Utilizing Lean Methodology and Information Technology to Improve the Efficiency of Pharmaceutical R&D *

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The topic chosen for discussion today is the study of an area where I had worked, implementing the lean manufacturing methodology. I am not from the pharmaceutical industry and know nothing about Information Technology (IT), but it is useful to discuss how the lean manufacturing concept can be implemented in a pharmaceutical industry engaged in research and development.

In any industry, quality, cost and delivery can be compared to the legs of a three-legged stool. Now, consider some statistics about pharmaceutical industry: It costs about $1.2 billion to develop the drug and it takes approximately ten years, on an average, on its research. The average annual turnover of a drug, which is just introduced in the market, can be assumed as $265,000. A blockbuster drug has annual sales of $1 billion and, generally, less than one percent of drugs that have been introduced in the market can claim sales of value greater than one billion dollars. So, it can be seen as to why it is important to reduce the cycle time and keep the cost down. Hence the pharmaceutical industry faces many challenges. The industry is also vastly different from other industries, having to cater to customers whose expectations are

not uniform. For example, any patient, visiting a hospital, desires the best care, and the best treatment, which naturally costs a lot of money. On the other hand, the insurance companies in the hospital are trying to keep the cost down. So how does the pharmaceutical company balance all of these interests?

Now, from a customer's perspective, it is the system or the processes or the interaction between the processes that delivers the product or the service to the customers. However, all the organizations are structured in the form of silos. One has to somehow break that silo mentality and move into a structured network systems mentality. So, when the pharmaceutical industry and the research and development organizations wanted to be more efficient and reduce the cycle time, they decided to bench mark and took a leaf from the manufacturing industry that had already identified ways to reduce the cycle time by using a system described as 'lean manufacturing' - also known as the Toyota Production System.

Toyota Production System:

In 1950's, Toyota faced bankruptcy and most of the banks, when approached, turned them down. However, one bank agreed to lend them money under two conditions. These two conditions led to the birth of what is known as 'Toyota Production System'. The first condition was that "you cannot build a car unless you already have a customer for it". The second condition was that "you cannot go and buy anything from your suppliers unless you use that product which you buy from your suppliers in the car that is being made for the customer who has already purchased the car".

Just-in-Time Principle:

It was the second condition which led to "Just in time". Why did the banks say that you cannot buy from your suppliers unless it's for the car which is sold? This was because in Japan land costs a lot of money, and hence the inventory cost was very high which was not the case in other countries. In order to save on the inventory cost, 'Just in Time' principle evolved.

The first condition led to cycle time reduction. That was how Toyota internalized all the methodologies in the same manner as to how Ford went about making the cars. Thus Toyota came up with their own methodology that led to Toyota Production System wherein the primary focus was "Cycle Time Reduction" and "Just in Time"

How R&D helps in lean manufacturing concept:

In any Research and Development (R&D) Environment, it is clear that R&D is not only about producing an output, it is also about producing information which helps in taking decisions. Thus, information on a product obtained through R&D also helps to find out not only to deal with information, but also help in making decisions.

So, while looking at R&D there are two success factors. The first one is how does one make that "go-no-go decision" and the second one is, having made that decision, how it0 is flawlessly implemented.

Concept:

The principal concepts of lean technology involve elimination of waste, where waste is nothing but non-value added activities; standardization of the work, which means one should have a set methodology and follow the methodology; elimination of defects which means that if you find defects in your processes, try and eliminate the same; and the last one is to make the value flow, meaning thereby, if there is any constraint, try and balance those activities such that the value is flowing to meet the customer's demand.

Components of 'waste' in pharmaceutical R&D:

Understanding of customers' requirements: Pharmaceutical Industry is governed by lot of regulations and it is necessary to interpret those regulations correctly, have the correct systems in place so that the regulations are complied with.

Under-utilisation of assets and capabilities: A constant watch is to be kept as whether what things are not being used and which are under or over-processed. Are there more procedures to be done on the patients?

Defects: Care must be taken at different stages so as not to overlook any defect or defects that might creep in in the process.

