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A Roadmap for Academic Health Centers to Establish Good Laboratory Practice-Compliant Infrastructure

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Abstract

Prior to human clinical trials, nonclinical safety and toxicology studies are required to demonstrate that a new product appears safe for human testing; these nonclinical studies are governed by good laboratory practice (GLP) regulations. As academic health centers (AHCs) embrace the charge to increase the translation of basic science research into clinical discoveries, researchers at these institutions increasingly will be conducting GLP-regulated nonclinical studies. Because the consequences for noncompliance are severe and many AHC researchers are unfamiliar with Food

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and Drug Administration (FDA) regulations, the authors describe the regulatory requirements for conducting GLP research, including the strict documentation requirements, the necessary personnel training, the importance of study monitoring, and the critical role that compliance oversight plays in the process. They then explain the process that AHCs interested in conducting GLP studies should take prior to the start of their research program, including conducting a needs assessment and a gap analysis and selecting a model for GLP compliance. Finally, the authors identify and analyze several critical barriers to developing and implementing a GLP-compliant infrastructure at an AHC. Despite these challenges, the capacity to perform such research will help AHCs to build and maintain competitive research programs and to facilitate the successful translation of faculty-initiated research from nonclinical studies to first-in-human clinical trials.

As academic health centers (AHCs) embrace the charge to increase the translation of basic science research into clinical discoveries, researchers at these institutions increasingly will be conducting their first-in-human studies requiring preclinical evaluation, assuming additional responsibilities that extend beyond their more familiar roles as scientists or clinicians.[1] They likely are unfamiliar then with the requirements of Food and Drug Administration (FDA) regulations, which can be daunting for researchers who have neither institutional support nor formal training in regulatory compliance.[2,3]

Good laboratory practice (GLP) regulations, enacted in the 1970s to deter researchers from submitting fraudulent studies and falsified data to the FDA,[4] aim to ensure that investigators conduct safety studies in controlled, documented, and traceable manners.[5] These regulations are intended "to assure the quality and integrity of the safety data"[6] necessary to support FDA Investigational New Drug (IND) and Investigational Device Exemption (IDE) applications for first-in-human investigations as well as for subsequent FDA marketing approval. The FDA-regulated processes for studying and marketing drugs and devices are outlined in Figure 1.

The consequences for noncompliance with these regulations are severe and range from FDA rejection of the nonclinical study data, to fines, injunction and prosecution, and placement of the AHC on a public noncompliance list on the FDA's website.[7] Additional consequences include damage to the AHC's reputation, potential financial harm, and an increase in future regulatory obstacles. It is risky then for researchers to attempt GLP research without institutional support and an understanding of these regulations.

In this article, we briefly describe GLP regulatory requirements, propose various models for the development and implementation of a GLP-compliant infrastructure within an AHC governing structure, and identify and analyze several critical barriers to achieving that infrastructure.

Regulatory Requirements for Conducting GLP Research

According to the federal regulations that govern the science, manufacturing, and research of FDA-regulated products, *nonclinical laboratory studies* are defined as "in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety."[6,8] These regulations address a wide range of research, including in vivo mutagenicity studies; acute, sub-chronic, and long-term toxicity studies; and carcinogenicity studies. Human and animal clinical studies are excluded, as are basic exploratory studies to determine the physical or chemical properties of a product independent of the animal test system. Although a common misconception, GLP regulations do not apply to the manufacture of a clinical product in a laboratory. Instead, the regulations define the areas and requirements of a quality system that must be present for a study to be deemed GLP-compliant. In addition to including details regarding the planning for facilities

and equipment, GLP regulations include specifications for the infrastructure systems that must be put in place. Below, we summarize these different elements of GLP regulations.

Testing facility management

The testing facility management oversees more administrative than scientific activities, and their responsibilities include designating the study director as needed and ensuring that an adequate quality assurance unit (QAU) is in place and that any communications from the QAU are received by the study director and then acted upon as appropriate. Additional testing facility management responsibilities include ensuring that the appropriate personnel are trained, the necessary resources are present, and that test and control articles are handled appropriately.

