EAG LABORATORIES | Eurofins Materials Science

WHITE PAPER

GMP, GLP or ISO 17025: How Do These Apply to Outsourced Analytical Testing?

By Joe Grappin, EAG Laboratories

"I NEED MY WORK DONE GLP — DOES YOUR FACILITY FOLLOW THE GLPS?"

"IS YOUR LAB GMP CERTIFIED?"

"DOES FDA ACCEPT ISO 17025?"

The regulatory landscape can be complicated for medical device development. The regulations are not entirely clear at times when compliance is required and on which standards are needed. Thus, subject to interpretation, this leaves companies to decide how to comply to the various regulations and standards. Contract laboratories must have a robust approach in quality to meet the diverse expectations from their customers. Few contract laboratories have the expertise to guide and consult with their customers and provide recommendations on the correct scientific study and the proper regulations. The contract laboratory should recognize the medical device client is tasked with having to know the complexities of bringing a product to market in a highly regulated environment in which quality requirements will change based on the product's stage in the development cycle.

As an analytical testing partner to the medical device industry, it is the laboratory's responsibility to have a deep understanding of these standards and regulations. Laboratories can help clients not only make the most appropriate choice in the analytical technique and test to solve their problems but also make sure the testing performed will meet the regulatory scrutiny needed to bring safe and effective products to market.

HISTORY OF REGULATIONS

To understand the regulatory and quality questions from a medical device client, it is important to understand the history of the regulations. GLP stands for "Good Laboratory Practices," yet why would a client ever want anything less from a laboratory? From the medical device client's perspective, GLP means 21 CFR Part 58: "Good Laboratory Practice for Nonclinical Laboratory Studies."[1] In the 1960s and 1970s, there was a growing concern over poorly designed, managed and executed nonclinical animal studies in the private and public sector. Significant events took place in 1975, and members of the FDA made allegations against research laboratories in the United States (Searle and Hazelton) relating to preclinical research studies. Both sites were subsequently investigated, revealing serious problems with the conduct of safety studies submitted to the FDA. Violations included poor record-keeping and data storage, inadequate personnel training, poor test facility management and even fraud.[2]

In December 1978, the FDA published final GLP regulations, and it made compliance with them the law in the United States in June 1979. These regulations were collected in Title 21: "Food and Drugs" of the Code of Federal Regulations (CFR) as Part 58: "Good Laboratory Practice for Nonclinical Laboratory Studies." These regulations applied to all nonclinical safety studies intended to support research permits or marketing authorizations of products regulated by the FDA. Subsequently, the FDA's Office of Regulatory Affairs (ORA) released two Guidance for Industry documents to ensure the proper and consistent interpretation of the directives by industry and by the FDA's field investigators. Further changes to the GLP rules were proposed in 1984, and finally in September 1987, the FDA published its "Final Rule" — Compliance Program Bioresearch Monitoring: Good Laboratory Practices, which was expanded to incorporate the following:

- **Requirement for a QA department.**
- **Requirement for protocol preparation (study plan).**
- **Characterization of test and control materials.**
- **Requirement to retain specimens and samples.**

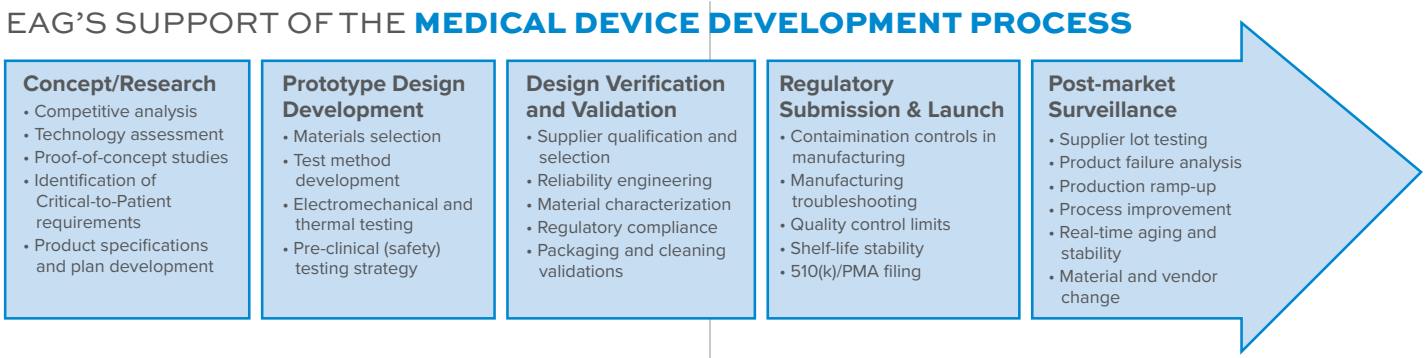
In addition to the United States' GLP regulations, many other countries have either implemented their own GLP regulations or have required safety studies for human medical products be performed in accordance with Organization for Economic Development (OECD) GLP guidelines.[3]

