PROPOSED GLP QUALITY SYSTEM DEFINITIONS

AS THE PROCESS OF REVIEWING THE FDA PROPOSED GLP QUALITY SYSTEM CHANGES CONTINUES, WE WANTED TO BREAK DOWN THE PROPOSED CHANGES, RATIONALE, AND INDUSTRY IMPACTS IN MORE DETAIL.

The Quality Assurance Unit (QAU) is an integral part of any GLP regulated facility and/or study. If the proposed changes are accepted, the way study documents are reviewed and inspections are performed may be impacted. Below are some of the FDA proposed changes, reason for the changes, and potential industry impacts.

THE PROPOSED CHANGE

§ 58.3 Definitions

As used in this part, the following terms have the meanings specified:
...
Attending veterinarian means a veterinarian who has training or experience or both in the care and management of the species being attended and who has direct or delegated authority for activities involving animals.
Batch means a specific quantity or lot of a test, control, or reference article that has been characterized according to § 58.105 and handled according to § 58.107.

Contracted person means a person who assumes, either directly or indirectly as an independent contractor, one or more responsibilities for the conduct of a nonclinical laboratory study.

Contributing scientist means an individual responsible for the conduct, interpretation, analysis, or any other service for a phase of a nonclinical laboratory study. An individual expert or specialist who is an independently employed contracted person, as defined in this section, is an independent contributing scientist.

Control article means any food additive, color additive, drug, biological product, electronic product, device, tobacco product, or any article other than a test article, reference article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.
Establish means define, document (in writing or electronically), and implement.

Facility-based inspection means an inspection which is not based on specific studies but covers general facilities and activities, for example, installations, support systems, computer systems, training, environmental monitoring, and equipment maintenance and calibration.

GLP Quality System means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management in the conduct of a nonclinical laboratory study.

Lead quality assurance unit (lead QAU) means the QAU responsible for quality assurance (QA) in a multisite nonclinical laboratory study. Testing facility management with executive responsibility selects the lead QAU.

Management with executive responsibility means those senior employees of a testing facility or test site who have the authority to establish or make changes to the quality policy and GLP Quality System at the testing facility and test site, respectively.

Master schedule means a compilation of information used for assessment of workload and the tracking of nonclinical laboratory studies.

Multisite study means any study that has phases conducted at more than one site.

Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions or in the applicable environment to determine their safety or toxicity or both. The term does not include studies involving human subjects, clinical studies, or clinical investigational use in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or basic exploratory studies to determine the physical or chemical characteristics of a test article.

Person includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

Phase means a defined activity or set of activities in the conduct of a nonclinical laboratory study.

Principal investigator means an individual who has specific responsibilities for one or more phases of a nonclinical laboratory study as delegated by the study director.

Process-based inspection means an inspection conducted to monitor procedures or processes of a repetitive nature that are very frequently performed. Process-based inspections are conducted on a prearranged schedule, which is not connected to the timing of any particular nonclinical laboratory study. Performance of process-based inspections covering processes or procedures that occur with a very high frequency (for example, certain mutagenicity studies) may cause some studies to be uninspected during the in-life period of the study, as defined in this section within the definition of Short-term study.

Quality means the totality of features and characteristics that bear on the ability of a nonclinical laboratory study to provide data that can be relied upon.

Quality assurance unit (QAU) means any person or organizational element designated to perform the duties relating to quality assurance (QA) of nonclinical laboratory studies. For any given study, the QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of the study.

Quality policy means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.

Raw data means all original nonclinical laboratory study records and documentation or exact copies that maintain the original intent and meaning and are made according to the person's certified copy procedures. Raw data includes any laboratory worksheets, correspondence, notes, and other documentation (regardless of capture medium) that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. Raw data also includes the signed and dated pathology report.

Reference article means any chemical substance or mixture, or analytical standard, or material other than a test article, control article, feed, or water that is administered to or used in analyzing the test system in the course of a study for the purposes of establishing the basis for comparison with the test article for known chemical or biological measurements.

Short-term study means a study for which the in-life period is completed within several days or a week at most. The in-life period of a study is that period during which data are collected.

Specimen means any material derived from a test system for examination, analysis, or retention.

