Universidade de Lisboa

Faculdade de Farmácia

Lifecycle management of process analytical methods for pharmaceuticals quality control

Bernardo Miguel Sarraipa Gameiro

Trabalho de Campo orientado pelo Professor Doutor João Almeida Lopes, Categoria Professor Auxiliar.

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

A esperança média de vida da população mundial, tem aumentado bastante nos últimos cem anos e isto, deve-se ao facto das novas descobertas na medicina, principalmente as descobertas de novas substâncias ativas que ajudam a combater patologias que já existiam ou novas que vão aparecendo. Com isto, houve um grande crescimento do mercado de medicamentos, pois estes permitem que algumas pessoas com condições médicas debilitadas mantenham a qualidade de vida, apesar do quadro clínico. Contudo os medicamentos, também têm reações adversas que podem prejudicar a qualidade de vida dos doentes e, para minimizar esta situação, é necessário supervisionar e garantir a qualidade dos produtos farmacêuticos. Consequentemente, em 1994 foi criada e terminada em 1996, a International Council for Harmonisation Quality Guideline 2 – Validação de Procedimentos Analíticos, com o intuito de conseguir validar novos procedimentos analíticos ou que já existiam, avaliando ensaios, impurezas, potência e qualquer outra medida quantitativa ou qualitativa. Garantindo que os medicamentos são seguros para o consumo dos doentes, fazendo assim um controlo estratégico do benefício-risco do medicamento ou da substância ativa. Todavia, com o passar dos anos, com o aumento da tecnologia e dos métodos analíticos, esta diretriz foi revelando algumas limitações, não sendo adequada para alguns métodos analíticos que foram surgindo recentemente. Por isso, foi necessário criar uma nova diretriz que conseguisse abranger todos estes novos métodos e, posto isso, em 2022, foi apresentado o texto provisório da International Council for Harmonisation Quality Guideline 14 – Desenvolvimento de Procedimentos Analíticos. Esta diretriz tem como objetivo conseguir regular o desenvolvimento de novos métodos analíticos, para que se melhore a comunicação entre a indústria farmacêutica e agências reguladoras. No entanto, esta nova diretriz, no seu texto atual encontra-se em vários aspetos incompleta, vaga, com falta de consistência na informação do documento e confusa, sendo necessário uma revisão do documento na íntegra, para que seja um acréscimo real relativamente à diretriz existente (ICH Q2).

Palavras-chave: Medicamento; Controlo de Qualidade; Métodos Analíticos; Ciclo de Vida; ICH.

Abstract

The average life expectation of the world population has increased significantly in the last hundred years, and this is due to the fact of new discoveries in medicine, mainly as discoveries of new active substances that help to fight pathologies that already existed or new ones that are appearing. With this, there was a great growth in the drug market, as they allow some people with debilitated medical conditions to maintain their quality of life, despite their clinical condition. However, medicines also have adverse reactions that can impair the quality of life of patients and, to minimize this situation, it is also necessary to supervise and guarantee the quality of pharmaceutical products. Consequently, in 1994, the International Council for Harmonization Quality Guideline 2 – Validation of Analytical Procedures was created and ended in 1996, in order to validate new or existing analytical procedures, evaluating tests, impurities, potency and any other quantitative or qualitative measurement. Ensuring that medicines are safe for patients to consume, thus making a strategic control of the benefit-risk of the medicine or active substance. However, over the years, with the increase in technology and analytical methods, this guideline has revealed some limitations, not being suitable for some analytical methods that have emerged recently. Therefore, it was necessary to create a new guideline that could cover all these new methods and, therefore, in 2022, the provisional text of the International Council for Harmonization Quality Guideline 14 – Development of Analytical Procedures was presented. This guideline aims to regulate the development of new analytical methods, in order to improve communication between the pharmaceutical industry and regulatory agencies. Nevertheless, this new guideline, in its current text, is incomplete, vague, with a lack of consistency in the information in the document and confusing, requiring a revision of the document in its entirety, so that it is a real addition to the guideline existing (ICH-Q2).

Keywords: Medicine; Quality Control; Analytical Methods; Life Cycle; ICH.

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Acronyms

APIC – Advanced Pharmaceutical Industries Co.

ANN – Artificial Neural Networks

ATP – Analytical Target Profile

COR – Completion of Reaction

CQA – Critical Quality Attributes

DoE – Design of Experiments

ECs – Established Conditions

EFPIA - European Federation of Pharmaceutical Industries Associations

EMA – European Medicines Agency

FDA – Food and Drug Administration

GC – Gas Chromatography

GMP – Good Manufacturing Practice

GTI – Genotoxic Impurity

HPLC – High-performance liquid chromatography

ICH – International Council for Harmonisation

ISO – International Organization for Standarization

ISPE – International Society for Pharmaceutical Engineering

LC – Liquid Chromatography

MAH – Major Accident Hazards

MODRs – Method Operational Design Regions

MS – Mass spectrometry

NMR – Nuclear Magnetic Resonance

NIR – Near-Infrared spectroscopy

PACMP – Post-Approval Change Management Protocol

PARs – Proven Acceptable Ranges

PAT – Process Analytical Technology

PCA – Principal Component Analysis

PLS – Partial Least Squares

PQS – Performance, Quality and Safety

PRI – Pharmabiotic Research Institute

QbD – Quality by Design

RAP – Impurity Determination Relative Area Percent

RMSEP – Root Mean Square Error of Prediction

RTRT – Real Time Release Testing

TLC – Thin Layer Chromatography

1 Introduction

1.1 Pharmaceutical production quality control

In the pharmaceutical world, quality control is one of the most important steps in drugs and drug products control, so it's normal that medicines need to be exposed to strict tests to go to the market. These tests are required to release a new medicine to the market, because they guarantee that this new substance is safe, therapeutically acceptable and within the specifications, according to the safety standards.(1)

Good Manufacturing Practices (GMPs) encloses a series of practices to ensure that medicines have high quality, and have the necessary requirements to go to market. So, GMPs standardize the production for every pharmaceutical industry and, by doing this, they restrict the errors in the production. To assure that these methods are followed by the manufacturing site, European Medicines Agency (EMA) coordinates inspections to verify these standards in the European Union (EU) and, in the United States of America (USA) is verified by Food and Drugs Administration (FDA), although the standards maybe different in these regions.(2)

1.2 ICH Quality guidelines

The International Council Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is formed by medicines regulatory authorities and pharmaceutical industry around the world.(3)

The council created and continues to create guidelines to help pharmaceutical industry to keep improving the medicines quality standards(4). These are the quality guidelines that exist, at the moment:

- Q1 – Stability;
- Q2 – Analytical Validation;
- Q3 – Impurities;
- Q4 – Pharmacopoeias;
- Q5 – Quality Biotechnological Products;
- Q6 – Specifications;
- Q7 – Good Manufacturing Practice;

- Q8 – Pharmaceutical Development;
- Q9 – Quality Risk Management;
- Q10 – Pharmaceutical Quality System;
- Q11 – Development and Manufacture of Drug Substances;
- Q12 – Lifecycle Management;
- Q13 – Continuous Manufacturing of Drug Substances and Drug Products;
- Q14 – Analytical Procedure Development.(5) (draft version)

1.3 Validation of analytical methods and lifecycle analytical methods management

The lifecycle management of analytical methods is first referred in ICH 12.(6) This document will provide us with the knowledge necessary to identify quality risks, to continue to improve and to ensure quality. Then, the Analytical Method Lifecycle Management approach starts with the Analytical Target Profile (ATP) concept and Quality by Design (QbD), that helps this concept by dividing it in 3 stages(7), as shown in Figure 1.

