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### Article

# Developing a system dynamic model for product life cycle management of generic pharmaceutical products: Its relation with open innovation

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# Article Developing a System Dynamic Model for Product Life Cycle Management of Generic Pharmaceutical Products: Its Relation with Open Innovation

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**Abstract**: The purpose of this study is to identify elements that influence the sale of generic pharmaceutical products during their life cycle in order to achieve more comprehensive planning and to prevent a decline stage of the product life cycle (PLC). We used a system dynamic model to identify the behaviors of demand, supply, and competition as three major subsystems of PLC in generic pharmaceutical products. We first investigated the PLC patterns of 527 medicines to identify their "reference mode", determined the causal loop of the pharmaceuticals phase of PLC based on both an in-depth literature review and experts' opinions, and finally simulated a quantitative dynamic model based on real-world data between 2012 and 2019 from Iran. Based on the results, "total demand and accurate forecasting", "marketing efforts", and "R and D activities of a firm" are the most critical factors involved in the formation of a generic drug PLC. An increase of 20–50% of manufacturers' marketing and R and D activities can raise sales by more than 50% in the decline stage of the PLC. The product life cycle can give generic manufacturers more insights into the processes leading to declining sales of their products. PLC may help to prevent a product from entering the decline stage even if the total demand for a generic drug is dropping in the market.

Keywords: system dynamic; pharmaceutical industry; product life cycle; open innovation dynamics

#### 1. Introduction

Product life cycle management (PLM) is a strategic process to manage a company's products effectively, from production to exit from a market [1]. PLM improves the processes of a company's product development and provides an ability to use product-related information to make better business decisions [2]. In recent years, the healthcare sector has sought helpful protocols and instruments for better decision-making to improve quality of care and to reduce expenditures and insufficient use of resources.

By using the PLM concept in the medical sector, we can create synergy between industrial products and patients [3]. However the nature of the healthcare system—with many actors (new patterns of diseases, patients with different attitudes and expectations, and too many providers [4]), rapid changes in the market, technology, rules and regulations, and new competitors' products—make PLM applications very dynamic. As a result, implementing the PLM strategy needs a stronger evaluation system for new opportunities such as the development of markets, regulations, and technology [5]. The use of product life cycle management in the pharmaceutical industry has also become an undeniable necessity. Evidence has shown that companies with a comprehensive strategy for PLM



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**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). have achieved much success in the financial and non-financial fields such as promoting patient adherence, increasing revenue, improving clinical benefits, and increasing the growth phase of the product life cycle (PLC) [6]. Drug development has usually focused mainly on the management of clinical trials results. Meanwhile, the industrial sector needs more comprehensive approaches such as PLM to introduce new products and to remove defective products from markets that could reduce operating costs and accelerate the development process of products [7].

Effective PLM strategies can also help open innovation in companies. Besides developing new products and technology, open innovation in a firm can be achieved through innovation in other prosses such as business models, marketing activities, or manufacturing [8,9]. Product life cycle management encompasses all aspects of innovation management during the life cycle stages through integrating information and processes [10,11], which were demonstrated in our SD model. Besides managing innovation related to developing new products in the early stages of the lifecycle [12], PLM can coordinate product information through all lifecycle stages. Also, PLM supervises the company's resources and shifts them from parts that may be wasted to somewhere that could be spent on innovation processes [13].

Identifying the main elements affecting the PLC over time has been considered the first step toward efficient product life cycle management [14]. Due to the lack of sufficient studies for product life cycle management in the generic pharmaceutical companies, in this study, we determined the elements to explain the PLC behavior of pharmaceutical products as a complex system of health care in Iran. Generic medicines are essential in offering the same therapeutic effect as brand medicines with more affordability and accessibility [15–17]. As a generic pharmaceutical market, the Iranian pharmaceutical market has grown rapidly in recent decades [18]. For example, the capacity of the Iran's domestic pharmaceutical industry increased from 30% in 1979 to 95% in 2016 [19]. Despite the acceptable progress, they are facing some domestic and international challenges to sale their products. For example, due to the concentration on price-setting by the government (Ministry of Health and Medical Science; [MOHME]) they have little chance to use price competition. As a result, they have tried to raise their market share by increasing their marketing efforts or maximizing profits by decreasing costs [20]. This unusual competitive market increases the importance of PLM in generic pharmaceutical companies. Our main objective is to evaluate this system's behaviors over time to identify the main factors influencing the pharmaceutical PLC and creating the decline phase. Recognizing the elements which lead to the decline stage of PLC in a competitive market of the generic pharmaceutical industry, a company will be able to avoid this phase through proper strategies and maintain their market share and performance.

