Green Chemistry and Quality by Design in Process Analytical Technologies and Drug Design

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Edited by

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and Bikash Ranjan Jena

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I dedicate this textbook to my parents, family members, relatives, wife, and son because they gave me strength, focus on healing, and courage to share my pharmacy knowledge to complete this textbook.

—Suryakanta Swain

I dedicate this textbook to all my well-wishers who always encourage me to achieve the higher goal and motivate me to write this type of textbook for pharmaceutical education and research

— Bikash Ranjan Jena

I didn't have a good idea, but I had an idea

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FOREWORD

Few textbooks address the most complex aspects of "Green Chemistry and Quality by Design in Process Analytical Technologies and Drug Design". Appropriately, the need for a book written in straightforward, clear, cogent, and pertinent language was recognized. The outstanding efforts of Editor-in-Chief Dr. Suryakanta Swain and co-editor Dr. Bikash Ranjan Jena have resulted in the publication of a comprehensive textbook on green chemistry, quality by design in process analytical technologies, and drug design in academic and industrial research. The subject matter is written with sufficient information about green chemistry and quality by design, as well as its theoretical foundation, and is presented in a straightforward manner to facilitate global comprehension among pharmacy students, researchers, and scientists. As a reader, whether you are a student or a teacher in India or abroad, I hope that researchers and academicians will find this textbook useful, as it should enhance your current knowledge, comprehension, and insights into the theoretical and practical concepts of the selected topics covered. I wish the editor-in-chief and co-editor the best of luck in their joint endeavour. I trust that their contribution to the literature of pharmaceutical sciences will continue forever. Dr. Suryakanta Swain, the principal editor of this textbook, is a renowned scientist with extensive academic teaching and research experience in pharmaceutical or health sciences. Dr. Swain has spent the last 16 years researching pharmaceutical targeting drug delivery systems using quality by design tools. He has a patent and has published articles of study and review, invited editorials or opinion articles, short communications, thematic issues, national and international books, and book chapters with reputable publishers.

—Prof. (Dr.) Sanjay Kumar
Vice-Chancellor,
Amity University, Kolkata, India

PREFACE

Our primary objective is to cover as much of the book's content as feasible. Thus, it is with great pleasure that we present this textbook “Green Chemistry and Quality by Design in Process Analytical Technologies and Drug Design”. This volume is exceptional in several ways. First, the text provided an in-depth analysis of the fundamentals of incorporating quality by design and ecological analytical chemistry into drug design and process analytical technologies. It will reveal and improve the QbD principles used in bioanalysis, process development, downstream processing, and combining QbD and green analytical chemistry (GAC) utilizing eco-friendly and green solvents for product development.

In addition, it will provide detailed information regarding applying the QbD concept and philosophy to quality control and process development. Quality by design is becoming an integral element of the modern approach to pharmaceutical process development. Therefore, this book will be more beneficial to Ph.D. research scholars, scientists/researchers, P.G. and U.G. students for pharmacy and chemical sciences for understanding the concept of quality by design and green chemistry for drug design, and it illustrates the necessary inputs that are related to product quality and process sustainability.

The current global data for the principles of analytical QbD approach combined with risk assessment tools (R.A.) and design of experiments (DoE) is leading to the development of robust chemical processes with proper analytical monitoring and control that ensure that product quality will be exceptional in comparison to existing textbooks in a lucid and researcher-friendly format for easy comprehension and applications in the current pharmaceutical research.

I am incredibly grateful to the co-editor of this textbook, who has sacrificed encouragement to write about all the selected contents of this book in order to inspire pharmacy students' imaginations. This textbook preparation took

longer than anticipated and contains more pages than anticipated. This book is useful for pharmaceutical students perusing M.Pharmacy degrees in pharmaceutical analysis/quality assurance, pharmaceutical chemistry, pharmaceutics, and other fields, and it helps them advance their careers in the pharmaceutical sector. Depending on the reader's needs, this book may fit into any of the previously listed categories. I am grateful to my co-editor and contributing authors for their regular and thorough assistance with the compilation, editing, and construction of flow charts and figures while creating this textbook. Finally, I'd like to thank my enthusiastic wife, Ms. Linarani Swain, for her love, patience, and unfailing support throughout the development of this textbook. I thank my son, Priyans Swain, for allowing me to write this book.