- Stage 1 – Method Design;
- Stage 2 – Method Performance Qualification;
- Stage 3 - Continued Method Performance Verification.(8)

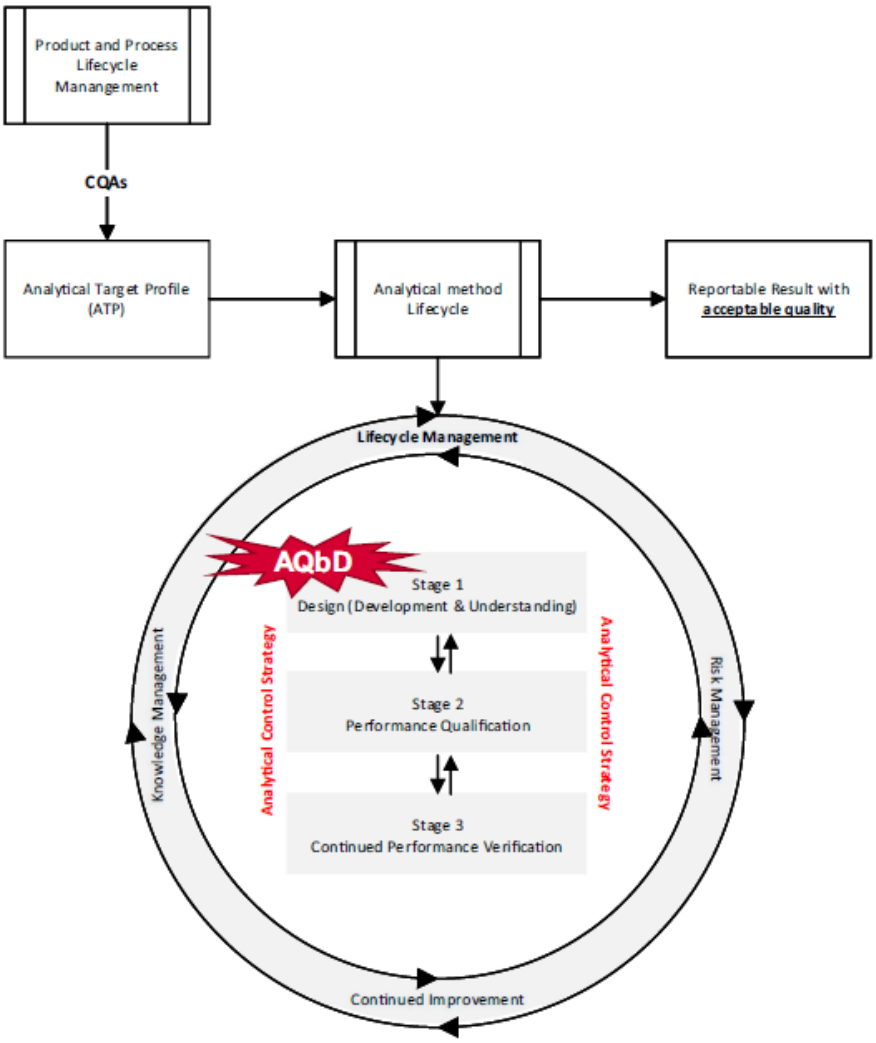


Figure 1-Analytical Method Lifecycle Management Concept (adapted from Volta e Sousa et al.)

After confirming these stages and in order to proceed to validate analytical methods, pharmaceuticals industries use the ICH Q2 guideline.(9) Therefore, they need to access to analytical information that can be used for number of purposes, like: decisions involving manufacturing process, products within regulatory limits to take decisions about legal affairs, national and international trade, health problems. Hence the importance of these methods being validated according to many rules.

Thereby, validation is defined by the International Organization for Standarization (ISO) and implies that analytical methods must have specific requirements and well clarified, so they can't mislead the process. In fact, validation represents that analysts have shown that the method is fit-for-purpose and shows that patients can trust the results.(10)

1.4 In-process control

The control in pharmaceutical industry oversees all medications to ensure that they are safe, secure with high quality, and profitable when they are released onto the market. Due to the restriction placed on the pharmaceutical sector, it is necessary that the substances used are controlled during the production process. Consequently, we may separate Monitoring from Control.

The control aims to maintain the continuous production of medicines and the quality that is characteristic of it and that it would never be capable of, if it were carried out manually.

On the other hand, the Monitoring is arranged on computers with monitoring systems, in order to be able to follow the process in real time. Therefore, specific interconnected sensors are needed to monitor the process.

When any substance does not comply with the measures imposed, the supervisors will be warned about it because of existence of alarms or any other warning mechanism. This happen because there are several types of control and monitoring during the production phase, like:

- In-line: a sensor is directly involved during the process;
- On-line: measurements are made in a secondary recirculation loop;
- At-Line: a sample is transferred from the process to be analysed at a nearby location and results are fast;
- Off-Line: a sample is removed from the process, where it will be analysed in a different location and the results take time.(11)

However, in-process quality control is carried out during the process, it can be at intervals or at the end of each step. (12) The aim of in-process quality control is to identify any problems, impurities, unusual fluctuations and where it occurs.(13)

To identify it, there are several types of sensors ranging from temperature, flow, pressure sensors to spectroscopy sensors. This is the only way we can guarantee that the final product is safe to use.(12)

The evaluation of the analysis made during the process, in addition to being analysed, will be classified according to the ICH Q7 guideline. In the process of quality control, several tests are carried out, such as:

- completion of Reaction (COR);
- impurity Determination Relative Area Percent (RAP);
- product Solution Concentration Analysis;
- process Solvent Exchanges;
- genotoxic Impurity (GTI);
- water Concentration;
- drying End-Point Determination;
- aqueous Solution Conductivity and
- aqueous Solution pH.

