

1. GLP Quality System

While many of the requirements of the existing regulation are consistent with a GLP quality system, FDA believes that modifications may be necessary to incorporate all basic elements needed for a

comprehensive GLP quality system, such as that set forth in the internationally recognized standard, Quality management systems-- Requirements ISO 9001, available from the International Organization for Standardization (ISO) at: <http://www.iso.org/iso/home.html>.

Ultimately, any GLP quality system proposed for a facility must be capable of ensuring the integrity of resulting data. FDA is considering

whether to include in the regulations a core set of essential elements

for such a GLP quality system, including specifically mentioning management responsibility for all activities at the facility and specifying a requirement for standard operating procedures for all essential functions.

I am concerned about the reference to ISO, and applying such standards to research, as I have seen many ISO certified laboratories that produce poor quality data. I believe the GLPs are a much better quality standard for research and have serve industry and the FDA well over the past 30 years. However, it is critical to emphasize that upper management (i.e. the entity that controls resources and that can effect change, and to whom a 483 would be issued) be made aware of ALL actual compliance issues within the facility and must respond to such. Currently, too many of the individuals fulfilling "management" roles in GLP have no control over resources and are essentially in middle management positions. If the highest level of management at a facility were required to receive the status reports on studies and facilities and address such issues, many of the problems would be resolved (although the current GLPs require such, many companies are viewing this differently). This entity should be better defined as the individual where the study personnel and QA's reporting lines intersect. I do support the flexibility to have many management duties delegated to lower levels of management (i.e. approving SOPs, assuring appropriate corrective actions are taken in response to each QA finding, etc.), similar to the Study Director delegating phases of a study or having an archivist with subordinates for specimen and electronic archives. It may be beneficial to adopt the OECD responsibilities regarding management, as these are no different from FDA but are nicely consolidated in a single area.

2. Multisite Studies

It is currently common practice for nonclinical laboratory studies to be performed across multiple sites (multisite studies), rather than

for a single facility to conduct all aspects/phases of a study. FDA is

considering revising the GLP regulations to specifically address the use of multisite studies through the addition of specific definitions

to describe personnel and study aspects specific to multisite

studies,
e.g., by requiring that an individual be designated as the responsible person for each site of a multisite study. Such an individual would be

responsible for any phase(s) of the study conducted at the site and would report to the study director.

This should definitely be added to the GLPs. However, there is a distinction between someone conducting a portion of the study on behalf of the SD (bioanalytical, clinical pathology, histopathology, biomarker analysis, etc.), who is defined in the OECD GLPs as a Principal Investigator, and an individual who would be considered a "contributing scientist" (TK, pathologist, statistician) that is simply taking the data that has been generated and providing the SD with an expert (independent) opinion. There is much confusion in the way OECD GLPs are written regarding the "control" the SD has. Although Study Directors should have control over all sites and data, etc., the "control" over another expert scientist who is simply evaluating or modeling data and providing an expert scientific opinion is totally different. The individuals offering expert opinions or that are contracted to perform specialized functions for a study (surgeons, cardiologists, ophthalmologists, etc.) are usually professionals and have their own businesses. These businesses should not be considered "test sites", as these individuals generally perform their functions at the testing facility. Of more concern than "multi-site" studies is the fact that many of today's studies are multi-discipline, and safety evaluations today may involve many more disciplines than toxicology. Examples of these would be tissue residue studies for animal health studies, stenosis for device studies, and vector evaluations for gene therapy studies. The expert needed to run the in-life portion of a study is not necessarily an individual that understands all other aspects of the study well enough to draw conclusions on the study, especially in areas such as animal health, biologics and devices. Trying to force this individual into a "study director" role is counter productive. In addition, a study director at a CRO has no true control over Sponsor generated activities or activities conducted by facilities contracted by the Sponsor. Therefore, I highly recommend that any revision to the GLPs place the bulk of the responsibility for data integrity on the SPONSOR. There should also be written flexibility so that the more complex safety studies can be conducted more in line with a clinical study model, where individual scientists are contracted by the Sponsor, and the Sponsor is responsible for compiling the individual scientist reports, evaluating the data and writing the final report (i.e. the Study Director is at the Sponsor). I have seen this model work very well for complex studies, and it eliminates many of the problems we see today concerning lack of transparency of Sponsor activities.

The GLPs should definitely retain the Study Director role as the single point of control, being responsible for the interpretation, evaluation and reporting of data. This person could easily be at the Sponsor, with a CRO toxicologist simply as a contributing scientist responsible for the toxicology portion of a study. Perhaps the definition of a Principle Investigator could be an individual who is

conducting a portion of a study on behalf of the study director and is generating data or samples, and the definition of contributing scientists could be an individual who is evaluating data and providing the SD with an expert opinion.

Adopting the OECD requirements for "test sites" and better defining the roles and responsibilities of "contributing scientists" would be welcome.

