Introduction
Testing of FDA-regulated products may be performed under different regulations, including Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP). This white paper outlines the differences between GLP and GMP regulations that are significant to testing, and provides guidance on when these regulations are applicable.

GMPs are the minimum practices, processes, and standards required for manufacturing, packaging, testing, storage, and distribution of drugs, biologics, human cells, tissues, cellular and tissue-based products (HCT/P), certain Class I medical devices, and all Class II and III medical products. These practices assure that the applicable regulatory requirements for safety, identity, strength, quality, and purity are met, and that the product is appropriate for its intended use. GMPs apply to marketed products and, depending on the stage of development, products used in clinical trials. The FDA GMPs for human medical products are defined in the following sections of 21 CFR:

- Drugs – Parts 210 through 211
- Biologics and blood products – Parts 600 through 680
- Medical devices – Part 820
- HCT/P – Part 1271

GLPs are a set of principles and requirements for planning, executing, monitoring, recording, reporting, and archiving nonclinical laboratory studies. These studies are performed to generate data for determining the safety of medical products. Testing under GLPs helps assure regulatory authorities that the data submitted in research or marketing applications accurately reflect the results obtained during studies, and that it can be relied upon in making risk/safety assessments. For the purposes of this document, references to GLP requirements refer only to those applicable to FDA-regulated products. Tests/studies that are not specifically performed to determine product safety and do not utilize a live organism as the test system do not require performance under GLPs. The FDA GLPs are defined in 21 CFR Part 58.

Brief History of GMP and GLP Regulations
The GMP regulations in place today were developed in response to a series of problems involving the quality and safety of medical products. The 107 deaths caused by “elixir of sulfanilamide” in 1937, the near 300 deaths caused by tainted sulfathiazole in 1941, the inactivated polio vaccine in 1955 that led to more than 100 individuals contracting polio, and the birth defects caused by thalidomide in the 1960’s each resulted in new, more stringent regulations. The current drug GMPs were first codified in 1963, expanded in 1978, and minimally revised in 2008. GMPs for biologics and blood products were first issued in 1975; medical device GMPs were enacted in 1978 and revised in 1996. Medical device GMPs are less prescriptive than drug GMPs, describing general quality system requirements rather than specific manufacturing controls; this could possibly be due to the fact that there exists a wider variety of medical device manufacturing processes as compared to drug manufacturing processes. Medical device GMPs are harmonized with the requirements defined in ISO Standard 13485, Medical devices – Quality management systems – Requirements for regulatory purposes. GMPs for human cells, tissues, and cellular and tissue-based products (Good Tissue Practices, or GTP’s), which were implemented in 1997, are primarily intended to prevent the possible transmission of disease from donor to recipient. Although many within the drug and medical device industries are familiar with the GMP regulations issued by FDA, it is important to note that the World Health Organization and many other countries have published their own GMP requirements or regulations, similar to those put in place by FDA.

In the 1960’s and 1970’s, FDA and EPA became aware of issues regarding the quality and integrity of safety data submitted in support of marketing applications for drugs and pesticides. These issues included inadequate or non-existent protocols and Standard Operating Procedures (SOPs), failures to comply with protocols and SOPs, inadequate data records, and, in some cases, falsified data. In response, FDA and EPA issued draft GLP regulations in 1976 and 1979, respectively, with final regulations issued in 1978 and 1983. In addition to US GLP regulations, many other countries have either implemented their own GLP regulations or require that safety studies for human medical products be performed in accordance with Organization for Economic Development (OECD) GLP guidelines.
When are GMP and GLP Regulations Applicable?

Medical product development generally occurs according to the continuum shown above.

While there are differences between how drugs, biologics, and medical devices are developed, the same general principles and requirements apply. Initial research and development (feasibility) is performed to determine:

- Whether or not a product is likely to be efficacious,
- If selected materials of construction are appropriate,
- If a product has an acceptable safety profile,
- If a process will reliably produce a product with acceptable characteristics,
- If product impurities exist, and
- To obtain information to allow setting of specifications.

These early studies are not regulated and are generally not submitted to regulatory agencies. Because these studies are critical in determining whether or not to proceed with development, which may involve significant costs, it is vital that good practices for experimental design and record keeping are followed.

21 CFR 58.3(d) clarifies that “basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article” are excluded from the scope of the GLP regulations. Nevertheless, many firms perform “functional preclinical studies” under GLP controls as a precautionary measure in the event that the study is submitted to a regulatory agency, and to maximize study controls.

