Using a LIMS to Improve Bottom Line Profitability

The Model T Ford is still discussed in business schools today because of how Henry Ford relentlessly drove quality and innovation. When first introduced in 1908 the Model T cost $825; by 1916 it cost $360. While reducing the cost by more than half, Ford increased the safety, reliability, and speed of the product. His laser-like focus on quality was legendary and his quote "Quality means doing it right when no one is looking", is still a mainstay of quality theory and practice.

Whether manufacturing cars, supplying clean water, or manufacturing pharmaceuticals, all repeated processes must include quality control to ensure products meet their defined requirements. Quality management is very often about measuring and minimising variance within and across batches to ensure adherence to acceptable limits. This in turn is all about keeping meticulous records, as well as managing and accessing that data.

Pharmaceutical Manufacturing Issues

The FDA (U.S. Food and Drug Administration) keep a public record of the warning letters that they send out to Companies and the citations they contain.[1] Looking at the last five years of data provides a useful insight as to the main issues they see when inspecting quality control regimes in pharmaceutical manufacturing companies. The data shown here is sifted to report only on the primary GMP regulations for drugs (FDA 21 CFR 211). The FDA data dashboard[2] also has some caveats regarding completeness of the data. Nevertheless, the data provides good insight as to their overall findings.

The top 10 GMP Drug Inspection citations for FDA financial years 2018–2022 are shown in Figure 1. This provides a summary of the issues they found. A description of each CFR number is provided in Table 1.

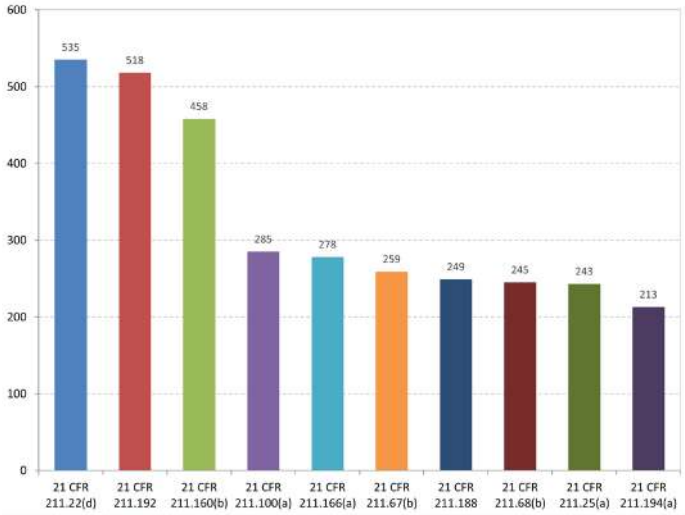

Figure 1: Top 10 GMP Drug Inspection Citations: FY2018–FY2022

#	Top 10 CFR Number - Description	Qty	LIMS Module
1	21 CFR 211.22(d) – The responsibilities and procedures applicable to the quality control unit shall be in writing; ...and followed...	535	Document Manager
2	21 CFR 211.192 – All production and control records, shall be reviewed and approved...	518	Electronic Approval
3	21 CFR 211.160(b) – Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures...	458	Test Limits
4	21 CFR 211.100(a) – Procedures ...to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess...	285	LES
5	21 CFR 211.166(a) – Testing program designed to assess the stability characteristics (shelf-life etc) of drug products...	278	Stability Manager
6	21 CFR 211.67(b) – Procedures shall be established and followed for cleaning and maintenance of equipment...	259	Instrument Calibration and Maintenance
7	21 CFR 211.188 – Batch production and control records shall be prepared for each batch of drug product produced...	244	Batch Manager
8	21 CFR 211.68(b) – Appropriate controls shall be exercised over computer or related systems to assure ...records are instituted only by authorized personnel...	236	Access Control
9	21 CFR 211.25(a) – Each person ... shall have education, training, and experience, ...to enable that person to perform the assigned functions...	215	Training Manager
10	21 CFR 211.194(a) – Laboratory records shall include complete data derived from all tests necessary to assure compliance with specifications...	181	Records and Reports

Table 1: Description of Top 10 CFR Numbers

Laboratory Information Management Systems

Laboratory Information Management Systems (LIMS) help manage quality control in tightly regulated industries, such

as pharmaceutical manufacturing. Much like Henry Ford, the built in controls and checks help drive the quality control of excipients and active ingredients within the manufactured product, and consistently manage quality over time. The quality control procedure in drug manufacturing consists of taking regular samples to ensure consistent quality of raw, intermediate, and final products. Here we outline one aspect of how using a LIMS can help prevent each of the top 10 quality issues highlighted by FDA inspections.

Document Management

The top issue, with 535 citations found through FDA inspections, is one of documenting and following procedures. A QC laboratory LIMS will usually manage the documentation concerning sample collection, testing, and result reporting. New document versions can be released to appropriate staff to electronically sign as proof they have read and understood them. A record of this information can be kept on their training record and is available for audit purposes. Document manager enables QC procedures to be put in place and followed by all staff, and is a key part of implementing 21CFR211 22(d). It can also be part of a competency management process that prevent staff undertaking specific tasks if a specific competency assigned to them is not up to date.

