurance for any product to be released to the clinic. Many of these SOPs and associated training materials could be adapted from other facilities or rapidly developed by external consultants. Many SOPs will require only minor tailoring to be appropriate for a specific facility, and all SOPs should reflect industry best practices. Once these procedures are established, operations should be monitored for compliance.

RECOMMENDATION 11: Assess all facilities at NIH producing sterile materials. Ensure all NIH facilities that produce sterile products for research administration to participants are compliant with cGMP and other regulations, and consider whether any of these activities could be outsourced or combined. Dis-incentivize duplication and evaluate which activities should be conducted at the CC and which should be outsourced or partnered.

Concluding Observations

Clinical research is a critical component of the NIH IRP; however, it suffers from shortcomings that potentially impact patient safety and research outcomes. The regulatory deficiencies observed in the PDS and IVAU are examples of sustained weaknesses in structure, facilities, practices and compliance at the CC. The working group concludes that if the recommendations proposed herein, together with those already being implemented by NIH management, are implemented, the IRP can provide the essential degree of patient safety while continuing its record of extraordinary scientific accomplishment.

Appendices

Findings regarding NIH intramural facilities manufacturing and compounding

OVERVIEW

Manufacturing novel drugs for small scale clinical trial use is a high risk process from a patient safety perspective, which requires qualified and robust Quality Service Unit (QSU) involvement to ensure success. Staff must be trained continuously on process and procedures with constant reference to written SOPs. Clearly defined dose release standards are required to prevent adulterated doses from being released from the program, and thereby prevent risk of patient injury or death. Engineering controls for the facility used to manufacture and compound patient doses must be rigorously maintained to standards described exactly in the Basis of Design (BOD) developed prior to construction, so that systems can be audited and continuously verified to be correctly operational. The BOD must be developed to align the installed systems with both best practice and with current regulations such as 21CFR Part 211, and USP General Chapters <797> and <800>. Routine, unannounced audits must be conducted on all administrative and engineering controls to verify compliance with SOPs and regulations.

Remarkably, in the case of both the IVAU and the PDS, the record shows that none of these widely deployed, basic patient safety safeguards were in place.

MANUFACTURING RISK ANALYSIS

It is not clear how decisions were made in the CC regarding whether to purchase commercial drugs at a local pharmacy or wholesaler, or to manufacture doses in the PDS. There was no documentation received by the working group that described any kind of Manufacturing Risk Analysis process. None of the staff that spoke with the working group could explain how those decisions were made, other than it was standard practice to have the PDS make drugs in response to requests from investigators. The patient safety risk in that strategy is high and requires the deployment of a robust QSU, since small campaign manufacturing bypasses all of the built-in quality and manufacturing standards used by commercial pharmaceutical companies. The combination of making product in house rather than first seeking a high quality, commercial product and a manufacturing program and facility that failed to meet regulatory requirements and quality control standards created a high-risk environment.

THE FACILITY

It was explained to the working group that the PDS facility was never qualified for drug product manufacturing, and this was known by pharmacy staff to be the case when the facility opened. In the 2015 inspection, FDA documented a long list of facility issues, and discussions with staff validated those

findings. Documents show unacceptably long delays between the time that staff reported a facility defect (wall paint failures, for instance) and the time that defect was repaired. Deferred maintenance is not acceptable in the compounding and manufacturing environment. Staff noted in emails the risk of mold growth, but those warnings did not seem to prompt any action by anyone. The lack of control was remarkable. There may have been no one empowered to advocate for patient safety in either compounding or manufacturing.

The working group heard from the NIH CC architect that the NIH CC uses no independent entity to verify that engineering controls for high-risk facilities meet appropriate regulations or standards prior to or after construction. NIH has a clear duty to insure that a Design Qualification (DQ) is performed to avoid a repeat of this unfortunate set of circumstances, and that the facilities used for manufacturing and compounding are fully qualified prior to use.

After PDS was opened, there were multiple alarms received by the operators that indicated inappropriate differential air pressure control. The alarms sounded so frequently, without resolution, that the alarms were eventually silenced. Subsequent investigation suggested that the Rees alarm system was never wired correctly, and that incorrect wiring resulted in false alarms. The problem with that explanation is that the type of wiring mistake described is considered to be virtually impossible in a qualified system that is annually re-qualified.