—Dr. Suryakanta Swain
Editor-in-Chief

ACKNOWLEDGEMENTS

I appreciate the substantial contributions of Dr. Bikash Ranjan Jena, co-editor, and all contributing authors and co-authors for sustaining the vitality of this textbook. I am grateful to everyone who shared their insights with me, including well-wishers, mentors, academic guides, academic colleagues, and industry colleagues. I thank my parents, father-in-law, mother-in-law, brothers, sister, sisters-in-law, and all other relatives, my wife, Mrs. Linarani Swain, and my beloved son, Priyans Swain. They provided substantial assistance throughout my complete life mission.

In addition, I'd like to express my heartfelt gratitude to the Honourable Vice-Chancellor of Amity University, Kolkata Campus, for his consideration in allowing me to prepare this textbook. This work was made possible thanks to his great support and blessing. Finally, I'd want to convey my heartfelt thankfulness to the management at Amity University for their great assistance and inspiration in developing this textbook. I am particularly grateful to Cambridge Scholars Publishing, U.K.'s publisher, acquisitions editor, managing editor, copy editor, and production manager for their contributions to the development, preparation, and publication of this textbook.

—Dr. Suryakanta Swain
Editor-in-Chief

INTRODUCTORY NOTE

Quality by design is predominantly used in industries as a measurement tool or as a systematic, patient-centric approach for monitoring chemical and technological processes by analytical and formulation scientists. It is the primary component of technology and product quality control. Process monitoring and control in analytical chemistry are included in process analytical technology (PAT), which is primarily used to address problems and determine the composition of products. QbD uses design of experiments (DoE), risk assessment, and PAT to better understand materials and processes. This enhanced comprehension makes QbD accessible and practicable for the pharmaceutical industry. QbD with green chemistry is a novel, unified approach to design and production that is both cost- and time-effective for rapid analysis and regulatory flexibility. The outcome of this book will emphasize the depth of comprehending the application of Quality by design in drug design to the production of finished products or dosage forms with the generation of robust methods using modern analytical tools. The authors have exerted their utmost efforts to emphasize a novel ideology of Quality by design applications in numerous aspects of the manufacturing process in the formulation and analytical sciences, which can be a cost-effective, robust, and holistic approach for less batch failure and to drive faster regulatory approval during drug product manufacturing according to ICH-recommended guidelines. Future ramifications of emergent modern applications of Quality by design and green analytical chemistry in drug design, process analytical technologies, and bioanalytical process development instruments are discussed. This book will cover all crucial aspects of incorporating Quality by design and ecological analytical chemistry into drug design and process analytical technologies. It will reveal and improve the QbD principles used in bioanalysis, process development, downstream processing, and combining QbD and green analytical chemistry (GAC) utilizing eco-friendly and green solvents for product development.

In addition, it will provide detailed information regarding applying the AQbD concept and ideology to quality control and process development. The principles of the analytical QbD approach, when combined with Risk assessment tools (Ra) and Design of Experiments (DoE), result in chemical processes with appropriate analytical monitoring and control that guarantee product quality. Quality by design is becoming an integral element of the modern pharmaceutical and chemical development approach. This book will be more beneficial to Ph.D. research scholars, researchers, and P.G. and U.G. students in Pharmacy and chemical Sciences for understanding the concept of Quality by design and green chemistry for drug design, and it illustrates the necessary inputs that are related to product quality and, ultimately, the sustainability of the process.

