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Formulation Innovation and Technological Capability in Pulmonary Drug Delivery: A Literature-based Conceptual Framework for Delivery Performance and Commercialisation Implementation

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ABSTRACT: Developing a successful pulmonary drug delivery product requires addressing multiple aspects, including, but not limited to, the formulation, the device, how the patient will use the product, manufacturing, and regulations. This research takes a user-centered approach to developing a conceptual framework to illustrate the intersection of innovation in pulmonary drug delivery formulations (NFI) and the "organization's capability in pulmonary drug delivery (ATC). The framework draws upon all pertinent literature and reflects regulatory supports (RS) as a buffer between the pulmonary drug delivery performance (PDDP) and Commercial Implementation (CIS). This research is a theory-focused, literature-synthesizing effort. No primary or secondary data, experiments, clinical or product sales data are analyzed. This research incorporates innovation and dynamic-capabilities theory, as well as pharmaceutical quality and methodology literature on construct specification, mediation, and moderation. The main conclusion drawn from the research is that delivery improvement does not necessarily require delivery system innovation. It also may require consideration of device, process, and other factors. Regulatory supports, RS, are positioned as a moderator of PDDP and CIS. PDDP is position as a proximal construct of the CIS, and CIS is concerned with the organizational unit's readiness and progress toward commercializing the product rather than profits or sales. The framework includes 8 relationships. These 8 relationships and 1 moderator, RS, are bound by theory. This paper proposes construct boundaries and provides a mechanism-based approach to identify barriers, along with a clarification of terms and a means to validate those barriers. Barriers may be identified via item clarity and instrumented by a set of delivery indicators. Barriers may be scoped to the product and jurisdiction. Barriers may be sequenced over time. Barriers may be isolated to the implementation and/or commercialization of a product.

1. INTRODUCTION

The pulmonary route can be used to administer a medicinal product to the respiratory tract and, in some cases, to the systemic circulation. A product designed for pulmonary administration has to contend with challenges of product performance, delivery, and the variability of the respiratory system and personal factors (e.g. inhalation technique) that make it difficult to guarantee

depositing a therapeutic dose of a medicinal product to the desired target(s) in the respiratory tract. As such, the delivery of a therapeutic dose of a medicinal product to the site(s) in the respiratory tract to effect a therapeutic benefit may not be certain.

Recent reviews have noted important milestones in dry powder particle design and the development of inhaler technologies, as well as a number of challenges associated with the powders' flow and cohesion, aerosolization, reproducible dosing and compatibility with various formulations and devices (Dhoble et al, 2024; Islam et al, 2024; Scherließ et al, 2022; Shahin and Chablani, 2023; Sou and Bergström, 2021; Telko and Hickey, 2005; Woodward and Fromen, 2024; Yue et al., 2023). These reviews show that inventive leaps in device or formulation design do not necessarily improve a delivery system. A range of formulation and device innovations require evaluation of their potential impact on the product, including the dose and the patient use scenario.

This work seeks to integrate these ideas with organisational capability and innovation theory. According to Teece (1986), the successful capture of the economic value from product innovation depends on the availability of complementary assets and a flexible commercial architecture. The emphasis of theory on capabilities and processes focuses on the integration and reconfiguration of a firm's resources and competencies to adapt to changes in its environment.

The model comprises five constructs: formulation innovation (NFI), ATC, PDDP, CIS, and RS. Of these, NFI and ATC reflect the preceding capabilities. PDDP is a performance stream which, in conjunction with NFI and/or ATC, influences CIS. CIS represents the degree of progress made in the product and/or process development and/or commercialisation. RS refers to a body of rules which, among others, describe the requirements of the regulatory body, the approach towards offering scientific advice, the time taken to give feedback, and the overall regularity of the body in fulfilling its functions. These rules may be combined to assess the overall appraisal of the body. In absence of evidence to the contrary, it is assumed that the rules do not influence PDDP and CIS.

The author recognizes that the examples cited to illustrate the model do not, of themselves, prove that the model is correct. The author's objective is to state a model, based on extant literature, and identify the cases within which it would be possible to provide evidence for, or against, the model. The author does not provide a case within which data, or results, of studies, support the model.

1.1 Problem statement

In the case of inhalation pharmaceutical products, there are multiple Formulation and Device Architecture related factors that affect the success of aerosolization and/or pulmonary deposition. There are many opportunities for Formulation and Device Architectural innovation. The extent to which a given Formulation and/or Device Architectural improvement impacts an innovation opportunity, is a function of reproducibility and manufacturability, product-related risk, evidence to support the innovation to address a regulatory need, and development choices (Dhoble, 2024; Sou and Bergstrom, 2021). It is a common practice for authors to consider innovation, technology, performance, and commercialization as distinct concepts.

Constructs can also be ambiguous. What is meant by "delivery performance"? It could mean emitted dose, fine particle fraction, aerodynamic particle size distribution, regional deposition, reproducibility, usability, or how good a survey respondent thinks a product is. Similarly, "commercialization success" may be defined by a number of business milestones including the attainment of regulatory approval, product launch, achievement of a given level of market acceptance or financial performance. Constructs must be operationally defined to the extent that their measurement or testing is feasible.

1.2 Research aim, questions, and objectives

The aim is to define a literature based conceptual framework to describe the relationships between formulation innovation and other related factors and technological capabilities, and their impact on the performance of pulmonary drug delivery and its commercialization, as well as to define the role of the regulatory authorities in this regard.

The purpose of the paper is to:

1. What is the role of formulation and technology in influencing the performance of the pulmonary drug delivery systems?
2. What are the organizational and/or technical means by which performance may be linked with implementation?
3. In what ways may performance serve to link the two means with implementation?
4. How does performance be linked with implementation, and what role may regulatory agencies play?

Five constructs have been identified, and with each a range of hypotheses have been postulated. A rough sketch of a concept map has been created. It is hoped that the research will aid in formulating a theory based assessment of the relationship between delivery performance and the implementation of drug therapy.

1.3 Contribution and scope

Three contributions are bounded by this work. First, it defines formulation innovation as the creative and intellectual process to identify and create solutions for a given formulation challenge, and defines technology capability as the ability to integrate various analytical, engineering, and scientific approaches and services to create, control, and implement a process and related system to address a formulation challenge. Second, this work defines proximal delivery performance and distal implementation performance. Third, this work incorporates contextual conditions and situational variables, and does not claim that the presence of a regulatory agency automatically enables success. This work describes the formulation of pulmonary medication, with special interest in dry powder inhalers. This work suggests that the framework developed is specific to the use of other inhaler types to deliver pulmonary medication.