Related literature and study background. Little is known about the life cycle of pharmaceutical products. For the first time, in 1967, Cox studied the PLC of 754 pharmaceuticals and determined different types of behavior in the PLC of medicines [21]. Other studies have tried to classify pharmaceutical sales patterns in different groups of medicines [21,22], and some of them have investigated the factors affecting PLC. For example, in 1991, one study by Jernigan and Smith discussed that the bell-shaped pattern is the most common form of PLC in medicines [23] or Henry Grabowski (1990) found that increasing the price of drugs leads to increase competition and shorter PLC of medicines [24]. In 1994, Bergstrom and Hoog found that switching between prescription medicines to over-the-counter (OTC) ones can influence the PLC pattern and increase sales volume [25]. Bauer and Fischer (2000) have studied the differences between new and old drugs in the cardiovascular group. They found that early entrants gain maximum sales faster than new entrants [26]. Fischer et al. (2010) reported that the quality and entry order of pharmaceutical products can affect the maximum sales and the time to reach the maximum in PLC curves [27]. Some studies have shown the positive effect of advertisements to physicians, pharmacists, and the patients on the sales of prescription and non-prescription drugs [28–30], and discussed that R and D and quality could affect sales in the pharmaceutical industry [31]. PLC studies in other

products have highlighted the importance of price and competition on the PLC curves. For example, Bass (1969) suggested that people buy a product under the influence of factory advertisements or other buyers' suggestions. [32]. Bass's model explains the diffusion theory, which shows how an innovation spreads through users' perceptions and interactions [33].

System dynamic model. Many studies used the system dynamic modeling to show the different relationships between variables. It has been used to model the different relationships and feedback between the variables in a specific system over time [34] and to analyze the system behavior such as a company, guiding policymakers to manage companies better [35]. The SD approach has been widely used in recent years to solve problems in different healthcare fields, such as supply chain management, healthcare policy, technology and information, aging, and population [36]. For example, Kazemi et al. (2011) proposed a system dynamic (SD) model for PLC and suggested several practical factors in the formation of PLC such as quality, price, product attractiveness, and consumer satisfaction [32]. Using a system dynamic approach, Safri et al. (2012) showed a causal loop for PLC of short-life products and described the factors involved in this cycle. They suggested three new, effective items on PLC such as uncertainty of demand, product innovation, and research and development of the manufacturer [37]. More recently, Carlos (2020) suggested a system dynamic model to evaluate the supply chain in the pharmaceutical industry. In his study, government, biological and economic environments, pharmacies, hospitals, and patients were the main subsystems that established the system behaviors [4]. Moosivand et al. (2019) developed a system dynamic model for the generic pharmaceutical supply chain. They suggested that collaborative relationships with suppliers, new technologies investment, and the establishment of information technology can optimize the supply chain and raise its resiliency [38]. Wu and Mao (2017), Yaghoubi and Hayati (2018), and Akhlaghinia et al. (2018) have tried to show the drug supply chain actors through a system dynamic model and elevate the system performance by showing different scenarios outcome [39–41]. Meanwhile, Abdollahiasl (2013) developed a comprehensive system dynamic model that qualitatively captures all national drug policy elements such as availability, quality, and affordability. Each of these subsystems encompasses their related variables, which are in a relationship with each other [34]. As reported by literature, since the PLC concept is formed with various factors over time, by using the SD method, we can show the different relationships involved in this set and the effects of each one on the sales of pharmaceutical products. Using this approach, we can find the problem's sources and also show the possible outcome of specific strategies to establish sustainability in PLC of generic medicines. Additionally, in this study, we show how effective PLM planning could influence open innovation in companies through our SD model.

#### 2. Materials and Methods

#### 2.1. System Dynamic (SD) Modeling Steps

The SD approach demonstrates the dynamic relationships to understand their possible consequences, and simulates dynamic relationships to discover the effects of different amounts of intervention, scheduling, delay, and feedback [42]. We explain the SD in the four following steps.

#### 2.1.1. Step 1: Problem Definition and Reference Mode

One of the essential steps in dynamic system modeling is the problem definition. In this step, the causes of existing problems in a complex system and its current situation will be investigated to identify the key factors' behaviors known as the "reference mode". For defining the problems in a system, the system dynamic method focuses on endogenous factors in a complex system and tries to decrease unimportant exogenous variables [32]; an exogenous variable is a variable that affects the system but is not affected by it. Therefore, removal of the variable is unobstructed since there is no actual closed system that can consider all of the variables associated with this system. It is preferable to simplify the

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system as much as possible, to include the main system-related variables, and to remove external variables that are not affected by the system [43].