The samples will be analysed by various tests like, Thin Layer Chromatography (TLC), High-performance liquid chromatography (HPLC), Gas Chromatography (GC), infrared, or Raman spectroscopy, among others.(14)

1.5 Real time release control testing

Real Time Release Testing (RTRT) is used, in the pharmaceutical industry, as a drug control strategy throughout its formation process, by a testing strategy in which fully automatic and integrated manufacturing is used. In other words, RTRT aims to guarantee the quality, safety and efficacy of the active substance and the product, evaluating the different parameters during the process, instead of using testing at the end of the production process. It's faster and a more effective process.(15) Therefore, the strategy of this analytical method is to control all process parameters and monitor the assigned products.

So, this path will apply Process Analytical Technology (PAT) such as:

- near-infrared spectroscopy (NIR);
- raman spectroscopy.

To be able to carry out a relevant control of the attributes. It can also be applied in the continuous production of active substances.(16)

Thus, RTRT manages to increase the influence of the enhanced process in quality control, as it allows to reduce the process cycle, the inventory requirements, the manufacturing costs and tests on the final product, and to increase quality assurance.(15)

Finally, the RTRT has been approved for daily use, so if something goes wrong with the process, it cannot be replaced by testing the final product, in case the equipment fails a specific testing and monitoring plan for daily use has been provided, until that the problem is corrected.(16)

2 Objectives

This online research has as main objective to identify and characterize the new ICH Q14 - Analytical procedure development, his advantages and needs, for quality control in the pharmaceutical industry.

It was then intended to:

- knowledge of ICH Q2 and ICH Q14;
- analyze if this ICH Q14 can replace the ICH Q2;
- understand the reason to the creation of ICH Q14;
- notice gaps in the ICH Q14;
- and, finally, if this ICH Q14 can apply to the real world.

3 Methods

This monograph on Lifecycle management of process analytical methods for pharmaceuticals quality control was performed after a bibliographic search using the following databases: PubMed, Google Scholar, EMA, World Health Organization (WHO), FDA, and links related to articles published from 1980 to 2022. In general, for this monograph, I consulted about 35 articles, using the following acceptance criteria: articles published from 1947 to 2022, literature reviews, guidelines, and books, associating these with some keywords.

Based on the information collected, I consulted other databases using the following keywords (both in Portuguese and English): “quality control”, “production”, “manufacturing process”, “quality control in pharmaceutical industry”, “production in pharmaceutical industry”, “definition of production in pharmaceutical industry”, “ICH Q2”, “ICH Q8”, “ICH Q12”, “ICH Q14”, “real time release testing” and “process control”, “NIR”, “Raman”, “NMS”, “MS”, “Gaps of ICH Q2” and “Gaps of ICH Q14”.

4 Discussion

4.1 An overview of the ICH Q2 guideline

4.1.1 The current ICHQ2 text: performance criteria for analytical methods

This guideline is an essential part to the daily work in pharmaceutical industry, the ICH created this document to discuss characteristics to take into account when the validation of the analytical procedures of the four most common types of analytical procedures:

- identification tests;
- quantitative testes for impurities' content;
- limit tests for the control impurities and
- quantitative tests of the active moiety in samples of the drug substance or drug product or other selected component(s) in the drug product.(17)

To understand the objective of the analytical procedure, we have to understand the difference between validation characteristics used in limit testing of impurities and those used for quantitative analysis of impurities. So, the typical validation characteristics includes:(18)

- accuracy;
- precision;
    - repeatability;
    - intermediate precision;
- specificity;
- detection Limit;
- linearity;
- range.

Each characteristics need to be validated which is necessary for the validation of different types of analytical procedures, as shown in table 1.

Table 1 - Typical Validation Characteristics.

Type of analytical procedure characteristics	Identification	Testing for impurities Quantitat. limit		Assay - dissolution (measurement only) - content/potency
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm. Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	-(3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

- \- Signifies that the characteristic is not normally evaluated
- \+ signifies that the characteristic is normally evaluated
- (1) In cases where reproducibility has been performed, intermediate precision is not needed.
- (2) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).
- (3) May be needed in some cases.

The revalidation may be an option, under some circumstances, such as, changes in the synthesis of the drug substance; changes in the composition of the finished product; and changes in the analytical procedure, which also require validation.(17)

4.1.2 Gaps on the ICH Q2 and necessity for an update

The ICH Q2 guideline – validation of analytical procedures, as its name indicates, presents us with a discussion of elements that we have to take into account when validating analytical procedures by regulatory authorities. However, with the evolution of analytical techniques, other methods emerged that cannot be evaluated with the current ICH Q2,(19) in order to be able to evaluate principles that analyze spectrophotometry and spectrometry methods such as Raman spectroscopy, Nuclear Magnetic Resonance (NMR), NIR or Mass Spectrometry (MS), which normally required other methods of statistical analysis.(20)

Raman Spectroscopy

The Raman spectroscopy is a non-destructive method of chemical examination that offers thorough details on crystallinity, chemical characteristics, phase and polymorphism, and molecular interactions. It is based on how light interacts with chemical bonds in a substance. Raman uses the principle of light scattering in which a molecule disperses incident light from a laser light source. Rayleigh scattering is the term for when most of the scattered light shares the same wavelength (or energy) as the laser source and offers little relevant information. On the other hand, Raman scattering is the little quantity of light (usually 0.0000001%) that is scattered at various wavelengths, depending on the chemical makeup of the analyte. So, a Raman spectrum has several peaks that display the strength and location of the Raman scattered light's wavelength. Each peak is associated with a particular chemical bond vibration, including single bonds like C-C, C=C, N-O, and C-H as well as groups of bonds like the breathing mode of the benzene ring, polymer chain vibrations, lattice modes, etc.(21)

Nuclear Magnetic Resonance (NMR)

NMR spectroscopy is a sophisticated method of characterizing materials. It is used to ascertain a sample's atomically precise molecular structure. NMR spectroscopy may identify phase changes, conformational and configurational changes, solubility, and diffusion potential in addition to chemical structure. (22) This method has historically been used to conduct research on atom nuclei rather than electrons. NMR spectroscopy information can be used to map the chemical surroundings of typical nuclei.(23) This energy transfer often takes place in a single step, moving from lower to higher energy levels. At a radio frequency, this energy transmission or absorption is made possible.(24) The energy is released at the same frequency as the nuclei's spin returns to its starting point and this energy transfer corresponds to a signal, which is then processed and produced as the corresponding nucleus's NMR spectrum in a variety of ways.(25)

Near infrared spectroscopy (NIR)

In order to monitor fermentation processes and determine the concentration of biologically significant bonds (aliphatic C-H, aromatic or alkene C-H, amine N-H and O-H) that absorb in the NIR region, NIR absorption spectroscopy, with a wavelength range of 12 820 to 4000 cm1, is increasingly utilized. Each chemical structure influences how the analyte's absorption bands are positioned, shaped, and sized. The NIR spectrum of complex culture medium can be used to simultaneously monitor nutrient contents, metabolite concentrations, product production, or biomass. To identify crucial processing factors that are crucial for product quality, chemometrics approaches are combined with NIR spectrum.(26)

