

# Tracking and Controlling Everything that Affects Quality is the Key to a Quality Management System

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**Abstract:** Every laboratory has a need to track and control the variables that drive the quality of the results. However, each laboratory is unique and what one organization deems to be a critical process to track and control will likely differ from other organizations.

Furthermore, there is more than just the end product or result that needs to be tracked and controlled. All of the intermediate products and resources play a significant role in producing the final product and each of these needs to be included in the LIMS.

At a high level, this article will present ideas and opinions on the following topics in relation to implementing a LIMS process tracking and control system in a laboratory: The difference between tracking and controlling processes; What to track and control in the lab; The "product" of the laboratory; Preventing mistakes in a laboratory; Comprehensive software platform options; The value of seeing a system as opposed to imagining it; The use of barcodes in the laboratory; and an assessment on using the Risk Based Approach in deciding what to include in the tracking system.

**Keywords:** Laboratory information management system, LIMS, quality assurance, quality control, risk based approach, software.

## INTRODUCTION

Laboratories are focused on producing results. Whether in a high throughput screening lab looking for drug leads or a diagnostics lab looking at a specific SNP or biomarker, all lab managers are focused on getting to the end product or result. However, in a laboratory there are many intermediate products that will be produced along the way which will contribute to the quality of the final product or result. To assure the quality of the end products or final results, all of the intermediate products along the way must be tracked and controlled as well. If the laboratory process is viewed as a chain, the results are only as good as its weakest link. While there are some commonalities among laboratories, the variables that each laboratory chooses to track and control will be unique, so each tracking and control LIMS must be unique as well.

## TRACK AND CONTROL

*Tracking* is based on historical events whereas *control* is based on future events. Tracking implies that there is a chain of custody or a complete history of the item being processed. For example, if a laboratory is running a particular assay, tracking means that they are capturing information for each step in the process such as:

- WHO performed the step;
- WHAT was the step that was performed;

- WHEN the step was performed;
- WHERE the step was performed.

In most cases, the quality control information being collected will never be looked at or used again unless there is a problem or a significant discovery. As soon as either of these events happen, the details of how a particular result was achieved become extremely important. Imagine a 384-well plate going through an HTS process. If one of the wells is identified as a hit, all of the information about the history of the compound in that well becomes extremely important. This information could include the complete history of the contents of the well, which reagents were used, the volume of the reagent, incubation time and temperature, the processes the sample went through prior to this assay etc. For the other 383 wells, all of this data is not important and will probably never be viewed. But for the hit, this data is what will be used to try to reproduce the results.

*Control* is future based. In an HTS process laboratory, there are many inputs that need to be controlled to maintain quality. When the technician goes to perform a step on a sample, what will the system allow to happen? Is the reagent qualified? Is the instrument calibrated? Is the sample ready for this step? Is the technician trained on the current SOP? If the technician gets the "go" signal from the LIMS, all of the validation criteria have been met and the assay can proceed. These are the controls that are in place to assure quality. For example, during the morning a laboratory manager releases an update to the SOP for a particular step in the process. Later that afternoon, a technician arrives at work and starts processing samples, unaware that the SOP has been updated. When the technician goes to perform the step, the system

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recognizes the “who” (technician) and the “what” (step) of the process. The LIMS then accesses the training record of the technician and recognizes that they have not read and signed off on the latest SOP for the step they are trying to perform. The technician gets a note on the screen telling them that there has been a change. The note includes a link to the latest SOP so they can read it, sign off that they understand it and then proceed with their work. In this scenario, the system had a control in place to prevent future work from happening until the updated SOP was read. The only way for this to happen is to have a single system controlling all of the inputs that affect quality.

In a regulated environment, auditors and inspectors are looking for this level of detail. They want to know if there is a process in place, if it is being followed, and if it is being recorded. A good rule of thumb when preparing for an audit is: If it isn't recorded, it didn't happen.

### TRACK AND CONTROL EVERYTHING

The word *everything* will mean something different to each laboratory. What one lab deems as the critical inputs that need to be tracked and controlled will vary significantly from other labs. If a lab is forced to track and control inputs that do not contribute to the quality of its results, the system becomes a drag on the lab and can quickly become a source of frustration to workers. On the other hand, if there are critical inputs that are not being tracked and controlled correctly, the quality of the results may be in question. The key is for each lab manager to have the ability to customize what to track and control based upon what they deem to be important. As these requirements evolve and change over time, having the ability to change the system as needed is essential. If changes are slow and costly, once again the LIMS can become a drag on the progress of the organization.

