Staying Fab in the Lab: An Insider's Insight into Good Laboratory Practice

Good Laboratory Practice (GLP) is a quality system for planning, performing, monitoring, recording, reporting and retaining nonclinical animal studies. Sticking to GLP ensures the validity of your nonclinical safety data – that it has integrity and reliability. It also ensures that study animals are treated ethically and that we follow appropriate welfare standards.

It is essential that all personnel involved in nonclinical research are well versed in GLP, and those working with preclinical data are aware of the conditions under which the data have been generated. This Insider's Insight has been prepared to introduce the principles of GLP, and why it is important to be aware of them as a medical writer.

Before you start

- Not all nonclinical research is subject to GLP regulations; generally, work in the early stages of drug development is exempt
- Major GLP guidelines have been developed for different countries, such as those by the United States Food and Drug Administration (FDA) and the Organisation for Economic Co-operation and Development (OECD)
- The GLP guidelines outline the core responsibilities of all parties involved in a study, as well as requirements for study equipment and infrastructure

Prepare to succeed

- Reporting the GLP status of a study can be used to assess its quality
- Confirm if the document you are working on requires the reporting of GLP status
- Reporting the GLP status of a study is usually performed in documents including Investigator's Brochures (IBs), Investigational New Drugs (INDs)/Investigational Medicinal Product Dossiers (IMPDs) and Common Technical Documents (CTDs)

Key Insights

Nonclinical studies conducted during the drug development process include different animal studies, which mostly follow the GLP regulations. It is important to have an appreciation of GLP if you are in any way involved in nonclinical research. Effectively, regulations and guidelines have been developed that outline the key requirements and responsibilities involved in following GLP. Examples of GLP include everyday routines of good practice for performing work in a laboratory, such as wearing appropriate personal protective equipment and general safety awareness. However, GLP also covers a range of other topics, including the specific responsibilities of each party involved with a study, how to report study findings, and the process for archiving study materials and data [1]. Aspects of GLP also apply to the suitability of the equipment used in a study – even the buildings and infrastructure in which the research is being performed. As a medical writer, knowing the GLP status of a study can be used to gauge of its reliability.

A History of GLP

A timeline for the introduction of some of the most notable GLP guidelines is summarised in Figure 1. Regulations for GLP were first introduced in the 1970s owing to a lack of quality and scientific integrity in nonclinical toxicology studies. The US FDA became aware of cases of poor laboratory practice all over the United States [2].

The agency performed an in-depth investigation on 40 toxicology labs and discovered considerable incidences of fraudulent activities and poor lab practices. Examples of some of these poor lab practices found were:

- Equipment not calibrated to standard form, thereby giving wrong measurements
- Incorrect/inaccurate accounts of the actual lab studies/experiments
- Inadequate test systems

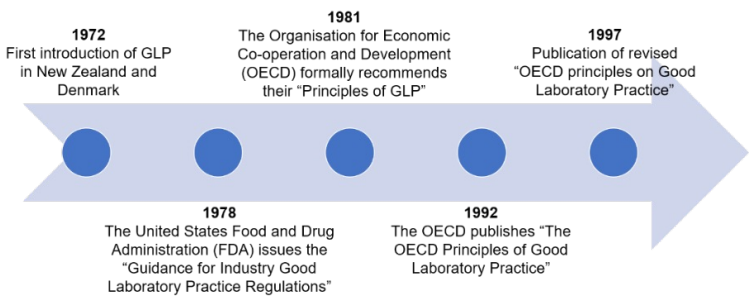

Figure 1: GLP Guideline Milestones

Practices seen at one lab made headline news at the time. Industrial Bio Test, a large commercial testing facility, worked for several large companies such as Procter and Gamble [3]. Mice that they had used to test cosmetics on, such as lotions and deodorants, had developed cancer and died. The company had disposed of the animals and buried their findings, and then stated that the products were suitable for human use. Those found to be involved in the company's production, distribution and sales operations were charged with criminal activities.

