
White paper

Totallab & Phoretix
software helping life
science labs become
compliant with GMP/ GLP
and FDA regulation 21CFR
part 11



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Purpose

Anybody who has looked at any guidance or documentation on good laboratory practice (GLP), good manufacturing practice (GMP) and FDA 21CFR will be familiar with the fact that there exists a multitude of guidance documents which inherently are written in the style of legal documentation and often difficult to follow.

This whitepaper has been written with brevity in mind and is meant to serve as only a brief overview of the key considerations for GMP/GLP labs who are involved in the analysis of 1D gels and blots while also offering a solution.

For clarity the paper is written in three sections, the first deals with regulatory considerations. The second section showcases the TotalLab teams' module for 21CFR compliance and the third section is an interview with a happy user of a TotalLab 21CFR product, this should help remove some of the haze caused by terminology and compliance framework; Joanne Lloyd who is a supervisor in a GMP lab at BioProducts Laboratory, she was involved with purchasing software for 1D analysis in the GMP lab.

Due to the desire to create an easily understandable and brief document, for more a more detailed discussion on compliance please refer to the appropriate guidelines issued by governing bodies such as the Federal Drug Agency (FDA).

A brief insight into how 21CFR affects regulation in life science laboratories

Life science organisations, today work in an environment filled with regulations, ensuring safety and quality of products. Adherence to policies for GMP and GLP helps organisations achieve the standards of safety required by the pertinent regulatory bodies. The 21CFR part 11 rule on electronic records and electronic signatures

issued by the FDA is one such policy which requires attention to security and integrity of electronic data and audit trails. In the laboratory context this often means that there should be electronic systems in place to manage electronic data analysis and any associated records. Specifically Laboratory Information Management Systems (LIMS) have been designed to maintain the integrity of laboratory records.

LIMS require original records to be maintained and only persons who have qualified access are able to carry out analysis. This ensures traceability of electronic records and the professionals involved in the analysis and supervision.

21CFR part 11 requires the use of electronic signatures and verifiable records to achieve higher levels of data security by ensuring electronic records and electronic signatures are considered trustworthy, reliable and equivalent to paper records.¹

Who is 21CFR part 11 aimed at and what considerations should be taken

FDA-regulated industries such as drug makers, biotech companies, contract research organisations, biologics developers etc. are required by 21CFR part 11 to apply and maintain controls to demonstrate compliance. The key idea is that all protocols implemented should be **transparent and verifiable** through **reports and documentation**. Controls required to demonstrate compliance include **transparent audit trails** for regular audits and system validation. Also, to ensure demonstrable compliance to rules regarding **security of data and analysis, system access tiers, electronic signatures and documentation** for software and systems involved in processing electronic data are required to be maintained.¹

The considerations taken to ensure demonstrable compliance to 21CFR inherently enforce many practices which fit in to the normal framework of GMP/GLP

guidelines and therefore practically complement existing GMP/GLP procedures.

Considerations in terms of electronic records according to GMP/GLP guidelines

Today an emphasis in GMP/GLP guidelines is on minimising the use of paper records. As a result there has been a substantial amount of guidance from various regulatory bodies and organisations interested in GMP/GLP on how to ensure electronic data is secure and verifiable.

The first major consideration is that a validated computerised system is a prerequisite for the acquisition and processing of electronic raw data within a GLP study. ²

According to the FDA's guidance on 21CFR part 11: *"We suggest that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no predicate rule requirement to validate a system, in some instances it may still be important to validate the system."*

We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs."

System validation is therefore a major consideration as it can impact on the end product quality.

Other areas which face major considerations are collection, maintenance and storage of data.

The following sections aim to briefly define key concepts which ensure electronic data is secure yet transparent and verifiable through reports and documentation;

- **Security of data and analysis**
- **System access control**
- **Documentation**

Security of data and analysis

In order to appreciate this area a clear definition of data is required. Additionally metadata, processing/ analysis of data and LIMS will also be briefly discussed.

Raw Electronic Data

Raw data has been defined in the OECD principles of GLP ⁽³⁾ as follows:

"Raw data means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period specified by the appropriate authorities."

Accordingly the Ordinance on Good Laboratory Practice² has defined electronic raw data as:

"Original test facility records generated by means of computerised systems and stored on digital media. In a broader sense this may include data processed subsequently, and stored on digital media, which are necessary for reconstruction and evaluation of the final results."

It goes on to say that the components of "raw electronic data represents the measured values and associated metadata (study number, time, sample ID) are attributes of the measured data and technical properties. Any processing of raw data such as integration, calibration and calculation should be described by the

process itself including processing parameters, equations and statistical methods. The process finally applied and the corresponding results should be preserved.”