For more detailed information, I refer the reader to the FDA forms 483 associated with this event.[5]

NCI FREDERICK

Several members of the working group toured the NCI Frederick manufacturing facility. Contract staff interviewed at that facility had a clear understanding of quality, manufacturing controls and patient safety. The QSU manager in Frederick has the qualifications and expertise to assist NIH management with the development of a QSU for the CC and the more limited scope of compounding that is expected to be done in the CC going forward.

There may be budgetary or contractual issues that prevent additional utilization of NCI Frederick; however, it would be worth the effort to explore a closer operating collaboration, particularly in the development and deployment of a QSU in the CC.

WHAT IS NEEDED NOW

- Evaluate now the suitability and fitness of the still-operating, non-sterile PDS manufacturing program and shut it down immediately if it does not have robust quality control. There was no evidence presented to the working group that suggests the non-sterile manufacturing program is controlled by formalized SOPs or by a qualified QSU. Both are required for non-sterile drug manufacturing. Further, there is no reason to believe that the deferred maintenance issue is any better on the non-sterile side of the house than it was on the sterile side. This should be considered an urgent need.
- Inspect all other intramural sterile production programs. Any reconstituted drug manufacturing program – both sterile and non-sterile – must be performed only in a fully qualified facility that

[5] http://www.nih.gov/news-events/news-releases/nih-suspends-operations-its-clinical-center-pharmaceutical-development-section

is in control, and that is operated by fully qualified staff that is in control. The working group heard about (roughly) 14 small sterile production programs operated in various NIH buildings, with almost no detail about them. Given the degree of non-compliance found in the PDS and IVAU and the high risk to patient safety, investigating these programs is of urgent importance. Qualified investigators should visit each program that manufactures or compounds drug to determine its fitness to continue. (See Recommendation 10).

- Populate and deploy an empowered and commercially experienced QSU to provide the appropriate and required patient safety component to whatever drug compounding and manufacturing functions NIH chooses to operate. The QSU will develop the full complement of required SOPs and training requirements. No manufacturing should occur without a QSU in place.
- Implement a robust Manufacturing Risk Analysis when a novel drug is first being considered for patient dosing. That analysis should rule out the availability of commercially prepared drug product prior to management approval of a unique manufacturing campaign. This includes sterile and non-sterile drugs and biologics. (See Recommendation 9)
- Ensure that sterile dose compounding is performed only in facilities operated in strict compliance with the prescriptive requirements of USP<797>. The facility must be compliant with USP<800> whenever there is any dose preparation in which any NIOSH-listed hazardous drug (HD) is used. The CC does require a qualified USP<797> / <800> pharmacy program to meet research and patient needs.
- Make the commitment to voluntarily operate all compounding programs in strict compliance with all Maryland state pharmacy regulations. That means subjecting the repaired USP<797>/<800> IVAU to voluntary inspection and recommendations by the Maryland State Board of Pharmacy. As noted in the body of the report, the Working Group heard from staff who explained that because NIH was a federal facility, standard state regulations and well-reasoned operating standards do not apply. That attitude is shocking as it relates to USP<797>, since the wide deployment of that standard has so dramatically reduced the prevalence of exactly the type of sentinel event that befell the PDS and IVAU. Everyone associated with manufacturing and compounding must understand their critical role in the overall enhanced patient safety program that will be deployed and rigorously operated by NIH.

Member Biographies

NORMAN R. AUGUSTINE (Chair)

Norman R. Augustine served as president of Lockheed Martin Corporation upon the formation of that company in 1995 and became chief executive officer later that year. He retired as chairman and CEO of Lockheed Martin in August 1997, at which time he became a lecturer with the rank of professor on the faculty of Princeton University, where he served until July 1999. Previously, he served as Undersecretary of the U.S. Army.

Mr. Augustine was chairman and principal officer of the American Red Cross for nine years, chairman of the National Academy of Engineering, president and chairman of the Association of the United States Army, chairman of the Aerospace Industries Association, and chairman of the Defense Science Board. He is a former president of the American Institute of Aeronautics and Astronautics and the Boy Scouts of America. He is a current or former member of the Board of Directors of ConocoPhillips, Black & Decker,

Proctor & Gamble, and Lockheed Martin, and was a member of the Board of Trustees of Colonial Williamsburg. He is a Regent of the University System of Maryland, Trustee Emeritus of Johns Hopkins, and a former member of the Board of Trustees of Princeton and the Massachusetts Institute of Technology (MIT). He served as a member of the NIH organizational study, as co-chair of the NIH Blue Ribbon Panel on Conflicts of Interest, as chair of the NIH Senior Management Review Board, as co-chair of the National Academies Traumatic Brain Injury Workshop, and as chair of the Scoop Jackson Foundation for Military Medicine. He holds 34 honorary degrees and was awarded the National Medal of Technology by the President of the United States. He is a member of the National Academy of Sciences, the National Academy of Engineering, the American Philosophical Society and the American Academy of Arts and Sciences.

