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"Implementation Of White Analytical Chemistry Assisted Analytical Quality By Design Approach Applied To Green Liquid Chromatographic Method"

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ABSTRACT:

As per the modern principles of white analytical chemistry (WAC), it is imperative to refrain from utilizing organic solvents that are carcinogenic and teratogenic in order to safeguard both the environment and analysts. A innovative idea for evaluating analytical techniques based on their economical effectiveness, greenness, and validation efficiency is white analytical chemistry. As a result, the reverse-phase high-pressure liquid chromatography (RP-HPLC) method for the simultaneous analysis was developed and validated using a WAC. In the field of chemistry, environmental protection as well as individual health and safety are being given more weight these days. As a result, there are more published studies explaining how to follow green guidelines, heed environmental agencies' recommendations, and handle chemicals more cleanly. Even the concept of "analytical quality-by-design" has been put up to highlight the importance of analytical chemistry in this industry's quality control system. But in theory, every sector of the chemical industry has a quality system, with a significant emphasis on chemical analysis and the corresponding quality control system. With time, more green chemistry ideas will find their way into the manufacturing of chemicals, such as minimizing waste output, using less materials and energy, and incorporating analytical measurements into large-scale quality-control operations. Green chemistry concepts will be included into QbD for a specific industry as a result of their integration with analytical chemistry.

In this present research review article, a general introduction to green chemistry is explained using analytical quality by design approach.

Keywords: White analytical chemistry(WAC), Green chemistry ,Reverse phase liquid chromatography(RP-HPLC), Analytical quality by design(aQBD)

1: INTRODUCTION

According to the concept of green chemistry, it pertains to "the application of techniques and methodologies that reduce or eliminate the use or generation of feedstocks, products, by-products, solvents, reagents, etc. that are hazardous to human health or the environment."[1, 2] In the green approach to chemistry, the design of a material or chemical process is given the most curiosity. Four of the twelve principles are concerned with design: designing more environmentally friendly chemical synthesis, designing safer chemicals and products, designing for energy efficiency, and designing for degradation. [3,4] Prior to the invention of green chemistry, the traditional approach to risk management focused on decreasing risk by limiting exposure rather than lowering risk by reducing hazards. [5]

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

Sustainable chemistry, clean chemistry, benign by design chemistry, and environmentally friendly synthesis constitute a few of the alternatives for "green chemistry." [6] For the safety of the analysts and the environment, it is recommended under green analytical chemistry principles that the consumption of hazardous organic solvents be minimized or avoided during the chromatographic analysis of pharmaceuticals. Only chromatographic methods can be evaluated using the principles of green analytical chemistry in terms of how they affect the environment, human safety, aqua-animal life safety, power consumption, sample consumption, and waste generation during sample analysis. White analytical chemistry (WAC) is a newly developed concept for evaluating analytical procedures for their effectiveness in sample analysis, greenness power, and cost effectiveness. Red, green, and blue (RGB) colours are blended to create the colour white. The RGB model is utilized in the WAC concept to evaluate the analytical procedure for sample analysis. With regard to linearity and sensitivity (R1), specificity (R2), accuracy and precision (R3), and robustness (R4), the Red model assessment uses four principles (R1 to R4) to measure the effectiveness of the analytical method's validation. The green model assessment takes into account four key principles of green analytical chemistry for assessing the eco-friendliness of analytical methods with regard to the use of poisonous and hazardous solvents (G1), waste generation (G2), power consumption (G3), and safety of human and animal life (G4). Four factors for evaluating the technique's cost effectiveness (B1), time effectiveness (B2), sample analysis stages (B3), and instrument handling abilities (B4) are included in the blue model's assessment of the analytical method. As a result, WAC has also added twelve assessments of the analytical approach based on principles. Additionally to assessing analytical for its cost-effectiveness, simplicity, and validation green analytical chemistry concepts. [7]

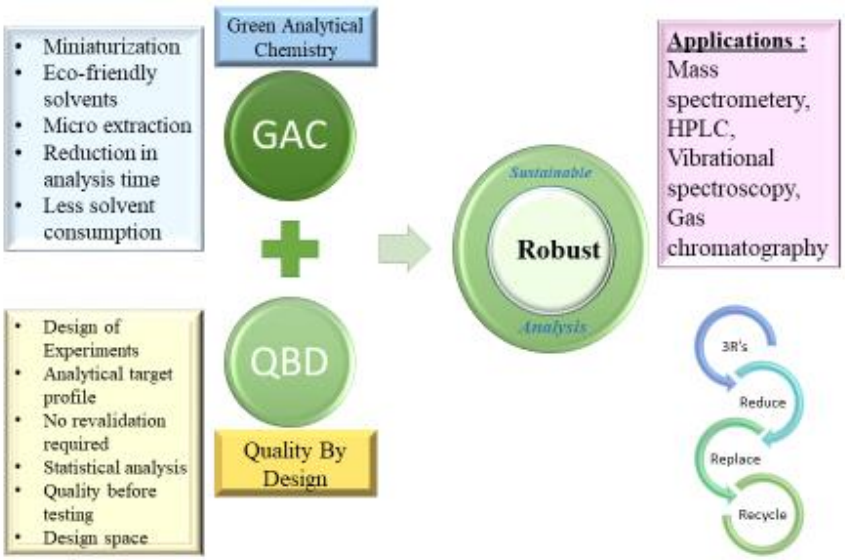


Figure 1: Green Analytical Chemistry and Quality by Design: A Combined approach towards Robust and Sustainable Modern Analysis [8]

Analytical Quality by Design: what exactly is it?

