ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR – ABEN
2019 International Nuclear Atlantic Conference - INAC 2019
Santos, SP, Brazil, October 21-25, 2019

Agência Brasileira do ISBN
ISBN 978-85-99141-08-3

STUDY OF THE DEMAND-SUPPLY FOR RADIOPHARMACEUTICALS IN IPEN: A SYSTEM DYNAMICS APPROACH

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ABSTRACT

Radiopharmaceuticals are unique medicinal formulations containing radioisotopes and are used in nuclear medicine for diagnosis and/or therapy for chronic diseases such as cancer, alzheimer and cardiac disorders. The increase in the incidence of these diseases in the Brazilian population and the trend of increasing demand for radiopharmaceuticals motivated the elaboration of this work from a system dynamics perspective. The aim of this paper is to present a System Dynamic Model for simulating the interaction between demand, capacity, workforce and production of radiopharmaceuticals produced by IPEN. The validity of this model is verified by running in Vensim PLE software using historical data. The model was based on the generic structure of commodity markets and main variables were considered to represent the market polices. The preliminary model presented was able to capture the expected behavior of the industry of radiopharmaceuticals. Two alternative scenarios were developed, one to analyze the impacts of investment in infrastructure of IPEN and the other to investigate the workforce investment. As result, the model performed well in representing the behavior of the market. In addition, scenario tests showed that investment in infrastructure and workforce investment have a significant impact in the dynamic of the system.

1. INTRODUCTION

Radiopharmaceutical is a medicine that differs from others because it is labeled with radioactive materials. It connects two components: a drug and a radioisotope. The use of radioisotopes in medicine is certainly one of the most important social applications of nuclear energy. [1].

From 1956 to 2006, the Union, through the *Comissão Nacional de Energia Nuclear* (CNEN), held a monopoly on the production, marketing and use of radionuclides for medical, agricultural and industrial use. Following Constitutional Amendment No. 49 of 8 February 2006, CNEN lost its monopoly on the production of short half-life radioisotopes. [2].

CNEN's main production unit is the *Instituto de Pesquisas Energéticas e Nucleares* (IPEN), which accounts for 95% of radiopharmaceuticals used in hospitals and clinics in Brazil. [3].

The production of radioisotopes and radiopharmaceuticals for use in nuclear medicine at IPEN has significantly increased demand for these products over the years and currently over 38 products are listed in the IPEN catalog. [4].

Nuclear medicine shows enormous potential in the treatment of heart disease, neuroendocrine and various cancers. According to studies conducted by the International Agency for Research on Cancer (IARC) published in February 2014, the number of cancer cases will increase by 50% by 2030, when nearly 22 million cases will be diagnosed worldwide compared with 14. million in 2012. This will be due to a sharp rise in the disease in developing countries. At the same time, deaths will increase from 8.2 million to 13 million per year. These trends are accompanied by population growth and aging and the adoption of risky habits such as smoking and sun exposure. [5].

System Dynamics (SD) is a method for modeling relationships between different variables of a complex system. There are many market studies using SD, but none focused on the radiopharmaceutical market.

The research question is: “How long can IPEN meet the demand for radiopharmaceuticals?” According to IARC, the radioisotope market should be larger in developing countries due to the increasing awareness of people about radioisotopes, increasing the incidence of chronic diseases, such as cancer, and population increase. Therefore, this analysis may allow us to understand the trends of this sector and to evaluate the implementation of policies and incentives to increase its production.

This article aims to examine the relationships of variables in the decision-making process regarding the productive capacity and investments of the workforce in IPEN Radiopharmacy.

2. RADIOPHARMACEUTICAL MARKET

Considering that much of the nuclear sector's activities are a monopoly of the union, market behavior is restricted and essentially depends on federal government policies and guidelines. [6].

The start-up of private short-lived radiopharmaceutical producers affected demand. CNEN is currently studying options for its operations in this market. [6].

The production of radiopharmaceuticals has particular characteristics due to the natural phenomenon of continuous radioactive decay, not allowing this input to be stored, requiring extremely efficient production and supply logistics. For this reason, some factors become critical, including the Public Service management model. The proper functioning of national nuclear medicine depends fundamentally on radiopharmaceuticals produced and supplied by CNEN. Thus, any difficulty in this area is reflected in the country's nuclear medicine activities. [6].

The relationship of CNEN's radiopharmaceutical units with their customers is formalized through a service agreement where the price of products is set by CNEN for all its units. The units have customer service by email or telephone that is the main channel for requesting the supply of radiopharmaceuticals. The frequency and quantity ordered depends on the exams scheduled in clinics and hospitals.

IPEN also has a specific system for ordering radiopharmaceuticals on its website. Radiopharmaceutical withdrawal is performed only by companies authorized by CNEN. The funds raised go to the Union's single account. The *Sociedade Brasileira de Medicina Nuclear* (SBMN) is the class association that brings together most of the country's nuclear physicians and represents their interests in CNEN [6].