VICTORIA CHRISTIAN

As chief operating officer of the Duke Translational Research Institute (DTRI), Ms. Christian oversees operations of a central institutional resource for translational researchers. With director Bruce Sullenger, Ms. Christian built DTRI from the ground up when Duke was first funded by the NIH Clinical and Translational Sciences Award (CTSA). Since then, Ms. Christian has worked with scientists across the Duke Research landscape to realize the potential of platform technologies and core laboratories, implement competitive pilot and seed funding mechanisms, and launch a series of high-impact research programs.

Ms. Christian's background includes a broad range of experiences in clinical and translational research in industry and academia. In 1990, she joined the Duke Databank for Cardiovascular Disease and coordinated a series of NIH-funded multicenter clinical trials in cardiac electrophysiology and implantable devices. Between 1997 and 2007, Ms. Christian held senior level positions at PAREXEL International and King Pharmaceuticals, and co-founded NITROX LLC.

Since returning to Duke in 2007, Ms. Christian has led operations for multidisciplinary teams on design and launch of the MURDOCK Study, milestones including FDA approval of a biological license application (BLA), construction and operation of a GMP cell processing facility, and on two major cooperative agreements funded by NHLBI. In 2009, Ms. Christian founded a second spin-out company, The Biomarker Factory LLC, with DTMI Director Rob Califf and partner, LabCorp, to discover and develop biomarkers, diagnostics, and decision support tools. In 2013, she founded Southeast Experts, LLC, a small independent consulting company that makes Southeastern academic scientists and trainees accessible by the private sector.

Ms. Christian serves as vice president of Duke Medical Strategies, Inc., as a steering committee member for the Duke Biobank, the Coulter Program, the BMS Alliance, the Stem Cell Research Oversight Committee, and as a member of the Biomarker Factory LLC Board.

LAURA FORESE, M.D., M.P.H.

Dr. Laura L. Forese is executive vice president and chief operating officer of NewYork-Presbyterian, an academic medical center and healthcare delivery network in the Greater New York area providing high quality, patient-centered care in collaboration with Weill Cornell Medicine and Columbia University College of Physicians & Surgeons.

Dr. Forese has ultimate operational responsibility for the NewYork-Presbyterian enterprise, which includes four major divisions: NewYork-Presbyterian Hospital, NewYork-Presbyterian Regional Hospital Network, NewYork-Presbyterian Physician Services, and NewYork-Presbyterian Community and Population Health. NewYork-Presbyterian currently includes more than $6.5B in total operating revenue and more than 3500 beds.

An orthopaedic surgeon, Dr. Forese graduated summa cum laude and Phi Beta Kappa from Princeton and Alpha Omega Alpha from Columbia's College of Physicians & Surgeons. She also received her MPH from Columbia's Mailman School after training at The (former) Presbyterian Hospital and was a faculty member for ten years at Columbia University. Since that time she has worked for NewYork-Presbyterian in a series of management roles with a focus on quality, safety, efficiency and service. A member of multiple healthcare and civic organizations, both public and private, she was recently named among the 50 most powerful women in New York by Crain's Business.

DONALD GAGLIANO, M.D.

Dr. Donald Gagliano has been vice president of Global Development Operations at Bausch & Lomb Incorporated since May 2013. Dr. Gagliano leads the scientific review of global business development opportunities and strategic initiatives for Bausch & Lomb's Pharmaceuticals business, as well as supporting special projects in its surgical business. Dr. Gagliano served as director of the clinical investigations regulatory office in the army medical research and materiel command. He directed a designated federal laboratory responsible for regulatory oversight and compliance of the army clinical investigation program and clinical collaborative R&D agreements. Earlier, Dr. Gagliano served as chairman of the medical education and training campus executive committee, U.S. army medical department center and school in San Antonio.