According to ICH Q8 guidelines, Qbd is defines as, "A structured approach to development starts with predetermined goals and places an emphasis on process control and product and process understanding, both of which are based on reliable science and quality risk management."[9]

The advent of AQbD has forced the industry to look beyond quality by testing (QbT) to guarantee product performance and quality. The knowledge gained throughout the development process can help with the creation of a design space and establishes the most appropriate process controls. Similar to process QbD, the outcome of AQbD is a well-understood, suitable for the task, and reliable method that consistently provides the Desired performance over the course of its lifecycle. With the use of AQbD, pharmaceutical processes and methods are better understood scientifically. Important quality attributes are also discovered, and their impact on the end product's quality is examined. The continual refinement of the process up until the last step is permitted, in Addition to giving the necessary design space for development. Reduced deviations and scientific variations help to increase resilience and prevent regulatory compliance issues.

Utilizing chromatographic analytical techniques like High performance liquid chromatography (HPLC), Gas chromatography (GC), High performance thin layer chromatography (HPTLC), and super critical fluid chromatography (SFC) is very common because of their many benefits over other nonchromatographic methods. They need fewer samples and are sturdy and adaptable. These methods reduce the possibility of human error by using automation. [10, 11]

Table 1 : **Comparison between QbT and QbD [12]**

Aspects	**QbT**	**QbD**
Pharmaceutical Development	Empirical	Systematic; Multivariate experiments
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation
Process Control	In-Process testing for go/no-go; offline analysis wide or slow response	PAT utilized for feedback and feedforward at real-time
Product Specification	Primary means of quality control; based on batch data	Part of the overall control strategy, based on the desired product performance
Control Strategy	Mainly by intermediate product and end-product testing	Risk-Based; controlled shifted upstream, real-time release
Lifecycle Management	Reactive time problem and OOS ; Post-approval changes needed	Continual improvement enabled within design space

Table 2: **DIFFERENCE BETWEEN REGULATORY PERSPECTIVE OF QbD and AQbD [13]**

Product Quality by Design (QbD)	Analytical Quality by Design (AQbD)
Quality Target Profile **(QTPP)** Definition	Analytical Target Profile **(ATP)** Definition
Critical Quality Attributes	Critical Performance Attributes**(CPA)**
Risk Assessment of Critical Material Attributes and Critical Processing Parameters	Risk Assessment of Critical Method Attributes and Critical Method Parameters
Design of Experiments and Development of Design Space **(DS)**	Design of Experiments and Development of Method Operable Design Region (**MODR)**
Manufacturing Process Validation	Analytical Method Validation
Implementation of Control strategy	Implementation of Control strategy
Continual Process Improvement	Continual Method Improvement

2: GREEN ANALYTICAL CHEMISTRY COMBINED WITH AQBD

2.1 INTRODUCTION TO GREEN CHEMISTRY [14]

In order to create more environmentally friendly and efficient products with less waste, green chemistry is a new field of study in chemistry that combines tools and techniques to assist chemical engineers in their research into the development of chemical products and processes that minimize or completely do away with the use of hazardous chemicals. In the realm of synthetic chemistry, green chemistry is now going to be a crucial instrument· A green chemist is someone who creates chemical processes and products that are safe for the environment, according to the Environmental Protection Agency. After their use, chemical products should be manufactured so that their components decompose into safe forms and are no longer released into the environment. Modern conditions have a direct impact on the environment, hence the development of greener analytical procedures has become essential. In particular, liquid chromatographic techniques are seeing an increase in the use of environmentally friendly chemicals in a variety of analytical procedures. Due to the foregoing, it is evident that when proposing or selecting an analytical method for the determination of a certain analyte, two fundamental characteristics must be taken into consideration. Two primary considerations are the method's greenness (low energy consumption, minimal waste generation, safety of reagents, no need for derivatization, and chemical recovery from residual products) and the metrological value of the results, such as selectivity, accuracy, sensitivity, and precision· The application of more environmentally friendly analytical methods is currently insufficient for pharmaceutical quality control. High Performance Liquid Chromatography (HPLC) is a more environmentally friendly method of analysis with many benefits, including operator safety and non-hazardous results. The suggested study outlines a novel chromatographic technique that substitutes ethanol, a less dangerous solvent than methanol and acetonitrile, for methanol in an environmentally responsible manner. The suggested study also demonstrates how simple it is to switch out conventional mobile phases with safer compounds and "greener" solvents without compromising the effectiveness of the procedure.

2.2 PRINCIPLES OF GREEN CHEMISTRY[15]

Poul Anastas created twelve green chemistry principles that address removing hazardous or harmful compounds from the synthesis, manufacture, and use of chemical goods. The goal of creating a green chemistry process is to apply as many of the twelve principles at different phases of synthesis, even though it is impossible to achieve all of the requirements at once.

2.2.1. POLLUTION PREVENTION: Waste prevention, as well as waste treatment and clean-up following creation, are its goals.

2.2.2. ATOM ECONOMY: It ought to be planned to optimize the amount of each material utilized during the process that ends up in the finished product.

