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AN OUTLINE OF QUALITY GUIDELINES FOR DEVELOPING AND VALIDATING ANALYTICAL PROCEDURES

Amit Saxena [*1] and Umesh Laxmanrao Kulkarni [2]

Development Quality Assurance [1], Mapaex Consumer Healthcare Private Limited, Bhopal - 462026, Madhya Pradesh, India.
Quality Assurance & Compliance [2], Slayback Pharma, Hyderabad - 500072, Telangana, India.

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Correspondence to Author:
Amit Saxena

Manager,
Development Quality Assurance,
Mapaex Consumer Healthcare Private Limited, Bhopal - 462026, Madhya Pradesh, India.

E-mail: amit_saxena1234@rediffmail.com

ABSTRACT: The International Council for Harmonization (ICH) which aims to harmonize, has altered how pharmaceutical regulations are applied and how drugs are being developed. Pharmaceutical companies use analytical techniques to perform research and development and to manage the inputs and outputs of a process. These analytical methods should routinely produce high-quality data to support decisions while controlling the remaining risks and uncertainties. This review article aspects the highlights of analytical procedure validation and development (ICH Q2 (R2) and ICH Q14). Both the guidelines have been produced by one panel of subject-matter experts and are currently accomplishing the crucial ICH landmark of Step 2 publishing for public comment. The ICH brings both regulatory agencies and pharmaceutical industries to discuss the scientific and technical aspects of drug approval. Since its beginning in 1990, ICH has regularly progressed to meet the international challenge of drug development. ICH's purpose is to promote better peace worldwide to ensure that secure, useful, and elevated medicines are being developed and registered in the most resource-efficient manner possible. The new guideline in this pair, ICH Q14, describes the science, risk-based approach, and quality systems to enhance the process and product quality for the development and maintenance of analytical procedures. While Q2 (R2) focuses on including a multivariate model that covers the validation principles for the use of analytical procedures. Applying these guidelines will improve regulatory communication between the industry and regulatory agencies and additionally facilitate post-approval changes to analytical techniquess.

INTRODUCTION: The governing bodies and pharmaceutical industry focus on product quality, safety, and efficacy but according to the US Pharmacopeia (USP) stimuli article [1] and the International Council for Harmonization (ICH) final concept paper [2] suggest "the concept of lifecycle management holistically".

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Together development and validation activities of an analytical method are critical as it is being used to monitor drug substances, drug products, excipients, degradation products, or impurities present in dosage forms [3, 4].

They must be precise, sensitive, and efficient while also being robust, and economical [4]. Accurate analytical analysis requires reliable and validated analytical methods. A shift in how analytical processes is created, validated, and used is currently taking place. The ICH primarily presents a safe path to congregate the drug regulators and the pharma manufacturers to talk over the logical and practical aspects of drug approval to resolve

the complex problems faced by industries to meet the progressively universal aspect of drug development to secure high-quality medications being created and enroll.

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Accurate analytical analysis requires reliable and validated analytical methods. A shift in how analytical processes are created, validated, and used is occurring. The ICH primarily presents a safe path to congregate the drug regulators and the pharma manufacturers to talk over the logical and practical aspects of drug approval to resolve the complex problems industries face to meet the progressively universal aspect of drug development to secure high-quality medications being created and enrolled. Pharmaceutical companies use analytical techniques to research and develop new manufacturing/analytical techniques for the inputs and outputs of manufacturing drugs. To measure the material qualities, analytical techniques should be reliable and are employed to offer data, or more general knowledge needed to decide. In June 2018, ICH assembly [5] decide to update the ICH Q2 (R1) guideline on analytical method validation and to create a new ICH quality guideline for the development of analytical methods (ICH Q14). The consideration points highlighted in the draft guidelines are as below.

ICH Q2 Contents [6]:

ICH Q2 Revision: Text of the main recommendation: Revised and generalized in comparison to the previous. Several subjects were shifted to Q14 (system suitability and robustness experiment) and the performance characteristics table from the original Q2 is revised.

Chapter's structure:

• Analytical procedure validation study

• Selectivity / Specificity

• Working Range

• Accuracy and Precision

• Robustness

• Glossary

It also contains two annexes; that discuss how to choose validation tests depending on the analytical method and provide examples of analytical techniques.

ICH Q14 Contents [7]:

ICH Q14 New: Principal policy text base in alignment with Q8, Q9, and Q10 guidelines.

• Analytical Target Profile (ATP)

• Knowledge and risk management

• Assessment of robustness and parameter ranges

• Change management of analytical methods

• Control strategy – Established conditions (EC)

• Lifecycle management and post-approval changes

• Development of multivariate analytical techniques

• Real-time release testing (RTRT)

• Submission of the analytic data in the dossier

It also includes three annexes - that offer examples of how the ideas in ICH Q14 might be employed, techniques for MODRs, and an example of the multivariate model. The proposed guidelines are intended to complement a series of guidelines, that were published years later, by ICH Q8 to Q12 [8-12] guidelines and the ongoing ICH Q13 for Continuous Manufacturing [13], which aims to merge both documents into one for simplicity and clarity [2].