LIST OF ABBREVIATIONS

APCI: Atmospheric pressure chemical ionisation
AQbD: Analytical quality by design
BBD: Box behnken design
CCD: Central composite design
CE-MS: Capillary electrophoresis mass-spectrometry
CPPs: Critical process parameters
CQAs: Critical quality attribute
DoE: Design of experiments
DSP: Downstream processing
EME: Electro membrane extraction
ESI: Electrospray ionisation
ETV-ICP-OES: Electrothermal vaporisation inductively coupled plasma-mass spectrometry
FMEA: Failure mode and effect analysis
GAC: Green analytical chemistry
GC: Gas chromatography
GMP: Good manufacturing practices
HF-LPME: Hollow-fibre liquid-phase microextraction
HPLC: High performance liquid chromatography
HPLC-EAT: High performance liquid chromatography and environmental assessment tool.
ICH: International conference on harmonization
ICP-MS: Inductively coupled plasma-mass-spectrometry
ICP-OES: Inductively coupled plasma -optical emission spectrometry
LA-ICP-MS: Laser ablation inductively coupled plasma -mass spectrometry
LC: Liquid chromatography
LC-MS: Liquid chromatography-mass spectrometry
LC-MS-MS: Liquid chromatography tandem mass spectrometry
LC-NMR: Liquid chromatography nuclear magnetic resonance
LC-PDA: Liquid chromatography photo diode array

LVI-GC-MS: Large volume injection gas chromatography tandem mass spectrometry
MILs: Microstructure based ionic liquids
NDA: New drug application
NMR: Nuclear magnetic resonance
OFAT: One factor at a time
OTC: Over-the-counter
OVAT: One variable at a time
PAT: Process analytical technology
PDA: Photo diode array detector
QbD: Quality by design
QTPP: Quality target product profile
R & D: Research and development
SBME: Solvent bar microextraction
SC: Supercritical
SDME: Single-drop microextraction
SOPs: Standard operating procedures
SPE-LC-MS: Solid phase extraction liquid chromatography-mass spectrometry
UFLC: Ultra-fast liquid chromatography
UHPLC: Ultra high-performance liquid chromatography
UPLC: Ultra performance liquid chromatography

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CHAPTER 1

APPLICATIONS OF QUALITY BY DESIGN AND GREEN CHEMISTRY FOR ANALYTICAL PROCESS DEVELOPMENT

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1. Introduction

Living in the twenty-first century, we cannot be sure of our health if we keep using items made from dangerous materials or in hazardous ways. Armenta et al. (2008), 497–511, say that a healthy environment is essential for a real dedication to health. Realizing this has led the pharmaceutical industry to develop a new idea to use processes and raw materials that are better for the earth. The emerging pharmaceutical business has always shown the world how important new ideas are. One of these ideas at the top of the list is the idea of sustainability, which leads to green science. Even though this idea has been discussed extensively in the last 20 years on many different levels, it still needs to be better understood and developed (Rios et al., 2013, 174–188; Van den Brink et al., 2015, 40–49).

Green analytical chemistry (GAC) is a philosophy that has recently come to the forefront of innovation as a "double-edged sword" to build competitive analytical methods that are better for the environment and more sustainable than traditional ones. GAC is a new way to think about creating and making drug molecules. It is based on 12 principles (Pena-Pereira et al., 2010; Anastas, 1999; 167-175). These ideas can be used as a road map to reduce or eliminate the dangers of chemical operations while focusing on green design standards. The main goal of GAC is to use processes that make less (and less dangerous) waste, use fewer toxic chemicals, make use of renewable materials, improve energy efficiency, and analyze processes in real-time to stop pollution and reduce the chance of accidents (Kirchhoff, 2005, 237–243; Musters et al., 2013, 87–96). This can be done by making new, more environmentally friendly methods or changing old methods and procedures using the QbD approach.

2. Concept of QbD paradigm for analytical science

QbD ensures that a product meets specific quality standards so that patients are safer and the product works better. At present, regulatory documents for the pharmaceutical industry stress how important it is to use the idea of "quality by design" (QbD) to understand the products and processes and ensure the quality of the products through design. The ICH rule Q8 (R2) backs up the idea of quality by design (QbD). QbD principles can be used to create a control plan for a product, mainly when much knowledge about the process has been gathered over time. During the lifecycle of a product, as people learn more about how the process works, the control plan can be improved (Pena-Pereira et al., 2010, 321-327; Anastas, 1999, 167-175; Kirchhoff, 2005, 237-243). So, QbD helps determine the factors affecting formulation and manufacturing-related parameters. This is indirectly good for developing strong formulations that get regulatory approval quickly. At the moment, QbD is doing well because of two big things. The first concerns how regulations make it hard to change process settings and update analytical controls. The second concerns how much it costs to do these investigations. This also shows that the QbD method is not trendy in the early stages of making new chemical entities (NCE) into drugs (Kirchhoff, 2005, 237–243).

