Facilities—Design and Sustainability for Harmonizing GLP

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"GLP Topics" addresses topics associated with good laboratory practice requirements. We intend this column to be a useful resource for daily work applications. The key objective for this column: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Manuscripts or case studies submitted by readers are most welcome. Please send your comments and suggestions to column coordinator Cindy Green at cindynwrs@seanet.com or to journal coordinating editor Susan Haigney at shaigney@ advanstar.com.

EXECUTIVE SUMMARY

Designing, upgrading, and continually maintaining good laboratory practice (GLP) facilities are critical factors in compliance with regulatory requirements and in producing top-notch study results, regardless of the setting. By having a working knowledge of the regulations, using preparation tools for working with architects, and maintaining compliance, the GLP work environment will generally take care of itself. In the end, the keys to success are in the organization, planning, and training.

INTRODUCTION

In the 20th Century, the architect Frank Lloyd Wright was quoted, "Less is only more where more is no good." There are some expressions that cannot be improved upon, especially when the topic is GXP facilities.

It doesn't matter whether the intended facility is related to laboratory design, manufacturing facilities, vivariums, or support roles—the better the planning, the more efficient the outcome regardless of whether the facility involves a remodel or new construction.

Facility design can be intimidating to individuals not well versed in architectural planning. And it really doesn't matter if you're starting from the ground up or simply making a small change to an existing facility. The task is daunting. The pressure is on to produce a working environment in which your co-workers will spend many hours, and blame you for the shortcomings. How do you handle the pressure? Follow these basic rules, and your completed facility will be better than you envisioned it.

REGULATIONS—SOCKS FIRST, SHOES LAST

As simple as it may seem, facilities are often designed without regard to the regulations that will govern the activities performed within its walls. A visit to the Internet will reveal myriad resources regarding GLP facility requirements, planning, and maintenance. Regulations, including 21 CFR Part 58, *Good Laboratory Practice for Nonclinical Laboratory Studies* (1) and the Organization for Economic Co-operation and Development (OECD) (2), provide strong background into what is required for GLP compliance. Good manufacturing practice (GMP) regulations for facilities may be found by perusing the United States Code of Federal Regulations (CFR) and international web sites (3-7). A few mouse-clicks should be the first task to be performed in facility planning. Rather than reiterate the regulations within this article, the following are key issues to keep in mind when it comes to designing compliant facilities.

The Test Facility Must Be Effectively Managed

The best study directors and quality units will struggle in an ill-conceived facility, and the results of any GXP study can become compromised without a critical eye to a laboratory that is poorly planned and managed. In such scenarios, samples can be mismanaged, records lost, testing results and quality control documentation absent, and poorly-maintained equipment contributing to erroneous results. While third party and regulatory audits can arrest these pitfalls to a certain extent, these events often come too late in the process or worse yet, not at all, leading to a drug or device fraught with downstream post-market problems in safety and effectiveness.

Testing And Control Articles

Testing and control articles must be considered within the facility design. The concept here is straightforward: design the facility in such a manner that receipt of specimens, test materials, supplies, and storage of these items are separate and easily identified. A cold room with shelves sporting faded hand-lettered signs reading "Tested" and "Finished" is no match for a separate, caged area within a cold room for storage of incoming versus tested samples. The key here is prevention of cross-contamination, mix-ups, and maintaining test material integrity.

Optimal Laboratory Planning Is Vital

Whether remodeling or building from the ground-up, the laboratory used to perform GLP studies must be carefully planned and the layout optimized for both effective use of space for equipment, required utilities, and comfort of the persons performing the tests. A general rule of thumb is 80 to 100 square feet and 8 to 10 linear feet of bench space per laboratory worker. Applying this rule should allow the GLP lab to comply with the OECD requirements that state: "The test facility should be of suitable size, construction, and location to meet the requirements of the study and to minimise disturbance that would interfere with the validity of the study" (2).

Additional items for consideration in planning a compliant GLP laboratory include the following:

- Use of epoxy sinks
- Design of separate lab drain lines from sanitary waste
- The use of plug mold systems to provide adequate electrical outlet
- Planning enough 240/220/208 volt outlets for equipment with special power requirements
- Designing instrument bench with a minimum depth of 36 inches to accommodate rear cabling and access to the front of the instrument
- Data cabling for computers and analytical instrument interfaces
- Piping gases from a central mechanical room to eliminate cylinders in the laboratory and improve servicing access
- Positioning the purified water system such that long pipe runs and dead-legs are minimized or eliminated.

