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Novel Formulation Innovation and Advanced Technology Capability in Pulmonary Drug Delivery: The Mediating Role of Delivery Performance and the Moderating Role of Regulatory Support in Commercialisation Implementation Success

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ABSTRACT: This study considers the innovation of novel formulations (NFI), advanced technologies (ATC), and their integration with other processes to achieve competitive advantage in the domain of pulmonary drug delivery performance (PDDP). It explores the association of PDDP with commercialisation implementation success (CIS) and the role of regulatory support (RS) in moderating the relationship of PDDP with CIS. It also examines the role of PDDP in the association of NFI and CIS, as well as ATC and CIS. A total of 326 completed workbooks were audited for two separate data sets. For each workbook, mean scores were computed for "four item responses for each of the five constructs, as well as an interaction term for centered PDDP and RS. The means for the corrected data set were 3.436, 3.466, 3.519, 3.495, and 3.499, respectively, for NFI, ATC, PDDP, CIS, and RS, respectively. The five blocks made up of four items had poor internal consistency (alpha = −.193 to .164). Using HC3-adjusted regressions, the relationships of NFI and ATC to PDDP (R^2 = .003) and the relationship of PDDP to CIS with NFI, ATC (R^2 = .001) were also estimated. The interaction of PDDP and RS was also estimated (B = −.045; p = .607). Based on these results, the research hypotheses, and the adjustments made to the regression models, it can be inferred that the research hypotheses were not supported, while the mediation hypotheses could not be evaluated. It is important to mention that the results of this research did not support the research hypotheses; rather the current measures did not provide sufficient evidence to accept the research hypotheses.

1. INTRODUCTION

Local delivery of therapy to the lung, via the airways, can be utilized to ablate or reversibly or irreversibly inhibit cells in the lung to treat various respiratory diseases. Some compounds that are delivered via the lung to treat disease, have the potential for systemic delivery and action. Particle, aerosol and formulation performance attributes are key in the design and realization of devices and systems for pulmonary drug delivery. The translational research, in the development of inhaled drug delivery systems, examines device compatibility and performance. While delivery and pulmonary drug formulation development

challenges may overlap, the aspects of the delivery systems may differ. For example, a delivery and platform may be suitable for a specific therapeutic indication, whereas another may require an entirely bespoke system.

There are a number of challenges associated with the development of delivery systems and platforms. For example, a novel device or platform may need to be integrated with advanced formulation and analytical systems in conjunction with quality, process and product (pharmaceutical) standards and manufacturing at varying scales. ICH Q8(R2) and ICH Q10 provide a framework that addresses challenges associated with the development of an innovation in the pharmaceutical and related industries (International Council for Harmonisation [ICH], 2009, 2008). These challenges may prevent a technology from being successfully transferred to industry.

Two organisational capabilities will be considered: novel formulation innovation (NFI) and advanced technology capability (ATC). NFI refers to an organisation's capability to develop and refine pulmonary medication formulations. ATC refers to an organisation's capability to employ advanced analytical and engineering concepts, skills, and techniques to accomplish a given task. It is proposed that NFI and ATC capabilities facilitate achievement in pulmonary drug delivery (PDDP). PDDP in turn is proposed to facilitate CIS. It is proposed that RS affects the association between PDDP and CIS. These definitions and propositions are theoretical and require validation.

The models and propositions advanced herein are theoretical and require verification. Different pulmonary medication products are based on multiple formulations, delivery systems, target patient populations, and therapeutic and pharmacological actions. Finally, not all advances in technology or pharmaceutical product development lead to improvement in commercial or marketplace position. The authors acknowledge the limitations of the models and propositions, and do not purport to explain commercialisation in its entirety.

The study aims to determine the relationships between NFI and ATC and PDDP, the relationship between PDDP and CIS, the relationships between NFI and ATC and CIS, the relationships between NFI and ATC and CIS via PDDP, and the role of RS on the PDDP-CIS relationship. The study will also review the original and corrected research worksheets, to confirm that the case study responses are consistent with the latest corrections.

1.1 Problem statement

In the area of pulmonary drug delivery, various breakthroughs have been made with regard to the development of formulations and delivery devices. However, the commercialisation of such breakthroughs relies on a number of integrative and interdependent factors. Because of these integrative and interdependent factors, it is often the case that a breakthrough in formulation and/or device design is overshadowed by integration challenges. These may include evidencing a case for marketing and access, and/or unwanted economic returns. In the absence of relevant data, it may not be possible to assess and mitigate these integrative and interdependent challenges.

The study aims to assess the extent to which the integrative and interdependent challenges associated with a drug delivery project are overcome, and the perceived delivery performance is enhanced. The study also aims to determine the relationship between perceived delivery performance and commercialisation. Furthermore, given the four-item constructs of the research tools, the study will assess the extent to which misleading composite scores are reported.

1.2 Research gap

A combination of the literature on NFI, the aerosol delivery system, and barriers to translation, coupled with research on innovation and organizational capability and performance, as well as guidance on regulations, should provide a body of literature describing the development of a pulmonary-delivery system. However, none of the cited literature integrates NFI, ATC, PDDP, CIS, and RS. The purpose of this study is to integrate these elements and evaluate measurement redundancy. The author has conducted a focused synthesis of the published literature.

1.3 Research questions and objectives

- RQ1: Is there an association between NFI and ATC with respect to PDDP?
- RQ2: Is there an association between PDDP and CIS, once NFI and ATC are considered?
- RQ3: Are the relationships between NFI and CIS as well as the relationships between ATC and CIS, effected by PDDP?
- RQ4: Does RS modify the relationship between PDDP and CIS?

The objectives of the study are to determine the sizes of the PDDP-CIS, NFI-CIS, and ATC-CIS paths, evaluate the indirect paths associated with the relationships of interest, assess the interaction between centred PDDP and RS, analyze the original and adjusted data, and determine the adequacy of the measurement to support substantive interpretation.