Electronic Approval

Production environments demand that QC checks are performed and formally approved on each batch of product. And yet this is the second most common inspection issue with 518 citations identified. A central theme of a LIMS is that everything you do is logged. Managing the review and approval process of all sample records becomes much simpler using a LIMS. Only authorised personnel may review and approve QC results, and approval can be performed by adding an electronic signature (username and password) to the results approval screen. Once this approval step is done the batch of material (either raw ingredients, or intermediate or final product) may be released from quarantine and used. Any future audit will be able to show who approved the product batch and when, so an accurate record is always kept for the purposes of 21 CFR 211.192.

Test Limits

The third most common FDA issue during inspection, with 458 citations, is that of applying appropriate specifications, standards, sampling plans and test procedures. Test results can be automatically checked within the LIMS against pre-built product rules defining, for instance, maximum and minimum limits outside which the product fails. Statistical process control

(SPC) may also be used across batches of the same product to ascertain process drift, or other key factors, in the production environment. Understanding specification values and applying these rigorously to production and control samples enables a good understanding of what 'good' looks like in terms of production quality.

Lab Execution System
21 CFR 211.100(a) covers the written procedures that ensure that drug products 'do what they say on the tin' (to quote Ronseal). Within the QC laboratory test procedures should always be documented and followed to ensure the same outcome every time. Steps however can easily be missed when under pressure and this is where a laboratory execution system (LES), which many LIMS include, can help. An LES breaks down a written test procedure into a step-by-step approach, ensuring that the laboratory technician does not miss a step. Following procedure, automatically comparing test results to specifications, and ensuring QC laboratory results are never ignored in preference to 'shipping product', will all help drive the number of citations down in this area of GMP.

Stability Studies
Pharmaceuticals have active ingredients that may decay over time. It is therefore important that drugs are subject to a stability study programme to assess the shelf-life of each. The fifth most common citation (with 278) is the absence of a stability study programme. Matrix Stability Study Manager, a LIMS module, supports this complex area of analysis. Study programmes can be set up to define storage conditions and time points and identify when samples should be taken for testing. Study programmes can run for many years improving the knowledge of the drug's stability over time to determine both the storage conditions and the shelf life appropriate for the product.

Instrument Calibration and Maintenance (ICMS)
The QC laboratory bristles with test instruments, each of which needs to be regularly maintained and calibrated. The LIMS instrument calibration and maintenance module allows the laboratory to document and record maintenance and calibration events on each instrument, as well as preventing instruments being used if the events have not been completed as required, or calibration identifies a problem. Demonstrating that analytical instruments are properly maintained and calibrated is a key QC laboratory function, and an area that attracted 259 citations over the 5-year period.

Batch Manager
The batch manufacturing functionality within a LIMS must include batch genealogy. This links together the raw materials, intermediates, and final product batches, allowing a complete view of exactly what is in every final product batch. In addition, if an issue is found with a specific raw material, or intermediate, any final product they have been used in can be identified. This is one way QC labs can comply with 21 CFR 211.188 which is number 7 on our list with 244 citations.

Access Control
21 CFR 211.68(b) demands that records are only created by authorized personnel. LIMS do this by managing access via username and password. In this way only authorized personnel can create or manage records. Different access rights can be allocated to different staff, so that some may only have access to sample registration functionality, for instance, while others have the ability to approve batches for release. In all cases a record is kept of who logged in, along with what records they created or changed, and when.

Training Manager
The training manager module keeps a record of each staff member's education, training, and experience. The LIMS can use this so that only qualified staff can perform certain functions, enter certain results, review and approve results and so forth. This enables tight control in a QC laboratory and ensures procedures are always seen to be followed, which was number 9 in our top 10 GMP issues.

Records and Reports
With 181 citations, the ability for a laboratory to properly record and recall all test data is the last in our top 10 GMP issues. The function of a LIMS is to ensure all test records are complete. For example, during registration the source of the sample, along with its lot number, date sampled, and other relevant details may be taken. Test results can be updated, and new revision saved, but the original result will always remain within the system, and available for inspection (unlike a spreadsheet or paper and pencil). A LIMS ensures the audit and chain of custody functions are available, allowing laboratories to work to, and fulfil, GMP standards.

Summary
LIMS help QC laboratories adopt good manufacturing practice, and ensure that procedures and standards are followed. The above provides examples of how the LIMS will help drive those standards, but there are many more aspects to both Matrix Gemini LIMS, and QC management generally. If you are a QC laboratory in pharma/biopharmaceutical manufacturing, then you should be using a properly implemented and validated LIMS to help drive quality improvement cycles. Remember that "Quality means doing it right when no one is looking".

REFERENCES

1. FDA warning letters https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters
2. FDA data dashboard (data source) https://datadashboard.fda.gov/ora/cd/inspections.htm

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