### WHAT IS THE “PRODUCT” OF A LABORATORY?

Every laboratory is tasked with producing results, usually in the form of information that will go toward further research or additional processes. The data produced is the goal or the end product of the laboratory processes. In the case of HTS laboratories, the end product is the identification of “hits” that warrant further analysis and research.

If the laboratory only concerns itself with tracking the assay itself, all of the variables that go into the result are not controlled. For example, in the process of finding the “hits” the sample will likely sit for a time in an incubator, will have one or more reagents added to it and will go through several instruments while being handled by multiple technicians. The instruments, reagents, lab personnel, available inventory and supplies are all resources that help to produce the result. Each of these resources has a life of its own that requires tracking and control.

Let's take a look at the instrument. A qualified, maintained, calibrated instrument that is working correctly and within the specifications of the laboratory is an intermediate product that the lab produces. Certainly, the lab does not center its focus on producing qualified instruments but because the instrument is an important resource in

helping the lab to produce the end product, it is necessary to track and control the instrument as well. The easiest way to do this is to attach a barcode label on the instrument and track all of the things that happen to it. For example, an instrument will be purchased, installed and qualified for use. Every time something happens to the instrument, the worker scans the barcode and records what is being done, creating the history of the instrument. It will need to be calibrated on a regular basis and have maintenance performed periodically. A comprehensive quality control system will include a module to manage the instrument. Each time samples are to be run through the instrument, the worker will scan the barcode on the plate or tube of the sample and will then scan the barcode on the instrument. The software system quickly checks the database to see if the instrument has a current qualification record and to see if the sample is ready for this particular step. If everything is a “go”, the screen prompts the technician to proceed. If the software checks the database and learns that the instrument has an expired calibration record, the screen prompts the worker to use a different instrument or to calibrate the instrument before proceeding. The software system is doing all of the background work and resource validation so the technician can focus on the assay and the science.

Imagine the headache and inefficiency of having to use separate systems to track and control instruments and track and control samples. If these are separate systems, there is no assurance in place that the instrument is ready for service at the time the step is performed. When they are integrated into a single system, quality and efficiency go up and mistakes go down.

Inventory control is another example of what a laboratory produces. It takes a certain amount of inventory for the laboratory to do the work of processing samples. If the inventory is not being tracked and controlled along with the laboratory processes, the lab will constantly find itself running out of critical supplies which will bring sample processing to a halt. The adequate inventory of supplies for the lab becomes an intermediate product that directly affects the timeliness and quality of the lab results or end product. A good quality control system will be seamlessly tied to the inventory control system (or better yet, they will both be part of the same system) and will automatically notify the lab when supplies start to get low.

### DETECTION OF MISTAKES LEADING TO PREVENTION OF MISTAKES

A good system will help a laboratory manager find the root cause of mistakes in the laboratory. A great system will help the lab manager prevent those types of mistakes from happening again. The following figures will illustrate how tracking the intermediate steps leads to the prevention of mistakes.

Fig. (1) shows eleven samples on the left hand side and eleven results on the right side. Each sample will go through a process to produce the result:

- Each sample will be processed by one of three technicians
- Each sample will have one lot of reagent added to it

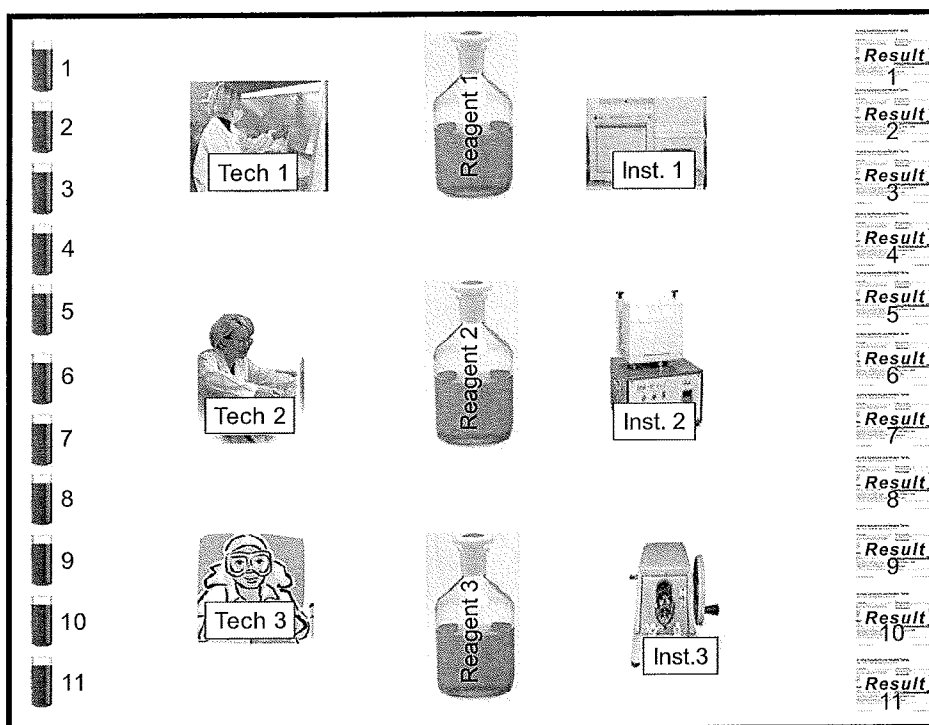


Fig. (1). Layout of a simple process.