Where does one start?

This brings us to discuss some of the building blocks in a lean operation, which resemble, to a certain extent, to what obtain in a manufacturing organization. The organization starts from standardized work as the base, and only then one can move on to workplace organization. Once this is clear, one proceeds to draw the value stream map, departmental layout and work in teams and then prioritization, the last being different from the manufacturing industry.

(I) Manufacturing industries have batch size reduction, but in an R&D type of an environment discussed here, when only one type of product or project is taken up

at a given time, prioritization assumes importance. Moving up the level is quality of source, and then visualization and then point of view/storage, i.e. keeping the equipment ready.

(II) Next is start up time reduction. This presupposes keeping all things needed before commencing the activity, like the software program or files etc.

(III) Total productivity equipments. In R&D type of organization discussed here, one should be equipped with computers and the needed software available in the best condition.

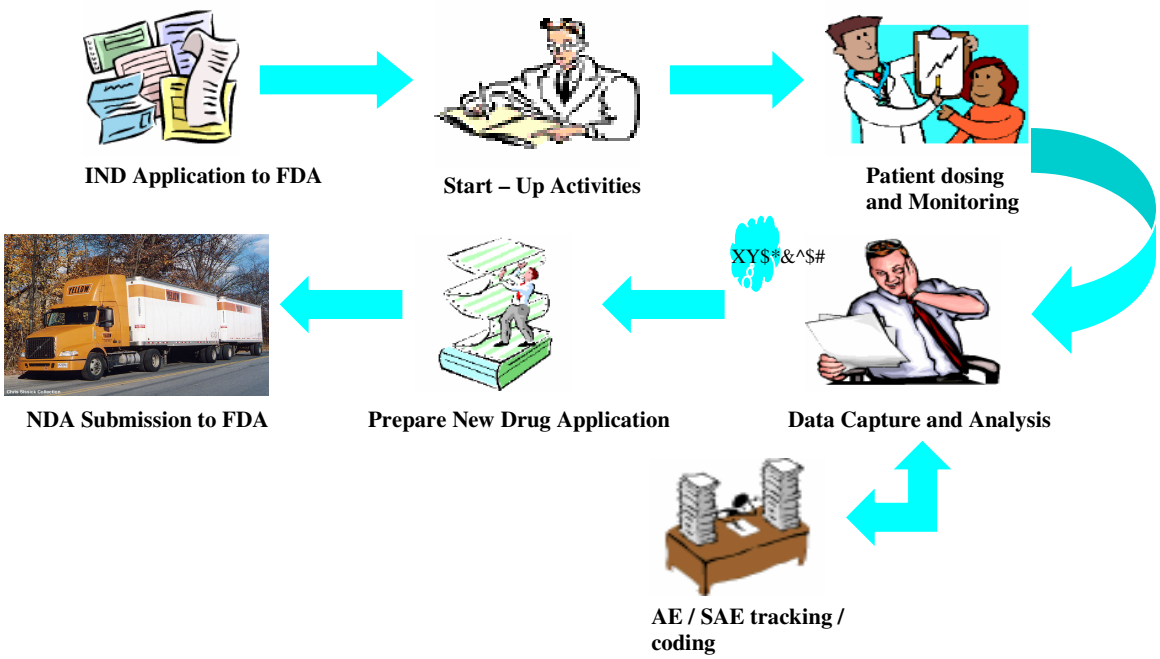
(IV) Last is Process Flow and balancing process activity.

Value stream map: In an organization, getting to the work is a process and the value stream map for this process would look something like this: the alarm clock will ring, starting from getting out of bed, brushing teeth, a shower, get dressed, have breakfast and drive to work. Almost similar will the value stream map be drawn to all the value added activities, steps by step.

In contrast, even after the alarm clock rings, delay in getting up, taking bath, dressing leisurely and rushing to office without breakfast, all constitute non-value added activities in the same process causing longer cycle time. Unless the situation is corrected and the bottleneck removed, the process suffers backlog, resulting in strain on the co-workers.

