

- ▶ Home
- ▶ Editorial Categories
- ▶ In the News
- ▶ Industry Directories
- ▶ Currently In Print
- ▶ 2007 Conference
- ▶ Events Calendar
- ▶ Classifieds
- ▶ Job Bank
- ▶ Subscribe
- ▶ Media Kit
- ▶ About Us

Search

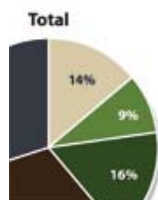
Articles

Entire Site

Search

Articles » 2007 » May 2007 » Table of Contents

## May 2007 Articles



**2007 Annual Outsourcing Survey**  
Gil Roth



**CRO Industry Update**  
Addressing expansion, adapting to trends  
Kristin Brooks



**Specialized Roles for Clinical Trial Site Design**  
How to optimize trial site management  
Kelli Henry



**CTM Supply Chain Management**  
How to bridge planning and execution  
Gil Roth



**Quality Assurance and Good Lab Practice**  
Examining the FDA's  
OECD's GLPs  
Paul Swidersky

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## Online Exclusives

**Jubilant News for Hollister-Stier**  
Joanna Cosgrove

### Departments:

**From the Editor**  
**FDA Watch**  
Financial Analysis  
**Managing Your Career**  
**The Lowe Down**  
Preclinical Outsourcing  
Data Watch

Bio News & Views  
**India Report**  
Top of the News  
Industry News  
Packaging & Tracking  
Custom Sourcing News  
Trials & Filings

Collaborations & Alliances  
Promotions & Moves  
Reader Showcase  
Associations & Events  
**Industry Calendar**  
**Classified Listings**  
**Advertiser Index**

- ▶ Home
- ▶ Editorial Categories
- ▶ In the News
- ▶ Industry Directories
- ▶ Currently In Print
- ▶ 2007 Conference
- ▶ Events Calendar
- ▶ Classifieds
- ▶ Job Bank
- ▶ Subscribe
- ▶ Media Kit
- ▶ About Us

Search \_\_\_\_\_

Articles

Entire Site

Articles » 2007 » May 2007 » Feature

## Quality Assurance and Good Lab Practice

Examining the FDA's □ OECD's GLPs

By Paul Swidersky

In 1979, good laboratory practice (GLP) regulations were put in place by the FDA to establish a level of consistency and reliability in the planning, conduct and reporting of non-clinical safety studies for food, drugs, and medical products and devices regulated by the Agency. The GLP regulations were designed to ensure quality and reduce fraud by requiring that specific documentation be kept regarding several key areas that include laboratory staff, facilities and operations, equipment, test and control articles, protocol, conduct of the study, quality assurance and archiving of data, records and specimens.

In 1980, the OECD (Organization for Economic Cooperation and Development) put forth a set of principles very similar to FDA GLP regulations. Like the FDA GLPs, the OECD GLPs were intended for non-clinical safety studies, but were also applicable to pesticides and industrial chemicals (regulated under EPA in the U.S.). These were developed under the auspices of the original OECD member countries. Today, OECD GLP principles have been adopted by the OECD's 30 member countries throughout North America, Europe, Eastern Europe and Asia. (The U.S. is a member.)

In general, a member country agrees to follow either the OECD GLP principles as adopted or, in the case of the U.S. and Japan, its own GLP regulations. Participating nations also agree to accept these standards as practiced by other countries. With these mutual agreements, when a laboratory from any member country conducts a non-clinical GLP study, the GLP compliance statement will be (or should be) accepted by other member countries.

Over the years, the agencies'/organizations' respective regulations and principles have been revised and updated. For example, the FDA revised its GLP regulations in 1987, and the OECD revised its principles a decade later. These updates were made to clarify any "grey" areas that had previously raised questions or were needed to address changes in research methodology, advancements in technology and their applicability to covering additional regulated studies.