- Each sample will then be processed on one of three instruments
  - Reagent 3 is added to the sample
  - The sample is then loaded onto instrument 2 for processing
  - Result 1 is produced
- Fig. (2) shows the path of one sample (sample 1)
- Sample 1 was picked up by technician 2

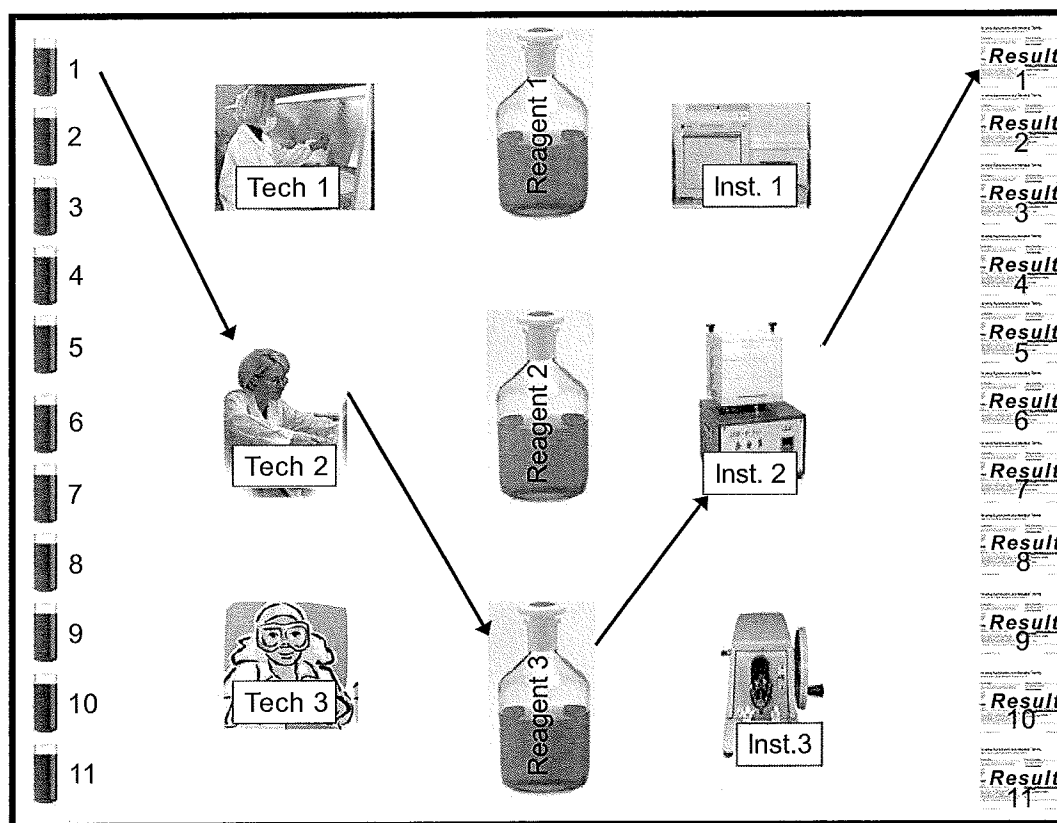


Fig. (2). Workflow of sample 1.