2. LITERATURE REVIEW AND THEORETICAL FOUNDATIONS

2.1 Pulmonary formulation innovation

There are a variety of factors that can affect aerosolization and deposition of a pulmonary formulation, including density, solubility, stability and moisture sensitivity. Other factors that affect the formulation can include particle shape and size, surface characteristics and the manner in which the particles are packed. Sou and Bergström (2021) discuss issues in the development of drug formulations and noted that a major obstacle in the development of drug products that are intended for the delivery to the lungs is the lack of experience in the clinical arena. Yue et al. (2023) discuss, among other things, the barriers to the use of inhaled medication, including the body's defense mechanism to remove inhaled medication. In addition, Yue et al. (2023) discuss the strategies and approaches used for the introduction of inhaled medicines, and the extent to which a carrier system used to deliver an inhaled medicine should be designed or engineered.

In the case of pharmaceutical formulations, a breakthrough by itself is not an indicator of value. A new approach in the engineering of particles or development of a carrier system may provide an improvement in the formulation attribute of interest, but may introduce new constraints in the safety, manufacturability or device compatibility of the system. Thus, NFI, in this context, refers to the organization's capability to define performance requirements and enhance formulations to meet the requirements.

Using the theory of dynamic capabilities, there are opportunities to further extend and strengthen the authors' arguments and connections to other aspects of organization, management and strategy.

2.2 Advanced technology capability

ATC encompasses an organization's capacity to invent, develop, analyze, and produce a product, as well as integrate, and employ essential data practices. For pulmonary products, relevant assets may include aerosol science and analysis, devices, processes, automation, modeling, and integration of data. The aforementioned resources are valuable to the extent that they are coupled with validated procedures, qualified equipment, and personnel, and relevant data.

Pharmaceutical development, including in ICH Q8(R2) and ICH Q10, encourages application of a risk management approach to the development of pharmaceutical products. While these Publications do not explicitly state advancement of technology improves commercial outcomes, they underscore the importance of comprehension, management, and control of pharmaceutical processes, as well as the lifecycle of the pharmaceutical product. ATC may be incorporated in the context of Product Development to Support Pharmaceutical Development. The outright ownership of the equipment is not indicative of ATC.

It is also possible to misapply a technology. Use of advanced analytics and modeling does not always guarantee product decisions. Similarly, automation may not resolve formulation deficiency. While it is suspected that ATC and PDDP are related, the nature and extent of such relationship will depend on how technology is employed.

2.3 Pulmonary drug delivery performance

PDDP refers to the capability of an organization to use an innovative drug delivery system to create a commercial product. It encompasses an evaluation of the performance of the delivery system to meet specified requirements. Evaluation criteria may include, but are not limited to, aerosol performance, robustness, consistency, and the ability of the delivery system to be compatible with the formulation. Competitors may vary in the criteria which they establish for evaluating delivery systems, thereby resulting in different rankings for comparable delivery systems. A score for PDDP, based on the perceptions of respondents to the survey, may differ from measurements obtained from aerosol analysis or clinical and/or regulatory evaluation of a product.

There are different methods of evaluating the validity of a survey. Some methods assume that each question in a survey reflects a single element (factor) of a broader concept. Based on the explanations provided in the workbooks, the assumption in the present analysis is that the four elements of PDDP evaluated in the survey represent a composite, or sum of elements, that

define an aspect of an organization. Thus, the analysis of the four elements of PDDP may help determine the overall level of the organization. Cronbach's alpha measures the extent to which the elements of a survey are related to the total score. In the present analysis, the focus is on determination and diagnosis, rather than substantiation.

2.4 Commercialisation implementation success

Success in implementation toward commercialisation readiness of a pulmonary product is defined as CIS. CIS should not be interchangeably used with actual sales, dominance in the marketplace, financial profits, legislative or regulatory approvals, or patient impact, unless explicitly measured. Implementation encompasses milestone sequencing, advanced preparation of evidence, and readiness of manufacturing and access to the market, as well as alignment with regulatory and other stakeholders.

Advancing a product for commercialisation involves more than the science and technology. It encompasses clinical differentiation, cost, reimbursement, usability, and several other factors. Teece (1986) stressed the importance of integration of different elements, including commercial and business, for successful exploitation of new innovations. This justifies the framework's differentiation of knowledge and skills (capabilities) versus implementation (integration). It also underscores that progress in science and technology may not guarantee success.

2.5 Regulatory support and regulatory science

Regulatory science (RS) is the degree to which regulatory requirements, standards, and expectations are clear, accessible, and usable. This does not mean lenient or prohibitive regulations. When advancement and planning of evidence is performed early for complex products (e.g. products for inhalation), factors such as product/device formulation and function, quality, attributes and attributes, process controls, and the intended clinical use and benefit must be integrated. Early interaction with the regulators can facilitate the planning and preparation of evidence to respond to the questions of the most interest and relevance.

Incorporating guidance and recommendations on good practice of the ICH could facilitate harmonization of pharmaceutical development, but the variability of the actual regulations could still be a barrier in practice. Therefore, it could be that in the absence of understanding of regulatory expectations, implementation of a given technology would require supporting evidence (moderator) to demonstrate the technology's performance. This may be difficult or even impossible to test.

2.6 Synthesis and construct boundaries

The framework combines the capability-based view and performance and contextual moderators. NFI and ATC are capability components. PDDP is a performance component. CIS is an construct component of implementation. RS is the contextual moderator of PDDP and CIS. The model purposefully limits the range of other considerations e.g. product-market fit, firm size, clinical evidence, R&D, reimbursement, product maturity, manufacturing economics and IP. The omitted factors may be relevant to the interpretation of the model given the limited evidence in the available data.

Wider evidence supports the rationale for the model and provides theoretical underpinnings. Effectiveness in the pulmonary delivery system is constrained by many barriers. Achieving deposition within the respiratory system is largely dependent on the characteristics of the formulation and the device. New, better inhaled formulations and delivery systems require the integration of a range of disciplines and new science. From a management perspective, the integration of various, and often unrelated, business and technical assets may explain the lack of commercial success for novel pharmaceutical products. Similar perspectives are reflected in pharmaceutical quality. Risk management and lifecycle quality systems address unmet needs and ensure the integrity of the product. These systems help address the gaps in the model.

