

Quality by Design (QbD) for Herbal Drug Products: Challenges, Opportunities and a Risk-Based Development Framework

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Abstract

Quality by Design (QbD) is a science- and risk-based pharmaceutical quality framework that shifts the paradigm from post-hoc testing of final products to designing quality into a product and process. Herbal drug products present unique challenges due to the complex nature of botanical materials, which may involve multiple variables such as taxonomy, chemotype, geographical origin, agroclimatic conditions, harvesting practices, processing, storage, and extraction procedures. All of these factors could contribute to undesired product quality variability affecting the safety, efficacy, stability, and performance of the final dosage forms. This article aims to discuss how QbD can be applied to herbal drug products by taking into account botanical authenticity, selection of quality markers, multivariate chemical profiling, quality risk management, design of experiments (DoE), analytical quality by design (AQbD), and process analytical technology (PAT) as well as lifecycle pharmaceutical quality management. Particular emphasis is placed on the importance of considering material-related aspects as upstream quality attributes by implementing a material-inclusive design space. The risk-based framework is proposed that starts with defining the quality target product profile (QTPP) and critical quality attributes (CQA) and linking them with critical material attributes (CMA) and critical process parameters (CPP). This is achieved through quality risk management, design of experiments, analytical development, and control strategy. The article also highlights emerging approaches such as DNA-based authentication, spectroscopy, chemometrics, metabolomics, machine learning, and digital tools as part of the quality management system rather than standalone solutions. Altogether, this framework is intended to enable consistent product quality, advanced process understanding, analytical control, and regulatory compliance by ensuring that inherent variability of botanical materials is characterized, understood, and appropriately controlled within predefined ranges.

Keywords: Quality by Design; herbal medicines; botanical drugs; quality risk management; design of experiments; quality markers; analytical Quality by Design; chemometrics; process analytical technology; lifecycle management.

1. Introduction

Herbal medicines and botanical drug products play a large role in global healthcare. Their quality is affected by biological, environmental and manufacturing factors that are fundamentally different from those influencing many chemically synthesized active pharmaceutical ingredients. Variability in species, plant part, chemotype, geographic origin, cultivation conditions, stage of harvest, drying, storage, and

manufacturing can alter the chemical profile of a botanical material. International guidance therefore focuses on identity, purity, composition, strength and control of contaminants throughout the herbal-product supply chain [1-8].

Traditional quality control often involves identity tests, microscopy, physicochemical parameters, chromatographic fingerprints, assays for marker-compounds, contaminant testing and finished-product specifications. These approaches are nevertheless vital. But a testing-intensive strategy may only identify a failure after material has gone into the manufacturing process. QbD provides a preventative approach in which the desired product profile is defined prospectively, potential sources of variability are identified, relationships between material/process variables and quality are studied experimentally, and an integrated control strategy is established [16-23].

The central problem with applying QbD to herbal products is that variability is not necessarily a manufacturing defect. Biological variability can be inherent to raw material. The goal is therefore not to make every botanical lot chemically identical, but to identify which dimensions of variability matter for quality and to keep those dimensions within scientifically justified limits. This entails integration of pharmacognosy, botanical authentication, analytical chemistry, statistics, process engineering and pharmaceutical quality management.

The review discusses the scientific and regulatory basis of QbD, its relevance to herbal products, identification of CQAs/CMAs/CPs, DoE, analytical strategies, chemometrics, PAT, control strategy and lifecycle management. It also proposes a practical framework for adapting QbD to the distinctive variability of botanical drug products.

2. Scope and Literature Search Methodology

This narrative review article presents peer-viewed literature and guidelines on herbal medicines, botanical drug products, pharmaceutical Quality by Design (QbD), lifecycle quality risk management, analytical procedure development, botanical authentication, chemical fingerprinting, quality markers, PAT and lifecycle management. Emphasis is placed on reviews published in PubMed-indexed and established journals in pharmaceutical sciences, pharmacognosy and analytical chemistry, as well as official guidelines of the World Health Organization (WHO), International Council for Harmonisation (ICH), U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). The literature was thematically grouped to identify limitations of current practices of quality control of herbal products and potential opportunities for their integration in the framework of lifecycle QbD.