On the other hand, the life cycles of current APIs are getting longer because fewer NCEs are getting approved, and existing APIs are being used in new ways. With more focus on drug safety and compliance, knowing more about the different toxins and how they change over time is essential. When QbD principles are used, they help people learn more about the product and how it is made, which makes the process of setting specifications better (Figure 1.1). Lastly, a better understanding of the product and how it is made can help regulators be more flexible (Van den Brink et al., 2015, 40–49; Swain et al., 2019, 240–250).

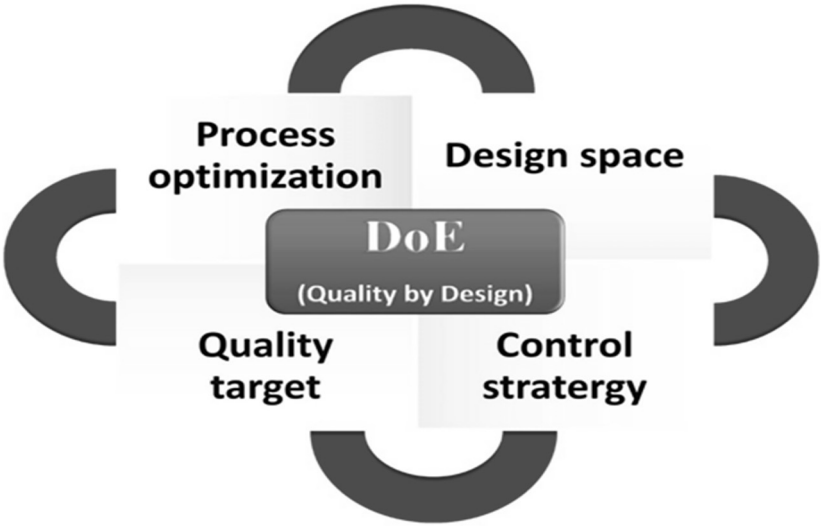

Figure 1.1. Schematic diagram reflecting a glimpse of QbD in drug development

3. QbD and green chemistry: a unified approach to analytical and product development

Presently, the purpose of including QbD in research is to demonstrate the utility of the QbD approach in developing separation methods in green analytical chemistry. The relevance of QbD and green analytical chemistry combination was emphasized by the case study of Active Principal ingredient and its related substance analysis by UHPLC. Following a QbD

approach, green chemistry principles were included in the analytical target profile to reduce the environmental impact and minimize analyst exposure during future routine use after implementing the method in the pharmaceutical industry. First, a scouting phase was enabled to select the stationary phase and the type of organic solvent. After applying quality risk assessments, the effects of selected critical process parameters on critical quality attributes (CQAs) were evaluated through a screening design. A response surface methodology was then carried out to simulate CQAs as a function of the retained factors, and the optimal separation conditions were determined by applying desirability functions to the simulated responses. Finally, the design space was constructed as the multidimensional subspace where the CQAs met the requirements, emphasizing quality risk management. The method was successfully validated by the accuracy profile approach and applied to a pharmaceutical product.