### Who Needs To Take Note?

As the global market for registering pharma products increases, and as greater testing services emerge, sponsors and contract labs need to understand both the FDA and OECD GLP requirements in order to ensure their adherence to them. For example, many companies based in the U.S. are currently contracting entire studies and/or portions of their work to labs in Canada, Europe, and vice-versa. To properly audit these facilities, a full understanding of each regulation is necessary.

Besides quality assurance personnel, company management, study directors, principal investigators, and sponsor representatives must also have a firm understanding of the GLPs and their differences in order to be able to contract studies and work among various facilities.

It is also critical that multinational companies conducting their own studies under either FDA or OECD GLPs understand these differences. In addition, government agencies frequently require that their research be conducted in compliance with the GLPs, thereby requiring government personnel to understand these GLPs as well.

### OECD & FDA GLPs: Key Differences

Parallels can be found in all areas of these two GLPs. This is not surprising, since the GLPs were established and well-defined by the FDA and OECD from the outset.

Yet despite these similarities between the FDA GLP regulations and its counterpart principles at the OECD, some significant differences exist. As the name suggests, the FDA GLPs are regulations and are required by law for non-clinical studies in the U.S., whereas the OECD GLP principles are voluntary procedures that must first be adopted as a regulation within each member country. Also keep in mind that some of the regulatory requirements governing the OECD GLPs can vary from country to country, even though the principles themselves remain the same.



When comparing the differences between these GLPs, it is important to take note of the numerous OECD GLP Consensus<sup>1</sup> documents. These consensus documents were published by the OECD to provide further guidance toward compliance of a GLP program. So please note that many of the differences discussed in this article may be the result of stipulations within these specific guidance documents.

Another key difference to note is that the U.S. does not require laboratories to be "accredited" or "certified" to conduct GLP work. In contrast, laboratories within the other OECD countries must first be accredited for GLP compliance by the respective country prior to conducting GLP studies for submission. It is also worth noting that accreditation by an OECD country is given to a facility only for the specific types of study to be conducted (i.e., the accreditation does not cover all possible studies). Within the U.S., the ultimate responsibility for GLP compliance resides with the study sponsor. It is the sponsor that must assure that any laboratory conducting GLP studies is, in fact, in compliance with the FDA GLPs.

### Terminology

Before examining in greater detail the differences between the FDA and OECD GLPs, it is important to keep in mind a few key distinctions within the terminology. For example, what are known as "test and control articles" within the FDA GLPs are referred to as "test and reference items" in the OECD GLPs. The following terms are defined by either the FDA, OECD or both:

#### Equivalent definitions, but different terms

| FDA       | OECD         |
|-----------|--------------|
| Article   | Item         |
| Protocol  | Plan         |
| QA Unit   | QA Programme |
| Equipment | Apparatus    |

#### Terms defined by OECD and not FDA:

1. Experimental start date
2. Experimental completion date
3. Master Schedule\*
4. Principal Investigator
5. Reference item
6. Short term study
7. Standard Operating Procedures\*
8. Study plan (protocol)\*
9. Study plan amendments
10. Study plan deviations
11. Test site
12. Test facility management\*
13. Test site management
14. Vehicle

\* Defined by OECD only, but a definition/description is found within the text of the FDA GLPs.

#### Terms defined by the FDA and not OECD

1. Person
2. Control article

#### Terms defined by both the FDA and OECD (the meaning is the same or equivalent)

1. Batch
2. Quality Assurance Unit
3. Raw data
4. Specimens
5. Sponsor
6. Study
7. Study initiation date
8. Study completion date
9. Study director
10. Test articles (items)
11. Test system
12. Testing facility

For this article, we will use FDA terminology whenever it has been defined; otherwise, we will use the OECD term.

## Comparing FDA and OECD GLPs

As mentioned, the FDA and OECD GLPs are divided into similar formats that address standard areas inherent to most contract laboratory environments. Before highlighting many of the existing similarities and differences between the two regulations, please note that other distinctions appear throughout the regulations. This article is designed to provide an overview of many of those key differences and is not intended to describe every possible difference.

