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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR PHARMACEUTICAL ANALYSIS: PRINCIPLE,PARAMETER AND APPLICATIONS- A REVIEW

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Introduction

Pharmaceutical analysis plays a critical role in both drug and pharmaceutical formulation quality assurance and control. Drug analysis is a fundamental requirement for analytical method development. The analytical tools used in the development and validation of analytical methods have decreased analysis time, improved precision and accuracy, and decreased analysis costs. As a result, the majority of pharmaceutical companies are making significant financial investments to build cutting-edge analytical labs. An analytical process should be created for testing the API, excipient, and finished product. Such a well-designed process should guaranty that it will reliably yield the desired and accurate outcome with a high degree of precision. The analytical method needs to be validated in order to obtain such specific results. Pharmaceutical sciences are important for Ensuring Patient Safety: It finds potentially harmful substances, hazardous by products, or impurities in pharmaceutical ingredients and final products. It Guarantees Correct Dosage: It measures the precise amount of the active pharmaceutical ingredient (API) so each pill or liquid dose delivers the intended medical effect. From Batch to Batch Consistency: It guaranties consistent composition and strength throughout various manufacturing production runs. In order to determine appropriate expiration dates, shelf life and stability testing tracks how a medication deteriorates over time at different temperatures and humidity levels. Regulatory Compliance: It offers the scientific information needed by international health organizations like the FDA or WHO to authorize and sell new medications. [1]

Analytical Method Development

Analytical method development is the process of creating and optimizing a reliable laboratory procedure to identify, separate, and quantify chemical components in a sample. Ensure Product Quality: It confirms that drugs and other chemical products have the correct identity, purity, potency, and stability. To Detect Impurities: It monitors degradants and hazardous or undesired by products that may compromise safety. Also Meet Regulatory Rules: Health authorities require scientifically proven and robust testing methods before approving products for public use. Support R&D Decisions: It provides critical data during formulation design, manufacturing, and shelf-life testing. Method development includes of three main stages: viability—where you determine if the method will work with your sample; development—where you improve the method; and validation—where the optimized method is validated to the relevant

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regulatory requirements. Analytical method development and Pharmaceutical product development happens at same time and depends on each other When think about the cost, time, productivity and effectiveness of the drug product, the idea of suitable method development is essential. A well-designed approach ensures the objective, which is crucial at every stage of the drug's development. It guaranties the lab's upgraded equipment. A validated analytical process plays a crucial role in achieving high-quality and precise testing results. . There are several types of analysis methods, including spectral analysis, electrochemical analysis, and chromatography analysis.[2]

General Considerations for Analytical Procedure Development [4][3]

1.Analyte standard characterization

determining which characteristics of the drug substance or drug product the analytical process needs to test.

2. Method requirements

choosing a suitable analytical method, technology, and related tools or equipment

3. Literature search and prior methodology

carrying out suitable development studies to assess analytical procedure performance attributes, including robustness, specificity, accuracy, and precision over the reportable range (including the calibration model, limits at lower and/or higher range ends

4. Choosing a method defining a suitable analytical procedure description that includes the analytical procedure control strategy (e.g., system suitability and parameter settings).

5. Instrumental setup and initial studies

Establish initial analytical condition that can provide a measurable response from the analyte .

6. Optimization

Analytical procedure is systematically optimized to obtain the best analytical performance to obtain a method that is precise, sensitive and robust for its intended purpose .

7. Documentation of analytical figures of merit

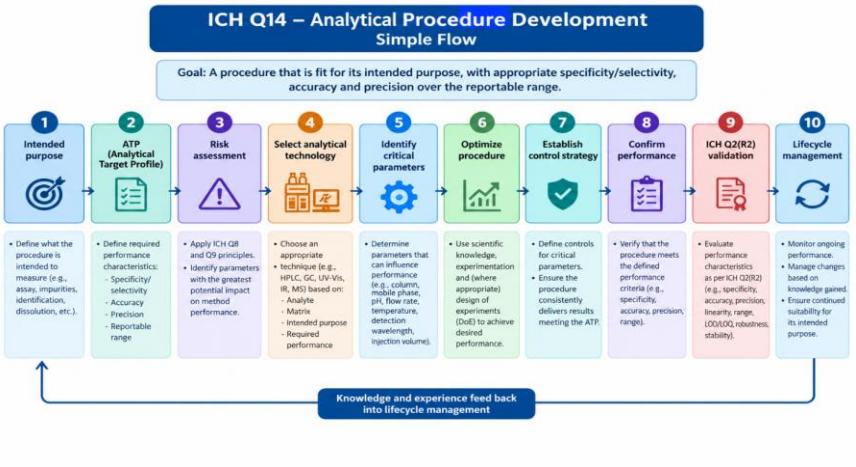
Generate documented evidence that is analytical procedure has the required performace .

8. Evaluation of method development with actual samples

Demonstrate that the developed method works effectively with real sample matrix , not just a laboratory standard .

9. Determination of percent recovery of actual sample and demonstration of quantitative sample analysis

Percentage recovery determines how much analyte can be recovered from the actual sample matrix during the analytical procedure .



Analytical Method Validation

Methods validation is the process of establishing documented evidence that offers a high level of assurance that a particular method and its auxiliary instruments will reliably produce results that accurately reflect the

quality characteristics of the tested product .Fitness for purpose, defined by IUPAC in the Orange Book as "degree to which data produced by a measurement process enables a user to make technically and administratively correct decisions for a stated purpose".

Method validation is a way for analysts to show that a method is suitable for its intended use and that the users can rely on the results that are reported..[5]Ensuring that every subsequent measurement in routine analysis will be sufficiently close to the unknown true value for the analyte content in the sample is the ultimate objective of analytical method validation..[6]

"Establishing a documented proof, which provides a high degree of assurance that a specific process will consistently produce a desired result at its prearranged specifications and quality characteristics" is how ICH Q2 (R1) defines method validation. It is, in essence, the process of demonstrating that analytical techniques are appropriate for their intended use and that they support the identity, potency, quality, and purity of drug substances and drug products. When a new method is created or when established methods are applied in various labs and by different analysts, method validation is necessary..[7]

Accuracy, precision, specificity, linearity, range, ruggedness, robustness, detection of limit, and quantitation limit are among the analytical parameters that can be verified, according to USP.