The modification of Q2(R2) contains multivariate calibration and launches new terms like working range and aids the design of a validation study. The draft Q14 guideline applies a long-recognized process known as quality-by-design (QbD) from Q8 that uses statistical, analytical, and review of risk assessment ideas from ICH Q9 in the design, development, and production of pharmaceuticals to guarantee the quality of those products [14]. QbD

concept for pharmaceuticals was outlined in ICH guidelines documents ICH Q8-Q11 [15]. It outlines minimal and enhanced methods for creating analytical procedures. In addition, it draws leverages from Q12 guidance on product lifecycle management requirements, such as established conditions (EC) and changing the testing method after approval. Together, Q14 and Q2(R2) refer to the proposed development and validation pursuit life cycle of an analytical method (describe along with flow (Fig. 1)) for assessing the quality of medicinal compounds (drug substances and drug products) and medical devices (in combination products).

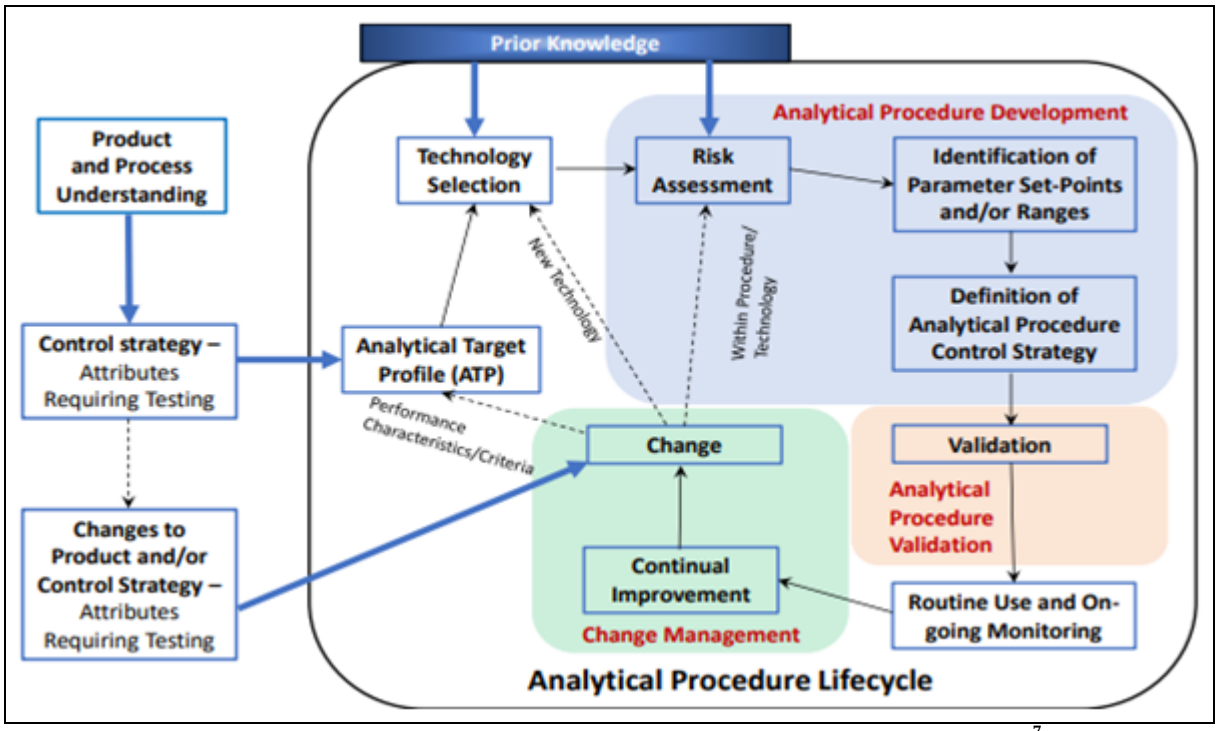

FIG. 1: PRODUCT DEVELOPMENT AND ANALYTICAL LIFECYCLE [7]

Thus, the USP already published a new general chapter on 'Analytical Procedure Life Cycle <1220>' [16] in USP-NF 2022, Issue 1, official as of May 1, 2022, as well as the ICH, introduced draft guidelines that offer a framework for putting the life cycle approach into practice by considering the validation activities that take place across the whole life cycle of an analytical technique.

This review article describes the concepts presented in draft guidelines on validation and development of analytical procedures [6, 7,] and a joint Q2(R2)/Q14 guideline Step2 presentation [3]. We will also point out several expected benefits and describe the overall life cycle of the analytical method, including multivariate model development and validation.

Background: ICH Q2 (R1) guidance primarily focuses on chromatographic techniques that came into force in 1995, a long time ago. Meantime the pharmaceutical sector is beginning to use novel procedures of an industrial approach, digital therapeutics [17], innovative technology techniques, and new sensor skills absorb into analytical measures performed by the Q2 (R1) paradigm, which is insufficient to judge the desirability of such procedures. Even it's not always easy to apply Q2 principles to new techniques that were developed (or used) in the interim, such as test procedures for biological products (CBPAs, quant. PCR, *etc*.), hyphenation technology (GC or LC or CE along with MS, LC-NMR, etc.), and procedure that require multivariate analytical evaluations (NIR, NMR, *etc*.) [2].

