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Operationalizing halal assurance within the quality-by-design pharmaceutical development lifecycle: A conceptual framework for biopharmaceutical development

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Abstract

Halal assurance is increasingly recognized as an important consideration in biopharmaceutical development. However, existing halal assurance and regulatory frameworks remain largely focused on organizational governance, material compliance, certification, traceability, and risk management, without explicitly operationalizing halal assurance within the Quality-by-Design (QbD) pharmaceutical development lifecycle. This Short Communication proposes a conceptual framework that operationalizes halal assurance across each stage of the QbD lifecycle, from the Quality Target Product Profile (QTPP) through Product Lifecycle Management. Rather than introducing a separate halal management framework, the proposed framework complements existing halal governance by embedding halal assurance within established pharmaceutical quality principles, thereby providing a practical foundation for systematic, proactive, and lifecycle-oriented halal biopharmaceutical development.

1. Introduction

Biopharmaceuticals, including vaccines, recombinant proteins, monoclonal antibodies, gene therapies, cell-based therapies, and other advanced biological products, have become increasingly important in the prevention and treatment of a wide range of diseases (Radenković, 2025). Unlike conventional pharmaceuticals, which are small-molecule pharmaceuticals, these products are developed and manufactured using complex biological systems involving living cells, culture media, biological processing aids, and multistage purification processes, rendering them inherently susceptible to process variability that may affect product quality, safety, and efficacy (Yeop *et al.*, 2025). Consequently, a systematic and science-based approach to pharmaceutical development is essential to ensure robust process performance and consistent product quality. The Quality-by-Design (QbD) paradigm has therefore become a cornerstone of modern pharmaceutical development by emphasizing predefined quality objectives, product and process understanding, science- and risk-based decision-making, and lifecycle management to achieve the desired product quality consistently (International Council for Harmonisation (ICH), 2009; ICH, 2023; Lee *et al.*, 2022).

Alongside advances in biopharmaceutical development, increasing attention has been directed toward ensuring that the products comply not only with regulatory requirements for quality, safety, and efficacy but also with halal principles. The expanding halal pharmaceutical market drives this growing interest, evolving regulatory frameworks, and increasing consumer expectations for medicines that satisfy both scientific and religious requirements (Herdiana *et al.*, 2024; Naimat *et al.*, 2024). In biopharmaceutical manufacturing, halal assurance extends beyond the assessment of active ingredients to include the halal integrity of cell substrates, culture media, recombinant materials, processing aids, and/or ancillaries, downstream purification processes, and the prevention of cross-contamination throughout the entire manufacturing lifecycle (Deliaz *et al.*, 2025; Zulkarnain *et al.*, 2021). Consequently, halal assurance is increasingly recognized as an integral consideration in biopharmaceutical development, highlighting the need for systematic approaches that can embed halal considerations throughout the product development lifecycle rather than relying solely on end-product certification.

Despite these advances, current approaches to halal assurance remain largely centred on ingredient permissibility, halal certification, halal management systems, traceability technologies, and halal risk assessment (Herdiana *et al.*, 2024; Pehin Dato Musa *et al.*, 2025; Tan *et al.*, 2023). In Malaysia, these elements are operationalized through the Malaysian Halal Management System (MHMS), which establishes organizational requirements for Halal Assurance Systems