Examination of the workflow should be included so that the correct layout is designed, including deciding whether to use free-standing island benches versus a "Bay" (i.e., a U-shaped design) or "T" lab bench layout, or any combination thereof, and planning casework to accommodate both the function and composition. For example, laboratories

performing minimal tests and using non-corrosive reagents may benefit from laminate countertop instead of the more expensive epoxy resins. It is also recommended that fume hoods and biological safety cabinets be positioned away from entry doors whenever possible to eliminate interferences in operation of the airflow by traffic and opening/closing of doors into outer corridors.

The plan should also address the future use of the laboratory and how easily changes can be made to the layout. If the laboratory test menu is not likely to change, it may be tempting to take a casual approach to future needs and to view the facility plan around existing or soon-to-be purchased equipment and workflow. However, technologies do change. Footprints of modern chemistry analyzers are minute compared to the sprawling instruments of just a few decades ago. In fact, the first clinical laboratory in which I worked had a dedicated room for a huge Tehnicon instrument that only performed 18 chemistry tests on 60 samples in one hour. To circumvent tearing down walls and interrupting laboratory services during remodels, a modular concept just may be the answer.

Modular laboratory concepts are certainly not new. Modules are now used in most of today's research building projects and for many other types of lab buildings as well. Modular labs utilize a regular repetition of structural elements and mechanical and utility requirements within a traditionally built facility. Modules can even be built off site in factories and delivered ready for placement. The manufacturer takes responsibility for design, construction methods, and costs. Design is usually in conjunction with an architect specializing in laboratory design. The manufacturer then constructs the modules inside a factory in a controlled environment. This approach can reduce the build time by as much as 12 months and increase the quality of final product due to factory-style quality control. However, in some cases modular design may increase cost, so a little homework is necessary.

Even if a factory-built modular lab is not in the budget, taking a modular-type approach can be beneficial. With plumbing, electrical, cabling, and other utilities placed under the floor, accessible from removable floor panels, modular benches can be moved and connected in a matter of days. Benches not requiring utilities can be moved in an afternoon, providing a flexible environment that can meet changing future needs.

In any case, the GLP lab design must take into account isolation of test systems and the isolation of individual projects that utilize substances or organisms known to be or suspected of being biohazardous. This includes incorporation of storage rooms for equipment and supplies, separate rooms or designated areas for receipt and storage of the test and reference items, and mixing of the test items with a vehicle. Clearly, if several GLP studies are to be performed within a given facility, the laboratory plan must address the study separation requirements to ensure that contamination or mix-ups cannot occur.

Meticulous Manufacturing Facilities Planning

Although this article discusses GLP facilities, a few notes on GMP facilities are appropriate here. A recent involvement in a GMP design required a review of the rough sketches of a floor plan intended for contract manufacturing of finished pharmaceuticals. The architectural firm was fluent in designing small clinics and related healthcare facilities, but GMP requirements were new to them. Because this was a new facility, opportunities abounded for making a world-class design, and the client was eager to use the plant as a showcase by implementing windows into the design through which investors, collaborators, and customers could view the unique methods of production without gowning and entering a controlled area. However, the design was focused on this central feature without examining the storage and flow of raw materials into, through, and out the plant. Additionally, certain critical elements were missing in the design. These included means to identify and separate approved materials from unapproved materials, gowning areas opening onto common hallways, requirements for servicing personnel to gown and introduce tools and equipment into the controlled environment, and a common warehouse intended for storage of everything (e.g., parts, com-

ponents, raw materials, and product). Fortunately, all parties involved were open to the concepts and requirements of the GMP regulations and the design was modified to accommodate the deficiencies, resulting in a compliant and highly workable plan. The moral is that simple common sense in design of an efficient process flow should always be the first consideration in a GMP facility.

Animal Care And Supply Planning

If the GLP laboratory facility is intended for conduct of studies on test animals, then it is critical that the areas used to house animals be carefully planned. This is especially important in today's climate where increasing pressure is placed upon researchers to employ alternate methods to using animals for research studies. Additional regulatory requirements will depend on the geographic area.

For example, experiments on vertebrate animals in the European Union are subject to Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes, adopted in 1986(8) . In the US, animal testing on vertebrates is primarily regulated by the 1966 Animal Welfare Act (AWA), which is enforced by the Animal Care division of the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA) (9-11).

Additionally, critical planning is required to ensure that species are separated, that individual projects are isolated and proper provisions for quarantine of animals are designed. Supplies, bedding, equipment, feed, and cold storage requirements must be maintained in separate areas from housing. This is one area that may be overlooked during the facility design.