While FDA does not regulate early stages of development, laboratories will generally follow a set of accepted research and development practices to ensure data reliability. These practices should not be confused with GLPs, which apply only to nonclinical laboratory safety studies (biocompatibility, toxicology, pharmacology, etc.) that support or are intended to support research or marketing applications for medical products. Additionally, GLPs only apply to studies performed in “test systems”: live organisms, plants, or microorganisms; or subparts of these test systems. This means that the GLPs do not apply to chemistry-based or microbiological quality testing. The applicability of GLP regulations is defined in 21 CFR Part 58, and reiterated by FDA in a 2013 draft guidance document, The Applicability of Good Laboratory Practice in Premarket Device Submissions: Questions and Answers.12

Some or all of the requirements defined in the GLP regulations may be applied to studies outside of the scope designated in 21 CFR Part 58; although laboratories may want to designate those studies as something other than “GLP,” as any study that appears on the GLP Master Schedule may be subject to review during routine FDA inspections.
Some of the key requirements for GLP compliance are:

- Each study is assigned to a Study Director, who is responsible for the overall conduct of the study, and for ensuring that the study is performed in accordance with GLPs. The Study Director is responsible for the protocol, study execution, and management of any issues that may arise during conduct of the study.

- A protocol, approved by the Study Director and the Sponsor, is developed for each study. The GLPs define specific information that must be included in each protocol.

- The Quality Unit monitors/inspects each study to ensure that the GLPs are followed, and that the integrity of the study is maintained (ie, that the protocol is adhered to) and the study report accurately reflects the data. Additionally, the Quality Unit maintains a “Master Schedule” of all GLP studies and periodically submits reports on the quality of studies to Study Directors and management.

- Facilities and equipment must be designed, maintained, cleaned, and operated according to SOPs.

- Each test article must be characterized, typically prior to being tested. For drugs, this usually involves determining “identity, strength, purity, and composition” of the active ingredient(s) and any other components that may impact safety, as well as product identification, lot number, and expiration date. For medical devices, characterization may include description or analysis of materials of construction, description of method of manufacture, product identification, lot number, and expiry. As stated in 21 CFR 58.105, responsibility for test article characterization may be assumed by either the testing facility or the Sponsor.

- Study records and specimens must be retained for defined periods of time.

Once a medical product has demonstrated potential effectiveness, the next step is to assess safety. During this “Design/Verification” or “Preclinical” stage, safety studies are typically performed in live models. If the results of these studies are intended to be submitted to FDA or another regulatory agency in support of a research or marketing application, then the studies must be performed under GLP requirements. Studies to determine pharmacology, kinetics and metabolism of drugs, immunogenicity, etc, which will be submitted in support of a drug or biologic application are also typically performed under the GLP regulations. These studies are usually designed to be representative of safety under actual product use, and may provide sufficient independent data to support a finding that the product will be safe for use. If the results of a safety study will not be submitted to a regulatory agency, there is no requirement that the study be conducted under GLP.

In some cases, clinical studies in humans will be required to further demonstrate product safety and/or efficacy. If clinical trials are necessary, they must be performed under Good Clinical Practice (GCPs), a set of ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with GCPs provides assurance that the rights, safety, and well-being of trial subjects are protected in a manner consistent with principles that have their origin in the Declaration of Helsinki; and that clinical trial data are accurate and credible. Clinical trials in the US must meet the requirements defined in 21 CFR Parts 50 through 56 and ICH Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance. Investigational drug products and biologics used in clinical trials must meet “relevant” GMP requirements. While this has been subject to interpretation, it is generally accepted that by late stage clinical development (ie, Phase III clinical trials), the investigational product must be manufactured and tested under full GMPs. GMPs are not applicable to the manufacturing and testing of medical devices used in clinical trials, with the exception of design controls (21 CFR 820.30).

Marketed medical products must, with some exceptions, be manufactured using GMP controls, which includes quality control testing. GMP requirements may also apply to the testing of product components such as active pharmaceutical ingredients and critical excipients, and testing performed as an element of supporting activities (e.g., stability studies, process validation). For GMP compliant testing, including testing performed at contract laboratories, the following requirements must be adhered to:
• Products submitted for testing before release to the market (“release testing”) must be tested against approved specifications that are consistent with those listed in marketing applications. For GMP testing submitted to contract laboratories, it is a joint responsibility of the application holder and the lab to ensure that tests are performed against the product specifications so that Out-of-Specification (OOS) or questionable results can be investigated. Note that FDA has cited contract laboratories for failure to test against specifications for GMP product testing.

• Each lot of product submitted for testing must be clearly identified by lot number or other traceable identifier.