3. Herbal Drug Products as Complex Pharmaceutical Systems

Botanical products are complex chemical entities, comprising numerous primary and secondary constituents. Their composition may vary during harvesting, drying, milling, extraction, concentration, drying of extracts, granulation, and storage [3-15]. Unlike a conventional purified API, a botanical extract may contain dozens or hundreds of detectable constituents, some of which may contribute to pharmacological activity, stability, toxicity, or process behavior. Botanical identity is a second source of complexity. Closely related species can share macroscopic or microscopic features, while differing in chemical composition. Substitution, adulteration, and economically motivated dilution, then, may remain undetected, if only one analytical dimension is examined. Microscopy, DNA-based approaches, chromatographic fingerprints, and spectroscopic approaches, contribute complementary evidence [9-13].

A third concern is contamination. Medicinal plants may be subject to heavy metals, pesticide residues, mycotoxins, and microbial contamination, depending on soil, water, agricultural practice, harvesting, and storage. WHO guidance recommends controls addressing contaminants and residues, and emphasizes appropriate quality-control procedures for medicinal plant materials [14,15]. A QbD strategy should incorporate these hazards at the earliest stages of development, rather than treating them exclusively as finished-product tests.

4. QbD: Principles and Regulatory Foundation

Modern pharmaceutical Quality by Design (QbD) is based on the idea that product quality is controlled through design and therefore should be built into both the product and its manufacturing process rather than being tested in the final product [16,17]. ICH guidelines Q8(R2), 9(R1), 10, and 12 provide a framework for pharmaceutical-development, quality-risk management, pharmaceutical quality system, and lifecycle management, respectively [18-21]. On the other hand, ICH guideline Q2(R2) and Q14 provide a framework for analytical procedure validation and evaluation [27,28].

The principles mentioned above may be applied to herbal drug development; however, additional considerations should be taken into account due to the specificities of botanical materials, such as botanical identification, agronomic variations, and the complexity of chemical composition. The World Health Organization (WHO) Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP) guidelines, the EMA guidelines for herbal medicinal products, and FDA's guidance for industry on botanical drugs are also relevant to the development of herbal medicines [24,33-35]. The objective is to obtain a product and process understanding that is sufficient to establish a control strategy by demonstrating the capability of a manufacturing process to provide a product with consistent quality derived from the understanding of the interdependence of material attributes and process parameters on critical quality attributes (CQAs).

5. Conventional Quality Control versus QbD-based Quality Assurance

Conventional quality control is commonly organized around specifications and testing of incoming materials, in-process materials and finished products. This remains indispensable for identity, assay, impurities, microbial quality and contaminants. Nevertheless, end-point testing cannot by itself explain the causes of variability or prevent recurrence.

A QbD-based system begins earlier. It defines the intended quality profile, identifies potential risks, characterises material variability, investigates process variables experimentally and integrates controls across the lifecycle. In herbal products, this changes the central question from whether a finished batch passes a specification to how botanical identity, composition, processing and storage interact to generate the final quality profile [3-8,16,17].

6. Quality Target Product Profile

The QTPP specifies the qualities that the final product should possess. It serves as a starting point for the development. The QTPP includes features like dosage form, route of administration, strength, dose, and release characteristics, stability, and microbial quality for herbal drug products, as well as limits on contaminants, identity, packing, and desirable, therapeutic performance characteristics. It should be based on its clinical use and regulatory requirements instead of laboratory findings.

7. Critical Quality Attributes

CQAs are physical, chemical, biological or microbiological properties, which should be maintained within an appropriate range to assure product quality. Potential herbal-product CQAs include botanical identity, botanical purity, marker or quality-marker content, chromatographic fingerprint, moisture, particle size, extractable-solids profile, dissolution or release, microbial quality, elemental impurities, pesticide residues, mycotoxins and stability-indicating attributes [3-15].