Application of IT in lean technology:

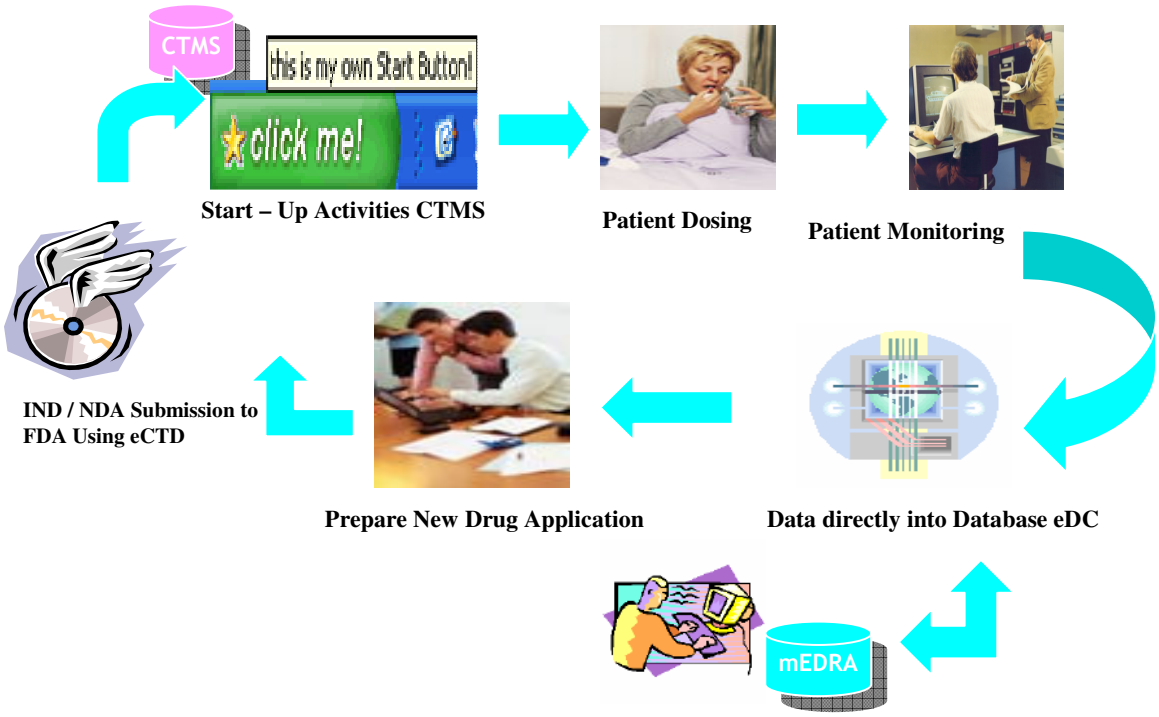
First it needs to be understood how the principles of lean are applied in the R&D type of organization. IT falls under two types. IT can be used to automate existing process, where the existing manual process put into a system to automate the process. This can be explained by means of two examples. One area is automation of the existing process using clinical trial management system and medical coding. The other area is where IT is a trendsetter, that is, where it comes with new methodology and dictates the process. Here, one applies lean after the technology has been put in place and then go back and continue improvement. For example, lean has been applied after development of new methodology in electronic data capture and electronic common technical document, as shown below.



Value stream map

The above is the high level values stream map of how a drug goes in to clinical tray. The activity starts from the point where the drug is being tested in human, but does not cover the value stream map of how the drug is tested before it arrives at this point. Before the drugs are tested on humans, one has to submit an Initial New Drug (IND) application to the food & drug agency (FDA) to seek permission whether the clinical drugs can be transported across state lines or not. Once the application is submitted to the FDA, the company has to undertake startup activities which, inter alia, include identifying the sites for trial of the drug and identifying the number of patients. Once these are completed, the actual dozing starts and the patients are lined up to physically take up the medication. As the patient takes the medication, there would be ongoing visits by monitoring case research associate and it would be his responsibility to make sure to collect all important information about the patient and it is this information that is going to be sent to the organization. An analysis of the information would help the company to ensure the drug is safe and effective. The company can also do some tracking on advance events and serious advance events (AE and SAE). The information obtained from tracking on AE & SAE is printed on a label kept inside the bottle containing the drug, which certifies safety and efficacy of the drug.