In the radiopharmaceutical market, the main associated risks are due to the fact that some inputs are imported, especially the molybdenum-99 (Mo-99) used in the production of the 99m Technetium Generators. In this case, CNEN is dependent on the supply capacity of the world market, the prices practiced in that market, as well as the exchange variation. The main strategy used by CNEN is the diversification of the number of suppliers, as far as possible.

In 2014, CNEN acquired Mo-99 from Argentina, Canada and South Africa and in 2015 began the acquisition of Russia. However, the definitive solution to this external dependency will only come when the implementation of the *Reator Multipropósito Brasileiro* (RMB), that will be completed in 2025, depending on the regularity of investments by the Federal Government.

With the increase in prices of international suppliers, CNEN rebalances the price of its radiopharmaceuticals to the domestic market, but this adjustment is not welcome by the SBMN. It is necessary to build an integrated policy with the participation of CNEN and the Ministry of Health. This strategy is appropriate for the expansion and strengthening of national nuclear medicine. [6].

Brazil has a growing demand for nuclear medicine services, with a rate of around 10% a year and one of the main challenges of the Brazilian nuclear sector is to meet this demand and allow the population increasingly to have access to these services [6].

According to the management report for the financial year 2018, one of the objectives is to increase the supply and production capacity of radioisotopes and radiopharmaceuticals in the country. CNEN aims to reach the supply of 550 Ci radiopharmaceuticals per week by 2019. [6]. Figure 1 represents the history of IPEN production.

The federal government's strategic guideline is to promote science, technology and innovation and to stimulate development with increased productivity, competitiveness and sustainability. [6].

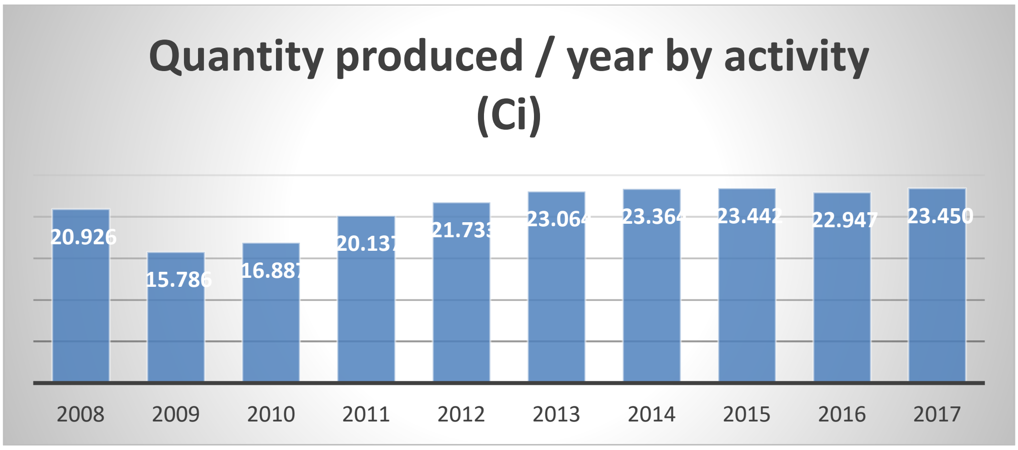

Figure 1 – IPEN Production

3. MATERIALS AND METHODS

This chapter deals with the methodology used for the development of the dynamic model of the radiopharmaceutical industry. The chapter begins by making considerations on the choice of Systems Dynamics as research method and proceeds to describe the process of formulation of the dynamic hypothesis and formulation of the simulation model.

3.1 Applications of Dynamic Simulation

According to Sterman (2000), a system is characterized as complex due to the multiplicity of its elements (natural, technical, economic and social), due to their interactions and also by the diversity of behaviors and properties that these elements exhibit. A complex system is characterized as dynamic when:

- ⇨ there is strong interaction between the various actors in the system;
- ⇨ there is a strong dependence on time;
- ⇨ has a complex causal structure due to feedback;
- ⇨ there are delays (behavioural or reactional) that are counterintuitive and difficult to predict.

System Dynamics (SD) is a method for modeling relationships between different variables in a complex system and enhancing learning in its internal dynamics. Jay Forrester led the first discussions in the 1960s. Forrester studies provided a set of concepts for understanding and modeling complex systems [7].

SD model these relationships with mathematical equations, structures of stocks and flows, and uses computer simulation models to analyze scenarios [8].

This paper built the system dynamics model using Vensim software, which is the simulation software for improving the performance of real systems [9]. Vensim provides causal tracking of structure and behavior and includes many types of analyzes, such as sensitivity analysis [10].

