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Resource Modelling for the QC Laboratory at XYZ Pharmaceuticals in Southern Africa

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ABSTRACT

Quality control (QC) laboratories are critical components in drug manufacturing and running them efficiently contributes to better, consistent supply of cost-effective quality products, while also and preventing deaths due to untimely delivery or unavailability of medicines. Having a resource modelling tool to estimate resources needed to handle a particular demand in a given system is essential for efficient running of QC laboratory.

This study was done to establish such a model at XYZ Pharmaceuticals. The list of all products manufactured by XYZ Pharmaceuticals Southern Africa was reviewed; and product families for all products were identified. Analysts 'hands on time (HOT) to process one sample of each of the product families was estimated.

The number of analysts required to support the workload at XYZ Pharmaceuticals was calculated using the HOTs for the different product families and the Maslaton's Calculation Model. A baseline resource model was established.

Keywords: hands on time (HOT), quality control (QC) laboratory, Lean Six Sigma, scheduling, planning, modelling

1. INTRODUCTION

Pharmaceutical manufacturers continue to operate in an increasingly competitive environment, contending with issues that run the range from lost revenue from expired patents, ballooning costs for new drug research and development, changes required by new regulations and other compliance mandates and global market pressures to reduce costs and improve quality and delivery (May, 2014).

The quality control (QC) laboratory plays a critical role in pharmaceutical production for both in-process and finished product testing. Laboratories not only monitor and control the quality of incoming APIs (active pharmaceutical ingredients), and other supplies used in the manufacturing process, but QC labs are also instrumental in the batch release process (May, 2014). They also have to follow strict regulatory guidelines (Lopes, Costigliola, Pinto, Vieira, & Sousa, 2018).

QC laboratories (labs) are a critical component in the manufacturing value stream for pharmaceutical products. However, lab environments are unique, as they possess their own special characteristics. They are hybrid, sharing many aspects of both service operations and manufacturing.

QC laboratories are responsible for quality, safety and efficacy of new medicines, and their management is a complex task that involves resource planning and scheduling, analysis prioritization, results documentation, etc. Inefficiencies at the laboratory level may delay obtaining results, negatively affect their quality and can have a major impact on the overall supply chain service level. This situation can be worse in cases where contract manufacturing or testing is done, where the organization has to deal

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with a large number of projects (Costigliola, Ataíde, Vieira & Sousa, 2017).

Significant attention needs to be paid to compliance, GLPs and safety. Equipment is often very expensive, highly sophisticated, extremely sensitive and requires proper operating and maintenance to avoid equipment breakdowns. QC laboratories serve as internal suppliers to the pharmaceutical manufacturing departments, but unlike many service operations, their processes and "products", i.e. timely test results, are mostly intangible and invisible in comparison with those of manufactured goods. (May, 2014).

Finding an optimum balance between staff time and machine time is of utmost importance in the lab, as is standardizing work to ensure that procedures are adhered to. It is common across pharmaceutical companies globally to find laboratory analysts and managers continually struggling with:

- being reactive at all times to the pressure of the workload, unable to pro-actively schedule activities on their terms.
- variable demand and uneven workloads;
- complex scheduling that combines routine testing with special tests and projects;
- large backlogs and missed deadlines, which trigger fast-tracking or expediting of work and further complicate scheduling;
- Individuals who are inflexible and have difficulty working in an environment that changes frequently. (May, 2014)

Such is the case at XYZ Pharmaceuticals, where analysts' schedules are driven by the demand and are always chasing after deadlines and lack real control of the system's pace. The nature of the demand and how it matches with resources has not been broken down and analyzed. Supervisors have been asked many times by management to determine how many analysts they need to match their workload but always have difficulty justifying the numbers they come up with. Therefore, even though operations are not happening in a worst-case scenario, where there is no vision at all, the existing vision is unclear. What is lacking is the visual understanding and the quantification of the demand. Also lacking, is a clear and precise visualization of the demand matches with resources, in addition to finding a better way to effectively manage flow and scheduling.