Study director

GLP regulations require that the study director oversees each nonclinical study. The study director should be a scientist or other professional of appropriate education and experience and is responsible for the technical conduct of the study, as well as the analysis, interpretation, documentation, and reporting of the results. The role of the study director is to take proactive steps in assuring that all applicable GLP regulations are followed. This individual serves as the single point of control, and as such, no assistant study director can be named.[9]

Quality assurance unit

A major step in complying with GLP regulations is designating a functional and independent QAU that is responsible for assuring that all aspects of the study are in compliance. These responsibilities include monitoring the study to ensure that the equipment, facilities, personnel, methods, practices, records, and controls comply with regulations. QAU personnel must have the necessary education, training, and experience to perform this function. They report directly to institutional management and are independent of the testing facility management, the personnel engaged in the study, and the study director.

Facilities

GLP regulations require that the research facilities be of suitable size and construction for the proper conduct of the study, including a separation of projects and areas devoted to animals, feed, supplies, test- and control-article handling, and lab operations. Personnel also must routinely maintain and calibrate all equipment used for GLP studies and clearly document the process.

Standard operating procedures

Written standard operating procedures (SOPs) are integral to any quality system that purports to ensure the quality and integrity of data. Regulations require that the SOPs cover all aspects of GLP-governed activities, including the operation of the QAU; the handling of animals, reagents, test methods, test article, and control characterization; and the handling, data organization, maintenance, and calibration of equipment. GLP regulations require formal, documented training on the SOPs for all study personnel. All deviations from the SOPs require authorization from the study director.

Study protocol

GLP regulations require a written and approved study protocol that defines the objectives and details all aspects of the conduct of the study. Any deviations from the study protocol must be documented; if they constitute a major change, these deviations have the potential to invalidate a study.

Records and reports

GLP regulations describe the contents of the final study report, the requirements for training records and for storage and retrieval of study records and data. The final study report details the results, requires specified signoffs, and must include a description and assessment of any circumstance that may have affected the quality or integrity of the data. Record-retention requirements also address timelines for storing raw data, specimens, and maintenance logs.

Building a GLP-compliant Infrastructure

Once leaders at an institution have decided to support the conduct of GLP studies internally or to contract them out to external firms, they must answer a number of relevant questions to determine the needs of both the investigators and the institution and to support the development of a GLP-compliant infrastructure. To increase the likelihood that those involved make informed decisions about the process, researchers should follow specific steps to conduct a needs assessment and a gap analysis and to select a model for GLP compliance. We describe these steps in more detail below.

Conducting a needs assessment

Before investing resources in the development of an institutional infrastructure, we recommend that investigators conduct a thorough assessment of current and anticipated future needs. While GLP regulations do not apply to basic exploratory studies, they do apply to the subsequent safety and toxicology studies. The use of a flowchart (see Figure 2) may help an investigator determine if a proposed study requires GLP compliance. Some pertinent questions to determine the overall scope and timeline for the development of an institutional GLP infrastructure include: 1) How many investigators might need to perform GLP-compliant studies in the future?; 2) How long will the studies last?; 3) How soon will they be ready to begin?; 4) What type of nonclinical studies will be required?; and 5) Are there any unique, study-specific needs (e.g. studies involving immunecompromised animals or the manipulation of infectious substances, which dictate space needs for both test article preparation and animal husbandry)?

Conducting a gap analysis

By assessing their institution’s future needs in developing a GLP-compliant infrastructure, as well as conducting an inventory of their current resources including a thorough assessment of their current animal facility status, leadership will be able to concretely plan for any new institutional infrastructure that must be developed. In addition, investigators should carefully consider opportunities to leverage their existing infrastructure in novel ways to prevent their institutions from having to establish new resources to support GLP-compliant work. However, any remaining gaps will require institutional investment in additional resources.

Selecting a model for a GLP-compliant infrastructure

Investigators at AHCs can choose from a variety of infrastructure models to implement their GLP-compliant research. Drawing from known examples of successful GLP infrastructure implementation and from reviewing the content of FDA post-inspection warning letters, we present here four possible models. We defined these models by the range of services that they provide to the institution and the locations of the institutional home(s) for training, support services, and coordination of compliance oversight. We outline the perceived advantages and disadvantages of these models below.