2.2.3. LESS HAZARDOUS CHEMICAL SYNTHESIS: The synthetic process ought to be engineered to use and produce materials with minimal or negligible harm to both the environment and human health.

2.2.4. DESIGNING SAFER CHEMICALS: Chemical products should be made with the least amount of toxicity possible without sacrificing the intended purpose.

2.2.5. SAFER SOLVENTS AND AUXILLARIES: Whenever feasible, the usage of supplementary drugs should be avoided.

2.2.6. DESIGN FOR ENERGY EFFICIENCY: Low temperature and pressure chemical processes demand energy, which needs to be understood**.**

2.2.7. USE OF RENEWABLE FEEDSTOCK'S: A feedstock's raw material ought to be replenish able.

2.2.8. REDUCE DERIVATIVES: When at all feasible, avoid unneeded derivatization such as the usage of blocking groups, protection, and deportation.

2.2.9. CATAYLSIS: Better stoichiometric reagents are the catalytic reagents.

2.2.10. DESIGN FOR DEGRADATION: When a chemical product's useful life is coming to an end, it should be made such that it breaks down into safe by-products and doesn't linger in the environment.

2.2.11. REAL-TIME ANALYSIS FOR POLLUTION PREVENTION: To enable real-time, in-process monitoring and control before the creation of hazardous chemicals, analytical methods must be further developed.

2.2.12 INHERNTLY SAFER CHEMISTRY FOR ACCIDENT PREVENT: The selection of materials for the chemical process should reduce the risk of explosions, fires, and chemical accidents. Chemistry can be motivated by this idea at various levels, including research, teaching, and public opinion**.**

2.3 INTRODUCTION TO SOFTWARE[16-18]

Since not all analytical techniques are equally green, a greenness assessment for the analytical procedures is necessary. The Green Analytical Procedure Index (GAPI) , Analytical Method Greenness Score (AMGS), analytical eco scale, and AGREE metrics are used to assess how environmentally friendly the proposed method is.

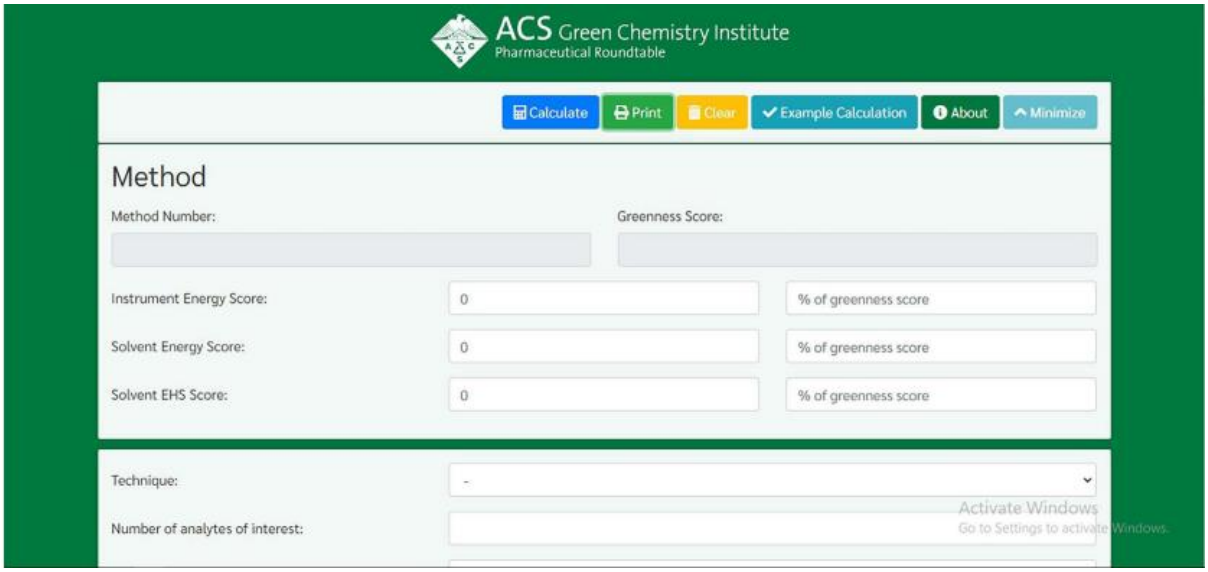


Figure 2 (a) GAPI pictogram; (b) AGREE metrics assessment (left) with its analogous scale for the indication (right); (c) AMGS spreadsheet.

The ecological assessment of the whole analytical process, from sample collection to final analysis, is taken into account by Plotka Wasylka's GAPI (Fig. 1a). It contains fragments of a pictograph that can be green, yellow, or red; green indicates safe operations, whereas red indicates unfavourable ones. MB Hicks et al. collaborated with ACS Green pharmaceutical round table websites to generate a few metrics that are combined in AMGS, a user-friendly semi quantitative tool.The number of pictograms and signal words provided by the "Globally Harmonized System of Classification and Labelling of Chemicals" (GHS) as well as the quantity of the chemicals are used by the analytical eco scale to determine penalty points. The analytical eco scale technique includes information on the type and quantity of each reagent, likely occupational familiarity, energy reduction, and waste. There were 100 total points, from which the penalty points were deducted.

