

Quality Control and Compliance in a Regulated Bioanalytical Laboratory-An Incessant Journey

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Abstract: *Basic Science and Regulatory considerations, with 'quality' as the focal point are two vital components of Regulated bioanalysis (RegBio). With the advancement in scientific practices through continuous learning, RegBio has progressed significantly in the past two decades. At the same time, technological advancements and new regulatory requirements have propelled local and international regulatory agencies to bring about constructive improvements to their regulatory guidance and other relevant documents. Thus, the dynamism of RegBio demands not only sound scientific knowledge but also correct understanding of regulatory aspects. The conceptualization, creation and implementation of an appropriate 'Quality Management System (QMS)' for a bioanalytical lab necessitate focussed and sustained efforts from the doers (analysts, laboratory professionals), quality control (QC)/quality assurance (QA) personnel as well as the management (leadership). With inference to decades of globalized practices and hands on experience, it is clearly understood that 'Quality' is a culture-driven phenomena, and needs to be inculcated in professionals and incorporated in the working culture of an organization at the very onset. This article focuses on the role of major stake holders of 'Quality Management System' for quality control and compliance in regulated bioanalysis, especially from India's perspective.*

Keywords: *Quality management system, Regulated bioanalysis, Management, Quality controller, Doers, Compliance.*

INTRODUCTION

In order to understand the 'Quality' perspective of RegBio, it can be conveniently divided into two eras; i) Pre-regulations era and ii) Post-regulations era. Pre-regulation era can be distinguished by relevant activities and developments prior to 1990s i.e. American Association of Pharmaceutical Scientists (AAPS)/Food and Drug Administration (FDA) workshops and subsequent reports thereof [1]. As such there were no mandatory guidelines for the conduct of bioanalysis in pre-regulation era, and often sponsors used to provide and enforce their own set of acceptance criteria to evaluate the basic method validation parameters. Post-regulation era started when renowned bioanalytical experts met in an international workshop on bioanalysis in Crystal City (CC), Arlington, VA in 1990. The outcome of the first CC workshop provided a solid foundation to develop the first report on the procedures and requirements for bioanalytical method validation (BMV) and study sample analysis [2]. After nearly a decade, the outcome of the second CC conference [3] led to the release of the first regulatory guidance by US FDA guidance in May 2001 [4]. This provided the bioanalytical community a sound tool to execute their day to day job [5].

From there on, the last decade has witnessed a significant and notable progress in RegBio due to better understanding of bioanalytical science, allied sciences and technological advancements. Excellent scientific progress has been made by overcoming recurring challenges in bioanalysis like speed,

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specificity and sensitivity. With the release of three major regulatory guidelines on BMV e.g. European Medicines Agency (EMA), 2011 [6], Brazilian Health Surveillance Agency (ANVISA), 2012 [7] and draft USFDA, 2013 [8] in the last 5-6 years there is a tremendous interest in RegBio. Additionally, International Conference on Harmonization (ICH) quality guidelines for the conduct of stability studies and defining thresholds for impurities testing based on Good Manufacturing Practice (GMP) risk management have ensured continuous improvement in pharmaceutical quality system [9]. In the current economic scenario, the field of bioanalysis has become global and with several guidance documents there is an additional burden on bio analysts with insignificant value addition to the quality, conduct or data of bioanalysis [10]. Thus, like other counterparts, the Indian bioanalytical community in the Contract Research Organizations (CROs) and the Pharma Industry too realized the demand for global harmonization of bioanalytical guidance to complement globalized bioanalytical practices from the practitioners as well as the regulators.

