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Contributing Factors for the Performance of Generic Drug Development Projects

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Abstract: Generic drugs represent significant part of the Brazilian pharmaceutical market, playing a major role in its health system. Recent studies show that a significant portion of applications for registration of new generic drugs is denied. These results gave rise to the question of this research, which sought to identify which factors contributed to the failure of the generic drug development projects (GDDP) in Brazil. The data collected through an electronic questionnaire were analyzed using the structural equation modeling method with partial least squares estimation (PLS-SEM). The results validate 5 indicators for the performance of the GDDP and 44 indicators for the contributing factors classified into three dimensions: Managerial, Structural and Technical. The results also indicated that management difficulties contributed directly to the performance of the GDDP. However, the contributions of technical difficulties and structural difficulties had only confirmed their indirect effects through mediation by managerial difficulties.

Keywords: drug development; generic drug; product development; project performance; research & development.

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1 Introduction

The pharmaceutical laboratories strive to quickly bring generic drugs (GDs) to market as a strategy to obtain competitive advantage (Kader, 2016). For Newman and Witzmann (2020), the launch of new GDs face difficulties as a result of complexities regarding the required product's performance, effectiveness, and safety. One of the indicators of these difficulties is the high number of requests for marketing that are rejected by the health authorities in different countries around the world (Srinivasan, Iser and Gill, 2010; Worku *et al.*, 2012; Carmo *et al.*, 2017). In addition to delaying the launching of the new GDs, inefficiencies in generic drug development projects (GDDPs) can result in higher costs for their production and, consequently, higher prices, which can lead to less competitiveness and profitability (Dylst *et al.*, 2013).

No studies were found in the literature that specifically address the performance of GDDPs or its contributing factors. The only publications related to GDs, either focus on the development of specific classes of drugs, or on general development processes. Thus, considering the gap found in the literature and especially the high rate of rejection of requests for registration of GDs reported by Carmo and colleagues (2017), the central question that this research sought to answer was: what are the factors that contribute to the performance of the GDDPs in the pharmaceutical industry installed in Brazil? To answer to this question, it was broken down into the following objectives:
a. Empirically validate the performance indicators and the factors that contribute to the performance of the GDDPs.
b. Empirically validate a multidimensional structural model that integrates the performance of GDDPs and their contributing factors.

2 Theoretical review and hypotheses

In the 1990s, Wheelwright and Clark (1992) stated that efficiency and speed in product launches would generate competitive advantage, which, according to Kader (2016), also applies to the development of new drugs. Generic drug development projects (GDDP) do not employ methods other than the most classic product development approaches. For Taylor (2016), despite the less complex development of the GDs, the development of the formulation and of the processes according to the regulatory requirements is necessary to obtain the approval of the regulatory agency for commercialization. GDDPs have the legislation as their main source of requirements. In Brazil, the most specific norm for drug development is the Normative Instruction - IN No. 47/2019 (Anvisa, 2019a). It refers to the approach called "Quality by Design" - QbD, which is also recommended by the FDA (2004) and The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use - ICH (2019).

We found by searching in the literature (Scopus® and Web of Sciences® databases) only a little number of publications dealing with the development of GDs, most of them about specific technical issues. In addition, we searched for Brazilian publications in the Google Scholar® database which basically resulted in theses and dissertations about specific aspects of the GDs development. About publications on the subject of performance of drug development projects, we could find only studies about innovative drugs, including the paper by Mendigorri, Valderrama and Cornejo (2016). Thus, as we

could not find references regarding the performance of GDDPs, aiming to define a conceptual model for this study, we preliminarily carried out an exploratory research. The conceptual model presented in Figure 1 resulted from this initial research combined with the review of the literature on drug products development.