4. Greenness of analytical methodology

The analytical Eco-Scale is an innovative and comprehensive technique for assessing the greenness of analytical methodology. Green analytical chemistry is a philosophy that blends sustainable development principles into analytical laboratories (Armenta et al., 2008, 497-511). There are various approaches to presenting the GAC concept, the most notable of which are the miniaturization of sample preparation techniques and final determination devices (Rios et al., 2013, 174-188; Van den Brink et al., 2015, 40-49). It is based on allocating penalty points to analytical process parameters that do not comply with the ideal green analysis. This approach compares different parameters and different steps of the analytical process. Traditional green chemistry metrics such as Atom Economy, E-factor, and Reaction Mass Efficiency were designed for organic preparations and may not always be applied to green analytical chemistry. The term “green chemistry” first appeared in the early 1990s, and it can be seen as chemists' contribution to the concept of sustainable development (Pena-Pereira et al., 2010, 321-327; Anastas, 1999, 167-175). The recent trends in analytical chemistry to apply new chemicals, such as ionic liquids, bio-based solvents, or deep eutectic solvents, require careful and comprehensive assessment before commenting on their greenness. Existing databases for assessing

green analytical methods only cover well-known procedures and instruments and thus do not encourage the development of new, more ecologically sound alternatives (Pena-Pereira et al., 2010, 321-327). The analytical Eco-Scale can be an excellent, semi-quantitative instrument alternative to established green chemistry measures. It is necessary to develop analytical chemistry-specific solvent selection systems, digestion chemicals, and assessment systems of derivatization agents (Anastas 1999, 167-327). The environmental impact of analytical techniques must be considered during the optimization process of solvents and reagents selection.

5. QbD prospective with green analytical chemistry (GAC): Multivariate applications

New methods and techniques that reduce/eliminate the use and generation of hazardous substances through all aspects of the chemical analysis life-cycle manifest the recent interest in green analytical chemistry.

Analytical QbD (AQbD) is a method for controlling genotoxic impurities (GTIs) systematically. GTI regulation is a critical function for every analytical scientist to do during method the development of every new chemical entity (NCE) intended for clinical application during industrial process manufacture (Kirchhoff & Mary 2005, 237-243; Musters et al., 2013, 87-96).

A crucial element of this process is the quality risk assessment (QRA), which can be well-performed using the Chemometrics design of experiment strategies as stated by the risk-assessment principles enshrined in ICHQ8 and Q9.

AQbD principles are established in order to set up an improved control strategy for the final steps in the production route of steroidal contraceptives, which has been produced for over 20 years within our facilities (Kirchhoff & Mary, 2005, 237-243; Musters et al., 2013, 87-96).

AQbD principles are used for the progress of the bioprocessing unit operations. The first step is risk analysis for identifying the process parameters that need to be examined experimentally to assess their impact on the performance of a given unit operation (Musters et al., 2013, 87-96).

The systematic evaluation control of GTIs during green synthesis can be well undertaken by appropriate screening of method parameters and critical process parameters (CPPs), finding the most influential variables for method optimization within the design space so that optimum product-process controlled strategies can be achieved through the QbD principles by meticulous finding of Quality target product profile (QTPP) (Mohamed et al., 2017, 1-11; Tariqul et al., 2020, 550-561; Supratik et al., 2022; 3637-3710, Sharma et al., 2020, 391-407).

As evidenced by numerous applications in industry quality control and R&D laboratories, the quality by design (QbD) approach has been widely used in the development of pharmaceutical products. QbD improves the understanding of processes and products with predefined goals based on statistical, mathematical, chemical, and quality risk management when compared to quality by testing (QbT) (Mohamed et al., 2017, 1-11; Tariqul et al., 2020, 550-561). QbD processes are divided into four steps:

Analytical target profile (ATP): It includes the purpose of an analytical method and its required performance criteria (Critical quality attributes - CQAs); Supratik et al., 2022; 3637-3710; Sharma et al., 2020, 391-407).

Risk assessment: This step focuses on data analysis and is related to sample preparation for further analytes determination. Then, additional potential variables, such as noise variables, can be identified. Measurement system analysis approaches can be used to evaluate them, as well as instrumental parameters, which can be evaluated using design of experiment (DoE) strategies (Hellweg et al., 2004, 418-427; Swain et al., 2019, 240-250). A brief overview of the Experimental design-based development strategy using the QbD paradigm is demonstrated in Figure 1.2.