#### 2.1.2. Step 2: Developing a Causal Loop Diagram

In system dynamic modeling, a causal loop diagram is used to establish the relationship between different variables in the PLC system. It is very applicable for explaining the system behavior and for identifying the model boundaries [44].

#### 2.1.3. Step 3: Developing a Stock and Flow Diagram

The casual loop model is then used to develop stock and flow diagrams based on the nature of variables. The stock variable is any accumulation of resources such as people, material, money, etc., and the flow variable is the rate stock variables converted to each other [45].

#### 2.1.4. Step 4: Testing the Model

Confidence tests for the SD models include structure and behavior tests. The structural tests compare the structure of the SD model with the real system structure, so the mathematical equations are compared with the relationship between the elements in the real system. Also, behavior tests determine whether the model behavior corresponds to the actual system behavior [45]. In Figure A1 we have summarized these steps (please see Appendix A for more details).

#### 2.2. Data Collection and Analysis

*Problem definition:* This study identifies the factors involved in the formation of PLC behaviors of generic pharmaceutical products by developing a comprehensive system dynamic model. To identify the "reference mode" and problem definition, we obtained the sales data of 527 generic medicines chosen randomly from official drug statistics [46] between 2002 and 2019. Using Origin Pro 2018 software [47], we plotted the PLC graphs and the fitted regression line with the R-square more than 0.8 [27]. Then we used the three following steps to run a system dynamic model:

- *First*, we conceptualized the dynamic hypotheses based on an in-depth literature review and experts' opinions.
- *Second*, we determined the causal loop of the pharmaceuticals PLC and confirmed their related relationships through a questionnaire to identify the causes of reference mode formation.
- Third, we ran a quantitative dynamic modeling based on real-world data and experts' opinions regarding the Iranian pharmaceutical industry.

*Data.* We used data from 2012 to 2019 for the Valsartan 80 mg (drug A, generic form of Diovan<sup>®</sup>), which belongs to the Osvah Pharmaceutical Co. in Iran (Company A). We chose to use Valsartan 80 mg since the Valsartan 80 mg sales pattern has the greatest R-square (0.8) based on our reference mode (one-peak sales pattern). Also, we had access to Valsartan 80 data between this time, but we did not have access to other products for the study time periods. This is public available data that have been published by the Codal website annually [48].

*Variables and analysis:* We followed three steps here; *first*, we identified the most common variables that have been reported by peer-reviewed literature, then and as a *second* step, we asked eight experts from the Iranian pharmaceutical industry to confirm the variables (See Appendix A, Table A1 for the PLC variables). At the *final* step we asked six academic experts to confirm the relationships between the variables through a designed system dynamic questionnaire. The final confirmed relationships between the PLC elements were entered into Vensim 6.4 DDS software [49] as the casual loops diagrams, and the qualitative system dynamic model were developed. We used a casual loop model to develop stock and flow diagrams based on the nature of variables. Using the formulated

equations based on the developed stock and flow diagrams in Stella 8.0 [50], we have performed the SD analysis in a eight-year period from 2012 to 2019 with one year intervals.

We also tested the model by the following methods: boundaries adequacy, sensitivity analysis, and comparison of the model behaviors with the actual system.

#### 3. Results

### 3.1. PLC Subsystems of Generic Pharmaceutical Products

Our findings showed that the PLC has three endogenous subsystems that establish the PLC behaviors: supplier's subsystem (API supplier, producer, and distributors), demand subsystem (disease, patients, physician, and pharmacies), and competition subsystem. Environmental factors were considered as exogenous elements, which were omitted from the quantitate simulation (See Figure 1.). Each of the three subsystems included some related factors that have been presented in Appendix A, Table A1.



Figure 1. Conceptual model of the product life cycle in pharmaceutical products.

#### 3.2. Determination of Reference Mode

Table 1 presents the results of the historical sales data of 527 drugs between 2002 and 2019 and the fitted regression line with R-square greater than 0.8. Sales trend of more than 20% pharmaceutical products of domestic manufacturers was observed in the overshoot and collapse pattern (Table 1). We were able to explain the interactions which caused the formation of our 'reference mode" overshoot and collapse behavior, which included an upward and downward trend of this behavior that may cause the oscillating behavior seen in 50% of the drugs in this study.