It may be observed when one looks at the value stream at the very high level and try finding out where these improvements were put in, one would come to know that IT and lean methodology were used at certain places to bring about improvements.



IND being submitted to FDA

The above diagram points at IND/NDA submission to FDA using eCTD. The IT solution was put there for submitting the application. The start up activities was another location where we put the IT solution. The monitoring was done through the electronic data capture and the electronic data capture AE & SAE coding and tracking was done using medical tracking system and then preparing the new drug application and submission.

Methodology: It would be necessary to discuss about the electronic data capture and the work flow in the electronic table capture. This is before the IT system was put in place - the patient visits the doctor, - the site transcribe all the data into the case report form manually, sometime once a week the monitor shows up, pulls out the case report form, takes a look at the information and send that information over to the organization so data management can enter it into the computer system. And when the data management enters it into the computer system, there follows a paper query process. The organization has pegged the cost of one query as $100 and so the entire process costs a lot of money.

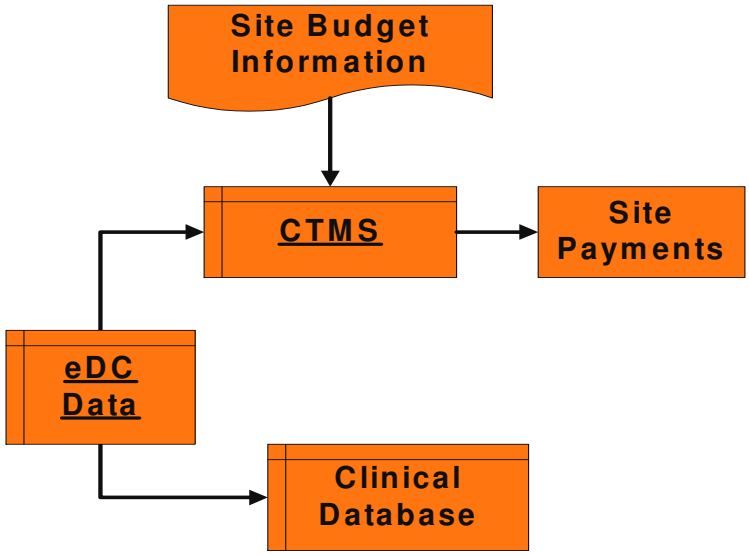
Now IT provides a solution to this particular case. The patient sits before a computer screen, which has inbuilt edits depending on the protocol as to the important data that are to be captured about the patient and the range for those values. The computer has the software

program with inbuilt edit checks and it keeps giving warnings and pop ups in case the physician puts in an apparently abnormal value.

Benefits: A major benefit from the above is that, unlike in the manual process, the entire process is quickened by the use of IT, enabling the safety review happening earlier. This helps in starting the analysis much earlier and, in case the physician is doing some treatment that has been not authorized by protocols, the organization can flag that earlier. As far as the quality of the data and quality of the information is concerned, there is less transcription in the data and so there are fewer errors. And there is definitely a time saving and cost reduction due to the implementation of EDC. The managers are also happy as they need not check the same thing over and over again and make those corrections so they are free to move on to the next work.

The second example discussed here is that of clinical trial management system. In the old method, i.e. the manual method, there was an isolated group with each study group having excel sheets to capture all the information. Now the group had three separate excel spreadsheets from three different studies and the information about the site in the studies did not match, with the result the said method proved to be very inefficient.