Although the first GLP guidelines were introduced in New Zealand and Denmark, they were quickly adopted more widely. The US FDA issued their own guidance in the late 1970s [2] followed by a regulatory alignment by the OECD, with the 'Principles of GLP' formally recommended in 1981 [4]. A revised set of guidelines 'The OECD Principles of Good Laboratory Practice' were published in 1992, with a further revision released in 1997 [5]. Currently, the guidance from OECD has been adopted by 38 member countries. The OECD operates with a Mutual Acceptance of Data (MAD) system, meaning that when a chemical passes a GLP safety assessment in one OECD country, it is accepted by the other member states. Reducing duplication due to MAD decreases costs (approximately €309 million per year), time and resource expenditure [6].

Purpose of GLP principles

- To promote the development of quality tests data
- Obtain reliable and reproducible data
- Obtain comparable data between countries
- Achieve international confidence in study data
- Avoid repetition of studies
- Enable reconstruction of studies
- Optimise animal conditions
- Shorten the registration time of the drug

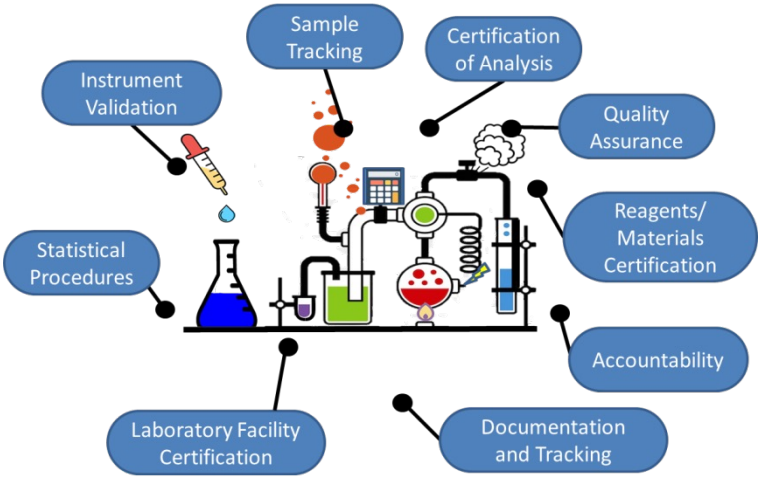

Figure 2: Elements of GLP

When Do I Apply GLP?

Compliance with GLP is generally applied during the nonclinical stages of drug development (Figure 3) [1, 7]. The OECD Principles of GLP [1] are applicable to the nonclinical safety and environmental safety testing of pharmaceutical products, pesticides, cosmetics, veterinary drugs, food additives, feed additives, industrial chemicals and medical devices.

Nonclinical Studies in the Process of New Drug Development

During the early preclinical development process, a crucial contribution to Go/No-Go development decisions, a drug candidate needs to pass through several steps, such as determining drug availability (studies on pharmacokinetics), absorption, distribution, metabolism and elimination (ADME) and preliminary studies that investigate drug candidate safety including genotoxicity, mutagenicity, safety pharmacology and general toxicology.

Figure 3: GLP in the Drug Development Process

Such early studies do not need to comply with GLP regulations. These studies aim at investigating the drug safety to obtain the first information about its tolerability in different systems. Any findings may be relevant for further decisions and may lead to later studies that would be required to be GLP compliant [1, 3]. Academic research is generally exempt from GLP, except for cases of nonclinical safety testing performed for intellectual property development on-site [8].

Clearly there are studies that must be performed under GLP conditions and are mandatory to ensure the safe exposure to humans, such as repeated-dose toxicity, genotoxicity and safety pharmacology. These studies must be performed before the IND/IMPD application. The collection of nonclinical studies should capture all information required for the safe transposition of drugs from animals to humans, generally based on the non-observed adverse effect level obtained from general toxicity studies (Figure 4).