Sponsor means: (1) A person that initiates and supports, by provision of financial or other resources, a nonclinical laboratory study; or
(2) A person that submits a nonclinical laboratory study in support of an application or submission to FDA; or
(3) A person that initiates a nonclinical laboratory study and functions as, and has the same responsibilities as, a testing facility, test site, or contributing scientist, as those terms are defined in this section.

Standard operating procedures (SOPs) means documented procedures which describe how to perform tests or activities normally not specified in detail in study protocols.

Study-based inspection means an inspection of a critical operation of the study which is scheduled according to the chronology of the given study. Management with executive responsibility at the testing facility and/or test site identifies which operations are critical before initiation of the study.

Study completion date means the date the final report is signed by the study director.

Study director means the individual responsible for the overall conduct of a nonclinical laboratory study.

Study initiation date means the date the protocol is signed by the study director.

Test article means any food additive, color additive, drug, biological product, electronic product, device, tobacco product, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act or under sections 351 and 354-360F of the Public Health Service Act.

Test site means a person who is responsible for one or more phases of a multisite nonclinical laboratory study. A test site includes management with executive responsibility and supporting SOPs relevant to the conduct of nonclinical laboratory studies.

Test system means any animal, plant, microorganism, or subparts thereof to which the test, control, or reference article is administered or added for study. Test system also includes appropriate groups or components of the system not treated with the test, control, or reference articles.

Testing facility means the person responsible for coordinating, conducting, or completing a nonclinical laboratory study, or any combination thereof. The testing facility designates the study director.

Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

Vehicle means any agent which serves as a carrier and is used to mix, disperse, or solubilize the test, control, or reference article for administration or application to the test system.

REASON FOR CHANGE AS DISCUSSED IN THE PREAMBLE OF PROPOSED FDA REGULATIONS

Attending Veterinarian: We propose adding a definition for an attending veterinarian. Our proposed definition is the same as the definition in USDA's Animal Welfare Regulations (9 CFR 1.1) but without specifics about educational requirements. We propose defining an attending veterinarian as a veterinarian with training, experience, or both in the care and management of the species being attended, with direct or delegated authority for activities involving animals. We propose this definition because we propose in part 58 certain provisions about animal welfare. For example, we propose that the study director must defer to the attending veterinarian when decisions regarding animal welfare arise, particularly when animals are in pain or distress.

Batch: We propose changing the definition of batch currently in § 58.3(n) to reference the relevant provisions in § 58.105 (Test, control, and reference article characterization) and § 58.107 (Test, control, and reference article handling). We also add that batch means a specific quantity or lot of a reference article (see section III.B.2.), we discuss the addition of a reference article definition.

Contracted Person: We propose adding a definition for contracted person to mean a person that assumes, either directly or indirectly as an independent contractor, one or more of the responsibilities for conducting a nonclinical laboratory study. Several comments to the December 2010 ANPRM state that the responsibilities of all persons (any legal entity) involved in multisite studies need to be addressed in the regulations. We propose the use of this term to allow us to address the comments without specifically identifying all possible contracted entities.
The comments also request that FDA include specifics for multisite studies as to how responsibilities are to be met and by whom. In response to these comments, we intend that a contracted person includes any person (for example, testing facility or individual) that the sponsor contracts with to conduct a phase (defined activity or set of activities) of a nonclinical laboratory study. Also, the term contracted person includes any person that is under a subcontract to conduct a phase of a nonclinical laboratory study.

Contributing Scientist: We propose adding and defining the term contributing scientist. A contributing scientist is an individual responsible for conducting, interpreting, analyzing, or performing any service for a phase of a nonclinical laboratory study. The current regulation in § 58.185 for reporting study results refers to "individual scientists or other professionals involved in the study" (see § 58.185(a)(12)). Our proposal replaces these scientists or other professionals with the term contributing scientist. In addition, when a contributing scientist is a contracted independent expert or specialist, we use the term independent contributing scientist. See, also, section III.C.6. where we discuss § 58.37 (Contributing scientist).

Control Article: We propose modifying the definition of control article currently in § 58.3(c) by changing "medical device for human use" to "device" to expand the regulations to include devices used in veterinary medicine. Also, the revised definition proposes to include a "tobacco product".

Establish: For this part 58 proposal, the meaning of establish is to define, document (in writing or electronically), and implement. We propose adding a definition for establish to help eliminate repeating in the applicable regulatory text the words that define establish. Our proposed definition is identical to the definition of establish in the part 820 quality system regulation in § 820.3(k).