Role of Quality Control and Compliance in RegBio

The Indian pharmaceutical industry has been following international standards of bioanalysis and related regulatory guidance for quite some time as they target highly regulated global market. Adhering to applicable regulatory guidance ensures high quality and uniformity of bioanalytical data submitted to targeted regulatory agency; nevertheless, it is worthwhile to discuss 'quality' attributes in bioanalysis. It is very important to ponder upon the fact that whether the term 'quality' signifies the same objectivity to the practitioners and internal regulators in the Indian scenario. Apparently there is a big difference in the mindset and understanding between the bioanalytical practitioners and the regulators. From the regulators point of view, quality implies direct compliance to their set of myriad requirements, while the bioanalytical practitioners believe in accomplishing the task based on targeted regulatory guidance by adopting current bioanalytical practices. Certain key issues like matrix effect and analyte stability in biological matrices are an integral part of method development and have to be systematically evaluated and documented. This requires tremendous efforts and scientific inputs on the part of practitioners to meet the expectations of global partners. Unfortunately, the Indian regulatory agencies could not keep pace with the continued advancements in science, technology, international regulations and best bioanalytical practices. This has inevitably led to a decline in quality science, industry's growth and learning, which are equally important in tackling new challenges in the regulated era. However, based on certain past experiences there are a few but noticeable steps towards improvement in overall functioning, recruitment process and infrastructure through increased level of interactions with the global counterparts.

Another important aspect of Indian bioanalytical community which deserves mention, especially the CROs is their experience of facing inspections from international regulatory agencies, namely World Health Organization (WHO), USFDA, ANVISA and Medicines and Healthcare Regulatory Agency (MHRA). In this context, there are two streams of bioanalytical professionals who work in parallel, those having the right attitude and behavioural attributes along with scientific and regulatory knowhow and the others who lack in correct attributes to handle the job at hand. Needless to say that facing international regulatory inspection demands not only sound scientific and regulatory knowledge but also the right attitude and behaviour in terms of honesty, preparedness, openness, backed with good communication skills. Some Indian bioanalytical scientists and organizations realized these attributes together with the scientific credentials and could clear the inspections successfully on time. While the others who could not imbibe these qualities failed miserably and got detached from the mainstream.

As far as the quality aspects of RegBio are concerned, an appropriate QMS can cater to the needs of a bioanalytical laboratory. The importance of quality and quality management system had been well understood and realized in India at a very early stage of development of RegBio. This is evident from excellent regulatory performance of some Indian CROs at the international regulatory inspections. Yet, there are certain gaps to be filled in terms of continuous training to the doers and quality controllers for globalized bioanalytical practices to cope with the dynamic nature of RegBio. Critical checks and controls are an integral component of QMS and for routine bioanalytical work in compliance with global bioanalytical practices and regulations. The checks and controls have to be integrated and monitored at all stages of bioanalytical process (planning, execution, controlling, monitoring and reporting). In case of any 'out of specification'/'out of acceptance limit' results or unforeseen events, the built-in quality checks and controls can facilitate an unbiased investigation, help to diagnose the problem, and devise preventive actions to avoid recurrence of such events in future. Further, it is prudent to understand the basic components of a QMS and their effective contribution to bring in and maintain the much desired quality

of bioanalytical operations. The major stake holders of QMS and their functions are summarized in Figure 1.

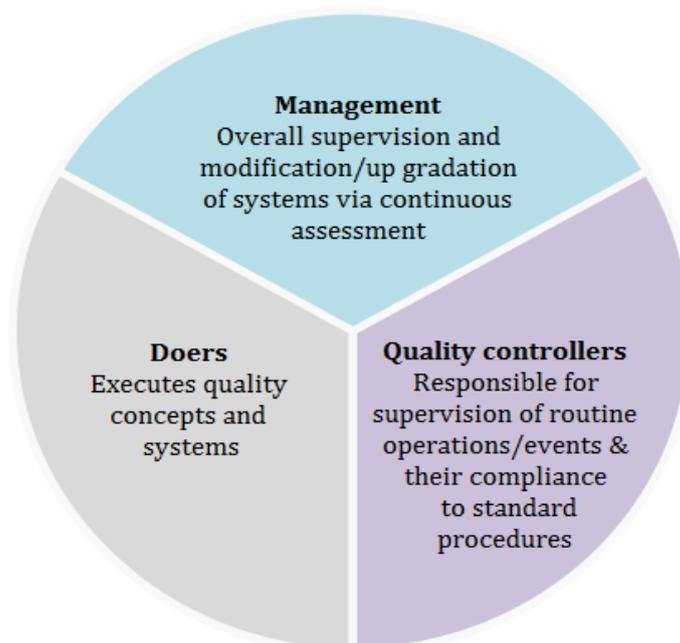


Figure 1: Major stake holders and their role in quality management system
Role of Management for Quality Control and Compliance in RegBio

Management is the overall decision maker for business and associated operations; and thereby the one is on them for any technical or financial matters. Considering this scenario, when the management is non-technical at most of the places in the Indian context, it is imperative to have a representative who is well-versed with technical, regulatory and financial aspects of bioanalytical operations generally designated as Test Facility Management or Head, Bio-Analytical or Chief Scientific Officer. From quality perspective, they are the final signatory for QMS whether these are quality documents like protocols, method standard operating procedures (SOPs) or closure of critical events like re-assay decisions and others.