Dr. Gagliano is an ophthalmologist in Bethesda, M.D., and is one of two doctors who specialize in ophthalmology at the Walter Reed National Military Medical Center. He received his medical degree from Rosalind Franklin University of Medicine and Science and has been in practice for 34 years.

HARLAN M. KRUMHOLZ, M.D.

Dr. Harlan M. Krumholz is a cardiologist and health care researcher at Yale University and Yale-New Haven Hospital. He is the Harold H. Hines, Jr. Professor of Medicine and director of the Yale Center for Outcomes Research and Evaluation (CORE), one of the nation's first and most productive research units dedicated to producing innovations to improve patient outcomes and promote better population health. He has published more than 900 papers. He is also a director of the Robert Wood Johnson Foundation Clinical Scholars Program, which prepares talented physicians to become future health care leaders.

He has led research and initiatives to improve the quality and outcomes of clinical decisions and health care delivery, reduce disparities, enable transparency in practice and research, and avoid wasteful practices. He is the architect of many of the nation's outcomes performance measures used in public reporting and policy incentive programs. He led a national campaign that led to reductions in treatment delays for acute myocardial infarction, based on his NIH-funded research. He established the Yale Big Data to Knowledge initiative, a multidisciplinary effort to use advanced analytics to solve health care problems, and co-directs the Yale University Research Computing Center. He is a leading expert for

national research initiatives in China and recently received the Friendship Award from the government, their highest recognition of foreign experts. He is a member of the National Academy of Medicine and was recently on the Advisory Committee to the Director of the NIH.

F. KURT LAST

Mr. Last has almost 25 years' experience in programming, design, commissioning, and operating GMP & GTP pharmaceutical manufacturing and research animal care facilities. His first position dealing with critical facilities was at Brown University where he led the Project Management Group within Plant Operations. He then moved into industry, rising to become Senior Director of Operations for a CGMP biologics manufacturing company, leading teams charged with Facilities (Research & Manufacturing) Operations; Calibration & Metrology; Research Animal Care, Security, and Environmental Health & Safety. In 1997, Mr. Last started Specialty Operations Solutions (SOS) that provided engineering controls and facility management services to academic and industrial clients.

In 2013, SOS was acquired by The WorkingBuildings Group of Companies. Shortly following the acquisition, Kurt was rehired by WorkingBuildings to lead and expand the firm's CGMP and sterile compounding practice group.

Kurt serves as GMP Facility Engineer and USP<797> / <800> engineering controls subject matter expert for universities and industrial clients across the country, including Duke University and the University of Alabama at Birmingham.

RICHARD B. MARCHASE, PH.D.

Richard B. Marchase, Ph.D., is the vice president for research and economic development at the University of Alabama at Birmingham. His administrative functions include strategic planning, regulatory oversight, recruitment, and space allocation for a research enterprise generating approximately $450 million annually. He functions as the principal university liaison for regional economic development issues and recently chaired the Board of Innovation Depot, the award-winning business incubator affiliated with UAB. He also serves on the Boards of the UAB Research Foundation, Triumph Services, BioAlabama, the Economic Development Partnership of Alabama Foundation, Alabama EPSCoR, and REVBirmingham. From 2012 to 2013 he served as UAB's Interim President.

Dr. Marchase received his undergraduate degree from Cornell University and was honored with the Hamilton Award as its Outstanding Graduate in Science and Engineering. He received his Ph.D. with Distinction from The Johns Hopkins University and did postdoctoral training at Duke University. He was named a member of the faculty there and was honored as a Nanaline H. Duke Scholar. In 1984, he received one of the inaugural Presidential Young Investigator Awards from the National Science Foundation. Dr. Marchase was recruited to the University of Alabama at Birmingham in the Department of Cell Biology in 1986. He was named chair in 1994, associate dean for research in the School of Medicine in 2000, and vice president for research in 2004. His research interests center on a novel calcium influx pathway important to both heart cells and neurons. He has numerous scientific publications and patents, has served on editorial boards for several biomedical journals, and has been Principal Investigator on over $50 million of research and infrastructure grants and contracts.