There was no ICH guidance on analytical method development before ICH Q14 and in the absence of development data, validation results are present. The lack of such a framework makes regulatory communication ineffective, especially when nonconventional (for example, real-time release test) analytical procedures are working.

It reduces the chance to outline a scientific rationale for adaptable regulatory methods for post-approval amendments [2].

Objectives of the ICH Q2(R2) and Q14 guidelines: Both recommendations, which are now in the public consultation stage, aim to fill a gap in the analytical method development kit. To evaluate the quality of pharmaceutical substances and products throughout the lifespan of an analytical procedure, both guidelines together outline the development and validation processes. ICH designed Q2 (R2) to provide direction and suggestions on how to conduct and assess the numerous validation tests for each analytical technique and serves as a glossary of words [3]. The purpose of this terminology and definitions is to eliminate the discrepancies between the various compendia and the three major pharmaceutical market regulators (Europe, Japan, and the United States). This recommendation relates to new or updated analytical techniques used for evaluating the release and stability of chemical, biological, and biotechnical active ingredients, and products. It can also be used for other analytical processes employed as part of the control strategy by a risk-based approach. The concepts of validation of analytical methods are provided, along with a basic framework that is relevant to goods principally falling under the Q6A and Q6B scope [18].

The ICH Q14 guideline is being proposed to harmonize the scientific and risk-based approach to the development and maintenance of analytical methods (analogous to ICH Q8 and Q11) and to provide the principles related to the document description. This new directive addressed the submission of analytical techniques and associated lifecycle data in the common technical document (CTD) format [2], to enhance regulatory communication between the industry and regulators. There are also details covered on the multivariate analysis model and real-time release studies [3]. In addition, facilitate principles for supporting the change to an analytical process based on risk assessment evaluation, method comprehension, and performance criteria are provided [3, 2].

ICH - Related Guidelines [16]: The harmonization guidelines have framed the pharmaceutical regulatory landscape and drug development by accompanying ICH guidelines, such as ICH Q8, Q9, and Q10 requirements, and future trends, such as ICH Q11, Q12, and Q13. How did these guidelines work in tandem to integrate validation and development guidance?

Pharmaceutical development ICH Q8(R2) [8]: This guideline provides directions on the content of the drug development segment for drug products as defined in ICH topic M4 of the CTD format. The parent Q8 document describes developing a systematic, knowledge-driven, scientific approach and tools (such as quality by design and risk management) that may be used for all dosage forms.

Quality Risk Management Q9 [9]: It describes the principles and techniques for quality risk management in this guideline and can address many aspects of pharmaceutical quality which keeps the entire project together.

Pharmaceutical Quality System Q10 [10]: To enable continuous improvement throughout the whole lifecycle of the product, this guideline applies a state of control to systems supporting the development and production of active pharmaceutical ingredients and pharmaceutical products, including biological, biotechnical active ingredients and products.

Development and Manufacture of Drug Substances Q11 [11]: This ribbon guidance demonstrates how to execute Q8, with the assistance of Q9 and Q10. It also advises on what details should be in Module 3 of the CTD. It is a guide for establishing and comprehending the drug substance's manufacturing process.

Lifecycle Management Q12 [12]: With the help of this new guideline, post-approval, chemical manufacturing control (CMC) adjustments are more effective and predictable throughout the product lifecycle which promotes transparency, fostering innovation and ongoing development between industry and regulators.

Continuous Manufacturing of Drug Substances and Products Q13 [13]: This novel recommendation is being proposed to include important technical and legal factors that support harmonization,

including technology utilized in the production of pharmaceutical ingredients and products. It provides a framework to manage continuous manufacturing changes and set forth established conditions.

Benefits of ICH Q2(R2) and Q14 [3, 6, 7]: We can summarize the key advantages of the proposed draft guidelines as follows:

ICH Q2(R2) describes the benefits of using sophisticated analytical techniques which leads to more robust quality monitoring by pharmaceutical companies. It offers direction and suggestions for deriving and evaluating different validation tests for every analytical technique including those for chemical, biological/biotechnological products, and statistical/multivariate data analyses. In addition, it includes principles outlined in ICH Q8, Q9, and Q10 that did not exist at the time of issuance in Q2 (R1).

According to the benefits of ICH Q14, there are ways to develop analytical methods over the course of their entire lifecycle by using defined performance attributes and related approval requirements. This way includes harmonizing scientific methods, key elements, and terminology for the creation of robust analytical procedures with an improved comprehension of the analytical processes. Additionally, more knowledge of analytical methods facilitates support for continuous improvement, including regulatory approval. It is also important to note that it reduces the effort throughout the lifecycle of the analytical maintenance while providing guidelines to demonstrate suitability for real-time release testing.

Traditional and Enhanced Approach to Analytical Development: New ways of thinking about how to assess and safeguard the quality of medicines more efficiently. The ICH Q8, Q9, and Q10 guidelines outline an approach that is first and foremost concerned with comprehending the procedure, encouraging innovation, maintaining control, and continual development to incorporate high-quality products from its start. Continuing this theme, the new draft guidance ICH Q14 aims to combine the traditional (also known as minimal) and enhanced approaches articulate into a comprehensive framework for analytical methodologies [7]. The major focal point is rapid method development and validation by method developers. The traditional strategy is still a good one, but the upgraded enhanced strategy provides more advantages.