Analytical Eco-Scale = 100 - total penalty points

A unique software tool for calculating the greenness profile is called AGREE. With varying weights that allow for confident flexibility, the input criteria in AGREE represent the twelve fundamental principles of green analytical chemistry. The twelve principles of green analytical chemistry were used to develop an aggregate scale with a range of 0 to 1. Each principle's product determines the overall result, which is related to all twelve of the green analytical chemistry principles. In Fig. 1b, a clockwise diagram is created, with the overall scores represented by a colour that corresponds to the greenness profile in the centre thereof. On the clockwise figure, the spontaneous red-yellow-green colour scale indicates the existence of the procedure according to the 12 principles; in contrast, each principle's weight corresponds to the width of its related segment. If the total score in the clockwise diagram's centre is close to one and the colour is dark green, the analytical method is more environmentally friendly. With a number assigned to each assessment criterion in the section, the colour indicates how well the procedure performed for each one.

2.4 INTRODUCTION TO Qbd DESIGN[19,20]

When greener chemicals are included in the building of analytical procedures, Quality by Design (QbD) provides useful insights into the influence of these compounds on method performance.ICH guidelines (ICH Q8), defines the concept of QbD "a methodical approach to development centered on product and process understanding process control based on scientific method and quality risk management, starting with predetermined objectives".

Understanding this could help in choosing an appropriate and precise process control and validation method. The notion of quality by design can be utilized in a scientific manner during the creation of an analytical method and its validation. Analytical quality by design, or AQbD, aids in the comprehension of the scientific pharmaceutical process, method, important quality attributes, and their impact on the product quality that is continuously improved upon until the method's completion. Enhancing the robustness helps prevent regulatory issues by lowering deviation and scientific variations. The advantages of chromatographic analytical techniques over non-chromatographic methods have made them widely recognized. These techniques include High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), High Performance Thin Layer Chromatography (HPTLC), Super Critical Fluid Chromatography (SFC), and Liquid Chromatography-Mass Spectroscopy (LC-MS). These methods demand a small amount of sample for analysis and are resilient, precise, accurate, and adaptable. The likelihood of human error is reduced by using these automated procedures.

2.4.1 ELEMENTS OF ANALYTICAL QUALITY BY DESIGN (AQbD)[21-23]

1. Analytical Target Profile (ATP)
2. Critical Quality Attributes (CQA)
3. Risk Management (RM)
4. Method Operational Design Region (MODR)
5. Control Strategy (CS)
6. Life Cycle Management (LCM)

2.4.2. TOOLS OF QbD

1. Design of Experiments (DOE)
2. Process Analytical Technology (PAT)
3. Risk Management Technology

STEP 1: ANALYTICAL TARGET PROFILE (ATP)

As the first phase of AQbD, ATP is the goal-setting process in the method-development approach. It is the analogous of QTPP in process design. In addition to the intended performance qualities, the ATP describes the collection of attributes determining which moiety will be quantified, in which product, by what method, over what concentration range, the proposed goal of the analytical procedure should be tied to the specifications and acceptability limitations. Precision, accuracy, range, detection limit, quantification limit, specificity, linearity, robustness, and ruggedness are among the technique performance requirements that are presumed to be predetermined targets. The development of a thorough understanding of the method's intended purpose necessitates an understanding of the moiety, its degradant, process impurities and the degradation pathways, as well as the drug's sensitivity to acid, base, oxidation, light, temperature, humidity, and critical quality attributes (CQAs) for the final product. [61] The following parameters are typically included in ATP for analytical procedures:

1. Target analytic selection (pharmaceutical items, API and contaminants)
2. Choosing the appropriate analytical technology, such as GC, ion chromatography, HPLC, HPTLC, and many more, based on the needs.
3. Requirements for the method (impurity profile and assay

Table 3: The method performance parameters as per ICH guidelines Q2 (R1)

PERFORMANCE CHARACTER	DEFINITIONS	ACCEPTANCE CRITERIA
Accuracy	The closeness of the results obtained to the true value	90-110%
Specificity	The ability to assess unequivocally the analyte in thepresence of other components that may be expected to be Present	No interference with main peak
Linearity	Ability to elicit test results that are directly or by well define mathematical transformation proportionalto the concentration of an analyte in the sample within a given range	Less than 0.999
Precision	The degree of agreement among individual test results	Inherent random variability

STEP 2: CRITICAL QUALITY ATTRIBUTES (CQA)

The analyst must determine which crucial method parameters have a direct impact on the technique's performance in this step. It will vary depending on the job. Three categories of critical method parameters exist: analyte-related parameters, instrument-related parameters, and operational condition-related parameters. Sample preparation, standards, reagents, column chemistry, mobile phase composition, pH, and mobile phase flow, column temperature, detector selection, resolution, retention time, tailing factor, detection limit, threshold purity, peak purity robustness, and other factors are important in chromatographic experiments. Critical quality criteria for the creation of analytical methods include the drug's physical and chemical properties as well as contaminants such polarity, charged functional groups, solubility, pH value, boiling point, and solution stability.