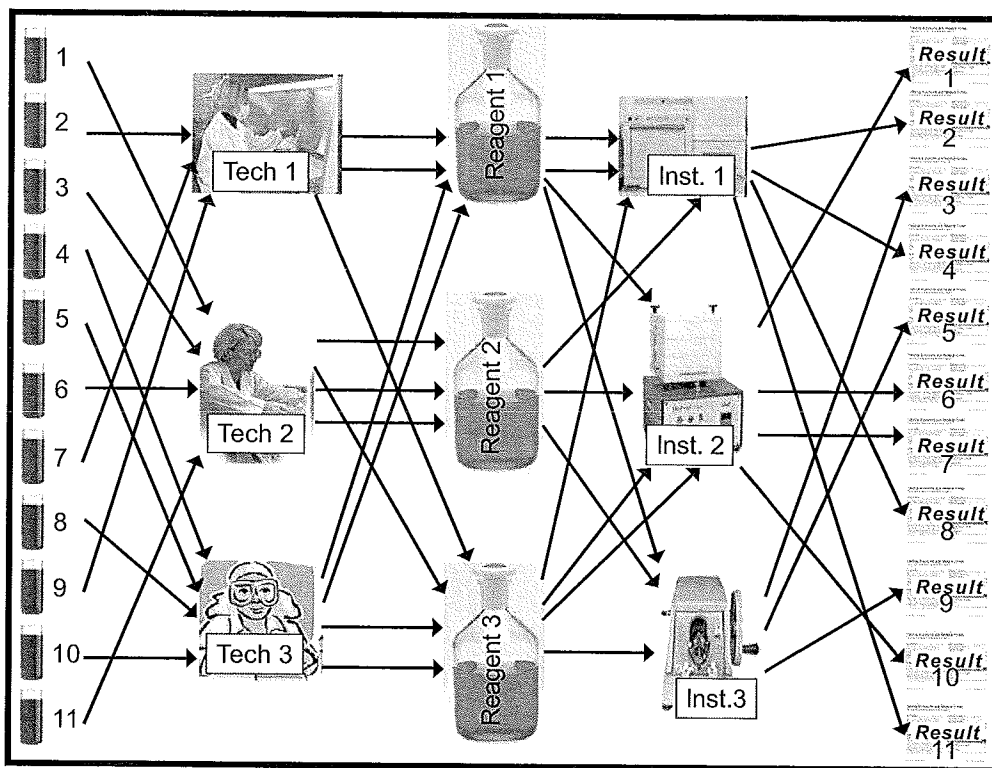


Fig. (3). The workflow of each sample.

The arrowed line represents the unique path or workflow that the sample went through to produce the result.

Fig. (3) shows the workflow path or chain of custody of each of the samples. A lot of data is being accumulated and it starts to become confusing to see the path that each sample has taken. However, databases do an impressive job of

collecting and managing this level of detail. Tracking at this level of detail with spreadsheets is very cumbersome and trying to search for data is even more difficult.

Fig. (4) shows four failed samples which are apparently unrelated.

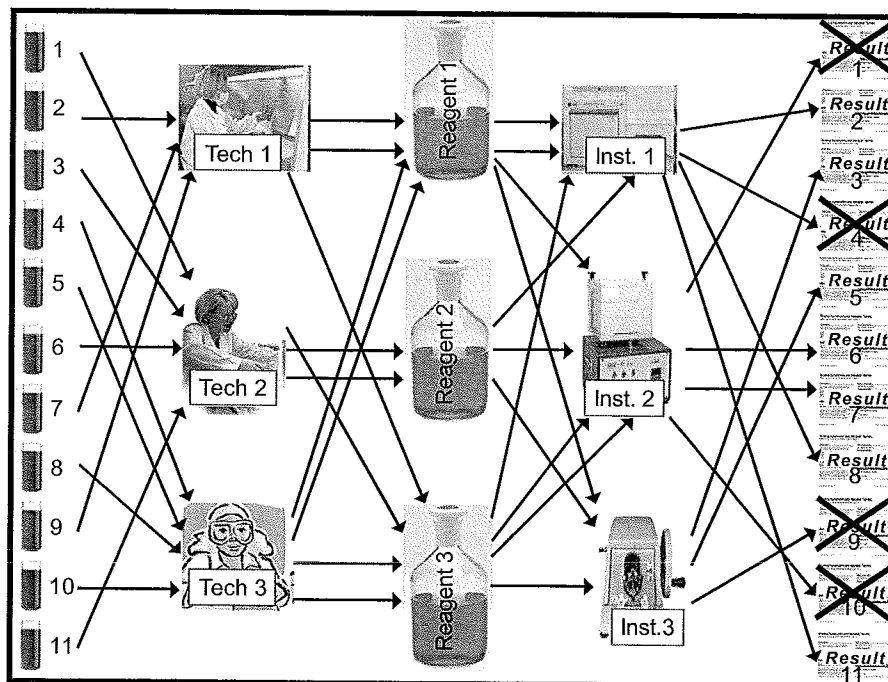


Fig. (4). Four out of eleven samples fail.

- Failed samples are represented by the X on the right column.
- Each of these samples has independently failed
- It is not immediately obvious what the cause of the problem is.

This is where tracking and controlling everything that affects quality becomes important. At this point, the laboratory can query the database to find out what is common about the four failed samples. If the tracking and control system is in place and being followed, the system will know which resources (technicians, reagents and instruments) were used to produce the results of both the failed and the successful samples. Querying the database for this information is a fast and efficient method for getting the information needed to solve the problem quickly.