Mass Spectrometry (MS)

In order to determine the mass-to-charge ratio (m/z) of one or more molecules found in a sample, MS is a valuable analytical instrument. The precise molecular weight of the sample's constituent parts can frequently be determined using these measures as well. Mass spectrometers are typically used to quantify known substances, identify novel compounds by molecular weight determination and assess the structure and chemical characteristics of molecules.(27)

The issue with typical chemometric validation applications is that they frequently do not evaluate quantitative criteria including trueness, precision, results correctness, linearity, and valid dose range. As a result, the ICH Q2 document's method validation regulatory requirements for the pharmaceutical industry are not always followed. Additionally, there is no information regarding the method's fitness for the purpose for which it is meant to be used or an assessment of the results' reliability resulting from the routine application of the NIR method in the future. The application of validation criteria given in the ICH Q2 document is the second primary way for validating an NIR multivariate quantitative method. The only inference that can be made using this strategy is the capacity to show a difference rather than an equivalent. These mistakes are fixed via the less popular equivalency approach. The responsibilities of the analyst and the methods he/she selects to reach this result determine whether an analytical method is regarded as valid. The purpose of this review is to emphasize how crucial it is to steer clear of incorrect judgments. Also, some strategies are insufficient to accept an NIR method as reliable and the tolerance interval-based accuracy profile technique is likely more adaptable and fully ICH compliant(28)

These reasons can be applied to others methods too, and because that argument ICH Q2 needed a review, it was created the ICH Q14, despite being directed to common analytical procedures, such as impurities, potency, identifies and other quantitative and qualitative measurements. The ICH Q14 will also be able to be used for other procedures, as a control strategy based on a risk approach.(19)

In this way, ICH2 Q2(R2) and ICH Q14 are intended to complement ICH Q6, ICH Q12 and ICH Q8, as well as being able to reconcile ICH Q13, in order to be able to reconcile the two documents in one in the future, and to improve and modernize the pharmaceutical industry.(20)

4.2 The ICH Q14 guideline

4.2.1 Comparison with the ICHQ2: a new guideline or an improvement?

With the evolution of the pharmaceutical industry and the advancement of the quality control technologies, the ICH Q2 does not address to all analytical procedures and so there was the need to create the ICH Q14, that will complement the ICH Q2. The ICH Q14 will carry new or revised analytical procedures for drug substances and products, that can be also used in control strategy (ICH Q10 - Pharmaceutical Quality System), resort a risk-based analysis.

In this guideline, we compare the minimal and enhanced approaches to analytical procedure development. The minimal approach is described in ICH Q2, by validate the characteristics which are referred using the four common types of analytical procedures. For the enhanced approach we should add one or more of the following topics to the minimal approach, to have a better development and information to an analytical procedure:

- An evaluation of the sample properties and the expected variability of the sample based on manufacturing process understanding;
- Defining the ATP;
- Conducting risk assessment and evaluating prior knowledge to identify the analytical procedure parameters that can impact performance of the procedure;
- Conducting uni- or multi-variate experiments to explore ranges and interactions between identified analytical procedure parameters;
- Defining an analytical procedure control strategy based on enhanced procedure understanding including appropriate set-points and/or ranges for relevant analytical procedure parameters ensuring adherence to performance criteria;

- Defining a lifecycle change management plan with clear definitions and reporting categories of Established Conditions (ECs), Proven Acceptable Ranges (PARs) or Method Operational Design Regions (MODRs) as appropriate.

This approach can be used to back and to expand and lifecycle management of analytical procedures. (29)

4.2.2 Performance criteria for analytical methods according to the ICHQ14

The performance criteria for analytical methods techniques are discussed in Section 8, where it is noted that multivariate models are built from samples. So, to extract the pertinent information from the analytical data and increase the resilience of the final model, a rigorous sample selection technique is required. The sample population should include all causes of variability that are anticipated to appear throughout manufacture and analysis, such as raw material quality, manufacturing process variability, storage conditions, sample preparation, and testing, based on the method and measurement principle. By using risk assessment techniques, it is possible to find sources of variability that may have an impact on the measurements and model outputs.

At a commercial scale, getting samples with the right amount of variability might be difficult. As a result, development laboratory and pilot scale samples are frequently used to supply adequate diversity to enhance the model's accuracy and robustness. To capture variability linked to equipment or processing conditions, it is advised to include samples taken from commercial scale operations. The sample distribution in the calibration and validation sets should also be carefully considered because it will have an impact on the model's capacity for prediction.

However, reducing the number of qualified suppliers for each compound can help in the selection of sufficient relevant samples that reflect the predicted variance a manufacturer would expect. The closest example of how to create an identification library is found in section 13.3 Annex C: Example of Multivariate Model Lifecycle Components, which describes how to identify incoming glucose samples using Raman. However, it doesn't seem like there is any guidance on creating a library if you wish to distinguish a material from other comparable structured compounds.(30)

4.2.3 Suitability of ICH Q14 for RTRT

Real-time release testing is one of the most anticipated innovations in the production, pharmaceutical industry, but it needs to be educated, documented, and explained to professionals. Which is not recognized in the current document. The development of the procedure for real-time release tests cannot be presented in ICH Q14 because it was mentioned in the document in a synthetic way and little, something that brings an innovation to the pharmaceutical world, ended up not complementing the relevant information to what it already is. Concluding only with generic knowledge, without any kind of concrete use, as well as the lack of how it can be adapted to the world of the pharmaceutical industry.

4.2.4 Flaws appointed to ICH Q14

Throughout the document we found some concepts that are important and were well applied. Also, we found many that are important, and some that were ambiguous and that do not make much sense, either because they are confused or because they are so generic that they do not contribute to the final document, as they end up not adding anything concrete, as showed in each point below.

So, in the next topics, we will take a sentence from the ICH Q14 (draft version), and then, explain why it's misleading.

4.2.4.1 Introduction

4.2.4.1.1 Objective of the Guideline

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"This guideline describes science and risk-based approaches for developing and maintaining *analytical procedures* suitable for the assessment of the quality of drug substances and drug products"

However, this sentence has some flaws because, according to International Society for Pharmaceutical Engineering (ISPE), it needs to have better expression of the purpose and application of the advice.

4.2.4.2 Scope

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“This guideline applies to new or revised analytical procedures used for release and stability testing of commercial drug substances and products (chemical and biological/biotechnological). The guideline can also be applied to other analytical procedures used as part of the control strategy”

However, this sentence has some flaws because, according to Pharmabiotic Research Institute (PRI), although the guideline claims to be applicable to novel analytical techniques, none of the OMICS methods have been covered in the annexes and examples.