Not every measured parameter is per se critical. The criticality of a particular attribute should be justified by means of scientific knowledge and risk assessment taking into account potential effects on safety, efficacy, product performance and manufacturability.

8. Critical Material Attributes

CMAs are the characteristics of materials that can influence CQAs. Examples for herbal manufacturing include authenticated species and plant part, chemotype, geographical origin, conditions of cultivation and harvesting, moisture, particle size, maturity, storage conditions, extractable composition and concentrations or ratios of relevant marker constituents.

Due to the inherent biological variabilities in botanical materials, QbD requires that a material strategy be established which will define the acceptable variability and its impact on the product performance. WHO GACP principles encourage control of cultivation, collection and primary processing [24]. Therefore, supplier qualification, representative sampling and characterization of multiple lots are key aspects of development.

9. Critical Process Parameters

CPPs are process variables that can be varied to affect CQAs. Milling, extraction solvent, solid-to-liquid ratio, extraction temperature, extraction time, agitation, filtration, concentration, drying, granulation, and compression and packaging conditions are examples of process variables that may be relevant, depending on the dosage form and route of manufacturing.

A variable should be identified as a critical quality attribute based on scientific justification and not on a predetermined belief. It is necessary to conduct development experiments to identify variables that have a meaningful impact on CQAs and those that can be controlled within an established operating range. Botanical QbD case studies illustrate how risk assessments and design of experiments can aid in understanding the extraction process and its variability [22,23].

10. Quality Risk Management

ICH Q9(R1) offers a powerful framework for identifying, assessing, controlling, communicating and reviewing risks to pharmaceutical quality [19]. Tools which may be used include risk ranking, Ishikawa diagrams, failure mode and effects analysis (FMEA) and hazard analysis which may be applied to botanical development.

The list of key potential risks for botanicals may include species substitution, adulteration, raw material variability, contamination, process variability and degradation. The risk assessment process should be iterative with initial theoretical risks being updated following authentication studies, analytical characterization, design of experiments (DoE) and process performance studies.

11. Design of Experiments

The DOE is a key QbD tool because it enables the systematic evaluation of a number of variables and interactions. Experiments that evaluate one variable at a time may miss out on interactions that are often important in processes such as extraction and formulation. The factorial, fractional-factorial, response-surface and mixture designs can be selected depending on the development objective.

For botanical products, the DOE can be used to evaluate solvent composition, time, temperature, solid-to-liquid ratio, agitation and drying conditions. Multivariate models can then be used to identify influential variables and set operating ranges or design spaces [22,23]. The design should include representative raw-material lots, if possible, so that process optimization is not based on an atypical botanical lot.

12. Design Space and Botanical Variability

A design space is a region of multidimensional space formed by the combination and interaction of input variables and process parameters, demonstrated to provide assurance of quality. For herbal products, the concept should include both the process variability and the relevant raw-material variability.

A material-inclusive design space can be established by deliberately including representative raw-material lots, chemotypes or compositional ranges in development studies. This approach is preferable to optimizing a process around an idealized lot, as it is closer to reality in commercial manufacturing. Botanical QbD case studies support the feasibility of linking raw-material and process variables to CQAs by means of multivariate experimentation [22,23].

13. Analytical Strategy

No individual analytical approach can fully characterize a complex botanical product. Therefore, an orthogonal analytical strategy is preferable. Identity can be supported by microscopic and DNA-based approaches whereas chemical composition can be investigated by TLC/HPTLC, HPLC, GC, LC-MS, NMR and spectroscopic fingerprints. Fingerprinting coupled with chemometrics can help in discrimination among species, suppliers and batches [9-13,29-31].

Analytical procedures should be fit for purpose and appropriately validated. Reference standards, suitability of systems, sampling procedures and criteria for data interpretation should be defined. ICH Q2(R2) and Q14 provide a modern framework for analytical validation and development [27,28].

14. Analytical Quality by Design

AQbD incorporates QbD principles into analytical procedures. AQbD starts the process with an analytical target profile (ATP) that describes the desired properties of an analytical procedure. The ATP is used to define the required performance characteristics (RPs) and analytical variables that may influence these characteristics. Design of experiments can then be used to identify a robust analytical region.