3.2 Dynamic Hypothesis

The Dynamic Hypothesis presents a theory with an endogenous focus that explains the reasons for the behavior of the system [8].

As stated previously, this work aims to investigate Until when IPEN will be able to meet the demand for radiopharmaceuticals.

The amount of radiopharmaceuticals produced by IPEN depends not only on price but also on many other factors such as production technology, availability, labor cost and many other factors of production.

In order to understand the behavior of the problem under investigation and develop the initial model, the Casual Loop Diagram (CLD) technique was used to capture the hypotheses about the causes of dynamics. CLDs represent the basic components of a system and the relations between them through positive and negative feedbacks. According to (Sterman, 2000), dynamic complexity arises from the interactions among the components over time. This feedbacks loops responds to the most complex behaviors of the systems. The positive connections are self-reinforcing, so an increase in one variable rise the other variable connected. Although, negative feedbacks are self-correcting, act to balance the system and limit the growth with it carrying capacity [8].

Figure 2 shows a positive feedback that self-reinforce the growth of radiopharmaceuticals demand and shows the balance feedback that limits the growth of radiopharmaceutical production.

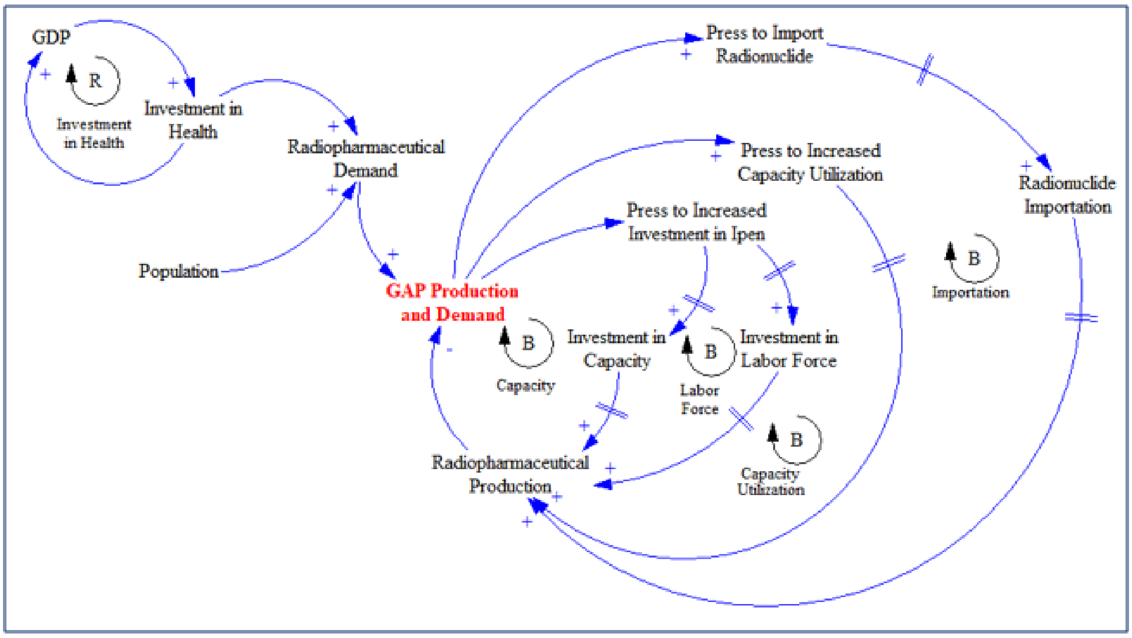

Figure 2 – Casual Loop Diagram – positive and negative feedback

The production adjusts to the demand with delay represented by the time necessary for the adjustment of the production to this demand.

The Capacity represented by the infrastructure required for the production of radiopharmaceuticals is a limiting factor of production and there is a delay between the identification of the need for new capacity, the acquisition of the new capacity and, the installation of this capacity.

The workforce is also a limiting factor as there is a lot of difficulty in hiring people, hired people have no experience and many of the experienced people are already retiring.
Capacity utilization varies according to company policies and capacity adjustment also causes a delay.

The increase in production leads to an increase in the import of radionuclides, which is not always readily available. Requests have to be made in advance and also incurs delays.

3.3 Model Formulation

The proposed model was constructed and simulated using VENSIM PLE plus software version 7.3.5. Stock and Flow Diagrams detail the relations presented in the CLD, emphasizing the physical structure, flow and accumulations of materials and information through the system [8].

The model presented in this paper is based on the generic structure of commodity markets suggested by Sterman (2000). The Stock and Flow Diagram (SFD) developed is divided into 5 sections: Economic and Population Section represented by Figure 3, Health Section represented by Figure 4, Workforce and Productivity represented by Figure 5, Capacity represented by Figure 6 and Production represented by Figure 7.

