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Understanding what, why and how for analytical method lifecycle approach

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Analytical method plays a very important role at all stages of pharmaceutical product lifecycle

USP<1220> and ICH Q14 are among most discussed topics today in analytical industry. With evolution of compliance and work-flow understanding, need to incorporate Quality by Design (QbD) principals in analytical methods has been long realized. Analytical life cycle management is holistic approach of implementing structured QbD approaches in analytical workflow (also segmented as stages I-II-III).

To better understand this concept, we can consider evolution of wheel as an example. No doubts that initially, when wheel was invented, it was a great invention. It was a paradigm shift in movement of goods/ loads from one location to another. But, initially wheels were made of stone, it was very heavy weight, that added to lesser efficiency or more force required to pull. Later physicians designed wheels with wooden frame (to reduce weight) with outer circumference covered with metal ring (to provide strength). In modern times, scientists worked on improving efficiency and created modern day metal frames, with rubber tyres. Is it the end of this evolution, definitely NO! as several researchers are continuously working on newer technologies to improve it further.

In similar context, when I look at pharmaceutical products, evolution/ adoption of newer technologies is not so fast & easy. Considering its possible implications on human health, a detailed assessment is made mandatory by regulatory authorities. But this has made industry follow some old technologies/ approaches that gives repeated failures and (in some cases) even limits detection of poor-quality products.

Recent recommendations from USP (**United States Pharmacopeia)** and ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) are in direction of providing a structured approach for design and development of these analytical strategies that support development of analytical methods with better control on variabilities. In simple words, we can say that Method lifecycle approach is preventive approach to control method variables and understand method parameters space better.

Lifecycle management approach brings a shift from current segmented approach towards a holistic approach. In current workflow, Analytical development team develops methods and gains understanding on impact of variables on method performance in a very limited space/ scope. Also, another missing portion is transfer of this knowledge space to subsequent

stages.

Due to unstructured development approach many variables are not properly assessed. Later Validation as per USP<1225> is completed and a final method protocol goes (Analytical procedure transfer USP<1224>) for next stage (*i.e.* QC lab) for routine usage (Analytical Procedure verification USP<1226>). Now with proposed USP<1220> all these stages (Development, Validation and Routine monitoring/ usage) will be covered under single chapter/ section.

To understand this upcoming transformation in analytical methods handling, I would try to answer rationales of What, Why and How for Analytical Method Lifecycle approach.

What is Analytical Method Lifecycle approach?

As defined in USP<1220>; The current concepts of validation, verification and transfer of procedure address portions of lifecycle but do not consider it holistically. The purpose of proposed new chapter <1220> is to fully address entire procedure lifecycle. Approach is based on Quality by Design concepts as described in International Council on Harmonization Q8 (R2), Q9, Q10 and Q11. The lifecycle management process provides a framework for defining the criteria for and development of an analytical procedure that meets the acceptance criteria. The procedure then becomes part of a continuous verification cycle to demonstrate that it meets the predefined criteria over the life of the analytical procedure.

Why is adoption of Analytical Method Lifecycle important?

During inspections, auditors find multiple instances of method failures as root cause for Out of Specification (OOS) results. OOS handling routes towards corrective and preventive actions (CAPA) for proper identification and correction for these attributes. But considering complexities in evaluation, many analysts initiate a development exercise i.e. push the method back to development team to understand problem and suggest solution/ modifications. Below are few audit observations that clearly indicate a lack of proper scientific decision making in handling analytical failures (Excerpts from warning letter issued by US FDA in 2016, 2017 & 2018).

Observation-1: During the period between January 1, 2018 and October 15, 2018, there were approximately 175 events identified as “repeated incidences” from QC, including at least 19 events due to column conditioning and 15 poor column performances that resulted in aborted or invalid HPLC sequence runs. ***Based on your assessment and identified root causes, insufficient actions were taken by the Quality unit to ensure the robustness and suitability of the analytical test procedures and the equipment***. Incident events with similar root causes were not thoroughly reviewed for historical trends and corrective actions were not implemented to reduce the occurrence of a typical events from similar root causes.

Observation-2: Proper controls are not exercised over computerized systems used for analytical testing to ensure drug products meet their specified quality attributes.