This approach is especially useful in chromatographic methods for complex herbal matrices because stationary phase, mobile-phase composition, pH, gradient, temperature, and flow rate variables have the potential to interact, and method robustness may be influenced by multiple factors. Risk-based analytical development approaches can help minimize method failures and increase confidence in fingerprint and marker determinations [27-30].

15. Botanical Authentication

Authentication is a fundamental quality attribute because all further development depends on the correct

botanical identity. Macroscopic and microscopic examination are useful for crude drugs. DNA barcoding can provide additional evidence if informative DNA is available. Chemical authentication and chromatographic fingerprinting address the chemical phenotype [9-13].

DNA approaches are not always appropriate. Processing can destroy DNA. Extracts or highly processed products can contain insufficient informative material. Chemical approaches may better reflect the constituents associated with product quality. A hierarchical approach to authentication using complementary evidence is preferable to relying on a single method.

16. Quality Markers

Marker selection remains a challenge due to the possibility that a readily measurable compound is not the basis for therapeutic activity. WHO guidelines describe marker substances for quality control and note the need for appropriate selection for herbal medicines [31]. Recent quality-marker research aims to link constituents to authenticity, quality, activity, process behavior and safety [25,26,32].

For complex botanicals, a multi-marker or fingerprint approach may provide greater assurance than a single constituent. The appropriate strategy depends upon the botanical, dosage form, therapeutic rationale and quality evidence available.

17. Process Analytical Technology and Real-time Quality Assurance

PAT can provide timely information on material and process behaviour to help in proactive control, and various spectroscopic techniques may help in such analysis. Their effective application depends upon representative sampling and adequate calibration, model validation and data governance.

Control strategy driven by real-time measurement of a PAT-relevant CQA can be a useful complement to traditional QC testing if the measurement has been demonstrated to have sufficient predictive capability for that CQA. PAT should not be viewed as an isolated technology but rather as part of a more comprehensive control strategy.

18. Control Strategy

The control strategy encompasses material controls, process controls, analytical controls, in-process tests, specifications, and monitoring. For herbal products, this includes supplier qualification, good agricultural and collection practices (GACP), botanical identification, fingerprinting of incoming material, testing for contaminants, controlled extraction processes, analytical validation, packaging controls, and stability studies [14,24,33–35].

Control is hierarchical; that is, a single test cannot compensate for inadequate control at another level. An effective control strategy will emphasize prevention and characterization followed by process control and analytical confirmation.

19. Stability

Stability programs should be based on more than just the loss of a single marker. Relevant changes may involve chromatographic fingerprints, ratios of markers, degradation products, moisture content, microbial quality, physical properties and interactions with packing. Stability-indicating analytical procedures should therefore detect relevant changes in composition in botanical matrices that may involve several simultaneous changes [27,35].

20. Contaminants

Contaminants present significant quality concerns in herbal medicines. WHO guidelines address the issues of contaminants and residues, such as pesticides and microbial hazards [14,15]. Heavy metals, mycotoxins, and microbial contamination can originate from the environment, agricultural practices, harvesting, water, and storage. Therefore, preventive measures should be taken at the level of suppliers and raw material producers, and laboratory tests should be conducted.

Using the QbD approach, it is possible to include the analysis of possible contaminants in the initial risk assessment. In this way, it will be possible to develop a system for preventing the spread of contaminants instead of detecting them at the final stage of production.

21. Pharmaceutical Quality System and Lifecycle Management

ICH Q10 focuses on management responsibility, knowledge management, change management, CAPA and continual improvement [20]. ICH Q12 develops the idea of product lifecycle by supporting structured management of post-approval changes [21]. For herbal products this is of particular importance since changes in suppliers, cultivation regions, processing equipment or analytical procedures may alter the chemical profile.

Lifecycle management should ensure preservation of product knowledge and scientifically evaluate changes in relation to established CQAs and the control strategy. Continued monitoring can help identify process drift and emergent issues before they result in quality failures.