In electronic system, an address book is created with the name of the investigator and the information of the investigator in the AMA format, which is the medical association format. And the groups had all the contact information with a database of the protocols that they used in all different studies. So it was very easy then from one central location to just with a click of a button to match it, investigate it and create a site. They could then populate the site with the contact information, essential documents like an investigator curriculum. It could also reuse the same data over and over again. Some of the benefits for the CTMS are single source for maintaining investigator information; it also tracks the essential documents, trip reports, subject enrolment and facilitating budget forecasting. Budget Forecasting is very important because CTMS is one location where they have negotiated contracts with the investigator. The contract stipulates based on the protocol the tests that need to be run on the patient, the contract stipulates how much the investigator will have to be paid – so you have the contract and the test; you can marry these two and you will have a pretty good idea of the money you need to earmark for each investigator.

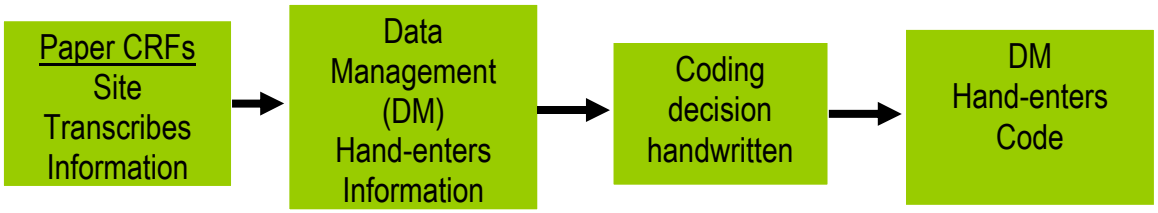


Integration of eDC and CTMS

An additional advantage, by linking up that electronic data capture and the CTMS and the way it was done, was that they had all the information on the electronic data capture form. When the monitor went out to the site and captured that information in terms of what had actually happened to the patient and what kind of test should be done, it was submitted electronically in view of the software program written to link up the CTMS and the electronic data capture. With the availability of all the procedures that were done on the patient and the things agreed on the contract, one can automatically marry these two to pull out an invoice from the investigator. This information is then submitted to the accounting department and be ready to expect to see an invoice of this amount from such and such investigator. So when the invoice came they could easily match up and say whether they were billed correctly or not. By this some of the processing steps became automated, eliminated multiple illustrations in the manual process and an improvement in accuracy and the efficiency of the investigative payment.

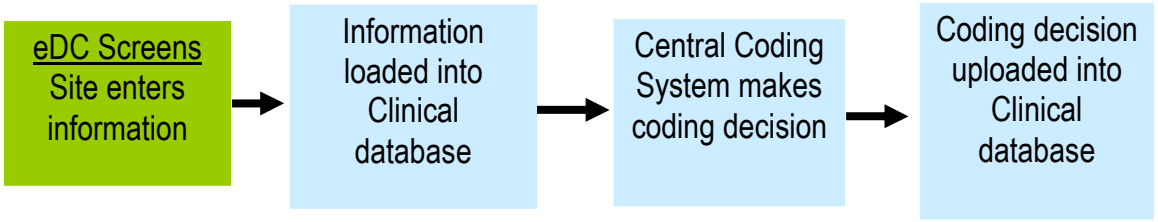
Medical coding: Now let's take a look in an area of medical coding where the system was put up. Medical coding is typically the tool that is used by pharmaceutical industry to identify the safety and efficacy and track all the serious aggressive events. How does it work?

Usually, a patient might call up and say: "After taking your drug, I felt dizzy" or something else. Any such opinion of either the physician or the patient needs to be captured verbatim, and this verbatim term is to be coded for the ease of tracking and trending.



Medical Coding – The Manual Way

The above was the manual process about four years ago, involving two departments – one was a pharma-covigilance department and the other, the data management department. The data management was in the statistics department because it was meant to handle all the data submitted to it, analyze and create reports. This information was coming into the company in two different ways: one through the paper case report form and other from the patient and the physician directly calling in. The two departments were documenting the same information; reconcile what information they were carrying; how it was being coded; and use same terminology so that their analysis things would not end up being flat. There were around sixty people meeting two to three times a week, just to go about to make sure that they are all coding it correctly and, to make matters worse, each department had a different medical dictionary and there were people within each department who were using different version of the dictionary. All this rendered the work too complicated.