The minimal approach identifies the characteristics that need to be examined for the active pharmaceutical ingredients or products along with choosing the right technology together with appropriate instruments for testing, also conducts the necessary development studies by defining an analytical procedure description and control approach [7] followed by validation studies, until problems eventually develop, and the method needs to be altered and revalidated.

The enhanced approach provides a scientific viewpoint, deeper understanding, and a methodical manner to learn and improve the analytical process. Based on knowledge of the manufacturing process evaluate the sample attribute, define the analytical target profile (ATP), assess risk, and perform single or multi-variate experiments [7]. The enhanced method permits the evolution and attestation of an analytical control space where several variables (across a range of values) can be adjusted as needed by developing a lifecycle change management strategy. More complete knowledge of indicated key factors will result in an additional reliable method that is trustworthy.

Analytical Target Profile (ATP): ATP for an analytical procedure is a predetermined goal that includes the method's general quality requirements. It is a mainstay of the enhanced approach and comparable to its quality target product profile [7] defined in ICH Q8(R2). The creation of ATP is the initial stage and upon creation of ATP, this control strategy establishes a connection between the critical process parameters and critical quality attributes. ATP is a reasonable way to define the assessment of an analytical course of action during the improvement stage and provides the standard for validation of analytical processes which assures the fitness of the final method [7]. ATP is determined by the method's supposed usage and focuses on the accuracy (bias) and precision of the reportable value of the method. Throughout a project's lifetime, the requirements of the method will

change either it will become more stringent or specific.

When using an ATP, numerous advantages can be attained:

• The ATP displays the gap and may be used as support for seeking resources for development.

• Using an enhanced approach, the performance parameters of the analytical process are stated [3].

• Makes it easier to select an appropriate technology to get the desired performance that ensures an analytical procedure is suitable during all changes across the analytical lifecycle of the product that can serve as a framework for lifecycle management [3, 7].

The key is ATP facilitates the choice of technology, the design, and the development of the analytical technique, along with its succeeding staging observation and ongoing improvement [7]. Translating these different stages of an analytical life cycle concept into analytical techniques depicted in **Fig. 2**

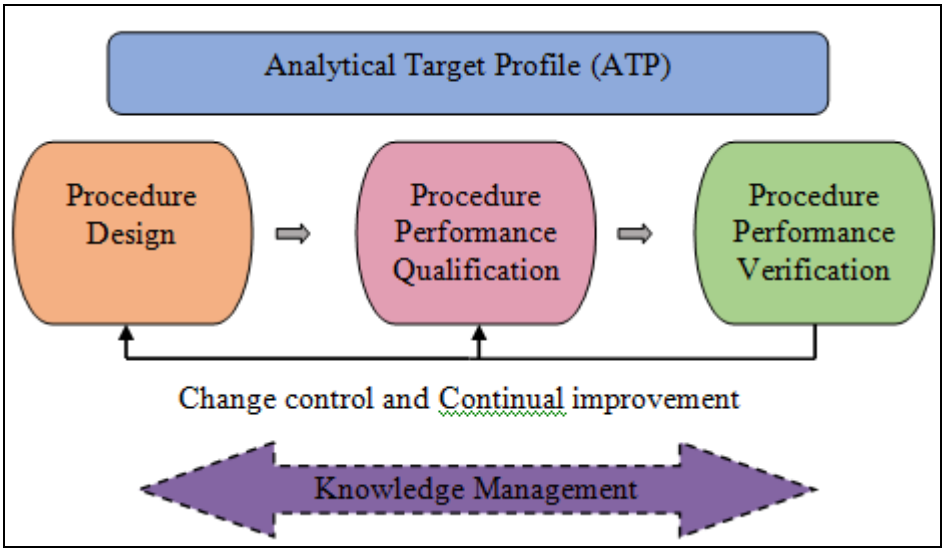

FIG. 2: THE STAGES OF LIFECYCLE MANAGEMENT IN THE ANALYTICAL METHOD

Knowledge / Risk Management: During the establishment of analytical procedures and lifecycle management, decisions are either expressly made or indirectly based on prior product knowledge which also guides in choosing the best analytical techniques and processes that are likely to meet ATP requirements. The best technology for a specific purpose is chosen by considering the latest best practices, cutting-edge development, and regulatory demands which in turn gives leverage to manage throughout the product lifecycle [3].

Knowledge management is the best approach for gathering, processing, storing, and sharing information to ensure the continued effectiveness of control strategies [1].

The pharmaceutical industry and regulators are looking for ways to better identify and mitigate risks and pinpoint possibilities for quality improvement throughout the drug lifecycle [7]. In the lifetime approach to analytical procedures, risk management is a crucial component to understanding the impact on process variables and reportable values, which helps develop control strategies. The new guidelines recommend the use of quality risk management (QRM) to support the advancement of a sturdy analytic method. This includes identifying and controlling factors that can significantly impact its performance and prioritizing the analytical variables to be tested empirically [7]. To determine the risk having the greatest impact, a formal risk assessment can be carried out by making use of quality tools (commonly employed methods like the Ishikawa diagrams (fishbone diagrams) [7], failure mode and effects analysis (FMEA)) or similar tools, for problem analysis in turn proactively preventing failures rather than detecting failures after the fact. The target of risk assessment is to understand the

impact on process variables and reported values, which helps develop control strategies.