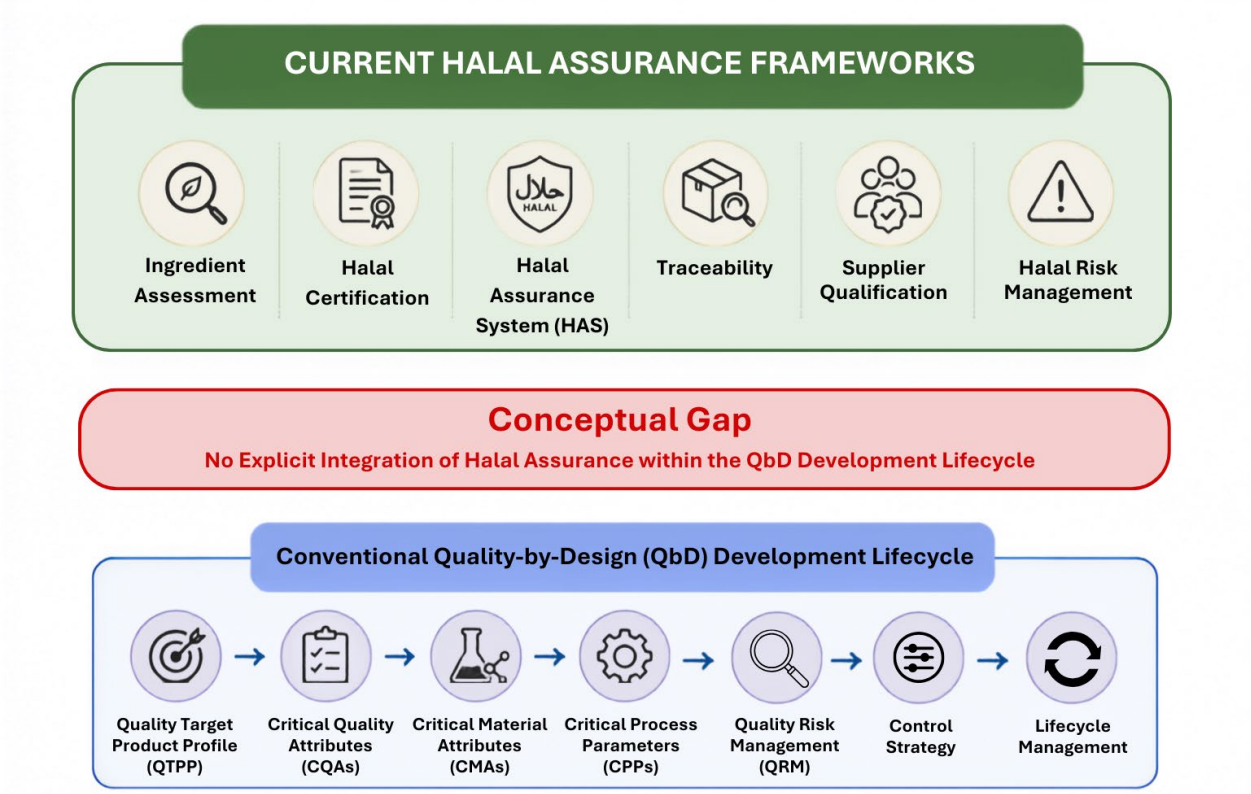

Figure 1: Conceptual comparison between the principal operational components of existing halal assurance frameworks and the conventional Quality-by-Design (QbD) pharmaceutical development lifecycle. The halal assurance components are conceptually synthesized from the Malaysian Halal Management System (MHMS 2020), Malaysian Standard MS 2424:2019, and the contemporary halal pharmaceutical literature, highlighting the absence of explicit operational integration of halal assurance across development-stage activities.

(HAS), including halal risk control, raw material control, traceability, internal halal audits, training, and other governance mechanisms to maintain halal integrity throughout manufacturing (Jabatan Kemajuan Islam Malaysia (JAKIM), 2020). Complementing MHMS, Malaysian Standard MS 2424:2019 establishes the general requirements for halal pharmaceuticals, including provisions applicable to biopharmaceutical products, by addressing materials, manufacturing, quality systems, documentation, personnel, and Halal Management Systems while including general requirements applicable to biopharmaceutical products (Department of Standards Malaysia, 2019). Nevertheless, the standard primarily emphasizes material compliance, manufacturing controls, and halal management requirements, while providing limited guidance on how halal assurance can be systematically operationalized within the Quality-by-Design (QbD) pharmaceutical development lifecycle, particularly for biopharmaceutical products.