2. METHOD: FOCUSED LITERATURE SEARCH AND CONCEPTUAL SYNTHESIS

A focused literature review and a conceptual combination of theories and constructs form the basis of this research. This work does not aim to synthesize, summarize or integrate several bodies of research. It adopts a structural and procedural approach to incorporate theories, constructs, and methodological instruments to research synthesis.

Searches were performed using keywords such as 'pulmonary drug delivery', 'inhaled formulation', 'dry powder inhaler', 'particle engineering', 'aerosol', 'device', 'pharmaceutical', 'QbD', 'regulatory', 'dynamics', 'compliments', 'mediation', 'moderation', etc. Titles, publication details, and/or web links of the publications were verified from the bibliography or from publisher/official sites. For the synthesis, preference was given to review articles, and when needed, primary articles were also included along with the ICH Q guidelines and related methods articles.

Exhaustiveness was not aimed for in this review. It was not required to have a reproducible database search. Multiple reviewers' screening of articles and a PRISMA flow diagram have not been included. Assessment of risk of bias of included studies has not been included. Page et al. (2021) provide information on PRISMA statement. As the authors state, this review is not a systematic review and, therefore, PRISMA statement will not be provided. This has no effect on the goal of the study which is to show how different variables influence each other (mediation and moderation).

The synthesis was based on sources that dealt with, or referred to, various aspects of the five constructs of the model. These include, but are not limited to, sources on, pulmonary delivery mechanisms and formulations/devices, design and development, and regulatory and pharmaceutical quality systems. Innovation-related sources are used to describe organisational value capture. It is worth noting that, though the components of the model are interconnected, the literature relied upon for the development of the model, does not necessarily provide sufficient evidence to validate the model.

The literature is synthesised based on the nature of the constructs described rather than based on the year of its publication. To determine technical relationships that exist between various components of a device, pulmonary drug-delivery sources are referred to. Requirements of pharmaceutical development and quality systems are described, using the ICH guidelines. Innovation theory is referred to describe organisational value capture. Future measurement of the paths requires identification and understanding of various concepts, and methods of review, described in the literature.

3. LITERATURE REVIEW AND THEORETICAL FOUNDATIONS

3.1 Pulmonary delivery as a coupled formulation–device system

Particle size and respiratory tract anatomy and physiology influence aerosol deposition. Inhalation particle deposition is affected by various factors including particle size and inertia, the rate and pattern of breathing, sedimentation and diffusion, and mucociliary clearance. In the case of aerosol delivery devices, one should not assume that the nominal or emitted dose is deposited in the intended site of action (SOA) to produce the desired pharmacological effect. Devices and formulations should be designed considering the entire delivery system, the interrelationships between devices and formulations, and how design impacts clinical endpoints (Labiris & Dolovich, 2003a; Newman, 2017).

The practical challenge in dry powder inhaler (DPI) design is to create formulations in which particles disperse and remain stable during passage through the device and dispersion upon inhalation. Factors affecting particle dispersion and stability include the solid particle's size and shape, and the energy and moisture content of the system. While there are a number of techniques for designing and engineering particles, formulations and devices should be developed in an integrated manner. A growing body of literature supports this view (Dhoble et al., 2024; Islam et al., 2024; Morton & Barling, 2024).

PDDP must be defined relative to product-specific endpoints. Examples of endpoints may include emitted dose, aerodynamic particle size, fine-particle dose and fraction, dose uniformity, in vitro performance, and/or device/flow related conditions. The endpoints and measures relied upon must be consistent with the product's intended use and the question(s) being addressed in the development. A general "delivery performance" score may be insufficient to address the endpoints of the product. In such cases, the measurement model and components of the score must be addressed.

3.2 Formulation innovation (NFI)

According to this framework, Formulation Innovation includes the modification, adaptation or development of drug and excipient particle architectures to fulfill given requirements of pulmonary drug delivery. It encompasses the engineering of dispersibility of drug and excipient systems to achieve required performance of solid state, moisture balance andother characteristics of the formulation, as well as device-formulation compatibility. A given formulation is considered innovative in a descriptive sense if it is different from previously developed formulations, however the value of the formulation should be evaluated against defined endpoints (Shahin & Chablani, 2023; Sou & Bergström, 2021).

Although the introduction of new formulations within a given timeframe may indicate progress, it may not necessarily improve one or more defined endpoints. A new formulation may actually worsen the product's attributes. For instance, in the context of inhalers, a new formulation may improve dispersibility of the active drug (or excipient) but increase instability or impact the formulation in a way that makes it physically incompatible with the intended device. For the purpose of this discussion, it should be noted that improved design of a pulmonary drug delivery product (PDDP) may include one or more of the following: formulation innovations, device/administration system innovations or other operational innovations.

The NFI assessment focused on the organizational dimension of the ability to create and improve candidates, learn from results of characterization, and choose the option most closely aligned with the intended product. The focus was on the assessment itself rather than the outcome. In the context of NFI assessment, objective counts of formulation candidates would not be the same as an assessment of a scale to determine perceived capability; the wording in the case of respondent assessment would need to be clear regarding whether it refers to idea generation or to the refinement of the candidates or the experiments, or to the successful performance of the candidates. Each of the studies in question would have to make an explicit choice regarding the unit of analysis.

3.3 Technological capability (ATC)

As used here, technological capability means the ability to employ and couple different analytical and technological tools including engineering, process and modelling technologies, and data and software to address challenges related to product development, especially in the pulmonary route of drug administration. It encompasses the ability to generate reliable and trustworthy measurements and integrate data, engineering and process technologies to gain understanding in product and process development and transformation. Ownership of equipment and technologies is not in itself a measure of capability. Capability is contextual and depends on the suitability of the technology, integrity of the data, and the competence of the personnel to interpret and integrate the data and technology within the overall decision framework of the organisation.

The ICH Q8(R2), Q9(R1) and Q10 guidelines provide industry guidance on the development of pharmaceutical products, the integration of various aspects of pharmaceutical development, and management of quality of pharmaceutical products; these guidelines do not, however, provide evidence that assessment of a particular technology capability would result in improved commercial outcomes.