Medical Coding after Lean

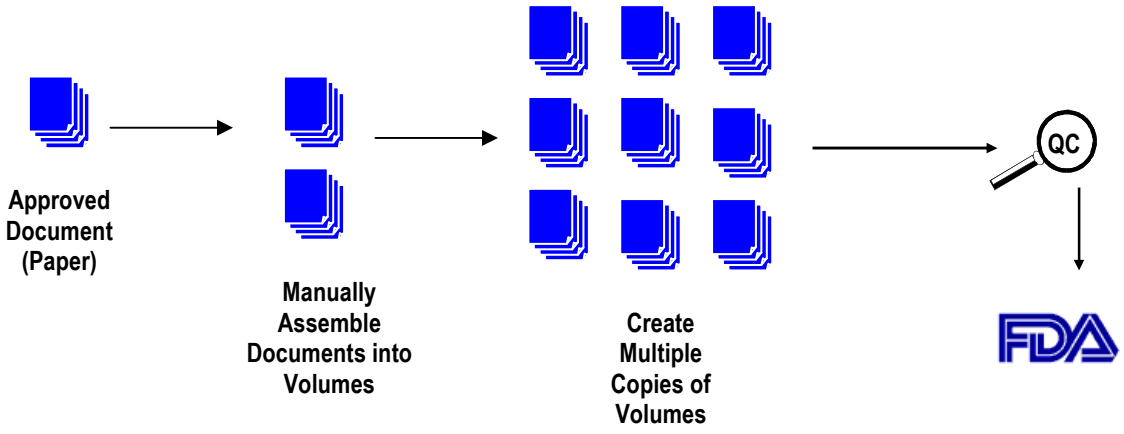
In Medical coding, after a lean, we identified a standard medical dictionary and the system was built in such a way that the dictionary acted like a thesaurus to the verbatim that was given after the conversation between the physician and the patient. Also out of the options it gives, the one you select is given priority over others, when a similar request is raised next time.

Some of the Benefits of medical coding are: 82-85% was automatically coded, a lot of rework eliminated, inconsistent coding eliminated and, of course, tracking and trending made easier.

The last one is an example of an IT-enabled new business process. A new development happened about two years ago, no matter where you are in the world and what drug you are developing, if you submit your application in the ECTD format, you can sell that anywhere in the world. In the past, if you had wanted approval in the United States you had to file according to the FDA, if you wanted approval in Europe, they had their own methodology. All these problems are crossed in the common technological document if you file in the ECTD format and you get approval, then you can market it anywhere.

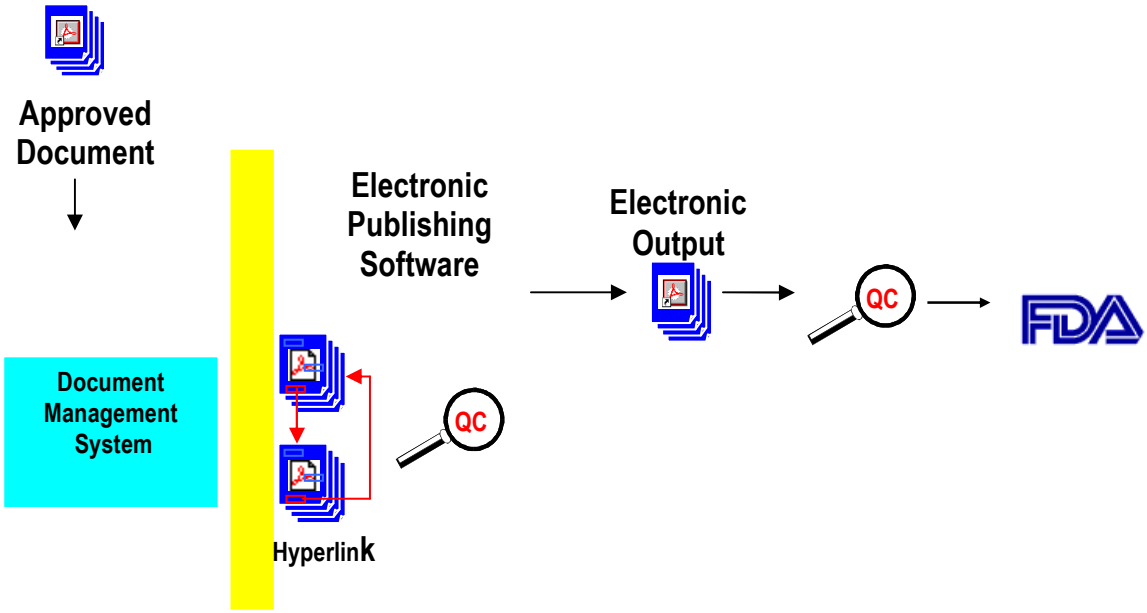
In so far as submission process is concerned, there are essentially two parts, one is the manual part and the other is the electronic part.