4.2.4.2.1 General Considerations for Analytical Procedure Development and Lifecycle Management

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“For a new application of such platform analytical procedures, the subsequent development can be abbreviated, and certain validation tests can be omitted based on a science- and risk-based justification. Details of the performance characteristics considered for analytical procedure validation are described in ICH Q2.”

However, this sentence has some flaws because, according to ISPE, it would be highly beneficial to have further clarification or extra examples or training materials to demonstrate the risk-based deployment of platform procedures across multiple products and applications.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“In general, data gained during the development studies (e.g., robustness data from a design of experiments (DoE study)) can be used as validation data for the related

analytical procedure performance characteristics and does not necessarily need to be repeated."

However, this sentence has some flaws because:

- According to Advanced Pharmaceutical Industries Co. (APIC), the policy in this sentence should be clearer about which development data can be utilized as validation data and which cannot.
- According to European Federation of Pharmaceutical Industries Associations (EFPIA), the validity of robustness data based on DoE development data is not entirely evident. An alternative example is the identification of developing peaks using liquid chromatography (LC)-MS, which can be employed for the specificity investigation in the validation.
- According to EFPIA, the statement, "In general" is a misleading claim that would accept any kind of information. Following a validation methodology, validation data are produced. As a result, development data can be used for validation but not for validation.
- According to Vaibhav Anandgaonkar. the "Validation data" usage hints that this statement is connected to data on method validation but never explain what this validation data is.

4.2.4.2.2 Minimal versus Enhanced Approaches to Analytical Procedure Development

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"An evaluation of the sample properties and the expected variability of the sample based on manufacturing process understanding"

However, this sentence has some flaws because, according to EFPIA "Expected variability of the sample", it's not obvious and it is not understood for what it wants to submit.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“Conducting uni- or multi-variate experiments to explore ranges and interactions between identified analytical procedure parameters.”

However, this sentence has some flaws because, according to ISPE, utilizing prior knowledge and applicable expertise is a quality by design component and, the accompanying control approach is a crucial component of the development of analytical procedures, but it misses some information that need to be explained.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“Employing predefined performance characteristics (e.g., in the ATP) linked to critical quality attributes (CQAs) and their acceptance criteria to provide purpose driven protocols for validation of analytical procedures and for future comparisons between current and new analytical procedures/technologies.”

However, this sentence has some flaws because, according EFPIA, since the analytical process does not always measure a CQA, and the sentence could be expanded to the rest of the text.

4.2.4.2.3 The Analytical Procedure Lifecycle

According to the ICH Q14 – Analytical Procedure Development, the following figure stipulated:

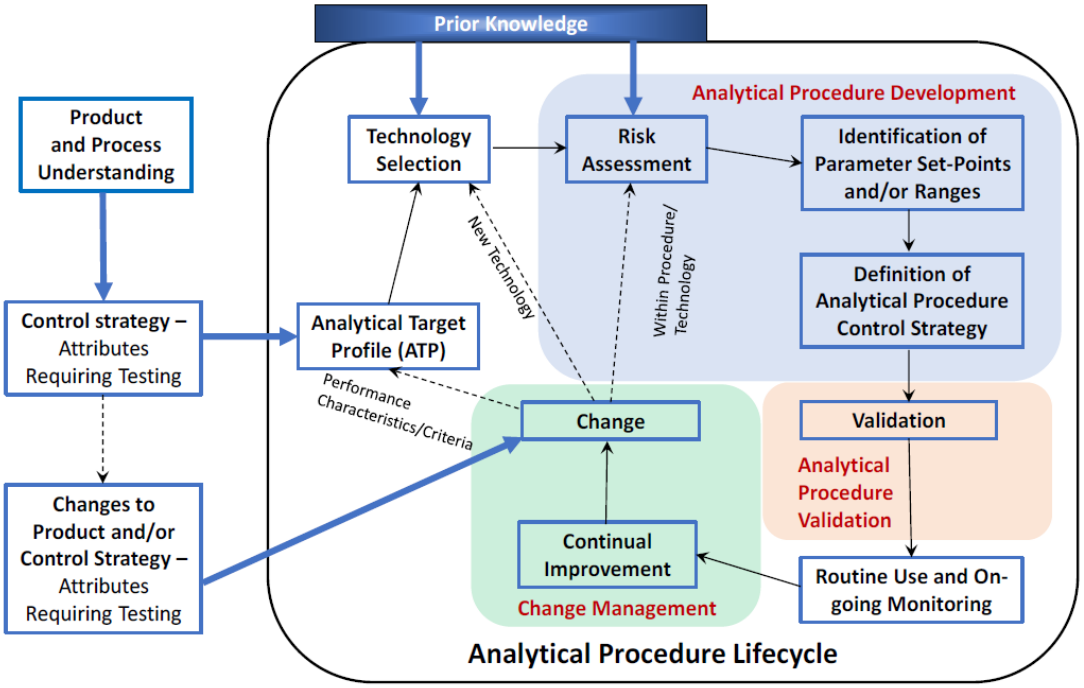


Figure 2 - The Analytical Procedure Lifecycle (adapted from ICH Q14).

However, this figure has some flaws because, according to EFPIA, a circle should be used to represent the blue box (the development of the analytical technique), and another arrow should point from the control plan back to the risk assessment (figure 2). Lines 153 to 155, "Risk assessment is typically performed early in analytical procedure development and is repeated as more information becomes available", but the image does not show it. Furthermore, the blue box must make specific mention of robustness studies. It's not desirable to have the analytical method control strategy separate from the product control strategy in the blue box.

4.2.4.3 ATP

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"Once a technology has been selected, the ATP serves as a foundation to derive the appropriate analytical procedure attributes and acceptance criteria for analytical procedure validation (ICH Q2)."

However, this sentence has some flaws because, according to EFPIA, the concept of analytical procedure attribute is never mentioned in ICH Q2. The two guidelines must be in harmony.

4.2.4.4 Knowledge and risk management in analytical procedure development and continual improvement

4.2.4.4.1 Knowledge Management

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"As with product and manufacturing process development (ICH Q10), knowledge management plays a critical role in analytical procedure development and during the subsequent lifecycle of the analytical procedure.

Prior knowledge is explicitly or implicitly used for informing decisions during analytical procedure development and lifecycle management. Prior knowledge can be internal knowledge from a company's proprietary development and analytical experience, external knowledge such as reference to scientific and technical publications or established scientific principles.

Prior product knowledge plays an important role in identifying the appropriate analytical technique. Knowledge of best practices and current state-of-the-art technologies as well as current regulatory expectations contributes to the selection of the most suitable technology for a given purpose. Existing platform analytical procedures (e.g., protein content determination by UV spectroscopy for a protein drug) can be leveraged to evaluate the attributes of a specific product without conducting additional procedure development.

As additional information is obtained, knowledge related to analytical procedures should be actively managed throughout the product lifecycle."