21 CFR PART 58: GLPS: HOW DO THEY APPLY TO ANALYTICAL TESTING OF MEDICAL DEVICES?

These requirements give insight into the standard and how they apply or don't apply to the analytical testing laboratory. 21 CFR Part 58 defines a Nonclinical laboratory study to mean in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects in clinical studies or field trials in animals. It also does not include basic exploratory studies into a test article's potential utility or to determine its physical or chemical characteristics.

During the scoping of a project, the analytical laboratory needs to uncover whether the requested work is to determine physical or chemical characteristics of a test article. Will the test system use cell lines and/or an animal model? Characterization studies on the test article, even after explanting the test article, are outside the scope of the 21 CFR Part 58 regulations. Although OECD GLP

GMP, GLP or ISO 17025: How Do These Apply to Outsourced Analytical Testing?



guidelines address analytical testing in more detail, 21 CFR Part 58 is the standard medical device clients must comply with to bring products to the United States market.

MEDICAL DEVICE GMPS

If GLPs do not apply to analytical materials testing on a test article, do GMPs apply? Well, that can be answered as, "It depends." Again, let's start with a little history. The GMP regulations in place today were developed in response to a series of problems involving the quality and safety of pharmaceuticals. These documented events go back to the 1930s, when patient safety was jeopardized because of poor manufacturing controls, resulting in increased regulations on the manufacturing processes of pharmaceutical products throughout the 1950s and '60s. The United States first implemented the 21 CFR Parts 210 and 211 in 1963, expanding these regulations in 1978 and slightly revising them in 2008.

The medical device GMP, 21 CFR Part 820, developed when the pharmaceutical GMPs were expanded, was last revised in 1996. The two GMPs are referenced below.

- **21 CFR Parts 210-211: "Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General" and "Current Good Manufacturing Practice for Finished Pharmaceuticals."[4]**
- **21 CFR Part 829 Medical Devices: "Quality System Regulation."[5]**

Note that there are separate GMPs for biologics as well as human-derived tissue and cell products.

Medical device GMPs are written describing general quality system requirements, such as requiring the use of calibrated instruments for measurements (21CFR820.72) and requiring the use of process validations (21CFR820.75). In contrast, pharmaceutical GMPs list specific laboratory controls such as where, when and how to test (21CFR211 Subpart I) as well as the design and construction of manufacturing facilities (21CFR211 Subpart C).

Medical device GMPs are also harmonized with the requirements defined in ISO 13485, Medical devices — Quality management systems — Requirements for regulatory purposes.[6] The key difference between the laboratory requirements of the pharmaceutical GMPs and medical device GMPs is medical device GMPs do not define calibrations nor validations, while pharmaceutical GMPs are very specific on those two items.

There are two main reasons behind these differences between pharmaceutical and medical device GMPs:

1. Medical device manufacturing has a wide variety of processes due to the various medical device products when compared to pharmaceutical manufacturing. For example, the manufacturing process for a contact lens is quite different than the process for a hip implant. In comparison, the manufacturing processes of various forms of oral dosage pharmaceutical products are similar, regardless of the disease application.
2. Pharmaceutical products have biological activity where potency is critical. Therefore, strict controls must be in place, as minor variations could impact the drug's efficacy and safety. In traditional medical devices, there are no active pharmaceutical ingredients (noncombination products), and in general the base materials of the device have a long history of being nonreactive.

Going back to the original question, if GLPs do not apply to analytical materials testing on a test article, do GMPs apply? Before answering, the analytical laboratory needs to know more about the material being tested and why the data is needed. If the data is in support of an in-process inspection of a device or material, 21 CFR 820 applies. If the material being tested is the active pharmaceutical ingredient, excipient or container closure/delivery system of a drug-device combination product, 21 CFR 210/211 applies. The requirements for testing on a drug-device combination product is well defined in 21 CFR 210/211, as is what to do in a supporting out-of-specification investigation.[7]

However, for clients manufacturing traditional medical devices, just stating that the laboratory is following 21CFR820.72, Inspection, measuring and test equipment, may not be enough. The level of control is uncertain, resulting in an incorrect expectation to adhere to pharmaceutical GLPs. This incorrect regulatory compliance could put the laboratory in a regulatory situation in which the requirements do not apply or could not be met. This could lead to

GMP, GLP or ISO 17025: How Do These Apply to Outsourced Analytical Testing?