22. Knowledge Management

Knowledge management plays a critical role in QbD since the knowledge generated during the development should be leveraged throughout technology transfer, commercialization, and post-approval lifecycle management. Botanical identity, supplier variability, fingerprints, process parameters, analytical performance, deviations, and stability should be captured in a systematic manner. A knowledge base enables the updating of risk assessments as new information becomes available and facilitates more efficient investigations. Digital systems can help to this end, but data integrity, validation, and governance should be prioritized.

23. Deviation, OOS and CAPA

QbD does not eliminate deviations, or out-of-specification results. However, a greater understanding of the process being investigated can provide valuable scientific insight into the investigation. A greater understanding of the relationship between CMAs, CPPs and CQAs can provide an opportunity to differentiate between raw material variability, process drift, analytical variability and unanticipated interactions.

CAPA's should be directed at root cause identification and learning that can update risk assessments, control strategies and knowledge management systems. Trending of deviations, OOS results and atypical fingerprint profiles can be incorporated into continued process verification.

24. Chemometrics, Metabolomics and Artificial Intelligence

Chemometrics offers a valuable tool to relate a complex chemical profile to a quality attribute. PCA, clustering, discriminant analysis and supervised classification can be applied to batch comparison, botanical authentication and detection of atypical profiles [12,13,29,30].

Metabolomics and machine learning approaches could be of help in further elaborating these concepts by making use of high-dimensional chemical data. However, issues such as overfitting, dataset bias, external validation, model interpretability and instrument-to-instrument transfer still represent a limitation. These approaches should therefore be regarded as emerging elements of QbD and not as a replacement of validated analytical procedures.

25. Digital QbD

Digital technologies can connect supplier information, analytical results, process data, stability data and quality events together within a lifecycle knowledge system. Electronic batch records and statistical process monitoring can provide improved traceability and identify drifts in processes earlier.

Herbal products would be particularly interested in such technologies due to numerous batches of botanicals and fingerprints that can accumulate during the production period. Its worth may be measured in standardized data structures, validated software, data integrity and appropriate governance.

26. Continuous Manufacturing

Continuous manufacturing can provide benefits in terms of process control and consistency, but it may be challenging to implement for herbal products, due to the potential variability upstream in botanicals. Continuous extraction or processing could be considered if upstream material attributes are controlled and there is adequate PAT (process analytical technology) to assure process consistency. ICH Q13 provides a framework for continuous manufacturing [36].

27. Major Challenges

The main barriers to the implementation of QbD in herbal products are biological raw material variability, limited reference standards, lack of active ingredient characterization, and the absence of quality markers, while the supply chain is complex, diverse, and inconsistent, and there is a lack of standardized procedures and regulations across jurisdictions [3-15].

In addition, small and medium manufacturers may lack access to advanced analytical equipment and statistical expertise. Thus, it is important to consider the level of risk and complexity of the product and apply an appropriate control strategy, rather than rely on advanced technology and analysis.

28. Proposed Risk-Based QbD Framework

A practical framework can be structured into ten steps: (1) define the QTPP; (2) establish botanical identity and intended quality attributes; (3) characterize raw-material variability; (4) conduct an initial risk assessment; (5) identify CQAs, CMAs and CPPs; (6) use DoE to establish relationships and optimize the process; (7) develop an orthogonal analytical strategy and AQbD methods; (8) establish a material- and process-inclusive control strategy; (9) verify process performance and stability; and (10) maintain the system through lifecycle monitoring and continual improvement.

The distinctive feature of this framework is that botanical variability is considered an upstream quality variable. Instead of choosing one raw-material lot and optimizing the process around that lot, representative variability is deliberately incorporated into development wherever possible.

29. Integration of ICH Q8–Q9–Q10–Q12

ICH Q8 provides the pharmaceutical-development foundation, Q9 provides risk-management principles,

Q10 supplies the pharmaceutical quality-systems structure, and Q12 provides lifecycle-management principles [18-21]. For herbal products, these should be complemented by WHO GACP and GMP guidance, WHO quality-control and contaminant guidance, EMA herbal-product quality guidance and FDA botanical-drug guidance [14,24,33-35].