3. CONCEPTUAL FRAMEWORK AND HYPOTHESIS DEVELOPMENT

3.1 Framework overview

The framework presents 5 constructs and 8 hypotheses. H1 defines a positive pathway from NFI to PDDP. H2 defines a positive pathway from ATC to PDDP. H3 defines a positive pathway from PDDP to CIS. H4 and H5 define positive pathways from NFI and ATC, respectively, to CIS. H6 and H7 define positive pathway from PDDP to CIS, through NFI and ATC, respectively. Lastly, H8 postulates that RS positively strengthens the pathway from PDDP to CIS.

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3.2 Conceptual framework

Black-and-white representation of the framework is shown in Figure 1. Positive pathways are represented by solid lines, and the 2 negative pathways are shown separately. The dashed line represents RS, which is a moderating factor for the pathway between PDDP and CIS. The framework is identical to the agreed-upon model. H7 is represented as ATC → PDDP → CIS.

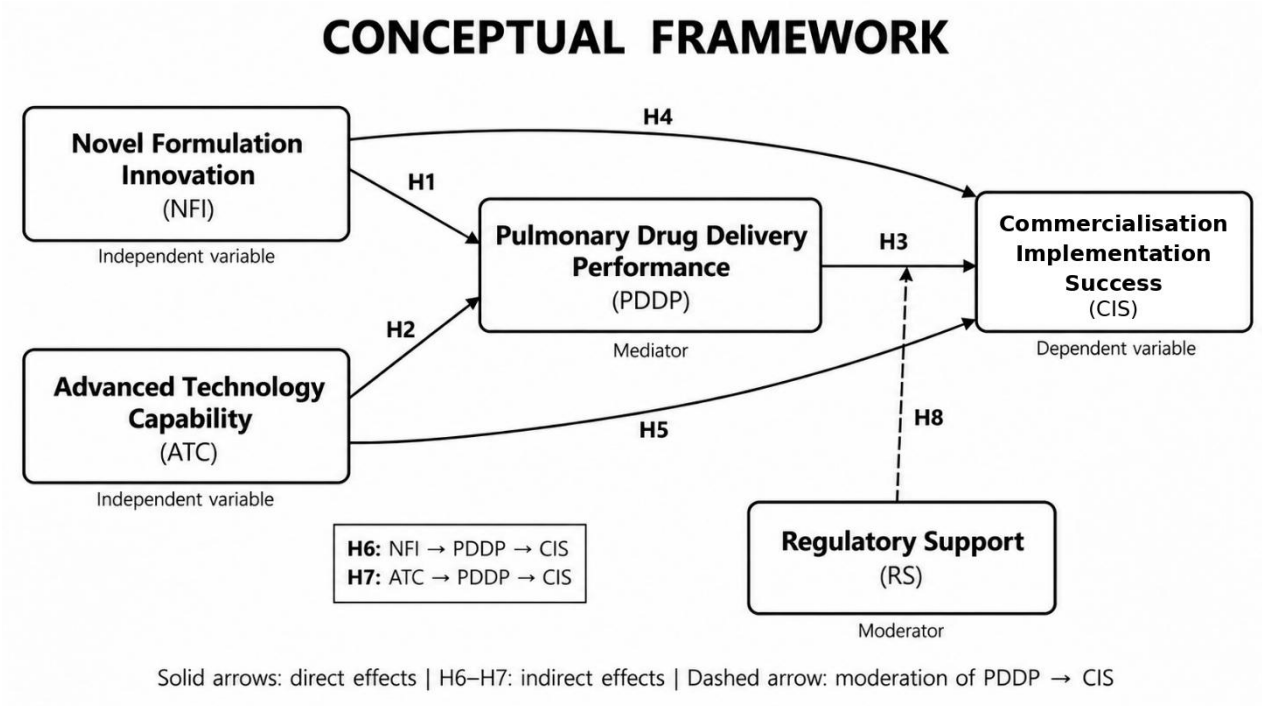


Figure 1. Conceptual framework linking formulation and technology capabilities to pulmonary drug delivery performance and commercialisation implementation success, with regulatory support as a moderator.

3.3 H1: NFI and PDDP

Pulmonary drug delivery is complex, and formulation can address delivery constraints using particle and excipient engineering. Further, formulation can be designed to meet delivery performance metrics. Formulation science and engineering innovations can positively impact pulmonary drug delivery. Like any advancement, trade-offs can occur. Therefore, the hypothesis is framed as an average positive association.

H1: Novel Formulation Innovation positively impacts Pulmonary Drug Delivery Performance.

3.4 H2: ATC and PDDP

Understanding of failure modes improves through process control, characterization and reproducibility. The ICH Guidelines describe the application of critical design and process parameters to establish control of critical product attributes, and thus quality (ICH, 2009). Therefore, it may be expected that ATC is positively related to PDDP.

H2: Advanced technology capabilities influence pulmonary drug delivery.

3.5 H3: PDDP and CIS

From a development perspective, it may be easier to advance a delivery system through a series of defined steps (e.g. development, quality and business/commercial) if that delivery system exhibits reproducible and defined behavior. However, there are other factors, such as the pharmacoeconomics and operational aspects of the business, that would also influence the commercialization of a product.

H3: The influence of PDDP on the commercialization of a product is positive.

3.6 H4 and H5: Direct capability paths

It is possible that NFI or ATC may influence CIS by other means besides the ones proposed in this study, e.g. by changing how a specific product is perceived by the target market, perhaps fulfilling an unmet market need. It is possible that ATC may influence CIS via better integration of the various process elements, greater control over a process, and/or greater/faster readiness to scale and improve a process.

H4: The presence of NFI influences the CIS of a product.