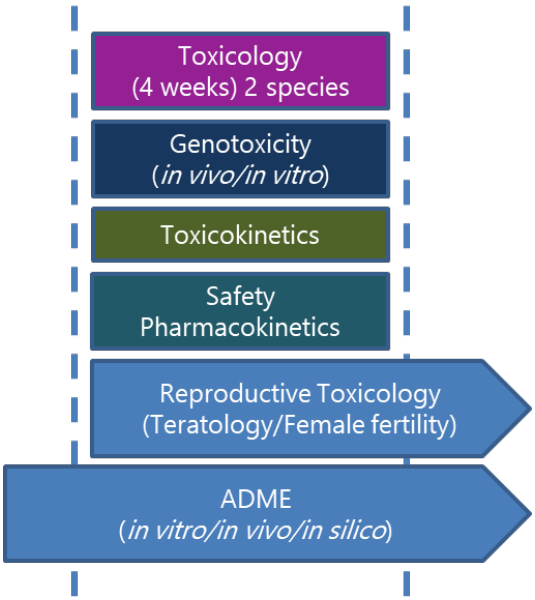

Figure 4: Preclinical GLP Application

Following IND/IMPD approval, other GLP experiments that evaluate toxicity, such as chronic toxicity, reproductive and developmental toxicity, carcinogenicity and genotoxicity, are carried out during the clinical phase of development. However, the necessity of performing such studies depends on the new drug clinical application purpose.

The Ten GLP Principles

The principles according to the OECD requirements are summarised in Figure 5. The full OECD guidelines provide detailed explanations fulfilling each principle. Definitions of any relevant terms are also provided in the most relevant guidelines [1, 5].