The ICH states that the following analytical parameters can be verified: linearity, range, system suitability, robustness, accuracy, precision, specificity, detection of limit, and quantitation limit. [8]

The FDA claims Accuracy, precision, specificity/selectivity, detection of limit, quantitation limit, linearity, range, system suitability, reproducibility, sample solution stability, and robustness are among the analytical parameters that can be verified. .

In accordance with European regulations Accuracy, precision, specificity, detection of limit, quantitation limit, linearity, and range are analytical parameters that can be verified.

Validation should ideally begin in the lab at the outset. Scientists find out in the lab precisely how the product reacts and what conditions must be met in order to create it. They discover the circumstances in which the product malfunctions, becomes unstable, becomes unusable, and when its quality starts to decline. This data can be used to establish requirements for validation once the laboratory has determined the boundary processing criteria. Validation should ideally begin in the lab at the outset. Scientists find out in the lab precisely how the product reacts and what conditions must be met in order to create it. They discover the circumstances in which the product malfunctions, becomes unstable, becomes unusable, and when its quality starts to decline. This data can be used to establish requirements for validation once the laboratory has determined the boundary processing criteria.

System validation is an ongoing process. A new system still needs upkeep, regular calibrations, and adjustments after it has been validated. As a result, the procedure is constantly being examined and assessed.

Types of analytical procedures to be validated

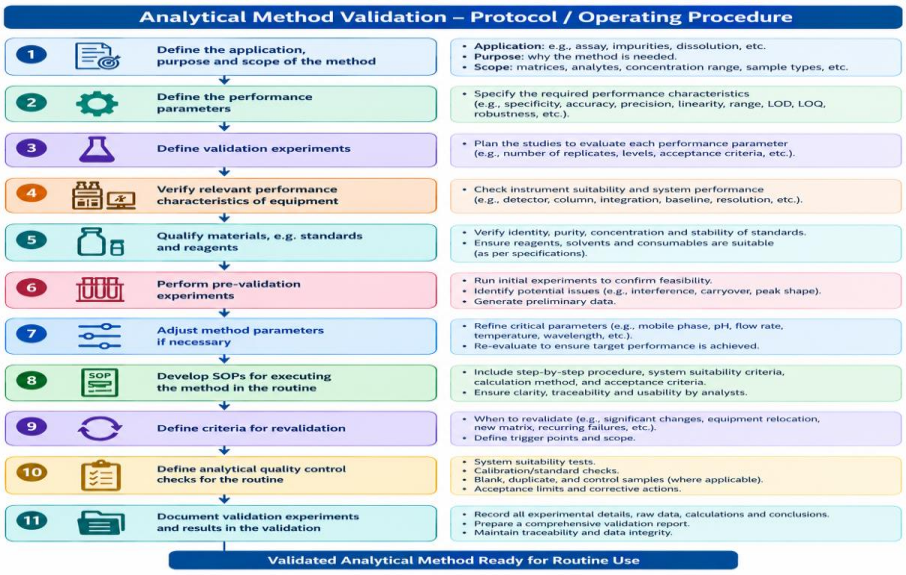
Identification tests Identification tests are used to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.

Quantitative tests and Limit tests for impurity control Testing of impurities can be performed by using a quantitative test or a limit test for the impurity in a sample. Different validation parameters are required for a quantitative test than for a limit test

Quantitative tests of the active moiety in samples of drug substance or drug product In this type, assay procedures are used to measure the analyte present in a given sample. The assay represents a quantitative measurement of the major component(s) in the drug substance.[9]

Steps of Analytical Validation

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Aim

To review the principles, approaches, and regulatory requirements involved in the development and validation of analytical methods used for the reliable identification, quantification, and quality assessment of pharmaceutical drug substances and drug products, with particular reference to ICH Q14 and ICH Q2(R2) guidelines.

Objectives

1. To review the fundamental principles of analytical method development and validation in pharmaceutical analysis.
2. To study the different analytical techniques commonly employed for pharmaceutical analysis, including HPLC, GC, UV-Visible spectroscopy, and other instrumental methods.
3. To understand the systematic approach to analytical method development, including selection of analytical technology, optimization of method parameters, and assessment of method performance.
4. To review the concept of the Analytical Target Profile (ATP) and its importance in developing analytical procedures that are fit for their intended purpose.
5. To study the important analytical performance characteristics such as specificity/selectivity, accuracy, precision, linearity, range, detection limit, quantitation limit, and robustness.
6. To review the requirements of analytical procedure validation according to the current ICH Q2(R2) guideline.
7. To understand the role of risk assessment and experimental design in analytical procedure development according to ICH Q14
8. To examine the importance of sample preparation, system suitability, standard and reagent qualification, and instrument performance during method development and validation.
9. To review the evaluation of analytical methods using actual samples, including recovery studies and quantitative determination of analytes.
10. To study the importance of documentation, SOPs, acceptance criteria, and analytical quality control checks for routine application of validated methods.
11. To understand analytical procedure lifecycle management, including monitoring, change management, and criteria for revalidation.
12. To summarize the current regulatory approach to analytical method development and validation and identify its importance in ensuring the quality, safety, and efficacy of pharmaceutical products.

Analytical Techniques Used in Pharmaceutical Analysis

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Method	Principle / measurement	Common pharmaceutical applications
UV–Visible spectrophotometry	Measures absorption of UV/visible radiation	Assay of drugs, dissolution studies, identification, quantitative analysis
IR / FTIR spectroscopy	Measures molecular vibrational absorption	Identification of APIs and excipients, functional-group characterization
Fluorescence spectroscopy	Measures emitted radiation after excitation	Trace analysis and analysis of fluorescent/derivatized compounds
NMR spectroscopy	Measures nuclear magnetic resonance	Structural elucidation, identification, impurity characterization
HPLC	Separates compounds using a liquid mobile phase and stationary phase	Assay, related substances, impurities, degradation products, stability testing
UHPLC	High-efficiency form of liquid chromatography	Rapid and high-resolution pharmaceutical analysis
GC	Separates volatile/thermally stable compounds in a gas phase	Residual solvents, volatile impurities, some APIs
TLC/HPTLC	Separation on a coated stationary layer	Identification, purity testing, screening and sometimes quantification
LC–MS/MS	Liquid chromatography coupled with mass spectrometry	Trace impurities, degradation products, bioanalysis, metabolite analysis
GC–MS	Gas chromatography coupled with mass spectrometry	Identification of volatile compounds and residual solvents
Potentiometry	Measures electrode potential	pH, ion analysis, acid–base titrations
Karl Fischer titration	Quantifies water	Moisture/water determination in APIs and formulations
Titrimetric methods	Quantitative reaction with a standard solution	Assay, acid/base content, oxidation-reduction analysis
Polarimetry	Measures optical rotation	Identification/purity of optically active substances
Dissolution testing	Measures drug release from dosage form	Tablets and capsules; quality and performance testing
Particle-size analysis	Determines particle-size distribution	Powders, suspensions, inhalation products
Thermal analysis (DSC/TGA)	Measures thermal transitions or mass changes	Melting behavior, polymorphism, stability, compatibility
X-ray diffraction (XRD)	Measures crystal structure/diffraction pattern	Polymorphism and solid-state characterization