Facility-Based Inspection: We propose introducing the term facility-based inspection to mean a QAU inspection that covers the general facilities and activities; for example, installations, support systems, computer systems, training, environmental monitoring, and equipment maintenance and calibration. This addition, along with the definition of process-based inspection (see section III.B.2.) would allow for greater efficiency instead of duplicating, for each study, inspection of those general facilities and activities. Our proposed definition also is consistent with the definition for facility-based inspection in the OECD document, *Quality Assurance and GLP* (Ref. 7).

GLP Quality System: We propose adding a definition for GLP Quality System to mean the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management in the conduct of nonclinical laboratory studies. As discussed in section II.B., we consider a fully implemented GLP Quality System the proper framework for building quality into planning, conducting, and reporting a nonclinical laboratory study while allowing flexibility for site-specific procedures.

Lead Quality Assurance Unit: We propose adding a definition for a lead quality assurance unit (lead QAU) meaning the QAU responsible for quality assurance (QA) in a multisite nonclinical laboratory study. We propose that testing facility management with executive responsibility selects the lead QAU. The location of the lead QAU may be at the testing facility, with another person conducting a phase of the study, or provided through a contractual relationship. This definition is consistent with the definition for lead QAU in the OECD consensus document, *The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies* (Ref. 6).

Management with Executive Responsibility: We propose adding a definition for management with executive responsibility to mean senior employees of the testing facility or test site who have the authority to establish or make changes to the quality policy and GLP Quality System at their testing facility or test site. We note that part 820 (see § 820.3(n)) adopted this term describing senior management to be consistent with the quality system specifications in ISO 9001:1994 (61 FR 52602 at 52609, October 7, 1996).

Master Schedule: We propose adding a definition for master schedule that means a compilation of information used for assessment of workload and the tracking of nonclinical laboratory studies. The master schedule will include information about all nonclinical laboratory studies conducted. For multisite studies, the master schedule also will include the phases conducted (see proposed 58.31(k)). Our proposed definition of master schedule is consistent with the definition in the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8). When we discuss § 58.31 (Management with executive responsibility, section III.C.2.), we elaborate on requirements concerning the master schedule.

Multisite Study: We propose adding a definition for multisite study to mean any study that has phases (defined in section III.B.2.) conducted at more than one site. Our proposed definition of multisite study is consistent with the definition in the OECD consensus document, *The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies* (Ref. 6).

Nonclinical Laboratory Study: We propose modifying the current definition in § 58.3(d) for a nonclinical laboratory study to add after "under laboratory conditions" the phrase "or in the applicable environment". This addition recognizes that the conduct of a nonclinical laboratory study is not limited to a traditional laboratory environment. We propose to make clear that the purpose for conducting nonclinical laboratory studies may be to determine relative toxicity. For example, because tobacco products are not safe, nonclinical laboratory studies help FDA evaluate the relative toxicities of those products. We also propose to update the regulations by changing "field trials in animals" to "clinical investigational use in animals",

which more accurately describes our intent. We propose a sentence structure change in the last sentence in this definition to clarify our intent, which is often misinterpreted due to the current sentence structure.

Phase: We propose adding a definition for phase to mean a defined activity or set of activities in the conduct of a nonclinical laboratory study. We propose this new definition to aid in understanding the new proposed definition of multisite study, which is any study that has phases conducted at more than one site. Our proposed definition is consistent with the definition of phase in the OECD consensus document, *The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies* (Ref. 6).

Principal Investigator: We propose adding a definition for principal investigator to mean an individual with specific responsibilities delegated by the study director for a phase of a nonclinical laboratory study. We propose defining principal investigator in general terms rather than specifying the principal investigator's single role in a multisite study as defined in the OECD document, OECD Principles on Good Laboratory Practice (Ref. 8). However, we propose that principal investigator responsibilities are those delegated by the study director, which is consistent with OECD principles. See, also, section III.C.7. where we discuss § 58.39 (Principal investigator).

Process-based Inspection: We propose adding a definition for process-based inspection to mean inspecting repetitive, frequently performed procedures and processes (for example, certain mutagenicity studies). This definition recognizes present practice and allows for greater efficiency, as noted elsewhere (section III.B.2.). Our proposed definition is consistent with the definition for process-based inspection in the OECD document, *Quality Assurance and GLP* (Ref. 7).