AT4C is different from NFI because it is possible for a company to have good analytical and process skills and not come up with new drug formulations. Alternatively, a company can come up with a novel drug formulation without having a refined and stable company infrastructure. Although the capabilities tend to occur together, the framework provides both capabilities as separate paths to PDDP to provide an opportunity to evaluate their individual effects.

3.4 Pulmonary drug delivery performance (PDDP)

PDDP refers to the formulation and the device's abilities to meet the requirements for the use of a formulation device system. Objective measures to evaluate performance should be identified and the test method documented along with the devices and conditions to be used in the test and the comparator. Acceptance criteria should also be defined. Examples of delivery performance measures include emitted dose, aerodynamic particle size distribution, fine particle dose, dose uniformity, and delivery system performance stability. The measures to be used depend on the needs and stage of the drug development. A specific measure to assess the performance of a delivery system may not exist (Dhoble et al., 2024; Labiris & Dolovich, 2003b).

To be clear, delivery performance measures do not equal patient outcomes. The same measure that is used to evaluate delivery performance may be used to evaluate other aspects of a product including safety and efficacy. The framework states that evaluation of PDDP is a surrogate for other downstream outcomes of a medical intervention.

3.5 Commercialisation implementation (CIS)

CIS describes the forward motion in the development and commercialization of a pulmonary product. This may be considered evidence of progress if supported by the evaluation of specific milestones in the development of the product and the evidence pathway. Other supports may include the readiness of the manufacturing and quality systems and processes, evidence packages, and coordination of regulatory, supply and market access activities.

CIS is distinct from regulatory approval, market entry, sale of the product, profitability, and improvement in health outcomes. CIS is evaluated at the development stage; evidence of improvement in health outcomes and market success is evaluated at the commercial stage. CIS may be supported by the attainment of development milestones or assessed as the readiness of a product or process. CIS may also be supported by evidence packages or other documentation. The judgement should be based on a stage-gate plan and the intended product pathway.

The concepts of innovation and theory of commercialization support the notion that delivery of a product may not guarantee success. Consideration of the ancillary factors may affect the outcome. These may include the regulatory and reimbursement environment and market conditions, amongst others. The ultimate commercial success of the product may depend on the interaction of these factors. The theory and supporting literature cited in the article does not attempt to assess the influence of these ancillary factors, which may be classified as outside the scope of the paper.

3.6 Regulatory support (RS)

RS is the degree to which a regulator communicates clearly, quickly and accessibly about expectations. It is the certainty with which a regulator interacts with a development team and the helpfulness of such interactions. RS is not relaxed oversight, nor does it guarantee a positive decision. The goal of RS is to strengthen the scientific basis for regulatory decisions. ICH quality guidelines assist pharmaceutical companies to structure development and help manage quality and risk throughout a product's lifecycle. Reliance on ICH quality guidelines does not mean that identical development advice is provided to all companies, nor that support has uniform effect.

RS may affect the relationship between PDDP and CIS as technical evidence relates to a regulatory pathway. The expected evidence may dictate the studies required and controls necessary to support a product. Unclear or changing expectations increase the work required to develop the product. How support varies by region and other development factors will also effect the relationship. Measurement of the above should differentiate access to scientific advice based on support offered.

3.7 Manufacturing scale-up, quality, and lifecycle control

In late stage drug development, the focus shifts from optimizing a formulation to ensuring it can be manufactured reproducibly at commercial scale. Scale-up may impact the form and performance of the active pharmaceutical ingredient. The principal concern at this stage is the ability to reliably manufacture a product that conforms to desired attributes in a controlled and reproducible manner at the targeted scale. ICH Q9(R1) provides a strategy to identify risks to the quality of a drug product and ICH Q8(R2) considers formulation and the manufacturing process in the context of pharmaceutical development (ICH 2009, 2023).

ICH Q10 applies this philosophical approach of emphasizing pharmaceutical quality as being fundamental to all components of a system for the management of pharmaceutical quality throughout a product's lifecycle, including knowledge management, performance of the activities of the quality system, and management review (ICH, 2008).

Instead of prescription, these guidelines describe various managerial approaches to the pharmaceutical industry (including the integration of CMC components within R&D, M&A activities, and sourcing strategies) and legal aspects of commercialization. These guidelines underscore that within the framework proposed, ATC is required to provide for the generation of reliable process knowledge and its implementation for process control; and PDDP is required to describe the phenomenon under consideration within the defined parameters of reproducibility as opposed to a best case scenario.

Tecnhical performance of a product remains a necessary element of, but not a substitute for, the readiness of the sector, system or organization for full implementation. Distinction between the two reinforces that for a given stage, a planned set of activities be documented to evaluate the readiness of a sector, system or organization for full implementation.

3.8 Technical endpoints and their interpretation

Pulmonary medications often rely on operational definitions of PDDP. An aerodynamic particle size distribution evaluates the behavior of particles in aerosols and is different from geometric particle size. Emitted dose represents the total dose that is released from the delivery device. A fine-particle dose refers to the total dose within the defined aerodynamic range. Dose uniformity represents the variance in the dose among the units in a given sample. Stability is the performance of a delivery system over a period of time. Reproducibility is the performance of a delivery system across different batches. Endpoints often assess different performance characteristics of a delivery system and may not be combined to determine a total score.

These endpoints are often dependent on the stage of development, dosage, the intended region of deposition, and the delivery system. A joint consideration of the delivery system and the formulation is essential, as the same substance may exhibit different behavior, depending on the delivery system and/or the condition under which the system operates (Dhoble et al., 2024; Islam et al., 2024; Scherließ et al., 2022; Shahin & Chablani, 2023). Thus, describing the condition, flow, and/or the operating status of the delivery system and stating the acceptability standard may be valuable. Although it may be useful to include perceived performance, it should not be counted as an objective performance outcome.

3.9 Clinical, human-use, and market translation

Techno-economic metrics help track and assess the performance of a product. However, these metrics do not demonstrate the clinical impact of a product or its effectiveness in the real world. The relationship between aerosol measurements and clinical impact varies by the product and evidence. Reliable in vitro-in vivo correlations in inhaled formulations are considered to be an important challenge in the field. Human-use factors, such as adherence, and how patients interpret and act upon instructions, also impact a product's performance (Newman, 2017).