Analytical Method Development: From Purpose to Lifecycle Management

The utility of a pharmaceutical analytical method is limited only by the decisions it supports. A wrong result failing a good batch wastes material and time; a wrong result passing a poor batch risks the health of patients. Thus, development is the point at which the reliability of future data is determined, and validation can only confirm, not create, that reliability.

The development of a method can be viewed as a chain of questions:

1. Why is the method needed, and what exactly must be measured?
2. Which technique is best suited, and why?

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3. What performance must the method deliver (the ATP)?
4. Which method parameters influence the result?
5. How are those parameters optimized?
6. Which of them are critical?
7. How is it decided that the method is acceptable?
8. How can risk be managed during development?
9. How can quality be built into the method (AQbD)?
10. How is the method managed after approval (lifecycle)?

The sections below address each question in turn.

2. Defining the Purpose of the Method: What Exactly Do We Want to Measure?

Every development project begins with a precise statement of purpose. Without it, a method may be technically excellent but unsuitable for the decision it must support.

2.1 Questions to Settle First

- **The analyte:** the active pharmaceutical ingredient (API), a specific impurity, a degradation product, a preservative, a metabolite, or a residual solvent.
- **The attribute:** identity, assay (potency), related substances, content uniformity, dissolution, water content, particle size, or residual solvents.
- **The sample and matrix:** drug substance, tablet, injectable, topical product, plasma, or urine, with the excipients or biological components that accompany the analyte.
- **The concentration range:** the expected level of the analyte, from percent-level for assay down to parts-per-million or ng/mL for impurities and bioanalysis.
- **The decision to be supported:** batch release, stability monitoring, process control, cleaning verification, or a pharmacokinetic study.
- **The stage of development:** an early-phase method can be fit-for-purpose, whereas a commercial method must be fully validated and robust.

2.2 Purpose Shapes the Method

The same molecule may need very different methods. An assay of a tablet needs high precision around 100% of label claim. An impurity method needs sensitivity and resolution at 0.05 to 0.1% levels. A bioanalytical method needs to detect nanogram quantities in a protein-rich fluid. Defining the purpose prevents wasted effort and sets the direction for every later choice.

2.3 Gathering Background Knowledge

Now that the objective is set, scientists gather existing information on the analyte such as its structure, molecular weight, pKa, log P, solubility, UV spectrum, stability, degradation products, formulation information, and any literature or pharmacopoeia method. Prior knowledge is an acknowledged input to development as per ICH Q14. [13].

3. Selection of the Analytical Technique: Why This Technique?

Technique selection is a reasoned match between what the analyte is, what the method must do, and what the technique can offer.

3.1 Selection Criteria

- **Analyte properties:** volatility, polarity, ionization, chromophore, thermal stability, molecular size.
- **Required selectivity:** can the technique distinguish the analyte from impurities, excipients, and degradants?
- **Required sensitivity:** does it reach the necessary detection and quantitation limits?
- **Matrix complexity:** simple solution, formulation, or biological fluid.
- **Accuracy and precision needs:** assay methods demand tighter performance than limit tests.
- **Throughput, cost, and availability:** especially for routine quality control.
- **Robustness and transferability:** can it be run reliably in other laboratories?

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- **Regulatory acceptance and sustainability:** pharmacopoeial precedent, solvent consumption, waste.

3.2 Common Technique Choices and Their Rationale

Technique	Why it is chosen	Typical application
Reversed-phase HPLC/UPLC with UV or PDA	Versatile, selective, precise, robust, suits non-volatile and thermally labile compounds	Assay, related substances, content uniformity, stability-indicating methods
Gas chromatography (FID, headspace)	Suits volatile and thermally stable analytes	Residual solvents, volatile impurities
LC-MS/MS	Very high sensitivity and selectivity in complex matrices	Bioanalysis, trace and genotoxic impurities, impurity identification
UV-visible spectrophotometry	Simple, rapid, low cost; limited selectivity	Simple assays, dissolution samples, bulk drug
HPTLC/TLC	Parallel analysis, low cost	Identification, screening, herbal products
FTIR, Raman, NMR	Structural information	Identification, solid-state and structural confirmation
Capillary electrophoresis	High efficiency, low solvent use, suits charged and chiral species	Chiral purity, ionic analytes
Titrimetry	Absolute, inexpensive	Bulk drug assay

3.3 Example of Justification

In the case of a tablet with a UV-absorbent, non-volatile, ionizable active pharmaceutical ingredient that has multiple potential degradents, reversed-phase HPLC along with PDA detection is justified based on the ability to separate the API from its degradents, quantification with precision, peak purity identification, and availability in QC labs [14]. On the other hand, for the detection of the same API in low ng/mL in plasma, LC-MS/MS can be justified because of the sensitivity and selectivity. Justifying the approach is a part of the development process.

4. Understanding the Analytical Target Profile

The analytical target profile is a predictive description of the performance criteria of the method. The profile is technique independent in that it describes what the method should do, but not how it should do it. [13].

4.1 Elements of an ATP

- The analyte and the attribute to be measured;
- The matrix or product type
- The intended range of reportable values
- The required performance characteristics, such as accuracy and precision, expressed in terms of acceptable uncertainty of the reportable result;
- The required specificity (for example, resolution from specified impurities);
- Sensitivity requirements (LOD/LOQ) when relevant.