H5: The presence of ATC influences the CIS of a product.

3.7 H6 and H7: Mediation by PDDP

According to this study, NFI and/or ATC may influence other variables, including CIS, via other factors. It may be possible to measure some of these influences. However, in the absence of adequate reliability and validity of the measures utilized in this study, this study will not speculate on the meaning of the measurement influences. It is assumed that the mediation hypotheses will be established at a later date.

H8: The mediation influence of PDDP between NFI and CIS will be established at a later date.

R7: PDDP is positively related to both ATC and CIS.

3.8 H8: Moderating role of RS

Regulatory Support may help project teams to shape the development pathway, including the regulatory pathway, based on the evolution of the product and evidence. The interaction is positive. However, the extent of the interaction is uncertain, particularly in relation to the maturity of the product and the regulatory framework.

R8: It is expected that regulatory support positively moderates the relationship between PDDP and CIS.

4. METHODOLOGY

4.1 Research design and dataset provenance

A cross-sectional analysis of research staff survey is the basis of this research. Each of the research staff supplied a workbook containing 326 records. Twenty item-response in each workbook are distributed among the five constructs. The workbook also contains respondent descriptors and composite scores. The workbook was edited to include centered PDDP and RS. For this study, the research staff workbook was the principal source of data and analyzed as supplied.

It is important to note, the design and analysis of this research does not independently confirm the process of selection or representativeness of respondents. The manuscript does not represent the researcher supplied files as probability samples or as representing the general population. The researcher workbook does not include many critical details of the study; this information must be completed from study records prior to submission.

4.2 Data integrity and recalculation

To examine the quality of the data, we checked both workbooks for format, item columns, fill-ins, distinct user identifiers, range of responses, agreement between stored means and interpretive constructs, and recalculation of construct scores, which are arithmetic means of corresponding construct items.

The interaction variable was calculated by subtracting the sample mean of the PDDP from RS, and multiplying the result by (PDDP - the sample mean of the PDDP). The corrected workbook also had an interaction column, which was not used, as it was not recalculated.

The uncorrected version had 326 records and 20 responses for each of the remaining respondents. The same was the case for the corrected version. However, the corrected version did not contain the item responses in the uncorrected version. Therefore, the correction is not just the addition of center score columns.

4.3 Measures and scoring

The scores for NFI, ATC, PDDP, CIS and RS were determined by calculating the mean of respective subscale scores (NFI1 to NFI4; ATC1 to ATC4; PDDP1 to PDDP4; CIS1 to CIS4; RS1 to RS4). Each subscale comprised of five items, and were evaluated on a Likert scale of 1 to 5. The full questionnaire was not provided; therefore it was not possible to determine the semantic meaning of the scales, confirm the wording of the items and response options, and determine the source of the scales.

Given that the arithmetic mean of the subscales was used to determine the score, a summary of the subscales and an evaluation of Cronbach's alpha was conducted. While alpha can be informative for reflective scales, it is not a measure of scale validity, and therefore, should not be used to justify the validity of a formative index. Low scores for Cronbach's alpha was viewed as an indicator that the scores require further evaluation.

4.3.1 Operational definitions and limits of item-level interpretation

Due to the nature of the files supplied, the definitions developed for this analysis are limited. The supplied corrected workbook contained NFI1 to NFI4, ATC1 to ATC4, PDDP1 to PDDP4, CIS1 to CIS4, and RS1 to RS4. The wording of the items and response options were not supplied, and therefore it was not possible to determine the semantic meaning of the items. It was also not possible to confirm that the items are worded verbatim the way they are described in this analysis.

NFI is calculated by taking the average of NFI1-NFI4, and is understood as respondent's perceived capability to innovate in pharmaceutical formulations. ATC is the average of ATC1-ATC4, and is understood as respondent's perception of advanced technology. PDDP is the average of PDDP1-PDDP4, and is understood as respondent's assessment of pulmonary drug delivery performance. CIS is the average of CIS1-CIS4, and is understood as respondent's perception of commercialisation. RS is the average of RS1-RS4, and is understood as respondent's perception of the presence of regulatory support. The names assigned to the items in this study are to be considered provisional.

It cannot be assumed that a given name for a variable reflects the true nature of the variable being assessed. PDDP2 could be assessing the reproduction of the correct dose, the characteristic of an aerosol, an individual's readiness, or other factors; which is not defined in the workbook. CIS items may be assessing the achievement of an implementation step, rather than the achievement of a commercialisation step.

The researcher needs to provide the complete questionnaire or codebook to this review board, which describes the exact wording and the justification for each of the 20 items, along with instructions and scoring. All recodings should reflect the original version of the questions. If the questions have been translated, this should be indicated.

4.3.2 Measurement model and reliability interpretation

As per the instructions in the workbook, the simple average of the four items in each block was computed. As stated above, this, in and of itself, provides no evidence that the sets of items form validated unidimensional scales. Cronbach's alpha provides one estimate of the average of the inter-item correlations. As stated previously, this does not provide evidence for content validity, dimensionality and measurement invariance. It should be noted that, depending on the context, negative values for Cronbach's alpha may be expected. As described previously, Cronbach's alpha is primarily an index of the average of the inter-item correlations. If those inter-item correlations happen to be of an average reverse-worded nature and have not been recoded, Cronbach's alpha is expected to be of a reverse or negative nature. Alternatively, blocks of items may combine more than one dimension or the variables in the block may be unrelated.

Prior to the interpretation of paths, evidence in support of construct validity should be assessed. Given that measurement errors can distort composite relationships, it is instructive to consider the evidence in support of convergent and discriminant validity (Fornell & Larcker, 1981). One approach to assess discriminant validity is provided by Henseler et al. (2015) and pertains to variance based structures. It should be noted that neither of these assessments of construct validity have been undertaken in the work reported here. The references are, however, useful in forming a basis for validation.