These definitions and guidelines on raw and associated data put responsibility on organisations practicing GMP/ GLP to have laboratory information management systems (LIMS) in place to correctly store and handle the electronic data. Additionally procedures related to any interfacing of instruments and persons to LIMS should also be clearly documented to ensure correct usage and clarity for external audits.

Procedures regarding collection of data is a major area discussed in guidance documents on GMP and LIMS but is not in the scope of this document, however the [‘AGIT Guidelines for the Acquisition and Processing of Electronic Raw Data’](#) can be referred to for an in depth discussion on the considerations required for collection of raw data.

Considerations in regards to processing of raw 1D image data

Raw image data files are generated in the analysis of electrophoresis gels and blots. Raw image files do contain usable results, such as, absence or presence of expected genetic material. However in order to quantify and identify results accurately processes such as background subtraction, calibration, etc. should be carried out in a secure and verifiable way by housing the processing in a LIMS. Also parameter settings used for analysis should be clearly documented for support of auditing.

Processing of image files should be done on copies of the raw image to ensure data integrity; this way the raw image retains all of its original data. These original raw data files should be stored in a secure location. Additionally, image file processing events should be identifiable by versioning. It is however sufficient to only store the final

processed image along with the protocol by which it had been processed and the original raw data file, as these three are sufficient material for the purpose of keeping a logical audit trail and achieving completely transparency for auditing.

Laboratory information management systems

LIMS are database systems designed to combine study and sample information with acquired data from laboratory instruments. In general, these systems “fully understand” the design of a study; various study activities, such as managing the samples involved, processing and documentation, i.e. sample related data, analysis of results, data reduction, calculation of means, and summaries. These activities are performed electronically, covering the whole range from data acquisition to final results within a GLP study. The possibility of laboratory instrument being controlled by the LIMS software is often limited, so the interaction and the interface between the LIMS and the instrument should be clearly described and the interaction should be part of the LIMS validation.²

LIMS are designed to house processing and storage of data in a compliant way and so are almost indispensable in GMP/GLP labs, the only alternative is to manually curate everything and have copies of everything for audits. With the use of computational methods maintaining hard copies is practically impossible.

System access

Tiers

In order for 21CFR and GMP/GLP guidelines to be satisfied, activities related to handling data and LIMS must be clearly documented and controlled. One crucial factor to control is; only authorised individuals should have access to the system, i.e. in terms of data handling & processing individuals have varying access rights on the data, and these

rights are definable by the function of individuals' role. In order to better understand this topic we must first understand that there are only really four types of functions which can be applied to the data; 1) Data entry, 2) Reading of data 3) Editing data and 4) Approving data. A supervisor of a study or lab should have all of these rights, lab personnel carrying out the analysis/ editing of the data should have all rights except being able to approve data, but a quality assurance officer or external auditor would have only read rights. In order to implement such a system with varying user privileges, a systems' administrator would need to implement tiered privileges against user LIMS logins.

Electronic Signatures

Each individual entering, accessing, processing and signing off data has to be traceable; in terms of auditing the LIMS must associate an inseparable link between time-stamped electronic signatures and all events related to a data record.

Signatures are legally binding affirmations of certain acts in regards to documents signed, and so an electronic signature implies the same responsibility on an individual when they are electronically signed into a system.

Electronic signatures are easily assigned to data access and functional executions within a LIMS system, as the users' login identity and password forms their electronic signature. However to satisfy GMP/GLP and 21CFR each user login ID should be unique, and no group ID's can be used in the LIMS framework. This ensures an individual is accountable to any type of data processing. Also user passwords should be secure (i.e. have a minimum number and combination

of characters) while also being routinely subject to change. Finally it is also highly recommended that user sessions should have an automatic screen lock/log out when a user has been inactive for a set time (e.g. 10 minutes).

Documentation

The use of the term documentation in this section has a very broad meaning. GMP/GLP laboratories are required to keep many documents to supplement their electronic records. However the aim again here is to briefly discuss this important area.

Perhaps the documentation most pertinent to this paper is related to documents associated with LIMS. In terms of operational procedures GMP/ GLP labs must have standardised operating procedures (SOP) in place, and in order for these processes to be verifiable there should be associated documentation, detailing full risk assessments and validation steps before implementation was possible; these SOP documents must also contain full details of the actual SOP or supplemental documents should exist. Documentation for LIMS should contain details such as parameter settings required for calibration of a gel images. There is also a further requirement for any changes to existing systems to go through SOP risk assessments and validation resulting in change control documentation, so if any parameters in the SOP of LIMS occur then these must have full documentation on risk assessment validation along with reasoning for the proposed/implemented change.