As a result, steady pressure is on supervisors to improve QC lab operations. In general, the challenges can be described as follows: finding a way to improve capacity and utilization of resources, reducing lead times while increasing reliability and speeding up the authorizations required for compliance, for both production and batch release (May, 2014).

Since problems in the QC laboratory are similar for pharmaceutical companies, many articles have been written on methods to increase efficiencies in the QC laboratory and enable QC management to have better control of the pace of operations. The research generally highlights the importance of being able to frame the problem and identify the causes before formulating solutions.

A management policy, Lean Six Sigma that explores improving the quality of process outputs by analyzing and abolishing the source of defects/errors and reducing variability in manufacturing and business practices is being used widely in QC labs. It is used to reduce the existing errors or mistakes in terms of defects per million (DPM). Furthermore, it improves the quality and efficiency of operational processes. Six Sigma essentially aims to make operations more reliable and accurate through the utilization of statistical methods (Vijayshri, Pranil, Lakhe, Jaju, & Deshmukh, 2017).

Lean Six Sigma (lean) thinking provides useful ways to address the challenge. However, while Lean Six Sigma has been used extensively in many process manufacturing industries, laboratories have lagged behind in applying Lean Six Sigma principles; however, they are starting to catch up. Many of these same principles can work in virtually any laboratory environment, including medical and clinical laboratories, as well as laboratories in other types of chemical manufacturing (Costigliola et al., 2017).

May (2014) highlighted the importance of establishing stability first in the lab processing using the 5s techniques (i.e. sort, set in order, shine, standardize, and sustain). The processes would then be linked in a flow diagram and the workload managed visually (May, 2014). Grovom (2013) highlighted how 5s is a foundation of lean. He emphasized determining needed equipment and procedures using 5s techniques. The same techniques can also be applied to determining needed human resources, i.e. analysts. 5s is capable of valuable improvements in pharmaceutical QC laboratories as demonstrated in other industrial labs. When 5s was rolled out at Roche Carolina QC Lab, it was noted how it could change culture in the laboratory by reducing wasteful habits, while benefiting inefficient and unorganized lab schedules, plans and systems (Grovom, 2013).

It was shown that for lean to be applied effectively in the QC laboratory environment, a good understanding of the lab functions is required. Functions to be considered include the context of the pharmaceutical manufacturing value stream, the work culture in a specific laboratory and company environment, and of how lean is applied in both manufacturing and service environments. When used effectively, lean principles can yield enormous productivity improvements in QC labs, improvements that are sorely needed in the current global pharmaceutical environment (May, 2014).

A project to test the effectiveness of lean principles was conducted at a QC laboratory of a global manufacturing company Pfizer, in Puurs, Belgium. Of note, their methodology showed that to conduct a study in the lab, it was not necessary to perform time-consuming studies on all products. Instead, a few products could be selected and the data could be extrapolated to make a model that could be used at different sites. The lab conducted inventory of only eight high-volume products using Kaizen principles to define, measure, analyze, improve and control methodology to analyze its value stream. They recognized that throughput improvements for the eight high‐volume products they had used were also applicable to the remaining products (DeWit, 2011).

Costigliola et al. (2017) perfomed a study where the main objectives were to come up with a standard model to measure performance of a QC laboratory. Information from the model then acted as a support tool for planning, scheduling and decision-making. He realized that all the stakeholders of a QC laboratory would primarily want to be able to estimate equipment and labour utilization, in addition to time needed to estimate an analysis. Initially, he had to understand the flow of products and information in the system. A work measurement and time study was then done over a period of one month by completing manual forms to estimate time taken for sample preparation, system setup, equipment cleaning and analysis data processing. Equipment hands-on tasks were separated from the hands-off tasks. The critical metrics in the study were throughput, equipment usage rate and employee utilization (Costigliola et al., 2017).