As a part of risk analysis, continuous monitoring is advised and the results of QRM shall be detailed in the applicant's pharmaceutical quality system (PQS) [7].

Robustness and Parameter Range: Robustness is not something you should test at the end, it should build from the start that is during development studies and it does not repeat during validation studies as per ICH Q2 or on a case-by-case basis [6, 7]. Robustness study varies for every technique; therefore, a plan is required to optimize the knowledge gathered while reducing the quantity of experimentation.

The enhanced approach outlined in Q14 is to achieve the reportable results of well-designed robustness studies that provide information about how variables affect and interact with other variables while changing as it demonstrates the accuracy of an analytical method.

In a traditional method, determining robustness involves changing each element individually and assessing the effectiveness of that change.

One path to potential regulatory flexibility is the use of a proven acceptable range (PAR) or method operating design region (MODR) which can permit method changes within the design space that can develop for a single parameter or a collection of parameters that depends on the layout and results of the development studies [3].

Control Strategy and Established Conditions for Analytical Procedures: The control strategy represents an organized set of safeguards developed using the knowledge that is already available about the analytical technique based on the results of development data and risk assessment in combination with robustness studies where appropriate [7], which can safeguard the accuracy of the measured result to ensure consistent performance of the analytical procedure operates as anticipated across the entire method lifecycle with the set of controls such as by identifying system suitability testing (SST) parameters and their acceptance criteria [3].

A set of explicit and well-defined instructions for carrying out procedures is the aim of an analytical control strategy.

The pharmaceutical sector is evolving!! ICH Q12 offers a context to accelerate post-approval chemistry manufacturing and control changes in a more foreseeable and well-organized way with the key concept being the established conditions (ECs). ECs for analytical procedures depend on the development plan, the intricacy of the analytical technique, as well as evidence of comprehension [7]. An analytical technique with defined analytical process parameters also set points may have many ECs when using a minimal approach.

In an enhanced methodology, a better appreciation of the analytical process factors and their influence on accomplishment makes it easier to identify the aspects that need to be under control, allowing for a more suitable set of ECs [3].

If ECs are a part of the drug license application and any changes will need regulatory clearance and are developed throughout the lifecycle development and validation phase.

Lifecycle Management and Analytical Procedures Post-Approval Changes: Throughout the course of a product, analytical techniques might change at any stage of the life cycle [7]. Depending on the status of the change, the degree of work is divided into full validation, partial validation, or comparative test and subsequent approval of the method may be required before the change can be implemented. The term analytical method life cycle describes the coordinated processes of development, qualification, validation, transfer, and maintenance related to good manufacturing practices and routine use till the retirement of method [19]. Applying lifecycle management principles to analytical processes offers the potential to apply the information obtained using scientific methods and quality risk management to continuous improvement which guarantees high reliability of analytical results. An established approved post-approval change control protocol and the product lifecycle change control plan assure acceptance of potential adjustments outlined in ICH Q12 guidance about the path to changes to

the chemistry, manufacturing, and controls (CMC) portion of marketing requests [7].

In the case where ECs are proposed, the proper reporting category should be determined by first evaluating the risk connected to such changes. The risk should be included in the reporting category (as shown in **Fig. 3**, a follow-up chart that determines the EC reporting category) [3].