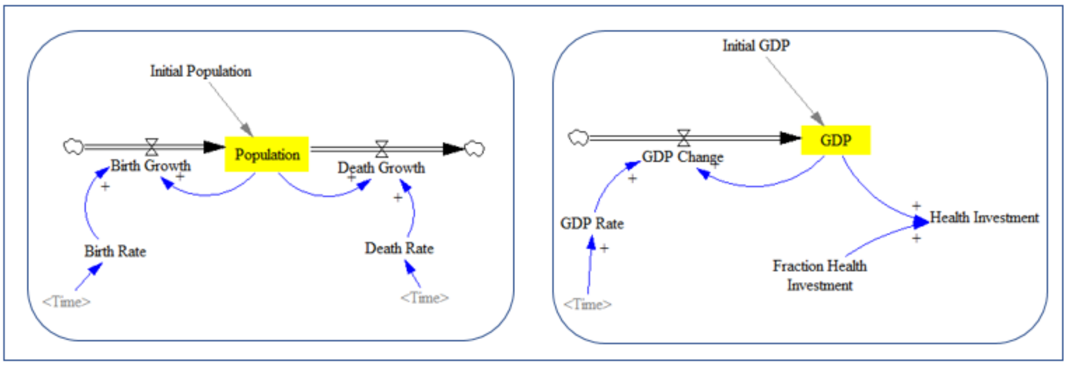

Figure 3 – Stock and Flow Diagram – Populational and Economical Section

The evolution of the Gross Domestic Product (GDP) was modeled because it influences the investment in health. The more investment in health, the greater the demand for radiopharmaceuticals. The population increase also has an impact on the demand for radiopharmaceuticals, since the greater the population, combined with the investment in health, the greater the demand for radiopharmaceuticals.

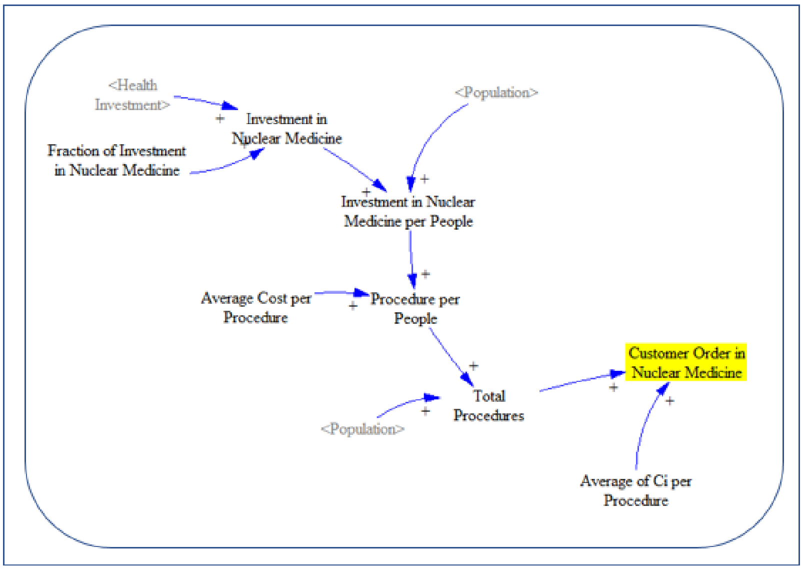

Figure 4 – Stock and Flow Diagram – Health Section

Demand for radiopharmaceuticals, represented by the variable orders from customers in nuclear medicine, depends on health investments, investments in nuclear medicine, and also depends on population size.