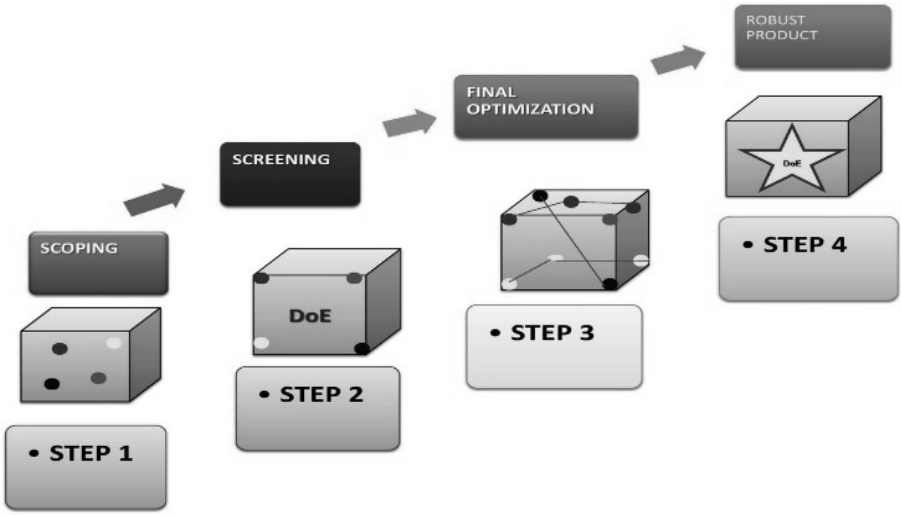

Figure 1.2. DoE enabled process for development of pharmaceutical product

From DoE results, the design space (DS) or MODR is obtained. DS shows the analytical chemistry conditions where an analytical method or production procedure can work without compromising the final result. This component establishes reliable methods for analytical chemistry laboratories (Sharma et al., 2020, 391-407; Hellweg et al., 2004, 418-427; Swain et al., 2019, 240-250).

Control strategy and validation: These are conducted via observation of several analytical statistics of merit, such as accuracy, and precision expressed as relative standard deviation (RSD) and coefficient of determination (R2), among others (Hellweg et al., 2004, 418-427; Swain et al., 2019, 240-250).

QbD was also applied in bioanalytical method development for olmesartan medoxomil (OLM) determination in rat plasma using ultra-performance liquid chromatography (UPLC) (Supratik et al., 2022; 3637-3710; Sharma et al., 2020, 391-407; Galuszka et al., 2013, 78-84).

When quality by design (QbD) and process analytical technology (PAT) were first introduced to the biotech industry, the substantial regulatory

agencies and the biotech industry spent significant resources to make their implementation easier, with mixed outcomes.

With the introduction of the twelve principles of green chemistry (GAC), guidelines were provided for chemists to develop clean, environmentally benign methodologies that are sustainable for the long term (Tobiszewski et al., 2015, 321-327; Henderson et al., 2015, 78-84). This overview highlights some advances in major green chemistry research areas: increased use of addition reactions and rearrangements and decreased reliance on elimination and substitution reactions. Research aimed at improving the selectivity of this chemistry is crucial and often depends on advances in catalysis. Alternative driving forces for the reaction include microwave irradiation, sonochemistry, and photochemical reactions. Reduction of, or, ideally, elimination of solvents. Use of alternative, environmentally benign solvents. Avoiding toxic materials and designing for reduced environmental exposure (Henderson et al., 2015, 78-84; Chaturvedi et al., 2017, 1358-1369; Galuszka et al., 2013, 78-84). An overview process indication is used in QbD while the optimization process during GAC and its implementation are depicted in Figure 1.3.