4.2 Illustrative ATP Statement

The procedure must quantify drug X in tablets over 80 to 120% of the label claim, with a reportable value that lies within ±2.0% of the true value with at least 95% probability, and with no interference from known degradation products or excipients.

4.3 Value of the ATP

The ATP converts the purpose into measurable requirements, guides technique selection, defines the criteria against which optimization and validation are judged, and provides a stable reference during later method

changes. A different technique can replace the original method at any time, provided the ATP is still met [13][15].

5. Identifying the Important Method Parameters

After the technique is chosen, all the variables that may influence the result are listed. Using HPLC as the model, they fall into groups.

Group	Parameters
Sample preparation	Extraction solvent, extraction time and technique (shaking, sonication), sample weight, dilution, filtration (filter type, discarded volume), solution stability
Chromatographic column	Stationary phase chemistry, particle size, column length and diameter, column lot and manufacturer
Mobile phase	Organic modifier, buffer type and strength, pH, additive, gradient program, preparation procedure
Instrument	Flow rate, column temperature, injection volume, dwell volume, detector settings
Detection	Wavelength, bandwidth, response time, data acquisition rate
Data handling	Integration parameters, calculation approach, system suitability limits

Not all of these parameters are equally important. Identification is based on prior knowledge, preliminary experiments (scouting), and chemical reasoning, for example, the effect of pH on the retention of an ionizable analyte. The list is then narrowed by assessing which parameters actually affect the method's performance attributes (Section 8).

6. Method Optimization

Optimization refines the initial conditions until the method meets the ATP with margin to spare.

6.1 Scouting and Initial Conditions

The development process begins with a generic screening procedure that involves the use of a C18 column, a broad gradient with an aqueous phase with a buffer and acetonitrile or methanol, and detection at the maximum absorbance of the analyte. This gives information on the retention behavior and number of components and it identifies problems such as poor peak shape**.**

6.2 Improving Separation

Resolution depends on efficiency, retention, and selectivity. Selectivity is the most powerful lever and is adjusted by:

- changing mobile phase pH, which alters the ionization and retention of acids and bases;
- switching the organic modifier (acetonitrile versus methanol);
- changing the stationary phase (C8, phenyl, polar-embedded, HILIC);
- adjusting temperature and gradient slope.

Efficiency improves with smaller particles, longer columns, and optimal flow, while retention is tuned through solvent strength.

6.3 Optimizing Sample Preparation and Detection

Optimal extraction conditions are ensured in order to achieve complete and reproducible extraction. In case of biological samples, protein precipitation, liquid-liquid extraction or solid phase extraction is studied for its recovery, purity and matrix effect and internal standard is chosen. Sensitivity and selectivity of detection are optimized.

6.4 One-Factor-at-a-Time versus Design of Experiments

Adjustment of one factor at a time is easy but inefficient and can never identify the interaction, e.g., between pH and organic matter. DoE employs factorial, central composite or Box-Behnken designs to study the effect of several factors at once, modeling the response (resolution, tailing and runtime), and pinpointing the optimum and robust conditions with fewer experiments. [15][16].

6.5 Stability-Indicating Optimization

When the method needs to be stability-indicating, the optimization is done by using stressed samples, which include acid, base, oxidation, heat, and light. The goal here is to ensure that the API is separated from any degradation products and that the peaks are spectroscopically pure. It is usually attempted to have about 5 to 20% degradation of the compound. [17].

7. Critical Method Parameters

Critical method parameter (CMP) is a variable in the method whose variation has a significant impact on the critical method attribute (CMA). A CMA refers to a performance feature of the method, which includes resolution of a critical pair, tailing factor, retention time, and accuracy of results.

7.1 How Critical Parameters Are Identified

1. Define the critical method attributes from the ATP (for example, resolution between the API and its closest-eluting impurity must be at least 2.0).
2. List all potential method parameters (Section 5).
3. Rank them using risk assessment tools and prior knowledge (Section 9).
4. Test the high-risk parameters experimentally by screening designs, such as fractional factorial or Plackett-Burman designs.
5. Confirm which parameters show statistically and practically significant effects.

7.2 Typical Critical Parameters in HPLC

For ionizable compounds, mobile phase pH is almost always critical. Organic modifier content or gradient steepness, column temperature, buffer strength, and column chemistry or lot number come next in terms of importance. Factors like injection volume or detector bandwidth are generally non-critical for a well-planned method. For sample preparation, extraction time, solvent composition, and sonication conditions can be critical to recovery.

7.3 Controlling Critical Parameters

The critical parameters have been assigned definite set points and ranges in the procedure with proper control and system suitability tests. The non-critical parameters may be assigned wider ranges since that would ease their implementation..

8. How Do Scientists Decide That a Method Is Acceptable?

A method is judged acceptable when objective evidence shows that it meets the ATP and is fit for its intended use. This is done in several steps.

8.1 Acceptance During Development

Prior to validation, preliminary criteria are used for the optimized method. These include resolution of at least 1.5 to 2.0 between critical peaks, tailing factor not greater than around 2.0, appropriate number of plates, satisfactory retention factor, peak purity of the analyte peak, and reproducibility in terms of replicate injections. Robustness is tested through intentional manipulation of the critical parameters to verify that the criteria are fulfilled.

8.2 Formal Validation Against Predefined Criteria

Acceptance is demonstrated through validation under ICH Q2(R2), with criteria set in a protocol before testing starts [18].

Parameter	Question answered	Common approach
Specificity	Is the analyte measured without interference from impurities, degradants, excipients, or matrix?	Blank, placebo, spiked and forced-degraded samples; peak purity
Linearity and range	Is the response proportional over the working range?	At least five concentrations; regression and residual analysis
Accuracy	How close is the result to the true value?	Recovery of spiked analyte at several levels
Precision	How reproducible are results?	Repeatability, intermediate precision, reproducibility (%RSD)

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LOD and LOQ	What is the lowest detectable and quantifiable amount?	Signal-to-noise or regression-based estimation
Robustness	Does the method withstand small deliberate changes?	Variation of pH, flow, temperature, composition, column lot
System suitability	Is the system performing correctly today?	Resolution, tailing, plate count, replicate injection %RSD

8.3 Judging Fitness for Purpose

Acceptance criteria vary depending on the kind of test. The recovery is expected to be near 100 percent in the case of an assay with low %RSD while trace level impurities have greater acceptance limits at low concentrations. The current guidance suggests that the performance be evaluated based on whether the total uncertainty of the reportable value is suitable for the ATP and the specification rather than through unrelated criteria [13][18]. The bioanalytical procedures adopt ICH M10 criteria of matrix effects, carryover, dilution integrity and incurred sample reproducibility. [19].