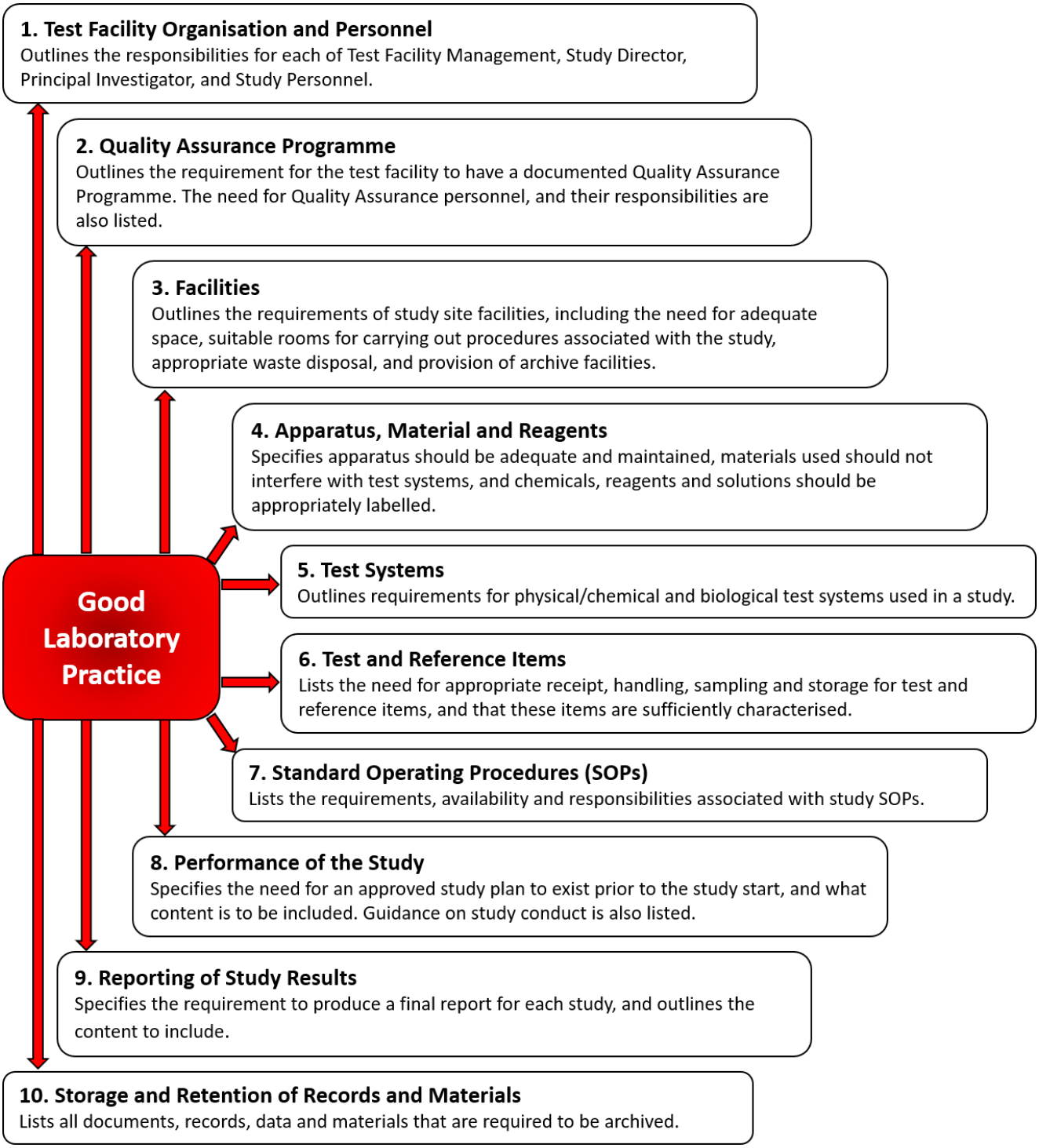

Figure 5: Ten GLP Principles

Not Just Study Personnel...

Although the GLP guidelines are critical requirements for personnel directly involved in conducting animal research, there are other parties also subject to regulatory framework:

Quality Assurance Unit (QAU): The involvement of a QAU is a requirement of the GLP guidelines. The QAU monitors the conduct of a study and typically conducts an audit to ensure all GLPs, standard operating procedures (SOPs) and protocols are being followed. It is important that the QAU is independent of study operations.

Contract Research Organisations (CROs): Independent from the interest of the study findings, CRO utilisation reduces the potential bias in reporting.

An Interview With Our Chief Medical Officer

Q How do you know that a study has been conducted to GLP specifications?

A It is important to note that GLP does not decide the technical design, methodologies and operations. It simply provides the framework within which testing is carried out. The technical design is often specified in test guidelines developed by regulators such as FDA and OECD.

Q Where should I report whether or not a study was performed under GLP?

A It is important to mention and comment on the GLP status in documents that list nonclinical studies, including IBs (see [7]), INDs/IMPDs and CTDs.

Q Is following GLP mandatory for all preclinical work?

A Prior to an IND/IMPD filing, GLP is r required only for safety studies. Such safety studies may comprise in vivo measurements of biocompatibility, metabolism, toxicology and pharmacology.

Q What are some of more common GLP errors made when performing nonclinical studies?

A Common areas for which errors from the GLP guidance can occur range from failure to properly calibrate or use laboratory equipment, researchers not wearing appropriate personal protective equipment, misinterpreting data or notes made during an experiment, lack of effective communication between researchers and risking bias by not assessing findings blindly.

And finally...

Good laboratory practice principles are flexible and a precise understanding of their application is essential. Each testing facility applies GLP principles within its own laboratories, taking into account both cultural and organisational aspects. In addition, the GLP quality system is dynamic, undergoing continuous modification (improvement). Consequently, there are often challenges applying the different interpretations underlying the principles of GLP. Cultural aspects can play a critical role.

Practitioners must use their knowledge of GLP principles, combined with the awareness of the issues linked to the conduct of various types of non-clinical laboratory studies in order to select the correct and adequate methods of application. It is also essential to engage in continuous discussion with representatives of regulatory authorities to ensure adherence with to the latest mandates.

Defining adherence to GLP is not the only means of assessing nonclinical studies. The Klimisch score can be used as a measure of the reliability of nonclinical toxicology study data. In this system, studies are assigned a score of 1 – 4. Only studies with Klimisch scores of 1 and 2 are deemed reliable data to address a study endpoint, lower scores are generally only cited in a supporting role. Consistent with study integrity, work adhering to GLP principles generally have Klimisch scores of 1 [11, 12]. Awareness of these measures can provide a quick and easy way to apply a discerning eye to any nonclinical research.

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Next Steps

We created this Insider's Insight to introduce and outline the key principles of GLP.

I hope you found this guide useful. If you would like to discuss support for any of your publication issues or challenges, please contact me at the email address below.

Dr Justin Cook
Head of Medical Writing
justin.cook@niche.org.uk

Get in touch

niche science&technology

+44 (0)20 8332 2588
www.niche.org.uk