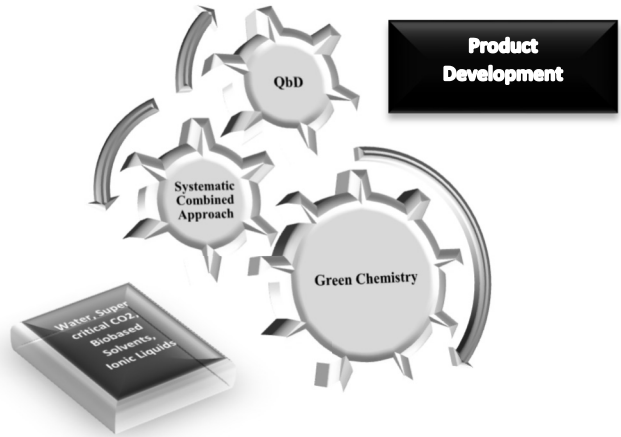

Figure 1.3. Schematic diagram elucidating QbD and green chemistry approach

6. Drug Development: Analytical Targets and the Fishbone Diagram

The fishbone diagram shows the most critical factors in terms of product quality and the long-term viability of the process. The Ishikawa fishbone diagram helps determine what caused a problem and how it happened. When creating processes and products that follow green chemistry (Vinayak et al., 2022, 255-261), all inputs, like materials, energy, and waste, should be considered regarding how well they work. As part of the Quality-by-Design (QbD) program, the pharmaceutical industry has recently emphasized research and development in analytical chemistry. To do this, the performance profile of the product must be evaluated to make a quality profile. From this, the most critical quality attributes for the process and analytical parts of process control must be found (Thompson, 1995, 261-270). There are many different analytical methods, procedures, and pieces of equipment.

Choosing the right one depends on what the analysis is for. The International Conference on Harmonization's (ICH) Guideline Q8 (R2) is a helpful tool for making an analytical process for quality-by-design (ICH, 2009; Jelena & Koel, 2022; 100136). “Quality by Design” is a “systematic approach to development based on sound science and quality risk management that emphasizes product and process understanding and process control from the start, with clearly defined goals.” It talks about how important it is to choose a suitable method of analysis and success characteristics for the analysis process to reach the study's goals. The way that QbD adds green limits to analytical target profiles is tied to risk assessment. This makes it easier to understand the factors that affect the performance and suitability of an analytical method. As a result, this gives us helpful information about how to improve the layout of the analytical process. Optimizing analytical techniques means carefully setting up an experiment to test new settings which are better for the environment on a goal profile. This optimization changes the process factors, how much energy and materials are used, and how much waste is made. So, methods that provide the necessary scientific information with the required sensitivity, accuracy, and precision will be safe and good for the environment (Armenta et al., 2008, 497–511). To ensure the quality of the result, it is essential to use chemometric and statistical tools as well as other quantitative methods. In this case,

multivariate statistical tools for data analysis and study design are essential. The processing of data is not a green chemistry idea in and of itself, but it can be seen as part of a lab system that is more efficient and wastes less. Raw measurement data can often be used to find important information without using chemicals or making chemical trash (Jelena and Koel, 2022, 100136). This is especially true when mathematical processes are used instead of chemical processing.

7. What problems QbD has right now and what chances it has in the future with green chemistry-focused development and approval

The goal of green chemistry, which grew out of this wide range of skills, was to give chemists and molecular designers an organized design framework that would help them think about how chemicals affect public health, the environment, and long-term sustainability. The global green chemistry community has made much progress in showing that this project, this design framework, can be more than just a theory and can be put into practice. Pharmaceutical development is a long and challenging process that starts with the idea of a formulation and ends with a finished drug. In any case, the pharmaceutical product must ensure that the patient gets a certain amount of quality. Even though pharmaceutical manufacturing technology has come a long way, many old ways of developing processes and making drugs are still used. The way things are right now, this is a big problem. QbD means that you cannot test the quality of the finished result; it should be built in by design. Using all twelve principles as a guide for design, the future of green chemistry will depend on breakthroughs that bring together and combine these advances. Designing for sustainability and less risk should not be seen as limiting. Instead, it should be seen as allowing people to explore and invent, crossing countries and scientific fields to find new ways to solve problems.

PAT is currently going through a process of redefinition that includes making it smaller, adding automatic sample systems and high-throughput measurement methods, and making data modeling and processing more complex in Analytical Quality by Design (AQbD). This is happening as part of the Analytical Quality by Design program. To be more specific, this