Model 1: Create an institutional GLP facility—In this central institutional model, administrators at the AHC would identify one space for all GLP work to be performed under a single set of uniformly-enforced regulations. Animal housing and procedure areas would be centralized, and technicians would be trained to follow GLP regulations for all research conducted in the facility. Testing facility management would be assigned to the facility and would handle all day-to-day functions, such as supervising the program staff, maintaining documentation in conjunction with the QAU, and serving as the point of contact for the principal investigator (PI) regarding financial and administrative issues. Management also would assign and interact with a number of study directors, who would in turn oversee the various studies being conducted within this centralized facility. In addition, the testing facility management would be responsible for interacting with the deans or other administration oversight entities.

The biggest drawback to this model is the significant cost required either to construct a new facility or to make significant changes to an existing one. The advantages, however, include an improved workflow and an easier way to ensure uniform procedures are being followed because all studies being conducted in the facility would be performed according to GLP regulations. In this model, the testing facility management could structure the study director position in one of two ways. Either the PI could serve in this role, interacting with the GLP core facilities manager, or the institution could employ a separate study director, relieving the PI of the study director responsibilities and allowing him to move into the role of subject matter expert. This latter approach provides the distinct advantage of giving a more independent and experienced study director control over the study and removing the PI from overseeing his own research, while still relying on his expertise in the field.

Model 2: Establish a number of decentralized GLP-compliant facilities—When a facility dedicated solely to GLP research is not practical, feasible, or necessary based on the structure of the AHC or the predicted volume of qualifying studies, an alternative approach is to establish a number of decentralized GLP-compliant research facilities. In this model, the necessary functional areas and equipment would be established at each location. Without a central location and a single testing facility management, as in Model 1, each physical location would need its own governing structure. The institution should then rely on a central QAU to assure that each individual unit is conforming to GLP regulations.

Compared to Model 1, the initial monetary investment in converting existing, decentralized facilities and infrastructure would be less, but the redundancy of personnel, resources, and training required to modify each facility would likely result in cost inefficiencies over time. This decentralized model also would require an organized effort to educate and raise awareness among researchers of the GLP-compliant studies being conducted in the proximity of non-GLP or basic research studies. Another drawback to this model is the increased number of qualified managers needed to oversee the disparate facilities. Finally, while this model likely would require more internal compliance guidance for individual groups of investigators, burdening the central QAU, training can be tailored to personnel-specific needs.

Model 3: Collaborate with another AHC to provide GLP services—Collaboration between two or more AHCs to conduct GLP research is another viable option. This model would require participating AHCs to identify and contribute unique expertise and resources to the end goal of performing GLP-compliant studies. An example of this shared partnership would be for one institution to house the facilities for the research while the other provided QAU services. The designated study director would remain in close communication with the management of the facility conducting the study and with the QAU.

With multiple institutions contributing resources, this model allows AHCs to leverage outside expertise and infrastructure resources to fulfill regulatory obligations, which likely would minimize the cost and staff burden for each individual institution involved. Further, some research institutions might be able to contribute components that others would be unable to provide. While specialized procedures, such as specialty assays, still might necessitate tailored training, other AHCs are more likely to agree to partnerships for a feasible price than commercial laboratories. In this model, AHCs should employ the same or a similar vetting process as they would when hiring an outside vendor (see Model 4), including ensuring that facilities housed elsewhere are comply with GLP regulations. In addition, the study director should work with the QAU to develop a careful plan for monitoring, including physical facilities inspections, to ensure GLP compliance. This model is consistent with the current National Institutes of Health (NIH) efforts to explore the efficient use and management of core facilities, including the use of collaborative or regional core facilities.[10]

Model 4: Contract a commercial GLP-compliant laboratory to conduct the research—An AHC could hire a contract research laboratory specializing in GLP studies. While this model may be the easiest to employ, as no in-house infrastructure is necessary and it requires less training and staff resources, it also has the highest recurring cost, as each GLP study would come with a large price tag. Also, oversight and accountability of research conducted at an outside laboratory are more difficult to manage. In this model, the advice of an internal researcher or outside consultant knowledgeable on the GLP regulations is critical to the process of identifying and selecting a qualified vendor. Investigators should inspect the potential laboratory to ensure that it meets regulatory and institutional requirements, as well as conduct periodic monitoring of the facility. Finally, this model may not be tenable for research that involves an essential assay requiring specialized techniques or methods developed and perfected within an AHC laboratory.