• Tests must be performed in accordance with documented, approved test methods. For contract testing, the application holder should also approve any non-standard test methods. Standard test methods (e.g., compendia, ISO, ASTM, etc) do not need to be approved by the application holder, but should be identified in product specifications.

• Tests must be validated or qualified, as applicable. For investigational medical products, the level of validation/qualification is usually dependent upon the stage of product development. Equipment used in testing should be calibrated, qualified, and maintained according to SOPs.

• The number/amount of sample(s) designated for testing should be sufficient to perform the test, and should include reserve sample(s) sufficient to perform the test one or more times in the event that a laboratory investigation is necessary. In cases in which samples are in short supply or cannot reasonably be supplied due to cost issues, this requirement may be waived, but additional sample(s) from the same lot should be available for investigative use if necessary.

• All OOS and questionable results must be investigated. For OOS investigations performed by contract labs, the Sponsor should review and approve the investigation, followed by a manufacturing investigation if the OOS result is found to be valid.

• The Quality Unit should review and approve all GMP test reports.
This table summarizes some of the key differences between tests/studies performed by NAMSA under GLPs and GMPs, as well as tests/studies performed under “Developmental” conditions.

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<th>DEVELOPMENTAL</th>
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<tr>
<td><strong>Type of Testing</strong></td>
<td>Open-ended safety testing, intended for submission to FDA as a component of research application (e.g., IND, IDE) or marketing application (eg, NDA, BLA, PMA, 510k). Usually only performed on one to several representative lots.</td>
<td>Determination of whether or not each product lot to be released to market meets specifications listed in marketing application. May also be performed on lots to be used in clinical trials. Stability studies may also be performed under GMP requirements.</td>
<td>Open-ended testing to determine product performance or safety. Not intended for submission to FDA or other regulatory agency.</td>
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<td><strong>Test Article or Product</strong></td>
<td>Usually a product in development; should be identical to product to be marketed. Must be fully characterized, but usually does not have approved product specifications. Responsibility for characterization (Sponsor or Test Facility) defined in study protocol.</td>
<td>Marketed product lots or lots used in clinical trials; may also include components of finished products or materials used in support of GMP manufacturing, such as bioindicators. Product or component must be manufactured using GMP controls. Generally has quality requirements (specifications).</td>
<td>Usually a product or material in development. Does not have to be characterized in advance of safety studies, and usually does not have approved product specifications.</td>
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<td><strong>Personnel &amp; Training</strong></td>
<td>Personnel executing or managing each study must have appropriate education, training, and experience to be able to perform assigned tasks. Training documented in a controlled system.</td>
<td>Personnel executing and supporting testing must have appropriate education, training, and experience to be able to perform assigned tasks. Training documented in a controlled system.</td>
<td>No specific requirement, although the same trained personnel performing GLP and GMP studies/tests perform Developmental studies.</td>
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<tr>
<td><strong>Study Director</strong></td>
<td>Each GLP study assigned to a Study Director responsible for the technical conduct of the study, interpretation, analysis, documentation, and reporting of results. The “single point of study control”; primary responsibility for study quality lies with the SD.</td>
<td>Not required. Responsibility for quality of testing lies with laboratory management, with oversight by the Quality Unit.</td>
<td>Not required. Responsibility for quality of testing lies with laboratory management.</td>
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<td><strong>Quality Unit Responsibilities</strong></td>
<td>The Quality Unit monitors each study to ensure GLPs are adhered to, and that the integrity of each study is maintained. They also review study reports to verify that they accurately reflect methods, and that results reflect the data.</td>
<td>Laboratory personnel and Quality Unit review/approve test data and reports to ensure that technicians followed the relevant test method(s) and SOPs, and that no errors occurred.</td>
<td>Laboratory personnel and Quality Unit review test data to ensure that technicians followed the relevant test method(s) and SOPs, and that no errors occurred. Laboratory approves reports.</td>
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<td><strong>Facility</strong></td>
<td>Facility must be of suitable size and construction to facilitate conduct of studies. General requirements apply, but facility does not need to be qualified.</td>
<td>Facility must be of suitable size and construction to facilitate conduct of studies. General requirements apply; facility may need to be qualified based on type of testing being performed.</td>
<td>No specific requirements, although, in most cases, same facilities used for Developmental testing are used for GLP and GMP testing.</td>
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<tr>
<td><strong>Equipment</strong></td>
<td>Equipment maintained; data-generating equipment calibrated. Computer systems used for studies must be validated.</td>
<td>Test equipment calibrated, qualified, and maintained according to SOPs. Computer systems used for tests must be validated.</td>
<td>No specific requirements. In most cases, same equipment used for Developmental testing is used for GLP and GMP testing.</td>
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### Summary
The GLP regulations are intended to ensure the quality and integrity of “open-ended” research studies of product safety, while the GMP regulations are intended to ensure the quality and safety of individual batches of regulated medical products through manufacturing and testing in accordance with pre-defined processes, methods, and specifications. Safety and safety/functional studies should be performed under GLPs, while release testing of marketed products should be performed under GMPs. Tests and studies for products not manufactured under GMPs and safety studies that will not be submitted to a regulatory agency in support of a research or marketing application should be performed under “developmental” conditions, although controls approximating GLP may be utilized.