Fig. (5) shows the workflow history of each of the failed samples that were identified.

- Multiple technicians are involved so it is probably not a technician problem
- All three instruments were used indicating that they are not the source of the problem
- Every sample that has failed had reagent 3 added to it

A system that tracks and controls everything that affects quality would be able to quickly identify the probable source of the problem, in this case, reagent lot 3.

This simple illustration included eleven samples, going through a single process with just three resources. When there are tens of thousands of samples going through

multiple processes with many different resources, the data becomes vast and varied, requiring an automated approach to finding and correcting problems.

Tracking and controlling all of the variables that affect quality led to the ability to quickly find the source of the problem. Once the problem is identified (reagent 3 in our illustration), the policies and procedures for the handling of the resources must be changed. This will prevent the problem from happening again. The lab manager will likely put more controls on how and when reagents are qualified. Once the LIMS tracks and controls at this level of detail, the lab will see a significant increase in the quality of the results.

One laboratory found that their cassette heads would not consistently operate within their quality control limits after going through the autoclave procedure more than 18 times. Upon recognizing this, the lab started putting barcode labels on each cassette head and tracking the life cycles, including how many times they went through the autoclave process. As technicians set up the assay, one of the required fields was to scan the cassette head. The system then checked to see how many autoclave cycles were associated with it and would flag the user if it had reached their threshold of 15. By tracking and controlling this variable, the quality of the lab results increased [1]. This leads to the next critical component of a tracking and control system.

#### FLEXIBLE AND ADAPTABLE PLATFORM

In the previous section, a bad lot of reagent caused a high rate of samples to fail. Now the lab manager needs to correct that problem immediately and permanently. This requires a highly flexible software platform that can quickly respond to

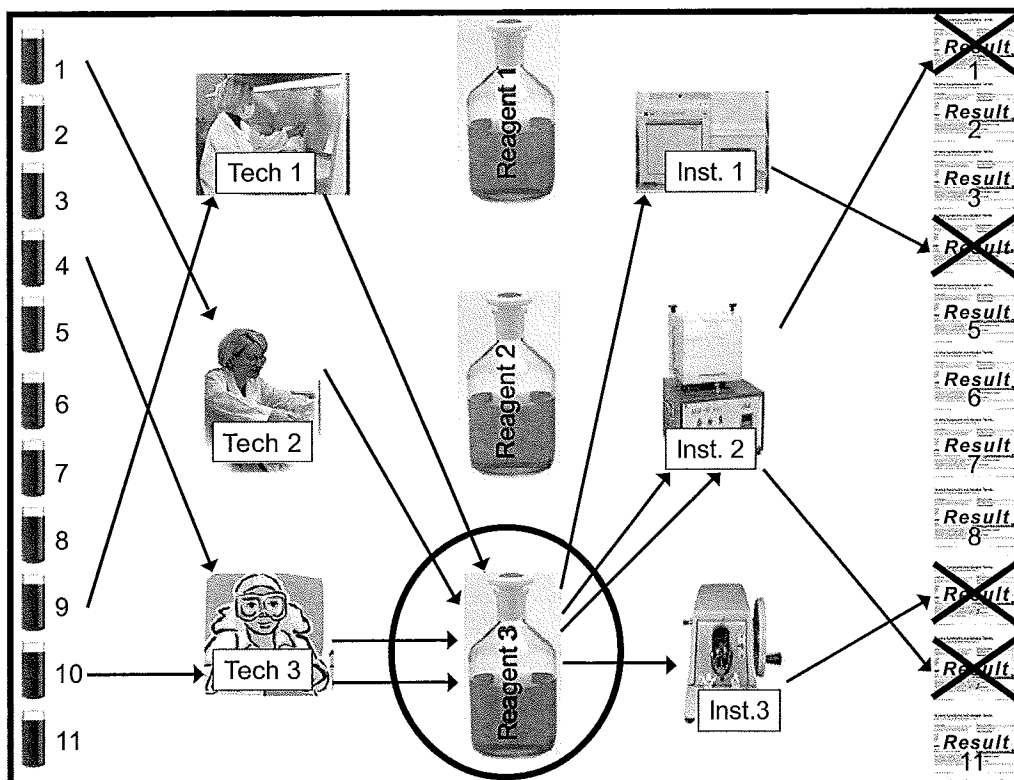


Fig. (5). Finding the source of the problem.

changing needs and requirements. If lab managers identify resources that need to be tracked and controlled for quality purposes but it takes weeks or months for the system to incorporate the changes, it creates a disconnect between what is needed at the bench and what is happening in the system. A good quality management system will empower the lab manager to incorporate tracking and control changes almost on the fly. This way, what is happening at the bench is being mirrored by the system and *vice versa*.