GLP Management Structures

While these four models describe the high-level issues related to facilities and resources, an AHC beginning GLP research will need to spend a considerable amount of time devoted to defining the necessary organizational and leadership roles, depending on the model that they chose. Figure 3 illustrates how an AHC might organize these necessary elements. The successful creation and maintenance of a GLP-compliant infrastructure requires that investigators engage with senior leadership to ensure an understanding of the sustained institutional commitment required and the potential financial and reputational harm of not complying with FDA regulations. For example, these regulations dictate that the testing facility management has the ability to replace the study director as needed. In an academic setting, where the study director could be a faculty member, the institutional authority with managerial responsibility over the study would need sufficient authority to remove the study director if necessary. Academic officials at the necessary administrative level, however, likely would not have the knowledge, expertise, or available time to govern a GLP facility, so a mapping of roles and responsibilities to multiple individuals would be required. For example, the typical hierarchy at a university (see Figure 3A) does not correspond directly to the typical hierarchy at a commercial lab (see Figure 3B), which was the setting of most preclinical studies at the time that GLP regulations were written.[8] To overcome this difference, Figure 3C provides one potential GLP governance structure that ensures the appropriate expertise and authority in testing facility management and compliance management by integrating the central GLP components into a typical AHC structure. We recommend the development of an institution-wide GLP policy and procedure manual, which involves all of the groups represented in the hierarchy. The internal ramifications for non-compliance with GLP regulations should also be included in this manual.

Developing and Implementing a GLP-compliant Infrastructure

Even with the choice between several structural models and with a commitment from institutional leadership, significant time and effort are required to create a GLP-compliant infrastructure within an AHC. In addition to establishing a managerial hierarchy for GLP studies, the AHC must engage several institutional stakeholders in the process, including the animal facility staff, department leadership, associated core facilities staff, compliance groups, and the relevant principal investigators and their laboratories. A well-developed central strategy for the management of documentation and record-keeping procedures is also essential. Although attention is naturally focused on the physical facility and critically-important equipment, other areas, described below, are essential to any implementation plan.

Writing the SOPs

Written SOPs detailing all of the activities of the facility are key to the successful management of a GLP-compliant laboratory. Accurate and complete SOPs ensure the standardization of procedures and appropriate documentation and record keeping. A successful SOP is drafted by the staff who will carry out that procedure and then edited by experienced technical writers. This workflow accommodates the necessary details as well as the appropriate structure and formatting, each contributed by qualified individuals, resulting in concise and thorough, but not overly proscriptive, SOPs. Outlines of the methods for storing, changing, reviewing, and archiving the SOPs are also necessary components.

Training

Once the SOPs have been written and approved, personnel are required to document that they have read, been trained on, and demonstrated proficiency in them. Documentation of training is as important as the training itself and plays a central role in GLP regulations. Documentation that the personnel who train the staff have the appropriate credentials is also required. While the concept of documenting every laboratory and operational activity may not be ingrained in those who normally work in an academic environment, it can be implemented with adequate training, the appropriate supervision from facility management, and sufficient monitoring from the QAU. Training also should include any students, postdoctoral fellows, and residents who are involved in the GLP studies.

Establishing the QAU

The creation of an independent QAU is critical to ensure that every study is sufficiently monitored and that all areas of the study are in compliance with GLP regulations. During the implementation process, the AHC is required to create and maintain written documentation of the QAU's responsibilities and procedures. This unit should be staffed by individual(s) trained in quality control and assurance. Depending on the number of studies, the QAU may not require full time staffing, or the institution may choose to add this role to the responsibilities of an existing employee. GLP regulations do not dictate the nature of the group but simply outline the responsibilities and state the required independence of the unit. In limited circumstances, if the groundwork for the QAU has already been laid and the SOPs have been approved, a PI from one project may be asked to serve as the QAU for a different project, as long as the PI is free of conflicts of interest and maintains complete autonomy from the study that he or she is inspecting.[9]