### Sponsor Requirements

Neither the FDA nor OECD includes specific sections within their GLPs that address sponsor requirements. However, the term "sponsor" has been defined in both GLPs and is used throughout both documents. In addition, the OECD has issued a consensus document that provides further guidance on the role and responsibilities of the sponsor.

Both GLPs assign specific responsibilities to the sponsor. Many implicit responsibilities arise from the fact that the sponsor initiates and submits the results of studies to regulatory authorities.

The OECD Consensus document includes the following:

- The sponsor must assume an active role in confirming studies are conducted in compliance with the GLPs. This is the same expectation by FDA.
- The sponsor must monitor/audit the contracted facilities prior to study initiation and during study. Not addressed by FDA but expected.
- Determine facility compliance status in national GLP compliance monitoring program (if applicable). U.S. companies contracting outside the U.S. need to be aware of this. Not required in the U.S.
- To avoid a mix-up in the identity of the test item for a study, a mechanism should be in place between the sponsor and testing facility to verify its identity prior to the beginning of the experimental phase. The FDA makes this a Test Facility management responsibility.
- Failure of the sponsor to conduct test item characterization in accordance with GLP could lead to study rejection. Not addressed by FDA, but it is understood that this could happen.
- Sponsor must provide to the testing facility any known risks of the test item to human health or to the environment, as well as any safety measures to be taken by the test facility staff. Not addressed in the FDA GLPs.

Although the implicit FDA GLP sponsor requirements seem clear, the OECD consensus document is very helpful in clarifying these responsibilities.

### Personnel Requirements

In general, the personnel requirements are the same between FDA and OECD; i.e., both require that all personnel engaged in the conduct or supervision of a study have adequate education (knowledge), training, experience, or combination thereof to perform their duties. Neither GLP is specific as to how this information is to be documented. But both GLPs require that this information be retained/archived. Therefore, whenever CVs, job descriptions, and training documentation are updated, earlier versions should be retained to ensure compliance.

### Test Facility Management – FDA = §58.31; OECD = §1.1

Many of the test facility management responsibilities are the same for both GLPs; however, OECD has additional requirements within the principles and within the requirements found in the Consensus Document for Study Directors:

1. Ensure that a statement exists which identifies the individual(s) within a test facility who fulfill the responsibilities of management as defined by the GLPs.
2. Management should consider the potential Study Director's current and anticipated workload. Same expectation by FDA.
3. Set qualification requirements for Study Director. There is no FDA expectation, though larger companies typically will have a document setting minimum qualifications.
4. Management must have written policies or SOPs to define under what circumstances a Study Director will be replaced, and the necessary procedures and documentation for the replacement. Same expectation by FDA.
5. Ensure documented approval of the study plan by the study director. Same expectation by FDA.
6. Ensure that the study director has made the approved study plan available to the quality assurance personnel. Same expectation by FDA.
7. Establish procedures to ensure that computerized systems are suitable for the intended purpose, and are validated, operated and maintained in accordance with the GLPs. While not specifically addressed, this is implied by FDA.
8. Ensure for a multi-site study that clear lines of communication exist between the Study Director, Principal Investigator, the Quality Assurance Programme and study personnel. Not addressed by FDA.
9. Ensure that when a phase (or phases) of a study is conducted at a test site, test site management (if appointed) will have the responsibilities as defined for test management, except for those that apply to study directors. Not addressed by FDA.

**Study Director – FDA = §58.33; OECD = §1.2**

Most of the study director responsibilities are the same; however, OECD has additional requirements both within the GLP principles and in the Study Director Consensus Document as noted below:

1. Ensure that the quality assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the quality assurance personnel as required during the conduct of the study. Same expectation by FDA.
2. Ensure that the study plan and the final report for a multi-site study identify and define the role of any principal investigator(s) and any test facilities and test sites involved in the conduct of the study. Not addressed by FDA.
3. Ensure that computerized systems used in the study have been validated. Same expectation by FDA.
4. OECD allows temporary replacement of the Study Director which should be considered with extended vacation, illness, accident, or scientific meeting. Temporary replacement is not allowed under FDA GLPs. At each change, the Study Director should check the current compliance status of the study. These interim GLP reviews should be documented and maintained with the data. Not addressed by FDA.
5. Study director is responsible for knowing the adequacy and GLP compliance of a contract facility (i.e., test sites). Same expectation by FDA.
6. Review study procedures and data, including computerized data. The type and frequency of the reviews must be documented in the study records. Same expectation by FDA, but does not address documenting these reviews.