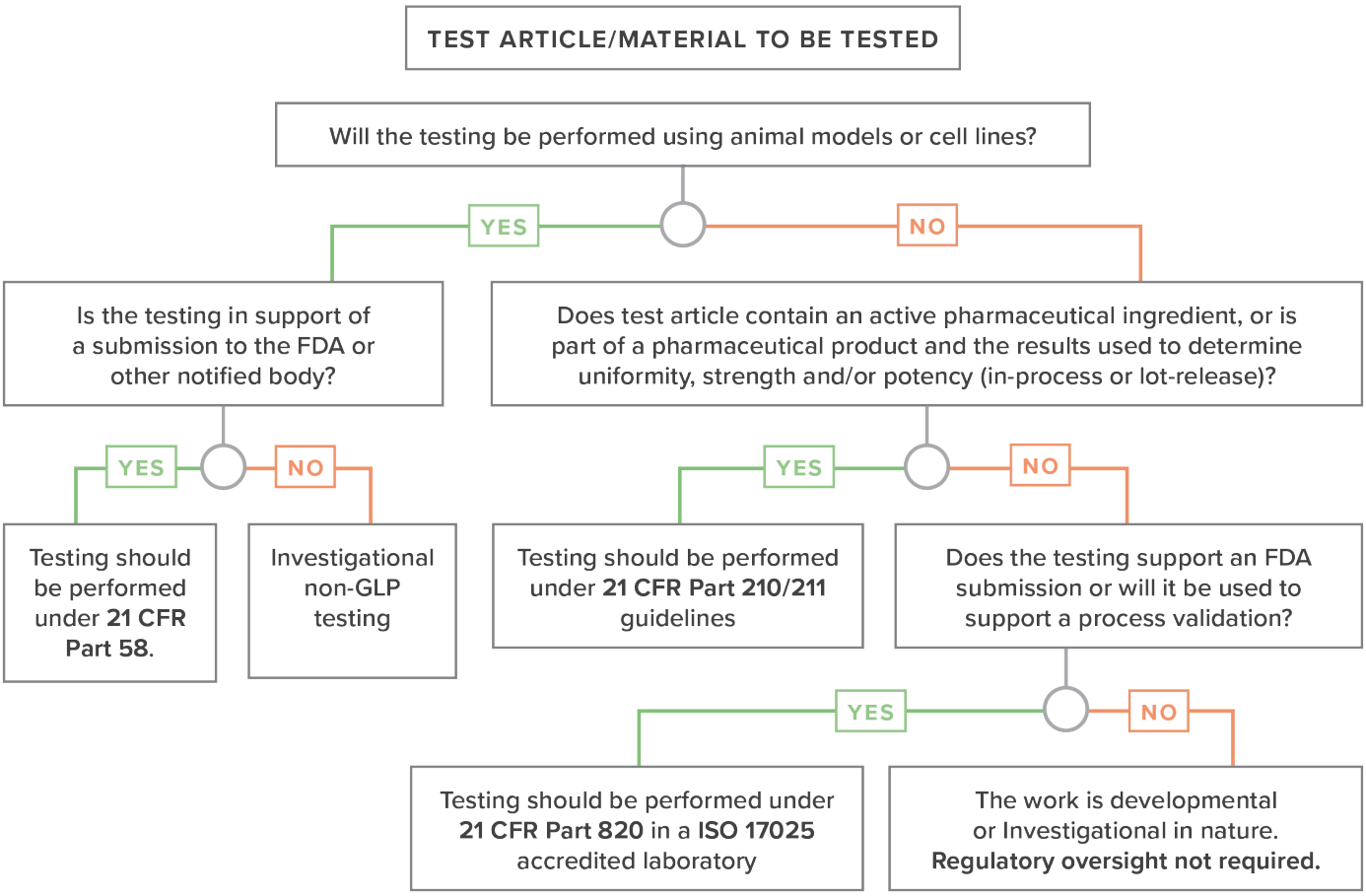


Figure 1: EAG Laboratories' recommend decision tree for determining what set of regulatory requirements are needed for the requested testing.

inaccurate out-of-specification investigations and/or FDA findings.