PLC Type	Linear (Upward and Downward Trends)	Binominal (Upward and Downward Trends)	Overshoot and Collapse	Oscillating	No Line Fitted
Number	60	54	110	267	36
Percent	11.38	10.25	20.87	50.66	6.8

Table 1. Different pattern of product life cycle in the generic pharmaceutical products.

#### 3.3. System Dynamic Casual Loops for PLC

According to the conceptual model (Section 4.1), dynamic hypotheses were designed in three parts: suppliers' subsystem, demand subsystem, and competition subsystem.

#### 3.3.1. Subsystem of the Supply-Side

Figure 2 presents the qualitative system dynamic model. As presented, the manufacturer has received active ingredients from the primary manufacturer to produce the final product. The availability of raw material and a capacity budget were crucial to maintaining the production capacity of a company. More sales to distributors can lead to more income (and profit), and the company can raise its capacity (Positive feedback loop R1). However, there are two balancing loops (negative feedback loops B1 and B2) that adjusted the loop R1: the effect of sale forecasting and supply raw materials (Loop B1) and the costs (Loop B2) that control the production and sales to distributors. Moreover, the other primary variables related to the manufacturer are the marketing (Feedback loop R3) and R and D activities (Feedback loop R2), which affect the sales to distributors and the drug quality, respectively.



Figure 2. Qualitative system dynamic model of the pharmaceutical product life cycle.

#### 3.3.2. Subsystem of Demand-Side

The demand subsystem consists of two major elements—"patients and diseases" and "physicians and pharmacies"—and each has its variables and relationships explained below.

- Patients and diseases: the number of patients depends on the disease incidence, which is affected by the population.
- Physicians and pharmacies: physicians play a role as gatekeepers between patients and pharmacies, and pharmacists as intermediate consumers have an essential role in drug selection. We found that loyalty to a manufacturer was an important factor to increase market share. The manufacturer's marketing activities can affect loyalty by increasing physicians' awareness and as a result increase consumption of related products (Feedback loop R4). Two other factors, including "product availability" and "product satisfaction", along with "advertisement" lead to loyalty and ultimately increase patients' consumption as a positive feedback loop R5. The intermediate consumers of pharmaceutical products are pharmacists; they usually choose the manufacturer of prescription drugs based on pharmacy inventory (availability), and quality and manufacturer advertisements (Feedback loop R6). Also, the number of pharmacies can enhance availability by increasing the pharmacies' stock across the country (Positive feedback loop R7).

#### 3.3.3. Competition Subsystem

Competition is another crucial component that affects the generic pharmaceutical market. The competition components consist of availability, price, advertisement, and quality of imported and domestic competitors, the volume of imported medicines, and the number of local producers and importers. Additionally, the total number of antihypertensive drugs from other groups affects the sales of drug A.

*Final causal loops of the pharmaceutical product life cycle.* Using the above-mentioned relationships between the subsystems, we developed a qualitative model of the product life cycle by using Vensim v6.4 DDS software. The basis of the system dynamic method is the maximum elimination of external variables of the system that are not affected from within the system [43]. Therefore, if their effect can be calculated from endogenous variables, these variables can be removed. We excluded the environmental factors as exogenous variables from the quantitative model. We then determined the stock and flow diagram based on the final casual loops of pharmaceutical PLC using Stella software 8.0. We reported our findings in Appendix A, Figure A2.

#### 3.4. Model Simulation: PLC System Behaviors

#### 3.4.1. Subsystem of the Supply-Side

Figure 3 shows the results of model simulation between 2012 and 2019. Based on Figure 3A, flow of raw materials and production rates in the first six years have experienced an upward trend along with the population growth and the increased number of patients, and a decline in 2018 due to reduced demand for drug A and increased again from 2019 onwards due to increasing demand for drug A. Product satisfaction has experienced a general increase due to the company's growth in R and D activities, which led to an increase in quality between 2012 and 2019. Meanwhile, loyalty declined in 2018 due to a decrease in the manufacturer's availability and advertising (Figure 3B). These situations, along with the decreased production rate based on incorrect sales estimation in 2019, caused more dropped sales, while total demand has been increasing in the country.



**Figure 3.** System dynamic simulation result during 2012–2019: (**A**,**B**) supplier subsystem; (**C**) demand subsystem; (**D**) competition subsystem.