The consensus document clearly adds additional study director responsibilities.

**Quality Assurance – FDA = §58.35; OECD = §2.1, 2.2**

Most of the quality assurance responsibilities are the same; however, OECD has additional requirements both within the GLP principles and in the Quality Assurance Consensus Document as noted below:

1. Verify and document that the study plan contains the information required for compliance with the GLPs. FDA does not have a protocol audit requirement; however, the QAU typically audits the protocol.
2. Inspections can be of three types, a) Study-based inspections; b) Facility-based inspections; and c) Process-based inspections. FDA does not discuss Facility-based or Process-based inspections.
3. QA inspection reports must also be provided to the Principal Investigator when applicable. FDA does not include PI's.
4. QA Final Report Statement – FDA requires that QA specifies dates inspections were made and findings reported to management and study director, while the OECD also requires two additional items: a) the phase(s) inspected; b) date(s) reported to principal investigator (if applicable).
5. OECD consensus document says that before signing the QA Statement, QA should ensure that: a) all issues raised in the QA audit have been addressed; b) that all agreed actions have been taken; and c) that no changes have been made to the report which would require further audit. FDA does not clearly define these requirements; however, it is typically expected.
6. OECD consensus document specifies that QA be: a) familiar with test procedures, standards, and procedures; b) understand the basic concepts of study; c) thorough understanding of the GLPs; d) have documented training; e) competence evaluated; and g) training continuous with periodic review. FDA does not specifically address QA training, etc., only personnel in general; however, training requirements are similar except for evaluating competence.
7. OECD consensus document states that national monitoring authorities may occasionally require access to the contents of QA reports to verify the adequate functioning of QA. FDA only gains access via a court subpoena or voluntary offer by the facility.
8. OECD states that records of all inspections, as well as master schedules, should be retained in the archives. FDA likewise requires retention of QA records and the master schedule, but does not require that records be placed in the archive.
9. GLP Master Schedule – OECD requires that the master schedule identify both regulatory and non-regulatory studies. FDA only requires that GLP studies be listed.

Many of the above requirements are significant differences for the quality assurance unit, particularly items 2, 3, 6, 7, and 9.

**Facilities – General and Animal (test system) Care Facilities – FDA = §58.41, 58.43, 58.45; OECD = §3.1, 3.2**

1. FDA and OECD are essentially the same for facility requirements.

**Test and Control Articles (Items) Characterization, Handling and Mixtures – FDA = §58.105, 58.107, 58.113; OECD = §6.1, 6.2**

1. One of the key and important differences is that FDA does not include a requirement for reference articles (i.e., analytical standards). OECD's definition of reference item can include both control items and reference items.
2. FDA states that a storage container shall be labeled with name, chemical abstract number or code number, batch number, expiration date, if any, and storage condition if appropriate. OECD does not require batch

- number.
3. For control article characterization, FDA states, "in those cases where marketed products are used as control articles, such products will be characterized by their labeling. OECD does not include this statement.
  4. For stability of test and control articles, as such or in mixtures, FDA states that this can be determined before study initiation or concomitantly according to SOPs. OECD states only that stability of the test item in the vehicle should be determined.
  5. FDA states that if more than one component of a mixture has an expiration date, the earliest date shall be shown on the container. OECD does not address this, but it would be the expectation.

As noted in item 1 above, the most significant difference is that FDA does not address reference standards, to which all characterization, stability, receipt, distribution and disposal requirements apply under the OECD GLP, not counting the requirements to their mixture with a carrier.