ISO 17025: COMPLEMENT TO GLPS AND GMPS

To address these uncertainties, laboratories can be certified to ISO 17025 "General Requirements for the Competence of Testing and Calibration Laboratories."[8] This standard is the main ISO standard used by testing and calibration laboratories. In most major countries, ISO/IEC 17025 is the standard for which most labs must hold accreditation to be deemed technically competent.

The standard requires the use of certified calibration materials as well as trending of instrument data and the competency of analysts. Each technique listed in an ISO 17025 certification must also have been evaluated for the uncertainty of the measurements and made available to the client. When reviewing GLP, GMP and ISO 17025, it can easily be seen that ISO 17025 complements the Medical Device GMPs as well as the GLPs to a lesser extent. More and more medical device clients look to laboratories having this accreditation during the vendor approval process.

If a medical device client is doing development work, do any of these — GLP, GMP or ISO 17025 — apply? Technically, no, as there are no requirements to comply to specific regulations for development work. Sometimes, due to the nature of the experiment and the techniques available, there may be no other option than to run an experiment/technique without calibrating to standards or reference materials. In these cases, it is always recommended to use a confirming technique to see if the data correlates.

To help with determining what set of regulatory requirements are needed for the requested testing, a decision tree is shown in Figure 1.

CONCLUSION

In summary, there is not one set of regulations that covers every medical device testing situation. Applying the wrong regulation or standard could slow down the development process and delay time to market. When choosing a good analytical testing partner, it is critical that the laboratory understands and can meet the regulatory scruting of the medical device industry, as well as provide excellent scientific support.

GMP, GLP or ISO 17025: How Do These Apply to Outsourced Analytical Testing?

ABOUT THE AUTHOR

Joe Grappin, M.S., has over 25 years working at analytical testing laboratories supporting the pharmaceutical and medical device industries. He started his career as an analytical chemist and was promoted to various laboratory manager and director roles where he was responsible for the quality and performance of the laboratory. Joe also actively participated in numerous GLP, GMP and ISO 17025 audits throughout his tenure. He then transitioned to a business development role at EAG Laboratories where he works with medical device manufacturers in development of analytical testing programs as well as aligning EAG offerings with the needs of the manufacturer.

REFERENCES

1. Code of Federal Regulations, Title 21, Food and Drugs, Subchapter A — General, "Good Laboratory Practice for Nonclinical Laboratory Studies," Part 58 (US Government Printing Office, Electronic Code of Federal Regulations, current as of January 25, 2018). http://www.accessdata.fda.gov/scripts/cdrh/ cfdocs/cfcfr/cfrsearch.cfm?cfrpart=58
2. GLPs and the Importance of Standard Operating Procedures Aug 01, 2003, Kevin Robinson BioPharm International, Volume 16, Issue 8 http://www.biopharminternational.com/glps-and-importance-standard-operating-procedures
3. Organization for Economic Cooperation and Development, OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, Nos. 1 – 16 (OECD, Paris, France). http://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypractice glpandcompliancemonitoring.htm
4. Code of Federal Regulations, Title 21, Food and Drugs, Subchapter C — Drugs: General, "Current Good Manufacturing Practice for Finished Pharmaceuticals," Parts 210-211 (US Government Printing Office, Electronic Code of Federal Regulations, current as of January 25, 2018). https://www.ecfr.gov/cgi-bin/text-idx?SID=0d6c9358cef8c49156a1144e37d7cf90&mc=true&tpl=/ecfrbrowse/Title21/21cfr211_main_02.tpl
5. Code of Federal Regulations, Title 21, Food and Drugs, Subchapter H — Medical Devices, "Quality System Regulation," Part 820 (US Government Printing Office, Electronic Code of Federal Regulations, current as of January 25, 2018). https://www.ecfr.gov/cgi-bin/text-idx?SID=e337425e36929390731dcea1f1030329&mc=true&tpl=/ecfrbrowse/Title21/21cfr58_main_02.tpl
6. ISO, (2016). ISO 13485:2016, Medical devices — Quality management systems — Requirements for regulatory purposes, Geneva, Switzerland. https://www.iso.org/standard/59752.html
7. Center for Drug Evaluation and Research, Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (FDA, Rockville, MD, October 2006). https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf
8. ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories https://www.iso.org/standard/66912.html.