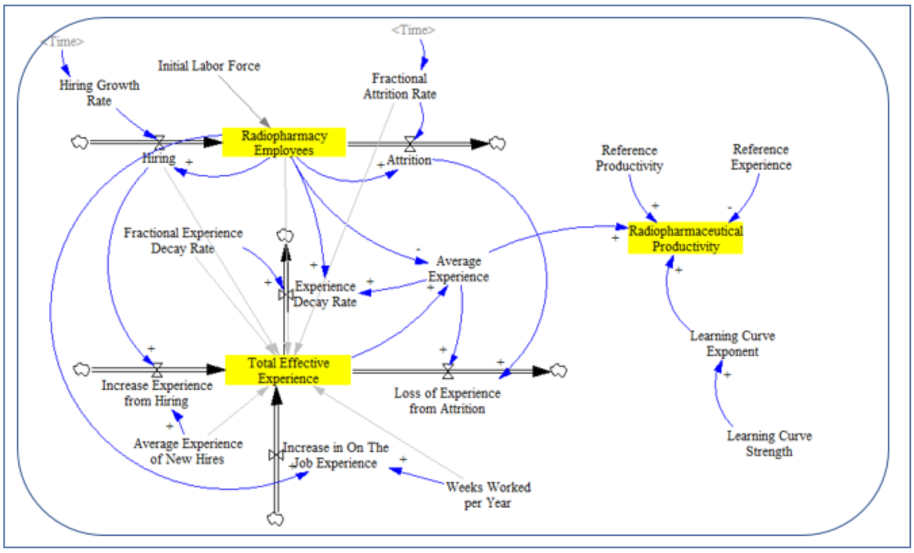

Figure 5 – Stock and Flow Diagram – Labor Force and Productivity Section

The decision to hire new employees, the hiring rate and the fractional attrition rate are assumed by exogenous and vary according to model testing. New employees bring some experience with them; departing employees take their experience with them. In addition, experience increases the longer the employee stays in employment and decreases as workers forget or when process changes make existing experience obsolete. Total effective experience (measured in person-weeks) is the effective number of weeks of service each employee has, plus all employees.

Each hired employee brings a certain effective experience. Employees who leave the workforce carry the average experience with them. Higher average experience should translate into higher productivity. The learning curve theory provides a variety of models for relating experience to productivity.

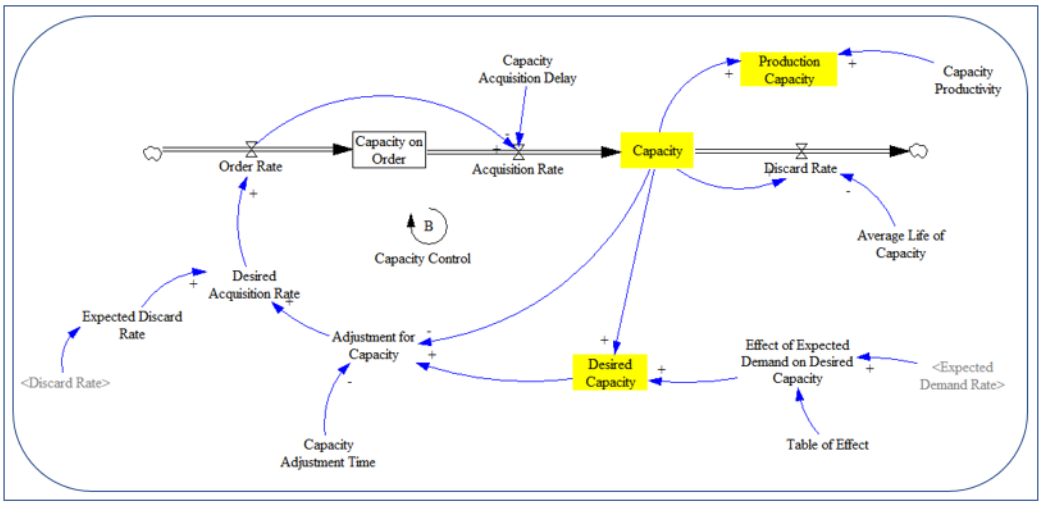

Figure 6 – Stock and Flow Diagram – Capacity Section

The decision to invest in new capacity is based on the desired acquisition rate, which is comprised of two other rates. One is the installed capacity depreciation rate, which must be replaced by new capacity. The other is capacity utilization adjustment.