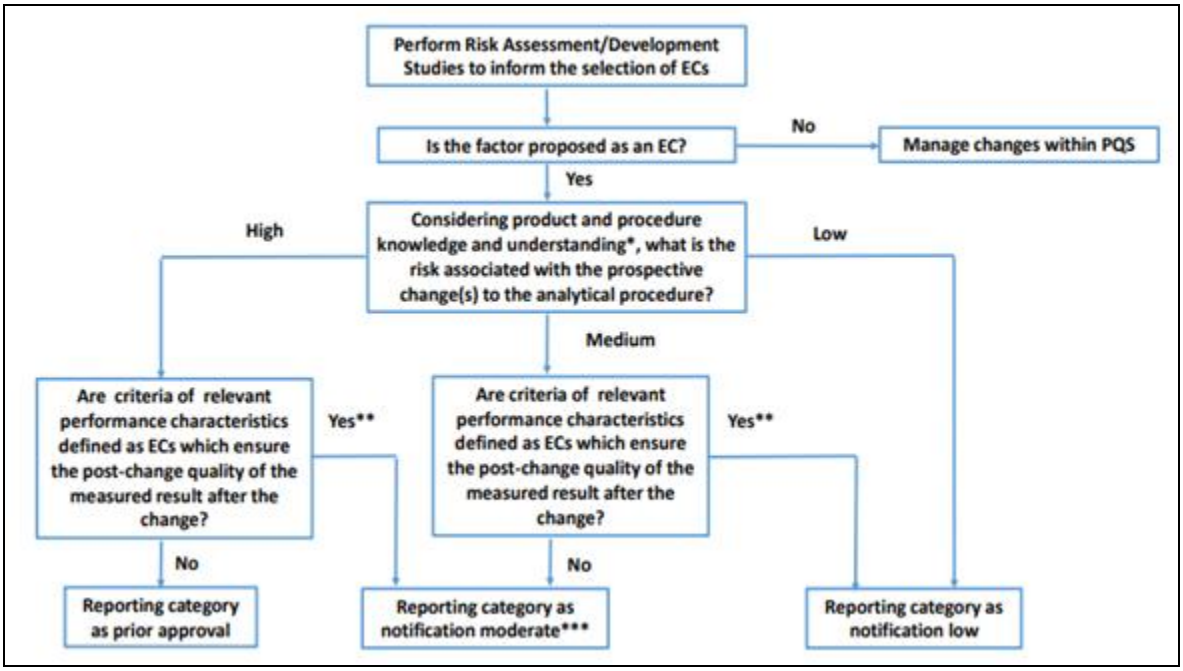

FIG. 3: RISK-BASED METHODOLOGY TO RECOGNITION OF ECS AND REPORTING CATEGORIES FOR RELEVANT CHANGES IN THE ENHANCED APPROACH [7]. * Analytical method control plan should be included. ** Enough data or past information should be accessible to create suitable upcoming bridge analyses. *** Certain modest risk adjustments that the corporation proposes could need prior approval based on input from health authorities.

To re-confirm the report category QRM can be used [7]. The findings of this risk assessment are taken into consideration when designing and determining the scope of the studies required to support the transition, including the most effective bridging study which is also known as the degree of evaluation work for changes that depends on two factors: the risk of the change itself and the level of knowledge associated with it, as shown in **Fig. 4** summarizes the depth of the actual work accomplished in each of the four corners and the preparation of the evaluation task [20].

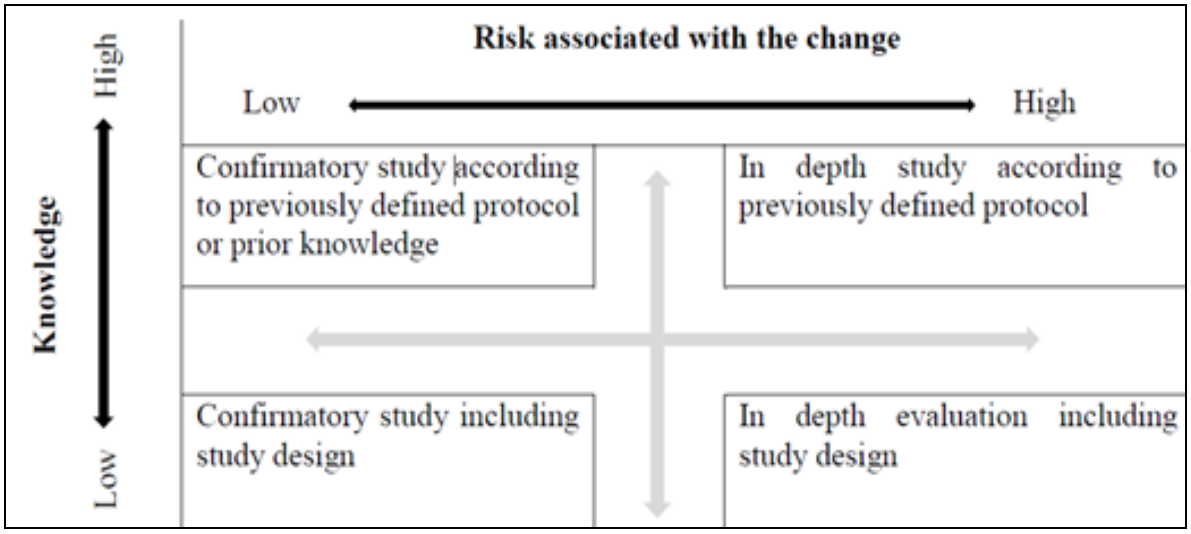

FIG. 4: DEGREE OF VERIFICATION WHEN CHANGING ANALYSIS METHOD ACCORDING TO KNOWLEDGE LEVEL AND RISK LEVEL [7]

Multivariate Analysis Model and Real-Time Release Testing (RTRT): The updated guidance also addresses multivariate analysis and RTRT. These are key elements of pharmaceutical manufacturing that are ongoing. The Q14 guidance and Q2 amendment cover the calibration of the model, confirmation, and validation of procedures. Models can be built and calibrated using several input variables like verified samples and a validated reference method [7]. However, each data set is used to evaluate model validation. The performance of the model can be reviewed while it is being used and it frequently needs updating and revalidation [18]. This is reflected in the lifecycle approach to change management. To create a reliable multivariate analytical approach, sample size, selection of model variable, distribution over the range, maintenance of model, and data pre-processing must all be supported by science [3, 7].

The Lifespan of a Multivariate Model is Iterative and has three Primary Parts: model establishment, routine production, and model maintenance [3] which is portrayed in Fig. 5 about the multivariate analysis model - the flow of construction, and the actual operation.