A flexible platform is one that can be continually tweaked and improved on the fly. Over time the system is fine tuned and completely dialed in to the process so it manages every aspect that contributes to the quality of the results. Lab managers who have these types of systems never look at their LIMS as being "done"; rather they look at the LIMS as a dynamic part of the lab that is constantly being enhanced and modified as the lab evolves, grows and changes.

An adaptable characteristic of a platform is the ability to completely change the system when needed. When a completely new assay is being developed or the lab is creating a new division with new science, new equipment and new risk profiles; a quality LIMS will be able to adapt to those new requirements. Many of the same resources from the current laboratory division will likely be used in processing the samples from the new division. Therefore, it makes no sense for a lab to purchase or build a new LIMS. This creates a confusing network of information islands as shown in Fig. (6).

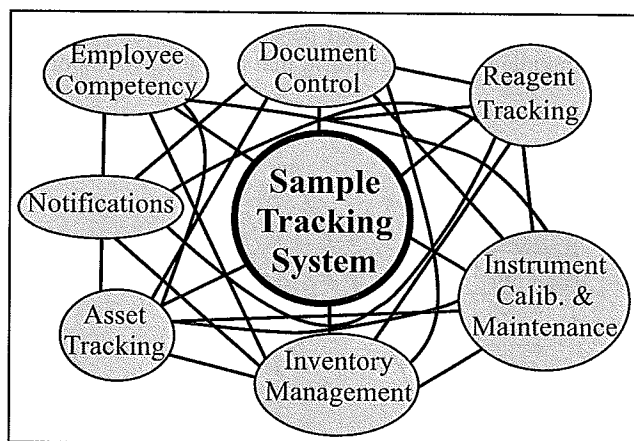


Fig. (6). A Confusing Web of Multiple Systems.

The alternative to the confusing web of islands of information is a single, comprehensive system that resides on a single platform as shown in Fig. (7).

By eliminating most or all of the island systems and consolidating onto a single platform for quality control, the laboratory can make the process improvements needed to increase the quality of the results. Therefore, a best practice is to find a LIMS that can be easily adapted to new processes, including processes that have not yet been identified. For this level of flexibility and adaptability to be achieved, a 100% web-based solution will make the most sense. This can be hosted either locally on the laboratory server or through a service provider. A web hosted option

makes it easier for two labs that are not physically connected to share sample and resource data back and forth.

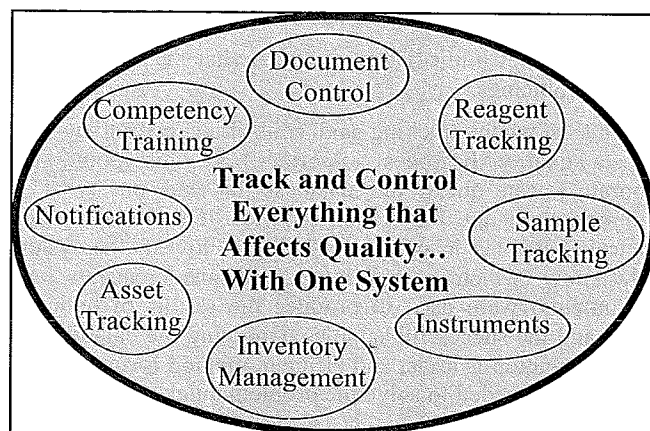


Fig. (7). Tracking quality and control on a single integrated system.

Another factor to consider is whether the LIMS is tied to a specific database or is database independent. The right LIMS will be compatible with any relational database and should be compatible with an existing database being used by the lab.

The LIMS should also have multiple options for connecting to other systems, instruments and other robots. At a minimum, the LIMS should have the options of database integration, an instrument servlet, and file export/import.

### HINDSIGHT VS FORESIGHT

A major worry that lab managers face when implementing a LIMS is whether they have thought of all the parameters and inputs and included those in the specification up front. This causes a lot of extra work pouring over the specification documents and reviewing them several times. All of this work is referred to as foresight.

Foresight is what the laboratory managers think they want before they get their system in place. Hindsight is what the laboratory managers know they need after they have their system in place and start to use it. Only after using it will they be able to definitively say how they really want the system to function. The goal of any LIMS project should be to get to hindsight as quickly as possible. Rather than try to get the perfect system in place up front, the best quality practice is to get a prototype built and have the experts start to use it. Based on the feedback, the developers then work to strengthen the weak areas, add the missing functionality and take out the parts that cost the lab valuable time and get in the way of the work. Many of these things don't become clear until the lab looks at their system with hindsight.