Electronic/Computerized Systems

Since the regulation was finalized, many laboratory systems have become fully automated. In addition, many facilities now employ computerized systems for managing general laboratory functions as well as for instrumentation in which such systems are integral components.

While the present regulation does not preclude such electronic systems, several of the current regulatory requirements are more consistent with

paper-based systems (e.g., an individual as archivist Sec. 58.190(c));

maintenance of copies of study protocols and the Master Schedule by the

quality assurance unit (Sec. 58.35(b)(1) and (b)(2)). FDA is considering updating the regulation to reflect the use of electronic and computerized systems. FDA believes that any modifications to the regulation to reference electronic/computerized systems should be general, to accommodate changes and advances in technology.

Agreed. However, it should be made clear in any revision that raw data for computerized systems is the electronic data, and audit trails must be established and maintained. Such electronic data must be archived under the control of the archivist. However, I caution to stay away from the terminology "validation", as this is often misused and may confuse "end-user" qualification with developer's validation. An individual should be responsible for the archives as currently required. However, there is nothing in the GLPs that precludes the archivist from having delegated subordinates (i.e. for electronic and specimen archives).

4. Sponsor Responsibilities

Whether nonclinical laboratory studies are conducted by a sponsor or at a contracted facility, FDA believes that the study sponsor should

clearly have responsibilities that the present regulation does not specifically mention, such as development and/or approval of study protocols. FDA is therefore considering amending the regulations to include additional specific responsibilities of sponsors of nonclinical laboratory studies.

Agreed. It would be beneficial to use Sponsor requirements as detailed in VICH 9 (CVM Guidance 85) on which to base such requirements. At a minimum, Sponsors should be required to assure

compliance of all contracted facilities and to effectively monitor studies to assure compliance with GLPs and protocols. As stated above, since many studies involve such varied disciplines, many Sponsors would like to use the expertise of facilities that also conduct their clinical assays (BA, biomarker, etc.) Flexibility should be included for the Study Director to reside at the Sponsor and oversee all parts of the study, as this would be the individual most qualified to pull all aspects of a study together and draw conclusions. A significant issue today (due to the multi-discipline nature of studies) is that the Study Directors at CROs do not have the in-depth knowledge regarding the mode of action of many of these compounds to truly assess safety concerns and draw conclusions on the safety of a product. Toxicology is only a portion of many safety studies, especially with studies such as gene and cell therapy and many biologics. The Sponsor is ultimately responsible for the submission, and actually has a vested interest in discovering safety issues BEFORE advancement to clinical studies and committing additional resources to a product that is not going forward.

5. Animal Welfare

In the United States, the Animal Welfare Act (7 U.S.C 2131-2159) governs the treatment and use of animals, including their use for research purposes. FDA is soliciting comments regarding whether and how to receive documentation of compliance with these existing statutory provisions or comparable international standards governing the ethical and humane use of laboratory animals in nonclinical laboratory studies. This issue is not specifically addressed in the present regulation.

Agreed. The GLPs could simply contain a statement that any use of animals in a study should comply with all animal welfare regulations whenever possible (exceptions would be animal efficacy rule studies and some early range finding studies).

6. Information on Quality Assurance Inspectional Findings

When an FDA bioresearch monitoring (BIMO) inspection of a nonclinical study identifies problems, FDA often finds it difficult to determine whether the quality assurance unit (QAU) failed to adequately inspect the study, or whether the QAU made recommendations for corrective actions and management did not adequately respond. FDA is considering the addition of a requirement that the QAU prepare a yearly summary of general inspectional findings that would reveal problems that are not necessarily study-specific and that includes the recommendations made to management to resolve those problems. Such a report would be maintained at the facility and be made available to FDA upon request, usually during the course of a BIMO inspection.

Although this is a good idea, it will probably be met with much

resistance and could compromise the objectivity of the internal QAU. In addition, this may be extremely difficult for smaller sites that rely on contracted or Sponsor supplied QA. I think the current problem FDA is seeing is a result of QA status reports not getting to a management level that can effect change. The individual at a company that would be receiving a 483 should be required to receive status reports as outlined in the current GLPs. In addition to study related findings, these status reports should detail all compliance issues at the facility, QA recommended corrective actions, and all actions taken by lower levels of management and/or study directors. Requiring Testing Facility Management to be an individual responsible for assuring compliance within a facility could solve most problems. Obviously, many duties could be delegated to lower levels of management.

7. Process-Based Systems Inspections

A number of procedures used in conducting a particular nonclinical laboratory study are common across many or even most studies conducted at the facility. Facilities often find it more resourceful to periodically inspect such procedures during systems inspections rather than repetitively as part of each study-specific inspection, as currently required in Sec. 58.35(b). For example, it may be appropriate to periodically inspect procedures such as slide preparation for pathology studies as part of a facility's process-based systems inspections rather than for each study. FDA therefore is considering permitting a combination of systems inspections and studyspecific inspections. The results of the appropriate systems inspection(s) would be referenced in the study-specific inspection reports relevant to those aspects of the procedures for the study under inspection.