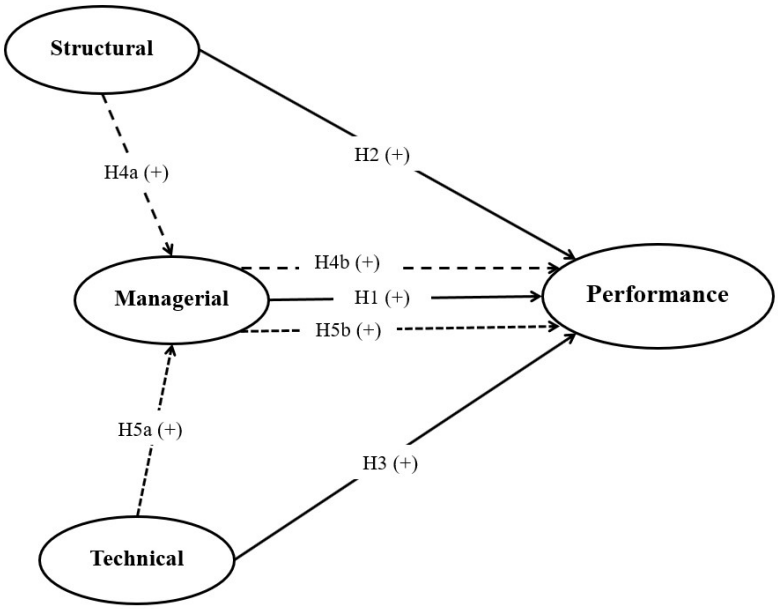

Figure 1 Conceptual model of the study.

For the configuration of the conceptual model, we considered that the GDDPs would fail because of different sets of reasons (R. G. Cooper and Kleinschmidt, 1987; Montoya-Weiss and Calantone, 1994; Page and Schirr, 2008). In the case of the performance of GDDPs, there is a specific indicator that is the approval by the regulatory body. In addition to this indicator, the Performance dimension of the conceptual model (Figure 1) has as its basic references the dimensions proposed by Shenhar, Levy and Dvir (1997).

The three dimensions of independent variables (Managerial, Structural and Technical) of the model are conceptually aligned with the understanding of the International Society for Pharmaceutical Engineering (ISPE, 2011) which considers that good project management practices in the pharmaceutical industry are related to business context, regulatory context, and technology. For Kanfer and colleagues (2014), the regulatory requirements, technical specifications and resources of the organization have to be considered by the development strategy. These dimensions are also aligned with the categories (Process, Strategy and Product) of the taxonomies proposed by Cooper and Kleinschmidt (1987) and Montoya-Weiss and Calantone (1994).

The composition of the managerial factors of the conceptual model is based on the PMI's (2017) approach to the project management and on the GD development processes proposed by De Paula (2004); Shargel and Kanfer (2005); and Yugue (2014). Because of no studies have been found addressing the influences of management factors on the results of the GDDP, we defined the following hypothesis:

Hypothesis 1 (H1) - Managerial difficulties are positively associated with the GDDPs' unplanned performance.

The hypothesis analyzes the positive relationship between the difficulties and the unplanned results of the GDDP because the objects of this study are the projects that have failed and the factors that influenced their failure. The failure is defined in terms of unplanned performance considering that projects are evaluated by comparing the results against what was planned.

The definition of the Structural Dimension was based on the model of influences of PMI (2017) which considers the company's external and internal environmental factors among the items to be considered in a project. In general, these factors are out of the reach of the project managers' decisions and include professionals, laboratories, equipment, ingredients, systems, and processes (Hansen and Tunnah, 2003; Anvisa, 2019b, 2019a). That said, the second hypothesis was established as follows:

Hypothesis 2 (H2) - Structural difficulties are positively associated with the unplanned performance of the GDDPs.

Studies such as that of Carmo and colleagues (2017) and Srinivasan, Iser and Gill (2010) suggest that failures to meet technical and regulatory requirements are among the causes for the disapproval of new drug registrations. Thus, the regulatory requirements form the basis for the technical factors considered in the conceptual model. Therefore, the third hypothesis was defined as follows:

Hypothesis 3 (H3) – Technical difficulties are positively associated with GDDPs' unplanned performance.

