

## Letter to Editor

# Emergence of Enhanced Quality Expectations in Pharmaceuticals

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Commercial viability of any drug product may often bring pain for patients who otherwise wait for their drug to improve their quality of life and breath. Dryness of drug products like thyroxin, warfarin, phenobarbitone, salbutamol inhalers, morphine etc. from the market leave patient on the mercy of nature. The heart wrenching healthcare professional burst out when lifesaving drugs are not available due to any reason. Voice of civil society rises in community where care of others is felt as a moral responsibility beside capitalism and/or socialism. It is also observed and quite possible that quality defects may create similar situations of drug shortage. Manufacturing facility or its control may go out unwittingly due to knowledge limitation. A quality defect that impacts delivery and performance of drug and/or carries harmful potential has always been a matter of top priority. In both cases, ability to detect, report and assess defines presence and thickness of protection wall for the public. Power to predict uncertainty and taking measures well in time is a challenge for industry and regulators to maintain uninterrupted supply of quality drugs. Journey of quality testing from representative samples to understanding the product and process ending up with the best efficient controls has undoubtedly reduced the grey corridor of failures. At the same time a lot of opportunity for industry and regulators is available to enhance the quality profile. With the innovation and expansion of knowledge, the

shape of both pharmaceutical quality and regulatory sciences is being designed in a way that has a great impact on product quality and strengthening the certainty throughout the lifecycle operations. Drive and direction of regulatory and modern sciences, such as science of quality risk management, quality by design, continuous manufacturing, quality metrics and creating a culture of quality are itself forecasting the roadmap of future. De-learning and re-learning are inevitable to live in the harmonized global village of pharmaceutical landscape. Absence of international professional knowledge based associations here in Pakistan like International Society of Pharmaceutical Engineering (ISPE), Parenteral Drug Association (PDA), Drug Information Association (DIA) etc. and reducing global initiatives within corporate organization are leaving a deep mark on the face of pharmaceutical business. Current absence of the Drug Regulatory Authority of Pakistan (DRAP) in the international arena through membership, Memorandum of Understanding (MOUs), Mutual Recognition Agreement (MRAs), Mutual Reliance Initiatives (MRIs), collaborative and joint working with other counterparts is increasing the burden of resistance in progress to make pharmaceutical business credible and reliable on the scale of modern science. Proportionality placement of DRAP and industry requires quality education, current knowledge and enthusiasm to guarantee the prosperity.

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Nobody wants to see complain for their drug products early in the morning and do its best to maintain quality as its inherent attribute. As a matter of fact, a lot of drug product recalls identify the weaknesses, residual negligence and space to improve. In a number of cases, failure to deliver the performance and fulfil therapeutic promises is visible and increases to the trouble of patients, sometimes with irreversible consequences. Every incident carries a series of actions that contributes in understanding the reasons and implanting the measures for better protection from its recurrence.

Reactive approach to an incident is becoming obsolete and is being replaced speedily with proactive approaches. Power to predict the happenings is derived by integrating the data (often unorganized, inaccessible and inconsequential) and scientific theories. Knowledge about failures or acceptance rates, changes in deviation trends, shift in complaint natures, change in output pattern etc. can be synchronized to make power of certainty visible. This ability can give an insight on the aging process and health status of manufacturing facilities to move forward.

It was a time when representative samples of products were screened through destructive chemical, microbiological and pharmacological testing for their registration and release of other units (e.g. tablet or syrup bottle) manufactured with taken samples as a part of batch. These testing include assay, weight, color, smell etc. With the passage of time, tests related to purity of product and dosage form performance were incorporated in the row. Likewise, control on impurities and degradation within drug product is defined in the same specifications spelling product quality attributes. In spite of testing, it is quite obvious that no one can guarantee quality of every unit (e.g. each tablet of batch) of the product upon testing unless capacity/strength of manufacturing process to absorb unavoidable shocks of variation is well understood, efficiently designed & controlled.