According to analytical technique, the CQA parameters for the HPLC method are as follows

1. Buffer used in the mobile phase, pH of the mobile phase, diluent, column, temperature of the column, organic modifier, injection volume, and detector
2. For the GC method: Program, pressure, injection volume, detector, oven temperature, sample concentration, gas flow, gas usage as a mobile phase, and
3. TLC plate, solvent system, injection volume and concentration, plate development time, visualization reagent for detection, and computation linked to legitimate and stated outcomes are all important factors for TLC and HPTLC methods.

STEP 3: RISK MANAGEMENT OR ASSESSMENT (RM)

It is well acknowledged in risk assessment that hazard is characterized as a combination of the likelihood and degree of harm occurring. This stage is crucial to determining the degree of accuracy and dependability of the approach. Risk assessment can be carried out in three steps, namely risk identification, risk analysis, and risk evaluation, according to ICH Q9.

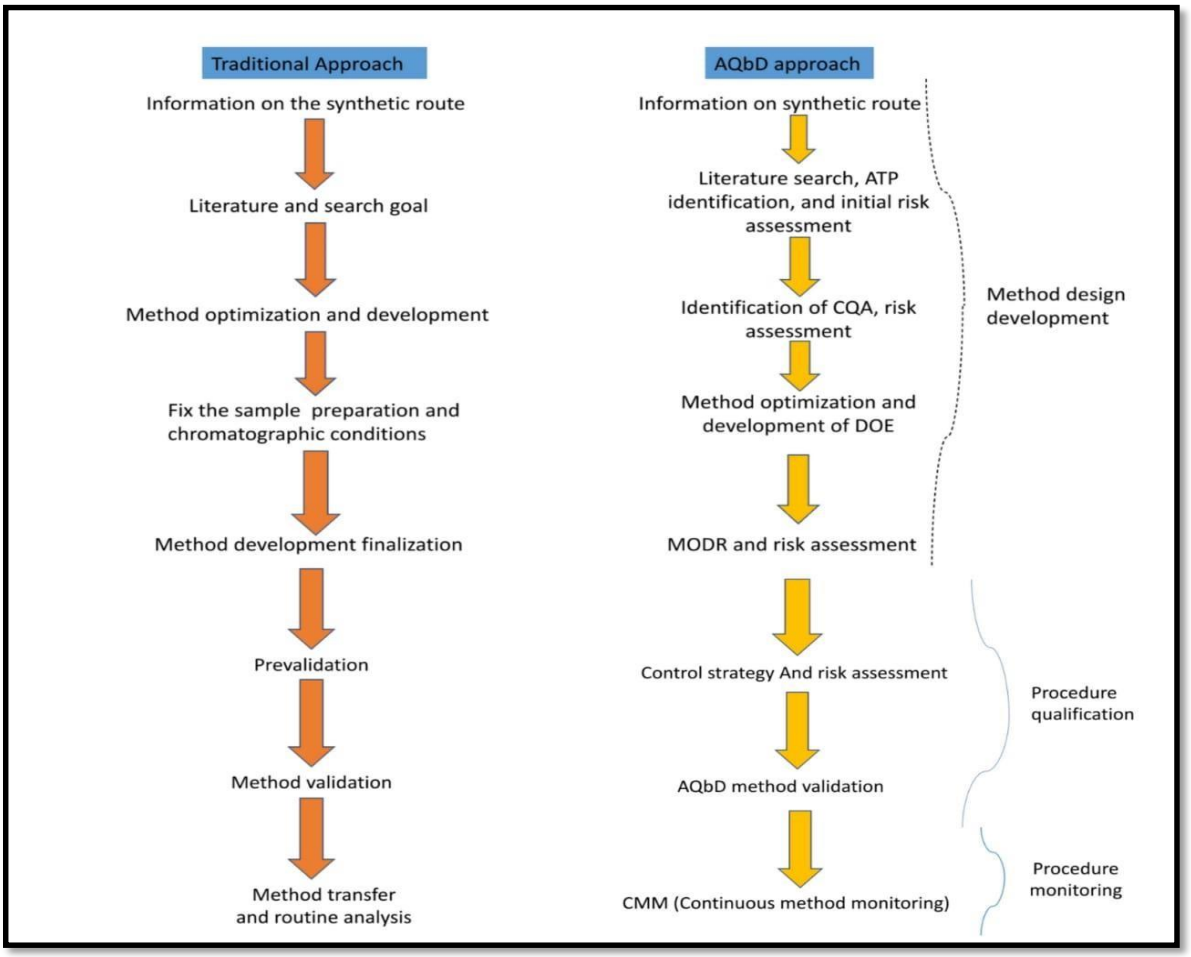


Figure 3: TRADITIONAL AND AQbD APPROACH FOR ANALYTICAL METHOD VALIDATION

Aqbd's widely accepted risk assessment instruments include the Fish Bone Diagram, Ishikawa Cause and Effect Analysis, FMEA (failure mode effect analysis0, and Prioritization Method. The failure type, impact, severity, causes, and corrective action with measures could all be evaluated during an FMEA evaluation utilizing a straightforward spread sheet. A failure is evaluated using a few metrics by an FMEA: 1) The degree of harshness on the analytical result; 2) Frequency; and 3) Detectability. The severity, occurrence, and detection level of each failure mode must be rated on a scale of 1 to 10 (1 being low, 10 being high) by the Following the rating, an RPN (risk priority number) might be determined.