If your lab is looking for a LIMS solution for 1D image analysis of gels and blots, read on, [visit our website](#) or [get in touch](#).

TotalLab and Phoretix: modules designed to work in a GMP/ GLP lab

TotalLab and Phoretix software have had modules designed to help life science laboratories involved in 1D analysis to be able to be compliant with 21CFR part 11 by implementing;

1. A system access and electronic signatures interface
2. A data integrity and security module
3. An audit trail system

By discussing the above points this section aims is to give readers the opportunity to appreciate how the design of these modules provides a LIMS which is pertinent to the needs and requirements of GMP/GLP and 21CFR compliant laboratories performing 1D gel/ blot analysis.

1. A system access and electronic signatures interface

The TotalLab and Phoretix modules control system access via the same login details as windows secure login. This creates an ease of use as multiple user ID's and passwords are not required and changes related to new users and password expiry can be implemented at the Windows identity level. For added security the software prevents the viewing or copying of passwords when logging in.

Also within the software security module there is a requirement to set up users with one of three levels of user privilege;

Supervisor: all access

User: all access except signing experiments in the Version Control tool

Viewers: only able to view experiments

These roles and privileges must be assigned upon installation, before the **software can be used, and therefore** any data input,

analysis/ processing signing-off will be permanently associated to electronic signatures.

2. A data integrity and security module

The TotalLab and Phoretix modules control for data integrity and security via the use of a 'Secure Storage Area' and a *Version Control Tool*. The Secure storage area allows users to write to it but not delete anything. This folder will store the following data files:

- Images added via the Version Control tool
- Checked in experiment files (a copy for each version checked in)
- Audit trail of the Version Control events

Firstly a system administrator must create a folder where the files will live, then only allow the correct users assigned above will be given access rights to the folder by the administrator. Finally the software allows storage on network drives (either the Secure Storage Area or local check out) for easy archiving. With these controls in place original raw data image files are kept secure as analysis/ processing is carried out on copies and these copies are auditable due to versioning through the version control tool, and all of the generated data can be kept securely on a network drive so that regular back-ups are more manageable.

3. An audit trail system

The TotalLab and Phoretix modules create three levels of audit trail, so that everything is accounted for, thus the process of data analysis is transparent and secure, results are repeatable and users can be held to account for all processing of the data.

Security Audit Trail

Whenever the Windows Security login is required, and when the software is closed, an event is created in the Windows Event Log. The Event Viewer can be displayed via

Administrative Tools in the Control Panel. This shows all login passes and fails for the IT administrator. Event logs can be archived and deleted only by users with the correct privileges (mainly administrators) and are therefore secure from tampering.

Adding or removing user privileges via the Admin Tool these actions are also recorded in the Windows Event Log.

Version Control Audit Trail

These audit trails are saved as in the Secure Storage Area, one per image. Reports can be created in the version control module by a single click and will contain all of the information related to user actions/ processing on the image data.

Experiment Analysis Audit Trail

The audit information required to repeat an experiment is stored with the data in the experiment file. Using the Audit report options in the Version Control tool it will be possible to view (and print/save) PDF reports of the Experiment data. These will contain all the parameters that are required to repeat the experiment.

Why would a laboratory conducting 1D gel/ blot analysis want to use TotalLab software to implement GMP/GLP practices or 21CFR compliance

As discussed in the first section of this document, there are many requirements upon a GMP/GLP lab in regards to maintaining electronic records in a way that audit trails will be transparent, to ensure laboratories operate in a responsible manner. In the detail of the guidance documents some of the requirements put forward are: security of data and analysis; controlled system access and user privilege tiers; electronic signatures; and documentation to support system SOPs in place and for auditing. As described in this

section the TotalLab/ Phoretix software solution is designed to meet all of these requirements while creating an easy to use interface. The ease of use is facilitated by integrating with the windows login ID's and passwords. The modular design which separates the three modules of security, version control and analysis, means that there is a strong ability to ensure data security by controlled login access (which also incorporates varying user rights on the data) and data analysis versioning(i.e. creating a new digital version for each processing step). The ease in ability to digitally sign off reports, or even print them; creates an easily auditable system.

If your laboratory wants to be 21CFR or GMP/GLP standard compliant and you are involved in the analysis of 1D gels, [try our trial for free](#) and see how easy and useful it is to use. If you want to know more feel free to [ask us a question](#).

We have had the opportunity to speak a valued customer, Joanne Lloyd from BioProducts Laboratory (BPL). BPL operates R&D, GMP and GLP laboratories; see the following section to find out why and how their R&D lab put into place Phoretix 21CFR to help with compliance.