Compliance management

The implementation of a new GLP program requires leadership endorsement and effective compliance management at multiple levels. A compliance manager plays several key roles in assessing compliance within the FDA-regulated infrastructure, including approving the

SOPs. This leadership role serves as the point of contact and responsible party for FDA review and provides the management structure to review QAU reports. When the QAU conducts the critical phase inspections and submits the report to the testing facility management and the study director, it is the responsibility of the compliance manager to provide the oversight to follow up and verify that the noted non-compliance findings are corrected in a timely manner. This position is also critical for maintaining proper communications and accountability and for verifying that corrective actions are taken when necessary. Overall compliance management within an AHC will require careful design and reporting structures to ensure the necessary personnel oversight and to maintain an environment that is conducive to GLP-compliant studies.

Funding

An AHC may provide the initial investment to launch a new GLP program, but investigators will need to secure an institutional commitment for the funds required for the continuation of the program. To remain financially stable, investigators should develop a business plan with cost analysis and break-even calculations, determine the running costs, and then establish a fee structure. For any program to be successful and to be maintained at the appropriate level, the AHC must pledge and deliver financial support. In the long run, a GLP-compliant program can be of significant value to an AHC and become a vital resource for projects that otherwise could not have been conducted at that institution.

In Conclusion

Federal regulations establish the requirements for performing GLP-compliant nonclinical studies. Comprehensive coordination of all the requirements outlined in these regulations is essential, as misrepresentation of GLP-compliance can have significant repercussions for the investigators and for the academic institutions who conduct such research. The creation of a GLP-compliant infrastructure, with all the appropriate levels of management, documentation controls, oversight and training, is a time-consuming process, involving a considerable coordination of efforts. To ensure the oversight and accountability required for optimal compliance, approval from the most senior levels of the AHC management is required. Since senior level management is not likely to have the background and expertise to oversee compliance with these regulations, employing additional trained and qualified personnel is necessary for the implementation of a GLP program.

Familiarizing academic professionals with the strict regulations required to conduct a GLP-compliant study requires a paradigm shift for the investigator who may serve as the study director, for the laboratory technician who is conducting the study, and for the institutional management who provide oversight and ensure compliance. In particular, one of the biggest challenges for AHCs to overcome during the creation of a GLP program is ensuring management control of the extensive documentation, which is specifically dictated by GLP regulations.

Despite the challenges, the successful design and implementation of a GLP-compliant infrastructure provides opportunities for significant benefits to AHCs. The immediate tangible benefits to the AHC that successfully navigates these hurdles include additional research contracts, more control over the quality and reliability of study data, a lower cost for nonclinical studies, an increased opportunity for the pursuit of translational research involving novel products, and the ability to use highly-specialized, locally-developed assays. To successfully translate novel therapeutics from the bench to the bedside, expertise and infrastructure to support compliance with FDA regulations is critical. The capability to perform GLP-compliant research will help AHCs build and maintain competitive research

programs and facilitate the successful translation of faculty-initiated research from nonclinical data generation to first-in-human clinical investigations.

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References

1. Collins FS. Reengineering translational science: the time is right. Sci Transl Med. 2011; 3:90cm17.
2. Berro M. Support for investigator-initiated clinical research involving investigational drugs or devices: the Clinical and Translational Science Award experience. Acad Med. 2011; 86:217–223. [PubMed: 21169787]
3. Hancock S. Meeting the challenges of implementing good laboratory practices compliance in a university setting. Qual Assur J. 2002; 6:15–21.
4. Schneider K. Faking it—the case against industrial bio-test laboratories. The Amicus Journal. 1983 Spring;:14–26.
5. Baldeshwiler AM. History of FDA good laboratory practices. Qual Assur J. 2003; 7:157–161.
6. U.S. Department of Health and Human Services. Food and Drug Administration. Good laboratory practice for nonclinical laboratory studies. 21 CFR 58. Effective 1979.
7. U.S. Department of Health and Human Services. Food and Drug Administration. [November 15, 2011] University labs inspection list. 2006. Available at: http://www.fda.gov/ICECI/%20EnforcementActions/BioresearchMonitoring/NonclinicalLaboratoriesInspectedunderGoodLaboratoryPractices/UniversityLabsInspectionList/default.htm
8. U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry: good laboratory practices, questions and answers. 2007
9. Weinberg, S., editor. Good Laboratory Practice Regulations. Vol. 168. New York, NY: Informa Healthcare; 2007.
10. U.S. Department of Health and Human Services. National Institutes of Health National Center for Research Resources. [November 15, 2011] Core facilities management and utilization. Available at: http://www.ncrr.nih.gov/core_facilities_management_and_utilization/