#### 3.4.2. Subsystem of Demand-Side

The results of the SD model simulation in the demand subsystem are presented in Figure 3C. Due to the increase in Iran's population and the relative stability of the hypertensive disease incidence (15%), the number of users of antihypertensive medicines has been estimated from 10.25 million in 2012 to 10.76 million in 2019 (5% increase). The total consumption of Valsartan 80 mg decreased by 32.8% in 2018 compared to 2017 due to the carcinogenic an-nitrous-di-amine reported in the Chinese raw materials of seven domestic companies (the factory A is not one of these seven companies) by the Iranian Food and Drug Administration in July 2018 [51], which caused the recall of this drug and reduced the demand (Figure 3C). After that, in 2019, the total demand grew again by fixing the contamination of raw materials and the domestic factories' production resumption of this drug.

#### 3.4.3. Competition Subsystem

Based on Figure 3D, the number of domestic competitors increased between 2012 and 2019, while the total consumption decreased in 2018 due to the carcinogenic N-Nitroso dimethylamine reported by the Iranian Food and Drug Administration [51]. Concerning the importation of brand medicines, we observed a declining trend in 2013 (Figure 3D). There were two importer companies for Diovan<sup>®</sup> in the market during the study time (except for 2014, with three importers). After 2015, the importation trend was constant while the domestic production increased mainly during 2012–2019.

The general results of the PLC subsystems simulation are as follows:

The overall demand trend for Valsartan 80 mg increased during the study period. However, in 2018 we observed a decrease due to contamination of API, recall of drugs, and reduced production of domestic pharmaceutical companies. The volume of imports has been almost constant during this period, which has helped domestic companies dominate the market. During this time, company A has not maintained its market share in the last years of the study period due to unstable management in production, advertising, and R and D. Therefore, this company's drug has reached the decline stage of the product life cycle.

#### 3.5. Model Validation

We performed the model boundary adequacy test by using two-step experts' opinions (interview and standardized questionnaires of the dynamic system). As shown in Figure 4, there is a high correlation (Pearson's coefficient = 0.973, *p*-value < 0.000) between the estimated model and the existing system based on historical data.



**Figure 4.** Comparison of historical data (real data) of the numerical sales of Valsartan 80 mg of Factory A with the model behavior.

We performed a sensitivity analysis to test the model and to show the impact of different company policies on the PLC situation (see Figures 5 and 6). For this part, we selected the 'advertisement', 'R and D activities' (determine the quality), and 'distribution points' (determine the availability) as three elements that construct loyalty and determine market share. Our finding is presented in Figure 5.

Figure 5A, compares three scenarios for advertisement activities and their impact on sale between 2018 and 2019. Line 1 in all of the graphs present the basic model. The line 2 (solid red line) presents changes in sales with no decrease in advertisement activities in the last two years; line 3 (solid pink line) shows the changes in sales with a 20% increase in advertisement activities in the last two years; line 4 (solid green line) shows the "50% increase in advertisement activities between 2018 and 2019. Our results show that these three scenarios (lines 2–4) may increase sales by 28–55% compared to the basic model in the last two years, while the demand for drug A declined compared to the previous year (2017). However, from a certain point, further increase in advertising will not have much effect on the sales of products.

Figure 5B, compares two scenarios for increasing R&D activities and their impact on sale during 2017–2019. The line 2 (solid red line) presents a 20% increase in R and D activities; line 3 (solid pink line) presents a 50% increase in R and D activities during 2017–2019. Based on the results, increasing R and D activities between 2017 and 2019 may raise sales in 2018 and 2019 due to the delayed effect of R and D activities on loyalty (Section 3.4.2). Although its impact is not as significant as the advertisement, it can be considered as a long-term strategy for increasing sales when the market situation is dropping for a specific drug.

Figure 5C, compares two scenarios for the number of distributors and their impact on sale during 2018–2019. Line 2 (solid red line) presents no decrease in the number of distributors; line 3 (solid pink line) presents a 50% increase in the number of distributors in 2018 and 2019. Based on those results, the increase of the distributors did not have much effect on the sales amounts.

Figure 5D, shows the mixed effect of the above scenarios on sales based on the maximum increase of the considered variables in each category mentioned in parts A, B, and C (line 2), and also on the increasing production rate based on accurate estimation of total demand (line 3, 20% increase in production rate). Based on line 2 (solid red line), by increasing 50% of the advertisement, R and D activities, and distribution points together the company raised the sales up to 51% and 79% in 2018 and 2019, respectively. Also, line 3 (solid pink line) shows a modification of the production rate based on accurate demand estimation in 2018 and raising it along with other scenarios may increase the sales by more than 100% in 2019 and prevent the decline stage of PLC.