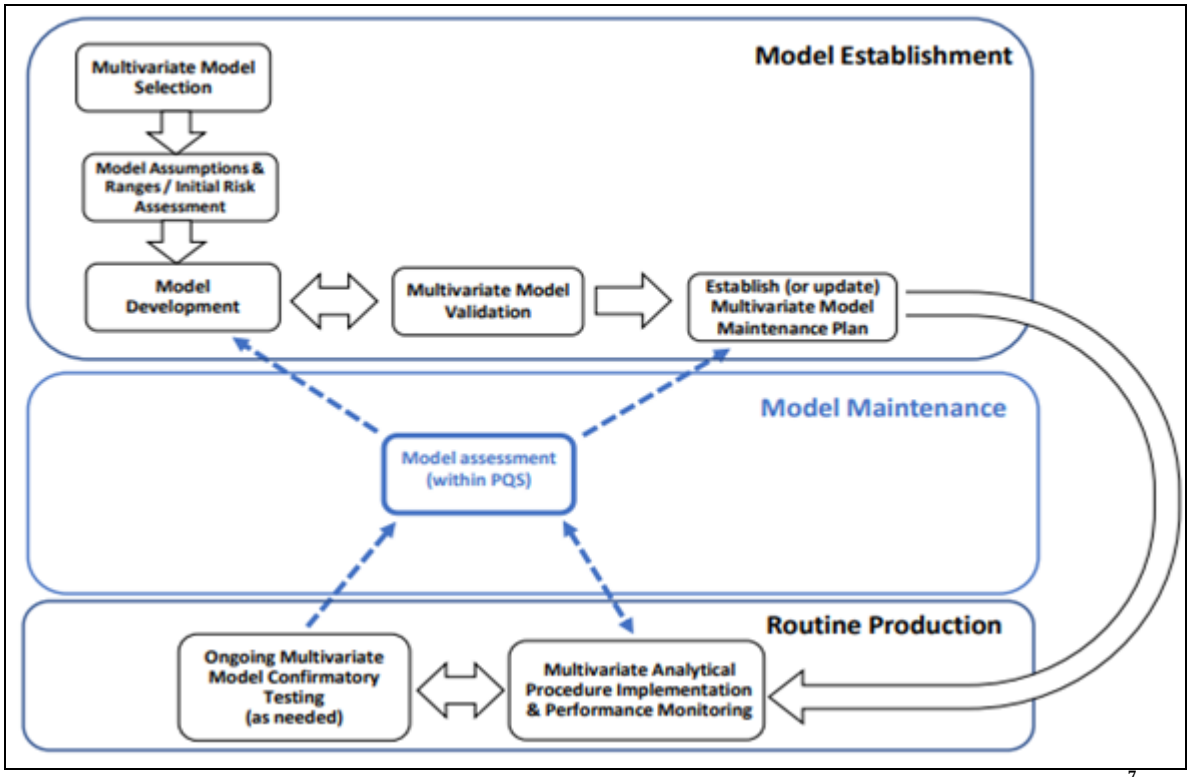

FIG. 5: LIFECYCLE OF AN ANALYTICAL METHOD USING MULTIVARIATE MODEL [7]

A proper blend of measurable material properties and process controls to predict CQAs is often used to assess and guarantee the quality of RTRT in-process and/or finished products [7]. There should be a clear justification for how the RTRT strategy relates to the product CQAs and acceptance criteria.

If the alternate test is set up ICH Q2 recommends that an RTRT procedure should be validated as necessary and adequately [3].

Analytical Method Validation Studies: Since it was introduced in the United States for the first time in 1978, one of the principles that have continued to be used and advanced is 'validation' [21]. Furthermore, FDA summarizes the fundamental guidelines and practices for process validation operation with product lifecycle concepts [22].

ICH Q2(R2) guidance describes all analytical procedures should be appropriate for their intended function and the design study is built on the foundation of the technology chosen and analytical method performance factors.

Parameters that are to be verified for the method validation test are framed in **Fig. 6**.

Type of measured product attribute / Analytical Procedure Performance Characteristics to be demonstrated (2)	IDENTITY	IMPURITY (PURITY) Other quantitative measurements (1)		ASSAY content/potency Other quantitative measurements (1)
		Quantitative	Limit	
Specificity (3)				
Specificity Test	+	+	+	+
Working Range				
Suitability of Calibration model	-	+	-	+
Lower Range Limit verification	-	QL (DL)	DL	-
Accuracy (4)				
Accuracy Test	-	+	-	+
Precision (4)				
Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

FIG. 6: STANDARD TRAITS TO EXAMINE METHOD VALIDITY FOR PRODUCT QUALITIES [6]

Indication of sign:

+ve essential parameter to be performed. -ve not essential parameter to performed. normally not assessed but for certain conditions, it might be required. QL: Limit of quantitation and DL: Limit of detection. It also focuses on incorporating prior knowledge for the design of the validation study and the lifecycle (partial, cross- and co-validation) approach [6] towards analytical procedure rather than the "all is well! after three validation batches". **Fig. 7** demonstrates how knowledge can be created while developing an analytical technique, as defined in ICH Q14, to help design validation studies.