Yet in the 1970s, Murphy, Baker and Fisher (1974) concluded that, in most projects, many of the determinants of performance are factors that project's managers would potentially have capacity to administrate. PMI (2017) considers that the project manager needs to understand the project's constraints and use his or her skills and political capabilities to successfully complete the project. Therefore, we considered the possibility of managerial factors acting as mediators of the relationships between the structural factors and the technical factors with the performance of the GDDP. According to Hair Jr. and colleagues (2017), an application of mediation is to "explain" why a relationship constructs exists, which justify the fourth and fifth hypotheses of this study. The hypotheses were split into components (a and b) that represent each of the two relations that characterize the mediating effect in a structural model.

Hypothesis 4 (H4) – The influence of structural difficulties on the unplanned performance of the GDDPs is mediated by managerial difficulties.

- *Hypothesis 4a (H4a): Structural difficulties of the developer are positively associated with the managerial difficulties regarding the GDDPs.*
- *Hypothesis 4b (H4b) = H1: Managerial difficulties are positively associated with the GDDPs' unplanned performance.*

Hypothesis 5 (H5) - The influence of technical difficulties on unplanned performance of the GDDPs is mediated by managerial difficulties.

- *Hypothesis 5a (H5a): Technical difficulties of the developer are positively associated with the managerial difficulties regarding the GDDPs.*
- *Hypothesis 5b (H5b) = H1: Managerial difficulties are positively associated with the GDDPs' unplanned performance.*

3 Method

Aiming to attend to the objective of empirically validate the proposed multidimensional structural model, this study adopted a quantitative approach with a descriptive-correlational scope. Based on the conceptual model (Figure 1) and considering the theoretical framework, an electronic questionnaire was developed for data collection. The questionnaire had been previously submitted to a content validation analysis and the results led to the exclusion of 5 of the original indicators.

As there is no specific profession or qualification to be a team member in GDDPs, there are no databases or lists of professionals working in these projects in Brazil. Thus, professionals participating in the LinkedIn® (social network site) who worked in GDDPs in Brazil were invited to respond to the survey. Invitation messages were sent to 2,210 professionals and the data collection was carried out from February to May 2019 by the QuestionPro® web survey service. From the questionnaires completely answered, 209 were qualified as valid. The collected data was then submitted to two groups of analyzes: descriptive statistics (sample characteristics) and multivariate analysis (structural model).

The Structural Equation Modeling with Partial Least Squares estimation (PLS-SEM) was applied for the multivariate analyzes (Sarstedt, Ringle and Hair Jr., 2017). Three groups of statistical tests were calculated to analyze the data (Henseler, Ringle and Sinkovics, 2009; Hair Jr. *et al.*, 2017): (i) evaluation of the measurement model; (ii) evaluation of the structural model; (iii) evaluation of the mediation effect. We used the SmartPLS® software - version 3.2.8 for the calculations.

The evaluation of the measurement model sought to analyze the relationships between constructs (latent variables of first order or exogenous) and their indicators. The following statistical tests were used (Henseler, Ringle and Sinkovics, 2009; Hair Jr. *et al.*, 2017): Convergent Validity - Average Variance Extracted (AVE); Discriminant Validity - Fornell and Larcker criteria and Cross-Loads; Indicator Reliability - Composite Reliability (CR) and Cronbach's Alpha (CA).

The objective of tests for the evaluation of the structural model is to verify its ability to predict the endogenous constructs, that is, to prove the relationships between the constructs and the validity of the model. The following statistical tests were used (Cohen, 1988; Hair Jr. *et al.*, 2017): Multicollinearity - Variance Inflation Factor (VIF); Effect Size (f^2); Structural Coefficients or Path Coefficients (Γ); Predictive Relevance (Q^2); and Coefficients of Determination (R^2).