These human factors impact the outcome of the product and its delivery, and, therefore, may impact the framework. If CIS is the focus of the framework, other outcomes may include clinical and market impacts. These may include patient and market acceptance, as well as the economics of the product. How these outcomes are measured and rationalized should be done in conjunction with the framework. Alternatively, a phased or staged approach may help determine the capability of the product, its performance and clinical evidence, regulatory status, and market and business impact. This approach should help clarify the gaps that exist between a product's launch and its delivery.**3.10 Unit of analysis and boundary conditions**

The main alternative is to define the model in terms of an organisation, a development programme, or a combination of a formulation and a device. Organisational capability is usually assessed at either the firm or team level. Aerosol performance, on the other hand, is assessed at the product or device level. Capability, in this sense, refers to the level at which performance is assessed. Therefore, if an organisation develops several products, an organisation-level capability score would not relate to the performance of the products. Similarly, a product-level score would not relate to the organisation's capability to implement that technology. In future studies, it would be preferable to model the variables at the same level or consider nesting in the model.

Different relationships may be expected to be applicable to different product platforms. Powder dispersibility and the user's ability to generate an adequate flow may be crucial to the performance of a powder inhaler, while a metered dose inhalator or a nebulizer may raise different formulation challenges. Products within the same therapeutic field are often at different stages of development and, therefore, may present different challenges and priorities. For a complete understanding of the system, it

is crucial to document the types of organisations involved. The types of organisations may be considered, along with the stage of product development, the challenges addressed by the products, the jurisdictions and the geographical locations, as background conditions.

Formulation–device compatibility as a design requirement

When designing aerosol delivery devices, the formulation and device design need to be developed in parallel, because aerosolization requires the interaction of formulation and device-generated airflow. Several formulation factors, such as powder cohesiveness, carrier interactions, particle size and shape, moisture, and the available energy to break inter-particle bonds can affect the amount of aerosol generated. Device design can create forces that affect a formulation's ability to aerosolize. Because of this, a formulation that performs well in one device may not perform similarly in another.The industry literature examining dry powder inhaler devices integrates the design of the formulation and device in an inverse manner (Dhoble et al., 2024; Morton & Barling, 2024; Scherließ et al., 2022).

This point clarifies that constructs like NFI should focus on the development of formulation for a specific product and device combination, as opposed to more abstract cases of innovation. This point also clarifies PDDP. When assessing a product, the endpoint should describe the device and the conditions of the test. It is important to note the device platforms employed in a study to assess the relative capability of the formulation being evaluated or the organization being researched.

The role of patient use and intended population

There are a variety of reasons for the difference between the performance of a medical device in the laboratory and the performance of the device in the hands of healthcare professionals and the end users. Some of the reasons for the variation are the devices' performance, the manner in which a healthcare professional uses the device, the users' level of adherence to the prescribed treatment and the training. Respiratory clearance and the anatomy and physiology of the respiratory system impact the degree to which a dose is deposited in the respiratory tract and the residence time (Labiris & Dolovich, 2003a; Newman, 2017). Therefore, the intended patient population and the required manner of use should be considered in the establishment of the performance requirements and the performance tests of the device.

With regard to the present framework, PDDP is defined and interpreted as delivery performance (technical performance) in the specified testing conditions. Clinical (patients) and health-related (users) usage conditions of the device are out-of-scope conditions and, thus, should be evaluated separately. Defining PDDP with the limitations stated above would allow establishing the hypothesized mediation model with high confidence.

Regulatory evidence as a translation mechanism

Although interactions with regulators shape the nature and the order of evidence, they should not be confused with the contents of the evidence. Guiding principles on pharmaceutical development (ICH, 2008, 2009, 2023) set the need for the pharmaceutical industry and manufacturers to integrate and link comprehensively, effectively and appropriately the understanding of the product, the critical risks and the manufacturing procedures. Not meeting the delivery performance requirements, effectiveness and safety of a product cannot be remedied by the reliance on the regulating agencies.

Because of this distinction, RS can be understood as complementing PDDP, rather than replacing it. Where performance information is lacking, well-based interpretations of regulatory intent may identify the nature of the performance evidence required, but may not be sufficient to resolve evidence gaps. On the other hand, where performance information is provided and reproducible, management expectations may facilitate a team's understanding as to what additional performance studies and documentation are required. Thus, the issues dealt with are of an implementation nature, rather than interpretative flexibility or regulatory forbearance.

Theoretical integration

The framework employs integrative strategies to balance complementary pulmonary drug delivery science, evolutionary theory, and economics. From a pulmonary drug delivery perspective, technical performance is defined by the ranges and tolerances of the components, materials, and other considerations employed in the design, manufacture, and analysis of a drug product. Dynamic capabilities shed light on the reasons why and how an organization may deploy and adapt resources to generate and sustain a competitive advantage (Teece, 2007). The hypothesis is also supported by the theory of complementary assets (Teece,

1986). Evidence from regulatory science adds a contextual perspective on how regulatory policies and interactions influence the extension of a product from a technically functional state to an implementation state (Honig & Zhang, 2019).

The model does not deny the possibility that the theories might constructively contribute to the evolution of the path analysis. The key underlying idea is that from these theories, constructs, or mechanisms, some propositions might be developed that, if tested, might be potentially confirmatory. It is envisaged that formulation and technological innovation may contribute to the enhancement of specified delivery-performance attributes; delivery-performance might facilitate the implementation process; both may influence implementation in ways that are not captured in PDDP; and the nature of the performance-implementation relationship may be modified by the kind and/or the level of regulatory support.

4. CONCEPTUAL FRAMEWORK AND PROPOSITIONS

4.1 Framework structure

The framework is illustrated in Figure 1. NFI and ATC are upstream capabilities; PDDP is the proposed bridge; CIS is downstream implementation; and RS, also downstream, is proposed to moderate the relationship between PDDP and CIS. H1 and H2 are capability-to-performance bridges; H3 is performance-to-implementation; H4 and H5 are capability-to-implementation; H6 and H7 are bridges facilitated by PDDP; and H8 shows the integration of the two bridges.