8.4 Continuing Acceptability in Routine Use

The method is accepted not just once but continuously: system suitability tests are performed each time, control samples and trending are evaluated, and all out-of-specification or unusual results are investigated for method-related reasons.

9. Risk-Based Method Development

Risk-based development focuses effort where it is most needed. It applies the principles of ICH Q9 to analytical procedures [20].

9.1 Steps of the Approach

1. **Risk identification:** list everything that could cause the method to fail to meet its ATP, drawing on prior knowledge and experience.
2. **Risk evaluation:** rank the risks to decide which parameters warrant experimental study and which need only routine control.
3. **Risk control:** reduce high risks through optimization, tighter control limits, additional system suitability tests, or a change in method design.
4. **Risk review:** revisit the assessment as knowledge increases or when the method changes.

9.2 Common Tools

- **Ishikawa (fishbone) diagrams** to identify potential sources of variability under headings such as method, materials, instrument, analyst, environment, and measurement.
- **Failure Mode and Effects Analysis (FMEA)**, which scores severity, occurrence, and detectability to give a risk priority number.
- **Risk ranking and filtering matrices** and cause-and-effect matrices for screening parameters.
- **Preliminary hazard analysis** during early development.

9.3 Benefits

Risk Assessment ensures that the experiments will focus on only a small number of important variables; it facilitates transparency and documentation of decision-making as well as the rationale behind the chosen control approach. It is the bridge between background knowledge and experimental studies in AQbD.

10. Analytical Quality by Design

Quality by Design (QbD), an approach which is incorporated from ICH Q8 on Quality by Design, applies the concept of AQbD in relation to analytical procedures where quality of the method is ensured in advance [14][20]. This begins with the ATP.

10.1 Stages of AQbD

1. **Define the ATP** and the critical method attributes.
2. **Select the technique** and develop initial conditions using prior knowledge.
3. **Risk assessment** to identify potential critical method parameters.

4. **Design of Experiments** to quantify the effect of the parameters and their interactions on the critical method attributes.
5. **Establish the Method Operable Design Region (MODR):** the multidimensional combination of parameter ranges within which the method consistently meets the ATP.
6. **Define the analytical control strategy:** set points, ranges, system suitability tests, and controls that keep the method within the MODR.
7. **Validate and verify** the method at selected working conditions.
8. **Continually monitor and improve** performance through the lifecycle.

10.2 Method Operable Design Region

The MODR serves as the main output of AQbD. As the impact of the parameters is established, working anywhere within the MODR will result in acceptable performance. Any modification within the MODR, such as a slight increase in pH and gradient, is thus not seen as a modification that would warrant a validation effort. [15].

10.3 Traditional Approach versus AQbD

Feature	Traditional approach	AQbD approach
Starting point	Method conditions	ATP and critical method attributes
Optimization	One factor at a time	Risk assessment and DoE
Operating conditions	Single fixed set point	Design space (MODR) with ranges
Robustness	Tested late, at validation	Built in during development
Changes	Often require revalidation or filing	Managed within the established region
Knowledge	Limited	Documented and scientifically justified

11. Analytical Procedure Lifecycle Approach

The lifecycle approach recognizes that a method does not end at validation. It continues through routine use, transfer, and change, and its performance must be assured throughout. ICH Q14, ICH Q2(R2), and ICH Q12 together provide the regulatory framework, and USP general chapter <1220> describes the lifecycle stages [13][18][22].

11.1 Stages

Stage	Purpose	Key activities
Stage 1: Procedure design and development	Create a method that meets the ATP	Define the ATP, select technique, risk assessment, DoE, define control strategy
Stage 2: Procedure performance qualification	Demonstrate the method performs as intended	Validation under ICH Q2(R2), method transfer, comparison against the ATP
Stage 3: Continued procedure performance verification	Ensure the method stays fit for purpose	System suitability, trending of results, control charts, review of deviations

11.2 Minimal versus Enhanced Approach

ICH Q14 describes a minimal (traditional) approach and an enhanced approach. The enhanced approach uses the ATP, risk assessment, multivariate studies, and a defined control strategy to establish **established conditions** for the method. These are the elements that must be reported to authorities if changed, while other parameters can be modified under the company's own quality system [13].

11.3 Method Transfer

When a method moves to a quality control or contract laboratory, transfer is shown by comparative testing, co-validation, or a justified waiver, using pre-agreed acceptance criteria. Clear identification of critical parameters and known sensitivities, for example to column lot or buffer preparation, reduces transfer failures.

11.4 Change Management and Continual Improvement

Performance data collected through routine use show trends, signs of drift, and opportunities for improvement. Changes, such as moving from HPLC to UPLC to reduce solvent use or analysis time, are assessed against the ATP. If the ATP is still met, the change can be handled through a risk-based and documented process, often with reduced regulatory burden under an established-conditions framework [13][22].

11.5 Retirement

When a method is superseded, the reasons and the bridging data comparing old and new performance are documented.

12. Conclusion

Analytical method development is most effective when treated as a connected sequence of scientific decisions. It starts with a precise definition of what must be measured and why, followed by a justified choice of technique, a clearly stated ATP, identification and optimization of method parameters, recognition of those that are critical, and objective criteria for acceptance. Risk assessment focuses effort where it matters, AQbD builds robustness through understanding, and the lifecycle approach ensures that performance is maintained long after approval. The combination of ICH Q2(R2) and ICH Q14 gives a coherent framework for developing methods that are specific, accurate, precise, robust, and fit for purpose throughout the life of the product.

Analytical Method Validation

Drug testing is done through measurement. A validation process provides assurance that a measured value, be it an assay value, impurity or concentration of drug in plasma, gives an accurate representation of truth within acceptable limits of uncertainty. Validation is mandated by regulatory agencies for methods used in marketing and manufacturing processes.