If an application holder decides to perform GMP testing at a contract firm, it is recommended that a Quality Agreement be put in place to define the responsibilities of each party.

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<td>Audits</td>
<td>Real-time, study-specific inspections conducted by Quality Unit during critical phases of each study. Process or systems-based audits may also be performed to verify GLP compliance.</td>
<td>Specific tests may be audited after test completion as a component of audits. GMP compliance is assessed through process or systems-based audits conducted by QA.</td>
<td>No specific requirements, although, in most cases, testing is performed under the same quality system as GLP and GMP testing (trained personnel, use of SOPs, etc.).</td>
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<tr>
<td>Documents</td>
<td>• <strong>Protocol</strong> – Each study requires a protocol approved by the Sponsor and Study Director prior to initiation. &lt;br&gt;• <strong>SOPs</strong> - Drafted by technically competent personnel, approved by Facility Management. &lt;br&gt;• <strong>Specifications</strong> – Generally not in place/not applicable. &lt;br&gt;• <strong>Study Data</strong> - Documented on worksheets, in LIMS, or in notebook. Reviewed by lab and Study Director, and audited by QA. Good documentation practices used. &lt;br&gt;• <strong>Reports</strong> – Detailed report describing study methodology, test system, statistical analysis, data summary, calculations, analysis, and conclusions; signed by Study Director and certified by Quality Unit. &lt;br&gt;• <strong>Archival</strong> – Records maintained for at least 2 years following FDA approval of research or marketing application, or at least 5 years after submittal to FDA.</td>
<td>• <strong>Test Methods</strong> – Drafted by technically competent personnel, approved by Quality Unit; typically approved by Sponsor if not a “standard” test method (e.g., USP, ISO, ASTM). Test method validated or qualified, as applicable. &lt;br&gt;• <strong>SOPs</strong> - Drafted by technically competent personnel, approved by Quality Unit. &lt;br&gt;• <strong>Specifications</strong> – Product specifications provided by Sponsor – generally approved by Sponsor’s Quality Unit. Consistent with marketing application, IND, or IDE. &lt;br&gt;• <strong>Test Data</strong> – Documented on worksheets, in LIMS, or in notebook. Reviewed by lab and QA. Good documentation practices used. &lt;br&gt;• <strong>Reports</strong> – May be in the form of a Certificate of Analysis or a more detailed report; approved by Quality Unit. &lt;br&gt;• <strong>Archival</strong> – Records maintained for at least 1 year following expiry date for lot.</td>
<td>• <strong>Protocol</strong> – Each unique study requires a protocol approved by the Sponsor and laboratory management prior to initiation. “Standard” test methods do not require a protocol or client approval. &lt;br&gt;• <strong>SOPs</strong> – If relevant SOP(s) exist, they are adhered to. If SOP(s) do not exist, activities documented. &lt;br&gt;• <strong>Specifications</strong> – Generally not in place/not applicable. &lt;br&gt;• <strong>Test Data</strong> - Documented on worksheets, in LIMS, or in notebook. Reviewed by lab. Good documentation practices used. &lt;br&gt;• <strong>Reports</strong> – May be a brief or detailed report, depending on complexity of study. Report approved by lab management. &lt;br&gt;• <strong>Archival</strong> – Records maintained as per standard NAMSA retention policy.</td>
</tr>
<tr>
<td>Test/Study Deviations</td>
<td>Deviations from protocol or SOPs managed by Study Director. Foreseen deviations managed as amendments; unplanned deviations assessed and documented. All deviations that may have affected the quality or integrity of the study included in the study report.</td>
<td>OOS results investigated as per FDA guidance. Test deviations documented and investigated as appropriate. Quality Unit facilitates and oversees investigation process. The application holder typically approves final OOS investigation report.</td>
<td>OOS typically does not apply. Test deviations documented and investigated as appropriate. Quality Unit facilitates and oversees investigation process.</td>
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<tr>
<td>CAPA System</td>
<td>Not required</td>
<td>Required</td>
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REFERENCES