An Interview with Joanne Lloyd: Project Scientist at Bio Products R&D Laboratory's Lab



Why become 21CFR compliant

1. What does it mean to your lab to be 21 CFR compliant?

Jo believes that 21CFR compliance is a grey area in terms of R&D but for products which are in the production cycle if anything is changed in the process of production then this requires a system level compliance to GMP. Jo's lab is involved in developing but also supporting licenced products. Jo says that any QC lab in pharma should be following GMP & 21CFR pt.11 compliance is an FDA requirement if products are to be sold in the USA. GMP should mean maintaining higher standards.

2. What does being 21 CFR compliant allow you to do? / If you were not 21CFR compliant what impact would this have on the way you currently operate?

Jo says that 'data integrity' is the key phrase here. Original images are seen as the proof image and so have to be maintained in the original form so the fact that the original is duplicated for analysis and stored separately this means that the original is secure and available for auditing purposes, whilst analysis is being carried out on a digital copy rather than a physical copy (which is the only alternative that could be used- suggested Jo). If the lab was not compliant then they would have to go through a process of justifying why they are not compliant.

21CFR pre-implementation considerations

3. Are you familiar with the procedure your lab took to implementing 21CFR? Did you need a consultant to help with implementation?

BPL operates with a 5 step policy in regards to implementation of any changes, this procedure is in place to ensure that the labs are operating within GMP, i.e. all changes are traceable/ auditable.

- I. The lab manager will be required to fill in a justification form as to why the software or equipment is required.

This form will then be sent to control change committee.

- II. The change committee will then approve in principle the change.
- III. A questionnaire will then be sent to the software manufacturer to answer.
- IV. Once the response is sent back to the lab manager, they then need to carry out a risk assessment to take all due considerations to the process of implementation, such as, 'How much validation is required'? i.e. does it do what it says, reproducibility, what is the technical protocol to be followed (e.g. background subtraction protocol)?
- V. The final step would be for the change committee to approve the implementation and then log it on their GMP system before implementation can take place.

Nb: Jo mentioned that in R&D work some procedures do not fall into 21CFR, however they do use alternative local procedures.

4. Other than TotalLab/ Phoretix software what other things did you have to update?

In regards to GMP internal regulation and 21CFR compliance, all equipment in the lab must be assessed and written procedures should be followed, which impact consideration when looking for new equipment.

Current Implementation

5. Can you tell me in your own words how you are currently implementing the software?
6. Do windows login passwords time out...?

Access is through windows login usernames and passwords, the passwords must contain letters and numbers and be of a certain length and the system requires the passwords to be frequently changed

7. *How many users/ supervisors do you have in the lab?*
8. *Do you keep your secure folder on a network drive or the local computer? How about the local working folders?*

Secure folders are kept on a network drive; the system operates with personnel local network drives and a system network drive for the company. The secure folder is kept on the company network drive while the local working folders are kept on the personnel local network drives. The policy in place does not allow work to be carried out on local machines as they are more difficult to back up regularly, whereas the secure folder and the local folders are backed up while on the network.

During auditing it is only really the secure folders which are checked, however if something has been signed off then the auditing takes into account this fact while it can check the local folders the work should be checked into the secure folder anyway with all auditing records associated. Signing off by supervisors is only really used when it has to be done for GMP, otherwise it is not, especially in the case of the R&D work.

How TotalLab/ Phoretix is helping with 21CFR procedure compliance

9. *I would like to know what you feel the Phoretix/ TL Quant 21CFR software allows you to do in terms of being compliant.*

A secure area for original experiment images is maintained- i.e. the raw data is maintained in a trusted environment and the analysis is carried out on a copied file. The second point is the software allows for controlled access, therefore only trusted users have access. Thirdly the software maintains an audit trail. The audit trail is not only helpful for auditing purposes but can also be useful for procedural checks to remind investigators of the process that has historically been taken in a certain analysis.

Jo did also mention that being able to unlock signed-off experiments can be useful.

10. *Are there any things about the software that you especially like or think are useful?*

Jo said due to the long experience of using Phoretix the staff are more comfortable with it over TL which is being implemented currently. The need for the TL Quant became explicit due to the multiplex R&D work advancing and now it needs to come into the GMP arena. So previously Jo's lab were using TL 1D which she feels was more easy to use as compared to TL Quant.

Jo particularly likes that they can just use the windows login ID to get into the software, it keeps things simple.

Remaining Challenges

11. *Are there any things about the software that annoy you?*

No grievances.

12. *If there was anything you would change about the implementation of the software, what would it be?*

Nothing came to mind.



[Get in touch with us if you are looking for a solution to your 1D gel analysis compliance.](#)

References

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