Quality: We propose adding a definition for quality, meaning the totality of features and characteristics bearing on the ability of a nonclinical laboratory study to provide reliable data.

Quality Assurance Unit (QAU): We propose modifying the current definition in § 58.3(*l*) to remove “except the study director” and “designation by testing facility management”. Also, we propose adding a sentence “The QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of the particular study.” We propose these changes for clarity and to be consistent with our inclusion of multisite studies and with the statement currently in § 58.35.

Quality Policy: We propose adding a definition for quality policy that is identical to the definition in § 820.3(u), meaning “the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.”

Raw Data: We propose modifying the current definition in § 58.3(k) to update the regulations to address copying requirements and computerized systems, and to specifically include the pathology report. We propose adding to the definition that raw data means “all nonclinical laboratory study records and documentation or exact copies that maintain the original intent and meaning and are made according to the person's certified copy procedures.” This additional regulatory text eliminates the need to provide examples of what we consider a copy. We also propose adding “correspondence” and “other documentation (regardless of capture medium)” to the examples of raw data. The addition of “regardless of capture medium” eliminates the need to provide examples of possible capture media. Also, we propose including as raw data “the signed and dated pathology report” to clarify what we consider as raw data.

Reference Article: We propose adding a definition for reference article consistent with EPA's GLP regulations in 40 CFR 160.3 and 792.3 for defining a “reference substance” to mean an article used to establish a basis for comparison of the test article for known chemical or biological measurements. We propose this addition to acknowledge the use of reference articles in certain studies.

Short-Term Study: We propose adding a definition for short-term study to mean when the in-life period (study period during which data are collected) is completed within several days or, at most, a week. Since the pre-specified, periodic timing of process-based inspections can result in the lack of an inspection of a short-term study, this definition is necessary to address our proposed addition of process-based inspections (see also the discussion of the definition of process-based inspection in section III.B.2.).

Specimen: We propose adding “or retention” to the end of the current definition of specimen in § 58.3(j) to read, “Specimen means any material derived from a test system for examination, analysis, or retention.” We propose this change because a specimen may be collected solely for retention purposes. Also, this proposed change is consistent with the definition in the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8).

Sponsor: We propose modifying the current definition of sponsor in § 58.3(f) consistent with our proposal to expand the scope of part 58, and to address possible roles of the sponsor in multisite studies. We propose revising the current

definition in § 58.3(f)(3) to include the possible roles a sponsor could play in a multisite study in addition to initiating and supporting the study. Those roles and applicable requirements are the same as those for a testing facility, test site, or contributing scientist as we propose to define those terms.
See, also, section III.B.3. where we discuss § 58.5 (Sponsor responsibilities).

Standard Operating Procedures (SOPs): We propose adding a definition for SOPs to mean documented procedures describing how to perform tests or activities normally not specified in detail in study protocols. We propose this addition because many proposed modifications in § 58.31 refer to required SOPs. This definition is consistent with the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8).

Study-based Inspection: We propose adding a definition for study-based inspection to mean the same QAU inspection specified currently in § 58.35(b)(3) for inspecting a critical operation of the study that is scheduled according to the study's chronology or sequence of events. Our proposed definition is consistent with the definition for study-based inspection in the OECD consensus document, *Quality Assurance and GLP* (Ref. 7).

Test Article: We propose modifying the current definition of test article in § 58.3(b) to change "medical device for human use" to "device" and to add "tobacco product". As discussed in section III.B.1. concerning the scope of part 58, we propose these changes to broaden devices to include FDA's CVM and to include FDA's jurisdiction of tobacco products.

Test Site: We propose adding a definition for test site to mean a "person" (currently defined in § 58.3(h)) responsible for a phase of a multisite nonclinical laboratory study. We propose that a test site includes management with executive responsibility and supporting SOPs for the conduct of a nonclinical laboratory study. For a different nonclinical laboratory study, a test site could function as a testing facility.

Test System: We propose modifying the current definition of test system in § 58.3(i) to add "reference" article consistent with our other proposed changes. See elsewhere in section III.B.2. for our proposed definition and explanation for adding a definition of reference article.