Knowledge pursuance from how to what and what to how provided enough command to shrink uncertainty of failures within batch and batch after batch. This traditional knowledge is being evolved in the shape of enhanced approach that speaks about established conditions and control strategies in manufacturing, holding, storing and distributing pharmaceutical products. Cost, objectivity and drug shortage threat is used to determine rationality and significance of both traditional and enhanced approaches. Its co-existence at the same time and age is well protected within science of risk.

The last two decades have seen tremendous advancement in the innovation of tools and introduction of approaches to achieve better insight into product and process understanding and to design quality in the product instead of relying on end product testing. This involves Quality by Design (QbD) and application of Process Analytical Technology (PAT) tools. QbD approach is indeed a process of designing quality into a product that promotes innovation and encourages continuous quality improvement. It gives a lot of flexibility in post approval variations and thus reduce regulatory load and fortifies certainty index. PAT is a tool to assess the process quality in real time and so helps in proactive working of any unwanted shifting of any specification from desired space.

Smart tools and innovative ideas that can reduce regulatory burden and improve efficiency attracts regulatory and quality sciences attention. Limitation of batch size is certainly to control uniform character (consistency) within a batch / batch after batch and to avoid potential of shifting towards inconsistency as well as unreasonable contamination possibility from the manufacturing environment and process. Demonstration of trusted and efficient control to resist the influence of factors impacting character of uniformity does not leave space to respect regulatory words over super science. Leading regulatory authorities

have yet approved continuous process from manufacturing of Drug substance to finished drug product delivery in one case while accepted conversion of traditional manufacturing process to continuous manufacturing process in other case. However, a lot of considerations are still under discussion to manage the knowledge for reaching on some workable approach throughout the pharmaceutical operations and in defining the batch.

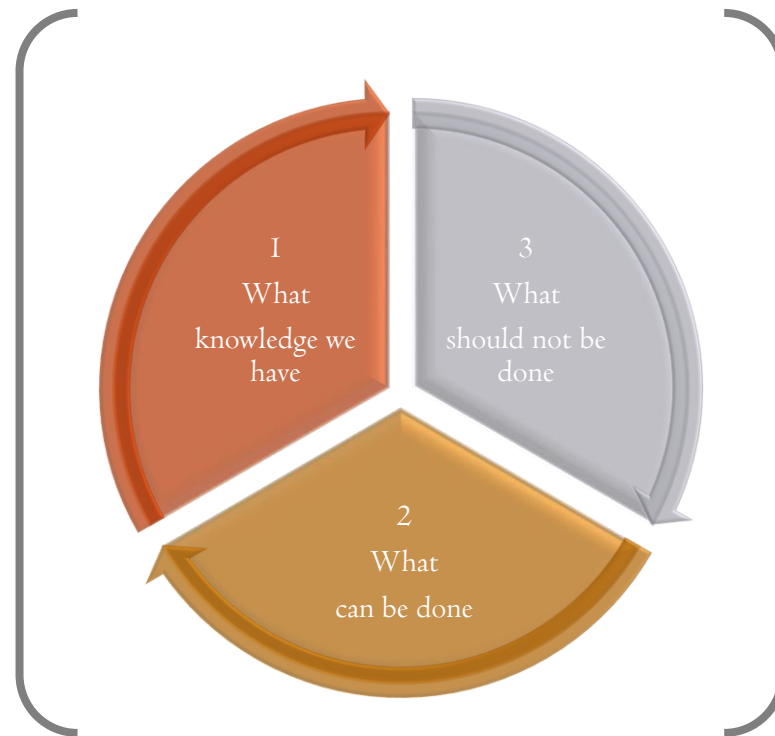
The intent of modern tools is to identify and assess potential risk for quality failures before they happen for efficient scrutiny and inspections within limited resources. Data integrity and signals generation through trends and patterns integration is arising to reshape the regulatory oversight methodology more successfully and proficiently. Creation of culture to resist behavior that believes on non-recording, non-reporting deviations and mistakes is inevitable. Quality improvement initiatives and clear demonstration by the top management about their own personal commitment to creating culture of quality is the indispensable foundation block. Clarity in delivering the messages, friendly quality competitions and freedom of expressing point of view are essentially required to bring everyone on stage where he or she can talk fearlessly.