The formula for calculating RPN is RPN = severity x occurrence x detection

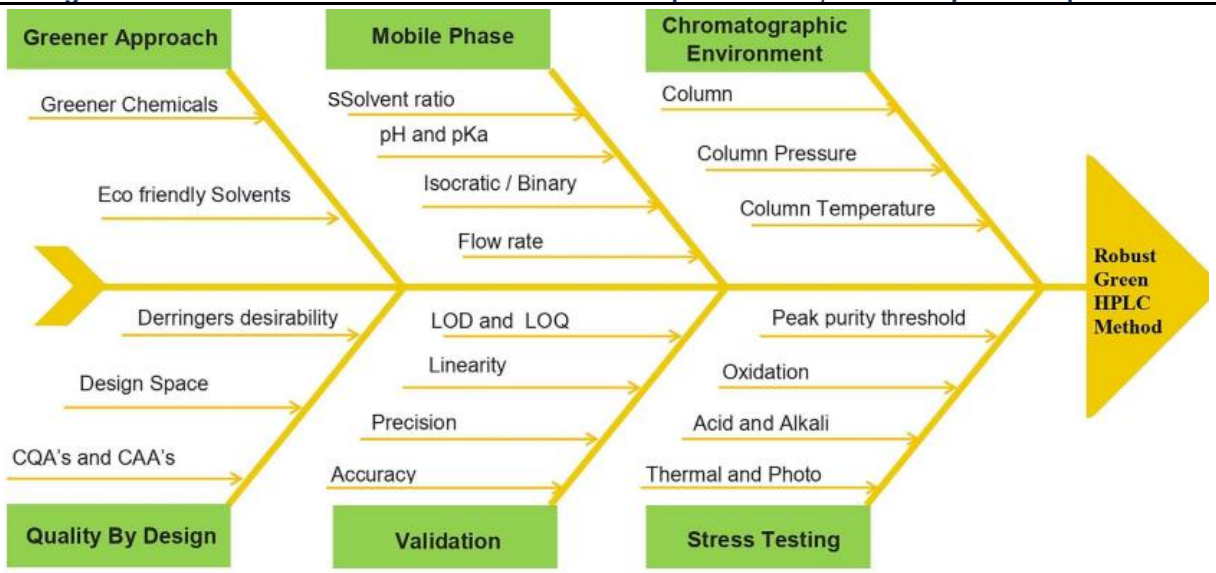


Fig 3. Fishbone diagram.

Figure 4: Ishikawa diagram showing the cause and effect analysis for a related substances method by RP HPLC method.

Table 4. Typical FMEA for a RP HPLC assay method

Recommended Actions	Responsibility	Target Date	Action Taken	SEV	OCC	DET	RPN
Actions taken or to be taken for decreasing the occurrence of the cause or facilitating the detection?	Person responsible for the recommended action?	Target date executing the recommended action?	Actual actions implemented.	How severe is the effect to the result? (1 = low, 10 = high)	How frequently is this likely to occur? (1 = low, 10 = high)	How easy is it to detect? (1 = low, 10 = high)	Risk priority number (SEV x OCC x DET)
perform DOE considering pH as critical method attribute and create a design space.	Analyst	10 days	pH range clearly defined in procedure	2	2	3	12
perform DOE considering different reagent grades as critical material attribute and create a design space.	Analyst	10 days	set of suitable reagent grades identified and clearly mentioned in the procedure	2	3	4	24

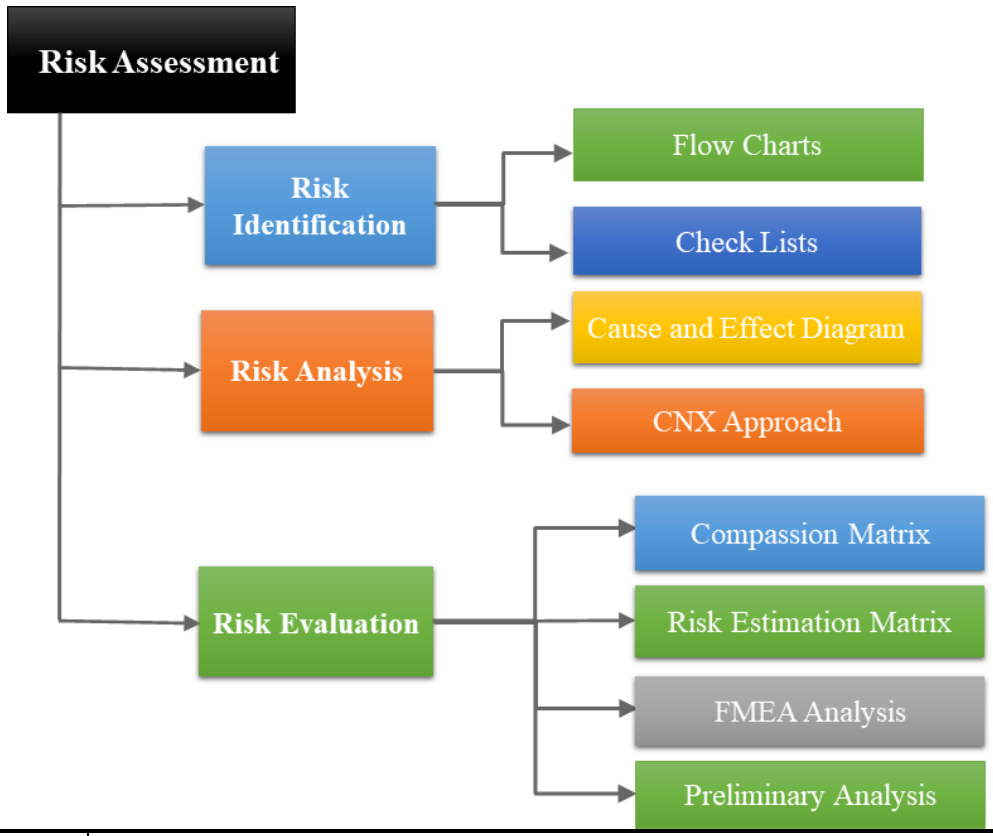
Table 5 : Typical FMEA for a RP HPLC assay method