Consultants from Tefen management indicated that a pharmaceutical QC laboratory would be more efficient by making the system lean through the following processes: identifying the value stream, gap analysis, elimination of waste, planning and control and, finally, continuous improvement (Tefen, n.d.) Rapid Micro Biosystems also recommended a similar approach starting with mapping out the value system, eliminating waste and improving the process (Rapid Micro Biosystems, 2014).

Harte (2018) initially encouraged establishing the lean goals by doing pareto analysis to identify products contributing to much of the workload and value stream maps. Lab performance was measured and cycle time was identified as an important metric. After analyzing the data, ways of improving performance were then identified (Harte, 2018).

According to Schäfer (2004), workflows needed to be identified first before engaging automated systems, which made scheduling easier. Maslaton (2012b) agreed that automating the schedule allowed the supervisor more time for other tasks that his/her role calls for, such as managing investigations, conducting audit trail review, leading root cause analyses, training the analysts, etc. Scheduling is also important in the laboratory to ensure efficiency. Scheduling is often done and left to the supervisors ’experience. Laboratory information management systems (LIMS) used by pharmaceutical companies only track the analyses performed and lack some features (i.e. information on processing times, work flow) essential for planning, scheduling and stock management. Advances in informatics, data analysis and knowledge management made industries aware of the power of information. This information can be organized and generate knowledge to improve the quality of the services and manufacturing processes. As a result, informatics is often being incorporated in the industrial setting. Industrial informatics represents an important field of study.Informatics is now not only related to Information Technology (IT) services and infrastructure, but is also used to design, simulate, and model manufacturing processes. (Costigliola et al., 2017).

The importance of resource planning in QC labs to meet both capacity and compliance is well recognized. However, Maslaton (2012b) focused on lab scheduling as the single most important process in the QC lab since scheduling contributes to all aspect of lab operation efficiency. He felt scheduling was the single most important process in the QC labs, as it contributes to all aspects of the lab operation efficiency. Most of the labs today are using whiteboard and Microsoft Excel-based tools, while using LIMS to define the assignments. Yet these are still primarily manual scheduling techniques or communication methods that are time consuming, especially for supervisors. Lean labs initiatives, as written by other writers previously mentioned, have helped simplify the lab scheduling process, but do not offer a robust and computerized scheduling solution. As a result, lab scheduling heavily relies on the

supervisor knowledge and experience to manage the schedule of his/her team (Maslaton, 2012b). For this reason, Westgard (1996) found it necessary for QC managers to continuously improve their analytical quality management skills.

Alternatively, De Wit (2011) realized that scheduling was more effective and successful if analyst teams were allowed to also participate in planning, scheduling and organizing their individual workflows. They can then operate as if they're running their own business by scheduling their work. Analysts know what is coming in and are able to organize workflow without the involvement of a supervisor. As teams, they will be able to discuss, review and rectify issues (DeWit, 2011).

Resource scheduling is the strategic level for QC operations, while resource modelling is the first step in planning. Creating yearly budgets can be stressful. There will be pressure to cut buying, costs and reducing staff while improvements in service levels will still be expected. That is when Lean Six Sigma approaches fall short due to complexities of the lab. Laboratory managers face the challenges of building a team comprised of the right number of analysts and ensuring that the available equipment is sufficient to process incoming samples within reasonable turnaround times (Lopes et al., 2018). Labour is the single largest expense in the QC lab, as the analysts and chemists are relatively highly paid compared to the manufacturing operators. Therefore, it would be beneficial to have an advanced modelling tool to accurately project the number of people needed to support the business based on a given forecast (Maslaton, 2012a). Too many analysts will increase costs leading to less funds available to invest in other quality activities and more expensive drugs. On the other hand, too few analysts lead to increase in overtime costs, stress, inefficiencies and inability to consistently deliver drugs to patients in a timely manner.

In 1984, a computer simulation model based on queueing theory was designed by quality control laboratories, demonstrating that the queuing theory is applicable to existing laboratory organisations. Descriptions of the sample input and the existing work capacity of the laboratory, along with the relationships between batch intake and batch processing of samples, were the critical parameters.