The process of building a system, putting it into the hands of end users, collecting their feedback, and implementing the changes is called the development feedback cycle. The shorter the cycle, the higher the probability of a successful implementation. Another way of looking at this is if it takes 18 months to implement a LIMS, by the time it is implemented, it will solve the problems the lab was having 18 months ago.

## HOW AND WHEN TO USE BARCODES TO AFFECT QUALITY

Laboratories can scarcely automate today without barcodes. Collecting all of the data that is necessary for a complete quality control system is greatly enabled by the use of barcodes. One lab manager was quoted saying, "The best way to improve quality in the lab is to put a barcode on everything in the lab and track it".

The use of barcodes has proliferated because it is both fast and accurate as is shown in Table 1 [2].

**Table 1. Comparison of Data Entry Techniques**

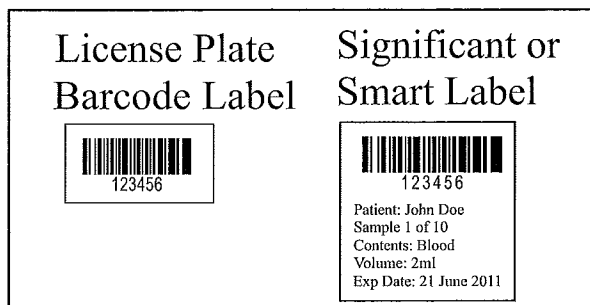
Method	Data Entry Time	Substitution Error Rate
Manual Keyboard	6 Seconds	1 per 300 Characters
Barcode Scanner	0.3 – 2 Seconds	1 per 10 Million+ characters

While barcoding is not the only method of data collection available, it is superior to most because there is no trade-off between speed and accuracy. Equally important is ease of use. Add to that the dramatic performance increases and cost decreases of microprocessors, and the rationale for barcode technology becomes compelling - fast, accurate, easy-to-use, and inexpensive.

While barcodes have been a part of our lives for years, few people actually understand the technology. Barcode scanning is based on a simple principle - Light is reflected in different amounts by different colored surfaces. To decode the information in a barcode, a small spot of light is passed over the bars and spaces *via* a scanning device. This barcode scanner can be a hand-held wand, a fixed beam device, or a moving beam device. The barcode will reflect the spot of light back into the scanner in varying amounts. That is, the dark bars of the barcode will absorb light, while the white spaces will reflect light. These differences in reflectivity are converted into electrical signals by a detector inside the scanner. The signals are converted into binary ones and zeros; these are used in various combinations to stand for specific numbers and letters within the character set of the symbology (barcode language).

Installation of an automated data collection system requires thinking and planning. On the front end, where data will actually be collected, there are two major system issues to be resolved: Part numbering and data availability. We will look at part numbering first.

Is the information included on the barcode label significant to the technician or is it just a sequential number? The answer to that question is a 'fork in the road' in automated data collection. A significant label contains information about the item it identifies. That information could include date, lot, assay, or other relevant data about the item. Non-significant part numbering systems use the 'license plate' approach to identification. That is, they simply provide a unique identifier for the item, and all the relevant data about that item is in a database [3]. (See Fig. 8) The part number, or specimen ID in many laboratories, is simply a specific path into the database where all of the relevant information is stored.



**Fig. (8).** License plate and significant number barcode labels.

There are advantages and limitations to each approach:

### Significant or Smart Labels

- Allows retrieval of information if system is unavailable
- Allows easy segregation by group and sub-group

*BUT*

- Requires on-site printing
- Results in larger labels

### License Plate Labels

- Easy to assign and maintain
- Reduces length of label size
- Changes to specimen require only a change in the database, not a new label
- Destruction of a label only requires the assignment of a new number, not a one-label reprint

*BUT*

- Requires access to database

The other major system issue is data availability. If significant numbering is desired, and the data is available some time prior to the labeling step, pre-printed labels (discussed below) may still be used. If the data is not available until shortly before labeling, on-site printing may be the *only* choice.

Regardless of numbering system chosen, most system designers advocate short identification numbers. Fewer characters to enter means reduced chances of error; shorter barcode messages are easier to scan than long ones.

When selecting what kind of barcodes will be right for the lab it is important to determine what the label will identify and how long it needs to work. Clearly, the performance requirements of a low density dot-matrix label slapped on a shipping carton for one-time scan differ substantially from the performance required of a uniquely-numbered label affixed to a sample tube or plate. In order to choose wisely, take the time to gather all relevant data, and then ask the hard questions. Assess the relative merits of significant part numbering systems, and determine when the data you need to scan will be available, and how costly label failure would be. You'll then be in a position to select the best label alternative for your application.