Collectively, these regulatory frameworks have substantially strengthened halal governance and compliance within biopharmaceutical manufacturing. However, they primarily provide organizational and operational requirements for maintaining halal assurance and do not explicitly integrate halal considerations into the scientific decision-making processes that underpin product and process development within the QbD paradigm (Figure 1). The six components presented under the "Current Halal Assurance Frameworks" in Figure 1 represent a conceptual synthesis of the principal operational elements consistently reflected across the Malaysian Halal Management System (MHMS 2020), Malaysian Standard MS 2424:2019, and the contemporary halal pharmaceutical literature (Department of Standards Malaysia, 2019; JAKIM, 2020; Herdiana *et al.*, 2024; Tan *et al.*, 2023; Pehin Dato Musa *et al.*, 2025). These elements comprise ingredient assessment, halal certification, Halal Assurance Systems (HAS), traceability, supplier qualification, and halal risk management, collectively characterizing the current operational focus of halal pharmaceutical governance. While these frameworks establish comprehensive organizational and compliance requirements for maintaining halal integrity, they do not explicitly align halal assurance activities with the scientific stages of pharmaceutical development described in the Quality-by-Design (QbD) paradigm (Department of Standards Malaysia, 2019; JAKIM, 2020; ICH, 2009; ICH, 2023). Consequently, halal assurance considerations are predominantly addressed through organizational governance and operational compliance mechanisms rather than being systematically integrated into development-stage activities such as defining product quality objectives, identifying critical material and process attributes, and performing Quality Risk Management (QRM) (Department of Standards Malaysia, 2019; JAKIM, 2020; ICH, 2009; ICH, 2023). This conceptual separation highlights an opportunity to operationalize halal assurance within the established QbD lifecycle while complementing, rather than replacing, existing halal governance frameworks.

In contrast, Quality-by-Design (QbD) is a systematic, science- and risk-based approach to pharmaceutical development that emphasizes building quality into a product from the earliest stages of design rather than relying solely on end-product testing (ICH, 2009; ICH, 2023). First introduced through the International Council for Harmonisation (ICH) Guideline Q8(R2) on Pharmaceutical Development and supported by