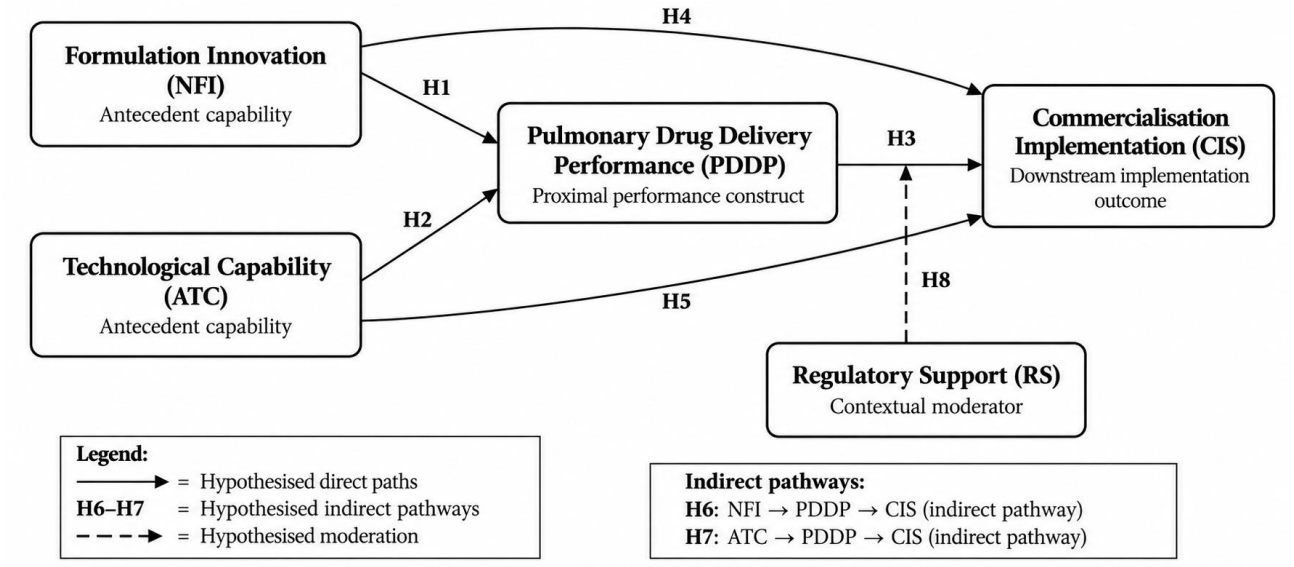


Figure 1. Literature-based conceptual framework linking formulation innovation and technological capability to delivery performance and commercialisation implementation, with regulatory support as a moderator.

Hypothesized direct paths are shown by solid lines. Indirect pathways happen through PDDP. H6 and H7 represent some of these indirect pathways. The dashed line shows the proposed role of RS in moderating the association between PDDP and CIS. This figure is illustrative and no real-data estimates have been provided.

4.2 H1: Formulation innovation and delivery performance

When attributes of a formulation are designed and assessed against an inhaler product, delivery performance may improve as a result of formulation innovation. Particle and formulation engineering affect the outcome of powder dispersion and aerosolization (Shahin & Chablani, 2023; Sou & Bergström, 2021). The outcome of formulation innovation on the delivery performance of a nasal or pulmonary inhaler may be assessed by a prespecified test and endpoint. It is, therefore, expected that the association will be positive.

H1: Formulation innovation has improved pulmonary drug delivery performance.

4.3 H2: Technological capability and delivery performance

The formulation may affect device interactions and other variabilities in a delivered dose. Capabilities to model and perform an aerosol analysis may be improved with engineering and science. Related bodies of knowledge such as Q8(R2) and Q9(R1), as well as inhaler design Q disks (Dhoble et al., 2024; ICH, 2009, 2023), suggest the association will be positive.

H2: Technology capability is positively associated with delivery performance.

4.4 H3: Delivery performance and commercialisation implementation

Delivery performance is how well a product can be manufactured consistently to meet requirements related to product function. For a product to be developed, product-related performance is essential. However, product performance does not show the clinical advantage of the product. Additionally, performance does not show the product's potential in the market and the income it may generate. Thus, the relationship is positive, but not definitive (Newman, 2017; Teece, 1986). Several factors beyond performance may influence a product's development and commercialization.

H3: There is a positive relationship between the performance of pulmonary drug delivery and commercialization.

4.5 H4 and H5: Direct capability–implementation relationships

NFI may be associated with CIS through knowledge and skills required to research and develop a product, generate the required evidence for product development, and plan and ensure the manufacturability of the product. ATC may be associated with CIS through the performance and implementation of a particular activity, e.g., process integration, and product scale-up.

H4: Under PDDP, formulation innovation is positively associated with commercialization.

H5: Under PDDP, technological capability is positively associated with commercialization.

4.6 H6 and H7: Indirect pathways through PDDP

According to the mediation analysis, formulation innovation and associated PDDP are likely to be associated with CIS. The combination of the component paths (i.e. indirect effect) is estimated through a path analysis, and confidence intervals are constructed for these estimates. The indirect effect should not be estimated based on the component paths and their levels of significance (MacKinnon, 2008; Preacher & Hayes, 2008).

H6: Performance in pulmonary drug delivery is posited to mediate the relationship between formulation innovation and its implementation in the commercialization of medicinal products.

H7: Performance in pulmonary drug delivery is posited to mediate the relationship between technological capability and its implementation in the commercialization of medicinal products.

4.7 H8: Regulatory support as a moderator

Depending on the nature of the feedback from regulatory authorities and the extent to which their expectations and requirements are clarified and communicated in a timely manner, performance in a given area of a drug delivery system may have a positive moderating impact on the implementation of the system. The expectation is that the support of regulatory authorities would have a positive impact on the implementation of a system; however, the support may have no impact, or a negative impact (Honig & Zhang, 2019; ICH, 2009, 2023).

H8: It is expected that the supportive role of regulatory authorities for the implementation of a system for pulmonary drug delivery would positively impact the implementation of that system.

4.8 Propositions and explanatory logic

There is a logical relationship among the propositions but they are not fully synonymous. Hypotheses H1 and H2 connect the two prior capabilities with the proximal technology outcome. Hypothesis H3 relates the technology outcome to progress in implementation. Hypotheses H4 and H5 connect the prior capabilities to implementation through pathways outside of PDDP. Hypotheses H6 and H7 connect prior capabilities with implementation via pathways outside of PDDP, as well. Hypothesis H8 explores if the presence of regulatory support ameliorates the relationship between PDDP and the Conflicting Information Style.

The directed relationships in the propositions are justified by the considered mechanisms. For H1, the product-related technology deficit should be of clinical relevance. In addition, the mechanism should be assessed through an endpoint that captures the change. For H2, the technological capability should be expressed in and validated through the clinical trial process and should be available for interpretation. For H3, PDDP should be assessed in relation to the next implementation gate. H4 and H5 should address manufacturability, and their interpretation should be contextualized by other mechanisms such as evidence generation, process control, and differentiation. H6 and H7 should be assessed. H8 should be assessed by considering the circumstances in which the regulatory support Measure is expressed.