However, this sentence has some flaws because, according to EFPIA:

- The text only one particular technology can be used. The ATP may alter in the future if another technology satisfies it.

- This chapter lacks a more direct mention of how the reuse of knowledge produced by the enhanced approach serves as a foundation for the operational "return on investment" for devoting resources to the enhanced approach.
- There is a lack of information on knowledge management, it would be beneficial to place more attention on it.

4.2.4.5 Risk Management

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“To maintain a state of control for analytical procedure performance, ongoing monitoring is recommended as part of risk review.”

However, this sentence has some flaws because, according to ISPE, the current wording could be misinterpreted as recommending analytical procedure performance monitoring for all analytical procedures in order to maintain a state of control when, in reality, risk assessment and the criticality of the attribute being measured would normally be the basis for its deployment.

4.2.4.6 Evaluation of robustness and parameter ranges of analytical

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“The robustness of an analytical procedure is a measure of its capacity to meet the expected performance requirements during normal use. Robustness is tested by deliberate variations of analytical procedure parameters. Prior knowledge and risk assessment can inform the selection of parameters to investigate during the robustness study. Those parameters likely to influence procedure performance over the intended period of use should be studied.

For most procedures, robustness evaluation is conducted during development. If the evaluation of robustness was already conducted during development, it does not need to be repeated during validation as discussed in ICH Q2. Data from validation studies (e.g., intermediate precision) can be used to complement robustness evaluation. For some analytical procedures with inherent high parameter variability (e.g., those

requiring biological reagents) wider ranges may need to be investigated during robustness studies. Robustness of multivariate procedures may require additional 185 considerations (see chapter 8). The outcome of the evaluation of robustness should be reflected in the analytical procedure control strategy."

However, this sentence has some flaws because:

- According to EFPIA, they don't explicit the connection between parameter ranges and robustness.
- According to EFPIA, during the robustness evaluation, sample and/or solution stability over the course of the analysis should be taken into consideration.
- According to ProPharma Group, Bertine Vorstenbosch - de Wijs, as mentioned in ICH Q2, robustness testing done during development need not be repeated throughout validation.
- According to Dr. Uwe Lipke, since reference solution stability is essential for producing accurate results, it should be specifically noted in here.
- According to ISPE, the intermediate precision is insufficient to assess a procedure's resistance to intentional parameter changes.

4.2.4.7 Analytical Procedure Parameter Ranges

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"In an enhanced approach, the ranges for the relevant parameters and their interactions can be investigated in multi-variate experiments (DoE). Risk assessment and prior knowledge should be used to identify parameters, attributes and appropriate associated ranges to be investigated experimentally."

However, this sentence has some flaws because, according to EFPIA, it does not mention that the procedure's important qualities must be identified at the end of the process.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“Analytical procedure validation is required only for those performance characteristics not covered by data from analytical procedure development. An analytical procedure validation strategy, e.g., as part of the analytical procedure validation protocol, can define the necessary extent of additional validation.”

However, this sentence has some flaws because, according to EFPIA:

- Despite the performance parameters being covered by the analytical procedure development data, if the analytical procedure validation is not included.
- Only certain components of validation would require this to be proper development dat.

4.2.4.8 Analytical procedure control strategy

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“For analytical procedures relying on multivariate models, sample suitability assessment can be verified using appropriate software tools which check if the sample fits within the model space.”

However, this sentence has some flaws because, according to EFPIA, it’s not referred what software should be used.

4.2.4.9 Established Conditions for Analytical Procedures

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“With an enhanced approach to development, there should be an increased understanding of the relationship between analytical procedure parameters and performance to facilitate identification of which factors require control and thus enable a more appropriate set of ECs. These can focus on performance characteristics (e.g., specificity, accuracy, precision).”

However, this sentence has some flaws because, according to EFPIA, applying the improved technique has several advantages, one of which is understanding the connection between analytical procedure parameters and performance. Understanding

the measurement criteria and the applicability of the available technologies are at least as crucial as they are absent in this situation. The current statement is deceptive since it suggests that ECs are made up of of analytical method parameters. Also, the knowledge gathered through the improved approach allows for the selection of both appropriate reporting categories and a suitable collection of ECs.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

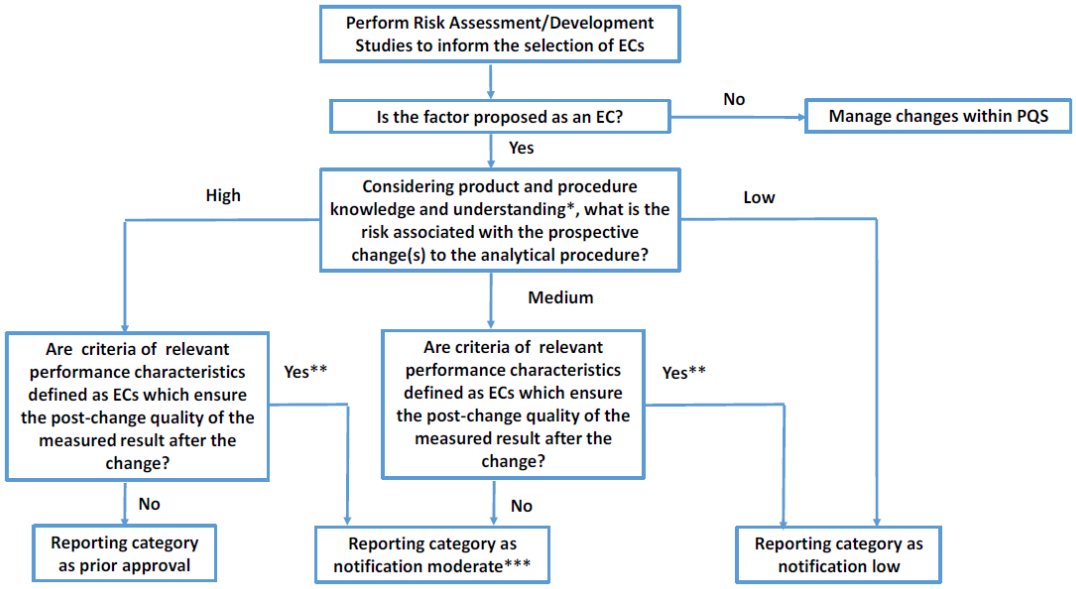
“Use of the enhanced approach should not lead to providing a less detailed description of analytical procedures in a regulatory submission”

However, this sentence has some flaws because, according to ProPharma Group, Liesbeth van Rooijen, comparing the text “parameters that are not ECs are typically not included in a minimal procedure description" in line 552 to 553, doesn’t show how it connects to this text is unclear.