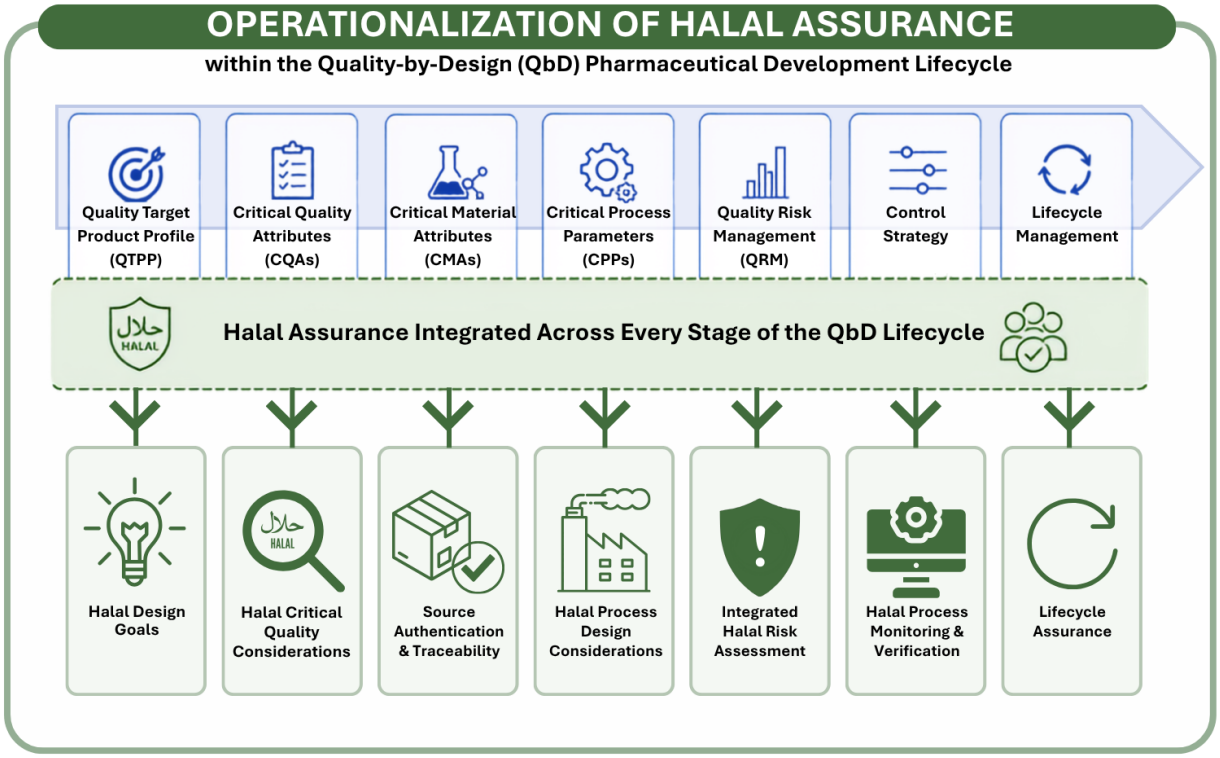

Figure 2: Proposed conceptual framework illustrating the systematic integration of halal assurance considerations across each stage of the Quality-by-Design (QbD) pharmaceutical development lifecycle, from Quality Target Product Profile (QTPP) definition to lifecycle management.

complementary guidelines on Quality Risk Management (Q9(R1)) and Pharmaceutical Quality Systems (Q10), QbD provides a structured framework for designing robust manufacturing processes that consistently deliver products meeting predefined quality requirements (ICH, 2008; ICH, 2009; ICH, 2023). The QbD paradigm is underpinned by several interconnected principles, including the definition of the Quality Target Product Profile (QTPP), identification of Critical Quality Attributes (CQAs), evaluation of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), application of Quality Risk Management (QRM), establishment of an appropriate control strategy, and continual lifecycle improvement (ICH, 2008; ICH, 2009; ICH, 2023; Simões *et al.*, 2024). Together, these elements enable systematic, science- and risk-based decision-making throughout pharmaceutical product and process development.

Accordingly, this Short Communication proposes an operational conceptual framework that systematically aligns halal assurance principles with the established Quality-by-Design (QbD) lifecycle for biopharmaceutical development (Figure 2). Rather than introducing a new halal assurance system or modifying existing QbD principles, the proposed framework serves as a translation layer that operationalizes halal assurance considerations within each stage of the QbD lifecycle. By integrating halal assurance considerations from the QTPP through Lifecycle Management, the framework promotes a proactive approach in which halal requirements are considered alongside quality, safety, and process development throughout the product lifecycle.

The proposed framework begins with the QTPP, which defines the intended characteristics of the final product and serves as the foundation for subsequent product and process development decisions (ICH, 2009; Lee *et al.*, 2022). Within the proposed framework, halal assurance is incorporated at this stage by incorporating halal requirements as predefined design objectives. These objectives subsequently inform decisions on material selection, process design, risk assessment, and manufacturing controls throughout the development lifecycle, consistent with the central role of the Quality Target Product Profile (QTPP) in guiding downstream pharmaceutical development activities (Rustandi *et al.*, 2026; Simões *et al.*, 2024). In the proposed framework, halal assurance is treated as a predefined design objective rather than solely as an end-product certification requirement. This approach enables proactive planning, supports risk-informed decision-making, and minimizes the need for corrective measures during later stages of development.

Following the establishment of the QTPP, the framework systematically identifies the Critical Quality Attributes (CQAs) and Critical Material Attributes (CMAs) that may influence both product quality and halal assurance. CQAs define the physical, chemical, biological, and microbiological characteristics that should be maintained within appropriate limits to ensure the desired product quality, whereas CMAs describe the critical physical, chemical, biological, or microbiological properties of raw materials and process inputs that may affect these quality attributes (ICH, 2009; Rustandi *et al.*, 2026; Simões *et al.*, 2024). Within the proposed framework, material evaluation is extended beyond conventional quality specifications to include source authenticity, halal status, traceability, supplier qualification, and the consistency of material attributes relevant to halal assurance. This is particularly important for biologically derived materials, including cell substrates, culture media,

recombinant materials, and processing aids, where variability in source and material characteristics may influence both product quality and the robustness of halal assurance (Herdiana *et al.*, 2026; Yeop *et al.*, 2025). Accordingly, materials that satisfy conventional quality specifications, but present unresolved halal concerns would be identified as requiring further evaluation during the CMA assessment stage, where they become inputs to subsequent halal risk assessment and process optimization.