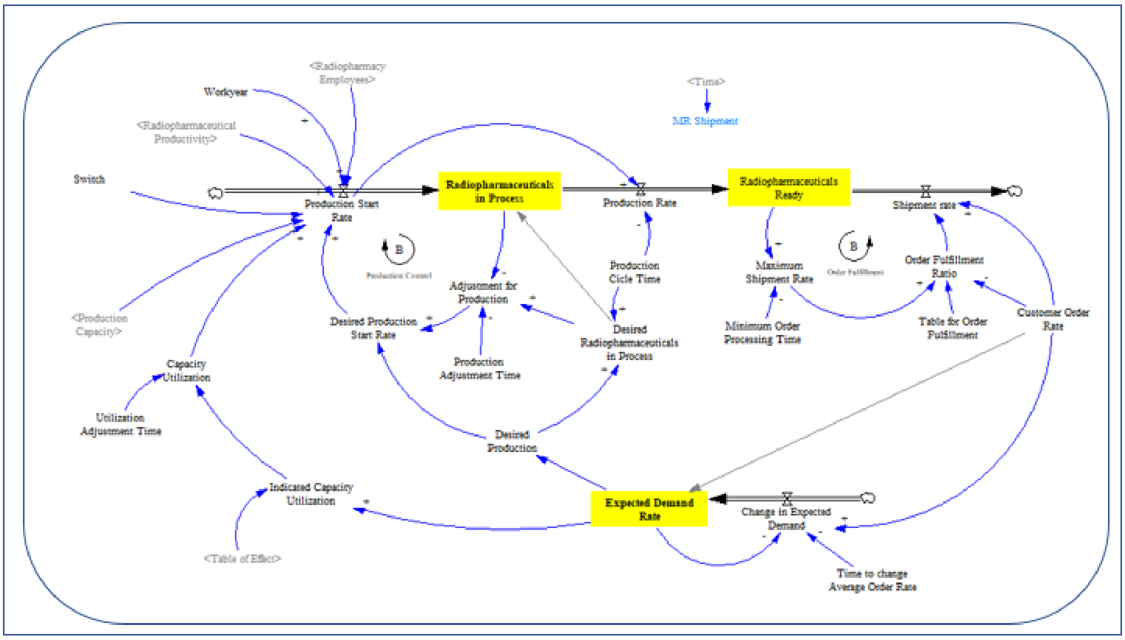

Figure 7 – Stock and Flow Diagram – Production Section

The production is captured as a two-stock chain with radiopharmaceuticals in process and radiopharmaceuticals finished. Backlogs and other stages of processing and storage, both upstream and downstream, not exist in the radiopharmaceutical production process. The order fulfillment ratio is the fraction of orders filled and is a function of the Maximum Shipment Rate relative to the Customer Order Rate.

The maximum shipment rate is determined by finished radiopharmaceuticals and the minimum time required to process and fill an order. Production is modeled as a delay. A third-order delay provides a reasonable distribution of completions around the average Manufacturing Cycle Time.

Capacity utilization captures variations in the intensity of production above or below the normal rate. Utilization may vary due to deliberate management decisions to respond to current production or production pressure (to meet demand) or due to undesired factors such as equipment breakdowns, materials shortages, or shortages of storage capacity for output.

Desired production depends on expected demand, and is then adjusted to correct discrepancies between the desired and actual levels of finished radiopharmaceuticals. Expected demand is modeled as an information delay of shipment data.

Figure 7 shows the stock and flow diagram with these detailed relationships, representing the dynamic behavior of production and demand.

This study used data from documents produced by CNEN, IPEN, DATASUS and documents from recognized institutions in Brazil. The period of analysis was from 2008 (when the CNEN made your data available) until 2030. In this manner, it is possible to assess the tendencies of the market for the next decade.

The validation of a model is focused on the verification of the model structure and the robustness of the model behavior. Forrester and Senge (1980) suggested 3 validations: structure and parameters, under extreme conditions, and dimensional consistency. The structure and parameters were validated based on other studies in the radiopharmaceutical industry and commodity markets. It shows consistency with the sector's behavior. The model was also tested under extreme conditions, by stressing important variables such as customer orders, demand, labor force availability and capacity availability. The results were consistent with the expected behavior. Finally, the dimensions test was done with the software Vensim.

4. RESULTS AND DISCUSSION

According to *Instituto Brasileiro de Geografia e Estatística* (IBGE), the Brazilian population is expected to reach 223 million inhabitants by 2030. As for GDP, according to *Banco Nacional de Desenvolvimento Econômico e Social* (BNDES) studies, considering the government's ability to control the GDP trajectory, it will grow smoothly until 2030 (Figure 8).

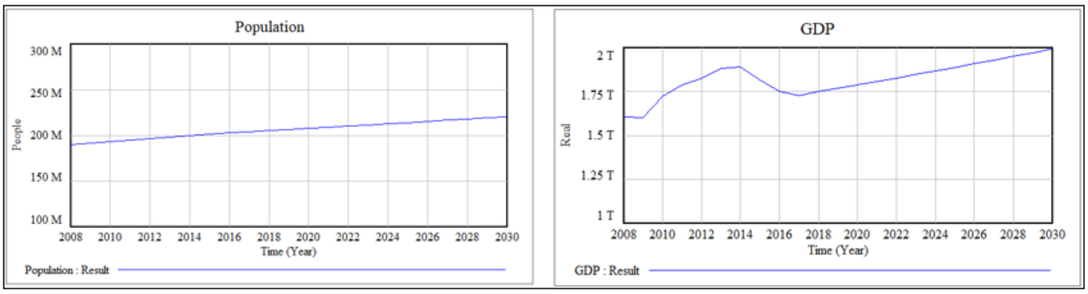

Figure 8 – Growth of population and GDP

In the economic and population context, there is a soft growth, leading to a relatively proportional increase in demand for radiopharmaceuticals, represented by customer requests as showed in Figure 9.