4.2.4.10 Lifecycle management and post approval changes of analytical procedures

According to the ICH Q14 – Analytical Procedure Development, the following figure stipulated:

Figure 3 - Risk-based approach to identification of ECs and reporting categories for associated changes in the enhanced approach (adapted from ICH Q14)

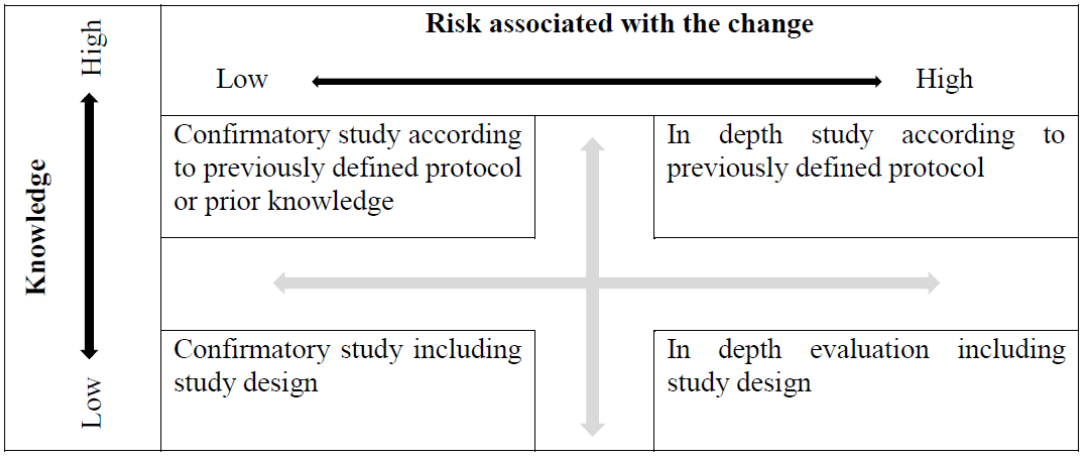


However, this figure has some flaws because, according to Dr.Uwe Lipke, the decision tree leaves (table 2) out various assessments and choices regarding modifications to analytical processes from the evaluation by competent authorities. The incorrect application of the so-called "Established Conditions" will not be evaluated in any way by the appropriate authorities. Furthermore, following such a revision, the registered dossier will no longer describe the actual analytical technique that was done. The work of inspectors will be impacted by this. The classification "notification low" results from underestimating the potential effects of a change (judgment about risk: low instead of medium or high). A type of IA version of notification low will be seen throughout Europe. When type IA variations are analysed, only the fulfilment of conditions can be assessed; risk assessment is not possible. The authorities receiving the notification low must determine whether the Major Accident Hazards (MAH's) conclusion is

appropriate because only the MAH may respond to the question about risk categorisation (low, high, or medium). Such an evaluation is not anticipated at this time.

According to the ICH Q14 – Analytical Procedure Development, the following table stipulated:

Table 2 - Relationship between knowledge, risk and extent of studies for changes to analytical procedures



However, this figure has some flaws because, according to ISPE, the Table 2's idea of comparing risk and knowledge levels from low to high is evident. But the Table 2's language may not always be consistent with Figure 3. What you must accomplish is stated in Figure 3, which may allow for similar strategies. Using the initial validation methodology and criteria, for instance, may still be suitable regardless of your level of knowledge (Table 2 implies only acceptable for high knowledge "according to previously defined protocol").

4.2.4.11 Development of multivariate analytical procedures

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“Multivariate analytical procedures are those where a result is determined through a multivariate calibration model utilizing more than one input variable. The considerations provided here are for models using latent variables that are mathematically related to directly measured variables. Other approaches, in machine

learning, such as neural networks, or optimization techniques could use similar principles although the specific approach may vary and will not be discussed in detail.

Development of a robust multivariate analytical procedure includes scientifically justified sample selection and distribution over the range, sample size, model variable selection and data pre-processing."

However, this sentence has some flaws because, according to EFPIA:

- The chapter 8 appears to stand alone and be unrelated to the ideas discussed in the previous chapters. For instance, there is no proposal on how to define ATP and EC for a multivariate model.
- Depending on the model type, an evaluation of model fit, such as R^2 and Q^2 for regressions, should also be included to make sure the model is appropriate and strongly correlates with the offline analysis.
- The proper chemometric algorithm to be utilized for creating the multivariate calibration model is missing, like Principal Component Analysis (PCA), Partial Least Squares (PLS) or Artificial Neural Networks (ANN).
- The absence of discussion or advice regarding neural networks and other related machine learning techniques makes this article too hazy to be of any use.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"The reference values are determined using reference analytical procedure(s) or prepared reference samples with known values. Care should be taken to ensure that uncertainty in the reference analytical procedure is sufficiently low in relation to the intended performance of the multivariate analytical procedure and that prepared reference samples are homogeneous."

However, this sentence has some flaws because, according to EFPIA, the word "Homogeneous" it's wrong, since we don't evaluate homogeneity's usefulness for model development, it's not useful in this opening situation.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“Careful consideration should also be given to sample distribution in the calibration and validation sets, as this will influence the model predictive capability.”

However, this sentence has some flaws because, according to EFPIA:

- There is no definition given for "calibration and validation sets".
- It’s not understandable how does the make-up of the validation set affect the model's capacity for prediction.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“The number of samples used to create a calibration model for quantitative analysis will depend on the complexity of the sample matrix and/or interference by the matrix in the analyte signal of interest (i.e., for more complex sample matrices, generally more samples are needed).”

However, this sentence has some flaws because, according to EFPIA, the statement “complexity of the sample matrix” it’s too vague and the assertion that the complexity of the sample matrix will always affect the calibration design is overstated.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“Variable selection is performed during model development. For example, wavelength range selection is frequently applied in spectroscopic applications to select a region of a spectrum that gives the best estimation of the selected chemical or physical property to be evaluated (modelled). Variable selection depends on the measurement principle, application and other factors, and should be justified.”

However, this sentence has some flaws because, according to EFPIA, the methodology links with molecule structure, therefore variable choice should be justified. Need a new explanation to better comprehend the statement.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"Examination of residuals to determine unmodeled features of the data (e.g., x-residuals or F-probability) outlier diagnostics to determine if the data is within the bounds of the model construction (e.g., Hotelling's T-squared or Mahalanobis distance) Software packages allow for the application of diagnostic tools for every model prediction."

However, this sentence has some flaws because:

- According to EFPIA, the suggested diagnostic methods, which are typically based on statistical constraints, are crucial for evaluating model performance.
- According to ISPE, when the chemometric model is being continuously monitored, Bias, Root Mean Square Error of Prediction (RMSEP), and the Test of Equivalency between the chemometric model and reference technique should also be utilized to make sure the model is functioning properly.
- According to ISPE, the suggested diagnostic tools are important to assess model performance and are usually based on statistical bounds.