Information is shared in discussion to generate knowledge that gives a strong value upon synchronizing with real time experience. Associations of subject matter professionals from different industries and their diversified experience comes up with worthy knowledge. Regular debate, discussions and conferences provide opportunity to exchange views, scientific judgments and real time bumpers in progress. The credibility and indigenous contribution both from regulatory and industry

has not yet crossed the residual level of global radar.

Harmonizing and globalizing efforts for quality of drugs demand reshaping of the regulatory authority from policeman approach to a knowledge based scientific organization that believes on continuous change, continuous learning, de-learning and re-learning, honesty, transparency, joint working, sharing of information, over and above respecting value of patient. It is unfortunate that DRAP or any segment of DRAP could not achieve or end up with any MOU, MRA, MRI or any membership in global initiatives like International Council for Harmonization (ICH) or Pharmaceutical Inspection Cooperation Scheme (PIC/S) so far.

It is time to think that 100's of meetings are sponsored by international agencies where DRAP leadership or nominees participated in recent years but why they lost the marathon where dozens of small countries from Eastern Europe, Russian, Eastern Mediterranean, South Asian, South American or North African region etc. got success. Identification of reason of failure is very important to know otherwise chances of repetition cannot be excluded. It is time to design millennium goals/project and strategy to protect project continuity. Strength of idea, rightness and robustness of the concept, complete strong plan with appropriate design and its religious implementation need to be tabled for worthy discussions. Openness, transparency, merit, credibility and knowledge based working requires core attention. To walk with the modern pharmaceutical world in a trustable and respectable manner one have to define the available knowledge capital, exclude what one should not do and include what can be done to start appearing on the global arena.



## US-FDA Progress as a Case study

21st Century broke the static approach and FDA came up with new measurable guiding principles through real time quality monitoring approach, quality risk, quality management, quality by design approach, data integrity and quality metrics etc. etc. in its first 15 years. They emphasized on performance based regulatory approaches to concentrate on desired measurable outcomes instead of processes and procedures. It should navigate to improve quantitative quality performance of individuals and organizational behavior, such as through quality metrics and by building a quality culture. Unlikely, relying on testing the batches, building quality in the product to achieve clinical performance through specification acceptance criteria is the fundamental area of interest. Migration from traditional approach to enhanced approach for putting more energy in controlling the variability of input materials and keeping the process parameters flexible is being encouraged from countervailing forces. Real time

monitoring through PAT assuring quality on line and diminish the requirement of end product testing. Variable process and variable input guarantee a more uniform output if pre-studied and controlled well.

The advancements in technology are making its way to continuous manufacturing (CM) from typical manufacturing of a batch. Enhanced process capacity and reduced product variability with an efficient manufacturing process to achieve meaningful product specifications based on clinical performance will be more secure in CM. A strong leadership to take lead in quality improvement and to make substantial investment towards quality is the prerequisite and grows upon substantial rewards on quality efforts. The stringent regulatory authorities are encouraging CM as well as putting a number of questions as they have limited experience at present. There are many challenges in evolving CM such as defining a batch, material traceability, segregation of non-confirming material, applying qualified tools for risk communication and knowledge management, performance indicators of control strategy,

establishing flawless relations of control points to finished product critical quality attributes and the process parameters objectivity, as well as efficient cleaning approaches for rapid switch over from one product to another avoiding cross-contamination etc. Side by side, the opportunities in CM are small facility area required for operation and maintenance, being highly flexible due to movable parts for a wide range of products and supervision through an integrated process control system.

Collaboration and effective communication with other regulatory counterparts and the pharmaceutical industries has been initiated in the recent past to extract benefits of opportunities in CM as well as to cope up with the challenges. Transparency, Openness and willingness to learn about the potential of new technologies are vibrant within the agency. The academia is being involved by them to keep organizing continuous discussions among professionals and formal forums to exchange scientific point of views are underway on CM and associate concerns.

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