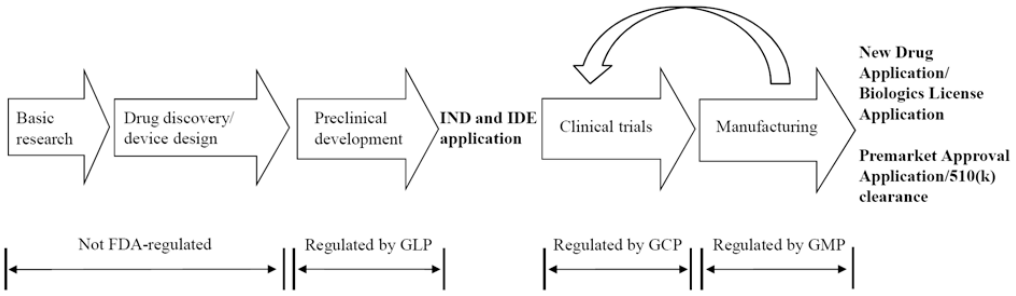

Figure 1.

Flow of Food and Drug Administration (FDA)-regulated processes from basic science research to clinical studies and product marketing. FDA regulations are indicated for each stage of the process, starting with preclinical development, which is covered under good laboratory practice (GLP) regulations, followed by clinical studies, which require submission of an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application and are governed by good clinical practice (GCP) regulations. The manufacture of products for marketing under a New Drug Application, Biologics License Application, Premarket Approval Application, or 510(k) clearance for devices and later-stage clinical studies, is governed by good manufacturing practice (GMP) regulations.