Building upon the identification of Critical Quality Attributes (CQAs) and Critical Material Attributes (CMAs), the proposed framework next evaluates Critical Process Parameters (CPPs) through the application of Quality Risk Management (QRM) to identify manufacturing steps that may influence both product quality and halal assurance. CPPs are process variables that should be monitored and controlled to ensure that the desired product quality is consistently achieved, while QRM provides a systematic process for identifying, assessing, controlling, communicating, and reviewing risks throughout product development and manufacturing (ICH, 2009; ICH, 2023; Simões *et al.*, 2024). Within the proposed framework, the existing QRM process is expanded to explicitly evaluate risks that may compromise halal assurance during manufacturing while complementing existing organizational halal risk management requirements. Although the Malaysian Halal Management System (MHMS) requires organizations to establish dedicated halal risk control as part of the Halal Assurance System (HAS), these requirements primarily support organizational governance and operational compliance (JAKIM, 2020). By contrast, QRM within the QbD paradigm serves as the established framework for evaluating risks associated with product and process development. Accordingly, the proposed framework complements the organizational halal governance established by MHMS by operationalizing halal assurance within the established QRM process of the QbD pharmaceutical development lifecycle, rather than introducing a separate development-stage halal risk management framework. These risks include the use of non-halal processing aids and/or ancillaries, shared manufacturing facilities, inadequate cleaning validation, cross-contamination, changes in raw material suppliers, and process modifications that may compromise halal integrity (Herdiana *et al.*, 2024; Naimat *et al.*, 2023). Integrating these considerations into routine QRM facilitates the early identification and mitigation of risks to halal assurance during process development. Consequently, appropriate risk control measures can be implemented before process optimization, technology transfer, or commercial manufacturing, thereby embedding halal assurance as a proactive component of process development and control throughout the QbD lifecycle.

Finally, the Control Strategy, which traditionally establishes a comprehensive set of controls to ensure consistent product quality throughout manufacturing, is expanded to incorporate halal assurance measures that preserve both product quality and halal integrity throughout the product lifecycle. In addition to conventional quality controls, the proposed framework

Table 1: Operational halal assurance considerations associated with each stage of the Quality-by-Design (QbD) pharmaceutical development lifecycle

QbD Lifecycle Stage	Primary QbD Function	Operational Halal Assurance Considerations
Quality Target Product Profile (QTPP)	Define intended product quality objectives.	Incorporate halal assurance as a predefined product objective, including intended market requirements, halal expectations, and overall product design considerations.
Critical Quality Attributes (CQAs)	Identify product quality attributes critical to safety, efficacy, and quality.	Evaluate critical quality attributes from both quality and halal assurance perspectives to ensure compatibility with predefined halal design goals.
Critical Material Attributes (CMAs)	Identify material characteristics that may influence product quality.	Assess material origin, halal status, source authentication, supplier qualification, traceability, and the suitability of biologically derived materials, excipients, and processing aids.
Critical Process Parameters (CPPs)	Identify and control process parameters affecting product quality.	Evaluate halal-sensitive manufacturing processes, including segregation, cleaning validation, cross-contamination prevention, and process modifications that may affect halal integrity.
Quality Risk Management (QRM)	Systematically identify, evaluate, control, communicate, and review quality risks.	Integrate halal assurance into routine risk assessments by identifying and mitigating risks that may compromise halal integrity throughout product development and manufacturing.
Control Strategy	Establish planned controls to achieve predefined product quality consistently.	Implement process monitoring, documentation, verification, supplier qualification, end-to-end material traceability, and complementary Halal Assurance System (HAS) activities to maintain halal integrity throughout manufacturing.
Lifecycle Management	Maintain product quality through continual monitoring, change management, and continuous improvement.	Evaluate changes in materials, suppliers, processes, facilities, analytical methods, and technologies from both quality and halal assurance perspectives to ensure sustained halal integrity throughout the product lifecycle.