**Figure 5.** Numerical sales in different scenarios for the SD model between 2012–2019: (**A**) different advertisement amounts, (**B**) different R and D amounts, (**C**) different distributors number, (**D**) increase in advertisement, R and D, and number of distributors. Line 1 in all graphs presents the basic model.



**Figure 6.** Numerical sales in different scenarios of API and warehouse planning between 2012–2019: **(A)** API availability related scenarios, **(B)** API supply and planning related to production rate and warehouse stock related scenarios.

In the next part of our sensitivity analysis, we investigated how some changes in API and warehouse-related variables that were constant during the study can affect sales due to their effect on the production rate. Figure 6A, shows two scenarios for the API availability and its impact on sales between 2012–2019. Line 2 (solid red line) presents a 20% decrease in API availability in the country; line 3 (solid pink line) presents a 50% decrease in API availability in the country during 2002–2019. Based on those results, a decrease in API availability can reduce sales to a great extent in 2015–2017. In the initial years of production, it may be due to the initial API stock (which was higher than the production rate in the first two years). The decrease of API availability had not affected the sales. Also, in 2018 and 2019, decreasing API stock has not affected the sales due to the low production rate.

Figure 6B, presents two scenarios for the API supply and their impact on sale during 2012–2019. Line 2 (solid red line) presents a two months decrease in the supply delay time (three months to one month); line 3 (solid pink line) presents a two months decrease in the supply delay time and a 20% increase in the API order rate. Based on line 2, the effect of decreasing API supply time could be seen during 2015–2017. They had no impact in 2018, since the demand for drug A had dropped and the residual factory stock had been enough to supply the market demand. Also, due to a decreased production rate in 2019, the API order (and so the production) raised sales between 2015 and 2017. Compared to 2018, total demand increased in 2019.

#### 4. Discussion

This is the first study attempt to investigate the life cycle of generic pharmaceutical products using a system dynamic method in Iran. In this study, the overshoot and collapse patterns were considered as a "reference mode" for the system dynamic model; the behavior of supply, demand, and competition subsystems as components of the pharmaceutical PLC were investigated throughout the formation of this pattern. We also examined the role of different policies of the manufacturer to prevent the reduction of product sales in the decline stage of the product life cycle.

Based on the results, more than two-thirds of the generic medicines in Iran have experienced at least one decline stage during their life cycle. We found this problem was caused mainly by the lack of a comprehensive plan to monitor the sales trends of generic drugs and forecasting systems based on that, production planning problems, unstable policies in R and D activities, and marketing management. Our study's main strength is to

demonstrate how generic pharmaceutical companies can minimize or eliminate the decline phase of PLC through inside managerial strategies.

#### 4.1. Elements That Determine the PLC of a Generic Medicine

Sales forecasting and production planning. The most crucial factor determining PLC of generic medicine is the general trend of demand for a product in the market and the forecasts made based on that trend. Therefore, periodic monitoring of the sales data in the market is crucial for planning of future production. Studies have shown that sales forecasting is an essential factor from various aspects, such as allocating the optimal production budget, planning the employees of the production sector, and determining the inventory of the factory [52,53]. In this study, the importance of sales forecasting accuracy was well demonstrated when market demand was increasing. Still, the factory reduced its production compared to the previous year, and therefore sales dropped. One helpful strategy to increase sales forecasting accuracy in a competitive market is to have close relationships with customers [54]. Based on our results, keeping in contact with physicians and pharmacists as two intermediate customers of generic drugs can help increase the sales forecast accuracy. Also, studies have shown that reviewing the competitors' sales history is another point that can increase the sales forecasting accuracy [55,56]. The pharmaceutical companies in Iran, with many competitors, should constantly monitor competitors' sales for more accurate forecasts and develop suitable strategies based on the PLC stage.

Our sensitivity analysis results showed that in the maturity stage of PLC (i.e., when the overall demand trend for a generic drug in the market is high), increasing API orders or decreasing the API supply delay time (and therefore increasing the production rate) could raise the peak of PLC since the production rate was below the demand rate in this period. This effect cannot be seen in reducing the API supply delay time at the decline stage due to reduced demand. The company needs other strategies such as more marketing efforts to sell the residual number of produced drugs by the push mechanisms [33].

Based on our results, three main elements determine the market share: availability, marketing, and R and D activities of the manufacturer. Our analysis has shown that by increasing these elements and modifying the production rate based on actual demand, a company can prevent the decline stage of PLC.