Paper Submission Process Before eCTD



Going back three iterations, after all the trails were over in which the statistical departments went in and created all the reports and the physicians looked at it, manual process would work like a proofed document. The proofed document is then manually assembled into volumes, which were then checked and, in case of any problems, the only place to approach was the head of the class! It was thus very labor intensive. Here is a partial automation. What happens is that with help from document management system, you create a document with Electronic Publishing Software. The document now contains a part electronic output and part paper output. The paper output and the electronic output have to be then hyperlinked on the outside, followed by a QC check and then the paper and the electronic outputs have to be matched together and submitted to FTA. If you have a problem at any one of those QC checks location, we have to go back right to the beginning!

Submission Process After eCTD



In the eCTD where it is completely electronic, we have approved document which goes to the document management system and electronic publishing software, hyper-linking and the QC checks are done all at once and submitted to the FTA.

Some of the benefits of it are that it helps with the submission, preparation and standardization across all submission types. The agencies have the ability to search electronically and easily navigate, so that there is no need to give them any paper copy. Life cycle management of submission document, meaning thereby, any historical document that has been submitted to the agencies for this particular drug, could be easily navigable.

Freeze up and wakeups: Just to give you a perspective, a new type of application is typically about 600 thousand pages and as papers that fills up two feral express trucks and, as the result of ECTD, it is only as thick as a pencil box.

Here are some figures that show some improvement time. If you are looking at a study set-up based upon all the lean process and IT, there is about 48.33% reduction. On the other hand, if you are considering the time elapsed between first subject and the last subject enrolled, it was 30.26%. This is because in order to have a closer look, we have to get all the patients enrolled before we can start dosing. Typically in the pharmaceutical industry, what one has is after the last patient has had the last dose, which means a certain amount of time has to elapse to make sure all the information is fitted in and come back to the organization. Once the database is locked, you can't import any more data. That is the data on which analysis has to be done, which gives 11 percent reduction in time. There is a 56% reduction in database release to report approved. There are certain other intangibles in other areas, on the outsourcing strategy if you look at an R&D environment, especially pharmaceutical. Companies

have to rely a lot on other suppliers and vendors to help them to do their work. To achieve the result of freeing of these times, companies get the capacity to bring in some of the things they had outsourced.

Advantages and limitations of Lean Technology:

1. Impact of supplier relationship: There is a better understanding of what the customer's requirements are.
2. You cannot do lean if you don't have open management commitment.
3. One needs to alleviate the fears of the company in accepting Lean manufacturing Technology and assure them know that no one's job is going to be in jeopardy.
4. Lean does not address organizational structure or change management
5. In the R&D type of organization, you have to have a strong IT partnership. A proper discussion with the IT people - both where you are automating a manual process and bringing a new solution in a place.
6. Technology is changing the business process and, in the pharmaceutical industry especially, a highly regulated validation of IT is a must, since developing systems is a costly affair. The question of validation would invite frequent difference of opinion and the governing board should be equipped with reasons about validation.
7. In conclusion, lean and IT do work together. Lean works in a non-manufacturing type of environment given the patience.