Preliminarily to the mediation tests (H4 and H5), the analysis of the relations between the independent variable and the mediating variable (VI -> Med) and between the mediating variable and the dependent variable (Med -> VD) pointed out that they were significant ($\beta > 0.20$). Considering this result, the mediating effects statistical tests were performed

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(Hair Jr. *et al.*, 2017). Finally, the path coefficient (> 0.20) and the p-value ($\alpha \leq 0.05$) were used as criteria for evaluating the hypothesized relationships in the model.

4 Results and Discussion

Of the 209 participants, most of them (63.2%) had considerable experience in GDDP with at least 5 years of experience. The Research & Development (R&D) was the department where they worked in with the highest frequency (74.2%). Most participants (91.4%) worked in private pharmaceutical laboratories and the largest portion of respondents (87.6%) worked in Brazilian laboratories.

In the first round of evaluation of the measurement model, the ID3 indicator (initial registration request failed) had a factor load below 0.50. However, considering recommendation of Vinzi and colleagues (2010), we decided for its maintenance because it is related to the effective success of a GDDP. By the same criterion, all indicators with a factor load of at least 0.60 were also maintained. Thus, as the factorial loads of all indicators were satisfactory, the four exogenous constructs (latent variables of first order) and their 49 indicators were empirically validated and therefore answered to the first research objective. The indicators that presented the greatest contributions to their respective constructs are presented in Table 1.

Table 1 Indicators with the greatest contributions to their respective constructs

Endogenous construct	*Exogenous construct*	*Indicator*
-	Performance (dependent variable)	Total costs (ID2)
Managerial	Development	Drug pre-formulation (DP6)
	Management	Project management (GT4)
	Portfolio	Technical feasibility (PF2)
Structural	Resources	Third-party professionals and/or services (RE6)
	Skills	Manufacturing process technology (CP2)
	Organization	Organizational structure (OR3)
Technical	Technical specifications	Analytical methods (ET5)
	Project requirements	Long time needed for development (RP2)
	Regulatory requirements	Compliance with health legislation (RR1)

Source: Research data.

The results of the first round of analysis of the measurement model did not present discriminant validity. For the adjustment, 7 indicators (RE4; ET7; GT3; PF4; RE5; ET8; and GT1) were excluded as they presented high factor loads in more than one construct. After these exclusions, the model showed satisfactory Average Variance Extracted (AVE) values. The resulting model integrating the Performance construct (with 5 indicators) for GDDPs with its three constructs of contributing factors (Structural with 13 indicators; Technical with 14 indicators; and Managerial with 17 indicators) is presented in Figure 2 in its final configuration.