Through a number of simulation experiments, it was demonstrated that investigating organizational features can lead to enhanced performance with an increased yield of analytical information (Janse & Kateman, 1984)

Klaessens et. al. (1988) were one of the early research collaborations to establish a model for the QC lab. They presented a decision support system, which e=they called LABGEN, by means of digital simulation. The system constructed simulation models of laboratory organizations by combining historical data with a rule-based framework compiled from expert knowledge to derive, test and compare laboratory organization structures in an interactive manner (Klaessens et al., 1988).

Ruiz-Torres et al. (2012) modelled a software prototype to address the complex scheduling problems, which was faced in a pharmaceutical industry QC lab setting, with implemented solution algorithms. Focusing mainly on the pharmaceutical industry, their problem dealt with assigning jobs to analysts as part of the quality control phase in order to minimise the total turnaround time and the number of tasks not meeting a required timeline. Considerations included overlapping tests, test batching, overlapping tests and resource assignments constrained by test specific capability requirements. It was noted that similar tasks could be put in a batch. However, batch sizes would differ depending on the product-test type combination. This marked a significant difference from previous literature in batching parallel machines (Ruiz-Torres et al., 2012).

Realizing that even though a good planning or scheduling system may be put into place, analyst competency may hinder their success. Ruiz-Torres et al. (2017) conducted another study on assignment of technicians to quality control tests in QC lab of the pharmaceutical manufacturing environment. The problem focused on constraints related to the capabilities of the analysts/ technicians, as well as various criteria related to efficiency, customer service and worker satisfaction. An analyst/technician satisfaction metric and a heuristic were utilized to maximize this measure (Ruiz-Torres et al., 2017).

Lopes et. al, building on Maslaton's research, realized that the lab resources, including both analysts and equipment, required consideration as samples of several types had to be tested. These samples included raw materials, intermediates and final products, in-process control samples, cleaning validation samples and stability samples, among others. The different samples could be categorized into different priority degrees (Lopes et.al., 2018).

Lopes et al. structured regime fails to capitalize on possible benefits that a free-for-all approach could entail. This was based on the understanding that the pool of resources could theoretically be shared between branches, as the analysts share the same qualifications, certifications and competences thus

can operate contiguously under proprietary resource allocation policies. They built a simulation model of a pharmaceutical QC lab to be employed as a benchmarking platform to estimate the performance of a new facility under alternative governance models.

Lopes et al.'s approach was devised to assess the impact of (1) different branches, (2) different analyst schedule configurations and (3) high-level sample allocation and scheduling policies on system performance under the two governance models (structured vs. free-for-all). The Discrete Event Systems (Cassandras & Lafortune, 2009) was then used as the methodology of choice to model quality control laboratories for simulation purposes. The discrete event simulation paradigm was implemented in modern commercial software that was based on the definition of entities that flowed through the system along the steps of an underlying logic framework. Under that agent-based structure, and taking QC laboratories into context, samples were modelled as entities, while equipment and analysts were treated as resources (Lopes et al., 2018).

Schäfer (2004) agreed with many researchers on the importance of scheduling and planning. He highlighted that the different modeling tools researchers were establishing needed to rely on concepts building a consistent framework. Components of the different modeling tools included samples, devices, sensors, results, database systems etc, He, therefore, defined a set of terms and definitions used in a dynamic scheduling environment. In detail, he described the entities, including their functionality, and attributes, as well as their logical and physical interactions. Concepts such as functional libraries, dynamic execution, workflows with activities and constraints and hidden transport were also described. He did not leave out calibration, maintenance, error management and discussion of how the entities interacted with the different components in the scheduling systems (Schäfer, 2004).

According to Maslaton (2012a), the key to imodelling in QC was simplifying the lab's complexity, while maintaining the desired level of accuracy. However, though it is tempting to collect 12 months data via time studies, this trap should be avoided as it is time-consuming yet not beneficial.

The aim of this study, in the QC lab at XYZ Pharmaceuticals, was to demonstrate whether an efficient resource modelling tool can be developed in a shorter period.