Your firm engages in extensive use of “Inhibit Integration” and other anomalous integration techniques for assessing US API’s such that unknown impurities are disregarded without scientific justification. Furthermore, unknown impurities are not accurately assessed or reported.

A review of chromatograms from your firm’s last 30 batches of drug product revealed that unknown impurities are routinely integrated as a part of the desired *API* (Active *Pharmaceutical* Ingredient). Your firm’s officials failed to explain why impurities would be as a part of the desired API peak.

Observation-3: ***Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity.***

Firm failed to establish adequate test procedures. For example, analyst manually integrated a high-performance liquid chromatography test for API, despite the fact that the chromatogram lacked peak resolution. When a chromatogram lacks peak resolution, detailed methods and appropriate oversight are essential to ensure test results, considered by the quality unit in batch release decisions, are scientifically valid. Firm lacked an approved protocol for manual integration or quality oversight of the practice.

How to implement Analytical Method Lifecycle approach in laboratory?

As mentioned in beginning; Analytical lifecycle approach comprises of 3 individual stage *i.e.* Stage-I (Procedure Design and Development), Stage-II (Procedure performance qualification/ Validation) and Stage-III (Continued procedure performance verification) and changes earlier segmented approach towards holistic approach of handling changes/ improvements.

To begin with; first and most important aspect of lifecycle approach is setting objectives, here its referred as Analytical Target Profile (ATP). This defines/ stipulates the performance requirements for analytical method. ATP is derived considering requirements of analytical method and performance attributes associated in laboratory environment.

Stage-1 is critical step towards analytical lifecycle management. It begins with 'Knowledge Gathering' approach to collate information about chemical structure, solubility, reactivity and stability of molecule/ compound. This information is helpful in selection of analytical technology and its suitability in achieving the ATP requirements. Second step is 'Risk assessment evaluation and control' to identify process variables and ascertain their impact on method performance.

It is recommended to include some guiding tools in decision making *e.g.* Ishikawa Diagram & Design of Experiments (DoE). Ishikawa diagram helps in identifying all possible variables and DoE helps in understanding effect of variables on process. Next step in development is 'Analytical Control Strategy', which includes establishing controls based of outcomes of DoE studies. These controls determine the process variability and provide an opportunity to establish/ set process parameters in best suitable operating limits. Control of variables may include direct restriction/ control on variable or incorporate replicates to reduce/ control random assay variability.

Next step is 'Knowledge Management' and reflects importance of information gathered during development to be passed to subsequent stages of method lifecycle for effective utilization. It includes systematic approaches to obtaining, understanding, retaining and transferring information to lifecycle stages for effective control strategies. Last step is 'Preparing for Qualification' that indicates a pre-assessment of experimental data to confirm absence of significant bias, before taking method for Stage-2.

Next stage (After development) is 'Procedure Performance Qualification' with objective to confirm that the procedure generates reportable values that meet the ATP criterion and remain apposite for test method. To avoid random variabilities, its recommended that laboratory that will be using the analytical procedure for testing should conduct qualification study. Based on ATP; criterions for qualification protocol are established and analytical control strategies can be modified based upon experimental outcomes/ observations.

Stage-3 'Continued Procedure Performance Verification' is a continuous exercise to confirm the suitability or fitness of analytical method. ATP is used as reference point for monitoring performance of method. Monitoring may include trending of analytical results, system suitability, out-of-specification results, stability data and other results. Primary objective of this exercise is to identify potential performance issues in analytical method and identify changes required in analytical method.

Analytical method plays a very important role at all stages of pharmaceutical product lifecycle *i.e.* Right from product development stage, till final product batch release from production. Selection of appropriate method attributes plays a very important contribution in determining suitability of method for its intended purpose. Drug product quality is confirmed by associated control strategies including procedure controls, environmental controls, materials control and selection of instrumentation.

With major analytical guidance documents being revised (to include guidance on systematic approach towards analytical method development, validation and performance monitoring), industries have the discretion either to retain conventional traditional development approach or adopt method lifecycle management principles in their routine work-flow. But looking at advantages of Analytical QbD work-flow, its difficult to avoid this approach for longer time. AQbD gives a structure to analytical method development and learnings gained are helpful is handling failures in systematic approach. Several researchers follow systematic design of experiments approach in development, but these learnings need to be handled in statistical approach for defining method operable range and should be transferred to later stages for effective utilization.

References

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