**Equipment (Apparatus) – FDA = §58.61, §58.63; OECD = §4**

Most requirements and all expectations are the same. The FDA GLP contains more maintenance requirements than OECD and is very specific on what should be documented for routine and non-routine maintenance. FDA also requires the designation of a responsible person. Both require calibration/standardization; however, the OECD states: "Calibration should, where appropriate, be traceable to national or international standards of measurement." This is the same expectation by the FDA.

**Standard Operating Procedures – FDA = §58.81; OECD = §7**

Both the FDA and OECD require that test facility management approve SOPs and any revisions. The majority of the required SOPs are the same; however, OECD has these additional SOP requirements:

- Computerized Systems -- Validation, operation, maintenance, security, change control and back-up. The FDA GLPs do not address this area; however, FDA's Part 11 regulations on e-records and e-signatures address computerized systems. FDA also applies the GLP requirements that equipment must be of appropriate design and adequate capacity to get to a similar expectation.
- Materials, Reagents and Solutions -- Preparation and Labeling.
- Quality Assurance Procedures -- Operation of QA personnel in planning, scheduling, performing, documenting and reporting inspections. The FDA requires the same thing, however, it is found within the QAU section.
- Test Systems -- Sighting and placement of test systems in test plots. This is not addressed by FDA, because test plots do not apply to the types of studies regulated by FDA.

**Reagents and Solutions – FDA = §58.83; OECD = §4.4**

Labeling requirements and non-use after the expiration date are the same for both FDA and OECD. OECD also states: "The expiry date may be extended on the basis of documented evaluation or analysis." This is the same expectation by the FDA.

**Animals (Test Systems) – FDA = §58.43, §58.45, §58.90; OECD = §3.2, §3.5. §5**

Although FDA defines the term test system (as animal, plant, or microorganism), they only refer to animals in these sections, whereas OECD uses the term "test system" throughout the GLPs. The OECD term "test system" is a broad definition that includes any biological, chemical or physical system or combination.

Animal care facilities, procedures, and supply requirements are the same. The single exception by OECD is the use of test systems in field studies.

**Protocol (Plan) – FDA = §58.120; OECD = §8.1**

The majority of the requirements are the same between FDA and OECD. The following differences include:

- OECD defines the difference between a protocol amendment and a protocol deviation, which are called protocol change or revision by the FDA GLP.
- OECD requires Test Facility management and the sponsor to sign and date the protocol, only if required by national regulation or legislation in the country where the study is being performed. And the FDA regulation, while requiring sponsor approval, does not require approval by testing facility management, though it is often done as a way of assigning the study director by management.
- OECD requires that the protocol be verified by quality assurance. FDA does not specifically require this, although it is typically the routine procedure for QAUs.
- OECD requires that protocol deviations be acknowledged and dated by the study director and/or principal investigator. FDA only specifically states that the study director sign and date, although it appears to require sponsor approval of all protocol changes.
- OECD addresses the use of a general study protocol, for short term studies, accompanied by a study specific supplement. FDA does not address short-term studies; however, they agree with the concept.
- OECD requires the name and address of the sponsor. FDA only requires the name of the sponsor.

- OECD requires the name and address of the test facility and test sites involved. FDA does not require test sites to be included, however, the expectation is the same.
- OECD requires the name and address of the study director and principal investigator(s) and the phases of the study delegated to the PI(s). FDA does not address principal investigators, however, the expectation is the same.
- OECD requires the proposed experimental start and completion dates. Not addressed by FDA.

None of the above differences are significant; however, they do clarify "grey" areas.

**Conduct of the Study** – FDA = §58.130; OECD = §8.3

The majority of the requirements are the same between FDA and OECD. The following differences include:

- FDA is very specific for specimen identification; i.e., they must be labeled by test system, study, nature, and date of collection, or the information shall accompany the specimen(s) to preclude error. OECD only specifies study ID and that the identification should enable traceability, as appropriate for the specimen and study.
- FDA states that records of gross findings for a specimen from postmortem observations should be available to a pathologist when examining that specimen histopathologically. OECD does not include this requirement.
- FDA specifies that manually recorded data shall be signed and dated on the day of entry. OECD does not specify "on the day of entry."
- OECD states that computerized system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. FDA, while using a different wording, has all the same requirements. In addition, FDA has the 21 CFR Part 11 regulation, electronic records and electronic signatures, which has very specific requirements for computerized systems and electronic data.