Further tests could also help define limitations of the model. The data may show that one of the antecedents is more relevant than the other, that indirect paths vary in importance, or that the relationship between PDDP and CIS varies with the type of product and stage of product development. The data may also show the absence of certain paths. The value of the framework lies in the definition of key constructs in a way that allows tests of theory. Thus, not all of the framework hypotheses need to be confirmed.

5. CONSTRUCT SPECIFICATION AND PROPOSED OPERATIONALISATION

The framework distinguishes conceptual definitions from empirical constructs. This paper does not include a questionnaire or datasets, and therefore does not claim that validated measures of these constructs exist. The table provides an example of potential empirical constructs that could be tested in the future.

Table 1 - Construct Definitions, Proposed Indicators, and Measurement Considerations for the Conceptual Framework

Construct	Conceptual role	Candidate indicators	Measurement cautions
NFI	Antecedent capability	Formulation development involving multiple cycles; use of particle/excipient engineering; refinement of aerosol formulations against specific criteria; assessment of formulation/device compatibility.	Do not equate novelty counts or patent counts with formulation performance.
ATC	Antecedent capability	Use of adequate analytical methods; aerosol/device testing; process validation through model/data; and integration of knowledge to make informed decisions.	Equipment ownership alone does not establish organisational capability.
PDDP	Proximal technical outcome	Assessments of emitted dose, aerodynamic particle size distribution, fine particle dose/fraction, dose uniformity, and stability. Testing of aerosol devices/systems under various conditions, and Relevant Flow condition testing.	Select measures according to platform and development stage; do not treat technical endpoints as clinical effectiveness.
CIS	Downstream implementation outcome	Meeting preset product development goals; readiness for manufacturing/quality; and progress in developing evidence and regulatory packages.	Separate readiness and milestone progress from approval, launch, sales, market share, and profitability.
RS	Contextual moderator	Clear preset requirements; relevant scientific/regulatory advice; and the ability to forecast how long it will take to receive scientific/regulatory advice.	Record jurisdiction, product category, and development stage; do not define support as leniency or approval.

Table 1 presents an example of the measurement structure. The example will be discussed with experts including pharmaceutical scientists, inhalation device specialists, regulators, manufacturability and quality specialists, and those involved in commercialization. It should be noted that if a construct represents multiple elements, justification is required as to why it is not formative or reflective, or if it is represented by other observed elements. Reliability of constructs does not validate their role and utility. (Cronbach, 1951; Fornell and Larcker, 1981; Henseler et al., 2015).

6. DISCUSSION

6.1 Interpretation of the integrated model

Various authors have provided justification for the integration of formulation, technology, and performance within the device, as well as the role of other stakeholders to support the delivery and commercialization of a pharmaceutical product. It is documented that the science and engineering of a medical device influences the formulation. (Dhoble et al., 2024; Islam et al., 2024; Sou & Bergström, 2021). Quality of a medical device is primarily attributed to the performance of the device, the process, the product, and the systems. It is also influenced by the actions of the organization over the life cycle of the product. (ICH, 2009, 2023).

The main proposition of this model is that the final stage of the process, the output, is implementation (PDDP). The other elements, NFI, ATC and CIS, do not necessarily represent the end outcome of the process. The model recognizes that innovation is required for technical advancement, but it does not necessarily mean that the advancement will create economic value. The model states claim is that complementary assets of an organization are critical to the realization of value.

6.2 Why formulation innovation needs product-specific evaluation

Formulation innovation is assessed by a product's intended use and profile. For a dry powder inhaler, the formulation of the powder and the properties of the dispersed particles affect the inhalation aerosol and the performance of the inhalation device. As with all formulations, there may be unacceptable trade-offs with the formulation. The major concern should be if the formulation supports the intended endpoint. If the formulation is viewed as a pill, there may be unacceptable trade-offs with the formulation. The goal should be to demonstrate that the formulation attributes are sufficiently robust to support the intended endpoint (Morton & Barling, 2024; Shahin & Chablani, 2023).

6.3 Technology capability as a deployed organisational resource

Capability refers to the integration and use of a given resource or technology, not the simple presence of the technology. It is possible for an organization to own a sophisticated analytical tool, but there may be no trained users of the tool, and/or the organization may not have established a mechanism to ensure traceability of the data, or to use the data in support of the design of the product. There may be a small team, which uses a given capability, and integrates the capability in an appropriate and effective manner to make decisions based on evidence. The theory supports the capability of the team, and the integration of the capability supports the decision-making of the organization (Teece, 2007).

6.4 The limits of delivery performance as a predictor of implementation

Mere progress in addressing delivery performance doesn't always guarantee implementation. Financing or manufacturing constraints, for instance, may delay a much-needed service. The means to innovate may be available, but other complementary assets or means to implement it may not (Teece, 1986). Thus, an understanding of the theory and a review of evidence may help justify weak science and open new research areas beyond the scope of delivery science.

6.5 Regulatory support and contextual variation

Support from regulators, broadly defined, is context-dependent and prescribes the nature of evidence and expectations of reviewers. It is, however, unlikely to be in the form of preferential treatment or an outcome. There are differences in global regulatory practices, and interactions with regulators may vary from scientific advice, to the level of evidence and expectations of quality of clinical and non-clinical data. The strength of evidence required by regulators may impact the timing of product approval. The support of regulators may, for instance, promote the acceptance of surrogate endpoints. The influence of the support, however, may not lead to the establishment of the evidence required to implement a change.

This means the moderator may be asymmetric across phases. Early regulatory feedback may occur while the design of the clinical study is still evolving and the PPDP has not yet been defined. Subsequently, late regulatory feedback may occur after the clinical study has been completed and the technical performance of the product has been established. If RS is assessed only once, the combined experiences may include events that occurred at different phases, and different decisions may have been influenced by the combined experiences. It is recommended that the timing of interactions with regulatory authorities be recorded with respect to the defining technical milestones in clinical studies. In such cases, the researcher should not interpret a single, unarticulated score as reflecting a given condition that is stable.

According to the model, it may be more appropriate to describe commercialization as a series of milestones as compared to a single broad assessment. Process validation, completion of the evidence package, readiness for product submission, and readiness for product manufacturing and market access may occur in different sequences and be affected by different circumstances. Hidden by a single CIS composite score. It is recommended that the researcher either delimit the implementation outcome to which the CIS is broadly applicable, or model a series of milestones.