Method	Failure Type	Potential Impact	SEV	Potential Causes	OCC	Detection Mode	DET	RPN
Outline method procedure, step or product being analyzed	Define could go incorrect (based on the Critical method parameter and Critical material attributes assessment)	evaluate the impact on the crucial output variables.	Evalute the severity to the result? (1 = low, 10 = high)	What reasons the key input to go incorrect?	Frequency of occurence (1 = low, 10 = high)	Existing control to prevent failure	Ease of Detectability (1 = low, 10 = high)	Risk priority numbe r (SEV x OCC x DET)
Assay method to quantify the content of API in the drug product by RP HPLC method	Placebo peak and analyte peak merged	Resolution between placebo peak and main analyte will reduce	10	pH of buffer (Critical method attribute)	5	pH mentioned in the procedure	2	100
Assay method to quantify the content of API in the drug product by RP HPLC method	Bad peak shape with tailing.	baseline hump at retention time of main peak will be observed	5	Grade of reagent eg., ammonium acetate used for mobile phase	4	Reagent grade mentioned in the procedure	2	40

Step 4: Method Operable Design Region (MODR)

With the help of a methodical series of tests known as MODR, analysts can quickly, scientifically, and methodically assess every possible element at the same time by establishing **Figure 5 : The sequences of steps involved in risk assessment and various tools involved in the process as mentioned in ICH Q9 guideline**

the relationship between variables and their answers. The method operable design region, or MODR, can be established during the method development phase and used as a source for a reliable and economical method. The Analytical Target Profile outlines the essential input variable's operating range. The MODR allows for flexibility in a range of input method parameters, resulting in precise method performance criteria and



response prior to FDA submission. Method validation and verification can be done once this is defined, if necessary. If there are more than four elements, screening designs must be used to eliminate the important components before optimization designs may be used to maximize the remaining factors. It Can be directly optimized using the optimization strategies if there are fewer than four factors.

Selection of Designs[24,25]

Screening

Qualitative variables can be filtered out during the screening process, which also identifies critical method parameters to be taken into account in the optimization experiments. Split factorial design and plackett burmann design are two options for the screening process; fractional factorial design may be preferred if the factors are more than four but less than six, and plackett burmann design may be used if the factors are more than six

OPTIMIZATION

Response surfaces, mixture designs, and factorial designs are among the options available for optimization. Evaluating the impacts and how the elements interact is the primary objective of optimization. Factorial designs can be chosen if there are more than two but fewer than five components. Response surface designs are used when the factors are reduced to two or four. Mixture designs are chosen when the optimization aim is related to the combination of critical component and factors. Simple lattice and restricted mixture are included in the response surface, whereas Box Behnken and Central Composite Designs are included in the mixture design. Dependant responses are measured for each experimental run for every possible combination of factors to be investigated after the experimental design has been chosen. After evaluation of model, all the responses should be specified for numerical and graphical optimization of all the factors .

SELECTION OF MODEL

The model of analysis, which is a mathematical link between factors and response, should be chosen based on the form of the anticipated response behaviour after all experimental runs. It might be Schaffer, cubic, quadratic, or linear. Analysis of variance (ANOVA test) should be performed in order to select a model. In many instances, statistical methodology, computation, and formula should be applied in accordance with method requirements in order to interpret the response result in a mathematical relationship. It could differ based on the method.

INTERPRETATION OF MODEL GRAPHS

With the use of a predicted response equation with distinct coefficients, model graphs can provide a clear understanding of how the response will behave at various levels of components at once. These coefficients include

1. 1D interaction: This illustrates how altering the level of a single element has a linear effect.
2. 2D contour: This shows the simultaneous influence of two independent influences on a single response.
3. 3D surface: It shows how three or more components interact with a 4D cube.

Following design development, a minimum of three confirmatory experimental runs within a predetermined range should be carried out. The Correlation Coefficient (R), which must be at least 0.9, will be used to compare the Observed Results of these confirmatory runs with the Predicted Results from the Model Prediction equation.