integrates halal-specific activities, including supplier qualification, end-to-end material traceability, process monitoring, documentation, and verification mechanisms to ensure that halal-critical materials, processing aids, and ancillaries, and manufacturing operations maintain halal integrity throughout manufacturing (ICH, 2009; Herdiana *et al.*, 2024; Pehin Dato Musa *et al.*, 2025). This integrated control approach complements existing Halal Assurance Systems (HAS) by strengthening transparency, facilitating regulatory compliance, reducing the risk of cross-contamination, and supporting the continuous verification of halal integrity from raw material sourcing to the finished product (Pehin Dato Musa *et al.*, 2025). Furthermore, Lifecycle Management extends halal assurance beyond initial product development by ensuring that changes in raw materials, suppliers, manufacturing processes, facilities, analytical methods, or technologies continue to be evaluated from both quality and halal assurance perspectives throughout the product lifecycle. Consistent with the Pharmaceutical Quality System described in ICH Q10, continual monitoring, change management, and continual improvement ensure that halal assurance is maintained as manufacturing processes evolve, thereby supporting sustained compliance with both regulatory and *Shari'ah* requirements (ICH, 2008). Consequently, halal assurance becomes embedded within the pharmaceutical quality system as a continuous lifecycle activity rather than a standalone certification exercise. The operational considerations associated with each stage of the proposed framework are summarized in Table 1.

The proposed framework, summarized in Table 1, provides a conceptual architecture for operationalizing halal assurance within the established Quality-by-Design (QbD) lifecycle for biopharmaceutical manufacturing. Rather than proposing a separate halal management framework, it demonstrates how halal assurance can be systematically embedded into existing pharmaceutical development activities, from defining product objectives and evaluating critical quality and material attributes to managing process risks, establishing control strategies, and enabling continual lifecycle improvement. By aligning halal assurance with internationally recognized pharmaceutical quality principles, the framework complements existing Halal Assurance Systems while promoting proactive risk prevention, transparency, and regulatory consistency throughout product development. Furthermore, the framework extends existing halal pharmaceutical guidance by providing a systematic approach for operationalizing halal assurance within the QbD pharmaceutical development lifecycle, particularly for biopharmaceutical products, where current standards primarily provide general requirements. Although conceptual in nature, the proposed framework provides a foundation for future validation using representative biopharmaceutical products, manufacturing platforms, and industrial case studies to assess its feasibility, adaptability, and practical application in halal pharmaceutical development. Beyond experimental validation, the framework may also provide a conceptual foundation for future supplementary guidance supporting the implementation of Quality-by-Design principles in halal biopharmaceutical development. If successfully validated, this framework may facilitate the systematic integration of halal assurance within established pharmaceutical quality systems, supporting the development of biopharmaceutical products that satisfy both regulatory quality expectations and *Shari'ah* requirements.

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3. Conflict of interest

The authors declare no competing interests.

4. AI declaration

Artificial Intelligence (AI) tools, including ChatGPT (OpenAI, San Francisco, CA), were used to assist in language editing, improving sentence structure, and clarifying grammar during the manuscript preparation stage. The authors reviewed, verified, and take full responsibility for the accuracy and integrity of the content. No AI tools were used for data analysis, result interpretation, or scientific conclusions.

6. Author contribution

Yumi Zuhanis Has-Yun Hashim: conceptualization, methodology, writing, reviewing and editing, supervision. Phirdaous Abbas: project administration, conceptualization, methodology, formal analysis, investigation, original draft preparation, writing, reviewing, and editing. Nurhusna Samsudin: reviewing and editing. Mohammad Aizat Jamaludin: reviewing and editing. Mohd Hafidz Mahamad Maifiah: reviewing and editing.

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