4.4 Statistical analysis

Descriptive statistics include means, standard deviations, and Pearson correlations. Three ordinary least-squares (OLS) regressions, controlling for heteroskedasticity with the HC3 procedure, were performed. In model 1, the dependent variable, PDDP, was regressed on centred NFI and ATC. In model 2, the dependent variable, CIS, was regressed on centred NFI, ATC,

and PDDP. In model 3, the dependent variable, CIS, was regressed on NFI, ATC, PDDP, and RS, and the interaction of centred PDDP and RS. All interactions and predictors were mean-centred prior to creating the interaction. Coefficients of the interactions and predictors are reported in terms of the (standardised) 1 to 5 composite score.

Although several paths in the path analysis suggest a mediation, the overall measurement diagnostics were unacceptable. A confirmatory mediation analysis should include a measurement model for which a bootstrapped confidence interval is reported to verify the mediation. In the presence of unacceptable measurement diagnostics, evaluation of the component paths, if significant, may provide unclear insights about the path the mediator(s) is taking to the outcome. In regression analysis, 0.05 is the threshold for statistical significance; however, confidence intervals and the overall explanatory power of the model may also be considered.

4.4.1 Model specification and interpretation

The first regression estimates the relationships of centred NFI and ATC with CIS. The second estimates the relationships of NFI, ATC, and PDDP with CIS. The third estimates the relationship of the product of centred PDDP and RS and centred RS with CIS. Interaction terms are expressed as the difference from the mean. For main-effect terms of the interaction, removing the mean may be interpreted as representing the effects of the variable at the population mean. Interaction terms may be insignificant even when the main effects are significant and vice versa.

Ordinary least squares draw inferences based on estimated standard errors. When model specification is inadequate or measurement error exists, interpretation is limited to the relationships among the variables specified in the model. The coefficients should not be interpreted as reflecting causal relationships.

In the mediation analysis, the first step is to estimate the indirect effect. This effect is represented by a product of paths. This study interprets indirect effects of paths where a sequence of regression coefficients is statistically significant. Because of the inadequate measurement models, this study does not verify any mediation effects.

Shared method effects are of concern when relationships in the data are the results of response styles or personal biases. Using self-reported data obtained at a single point in time, these effects are difficult to avoid; therefore, it is prudent to implement different validation strategies in the design to rule out these effects as much as possible (Podsakoff, MacKenzie, & Podsakoff, 2003).

4.5 Ethical and reporting considerations

The data file contains IDs and job title. The absence of names does not indicate the respondents cannot be identified and hence that the conditions for ethics are satisfied. The author must give details of review of ethics, if any; process of informed consent, if any, and confounding, and the safeguards taken for the protection of the respondents. The author must provide details of the data stored, processes, and their transfer. These have not been assumed and are not provided in the current work.

5. RESULTS

5.1 Comparison of the initial and corrected datasets

Both data sets contained 326 records, 20 item-response variables and differed in their specific item responses. Generally, it was found that the corrected data sets resulted in more adequate and higher average construct scores as compared to the initial data sets. Based on this, the corrected data sets are thought to contain more adequate data in an improved format as compared to the initial data sets. The initial data sets are presented in this document for illustration and for verification of the data manipulations. The corrected data sets are the primary data sets for this study.

Construct	Initial M	Initial SD	Corrected M	Corrected SD
NFI	2.963	0.705	3.436	0.602
ATC	2.949	0.706	3.466	0.520
PDDP	3.008	0.763	3.519	0.525
CIS	3.033	0.678	3.495	0.577
RS	2.947	0.731	3.499	0.555

The construct means of the initial data sets ranged from 2.947 (RS) to 3.033 (CIS). The means of the corrected data sets ranged from 3.436 (NFI) to 3.519 (PDDP). It can be concluded that due to the changes of the item responses of the corrected data sets, the construct means also changed. The two data sets were not fused or averaged, and it was the corrected data sets that were used for the primary results of this study.

5.2 Measurement reliability

Construct	Initial alpha	Corrected alpha
NFI	0.013	0.164
ATC	0.039	-0.193
PDDP	0.107	-0.145
CIS	-0.131	0.067
RS	0.138	0.035

The first version of the data set produced alpha values of .013 for NFI, .039 for ATC, .107 for PDDP, -.131 for CIS, and .138 for RS. Alpha was estimated at .164 for NFI, -.193 for ATC, -.145 for PDDP, .067 for CIS, and .035 for RS, in the second data set. Thus, the issue related to scale coherence was not resolved with the correction. According to the literature, a negative alpha value signifies that the observed item covariance does not conform to a positively keyed reflective scale. Low positive alphas do not meet expectations for a reliable and valid scale.

It should be emphasized that the results do not signify that the assessed constructs are unimportant. It means that the four items, when combined and scored in their current form, do not behave like reflective scales. Some of the reasons for this could include using item wording to assess non-equivalent facets, response option mistakes, item order mistakes, or using wrong reflexive composites. Without examining the codebook and the questionnaire, it would not be appropriate to provide any construct validity coefficients.

5.3 Corrected-data correlations

Construct	NFI	ATC	PDDP	CIS	RS
NFI	1.000	0.022	0.054	-0.003	0.011
ATC	0.022	1.000	0.007	0.005	-0.012
PDDP	0.054	0.007	1.000	-0.029	0.053
CIS	-0.003	0.005	-0.029	1.000	0.010
RS	0.011	-0.012	0.053	0.010	1.000

Most of the corrected-data correlations were very close to zero. NFI correlates with PDDP and CIS with values of r = .054 and r = -.003, respectively. ATC correlates with PDDP and CIS with values of r = .007 and r = .005, respectively. PDDP correlates with CIS with value of r = -.029. NFI correlates with CIS with a value of r = .010. The low values indicate that the relationships do not exist in the population.