Properly Plan Specimen And Data Storage Facilities

Would you expect to go to your local bank and see open shelves with shoe boxes labeled with your name and containing your money? As ludicrous as this may seem, this is the way some GXP study specimens and data are handled. Confidential procedures, documents, and study data are often stored in general access areas and samples are kept in a refrigerator that also holds lab reagents or, worse yet, lunches. A quick look at 21 CFR § 58.51 should make anyone aware that this single regulatory sentence translates to limiting access to these items and organizing the storage part of the facility so that it is easy to obtain completed records and the samples themselves.

GLP FACILITY PLANNING 101

With the basic knowledge of what regulators will look for in a study facility, and with so many things to consider, how does one know where to start?

Begin With A Program Statement

The program statement is the first and often ignored element to a successful GLP facility. It puts you, architects, and ancillary personnel on the same page. The program statement should be a brainstorming session that includes the items listed in Table I.

Layout The Scenarios

Once the program statement has been drafted, the interactive scenarios are documented. An extremely useful tool is a bubble diagram (see Figure 1). This step is the most important in the process and should include consideration about efficiency and ergonomics. Bubble diagrams are answers to basic questions, such as the following:

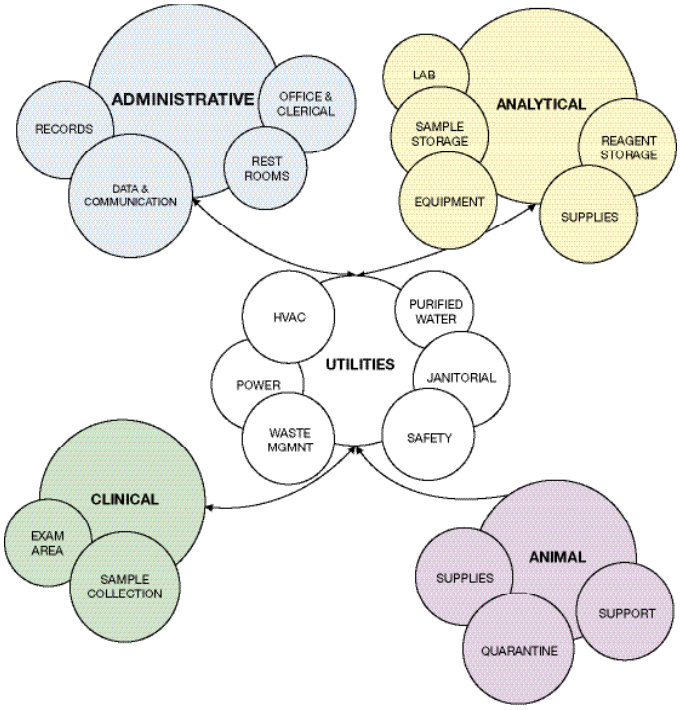
- What will be the functional areas and what will they require?
- For GLP facilities: How will patients, records, and samples be managed, identified, transported, stored, and retrieved?
- For GMP facilities: What is the process flow and how will supplies, components and materials be ordered, received, accepted, stored, maintained, used in the manufacturing process, quarantined, tested, stored, and distributed?
- What patient facilities will be required?
- How will people communicate?
- What will be the equipment requirements?
- How can space be most efficiently utilized?
- What utilities will be required?

TABLE I: Example program statement for designing or upgrading a GLP facility.

Statement category	Comment
Program expectations	What do you want to accomplish at the end of the program?
Type of GLP facility	Research, clinical, teaching, manufacturing, etc.
Scope of GLP program, testing, or work	Include every item that will be required to accomplish the study, even if you think you don't need it
Hours of operation	Impacts decisions on alarms, entry lockouts, lighted parking
Estimated laboratory test volume	Test volume will aid in laboratory planning and floor space requirements
Personnel requirements	Determines office and cubicle requirements, director, supervisory, technical clerical, and support staff
Number of employees	Impacts functional, support, and ancillary requirements such as break rooms, placement and number of bathrooms, lockers, number, and placement of janitor closets

The bubble diagram is not a floor plan. It relates to function rather than layout and will ultimately be used during the architectural design. To produce the best bubble diagram, input should be sought by all people who actually will have to work in the functional areas. This can be accomplished by meetings of individuals in each functional area before development of the bubble diagram. The goal of such meetings is to produce an area consensus statement that is presented by one representative of the functional area during development of the bubble diagram. An informal meeting is best for this activity, and should include all employees. It is important that all ideas are presented and the overall impact on the project weighed. Don't unilaterally dismiss an idea, as it could be important to the efficiency of the facility. Allow time for input beyond the consensus statement, and from individuals unrelated to the functional area. It is not uncommon that the previous work experience of an administrative person could bring an idea that would enhance a technical functional area such as a sample pass-through to the laboratory or cold room.