## RISK BASED APPROACH

The application of a Risk Based Approach (RBA) to quality in a lab setting provides a basis to align available resources, the people, processes and technology, with the organization's goals and any applicable compliance requirements. The FDA has encouraged the use of the RBA since 2003 [4], (as well as other standards or regulatory agencies) and the approach can be used effectively whether an organization is mature or rapidly evolving.

From the RBA perspective, an organization's approach to tracking and control starts with an assessment of the overall risk level of the organization. This establishes the overall risk threshold an organization or laboratory will target, and scale efforts according to high risk products and processes within the organization. In a setting where there are multiple medical products, compounds or components, targeting high risk areas can reduce overall risk, support quality outcomes and improve ROI. A one-size-fits-all approach may appear simple, but may also result in higher costs.

Adopting this methodology for lab environments involved with high throughput screening and/or combinatorial chemistry encourages an organization's upper management to work together with the lab managers to define high-level threats or vulnerabilities and acceptable risk thresholds. Often this is delineated in a risk matrix for users to assess systems or processes as having or not having various vulnerabilities of importance to the organization and any compliance requirements involved. An example being the loss of sample history for lead compounds is unacceptable as is the use of unqualified instrumentation when screening a patient's blood sample.

Having the risk matrix defined, lab managers are empowered to prioritize and make decisions on the level of rigor desired for the tracking and control of all artifacts used by or passed through the lab. Creating an assessment tool such as the example in Fig. (9), for software systems in a lab, can further simplify the decision process. In this example there are high, medium and low risk levels that dictate the scale of rigor (tracking/barcoding, control, documentation and training) required across a spectrum of minimal detail required at level A, to comprehensive for level E outcomes [5]. The processes or systems can also be spread across categories, as in this example there are three categories for the software systems in use.

Risk Classification		Software Category		
		1	2	3
1 Low	A	B	C	
2 Medium	B	C	D	
3 HIGH	C	D	E	

Fig. (9). Risk Assessment Tool.

Using a Risk Based Approach answers the question, "What is the worst thing that can happen if this variable is not tracked and controlled?" To track and control everything that affects quality in the laboratory, the lab manager and the quality experts will appreciate the tools offered by the RBA for assessing the entire process and all of the inputs. The tools can support a multidimensional model when desired, of increasing rigor as complexity, software systems or process categories and business risks increase. Fig. (10), demonstrates increasing documentation rigor and can just as easily address rigor for tracking, control, training, etc.

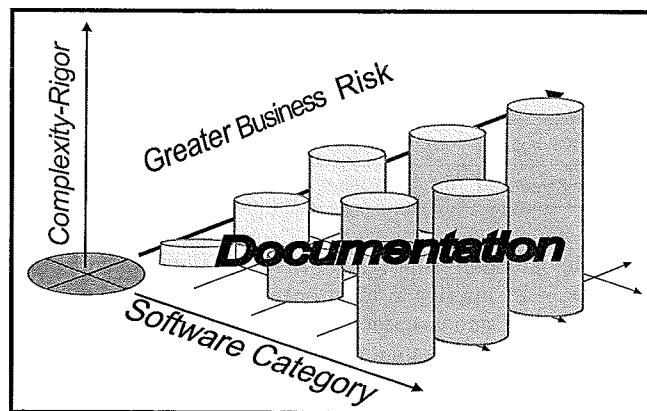


Fig. (10). Multidimensional Scalability Assessment.

Developing a risk matrix and an assessment tool appropriate for the organization's technology, goals, objectives, business and compliance risks will enable an agile lab environment to respond to change with the appropriate levels of rigor; thus supporting quality outcomes. Partnering this process with an adaptable LIMS platform is an effective and efficient combination for a lab manager to rapidly incorporate both Foresight and Hindsight into optimizing lab operations.

## CONCLUSIONS

The business logic for tracking and controlling must come from the scientists and the laboratory process experts. As scientists, process experts and IT professionals work together using the Risk Based Approach to determine what affects quality for the laboratory, they will need a system that will respond to those specifications. Furthermore, that system must also have the ability to respond to the new requirements that will surely come up as the business evolves. Humans will make mistakes. Good systems will help to prevent those mistakes from happening and let lab managers sleep at night.

## ABBREVIATIONS

- HTS = High Throughput Screening
- ID = Identification
- IT = Information Technology
- LIMS = Laboratory Information Management System
- RBA = Risk Based Approach
- ROI = Return on Investment
- SNP = Single Nucleotide Polymorphism
- SOP = Standard Operating Procedure

**CONFLICT OF INTEREST**

Carl Hull is the Vice President of Sales for UNICConnect, which sells the UNIFlow LIMS platform to laboratories.

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