*Research and development activities.* R and D activities (which cause increased product quality) can significantly increase the sales of pharmaceutical products during the decline of the product life cycle. Along with our results, studies have shown that modifying a firm's R and D activities can return product sales in the decline stage or drop the product [57]. However, we cannot ignore some challenges affiliated with the Iranian generic pharmaceutical companies such as setting MOH prices that may lead to a lack of companies' resources to invest in R and D. It is fair to say that they rely on formulation rather than R and D-based activities, not a competitive market. At the same time, there is little interest in exportation either depending on the domestic market or the burden of sanctions [58–60]; as a result, there is little exportation to neighboring countries [61,62]. Considering all challenges as mentioned earlier, planning R and D activities through cost-effectiveness, such as merging with marketing sectors, the Iranian pharmaceutical companies can gain more profits (at least from the existing domestic market).

*Marketing*. The significant role of marketing activities on the sales of pharmaceutical products has been reported by previous studies [31,53,63,64]. Studies have shown that advertising increases the awareness of people and physicians about the drug and that depending on the gained reputation for a manufacturer, the use of the company's products and sales will increase [32,65]. Some studies have shown that this awareness exists among pharmacists, and the manufacturer marketing activities such as direct referral of factory representatives to pharmacies or the use of internet marketing methods as well as creating financial incentives in pharmacies may increase pharmacists' recommendations to use a particular drug and increase its sales [30,66]. Concerning generic pharmaceutical products, the physician who prescribes the drugs and the pharmacy that delivers them to the patient

are the two essential elements of advertising targeting. Studies have also emphasized the role of both product quality and marketing activities in customer satisfaction [67,68]. Effective marketing and the exchange of information about product quality significantly affect product sales [68]. Other studies have shown that quality can prolong the growth phase of PLC, shorten peak sales, and increase peak sales [27].

In other words, integration of R and D and marketing can increase the companies' performance [69,70] through cost reduction, resource and risk sharing, new technologies access, and entering new markets [68]. For the generic pharmaceutical industry with few financial resources for investment in the R and D sector [59], the integration of marketing and R and D sectors can reduce the costs and increase the company's performance due to more coordination and cooperation of these two parts.

Availability. Concerning the availability element, a more than 27% increase in distribution points has little impact on sales due to the development of good coverage of these distributors nationwide. It is mainly due to the same products in the distributors' portfolio [71]. In 2014, Izadi and Kimiagari showed the optimum distribution centers in the generic pharmaceutical industry, such as Iran, with 9–11 distribution centers. Besides maintaining the proper accessibility to drugs in the country, the optimum number of distribution centers leads to more integration and coordination between distributors and manufacturers and reduces inventory-holding costs [72]. Another study showed that by mechanizing the distribution points, reducing the number of distributor companies can increase control and supply chain efficiency in the generic pharmaceutical industry [73]. So, according to similar products in the portfolio of distributors companies, generic manufacturers should consider the number of distributors they are in contact with as a strategy to optimize their product availability and reduce cost.

#### 4.2. System Dynamic Model of PLM and Open Innovation

With more advances in industries, firms are shifting towards intelligent manufacturing planning with dynamic multi-factor modeling, simulation, and smart decision-making systems to boost production capabilities [74]. Due to the complexity and variety of portfolios in such a modern product development environment, the PLM can reduce product development cycles, quality problems, and cost [75]. At the same time, it can innovate the firms' products and business strategies, paving the way for open innovation, leveraging the intellectual assets, and enhancing competitiveness and performance [76].

As various actors are involved in the PLM system over time [39–41], the system dynamic model of PLM includes all needed characteristics (multi-scales, capacity for showing different relationships and feedbacks, strategic planning) [34,35] to utilize various methods towards providing aspects of product lifecycle management [77]. Product lifecycle management systems allow firms to integrate all of the business processes and information related to products portfolio at every managerial and technical organizational level [77,78]. Concerning data management, the PLM supports firms to administer a wide range of product information through the lifecycle stages; it consists of information related to the design of a product or service, market information, customer requirements, and all of the stakeholders involved in the supply chain [79]. This outside-in company's flow of information is necessary to perform open innovation processes and find new opportunities in the market [80].

Our developed SD model helps innovative processes in the generic pharmaceutical companies in three manners:

*First*, the PLM model shows strategies for enhancing production efficiency through proper raw material planning based on accurate sales forecasting. Inefficient production leads to resource wastes and reducing productivity, as an essential element for innovation [13].