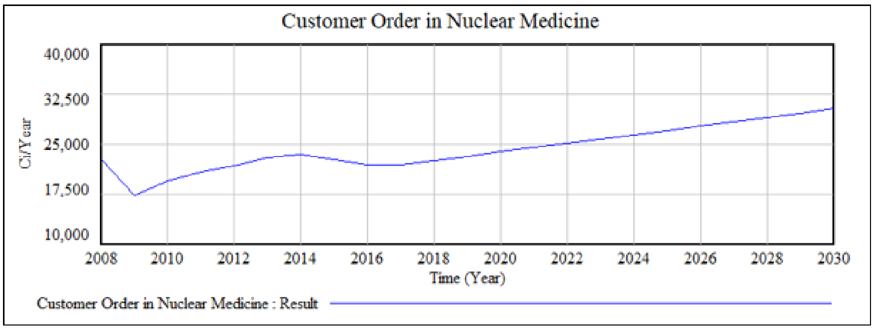

Figure 9 – Demand for radiopharmaceuticals

Today IPEN's radiopharmaceutical production meets demand, but if it continues in this way, it may fail to meet this demand as showed in Figure 10, where Standard Production represents IPEN's radiopharmaceutical production and customer order represents the current and expected demand. Figure 10 shows that there was a period in which IPEN was unable to meet demand due to problems of supply of molybdenum, but to this day IPEN has managed to completely meet the demand. Assuming that IPEN now works to the limit of its capacity, if it continues in this way, it cannot meet the demand.

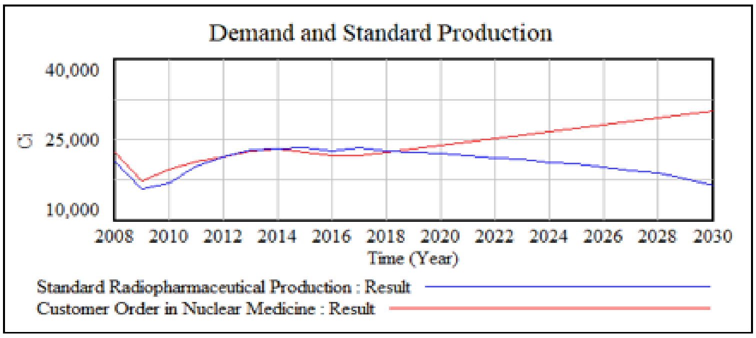

Figure 10 – IPEN radiopharmaceutical production x demand

The production of radiopharmaceuticals from IPEN depends on several factors, mainly infrastructure, labor and raw material availability, where today the main raw material used is molybdenum. In this study, we will only represent infrastructure and labor.

Today, IPEN has an experienced workforce, but there are no hiring and the current workforce is retiring and there is no passing of knowledge. Figure 11 demonstrates the projection of the decrease in the workforce and IPEN experience.

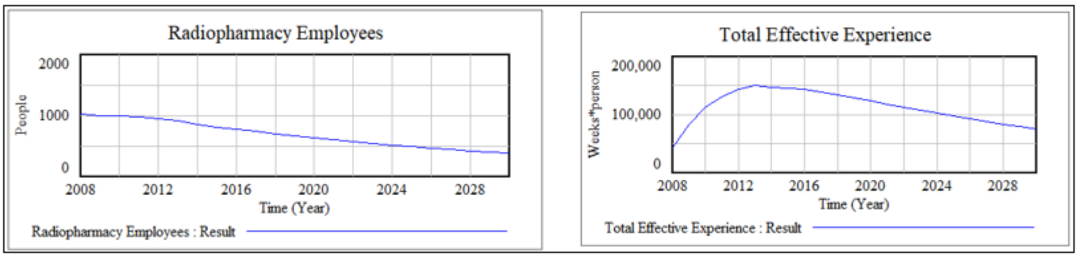

Figure 11 – Labor Force

IPEN's radiopharmacy has an old infrastructure that needs to be refurbished and extended to meet *Agência Nacional de Vigilância Sanitária* (ANVISA) standards of good manufacturing practice. Figure 12 shows IPEN's current infrastructure, considering its 30-year lifespan.

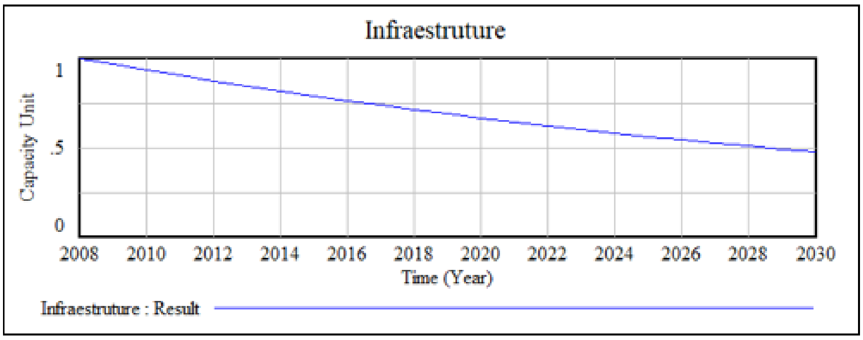

Figure 12 – Infrastructure

A scenario-based analysis was done in order to assess the behavior of the model. These analyses set the switch in two positions: 1- Capacity (Figure 13); 2- Workforce (Figure 14).

In scenario, 1 capacity doubled in 2021 and the result is shown in Figure 13. An increase in production capacity above demand in 2021 is observed and this fall back to a level below demand in 2028.