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

"Model assessment is performed within the Performance, Quality and Safety (PQS) and utilizes knowledge management and risk assessment. If an issue is identified, model development and revalidation may be needed, for example, to add samples into the calibration set and remove those that are no longer relevant. In some cases, the model may be performing appropriately, but additional experience may identify the need to modify the limits of the model maintenance plan."

However, this sentence has some flaws because, according to EFPIA, a second clause was included to make it clear that the PQS will also be used for model building and revalidation, in addition to model assessment.

4.2.4.12 Development of analytical procedures for real time release testing: special considerations

According to the ICH Q14 – Analytical Procedure Development, the following is stipulated:

“As appropriate, an RTRT procedure should be validated as recommended in ICH Q2 and it should be demonstrated that the process measurements have appropriate specificity for the targeted product quality attribute.”

However, this sentence has some flaws because, according to EFPIA:

- They need to define what "RTRT procedure" means. Include or edit the definition in the glossary if necessary.
- Without mentioning the components of Q14 to take advantage of the advantages provided by the improved approach throughout the lifecycle of the RTRT method, Chapter 9 simply discusses the minimal approach (ICH Q2) to validation.

4.2.4.13 Annex C: Example of Multivariate Model Lifecycle Components

According to the ICH Q14 – Analytical Procedure Development, the following table stipulated:

Table 3 - Example of Multivariate Model Lifecycle Components

Model Description	On-line NIR to determine blending ranges to achieve blend uniformity during development	Measurement of Content Uniformity and Assay of uncoated tablets by NIR used for product release	Glucose Raman model used for qualitative identification testing on incoming raw material release for GMP use
	Model Category – Low Impact	Model Category - High impact	Model Category – High impact
	User requirements	Defined model requirements (e.g., ATP)	Defined model requirements (e.g., ATP)
Risk Assessment	Initial assessment based on existing knowledge, laboratory and pilot studies, or DOE, as appropriate.	Formal risk assessment based on knowledge gained during initial development.	Formal risk assessment with knowledge gained during initial development
Model Development - Calibration	Scientifically sound approach based on laboratory and pilot data and previous experience.	Formal design-based approach (*e.g.*, DOE) covering appropriate ranges of relevant variability sources with established acceptance criteria that are suitable for intended use.	Formal design-based approach covering appropriate ranges of relevant variability sources (raw material, lots, packaging, instruments-to-instrument, user, software limitation) with established acceptance criteria that are suitable for intended use. Establish an identification threshold that has the same probability of detection as the existing method and a suitable alternative testing method should the Raman method fail.
Validation (Verification)	Assess specificity and robustness, optionally assess linearity and/or precision	Full validation covering applicable performance characteristics across reportable ranges with established acceptance criteria (ICH Q2).	Full validation covering applicable performance characteristics across reportable ranges with established acceptance criteria (ICH Q2). Include establishing suitable comparability of Raman method to existing method for release (can be reference method)
Performance Monitoring	Routine monitoring – maintain data sources (instruments), automation connectivity, and data integrity.	Routine monitoring – maintain data sources (instruments), automation connectivity, and data integrity.	Routine monitoring – maintain data sources (instruments), automation connectivity, and data integrity.
	Real-time diagnostics – implement initial diagnostics to confirm model performance in real-time.	Real-time diagnostics – implement routine diagnostics to confirm model performance in real-time.	Real-time diagnostics – implement routine diagnostics to confirm model performance in real-time.
	Periodic monitoring – if applicable, compare model predicted results to reference method at a frequency that is scientifically justified or on an event driven basis as needed.	Periodic monitoring – compare model predicted results to reference method at a frequency that is scientifically and statistically justified or on an event driven basis.	Periodic monitoring – compare model predicted results to reference method at a frequency that is scientifically and statistically justified or on an event driven basis.
Model Maintenance	Model Update - updates are common during the process development stage as new experimental data becomes available	Model Update - updates should be triggered based on Model Monitoring and Maintenance Strategy.	Model Update - updates should be triggered based on Model Monitoring and Maintenance Strategy.
	Change Management per PQS	Change Management per PQS	Change Management per PQS

However, this sentence has some flaws because, according to EFPIA:

- Although the table only contains information for synthesized compounds, the tile is more generic. There is no illustration of RAMAN or biotech goods. There is no definition for ATP, EC, Post-Approval Change Management Protocol (PACMP) for a multivariate model.

- In the last line of table need to be added more information to the text to clarify what is meant by "change management." By doing this, the analyst's flexibility is maximized.
- For brevity, cells in the table with the same command can be combined.
- For the examples presented, the table ought to contain a header row.
- In the case of the blending example, this may not accurately represent real-world situations because unsupervised models are frequently employed, they may not go through a thorough validation process, or they may merely be created for informational purposes.(31)

5 Conclusion

The pharmaceutical industry has grown a lot from the last past years, with the emergence of new drugs, it's normal that their production has increased. Manufacturing, extraction, processing, purification, and packaging of chemical substances for use as drugs on people or animals are all included in the pharmaceutical sector. The synthesis of the active ingredient or medication (primary processing, or manufacture) and secondary processing, the transformation of the active drugs into products appropriate for administration, are the two main processes of pharmaceutical manufacturing. So, bearing in mind that medication can have serious consequences for human health, it is normal to carry out several evaluations of medications so that they harm as little as possible.

Therefore, one of the most crucial steps is quality control, because medicines must be advertised as being stable. The predictable formulations that are clinically effective with the aim of minimizing errors, quality control must find ways to be stringent and sophisticated analytical techniques for their evaluation is occurring concurrently. For this reason, in order to maintain this level of quality, the ICH Q2 was created, with the objective of validating analytical procedures that can guarantee the quality of the final product.

ICH Q2 offers instructions and suggestions on how to develop and assess the numerous validation tests for each analytical technique. Along with describing the actual experimental data needed and along with the statistical interpretation for the validation of analytical procedures, it also discusses the characteristics that must be taken into account during the validation of the analytical procedures that are included in registration applications.

However, the ICH Q2, over the years, became outdated and it was not possible to apply it to the new methods. For this reason, it was necessary to develop a new guideline that encompasses what the ICH Q2 did not address and with this purpose, ICH Q14, was developed.

This guideline outlines scientific and risk-based methods for creating and sustaining analytical processes appropriate for evaluating the quality of drug substances and drug products. It pertains to new or updated analytical techniques used to analyze the release

and stability of chemical, biological, and biotechnological commercial pharmacological ingredients, and products. Additionally, it can also be used with other analytical techniques employed as part of a risk-based control strategy.

Despite the great promotion of this new guideline, it fell short of expectations. The document itself was vague on many criteria. It shows lack of consistency, confusing in some topics, so it needed to be more detailed with some information and added more examples for a better understanding of the document.

Even so, this guideline has enormous potential to develop more analytical procedures and to be able to improve the quality of medicines in the near future, but for this it is necessary to resolve the gaps in the current document or to prepare a new one.

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