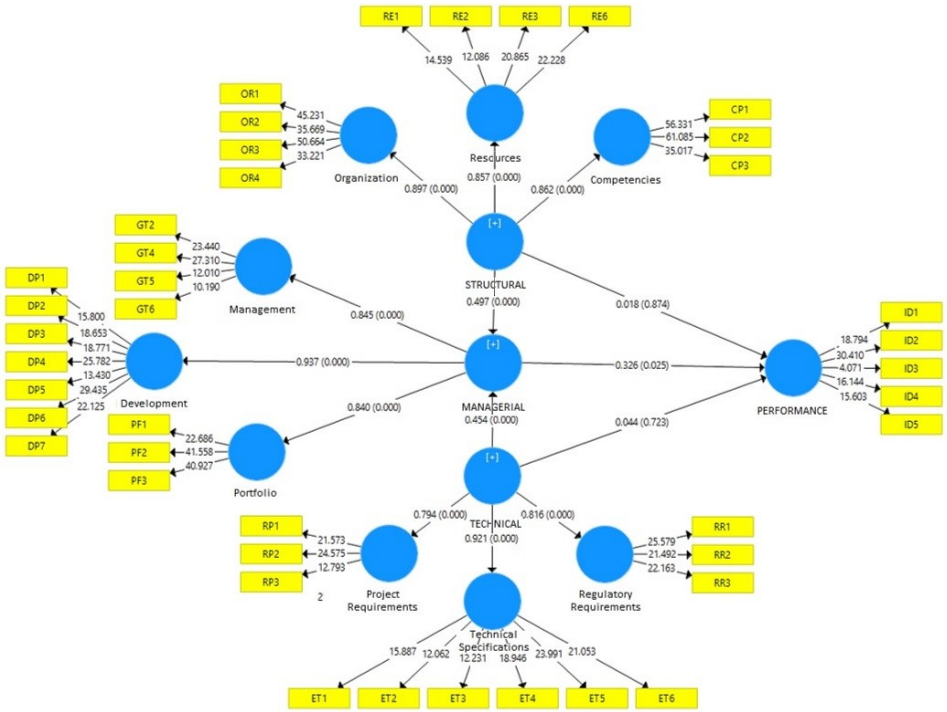

Figure 2 Model of structural equations with coefficients of determination.[1].

The second criterion to attest to the discriminant validity was also met, since the shared factor loads of the indicators with their respective constructs were greater than any of their crossed loads in other constructs. Concerning the analysis of the reliability of the measurement model, although some constructs presented Cronbach's Alpha values below 0.70, the values of the Composite Reliability of all the constructs were satisfactory, indicating internal consistency of the constructs (Hair Jr. *et al.*, 2017).

In the initial evaluation of the structural model, the values of VIF (Variance Inflation Factor) indicate the absence of multicollinearity (VIF < 5). The results of the calculation of the coefficients of determination (R^2) were classified as having medium effects based on the parameters for the area of social and behavioral sciences (Cohen, 1988).

The results for the effect sizes (f^2) indicated that the Structural ($f^2 = 0.406$) and Managerial ($f^2 = 0.354$) constructs have great effects and that the Technical ($f^2 = 0.255$) construct has a medium effect, which are useful for adjusting the model. For the predictive relevance, as the Q^2 values obtained were greater than 0, the accuracy was considered satisfactory (Hair Jr. *et al.*, 2017).

The analysis of the path coefficients of the structural model (Figure 2) indicated that the relationships between the exogenous constructs and the endogenous constructs were significant (p-value ≤ 0.05), confirming the contribution of each of them to the model. Finally, for the verification of the research hypotheses, the nomological validation of the research hypothesis was carried out by considering the p-value ($\alpha<0.05$) and the path

[1] The model is an output of the SmartPLS software.

coefficients (greater than 0.20) (Hair Jr. *et al.*, 2017). The results of the tests are displayed in Table 2 and can also be seem in Figure 2.

Table 2 Results of the hypotheses tests

	Hypotheses	*Path coefficient (β)*	*p-value (α<0.05)*	*Result*
H1	*Managerial difficulties are positively associated with the GDDPs' unplanned performance.*	0,326	0,025	Confirmed
H2	*Structural difficulties are positively associated with the unplanned performance of the GDDPs.*	0,018	0,874	Not confirmed
H3	*Technical difficulties are positively associated with GDDPs' unplanned performance.*	0,044	0,723	Not confirmed
H4	*The influence of structural difficulties on the unplanned performance of the GDDPs is mediated by managerial difficulties.*	0,280	0,001	Confirmed
H4a	*Structural difficulties are positively associated with the managerial difficulties regarding the GDDPs.*	0,784	0,000	Confirmed
H4b	*Managerial difficulties are positively associated with the GDDPs' unplanned performance.*	0,357	0,001	Confirmed
H5	*The influence of technical difficulties on unplanned performance of the GDDPs is mediated by managerial difficulties.*	0,261	0,003	Confirmed
H5a	*Technical difficulties are positively associated with the managerial difficulties regarding the GDDPs.*	0,768	0,000	Confirmed
H5b	*Managerial difficulties are positively associated with the GDDPs' unplanned performance.*	0,340	0,002	Confirmed

Source: Research data.