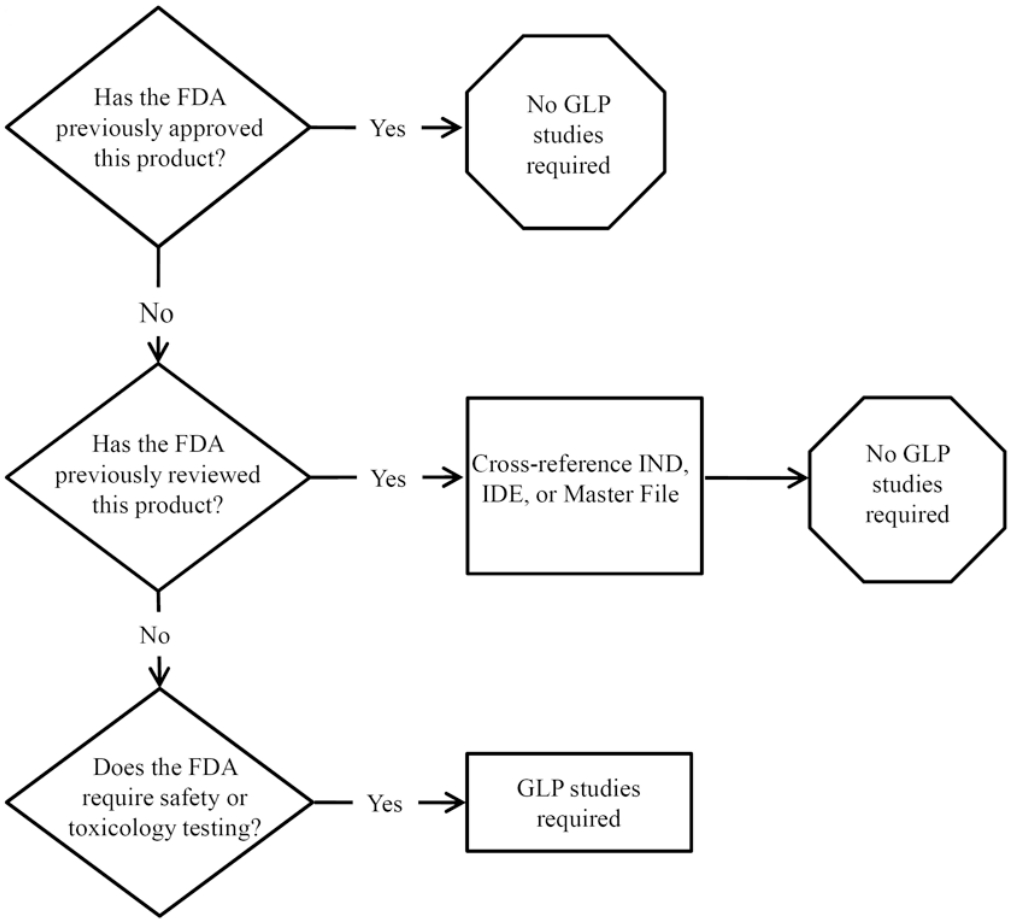

Figure 2.

Flowchart for determining whether studies generating nonclinical data intended to support an Investigational New Drug (IND) or Investigational Device Exemption (IDE) submission likely require compliance with Food and Drug Administration (FDA) good laboratory practice (GLP) regulations. This simplified flowchart provides context for GLP studies and is not an exhaustive guide for all GLP requirements.

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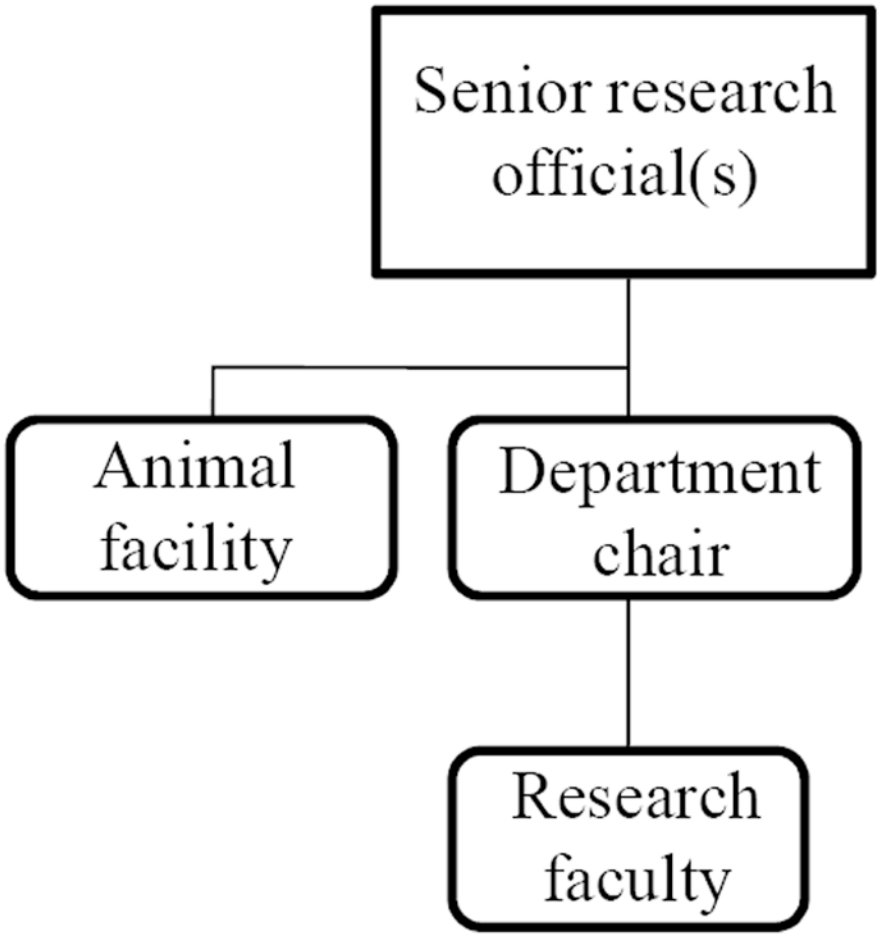