Figure 1:
Example bubble diagram used for planning a GLP facility.



Equipment, Utilities, And Required Space

Before a single wall is drawn, the general layout for each functional area is defined by using general box diagrams. Each box should represent a potential room for each functional area and contain required contents of the room (see Figure 2). At this time, a full list of equipment and required footprint space and utility needs is developed. Using the example in Figure 2, the size, weight, power requirements, and

waste handling of the chemistry analyzer is input in a list or spreadsheet.

This activity is repeated for each piece of equipment until the complete room contents are assembled. Function and equipment sizes will dictate the required amount of space for each room. However, do not overlook the space requirements to comply with the ADA Standards for Accessible Design (28 CFR § 36) that include such items as dimensions for entrances, bathrooms, hallways, space between benches or workspaces, telephones, and alarm placement. General space requirements are presented in Table II. However, each GXP facility must be planned for optimal use of space and maximum efficiency; general space requirements are rules of thumb and may not apply in all cases.

Using the information from the box diagram, equipment list and dimensions, the information is combined and examined to determine whether cross-functional areas exist. For example, a laboratory may require utilities such as purified water systems and piped gases, the clinic may require an autoclave, and vacuum may be required in multiple areas. In these cases, a central mechanical room can function to house the utilities, making servicing and maintenance centrally located and saving valuable space.

Next, the general layout can be initiated, taking into account how the functional areas spatially interact; where access must be restricted; how safety and evacuation routes must be introduced; where storage, purchasing and receiving areas are most efficiently placed; and where other key details are

Figure 2:
Block diagram including GLP equipment requirements.

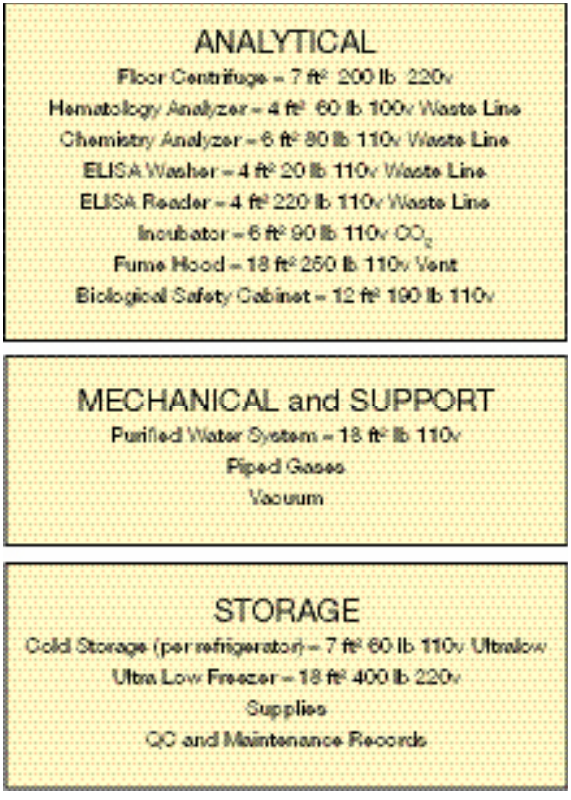


TABLE II: General space recommendations for a GLP facility.

Functional area	General space requirements
Accessible routes (i.e., space between lab benches)	Minimum 60-inch width for compliance with ADA regulations
Administrative and clerical	70-80 ft² per person
Circulation space	Allow 20-30% of total usable area for corridors and circulation
Conference rooms	25 to 30 ft² per person with 32 inches per person at the table for compliance with ADA
Exam room	Minimum 8 ft x 10 ft
File room	7 ft² per file cabinet plus a 5-ft wide aisle
Hallways	Minimum 60-inch width for compliance with ADA regulations
Laboratories	80 to 110 (mean of 95) ft² per person
Library	Allow 12 inches for bookshelf width; 175 to 450 ft² with seating for 4-6
Lunchroom/ breakroom	15 ft² per person, plus a kitchen area
Offices	Minimum 8 ft x 10 ft
Reception area	125 to 200 ft² for receptionist and 2-4 people 200 to 300 ft² for receptionist and 6-8 people

introduced into the facility design. The focus here is on efficiency. This step is best left to an architect specializing in the design of clinics, laboratories, or healthcare facilities.