Table 1. Products Manufactured by XYZ.

TYPES OF PRODUCTS MANUCTURED BY XYZ
Antibiotics
Antitubercular
Antifungals
Analgesics/Antipyretics
NSAIDs
Xanthine Oxidase Inhibitors
Antihistamines
Antiamoebics
Diuretics
Antacids
Anti-ulcer
Antiepileptics
Antivirals
Cough and Cold Remedies
Antidiabetics
Antivirals

Table 1 shows the different categories of medicines manufactured by XYZ Pharmaceuticals.

2. METHODS

The following methodology, to come up with a resource modelling tool for the QC lab at XYZ Pharmaceuticals, was implemented:

A. Three main product families were identified:

1. Reviewed updated product list

2. Defined product families based on similarities in testing

B. Bills of tests for each product family were generated.

1. Test procedures of random 10 products in each family were reviewed.

2. Bills of tests for each family that included all tests applicable to it were compiled.

C. Forms for each family with bills of tests were created and issued to analysts.

D. For a period of 30 days, the Chief Chemist who is the supervisor, would give analysts a form for the family type of sample he would have issued to them for testing.

E. Analysts filled in:

- the hands on times to test samples of products from the different families.

This included times to do each test as per the product's pharmacopoeial specifications. Average times for each test/activity were determined.

F. Total hands on time (HOT_T) for each family was determined by adding the average times taken to conduct all tests such as. hardness test, disintegration test etc, of the product representing the family, as per its pharmacopoeial specifications. Overall total hands on time ($OHOT_T$) in a year was calculated by multiplying factored HOT_T of the different product families by the average batches manufactured annually based on historical data. The factors were derived from dividing the number of products in a particular family by the total of the company's product portfolio.

G. The total number of analysts required to handle the current workload was calculated using Maslaton's model (Maslaton, 2012). The following assumptions and rules were taken into consideration (see Table 2).

Table 2: Maslaton's Model Assumptions

Key Assumption – On average, 30% of analyst time is spent on non-testing activities such as data monitoring/trending, calibrations, glassware cleaning, instrument troubleshooting, collecting reference standards, etc.
Other assumptions – two weeks plant shut down, three weeks of vacation and leave days, one-week public holidays, six weeks spent on non-testing activities (i.e. calibration, collecting reagents, investigation etc.)

3. RESULTS AND DISCUSSION

RESULTS

Table 3: Product Families

IDENTIFIED PRODUCT FAMILIES	
Tablets/Capsules	- Family A
Syrups/Suspensions	- Family B
Creams/Ointments	- Family C

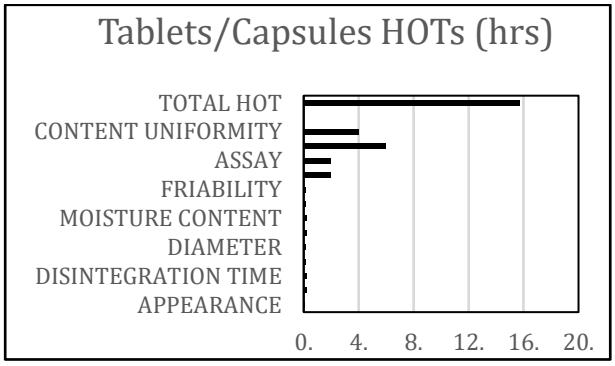
A total of 39 finished product samples was tested during the period under the study. 16 were in family A, 13 in family B and ten in family C.

FAMILY A

Table 4: Tablets/Capsules HOTs (Hours) – Hands on time calculated for measuring qualities of Tablets/Capsules.