5.4 Model 1: NFI and ATC predicting PDDP

Predictor	B	HC3 SE	95% CI	p
NFI_C	0.047	0.048	[-0.047, 0.142]	0.327
ATC_C	0.006	0.056	[-0.104, 0.116]	0.912

The NFI and ATC combined explained 0.003 (adjusted 0.003) of the variance in PDDP. NFI was not near the predicted value and was not significant (p = .327). Same case with ATC (p = .912). Therefore, neither NFI nor ATC predicted PDDP in the population. Hypothesis 1 and 2 were not supported.

5.5 Model 2: predictors of CIS

Predictor	B	HC3 SE	95% CI	p
NFI_C	-0.001	0.053	[-0.105, 0.103]	0.983
ATC_C	0.006	0.062	[-0.116, 0.128]	0.923
PDDP_C	-0.032	0.059	[-0.147, 0.084]	0.591

Model 2 accounted for 0.1% of the variance in CIS (adjusted R^2 = -0.8%). NFI was not significant (B = -0.001, p = 0.983); ATC was not significant (B = 0.006, p = 0.923); and PDDP was not significant (B = -0.032, p = 0.591). Thus, hypotheses H3, H4, and H5 were not supported. The very low R^2 of the model suggests the three composites account for very little variance in CIS.

5.6 Model 3: moderation by regulatory support

Predictor	B	HC3 SE	95% CI	p
NFI_C	-0.001	0.053	[-0.106, 0.104]	0.987
ATC_C	0.008	0.063	[-0.115, 0.131]	0.897
PDDP_C	-0.035	0.059	[-0.151, 0.081]	0.553
RS_C	0.012	0.054	[-0.093, 0.117]	0.816
INT	-0.045	0.088	[-0.219, 0.128]	0.607

The complete model accounted for R^2 = 0.2% of the variance in CIS (adjusted R^2 = -1.4%). The interaction term was B = -0.045, SE = 0.088, and 95% CI [-0.219, 0.128), p = 0.607. The confidence interval includes zero, therefore the interaction was not significant. Therefore, H8 was not supported. Given the interaction term's negative point estimate, one would be tempted to draw the conclusion that the presence of adequate regulatory support would attenuate the relationship between performance and commercialization. However, given the limits of the data, no definite conclusion can be drawn.

5.7 Initial-data regression comparison

The initial data set led to similar broad conclusions. For the initial PDDP model, R^2 = .004; NFI was not significant (B = .030, p = .614) and ATC was not significant (B = –.065, p = .241). For the initial CIS model, R^2 = .004; NFI (B = -.039, p = .448), ATC (B = .033, p = .574) and PDDP (B = .029, p = .545) were not significant. For the initial moderation model, R^2 = .004, and the interaction (B = .027, p = .725) was not significant. Thus, the initial and corrected data and model files differ in various estimated parameters and descriptive statistics. However, none of them provided evidence in support of the formative paths of interest, based on the current scoring scheme.

5.8 Hypothesis summary

Hypothesis	Proposed relationship	Decision using corrected data
H1	NFI → PDDP	Not supported
H2	ATC → PDDP	Not supported
H3	PDDP → CIS	Not supported

H4	NFI → CIS	Not supported
H5	ATC → CIS	Not supported
H6	NFI → PDDP → CIS	Not established; measurement concerns
H7	ATC → PDDP → CIS	Not established; measurement concerns
H8	RS moderates PDDP → CIS	Not supported

5.9 Operational meaning of the empirical results

The corrected files resulted in means ranging from 3.436 to 3.519, for the five-point Likert scales. Means do not represent overall high or strong scores unless it is indicated by anchors, and in the absence of any such ruling, they should not be interpreted that way. Standard deviations of the items ranged between .520 and .602. Standard deviations indicate variability in the scores; they do not represent the overall significance or relevance of the scores.

Correlations between recalculated means of the items are as follows: NFI correlates with PDDP at r = .054, with CIS at r = -.003; ATC correlates with PDDP at r = .007, with CIS at r = .005; PDDP correlates with CIS at r = -.029; and RS correlates with CIS at r = .010.

The recalculated means of the items described above are poor indicators of the underlying relationships in the population; however, they do indicate that correlations, if any, are very low. The explanatory models based on the recalculated data are poor, with an R^2 of .003 for the PDDP model. The model containing NFI, ATC and PDDP, and the moderation model, have an R^2 of .001 and .002, respectively. The interaction term, B = -.045, HC3 SE = .088, 95% CI [-.219, .128], indicates that the moderating effect, if any, is not supported by the data. The point estimate is negative, but it does not indicate the presence of a harmful effect of the moderator.

For H1 and H2, coefficients are B = .047 (p = .327) for NFI and B = .006 (p = .912) for ATC in the PDDP model. For H3 to H5, coefficients in the CIS model are B = -.032 (p = .591) for PDDP, B = -.001 (p = .983) for NFI, and B = .006 (p = .923) for ATC. The estimates do not support the theoretical, positive, expected relationships. It is not appropriate to conclude that the relationships do not exist, as the scales do not appear to be coherent. The most appropriate conclusion is to say that the relationships are "not statistically supported" in the present analysis.

There is an emphasis on the estimation of coefficients, confidence intervals, and overall model fit as opposed to p-values; therefore, the results are generally consistent with recommended practices for transparent research (Lakens, 2013). As noted by Chafkin and Shimer (2020), the costs and uncertainties associated with pharmaceutical development may influence the decision to undertake or not undertake research and may affect a sponsor's investment prioritization and portfolio diversification, but these aspects were not assessable in the current study.

6. DISCUSSION

The main finding is that the estimated relationships represented by the paths or the regulatory interaction in the final version of the model were not statistically significant. The direct relationships explained very little of the variance in the model. The initial value structure relationships were also very close to 0. Results from measurement diagnostics were more informative: most of the scales showed very poor reliability, including negative, or no, measurement. The best that can be said is that the measurement does not reliably support the framework.

First, measurement quality suffers. Each block of items should be interrelated in a positive fashion (i.e., covary positively). It is possible that some items in a block are negatively related. If negative alpha is due to measurement error, such issues can be resolved by determining the reason for negative covariance (e.g., items have been incorrectly worded and/or coded). The negative covariance may be due to combining items that actually measure different facets of the construct. Because the dataset does not include the wording of the items, the Workbook is limited in determining the cause of negative covariance of the items.