Validation should be distinguished from related activities:

- **Development** designs and optimizes the method.
- **Validation** demonstrates through planned experiments that the method meets predefined criteria.
- **Verification** confirms that a compendial or already validated method works in a particular laboratory.
- **Transfer** qualifies a receiving laboratory to run an established method.

The type of test determines which parameters are evaluated. The USP and ICH distinguish identification tests, quantitative tests for impurities, limit tests for impurities, and assay tests for the active ingredient or other selected components [23][26]. Table 1 summarizes the parameters typically evaluated.

Parameter	Identification	Impurity (quantitative)	Impurity (limit)	Assay, dissolution, content uniformity
Specificity	Yes	Yes	Yes	Yes
Accuracy	No	Yes	No	Yes
Precision	No	Yes	No	Yes
Linearity/response	No	Yes	No	Yes
Range	No	Yes	No	Yes
Detection limit	No	No	Yes	No
Quantitation limit	No	Yes	No	No
Robustness	Evaluated during development for all procedures			

Table 1. Parameters normally considered by test type (after ICH Q2(R1) practice; Q2(R2) retains the same logic with updated terminology).

ICH Q2(R2), adopted in 2023, keeps these performance characteristics but modernizes the terminology (for example, the response/calibration model and reportable range) and extends the scope to multivariate and spectroscopic procedures [23].

2. Specificity

Definition The capacity of the test to evaluate the analyte unequivocally in the presence of substances which can reasonably be anticipated to be present, e.g., impurities, degradants, excipients, and matrix constituents.

"Specificity/selectivity" is the terminology used in ICH Q2(R2). [23].

Purpose. To prove that the measured signal arises only from the analyte, so that the result is not falsely high or low. Specificity is the foundation on which the other parameters rest.

How it is evaluated.

- Inject blank, , reference standard, and sample, and compare chromatograms for interference at the analyte retention time.
- Spike the sample with known impurities and degradants and demonstrate resolution from the analyte.
- Analyze forced-degraded samples (acid, base, oxidative, thermal, photolytic) and assess peak purity using photodiode array or mass spectrometry.
- For identification tests, show positive results for samples containing the analyte and negative results for structurally related compounds.
- Where full separation is not possible, compare results with a second, orthogonal procedure.

Interpretation. No significant interfering response at the analyte peak in blank or placebo; resolution between the analyte and the closest-eluting peak commonly at least 2.0; peak purity indices indicating a homogeneous peak; and satisfactory mass balance in stressed samples.

Pharmaceutical significance. A non-specific method can report degraded or contaminated product as acceptable, mask harmful impurities, or give unreliable stability conclusions. Specificity therefore directly protects patient safety.

3. Accuracy

Definition. The closeness of agreement between the value found and a value accepted as a true or reference value. It is often reported as percent recovery.

Purpose. To show that the method has no significant systematic error (bias) and that the analyte is fully recovered from the sample matrix.

How it is evaluated.

- For drug substance: apply the method to a reference material of known purity, or compare with a second well-characterized procedure.
- For drug product: spike placebo with known amounts of the analyte (or use standard addition when a placebo cannot be prepared).
- ICH recommends a minimum of nine determinations over at least three concentration levels covering the specified range (for example, three concentrations with three replicates each) [34].
- Report percent recovery for each level together with the mean and confidence interval.

Interpretation. For assay of a drug product, mean recovery is commonly required to be within 98.0 to 102.0%. For impurities and low-level analytes, wider limits are acceptable (for example, 80 to 120%, depending on level). For bioanalytical methods, ICH M10 expects mean accuracy within ±15% of nominal (±20% at the lower limit of quantitation) [29]. Consistent bias at one level suggests incomplete extraction or interference.

Pharmaceutical significance. Accuracy ensures that potency and impurity values reflect the true content, which determines whether a batch is correctly released or rejected and whether patients receive the intended dose.

4. Precision

Precision is the closeness of agreement among a series of measurements obtained from multiple samplings of the same homogeneous sample under prescribed conditions. It is expressed as standard deviation, relative standard deviation (%RSD), or confidence interval, and is considered at three levels.

4.1 Repeatability

Definition. Precision under the same operating conditions over a short interval of time (intra-assay precision): same analyst, instrument, reagents, and day.

Purpose. To show the smallest expected variability of the method and that the measurement system and sample preparation are inherently consistent.

How it is evaluated. At least six determinations at 100% of the test concentration, or at least nine determinations covering the specified range (for example, three concentrations with three replicates each) [23]. The mean, standard deviation, and %RSD are calculated.

Interpretation. For drug product assay, %RSD of 2.0% or less is commonly accepted. Higher values are acceptable at low concentrations, and the acceptable variability increases as the analyte level decreases, consistent with the Horwitz relationship.

Pharmaceutical significance. Low repeatability variability ensures that a result near the specification limit can be interpreted with confidence and reduces unnecessary out-of-specification investigations.

4.2 Intermediate Precision

Definition. Within-laboratory variation arising from random events such as different days, analysts, instruments, columns, and reagent lots.

Purpose. To show that the method gives consistent results under the normal variation of routine use within one laboratory.

How it is evaluated. A planned experiment in which the same homogeneous samples are analyzed by different analysts on different days using different equipment, where available. Variance components are estimated, often with analysis of variance (ANOVA), and the overall %RSD is compared with repeatability. Statistical tests such as the F-test or Student's t-test may compare analyst or day means.

Interpretation. The overall %RSD should meet the acceptance criterion and should be only modestly higher than repeatability. A significant analyst, day, or instrument effect indicates uncontrolled method steps requiring improvement.

Pharmaceutical significance. Quality control laboratories run methods for years with changing staff and equipment. Intermediate precision predicts whether results will remain consistent in that real environment.

4.3 Reproducibility

Definition. Precision between laboratories, as assessed in collaborative studies.

Purpose. To demonstrate that the method performs consistently when run by different laboratories, which is essential for standardization and transfer.

How it is evaluated. An interlaboratory study in which several laboratories analyze identical samples by the same written procedure. Between-laboratory standard deviation and %RSD are calculated, often following ISO 5725 principles. It is usually required for methods proposed for pharmacopoeial inclusion and is not always needed for routine in-house methods [23].

Interpretation. Between-laboratory %RSD should be acceptable for the intended use and, as expected, higher than repeatability. Large differences between laboratories point to ambiguous procedure instructions or critical but uncontrolled parameters.