Management plays a key role in conceptualization and even for the implementation of working culture of an organization. Identifying and nurturing the quality intensions to do the things in the right way is decisive and is there in stake holder's mind when a healthy work culture is to be inculcated in the organization. Thereafter, implementation is the responsibility of the actual doers; however, the working culture of an organization builds through the vision and intensions of management. Focused and continual efforts of doers, quality controllers and managers are required to maintain the quality standards of operations in routine analysis. In the same context, developing a conducive and quality oriented work culture in a well established and high performing setting in a bioanalytical laboratory is paramount.

An organization motivated with proper vision, quality thinking and a conducive work culture at all levels can effectively facilitate conceptualization, creation and implementation of an efficient QMS to build and maintain quality in routine operations. Management has to remain in constant touch with key stake holders to understand and fulfil their genuine needs, and to provide all required resources (infrastructure, manpower, instruments, finance and safety etc.) to doers, managers and quality controllers to execute their routine operations with desired quality standards as per the best global practices. This is indeed demanding under highly compelling conditions with constant changes in the economic scenario. On the whole as it is said that culture flows/percolates from top (management) to bottom (actual doers), management shall have to play a mentor's role to take care of QMS and overall quality aspects of operations and also to add value to existing QMS via scientific, regulatory or financial advice on timely basis.

From an Indian CRO perspective, in most of the cases the management is either non-technical, inexperienced, has a rigid mindset or to some extent lacks in vision, which hampers global business prospects. Additionally, putting faith in non-technical or out of touch techno-commercial senior personnel further impediments high performing employees. Due to such confounded attitude of the management,

some highly successful Indian CROs have faced serious jolts from quality front during various local and international inspections. As a result they lost a good number of well established clientele and thereby the existing and upcoming business opportunities. On the brighter side, some progressive CROs who took good care of maintaining 'quality' as well as all the stake holders remained in the mainstream, while the others were left out.

Role of Quality Controllers for Quality Control and Compliance in RegBio

Quality controllers build the bridge between Management and Doers/Executors. Actually, 'Quality' is achieved by doers through their skills and excellence in operations and maintained by quality controller/quality assurance through various systems and performance audits; compliance programs; trend-analysis; training and other quality programs. As a general concept, maintaining quality is always tougher than achieving it. Quality controller plays a vital role of communicator in a laboratory. Focussed and meticulous efforts of quality controllers are required to not only maintain quality and quality standards in laboratory but also to aid error free, reliable and consistent laboratory data.

From an Indian CRO perspective, in the pre 2000 era, Quality Assurance (QA) personals were solely responsible for all types of quality efforts like system audits or performance audits - in-process, study specific, for cause etc. Noticeably they used to perform their audits by evaluating all aspects of the study (system, study data etc.) through 100% verification criteria and used to report directly to the management. But the whole process was not considered efficient in terms of quality, speedy and on time delivery as few auditors used to perform lot many jobs at the same time and in the process of expediting too many tasks would eventually end up compromising the quality. Nevertheless, post 2000 era witnessed an introduction of new quality concept in India through which the whole quality system was divided between two stake holders instead of one. The new stake holders were named as QC, Quality Monitor (QM) and QA personnel. For quality improvement and efficiency, the QC/QM came into foray to take care of quality control aspects of the concerned department, with direct reporting to the head of the department instead of the management. This helped in timely execution, compliance, corrective-preventive actions and completion of projects. Further, QC/QM used to execute their audits by applying 100% quality checks to target areas such as study data (chromatograms) or calibration records. While the QA team used to expedite their audits by applying 10-30-100% checks based on the criticality of the target, for example, the QA audit to method validation is done by 100% criteria. This approach gained phenomenal popularity among Indian bioanalytical scientists and quality controllers and proved quite efficient in achieving and maintaining 'quality' and quality standards in the laboratory. Eventually, management also endorsed the usefulness of this new approach and is now being accepted by majority of the existing CROs and bioanalytical laboratories functioning within pharmaceutical R&D centres or in pharmaceutical premises.