The second point also pertains to theory. According to ICH (2009) the development of devices and the innovations in their formulations are interrelated. The survey does not support this interrelationship, as organisations that provide greater formulation innovations do not report greater delivery innovations. As mentioned earlier, the reverse may be true, due to negative reliability. The fact that the survey supports no relationship between formulation and delivery innovations does not support the notion that this relationship does not exist.

Third, this research illustrates how far there may be between the lab and the marketplace. Here, delivery performance may be a significant milestone for development; however, CIS may be dependent upon other factors outside this research, such as clinical data, the unmet need in the target market, the economy of the manufacturing process, reimbursement, the supply chain, intellectual property, the ability of the product to be used by patients, and competitive positioning. It may be useful to develop a model that would consider the aforementioned factors to more fully evaluate an innovation.

Fourth, the authors suggest that the product development lifecycle (PDDP) and clinical involvement systems (CIS) may be moderated by a number of factors. There is evidence to suggest that, depending on the jurisdiction and the stage of the development, the product quality system may focus on the planning and design of the product. It is unlikely that perceived regulatory support would moderate the relationship between the PDDP and CIS.

Lastly, the importance of version control is illustrated by the comparison of the original and modified datasets. The modified dataset has greater construct means than the original dataset and contains different responses to the item. However, the reliability issue remains. The authors of the report presented the original dataset for comparison, but based the analysis on the modified dataset.

6.1 Implications for interpreting capability and commercialisation

Capabilities are positioned relatively close to development and an implementation outcome further away. A formulation or technology may affect a proximal milestone and not impact the final commercial outcome. Innovations may not be economically beneficial even if they are successfully commercialized. Based on Teece's work, a primary element in determining the economically beneficial outcome of an innovation is the combination of the complementary assets and the commercial structure (Teece, 1986). Teece's work on 'dynamic-capabilities' supports the theory that continuously adapting and recombining the elements of a business in response to changes in the environment can also be a source of competitive advantage (Teece, 2007). The theories, however, do not corroborate the survey composite constructs in this study.

In developing a pulmonary drug product, device and formulation development are interdependent. Stability and manufacturability of the formulated product can impact the final design of the delivery system. Barriers to efficient delivery and formulation of powder products for inhalation can be impacted by a number of factors, including device design and the user's ability to incorporate the device into the product (Labiris & Dolovich, 2003, 2003b; Telko & Hickey, 2005; Sou & Bergström, 2021; Dhoble et al., 2024; Islam et al., 2024). While the cited literature describes the barriers to efficient delivery of pulmonary drug products and supports the need to include delivery in a product development project as a separate construct from formulation, survey construct average is not the same as fine particle mass, emitted dose, or clinical benefit.

Achieving Commercialization depends on several factors including regulations, product quality, manufacturing and supply capabilities, the supply chain, clinical evidence, reimbursement, and market conditions. Pharmaceutical development and life cycle quality guidelines describe the role of processes, risk, and quality. However, these guidelines do not show that perceived regulatory provisions affect the relationship between process and cumulative incremental product/service development costs (PDDP–CIS) in this study (ICH, 2008, 2009, 2023). Regulatory Science supports the inclusion of Regulatory Science (RS) in the study, but does not support the statement in H8 is correct (Honig & Zhang, 2019).

6.2 A staged validation and replication plan

The first step should be the recovery and documentation of the original questionnaire and response anchors. These should be evaluated by subject matter experts to determine if they represent the constructs they are intended to measure, and whether the assigned constructs are distinguishable from one another.

Next, a pilot study should be conducted to evaluate the correlation of the items to one another and determine whether the items reflect the constructs. If this measurement is adequate, the study should be conducted with a separate sample to validate and verify the measurements, and test the hypotheses of interest including direct and partial effects.

The focus of future work should be on the distinctions between respondent perceptions of delivery performance and actual delivery performance, and between readiness to implement and actual commercialization. In the spirit of this research, methods to ensure that distinctions are documented should be prioritized.

7. THEORETICAL IMPLICATIONS

The study provides a combined model of formulation innovation, technology capability, delivery, and commercialization. The model illustrates examples of operationalization and demonstrates its limits. Results showed that integration of elements of a model through conceptual thinking would not constitute a valid measurement model. Measurement models require the researcher to justify and defend the relationship between the constructs and their indicators.

From an empirical stance, the framework refers to proximal and distal outcomes. PDDP is proximally related to product development, while CIS reflects more distal outcomes. The framework invites researchers to locate the boundaries of an organisation within which the capability in question is employed. Future studies should identify the elements that occur between distal and proximal outcomes, and the capability in question that is presumed to influence those elements.

Since poor item-level consensus was found in the empirical study, the theoretical conclusion would be that the researchers demonstrated reasoning and justification for pathways and boundaries, and provided evidence that these pathways and boundaries remain untested. It was shown that the research hinges on theory and invites further work in the area. A study employing a product unit of analysis would be helpful to support the theoretical framework and guide the sequence of capability, performance and implementation.

RS acts as a moderator because it is expected to affect the pathway from technical evidence to implementation. However, one RS mechanism is not always the same as the next. For instance, requirements may be clear, but uncertainty may remain. There are other factors such as whether or not the process is expected to take a certain amount of time. Honig and Zhang (2019) describe the importance of the evidence and regulatory decision-making process and provide examples where evidence is not aligning with the standards and requirements of a given regulatory decision. A positive interaction of evidence and regulatory requirements may be assumed. Future work should indicate different effects from evidence if a theory predicts those effects.

There are other considerations. Implementation decisions made early in the product lifecycle may affect later decisions. For instance, the type of technology used in a given product may have a bearing on the commercialization potential of that product. Even so, a product may be equipped with state of the art technology and remain unable to benefit a given market due to limitations in other areas of the product lifecycle (e.g. regulations or manufacturing). From a regulatory and policy perspective, the field is still developing. The low R-squared values from this study are reflective of the theory's constraints. However, these values do not indicate which theoretical constraints are limiting the most.