Dr. Marchase has been active in a host of national organizations, including the Association of American Medical Colleges and the Association of Public and Land-grant Universities. He currently serves on the

APLU Board of Directors and chairs their Council on Research. He served as President of the Association of Anatomy, Cell Biology, and Neurobiology Chairs and as both President and Vice President for Science Policy of the Federation of American Societies for Experimental Biology (FASEB), which represents over 120,000 scientists and is recognized as the principal voice of the biomedical research community on issues related to research funding and policy. He was honored by the Juvenile Diabetes Research Foundation with the Mary Jane Kugel Award and by the American Association of Anatomists with the A.J. Ladman Award for Exemplary Service. Dr. Marchase was named a Charter Fellow of the National Academy of Inventors in 2012 and is a member of the Editorial Board of its journal, *Technology and Innovation*. His appointment to the Advisory Committee to the Director of the National Institutes of Health is in process.

EDWARD D. MILLER, M.D.

Dr. Edward D. Miller served as chief executive officer of Johns Hopkins Medicine and the 13th dean of The Johns Hopkins University School of Medicine. He retired from this position on June 30, 2012.

As part of Dr. Miller's vision to improve access through the development of a regional, integrated health care delivery system, Howard County General Hospital was acquired and integrated into Johns Hopkins Medicine. Dr. Miller also led the effort to integrate Suburban Hospital and Health System in Bethesda, Maryland, Sibley Memorial Hospital in Washington, D.C., and All Children's Hospital in St. Petersburg, Florida, into Johns Hopkins Medicine.

Under Dr. Miller's leadership, Johns Hopkins Medicine broadened its international presence to include relationships with hospitals and other health care-related institutions in the Americas, Europe, the Middle East and Asia, including an agreement to help Malaysia develop its first fully integrated private four-year graduate medical school and teaching hospital.

One of his most significant accomplishments as Dean/CEO has been the massive rebuilding and renovation projects that have transformed the East Baltimore medical campus into a medical center where the most modern of buildings sit among the most historic including one of the largest hospital construction projects in the nation—two new state-of-the-art hospitals for adult and pediatric patients. Other campus construction projects completed include clinical and research buildings for the Sidney Kimmel Comprehensive Cancer Center, the Broadway Research Building, the Anne and Mike Armstrong Medical Educational Building, and the new Robert H. and Clarice Smith Building that is part of the Wilmer Eye Institute.

Under Dr. Miller's direction, a new school of medicine curriculum, Genes to Society, was developed and introduced, representing the first wholesale academic overhaul at the school in two decades.

An anesthesiologist who has authored or co-authored more than 150 scientific papers, abstracts and book chapters, Dr. Miller joined Johns Hopkins in 1994 as professor and director of the Department of Anesthesiology and Critical Care Medicine.

Dr. Miller is a member of the Institute of Medicine of the National Academy of Sciences and is a fellow of the Royal College of Physicians and the Royal College of Anaesthetists.

Born in Rochester, N.Y., Dr. Miller received his A.B. from Ohio Wesleyan University and his M.D. from the University of Rochester School of Medicine and Dentistry.

JOHN H. NOSEWORTHY, M.D.

Dr. John H. Noseworthy is president and chief executive officer of Mayo Clinic, a not-for-profit organization operating in six states that is dedicated to medical care, research and education.

Prior to his current appointment, Dr. Noseworthy served as chair of Mayo Clinic's Department of Neurology, medical director of the Department of Development, and vice chair of the Mayo Clinic Rochester Executive Board.

During his tenure as CEO, Dr. Noseworthy and his leadership team have implemented a plan to ensure that Mayo Clinic remains a trusted resource for patients amid a rapidly changing health care environment—extending Mayo's mission to new populations, providing care through more efficient delivery models, and increasing the personalization and immediacy of health care for all people. Examples of new initiatives include a proton beam cancer therapy program with two treatment centers—one in Phoenix and one in Rochester, Minn.—and development of a Mayo Clinic–affiliate network of high-quality medical practices throughout the country.

Dr. Noseworthy is a professor in the Department of Neurology. He specialized in multiple sclerosis and spent more than two decades designing and conducting controlled clinical trials with generous support from the Medical Research Council of Canada, the Multiple Sclerosis Society of Canada, the National Multiple Sclerosis Society (USA) and the National Institutes of Health. Dr. Noseworthy also is the author of more than 150 research papers, chapters, editorials and several books, including the three-volume textbook *Neurological Therapeutics: Principles and Practice* now in its second edition. He also served as editor-in-chief for *Neurology*, the official journal of the American Academy of Neurology.