Role of Doers for Quality Control and Compliance in RegBio

With inference to above section, an efficient QMS can be conceptualized and created through proper vision, conducive working culture and quality thinking of management and actual doers. However, aspects related to its implementation require a different set of skills, thinking and training for accurate and consistent execution and outcomes. Identification of right professionals to design quality management systems and documents like SOPs, method protocols, and other work instructions allows the organization and its team to develop scientifically sound and practically viable systems to achieve consistent quality outcome. On the other hand, training on well established QMS and on subsequent advancements takes lot of 'quality' time of senior scientists/managers and quality controllers. In the Indian industry, most of the successful CROs attained and maintained very good growth rate, which resulted in high demand for trained bioanalytical manpower. Nevertheless, due to a dearth of trained professionals there was a tremendous challenge for the trainers (senior analyst/ scientist/mangers) to attract, train and retain doers and to provide desired quality outcome relentlessly in addition to their time bound tasks.

Having gained all the critical insights over the years, the Indian Pharmaceutical Industry and CROs, have clearly understood the well-established fact that a good QMS in bioanalytical labs needs appropriately trained manpower (doers) as recurring errors of beginner or inadequately trained doers may spoil the whole purpose of an efficient QMS. The major contributing factors to inadequate training to a beginner in bioanalytical laboratories can be numerous and not limited to, i) no availability of specific qualification or certified courses/degrees on bioanalysis, ii) most of the educational courses/degrees lack in imparting and training on practical aspects hence, students from pure science or pharmacy background are ill equipped to handle advanced instrumentation and tackle allied procedures, iii) lack of availability

of specialized training institutes, iv) limited number of multinational company CROs or Pharmaceutical R&D centres, v) unavailability of local quality research organizations, and vi) lack of true bioanalytical experts or trainers. This severely hampers employment opportunities in specialized areas and thus a budding talent needs to put in a lot of smart efforts and quality time to learn the basics of chemistry, instrumentation, bio-transformation, quality and regulatory aspects of bioanalysis. In addition to these important aspects, a newcomer in a bioanalytical lab has to be trained for good laboratory practices (GLP), good clinical practices (GCP) and good manufacturing practices (GMP) for desired outcome. This entire process requires a specific mindset for innovative and progressive thinking to take care of all critical phases (method development, validation, sample analysis and post analysis phase) of bioanalysis, and to cope with constantly changing dynamics of RegBio. In this age of stiff competition with highly demanding timelines and pressing schedules, it is obvious to find that a recruit in his pursuit to complete the job at hand inadvertently compromises on 'quality'. This predicament leads only to so-called 'manual output' and less of quality learning.

CONCLUSION

The transition phase from non-regulated to regulated bioanalysis has been unduly long especially in the Indian context. This has compounded the predicament of keeping pace with global partners in the post-regulated era. As a result it was difficult to realize the quality aspect, scientific and collective growth for all the stake holders. Nevertheless, looking at their global counterparts, there is a swift change in the Indian market as most of the Indian bioanalytical lab have endorsed 'Quality' as a 'Laboratory Fate Deciding Factor' (LFDF) and accepted it as a key driver to define the life span of their laboratories. Controlling the quality and compliance levels to achieve reliable and reproducible laboratory data constantly is the most demanding and never-ending challenge which is faced by the bioanalytical scientists globally. We believe when it comes to reliability, 'Quality' is integral to operations and practices of organizational professionals. As decay in quality standards is quite inevitable due to human interventions, the strategy to avoid its recurrence requires well directed efforts, active participation and sustained contribution from the key stakeholders like doers, quality controllers and management. Hopefully our perspective will repose the significance of inbuilt quality for bioanalytical operations and thereby for RegBio.

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