STEP 5: CONTROL STRATEGY

A control strategy is built into the product AQbD to guarantee that the instantaneous method performance meets the necessary ATP. The data gathered during the method development phase, statistical data from DoE, MODR, robustness studies, forced degradation studies, stability studies, compatibility studies, and method verification process all contribute to the control strategy. With the help of the aforementioned data, the methodology's capacity to meet the ATP is accurately forecasted. There is no reason why the control strategy should deviate from the standard process. Providing caution remarks on conventional testing protocols, such as the use of specific grade reagents, technique sensitivity to pH, and organic ratio in mobile phase, can be as easy as that**.** [81]

STEP 6: LIFE CYCLE MANAGEMENT

The recognized procedure known as Quality by Design (QbD) guarantees the suitability of a particular analytical method for the intended purpose in analysis through method validation, verification, and transfer. When combined, this is referred to as the "lifecycle management of analytical procedure," which begins with the creation of ATP and lasts until the technique is put to use. The performance qualification and acceptance requirements, such as precision study at the site of routine usage, are the primary emphasis of these efforts. These performance requirements offer reassurance that the procedure is managed over its entire lifecycle.

2.4.2 QbD METHOD VALIDATION [26-28]

*Figure 6 :*The list of method validation parameters used in QbD approach

Table 6 : The method validation parameters consideration for QbD

Parameters	Assay Characterization	Specificity	Linearity	Range	Accuracy
Definitions	Understanding of the factors that influence the mean and standard deviation/CV of the assay	To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample	The linearity of an analytical procedure isits ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample	The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including the second centrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, Accuracy and linearity.	The accuracy of an analytical procedure expresses the closeness of agreement between the values which is accepted either as a conventional true value or an accepted reference value and the value found.
Typical Factors	Excipients, Concentrations, Assay Methods (# Dilutions)	Sample preparation method, controlled impuritieso r sample matrix	3-5 concentrations aretypical with 3 min	Concentration	Well characterized standards with known potency etc.

Recommended Data and Analysis Procedure			For the establishment of linearity, a minimum of 5 Concentration Is recommended. Other approaches should be justified. ICH Topic Q2 (R1) Partied. Examination Of residuals will indicate where the linear range has been established		Minimum of **9** determinations over a minimum of 3 Concentration levels covering the specified range (e.g.3 concentrations and 3replicate each of the total analytical procedure). ICH Topic Q 2 (R1) Part II. 10+ determinations is Even better for accuracy.
TIP	QRM, Process Mapping and FR Matrix to identify key factors in the analytical method	Assay or analytical method designed to detect the specific drug attribute	Linear fit, Ad R square, equation (slope/intercept)and residuals plots	Make sure concentrations exceed drug application ranges and refer to linearity study for range	Measure mean shift from reference standard
JMP Platform	DOE, Full Factorial, Custom Designs	Fit Model and orFit Y by X	Fit Y by X or Fit Model, Residuals	Fit Y by X	Fit Y by X, Distribution and Graph Builder

During method validation, representative drug substances (DS) and drug product (DP) materials ought to be employed. When measuring and testing genuine products, these identical materials and standards will guarantee that the limits of detection and quantitation are appropriately computed, validated, and operating. Another factor to consider is the DS/DP's maturity. Use the appropriate sample size and sampling technique as specified in the method SOP for all method validation tests. Achieve satisfactory outcomes for each analytical method's method validation. Make that each validation method variable has acceptance criteria defined, and then adjust or enhance the assay to meet the requirements of the validation testing. The analytical method's suitability for use and readiness for transfer to other internal organizations or external CROs/CMOs must be determined at the end. This is verified by satisfying every acceptance criterion about linearity, bias, accuracy, etc. Usually, equivalency tests are employed in method transfer.

3. APPLICATIONS: [29, 30]

Chemo metric-based AQbD and green chemistry approaches to chromatographic analysis of remogliflozin etabonate and vildagliptin, which are two antidiabetic drugs1. The method used less toxic organic solvents and achieved optimal separation of the drugs in their fixed-dose combinations.

Quality by design approach for green HPLC method development for simultaneous analysis of two thalassemia drugs, deferasirox and deferiprone, in biological fluid23. The method integrated AQbD and GAC to maximize efficiency and minimize environmental impacts, as well as energy and solvent consumption. The method was also used to study the pharmacokinetic parameters of the drugs in rat plasma.

Green chemistry applications in various industries, such as food and flavor, pharmaceutical, paper and pulp, polymer, sugar and distillery, textile and tannery, and agrochemicals4. The applications involve the use of safer chemicals, renewable resources, waste minimization, energy efficiency, and green technologies.

CONCLUSION :

The methodical approach to method development known as Quality by Design (QbD) emphasizes understanding and control of chemical processes and products while using stated objectives. As can be observed, there are already papers that combine the principles of QbD with those of green chemistry to enable the development of more ecologically friendly analytical procedures. In these procedures, analytical methods are optimized within predetermined measurement uncertainty with specified robustness parameters, meeting customer expectations for quality in the process. Analyzing analytical techniques accessible based on metrics of green analytical methods is very helpful in the formulation of the analytical target profile during the quality design stage. This makes it possible to choose a safer analytical procedure while lessening its impact on the environment. Analytical chemistry methods can be made more environmentally friendly by using instruments that are appropriate for the job and producing the required performance. This goes beyond simply using fewer solvents and hazardous chemicals, which reduces waste associated with a given chemical measurement procedure. As a result of the instruments chosen for a particular scenario, less risks to the environment and the analyst's health and safety are present, in addition to saving materials and energy.Modern Style: Utilizing Limited number of extra tests using experiment methods are employed to ascertain acceptable ranges of method variables and their effect on the measurement procedure's repeatability and reproducibility, which includes sample preparation and the analysis of data is astounding.

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