Pharmaceutical significance. Reproducibility supports method transfer between a company, its contract laboratories, and regulatory laboratories, and underpins confidence in compendial methods worldwide.

5. Linearity

Definition. The ability of the procedure, within a given range, to obtain results that are directly proportional to analyte concentration, either directly or after a well-defined mathematical transformation. ICH Q2(R2) describes this more broadly as the response (calibration model), which can be linear or non-linear [23].

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Purpose. To establish the relationship between signal and concentration so that unknown samples can be quantified reliably from a calibration curve or reference standard.

How it is evaluated.

- Prepare at least five concentrations across the intended range, ideally independently.
- Plot response against concentration and fit by least-squares regression ($y = mx + c$); use weighted regression when variance changes with concentration, as in bioanalysis.
- Report the slope, intercept, correlation coefficient, coefficient of determination, and residual sum of squares, and inspect a residual plot.

Interpretation. For assays, r is commonly expected to be at least 0.999 and for impurities at least 0.99, but a high correlation coefficient alone does not prove linearity. Residuals should be randomly scattered, the intercept should be small relative to the response at the target concentration, and back-calculated concentrations should be accurate. Curved residuals indicate a non-linear model is needed.

Pharmaceutical significance. A sound calibration model prevents systematic over- or under-estimation across the concentration span, for instance in dissolution profiles that span low to high drug release.

6. Range

Definition. The interval between the upper and lower concentrations (including these concentrations) of analyte in the sample for which the procedure has demonstrated suitable accuracy, precision, and linearity. ICH Q2(R2) refers to the reportable range and to the working range of the procedure [23].

Purpose. To define the concentrations over which the method can be used with confidence, ensuring that all expected sample results, including values near the specification limits, fall within validated limits.

How it is evaluated. The range is not a separate experiment but is derived from the linearity, accuracy, and precision data, confirming that all three are acceptable at the lower and upper extremes. ICH recommends the following minimum ranges [23]:

Test	Minimum recommended range
Assay of drug substance or product	80 to 120% of test concentration
Content uniformity	70 to 130% of test concentration
Dissolution	±20% over the specified range of the test
Impurities	From reporting level to 120% of the specification

Interpretation. The range is accepted when precision, accuracy, and response are demonstrated at both ends. If performance deteriorates at an extreme, the range is narrowed accordingly.

Pharmaceutical significance. A properly defined range ensures that out-of-trend or marginal results can be measured without extrapolation or unplanned dilution, protecting the validity of specification decisions.

7. Detection Limit

Definition. The lowest amount of analyte in a sample that can be detected, but not necessarily quantified, under the stated experimental conditions (LOD).

Purpose. To establish the sensitivity of the method for limit tests and to confirm the presence or absence of an analyte, such as a toxic impurity.

How it is evaluated.

- **Visual evaluation** of samples with known concentrations (mainly for non-instrumental methods).
- **Signal-to-noise ratio:** comparison of the signal from low-concentration samples with blank noise; a ratio of about 3:1 (2:1 is sometimes accepted) is generally considered acceptable.
- **Standard deviation of the response and the slope:** $LOD = 3.3\ \sigma / S$, where σ is the standard deviation of the response (blank, regression residual, or intercept) and S is the slope of the calibration curve.
- The calculated limit is confirmed by analyzing an appropriate number of samples at that level.

Interpretation. The LOD must be low enough to detect the analyte at levels below the limit of concern. It is a detection capability only, so no numerical result should be reported from it.

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Pharmaceutical significance. Detection limits are critical for trace contaminants such as genotoxic impurities, residual solvents, elemental impurities, and for cleaning validation in shared manufacturing equipment.

8. Quantitation Limit

Definition. The lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy (LOQ).

Purpose. To define the lowest concentration at which a numerical result can be reported reliably, which is the basis for quantifying impurities and low-dose analytes.

How it is evaluated.

- **Signal-to-noise ratio:** typically 10:1.
- **Standard deviation of the response and the slope:** LOQ = 10 σ / S.
- **Experimental confirmation:** analyze samples prepared at the LOQ and show acceptable accuracy and precision (a commonly applied criterion for chromatographic impurity methods is %RSD of 10% or less).

Interpretation. The LOQ should be at or below the reporting threshold for the analyte. For impurities in new drug substances, ICH Q3A reporting thresholds are as low as 0.05% for products with a maximum daily dose up to 2 g [26]. In bioanalysis, the lower limit of quantitation must show accuracy and precision within ±20% [29].

Pharmaceutical significance. A suitable LOQ allows control of degradation products and impurities at levels set for patient safety, supports stability monitoring as degradants emerge, and underpins pharmacokinetic studies where drug concentrations fall to very low levels.

9. Robustness

Definition. A measure of the capacity of the procedure to remain unaffected by small but deliberate variations in method parameters, providing an indication of its reliability during normal usage.

Purpose. To identify the parameters that influence method performance and to set appropriate controls and system suitability criteria. Robustness is best examined during development, and the results are confirmed or included in the validation package [23][24].

How it is evaluated.

- Vary parameters one at a time or, preferably, together using Design of Experiments (for example, fractional factorial or Plackett-Burman designs).
- Typical HPLC variations include mobile phase pH (±0.2 units), organic content (±2% absolute), buffer concentration, flow rate (±10%), column temperature (±5 °C), detection wavelength (±2 to 5 nm), and different column lots or manufacturers.
- For sample preparation, vary extraction time, solvent volume, and sonication, and assess solution stability.
- Monitor critical responses such as resolution, tailing factor, retention time, and assay result.

Interpretation. The method is robust when system suitability criteria are met and results remain within acceptable limits across the tested variations. Parameters that cause significant changes are identified as critical, and their permitted ranges are written into the procedure.

Pharmaceutical significance. A robust method transfers easily between laboratories and instruments, minimizes failed runs and out-of-specification investigations, and reduces the need for revalidation after minor, expected changes.

10. System Suitability Testing

System suitability testing (SST) verifies, at the time of analysis, that the complete analytical system (instrument, reagents, column, and operator) is performing adequately for the specific method. It is not a substitute for validation or instrument qualification; it is performed with each run or sequence [27].