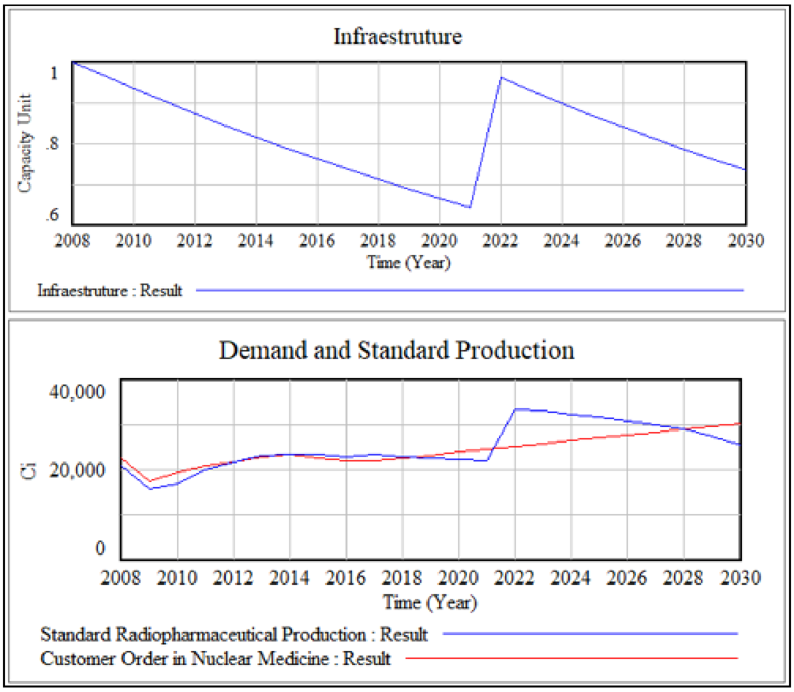

Figure 13 – Scenario 1 – Adjustment of Capacity

In scenario 2 was simulated the hiring of 270 people in 2021. Figure 14 shows the evolution of the staff with this hiring, the evolution of actual experience and productivity. Lastly, the difference between demand and productivity is analyzed considering these contractions. It can be observed that with these contractions, production is above demand until 2028, when it falls again.

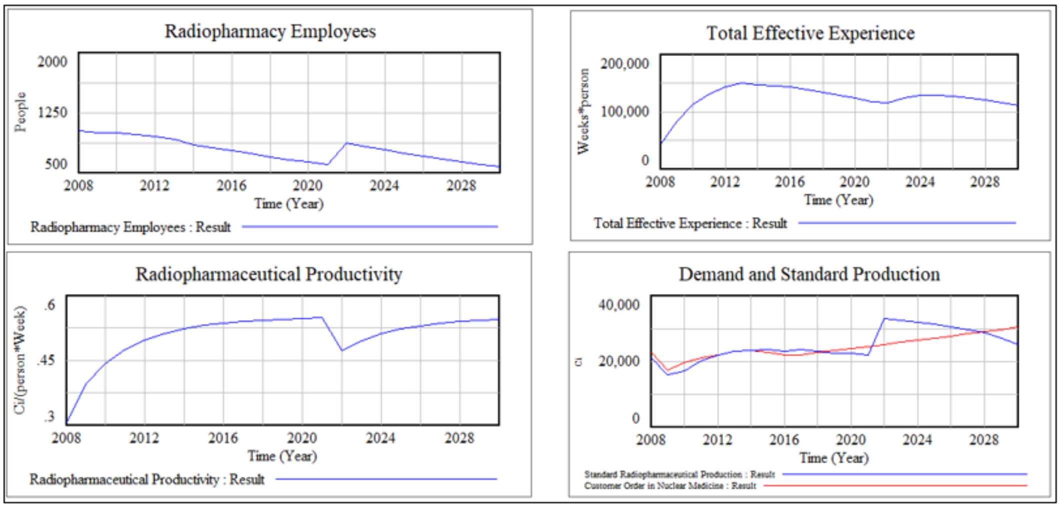

Figure 14 – Production

5. CONCLUSIONS

This paper modeled the production demand and radiopharmaceuticals of IPEN, to allow the analysis of the impact of different variables and market policies in the decision making of the production process. Some of the main variables are considered exogenous in this initial model such as customer order rate, hiring growth rate and attrition rate. The simulation presented capacity and workforce as a production constraint. Because of this limitation, two scenarios were considered, varying workforce and capacity. Both scenarios showed that investments in workforce and capacity release production constraints. For future work, the model can be expanded to find the behavior and relationships of important variables considered exogenous in this work, such as profitability and prices.

ACKNOWLEDGMENTS

The authors would like to thank CEN, FAPESP, and the CPG IPEN/USP for the financial sup port.

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