Test	**HOT**
APPEARANCE	0.083
IDENTIFICATION	0.25
DISINTEGRATION TIME	0.25
THICKNESS	0.167
DIAMETER	0.167
UNIFORMITY OF WEIGHT	0.2
MOISTURE CONTENT	0.25
HARDNESS	0.167
FRIABILITY	0.167
DISSOLUTION	2
ASSAY	2
RELATED SUBSTANCES	6
CONTENT UNIFORMITY	4
TOTAL HOT	15.701

Fig 1: Family A HOTs

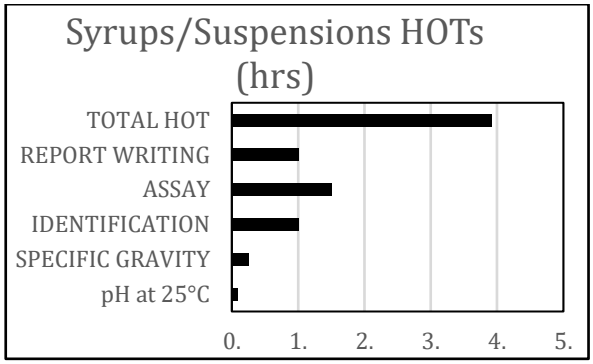


FAMILY B

Table 5: Syrups/Suspensions HOTs (Hours)

APPEARANCE	0.083
pH at 25°C	0.083
SPECIFIC GRAVITY	0.25
IDENTIFICATION	1
ASSAY	1.5
REPORT WRITING	1
TOTAL HOT	3.916

Fig 2: Family B HOTs

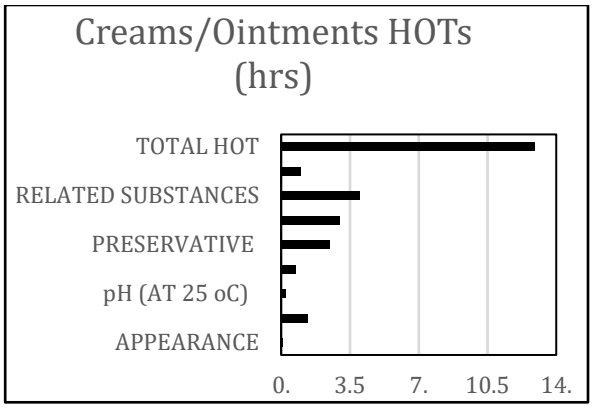


FAMILY C

Table 6: Creams/Ointments HOTs (Hours)

APPEARANCE	0.083
IDENTIFICATION	1.33
pH (AT 25 °C)	0.25
SPREADABILITY	0.75
PRESERVATIVE	2.5
ASSAY	3
RELATED SUBSTANCES	4
REPORT WRITING	1
TOTAL HOT	12.913

Fig 3: Family C HOTs



SUMMARIES

Table 7 –Total Hands on Time for the identified three product families

PRODUCT FAMILY	**HOT_T (HOURS)**
TABLETS AND CAPSULES	15.7
SYRUPS AND SUSPENSIONS	3.92
CREAMS AND OINTMENTS	12.91

Fig 4: Comparison of families Total HOTs

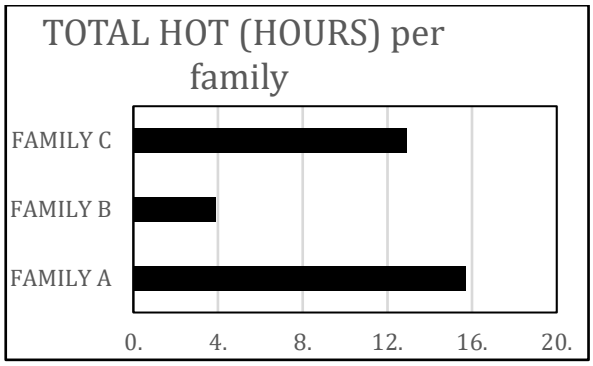
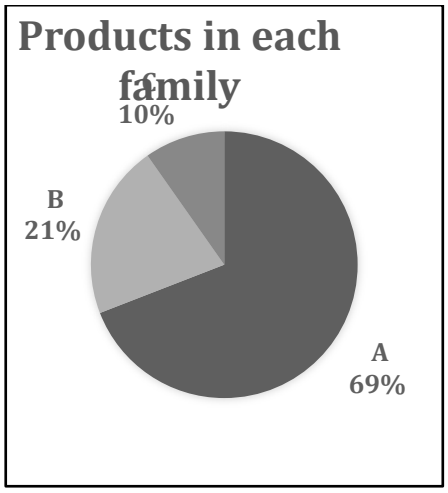