SST parameter	Purpose	Typical limit

Resolution (Rs)	Separation of critical peak pair	At least 2.0
Tailing (symmetry) factor	Peak shape	Not more than 2.0
Theoretical plates (N)	Column efficiency	Method specific
Capacity factor (k')	Adequate retention	Usually greater than 2.0
Repeatability of replicate injections	Injection and system precision	%RSD of 2.0% or less for five or six injections of standard
Signal-to-noise at quantitation limit	Sensitivity	At least 10 for impurity methods

SST limits are established from development and validation data. If SST fails, the analytical run is invalid and results must not be reported until the cause is corrected.

11. Stability-Indicating Analytical Methods

A stability-indicating method (SIM) accurately measures the active ingredient free from interference by degradation products, process impurities, and excipients, and can detect changes in quality attributes over time. Regulators expect SIMs for stability studies performed under ICH Q1A(R2) [28].

Validation of a SIM places particular emphasis on specificity, demonstrated by forced degradation under acid, base, oxidative, thermal, humidity, and photolytic stress, typically targeting about 5 to 20% degradation [30]. The validation package should show:

- resolution of the active from all significant degradants and impurities;
- peak purity of the active peak in stressed samples (PDA or MS);
- acceptable mass balance between loss of assay and formation of degradants;
- adequate quantitation limit for degradants at the reporting threshold;
- accuracy and precision for impurities, often using relative response factors.

Forced degradation also reveals degradation pathways, informing formulation, packaging, and storage conditions.

12. Regulatory Requirements

Various authorities and compendia provide the framework for validation.

- **ICH Q2(R2):** the harmonized guideline on validation of analytical procedures, adopted in 2023, replacing Q2(R1) [1].
- **ICH Q14:** analytical procedure development, including the analytical target profile, enhanced approach, and lifecycle concepts [24].
- **ICH M10:** bioanalytical method validation and study sample analysis [29].
- **FDA:** guidance on analytical procedures and methods validation for drugs and biologics (2015), and current good manufacturing practice regulations requiring methods to be validated and shown suitable under actual conditions of use (21 CFR 211.165 and 211.194) [31].
- **USP:** general chapters <1225> (validation of compendial procedures), <1226> (verification of compendial procedures), <621> (chromatography), and <1220> (analytical procedure life cycle) [27][32].
- **Other pharmacopoeias and agencies:** Ph. Eur., Indian Pharmacopoeia, EMA, WHO, and national regulators, which are largely aligned with ICH.

Regulatory documentation typically includes a validation protocol with predefined acceptance criteria, raw data, a validation report, and any deviations. Revalidation is expected after changes to the synthesis of the drug substance, composition of the product, or the analytical procedure itself, in proportion to the change.

13. Application in the Pharmaceutical Industry

- **Quality control and release testing:** assay, impurities, dissolution, content uniformity, and identification of raw materials, intermediates, and finished products.

- **Stability studies:** validated SIMs support shelf-life and storage-condition assignment.
- **Process development and monitoring:** in-process controls, cleaning validation, and process analytical technology.
- **Bioanalysis and clinical studies:** pharmacokinetics, bioavailability, and bioequivalence, using LC-MS/MS methods validated per ICH M10.
- **Generic drug development:** comparative dissolution and impurity profiling to support abbreviated applications.
- **Regulatory submissions and inspections:** validated methods form part of the quality section of dossiers and are examined during inspections.
- **Technology transfer:** validation and transfer data enable manufacture and testing at multiple sites and contract laboratories.

14. Recent Advances

- **ICH Q2(R2) and Q14 alignment:** validation is now linked with development knowledge, enabling use of prior development data in validation and covering spectroscopic and multivariate procedures such as NIR and Raman [23][24].
- **Combined evaluation of accuracy and precision:** approaches based on total error, tolerance intervals, and accuracy profiles evaluate whether future results will fall within acceptable limits, in line with fitness for purpose [33].
- **Analytical Quality by Design:** risk assessment and Design of Experiments define a Method Operable Design Region, giving robustness that is built in rather than tested late.
- **Lifecycle management:** continued procedure performance verification, trending, and control strategies replace one-time validation (USP <1220>) [32].
- **Advanced instrumentation:** UPLC, high-resolution mass spectrometry, two-dimensional LC, and supercritical fluid chromatography broaden what can be validated, including trace impurities and complex biologics.
- **Automation and digital tools:** automated sample preparation, laboratory information systems, electronic validation protocols, and software for statistical evaluation reduce manual error and speed up studies.
- **Green analytical chemistry:** solvent reduction, shorter run times, and greenness metrics are increasingly considered during validation planning.

15. Challenges and Future Perspectives

Challenges

- Validating methods for complex modalities such as peptides, oligonucleotides, proteins, and cell and gene therapies, where reference standards and orthogonal techniques are limited.
- Reaching very low quantitation limits for genotoxic and nitrosamine impurities in complex matrices.
- Interpreting new terminology and flexibility in ICH Q2(R2) consistently across companies and regulators.
- Choosing meaningful acceptance criteria rather than relying on habitual limits.
- Method transfer failures from poorly documented critical parameters.
- Maintaining data integrity (ALCOA+) in electronic workflows.
- Balancing thorough validation with development timelines and cost.

Future perspectives

- Wider adoption of lifecycle and AQbD approaches, with established conditions and continuous verification.
- Use of machine learning for method development, prediction of robustness, and detection of drift in routine data.

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- Real-time release testing and in-line spectroscopic methods validated as multivariate models.
- Harmonized global expectations for validation and easier reuse of data across regions.
- Digital twins and automated, paperless validation workflows.
- Increased emphasis on sustainability as a validation consideration.

16. Conclusion

Analytical method validation provides documented evidence that a procedure is fit for its intended purpose. Each parameter answers a specific question: specificity asks whether the right analyte is measured, accuracy whether the result is correct, precision whether it is reproducible at three levels, linearity and range over which concentrations it works, detection and quantitation limits how low it can go, and robustness whether it withstands everyday variation. System suitability tests protect each analytical run, and stability-indicating validation ensures that product quality changes can be detected throughout shelf life. With ICH Q2(R2) and ICH Q14, validation is now part of a continuous, knowledge-driven lifecycle, supported by advances in instrumentation, statistics, and automation, which promises more reliable data and safer medicines.

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