*Second*, we have shown the importance of information sharing—as the core of open innovation [81]—through the PLM processes differently. Studies have shown that constant monitoring and acquiring customers' needs [82] and competitors' offered services [83] is

a critical strategy for knowledge transfer in open innovation processes [81] and should be considered as a crucial strategy for accurate sales forecasting and production planning for companies. Also, the share of information between marketing and R&D through the integration of these two parts could help both works with more coordination and meet customers' needs.

*Third*, the SD model shows how raising the producer loyalty throughout enhances the customers' (physicians and pharmacists) satisfaction. Sharing more information from outside a company about customers' needs (physicians, patients, families), besides increasing loyalty, can involve customers as part of innovation at the beginning, developing, or changes in products; this may lead to more customers' loyalty as a part of open innovation [84–86].

Overall, developing effective PLM strategies in firms—which were developed in detail in this studymay help open the innovation dynamics by involving all of the sectors and stakeholders in its implementation and benefits companies by more coordination, integration, and sharing more information between internal and external sources to achieve the goals [87,88].

Some aspects of this study need explanations. Regarding system dynamic modeling, it is not always possible to collect all required information from the real world in practice; researchers have used different techniques such as sampling and averaging the measured data to estimate data and to run models. We agree that the estimated information may be different from the actual data. In this study, we tried to minimize these limitations as much as possible by using existing data and expert opinions.

#### 5. Conclusions

This study used data between 2012 and 2019 from the pharmaceutical industry in Iran to simulate a system dynamic model. We found that "the demand trend for a generic medicine in the country", 'accurate forecasting', and 'marketing and R and D activities', are three crucial elements of the PLC for the Iranian pharmaceutical industry with generic products. The study provides information about PLC components and their relationships and encompasses the consequences of different decisions on this complex system through a generalizable simulation approach. The study results provide a clear view of the generic pharmaceutical industry that the generic pharmaceutical companies in other countries can benefit from it.

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### Appendix A



Figure A1. System dynamic modeling steps.

Table A	1. Pro	duct life	cycle	subsystems	and	related	variabl	es
			2	2				

	Variables	Unit
	Factors related to supply of raw materials	
	1. Inventory of raw materials	Percent
	2. Delay in supply of raw materials	Number
	Factors related to manufacturers	
	3. The amount of advertising activities	Percent
	4. Production rate	Number/year
	5. Warehouse stock	Number
	6. Sales to distributor	Number/year
	7. Company income	Rials
щ,	8. Market share	Percent
ste	9. Costs	Rials
sy	10. Research and development activities	Percent
sul	11. Production capacity	Number
ly	12. Sales forecast	Number
dd	13. Raw material order rate	Number
Su	14. Delay in raw material order	Number
	15. Total number of product portfolio	Number
	16. Product quality	-
	17. Product availability	-
	Factors related to distributors	
	18. Number of distribution points	Number
	19. Sales to pharmacies	Number/year
	20. Discount rate (incentive)	Number
	21. Percentage of distribution centers	Number
	22. Warehouse stocks of distributors	Percent

	Variables	Unit
	Factors related to the disease and patients	
	23. Population	Number
	24. Mortality rate	Number/year
	25. Birth rate	Number/year
	26. Disease prevalence	Number
	27. Total number of people sought for treatment	Number
R	28. Total consumption of antihypertensive drugs	Number/year
iter	29. Number of people treated	Number
sys	30. Price satisfaction	-
qn	31. Quality satisfaction	-
ds	32. Product satisfaction	-
an	33. Existence of insurance coverage	0/1
em	Factors related to the pharmacies	
Ď	34. Number of pharmacies	Number
	35. Warehouse stocks of pharmacies	Number
	36. Sales to patients	Number/year
	37. Loyalty to the manufacturer	-
	Factors related to the physicians	
	38. Product satisfaction	-
	39. Loyalty to the manufacturer	-
E	Factors related to the competition	
ste	40. Number of competitors from other families	Number
sy	41. Consumption of competitors from other therapeutic families	Number/year
Sut	42. Consumption of domestic competitors of drug A	Number/year
Ę	43. Number of domestic competitors	Number
Ē	44. Number of foreign competitors	Number
) eti	45. Price of foreign competitors	Rials
lu	46. Volume of competitors imports	Number/year
ۍ	47. Import volume of competitors of the same family A	Number



**Figure A2.** Stock and flow diagrams of generic pharmaceutical PLC in Stella software 8.0. Notes: Some assumption was considered to develop the system dynamic model: (1) The drug is a prescription medicine. (2) Iran's FDA sets the price of all generic medicines, and the medicine are under the insurance coverage, so all of the producers' price are the same and price satisfaction was considered 100%).

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