The resulting system can be visualized as a lifecycle loop: botanical sourcing and characterization inform development, which establishes the control strategy, manufacturing generates process and quality data, monitoring updates knowledge, and lifecycle changes trigger renewed risk assessment.

30. Novelty and Scientific Contribution

The novelty of the proposed approach is not in the application of particular QbD tools for herbal products but in the combined consideration of upstream factors related to biodiversity and chemical profiling with analytical QbD and process understanding and lifecycle quality management, thus, shifting the paradigm from testing to the integrated quality system based on risk assessment.

The framework emphasizes the need to reconcile herbal medicines' multiplicity with the need for standardized and controlled production. In other words, the approach is geared towards acceptance and control of complexity rather than seeking uniformity through averaging. On the other hand, it also helps to avoid overrating the current capabilities of innovative tools such as AI or metabolomics.

31. Practical Implementation Roadmap

Implementation can be staged, with Phase I focusing on botanical identity, supplier qualification, raw material specifications, and baseline chemical fingerprints. Phase II would then identify critical quality attributes (CQAs), critical material attributes (CMAs) and process parameters (CPPs) and perform a formal risk assessment. DoE and AQbD would be applied in Phase III to optimize the process and analytical system. A control strategy, process verification, and stability program would be established in Phase IV, while lifecycle management, trend analysis, and continual improvement initiatives would be initiated in Phase V.

Authentication, supplier qualification, control of contaminants, and chromatographic characterization may offer more value to a resource-constrained organization than investment in cutting-edge AI or PAT technologies without the requisite data infrastructure.

32. Research Gaps

Important research gaps include standardized approaches to define botanical variability, validated multi-marker approaches, a better understanding of the relationship between chemical fingerprints and clinical performance, standardized chemometric workflow approaches, regulatory pathways for enhanced PAT applications and robust integration of DNA and chemical authentication. More industrial case studies are also required to demonstrate the impact of QbD on process capability, deviation rates, batch consistency and lifecycle costs.

33. Discussion

QbD is particularly relevant to herbal medicines since many sources of variability occur before manufacturing begins. A conventional finished-product specification can identify an unacceptable result, but it does not necessarily explain why it occurred or prevent recurrence. Linking up raw-material attributes to process parameters and final CQAs provides a more preventive model.

The framework should nevertheless be scientifically proportionate – not every herbal product requires metabolomic, machine-learning, Raman spectroscopy or continuous manufacturing! The core of QbD lies in knowledge and risk management – advanced technologies are tools that become valuable when targeting a defined quality problem.

The most important conceptual shift, therefore, concerns a transition from testing-centered quality control to knowledge-centered quality assurance, including knowledge of botanical identity, agricultural origin, chemical composition, processing behavior, analytical uncertainty, stability and supply-chain risk for herbal products!

34. Limitations

This review is a narrative synthesis, and not a systematic review or meta-analysis. The framework needs to be prospectively validated in industrial case studies in different botanical species, dosage forms and jurisdictions. Evidence supporting the application of advanced technologies such as AI, metabolomics and PAT is heterogeneous, and acceptance by regulators may vary across jurisdictions and product classes.

35. Conclusion

Quality by Design presents a pathway to improve the quality of herbal drug products, if its application considers the specific properties of botanical substances. An herbal QbD-approach should be based on establishing the identity of botanical materials, defining product and process critical quality attributes, applying design of experiments to identify critical material attributes and process parameters, designing methods according to their analytical requirements, and using the collected information to establish a control strategy for the product lifecycle. Advanced tools such as chemometrics, DNA-based authentication and spectral analysis, PAT and digital technologies can be applied to support the QbD-assurance if their added value is demonstrated.

The risk-based approach suggested by the authors shifts the paradigm of quality control by considering botanical variability as a controlled variable, which offers to significantly improve the consistency of herbal medicines. Thus, it may be concluded that the proposed method is capable of increasing batch consistency, analytical reliability, process robustness and regulatory efficiency, contributing to the production of safe and effective herbal medicines.

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