Testing Facility: We propose removing and replacing most of the current definition of testing facility in current § 58.3(g) to update the regulations consistent with the conduct of multisite nonclinical laboratory studies. Our proposed definition is as follows: "Testing facility means a person responsible for conducting, coordinating, or completing a nonclinical laboratory study, or any combination thereof. The testing facility designates the study director."
We propose this change because, in a multisite study, the testing facility might not be the person treating the test system with the test article as specified in the current definition. Rather, the person treating the test system with the test article might be a contracted or subcontracted person. Therefore, this general definition of a testing facility is necessary to capture all possible contractual relationships in a multisite study.

Validation: We propose adding a definition for validation to mean confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use of a system or process can be consistently fulfilled. This proposed definition is similar to the definition in § 820.3(z), and addresses comments to the December 2010 ANPRM requesting a definition for validation of a system or process

Vehicle: We propose adding a definition for vehicle to mean any agent that serves as a carrier and is used to mix, disperse, or solubilize the test, control, or reference article for administration or application to the test system. This proposal recognizes the use of vehicles in the conduct of nonclinical laboratory studies. Our proposed definition is consistent with the definition of vehicle in the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8), for describing a carrier for test, control, or reference articles.

POTENTIAL IMPACT OF THE PROPOSED CHANGE

In an effort of clarification, 22 new definitions were added and others modified in Section 58.3 as part of the proposed changes to the FDA GLP regulations. This section of the proposed regulations is a good reference for an overall view of the type of changes made throughout the document. Though some definitions add valuable information and tie together some of the intentions of the proposed changes, others are thought to need more work and have generated more questions than answers.

One new and important definition is *GLP Quality System*. The proposed regulations are centered on this idea of a framework for quality in all aspects of studies. This, along with added definitions of *quality* and *quality policy*, highlights the agency's focus to improve the quality and integrity of studies through these proposed regulations. Specific to the definition of *quality policy*, questions have been raised about what this policy is supposed to look like. Is it a specific

document? Who needs to have it (e.g. sponsors, test sites, any person performing a phase of the study)? What does it need to include? It is important to ask these questions now so that when the regulations are finalized, companies know what needs to be done to maintain compliance.

Another noteworthy change highlighted in the definitions section is that the definitions for *test facility* and *test site* have been included and contain a specification regarding the "person responsible" rather than the facility/ site as a whole, changing the point of responsibility and risk. This specification coordinates with the addition of definitions of *contracted person*, *contributing scientist*, and *principal investigator*, as well as the mention of an "independent contributing scientist." These are important definitions, especially with the addition of regulations having to do with multisite studies, but many believe these definitions are ambiguous and overlapping. It is also noted that some of these changes are not consistent with OECD guidelines. With regards to the *contributing scientist* specifically, questions have been brought up regarding what is considered a "service for a phase" of a study. The proposed definition could expand who is typically thought to be a contributing scientist, and therefore affect study procedures, documentation, and reporting. *Contracted person* is another definition in question. Some think it should be removed as it is believed to be adequately covered by the other associated definitions. Hopefully these definitions will be refined before becoming final. Either way, it will be very important to outline these titles, associated responsibilities, and interactions with management in company SOPs. The proposed changes also include an updated definition for *raw data* that introduces the term "certified copy procedures." This implies that a procedure for copying will be expected to be standardized and documented which may not be common practice in many companies. It is noteworthy to mention that the definition of *raw data* was also updated to include clarification that the signed and dated pathology report is considered raw data.

With regards to the remaining newly added terms, some definitions, such as *reference article,* are deemed necessary and adequate, while others, such as *validation* and *short term study,* include room for improvement. The definition for *validation* has been perceived as being too vague. The expectations for the extent of validations is not clear from the definition. Some say that the definition should be updated to exclude process validation or possibly be modified to specify that it is meant for computerized systems. The issue with the definition of *short term study* is similar, in that it is viewed as a necessary addition but clarification is needed. The definition states that "The in-life period of a study is that period during which data are collected," however, the definition of *raw data* includes the final signed and dated pathology report, which is typically not part of the traditional meaning of in-life period. Additionally, one definition that was hoped to be included but was not added is the definition for deviation.

Overall, the additions and changes to the definitions may have more impact than one may have expected. Roles and responsibilities, as well as quality and copying procedures, should to be reevaluated. At minimum, a large number of SOPs will need to be updated with the changes in terminology proposed.