Agreed. However, if this flexibility is given, it is critical that the provision include a requirement to adequately inspect all study activities unique to a given study. It would also be helpful to help define what type of studies and activities could be covered by process-based inspections, and clarify that any finding discovered during a process based inspection be reported to all applicable study directors.

8. Test and Control Article Information

When reviewing and inspecting nonclinical laboratory studies, particularly those submitted for new drugs (human and animal), basic information about the test article, such as strength, purity, stability, and for mixtures thereof, concentration and uniformity, is often absent from the laboratory's records, therefore precluding appropriate interpretation of the study results. Although the

current regulations require that these parameters be determined (Sec. 58.105(a) and (b) and Sec. 58.113(a)), the regulations do not specify who is to receive this information or include a timeframe for delivery of the information to the facility performing the nonclinical testing. FDA is therefore considering additional requirements under the sections in the regulations discussing test and control characterization (Sec. 58.105) and mixtures of articles with carriers (Sec. 58.113), including timeframes for provision of this information to the study director. In addition, sponsors have requested the ability to cite compliance with the applicable good manufacturing requirements (i.e., parts 210 and 211, etc. as relevant) regarding the specifications, quality, and integrity of the test article. FDA is considering whether to accept compliance with either the specifics that would be required under a revised part 58, subpart F or the relevant good manufacturing requirements.

If adequate GMP procedures are in place, GMP analysis may be appropriate. However, many "GMP" analyses are done in the GMP R&D laboratory. Specific requirements should be added to mitigate differences between GMP and GLP (such as archival of records, QA oversight, etc.). As previously stated, even with the characterization information, there are many properties with new drugs that impact safety evaluations. Study Directors located at the Sponsor, would have more in-depth knowledge of the molecular entity, and the evaluation of the study would be enhanced. However, in a routine toxicology study where the Study Director is at the CRO, it is critical to outline Sponsor responsibilities as far as supplying characterization information. FDA should also consider adding a provision to the GLPs (similar to EPA), defining expectations for conducting characterization studies as "stand-alone" GLP studies. Test articles are often manufactured and characterized well before the location of the individual GLP studies are known. In addition, a single batch/lot of test article could be used for numerous studies.

Due to the increased importance of bioanalytical data and in an effort to harmonize with OECD and EPA GLPs, it would be beneficial to expand this section of the GLPs to include analytical reference standards.

9. Sample Storage Container Retention

FDA's regulations currently require that facilities maintain test article storage containers for the duration of the study (21 CFR 58.105(c)). FDA believes that compliance with the regulatory requirements for the handling of test and control articles, which include documentation of receipt, distribution, and use of each batch (Sec. 58.107(d)) provides adequate information about the use and

integrity of study samples. Therefore, FDA is considering eliminating the requirement at Sec. 58.105(c).

Agreed

Other considerations:

The scope of the revised GLPs should include animal rule studies and medical devices for animals.

Although feasible and practical in many cases, care should be taken regarding any harmonization effort with OECD or EPA. The intent and scope of those GLPs are entirely different from FDA with the complexity of FDA safety studies being far greater than those currently conducted under OECD and EPA GLPs. Although portions of both may be able to be somewhat harmonized, the complexity of FDA regulated studies precludes many harmonization efforts. Also, please note that the EPA GLPs are 22 years old, while OECD GLPs are 13 years old. OECD GLPs and associated consensus documents are based on total consensus of the member countries, and therefore many critical items required by FDA GLPs were not incorporated into the OECD GLPs (i.e. archival of electronic data at test sites, status reports to management, reporting unforeseen circumstances in the final report, etc.).

With the current passage of the food safety act, consideration should be given as to whether a single set of GLPs is adequate. Routine testing, such as most studies required for food additives, would require much less flexibility than those safety studies on new drugs, biologics or cutting edge therapies.

If food and feed additives are going to remain under the scope of the FDA GLPs, then additional directive should be included as to when GMO crops and animals are considered "food additives". Currently, EPA regulates GMO crops that contain pesticidal products (herbicide resistance and BT). However, more crops are being developed to be drought resistant or have enhanced traits (such as addition of vitamins, higher oil content, etc.). Clarity is needed regarding when genetically modified organisms (plants or animals) fall under the category of a "food additive", and therefore require safety testing in compliance with GLP.

FDA should also consider developing a registration program for new GLP laboratories. This program would simply require that facilities register with FDA prior to submitting GLP studies. Such registration would include submission of all pertinent GLP required documents and would be at no cost for the facility with FDA's current inspection program going on as is. However, this registration should eliminate the problems currently seen with facilities submitting GLP studies that are completely unaware that GLPs are regulation and not simply good practices in their opinion. Of course, any facility that has successfully been inspected by FDA would be grandfathered in and would automatically receive a registration number.

Thank you,

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