6.6 Theoretical implications

The study has an integrated framework that serves to link several previously disparate concepts. It outlines the integration of technical performance science to other management and regulatory science concepts. It establishes that regulatory conditions may be a constraint on the implementation of technologies. It outlines a logic framework and schematic to represent the concepts. The field may evolve the framework and propose changes to the logic and schematic if supported by evidence.

6.7 Boundary conditions and competing explanations

Positive paths in this model are generally ambiguous. For instance, changing the formulation may not improve an relevant endpoint, even if the change is considered to be an improvement by the sponsor. There may be analytical capacity available to assist in the decision-making process, but it is not fully integrated. Finally, better aerosol data may have been developed by a competitor who has resolved the main clinical and business obstacles to the introduction of the product. The PDDP-CIS relationship may be weaker for various reasons. The reasons presented in this section are not excuses to change the interpretation of the results in a misleading way. If possible, they should be assessed.

The model considers other factors as well. The relationship observed between PDDP and ATC may reflect the level of maturity of the competing product. The relationship between PDDP and CIS may reflect the fact that products that are further along in the development process provide performance data in a timely manner. The nature of a cross-sectional analysis does not allow the researcher to define maturity prior to the introduction of a product.

The impact estimates and uncertainty for the study should be reported, not just p-values. Effects of interest should be reported in terms of both statistical and practical significance. Longitudinal data with complete records at the product level would help illustrate how the proposed mechanism operates, and differentiate the mechanism from reverse causation and confounding.

6.8 Practical implications

New product development teams should interpret the presented framework to link ‘novelty’ claims to performance evidence that is specific to the product of interest, compared to competitors’ products. Relatedly, investment in R&D should be justified with respect to a clear outline of the decision, appropriate methodology, data to support the rationale, and a clear process that ensures repeatability. Regulatory and quality teams should engage early on to help ensure development activities are aligned to the pathway of interest. Other teams should consider how to differentiate their product in light of performance, supply, regulation, manufacturing, and cost when the product becomes available to the public.

7. PROPOSED EMPIRICAL VALIDATION STRATEGY

The author recommends testing the framework in stages. First is the determination of the level of analysis, which may be at the level of a product development program, a product-device combination, or a firm. These levels of analysis may not be substituted for each other. It is likely that the product specific PDDP indicators will be studied at the level of the program, while for the level of the firm, several product development programs may need to be combined or subsitituted, and the indicators may need to be aggregated.

Once the level of analysis is determined, constructs and their corresponding indicators must be defined prior to data collection. It is recommended that each of the defined constructs and their corresponding indicators be reviewed to determine if they capture the domain of the construct. Cognitive interviews may also be used to determine if respondents understand a given indicator as designed. If a questionnaire is constructed, it is also recommended that all of the aforementioned features of the item be documented.

Prior to data collection, the measurement models to be utilized should be determined. In such cases where the researcher determines that a given measurement models may lead to asymmetrical item response patterns, the measurement models should

be determined, and rigor should be exercised. If a variance based measurement model is used, it should be justified and documented.

Fourth, in cases where it is possible, incorporate multiple types of substantiation. Objective technical data can come from product tests or development records. Achievement of milestones can be substantiated through gate records. Support can be assessed by defined perceptions. Reliance on a single source can be lessened with input by multiple individuals. Common-method bias should be assessed as a threat to the validity of the study, not be automatically assumed to explain relationships (Podsakoff et al., 2003).

Fifth, examine structural relationships only after confirming the adequacy of the measurement model. Effect sizes and confidence intervals should be computed to estimate direct relationships. Indirect effects for relationships represented by H6 and H7 should be estimated and interpreted. To test H8, an interaction term should be estimated, and conditional-effects should be interpreted. Mediation analysis should not be drawn based solely on independent tests (Baron & Kenny, 1986; MacKinnon, 2008; Preacher & Hayes, 2008). If the research design is cross-sectional, effects should be considered as association and not be interpreted as meditation. If the design allows, effects should be captured in a reverse order (capability measures first, and implementation outcomes later).

Factors impacting sample size determination should include the smallest effect size of the primary outcome of interest that is deemed meaningful from a scientific or clinical perspective, stakeholder input or judgment, the level of complexity of the research model, the number of indicators and parameters, and the expected quality of the data. A sample size determination approach that relies on a simplistic, rigorous case limit for each item, for instance, should be justified in light of the proposed model and other sample size determination approaches. Research participants should not be considered independent from one another a priori based on the presumption that participants are nested within teams and organizations. Data collection should be planned to address lack of data, redundant data and variability in the product platform.

Structural equation modelling (SEM) and regression-based path analysis should be considered based on the research objective and the measurement model. A researcher's propensity to prefer SEM over other techniques should not be mistaken for justification in cases where the measurement model does not support the estimation of a latent variable. Clarification of variables should be driven by the principle of transparency. Hence, regression analysis should be used where technical endpoints are measured. Biringen's (2013) Path model can be justified in a similar vein to explain moderation and Mediation. Any research technique or instrument used in a health research context should be described in a manner that reveals the instruments assumptions, justification for model specification, uncertainty, limits and boundary.

The evidence should be categorized into three layers. The capability layer could include formulation-development and technology practices, which could be assessed through structured audits or multiple informants. The technical layer could include records from tests conducted on a product. The implementation layer could include evidence of achievement of milestones along with evidence of readiness to proceed to the next step. Evidence could also include the stage and jurisdiction, which could be described using ordinal scale. Such design could lessen the risk of one respondent being the main reason for the positive/negative views held about a given construct.

All hypotheses should be disclosed, including counter-intuitive or null findings. The sample size, primary outcomes, and exclusions should be predefined. The rationale for any deviations from the prescribed analysis should be disclosed. The measurement and structural evidence should be disclosed in the model. The model should not be considered supported unless the structural and measurement evidence warrant it.

7.1 Design implications for future comparative studies

Studies could focus on the relationships proposed in this research, for various inhaler platforms, formulation classes, stages of development, and regulatory jurisdictions. Such studies should be prespecified. For Powder Inhalers, the relationships may be most pertinent for the selection of the propellant, while for other platforms and classes, the focus may be on the formulation and device. The comparisons should be pre-defined.

The measurement-equivalence problem occurs when multiple platforms are being assessed. What is measured may be different across the assessed platforms. So, if the endpoints measured are different, a combined total score may actually cover up the

differences. It is important for researchers to know what endpoints can be measured across different platforms. Researchers also should report measurement endpoints based on the delivery technology.