Born in Melrose, Mass., Dr. Noseworthy received his M.D. from Dalhousie University in Halifax, Nova Scotia, Canada. He completed his neurology training at Dalhousie University and the University of Western Ontario, and a research fellowship at Harvard Medical School. He joined Mayo Clinic in 1990. He has received the Alumnus of the Year award from Dalhousie University (2005), an honorary doctorate of science degree from the University of Western Ontario (2012), an honorary doctorate of laws from Dalhousie University (2015), and was named an Officer of the Order of the Orange-Nassau (2015). He is a Health Governor of the World Economic Forum.

KATHY L. HUDSON, PH.D.

Dr. Kathy L. Hudson is the deputy director for science, outreach, and policy at NIH. She directs the communications, legislation, and science policy efforts of NIH and serves as a senior advisor to the NIH director. She has led the creation of major new strategic and scientific initiatives for NIH; she was a key architect in creating the National Center for Advancing Translational Sciences (NCATS), NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, the Accelerating Medicines Partnership, and the Precision Medicine Initiative. She leads the agency's efforts to advance biomedical science through policy development and the creation of innovative projects and partnerships. Dr. Hudson works with Congress, other government agencies, research institutions, patient advocacy organizations, industry, and professional societies to establish collaborative efforts to advance biomedical research and policy.

Dr. Hudson's professional experience includes serving as the acting deputy director of NCATS, the NIH chief of staff, and the assistant director of the NHGRI. She was the founder and director of the Genetics

and Public Policy Center at Johns Hopkins University as well as an associate professor in the Berman Institute of Bioethics, Institute of Genetic Medicine, and Department of Pediatrics at the university.

Dr. Hudson holds a Ph.D. in molecular biology from the University of California, Berkeley, an M.S. in microbiology from the University of Chicago; and a B.A. in biology from Carleton College.

LAWRENCE A. TABAK, D.D.S., PH.D.

Dr. Tabak is the principal deputy director of the National Institutes of Health (NIH). He previously served as the acting principal deputy director of NIH (2009), and as director of the National Institute of Dental and Craniofacial Research from 2000-10.

Dr. Tabak has provided leadership for several trans-NIH activities, including the NIH Roadmap effort to support team science, the NIH Director's initiative to enhance peer-review, and the NIH's implementation of the American Recovery and Reinvestment Act. He has co-chaired working groups of the Advisory Committee to the Director of NIH, the Diversity of the Biomedical Research Workforce, Information Technology and Informatics, and the NIH Intramural Research Program. Dr. Tabak coordinated a trans-NIH effort to enhance the reproducibility of scientific findings. Most recently he led the team that developed an NIH-Wide Strategic Plan.

Prior to joining NIH, Dr. Tabak was the senior associate dean for research and professor of dentistry and biochemistry & biophysics in the School of Medicine and Dentistry at the University of Rochester (NY). A former NIH MERIT recipient, Dr. Tabak's major research focus is the structure, biosynthesis and function of glycoproteins. He continues work in this area, maintaining an active research laboratory within the NIH intramural program in addition to his administrative duties.

Dr. Tabak is an elected member the National Academy of Medicine (formerly IOM) of the National Academies. He received his undergraduate degree from City College of New York, his D.D.S. from Columbia University, and a Ph.D. from the University of Buffalo.

CARRIE D. WOLINETZ, PH.D.

Dr. Carrie D. Wolinetz is associate director for science policy and director of the Office of Science Policy (OSP) at the National Institutes of Health (NIH). As leader of OSP, she advises the NIH director on science policy matters of significance to the agency, the research community, and the public, on a wide range of issues including human subjects protections, biosecurity, biosafety, genomic data sharing, regenerative medicine, the organization and management of NIH, and the outputs and values of NIH-funded research.

Prior to joining NIH, Dr. Wolinetz worked on biomedical research policy issues as the deputy director for federal affairs at the Association of American Universities (AAU) and the director of scientific affairs and public relations at the Federation of American Societies for Experimental Biology (FASEB). She also served as the president of United for Medical Research, a leading NIH advocacy coalition. Outside of NIH, Dr. Wolinetz teaches as an adjunct assistant professor at Georgetown University in the School of Foreign Service's program on Science, Technology & International Affairs.

She has a BS in animal science from Cornell University, and she received her Ph.D. in animal science from The Pennsylvania State University, where her area of research was reproductive physiology.

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