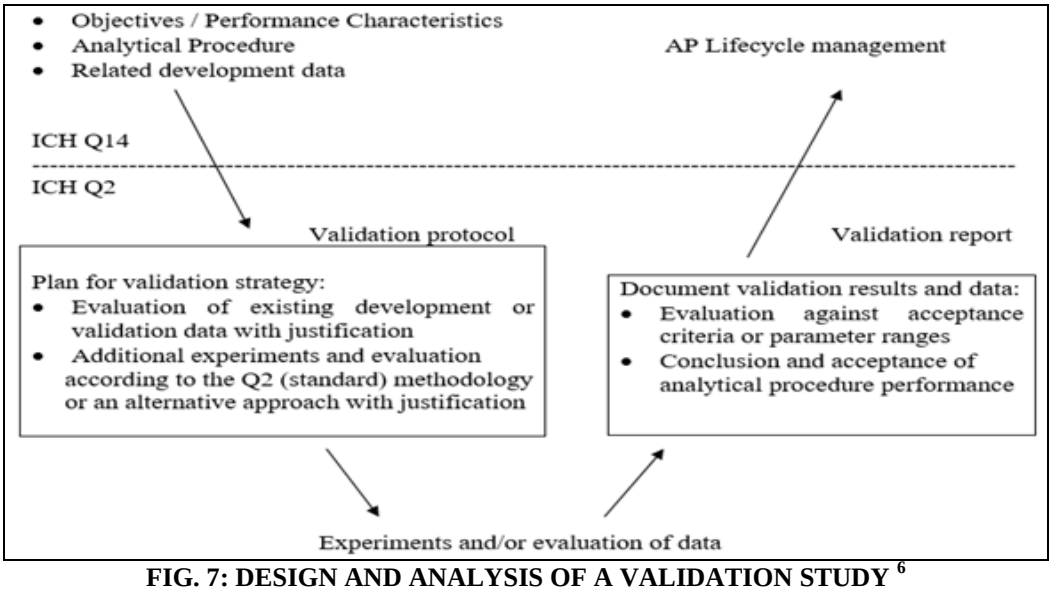

FIG. 7: DESIGN AND ANALYSIS OF A VALIDATION STUDY [6]

Validation tests confirm an analytical procedure's fitness for its intended purpose, which is planned experiments. The document also discusses how to measure the specificity of an analytical test as well as how to examine a test's accuracy, precision, and robustness.

Specificity / Selectivity: The analytical approach itself provides the evidence necessary to demonstrate the method's specificity or selectivity when there is no interference, and the results can compare to those of an orthogonal technique [6]. When performing identification tests, it's important to show that you can recognize the target analyte based on traits of its molecular structure or other characteristics [3].

Accuracy: Should be established within the reportable range of an analytical technique, which is commonly analyzed by comparison with reference material or through the orthogonal procedure and by spiked samples [3]. It can independently assess both accuracy and precision, with each having a set acceptance threshold [6].

Precision: An assessment of precision is part of the validation process for assay tests and tests that quantitatively determine contaminants or purity [3]. Authentic, homogeneous samples or samples that have been artificially created should be used to study precision tests. Usually, repeatability, intermediate precision, and reproducibility tests are established [6].

Working Range / Reporting Range: Multivariate calibration and new vocabulary are added by Q2(R2) namely changing the position of "range" to 'reportable range' and 'working range' which encircles the preceding linearity properties, detection, and quantification limit.

Reporting range works well for describing a product's quality attributes, indicating that it should be demonstrated with adequate accuracy, precision, and specificity. Therefore, it is a value that is independent of the analytical technique used [6, 20].

Whereas the working range depends on the selection of an analytical technique. The reportable range leads to a particular working range that depends on the measured volume or concentration range of a sample and the analysis technology is chosen. For linear analysis, it is important to validate 'linearity' for the working range, and for nonlinear analysis and multivariate analysis, the link between the theoretical value and the actual value is evaluated within the reportable range [6, 20]. The lower limits of the range can be calculated using a variety of methods including accuracy and precision, signal-to-noise basis, the standard deviation of the response, and the slope basis [3].

Information Submission Regarding Analytical Procedure: Q14 lists the information that should be included in the application materials and where to place it [7]. The guidance emphasizes how to present knowledge from analytical procedure development in different CTD sections for performance attributes, acceptability criteria, the procedure utilized as a part of the control strategy, and enhanced approach (e.g., MODRs, PARs). Additionally, specific guidance is provided for the submission of multivariate methods, including RTRT, and their validation data.

Annex: Describes mock examples to help understand the text of both guidelines. It illustrates how the concepts described in ICH Q2(R2) and ICH Q14 could be applied to various analytical method formations.

CONCLUSION: These guidelines guide as a framework for easier, more logical, and better documenting of the things we already do. It will help us to keep the focus on the science and the purpose of the method. Whichever method you use should not matter if it offers accurate measurements that are simple to use. We can conclude that each guidance encompasses unified scientific and technological concepts which provide understanding, control, and characterization of analytical methods throughout the whole analytical method lifecycle. Both regulator bodies and pharma manufacturers accept this strategy that makes greater use of analytics to better comprehend and promote quality. It serves as a roadmap that marks the development of this concept and aids in encapsulating the present and foreseeable goals of the pharmaceutical industry's armature.

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