**Multi-site requirements**

The FDA does not address multi-sites. The OECD defines multi-site studies under the definition of Test Facility and uses the term within the principles. In addition, the OECD published a consensus document titled, "Organisation and Management of Multi-Site Studies." Under FDA, all sites in a study are expected to comply with the GLPs unless noted otherwise in the protocol.

**Reports** – FDA = §58.185; OECD = §9.1, 9.2

The majority of the requirements are the same between FDA and OECD. The following differences include:

- OECD requires the study director to include a statement indicating the extent of compliance with the OECD GLPs. FDA GLPs do not require a GLP compliance statement. The FDA GLP compliance statement requirement is found in the various submission requirements, such as 21 CFR Parts 312 and 314.
- OECD addresses a short-term study report as a standardized final report accompanied by a study specific extension. FDA does not define or discuss short-term studies.
- OECD specifies that reports of principal investigators or scientists involved in the study should be signed and dated by them. FDA does not specify principal investigators, but they are covered as "individual scientists or other professionals."
- FDA specifies that test and control articles characterization information be included. OECD does not require that characterization information for reference items be included, only for test items.
- OECD requires the name and address of the sponsor. FDA does not require this; however, it is expected.
- OECD requires the name and address of the principal investigator(s) and the phase(s) of the study delegated, if applicable. FDA does not define or discuss principal investigator(s).
- OECD requires experimental start and completion dates. FDA does not define these dates or require this information.
- OECD requires a reference to OECD Test Guideline or other test guideline or method. FDA does not specifically require a reference to any test guidelines used.

**Storage, Retrieval/Retention of Records and Data/Materials** – Archives – FDA = §58.190, 58.195; OECD = §10

- OECD requires that test and reference items, QA records, personnel qualification files, standard operating procedures, and master schedules be retained in the archive. FDA does require that these items be retained; however, they do not specify that they be retained in the archive.
- The FDA defines retention periods for archiving all required study data, etc. based on the submission requirements to the FDA. OECD does not discuss retention periods, presumably, these time periods are determined by each country.

**Disqualification of Testing Facilities – FDA = §58.200-58.219; OECD = N/A**

The FDA provides details as to the grounds on which a testing facility may be disqualified. The OECD GLPs do not address this area, because the grounds for disqualification are left to each country in which the test facility/site is located, and accreditation is required to be renewed periodically (typically every two years).

Looking back, 20 years have passed since the FDA revised its GLP and 10 years have passed for OECD. Clearly, the OECD GLPs have addressed many of the "grey" areas in the FDA GLPs, and have also added some additional requirements. The U.S., as an original OECD member that helped develop the GLPs, continues to be a major part of the global research community. Now would be an opportune time to adopt these international GLPs in the U.S. There is some precedence for this approval, in that the FDA has adopted the International Conference on Harmonization (ICH) Good Clinical Practice (GCP).

**References**

**GLPs**

1. FDA GLPs, 21 CFR Part 58 (as revised in 1987)
2. OECD Principles of Good Laboratory Practice, ENV/MC/CHEM(98)17 (as revised in 1997)

**OECD Consensus Documents**

1. Role and Responsibilities of Sponsors (1998)
2. Role and Responsibilities of the Study Directors (1999)
3. Guidance for the Conduct of Laboratory Inspections and Audits
4. Quality Assurance and GLP (1999)
5. Organisation and Management of Multi-Site Studies (2002)
6. Application of GLP Principles to Field Studies (1999)
7. Application of GLP Principles to Short-Term Studies (1999)

***Paul Swidersky is the founder, president and chief executive officer of Quality Associates, Inc. He has more than 35 years of experience in scientific research and has been working in QA since the inception of GLPs in 1979. He can be reached at [pswidersky@qualityassociatesinc.com](mailto:pswidersky@qualityassociatesinc.com).***

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