Table 8 – Number of products in each family

PRODUCT TYPE	**NO. OF PRODUCTS**	**FACTOR**
FAMILY A	85	0.691057
FAMILY B	26	0.211382
FAMILY C	12	0.097561
TOTAL	123	1

Fig 5: Number of products in each family



THE CALCULATION MODEL

Fig 6: Calculation Model

CALCULATION MODEL
52 weeks * 43.75 hours (8.75 hours per day excluding breaks * 5 days a week) – 12 weeks (analysts unavailable for testing) * 43.75 = **1750 hours** Overall Hands on Time ($OHOT_T$) for one year = ((0.69*15.7) + (0.2*3.92) + (0.11*12.91))*500 (batches manufactured per year) = **6473.6 hours** Analysts required for finished products bench testing = ($OHOT_T$) per period / Total working time per period = 6473.6 hours / 1750 hours = 4.81 i.e. **5 analysts**

Using the HOTs of the different families, product type factors presented in Table 7 and indicated assumptions, the number of analysts required for routine testing of finished products samples was found to be five.

DISCUSSION

Based on data analysis using data limited to 30 days, this study showed that five analysts are required for bench testing of finished product for the QC demand at XYZ Pharmaceuticals. It would be useful for the QC team of XYZ Pharmaceuticals to continue the study by comparing data collected in the previous three to six months to fully validate the model. The samples and their type factors will be input to the model as forecast and running calculation will give the required number of analysts for the period. If the result matches within +/- 10% to the actual number of resources (i.e. analysts who tested the samples in those periods), the model can be adopted as is. Thus, the lab resources can be declared successfully modelled. It is however, important to factor vacations, overtime, etc. during the periods by adding or subtracting. For instance, if 15% overtime was experienced, resources should be normalised by the same factor (Maslaton, 2012).

If the results are found to be too high, it may mean estimates were too relaxed maybe HOTs for example, or certain activities were double-counted therefore review and an investigation will be necessary. On the contrary, extreme differences; for example if a result of 30 analysts was found from the calculation, and yet in reality 60 analysts had done the work in the chosen period, may mean estimates were too aggressive or some work was missed (Maslaton, 2012).

Once results are established within -/+ 10%, this can be the baseline model. If a company is still interested in conducting full-time studies, they can move forward since grouping and forecast would have been done, focusing on bigger issues such as the highest contributing tests to overall staffing/instrument requirements (Maslaton, 2012).

It will be normal to question the benefits from such a model, considering complexities of the lab and significant effort that would be required to build a resource model tool other than estimating number of analysts or instruments in the lab. There are many other opportunities for improvement that can be used to refine strategies and accustomed operating models, such as:

- identify tests with most HOT/FTE;
- identify desired campaign size method/product;
- identify ROI for projects leveraging the standards that were collected for scheduling, costing and efficiency calculation;
- define training road map based on HOTs for each method;
- establish campaign size for analyst;

- through the estimates for given periods, re-prioritize projects in the lab to meet the desired service level for estimated demand;
- use Lean and Six Sigma to reduce HOTs;
- limit vacations during certain periods etc.;
- refine KPIs (Maslaton, 2012).

4. CONCLUSION

This model is important for companies as it helps them determine the human resources they require to efficiently operate a QC laboratory, in a short period. Time and resources that would otherwise be wasted on conducting are saved. The model can also be easily implemented.

5. RECOMMENDATIONS FOR NEXT STEPS

The study will be benchmarked by another of XYZ's R&D QC Laboratory as one of the validation tools. Other pharmaceutical QC laboratories are encouraged to benchmark this study to validate and improve the model internationally. This would strengthen the case study as a template that can be used confidently by other QC laboratories.

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