The relationships relied upon by the model may vary by product type and product development stage. For example, the engineering and integration of a device to deliver the dry powder to a user's lung may be the main considerations in developing one type of an inhaled product, whereas other considerations may apply to other product types. Publications focusing on pulmonary drug delivery demonstrate that various factors, including the composition of the product and the characteristics of the device and the aerosol, play an important role in achieving the product goal (Labiris & Dolovich, 2003a, 2003b; Telko & Hickey, 2005; Sou & Bergström, 2021; Yue et al., 2023). Thus, it is likely that broad capability measures may not be applicable to all product types.

The author suggests that focusing on the capabilities of product development and the barriers to product implementation provides an understanding of how products are commercialized. Based on the author's model, NFI and ATC are associated with PDDP. It is also suggested that PDDP is associated with CIS, and that RS may modify the association between PDDP and CIS. The author states that the relationships suggested by the author remain to be tested and validated. It is noted that in the current study, the components of the item scales do not reflect a consensus among experts, and as such the components of the scales may not measure what they are intended to measure.

8. PRACTICAL IMPLICATIONS

8.1 Formulation and R&D teams

Formulators and R&D teams should define the anticipated benefit prior to the development of a formulation. They should identify the acceptance criteria for benefit assessment. For an inhaled product, criteria may include aerodynamic particle size distribution, emitted dose, fine particle fraction, stability, reproducibility of dose, and formulation and device compatibility. Justification for the criteria should be explained with supporting evidence. A perception score for a formulation should not be applied as a surrogate measure to define benefit.

8.2 Technology and manufacturing teams

Funds dedicated to capital equipment should be justified in the context of process and/or product development. Equipment, automation, and other enabling technologies should be employed to design and manufacture the product or to control the process. It should be expected that the equipment is supported by and integrated into suitable business processes.

8.3 Regulatory and commercialisation teams

The regulatory and quality functions of an organization should collaborate to define and implement the product development strategy and evidence to be generated. Prior planning for product commercialization should contemplate differentiation, usability, price, market access, and other factors that affect service availability and continuity.

8.4 Implications for responsible empirical reporting

This case study provides an example of why researchers should not manipulate data to enhance statistical significance. In the case of this study, the research team determined that reverse-keying was the most reasonable approach to increase reliability of the measurement. However, reporting a "better" estimate without addressing measurement challenges and limits of the instrument would not resolve the validity issue.

Reverse coding, omission of items, exclusion of respondents, or other approachs to alter the measurement of an outcome should be done in accordance with research team's methodological framework and explained in detail to stakeholders. Transforming a data set in a way that improves the estimate would not benefit the validity of a study.

The research team used the corrected data set as the base for the analysis as the authors stated that data set was the corrected version. The research team used the original version of the data set to illustrate how the estimates changed. The two data sets are not merged. The calculations appear to be correct, however the research team does not know the rationale for the data owner's changes. Based upon the current evidence, the research team cannot say how the data was transformed historically.

The greatest need is to assess and refine the measurement instrument. The original versions of the measurement instrument should be located and aligned to the measurement items. Any recoding should occur based upon the actual measurement instrument rather than be change to enhance statistical significance. All recodings should be documented in a data dictionary. The data should be analyzed in a reproducible way to assess the overall changes that occurred to the data.

9. LIMITATIONS AND FUTURE RESEARCH

There are multiple limitations to interpreting these data. First, there are gaps in the workbooks. For example, the wording of the questionnaires, response anchors, sources of the items, and coding instructions are not included. Second, the workbooks do not allow for firm conclusions concerning the validity of the constructs measured by the composites. Third, the workbooks contain no information concerning the sampling frame and recruitment process, the non-response, or regulatory jurisdiction. Fourth, the documents do not indicate whether the sampling frame is indeed representative. Fifth, the WHO CIS evaluates the extent to which a product's introduction and use is successful and not the product’s sales, profits, legality, or other actual commercial impacts. Sixth, the researchers do not take into account a variety of product and market factors that may influence the success of a product's adoption.

It is also likely that future research may document and include the aforementioned gaps in the workbooks. Before research involving reflective scales, reliability may need to be confirmed. In cases where a potential construct may be formative, it is also important to gauge the degree of association of the various indicators to the construct and the degree of association of the indicators with one another.

A stronger design would feature a focal product, development program or delivery platform and indicate its status, e.g. 'in development', type of organization, and the jurisdiction or authority under which it was developed. Data should be recorded in a longitudinal fashion to reflect the capabilities of the organization, the performance of the organization in fulfilling the contract, and the outcomes of the implementation of the program or project. Where available, the judgment of researchers or evaluators should be compared with relevant performance indicators, e.g. the outcome of a test, achievement of an educational milestone, etc. The effects of mediators and moderators should be reported as indirect effects and conditional effects, respectively. These analyses should be performed after confirming that the performance indicators are valid.

10. CONCLUSION

The study does not evaluates the role of formulation, technology, and regulation in an innovating industry to be of less relevance. The lack of confirmatory data assesses the role of the above mentioned to be of less relevance. Therefore the study evaluates the roles of the above mentioned to be of less relevance.

The assessment framework should be verified. The rebalanced dataset should be assessed against its documented modifications. The analysis framework should be assessed. In the same spirit, other studies should assess respondent perceptions and delivery and implementations" outcomes. Where data is available, studies should evaluate indirect effects, and confidence levels.

In the assessed data, means for constructs ranged from 3.436 (NFI) to 3.519 (PDDP). Cronbach's alpha was between -.193 and .164. The direct effect models and PDDP's interaction with Regulatory Structuring were not statistically significant. Therefore, H1 to H5 were not supportive. Because of measurement limitations, effects of H6 and H7 could not be assessed.

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