Don't Forget The Details

Certain details often escape even the most experienced planners and architects and must be dealt with after the build is complete, adding unexpected expenses. While the following list is not intended to be complete, it will provide an idea of items often overlooked in the design and operation of a GLP facility:

- Bulk supply receiving and storage areas
- Biohazard and chemical waste disposal storage space
- Safety equipment requirements
- Quarantine areas
- Surge protection (e.g., most modern laboratory analyzers, readers, and spectrophometers include computers or computer-associated components)
- Clerical supply storage
- Technical worker clerical workstations\cubicles
- Room for large office machines (i.e., document processing centers)
- Mail room
- Phlebotomy and/or cot areas
- Janitorial supply storage
- Waste disposal areas (i.e., cardboard and plastics recycle storage)
- Additional electrical outlets for future expansion (extremely important).

MAINTAINING GLP FACILITY COMPLIANCE

An ancient Chinese proverb states, "If you are planning for a year, sow rice; if you are planning for a decade, plant trees; if you are planning for a lifetime, educate people." Nearly every GLP facility is neatly arranged with up-to-date record storage, impeccable maintenance, and calibration records and is nearly perfect—for the first six months following the remodel or new build. Then something starts to happen. Reagents and chemicals begin to outdate. Shelves, refrigerators, and freezers become cluttered. Maintenance performance on equipment increasingly reaches the outer limits of allowable time intervals such that in extreme situations, only 10 or 11 monthly maintenance events occur within a 12-month calendar year. Calibration, temperature recording, and daily tasks slip from their previously regimented diligence. Excuses include workload, personnel turnover, apathy, and poor supervision. The culprit is usually improper or inadequate training, stressing the requirements and elements inspectors will scrutinize during study audits and laboratory inspections.

These principles are neither secret nor difficult to understand, yet innumerable US Food and Drug Administration warning letters have been issued for poor attention to detail regarding maintenance of the facility to meet GLP requirements. A substantial number of such warning letters cite the failure to document activities related to facilities management. FDA bases many of its decisions on documentation reviewed during an inspection, because documentation is both the central indication of how well a laboratory is run and a measure of the quality of the results that are produced by the GLP lab. Along with this is the attention to general "no brainers" such as the quality of housekeeping including cleanliness, lack of clutter, and conveniently located space so the quality of work, safety of personnel, and testing services are not compromised.

It is imperative that every individual working in every capacity within the GLP laboratory be afforded the education required for sustainable compliance with regard to maintenance and upkeep of the facilities and the instrumentation by which GLP results are produced. Management must recognize that while the output of laboratory results is an important measure of a laboratory service, adequate time must be allowed for maintaining, recording, and reporting problems related to the facility in which tests are performed, and must be accounted for in the master schedule. Table III lists key elements for sustainability of GLP compliance.

CONCLUSIONS

There is no magic to GLP facility upgrading, new design, and maintaining compliance. The keys to success are planning, attention to detail, and adequate personnel training to ensure that all elements

TABLE III: Key items to ensure GLP sustainability after building a new facility or renovation that are often mismanaged or neglected. Lack of ongoing attention to these details can result in regulatory action.

Facility compliance element	General space requirements
Floors, walls, ceilings, and cabinet maintenance	Maintain and review documentation of internal inspections for dirt, damage, and proper function as well as maintaining documented proof of remediation or repairs.
Procedures	Ensure that appropriate and technically valid facility-related standard operating procedures (SOPs) are established and followed and that all original and revised SOPs are approved.
Purified water system	Maintain and review records of resistivity, filter changes, records of repairs due to leaks, timely water analysis to ensure proper purification.
Refrigerators, freezers, and incubators	Temperature charts up to date, timely equipment cleaning records, CO^2 incubator monitoring records complete.
Safety and safety systems	Ensure that fire extinguishers, laminar flow biosafety cabinets, fume hoods, eye washes, and showers are functioning and that maintenance and inspection records are current.
Specialized storage	Ensure that facilities include specialized storage to ensure separation of flammables from other chemicals, separation of liquid chemicals from solids, compliant chemical, radioactive materials and biohazards waste storage, and verify that labeling of storage areas and cabinets meet local and federal regulations.
Top-level facility records	Maintain all records associated with facility commissioning, equipment installation, mechanical and architectural drawings and their revisions, and major repairs to the facility or major equipment (i.e., HVAC systems).

are in check and that facilities-related documentation is complete. Using the aforementioned tools, the facility won't take care of itself, but it will provide the environment to produce top-level study results. Hard work? Yes. Worth the effort? Unquestionably.

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GLOSSARY

Master schedule. Master schedule means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility.

Quality unit(s). An organizational unit independent of production that fulfills both quality assurance and quality control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine. The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

ARTICLE ACRONYM LISTING

APHIS	Animal and Plant Health Inspection Service
AWA	Animal Welfare Act
CFR	Code of Federal Regulations
FDA	US Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
OECD	Organization for Economic Co-operation and Development
USDA	United States Department of Agriculture

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