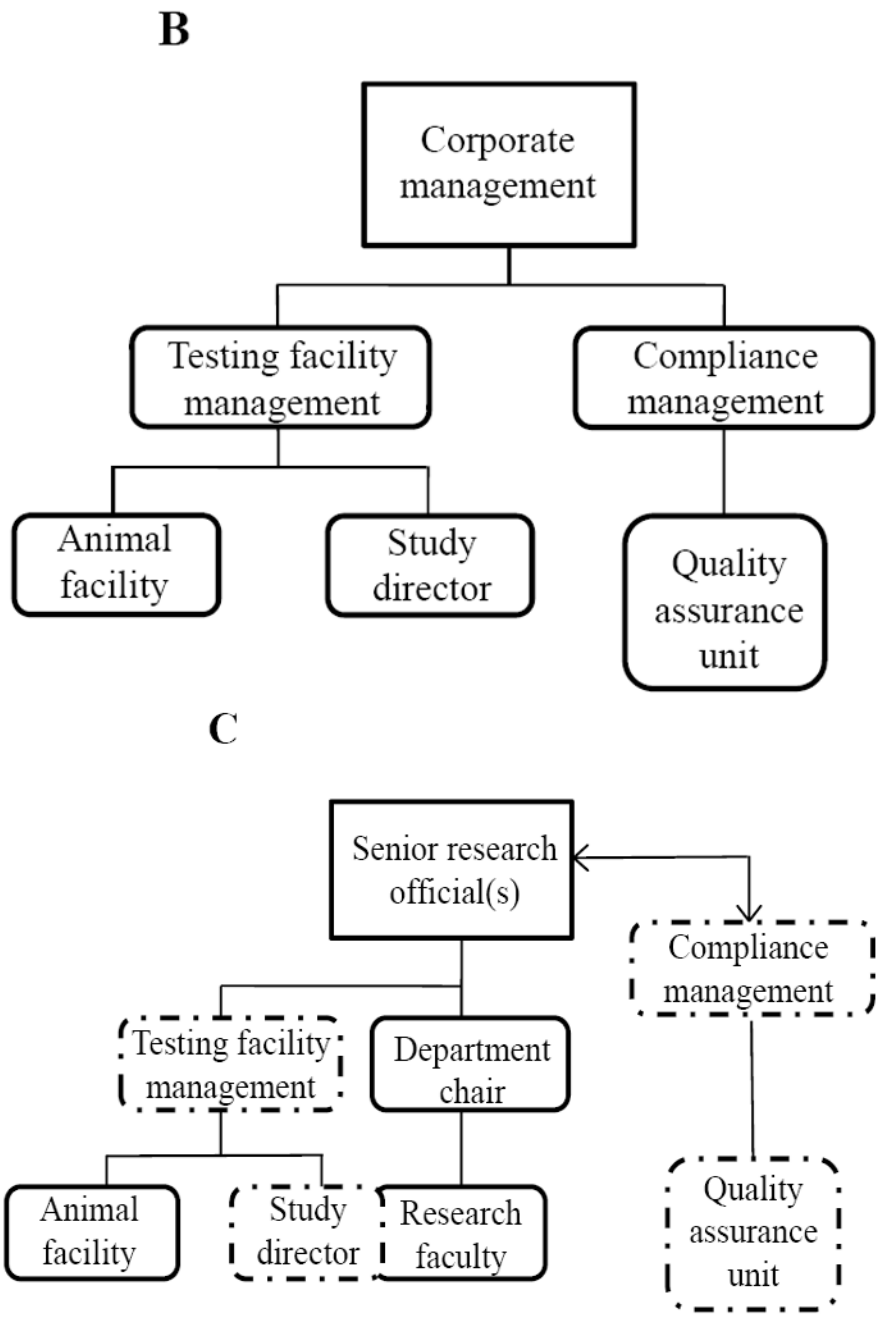

Figure 3.
Comparison of the structure of the research organizations at a typical academic health center (AHC) (panel A) and a typical commercial laboratory (panel B). Panel C depicts a potential combination of the two for AHCs conducting research that meets the FDA's good laboratory practice (GLP) regulations by adding management and oversight functions that are not usually part of the AHC research structure. Dotted lines indicate roles that must be added to comply with GLP regulations. Overlapping dotted and solid lines indicate potential co-located roles. Arrows indicate coordinated responsibilities.