There are other ways to distinguish capability deployment from capability accumulation. For example, it may be assumed that the inability to produce a certain end product represents a lack of capability. If an analysis system is in place but the product development team uses a different system to direct their next course of action, the product development team is deploying an analytical system to help direct the next course of action. A system in place that helps the product development team achieve a specific technical end product represents capability and system performance. In order to measure these systems, they must be assessed at different points in time. A mediating system is assumed to achieve a specific end if a product development team achieves a specified end.

7.2 Evidence integration and triangulation

Technical, organizational, and implementation evidences may come from a variety of sources. It is not necessary to assume that a source of evidence is superior to the others. The focus should be on what types of evidence are available in order to support a given construct.

In the absence of direct evidence, respondent reports are still useful to draw reasonable hypotheses concerning the subject's capacity or the advancement of the subject's effort. There are differences between respondent assessments and evidence produced in a laboratory. Commercial readiness is different from product launch. The use of precise language to describe different kinds of evidence aids in focusing on critical differences.

Limitations of triangulation are evident in the integration of different types of evidence. Responses to surveys and test results may reference different product lots. A survey respondent may be summarizing an organization's overall capability, while a test result may be specific to an individual product lot. If no evidence supports that the product and surveilled period represent the same point in time, the product and survey should not be integrated and considered as evidencing the same outcome.

7.3 Reporting standards for conceptual and empirical claims

When stating hypotheses, theories, and conclusions, the author distinguishes between the hypotheses and theories described in the reviewed literature, and the assertions of the model. The author notes that the reviewed literature documents studies and components of medical devices, formulations and delivery systems, as well as theories of Value Capture and Innovation. The eight hypotheses described in the report are conclusions and predictions based on the aforementioned literature. The distinction is expressed throughout the report by the use of the words "propose" and "expect" to describe pathways and components of a system, as opposed to evidence and results.

An empirical article will need to present results in a similar way as before. Before any interpretation, coefficients and uncertainty intervals should be presented. Results that are not significant should not be interpreted to mean that there is no relationship. Interpretation of the results should also consider the possible reasons for observed associations, including the measurement model, the level of analysis, and the design and analysis considerations. For example, user behavior may influence the result even if the technical and implementation indicators are designed to measure different things.

8. INTEGRATIVE SYNTHESIS OF EVIDENCE

Pulmonary drug delivery is mainly inter-related (Labiris & Dolovich 2003a, 2003b; Newman 2017; Scherließ et al 2022; Sou & Bergström 2021). Innovations in formulation may not lead to better delivery. The main body of evidence is around the specification of the product and device. The evidence does not address relationships with pulmonary drug delivery.

The integrated evidence highlights the importance of integration of diverse resources and the ability of an organization to deploy resources to achieve innovation. As explained in Teece (1986, 2007), while the integration of the resources may result in the development of pharmaceutical products, the specification of the integration and the endpoints may help to assess the commercial potential of the product. The evidence helps to address an important gap in the literature.

Because the available data does not show the specifics of the hypotheses, the hypotheses should be viewed as expectations, or theories that await testing. Additional data can confirm or disconfirm some of the hypotheses. Data can also support or reject expectations or theories. It may also validate the author's assertion that a number of factors, including product-specific performance, organizational deployment and implementation, must be taken into account.

Table 2 - Evidence Domains and Their Roles in the Conceptual Framework

Evidence domain	What the literature supports	Role in this paper
Pulmonary physiology and aerosol science	Deposition and delivery depend on particle behaviour, respiratory physiology, device design, and user technique.	Defines the technical boundaries of PDDP and supports a coupled formulation–device view.
Formulation and particle engineering	Formulation attributes can be engineered, but improvements involve product-specific trade-offs and require measurement.	Provides the mechanism for the NFI → PDDP proposition.
Engineering, analytics, and quality systems	Development requires reliable measurement, process understanding, risk management, and lifecycle controls.	Defines ATC as deployed capability rather than equipment ownership.
Innovation and dynamic capabilities	Innovation value can depend on complementary assets and organisational integration of resources.	Explains why direct capability paths and downstream implementation are theoretically plausible.
Regulatory science and guidance	Regulatory expectations shape evidence planning and quality-system decisions; they do not guarantee approval.	Motivates RS as a contextual moderator, not a direct substitute for performance.
Methods literature	Constructs require clear operational definitions; indirect effects and interactions require explicit estimation.	Informs the proposed validation and reporting strategy.

9. LIMITATIONS AND FUTURE RESEARCH

The author acknowledges the focused nature of this review and does not claim to have systematically reviewed all literature related to pulmonary drug delivery, innovation and regulation. The author designed the search to model and framework construction, not to synthesize or integrate evidence. The purpose of the search was not to analyze or summarize data, thus no data was analyzed or summarized to support or refute the hypotheses.

A number of other factors may also affect the proposed relationships, including clinical differences and manufacturing costs. Product maturity and organizational or funding resources may also be factors. The hypotheses are also generally applicable to products other than inhaled dry powder products, including pressurized metered dose inhalers and nebulizers.

These factors do not necessarily invalidate the proposed hypotheses. Rather, the hypotheses should be tested under the boundaries defined by the factors.

10. CONCLUSION

This literature-based conceptual paper has proposed a framework to connect formulation innovation and technology to the delivery of pharmaceutical products to the lung. It has been proposed that the integration of various elements of the framework, including formulation, device, analytical and process capabilities, as well as organizational resources, should contribute to the commercialization of pharmaceutical products. It has been proposed that the integration of these various elements would be supported by regulatory agencies. The reviewed literature has been proved to be relevant and supportive of the elements of the framework. It has not been demonstrated to be supportive of the validity of the eight hypotheses.

From the author's perspective, the most important contribution of the framework is the ability to distinguish constructs. The author has defined the term formulation innovation as the formation and enhancement of formulation architectures and the term technological capability as the repertoire to integrate and orchestrate various elements of the framework, including analytical, process and other resources. The author has defined the term capability of PDDP as the attainment of specified" technical outcomes in Pharmaceutical Delivery. The author has defined the term CIS as the state of being prepared to implement

a pharmaceutical product and the term RS as the perception and interpretation of the standards and guidance of a regulatory agency.

It is suggested that various elements of the framework be measured and tested to validate the hypotheses. It is suggested that future work, which uses the elements of the framework to validate hypotheses, will help establish the framework.

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