The results of the path coefficient analysis indicated statistical evidence of the direct relationship between managerial difficulties and the GDDPs' unplanned performance, which confirms the hypothesis (H1). This result is in line with the understanding that the management's characteristics and decisions influence the chances of success of projects (Shenhar, Levy and Dvir, 1997; Mendigorri, Valderrama and Cornejo, 2016; PMI, 2017).

The result of the path coefficient analysis of the Structural → Performance relationship is not significant, leading to the rejection of the hypothesis (H2). This result was not expected, since structural difficulties and deficiencies were considered important inputs and constraints to the projects (Shargel and Kanfer, 2005; Mendigorri, Valderrama and Cornejo, 2016; PMI, 2017). Likewise, the result of the path coefficient analysis of the Technical → Performance relationship had no statistical significance and did not confirm the hypothesis (H3). This result was also not expected, since references were found about the dependency of the projects on the product's and regulatory requirements (Kennedy, 2008; ISPE, 2011; Carmo *et al.*, 2017; PMI, 2017; Anvisa, 2019a).

Regarding the tests to verify the mediation effects, both the relationship between the structural difficulties and the GDDPs performance and the relationship between the technical difficulties and the GDDPs performance showed positive and significant results, confirming H4 and H5. This means that Managerial factors work as intervening variables by receiving Structural factors ("inputs") and translating them into the Performance ("outputs"). In the same way, Managerial factors work as intervening variables by receiving Technical factors and translating them into the Performance.

Considering that the hypothesis H2 and H3 were not confirmed, the results of the analysis partially validated the proposed structural model, what answers to the second research objective that aimed to empirically validate the multidimensional structural model.

5 Conclusions

The findings of the research answers to the question that emerged from the low success rate of the request for marketing approval of GDs and contribute to fulfill a gap in the literature. The results regarding the contribution of each factor to the performance of the GDDPs indicates the components that are the most important influencers. It includes but is not limited to project portfolio management, technical feasibility analysis, resource constraints and product requirements management, organizational culture, integration among departments, risk management, and Quality by Design approach.

Considering that the first launched GDs of a certain drug substance normally achieve a relevant competitive advantage over competitors, the results of the model analysis suggest that the imposition of shorter deadlines for GDDP influences the performance by imposing pressure to compress the schedule, which may have repercussions on other dimensions of the projects due to competing demands (tradeoffs) involving schedule, costs, and quality.

Strategic issues related to project portfolio decisions, technical feasibility evaluation and pre-formulation analyzes have the potential to cause inefficiencies in the use of the resources. From a more operational point of view, the great contribution of the difficulties related to the organizational structure (Structural construct) is possibly related to the dependence of the GDDP on resources and activities from different departments, which often do not adequately answer to the needs of the projects.

In addition to the direct contribution of the management difficulties to the performance of the projects, the confirmation of the mediation effects of the management over other two relationships (Structural and Technical) highlight the importance of the GDDPs' management. The insufficient adoption of project management methodology that emerged from the measurement model analysis is one the major contributors.

Considering the importance for health systems and the scarce literature about GDDPs, this study produced original contributions by proposing and validating 5 performance indicators and 44 contributing factors to the performance of the GDDPs as components of the three constructs: Structural, Technical and Managerial. It also proposed and validated a multidimensional model and its measurement scales. Other contributions are the confirmation that management difficulties and deficiencies directly influence the unplanned performance of the GDDPs, and that structural and technical difficulties and

deficiencies indirectly influence on the unplanned performance of the GDDPs through the mediation of management difficulties and deficiencies.

The output of this research provides insights for improvements on GDDPs. Eventual practical improvements can potentially increase the success rate, favor obtaining competitive advantage and, at the end of the chain, benefit the population and the national health system by providing more access to GDs, in less time and at lower cost.

Care must be taken to generalize the results due to not random sampling. In addition, the focus on the relationship between deficiencies and unplanned results must be considered. The fact that similar studies have not been identified in the literature implies gaps that will not be filled with a single study and that can also give rise to other questions on the topic.

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