

# Micronutrients as an Innovation Opportunity for the Pharmaceutical Industry: A Case Study of Vitamin D in Brazil

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## **Abstract**

*This paper aims to demonstrate the micronutrients as an attractive alternative of innovation for Pharmaceutical Industries with limited resources. A case study of vitamin D as a pharmaceutical supplement is launched in the Brazilian Market. The results demonstrate that some opportunities of several new products for populations with nutritional deficiency—the so-called micronutrients for hidden hunger, that is any deficiency unnoticed where micronutrients assume metabolic functions in humans. This deficiency unnoticed lead to disease onset or an organism dysfunction. WHO estimate that more than 2 billion humans are affected by hidden hunger. Scientific studies show that these ills cause serious problems for pregnant women, elderly and children. Thus, the micronutrients in a normal diet comes up the news opportunities for pharmaceuticals industries as well as vitamin supplements. Pharmaceutical industry is the most innovative company in healthcare. Launcher a blockbuster as a new product through of radical innovation is so hard and with higher costs. In this sense, the micronutrients are an attractive alternative of innovation for pharmaceutical industries with limited financial resources. So, pharmaceutical supplements appear as an incremental innovation of known chemical substances.*

## **Keywords**

*micronutrients, vitamin D, public health, pharmaceutical industry competitive intelligence*

## 1. Introduction

According to Sakar (2007), innovate derives from Latin in+novare and its meaning can be expressed as doing something new, renewing or altering something. Drucker (2010) points out that innovating is the ability to transform something that already exists into a resource that generates wealth. Therefore, innovation is the process that includes the technical activities, design, development, and management that result in the marketing of new (or improved) products, or in the first use of new (or improved) processes. It may be a new marketing method, or a new organizational method in business practices, workplace organization, or external relations (Freeman, 2008).

Organization for Economic Co-operation and Development (OECD) highlights innovation encompasses several scientific, technological, organizational, financial, commercial and marketing activities. Technological innovation activities are the set of scientific, technological, organizational, financial and commercial steps, including investments in new knowledge, leading to or attempting to implement new or improved products and processes (OECD, 2005).

In this innovation context, the pharmaceutical industry is a global example of this innovative capability. In 2014, according to IMS HEALTH (2015), innovative medicines accounted 24% of total global drug sales, accounting only 19% of global sales in 2009 (IMS Institute for Healthcare Informatics, 2013; Healthcare Informatics, 2015). In ten years, R & D investment by these companies has reached US\$ 1.2 trillion and should continue to grow there about 2.4% pa. until 2020. Considering the 100 global companies that have invested more in R & D, it is observed that 22 are pharmaceutical companies, outperforming the automotive and electronics industries (Evaluate, 2015).

Innovations are characterized by as radical, incremental, disruptive or frugal. Radical innovations resulted in drugs whose therapeutic indications differed substantially from existing drugs on the market, thus it creating a new class of drugs. Already the incremental is an improvement of an already existing drug and whose performance has been improved significantly or the research of that same existing drug are directed to a second therapeutic indication. Concerning disruptive innovations, they provoke a rupture in established business models. Usually favor the appearance of new products with performance equivalent to the market standard, but lower than the leading product from radical innovation, however, adopts a new approach making it cheaper and more convenient or easier to use. The frugal innovation discovers new business models, reconfigures value chains, and redesigns products to serve users who face extreme affordability constraints in a scalable and sustainable manner. Furthermore, it involves either overcoming or tapping institutional voids and resource constraints to create more inclusive markets (Vieira, 2006; Kotler, 2011).

In this context, the area of human health is the one that has demanded the different types of innovation for the improvement of the quality of life of humankind. According to the Food and Agriculture Organization of the United Nations (FAO), about 800 million people remain chronically undernourished and more than 2 billion suffer from micronutrient deficiencies (essential vitamins and minerals required from diet to sustain cellular functions and molecular mechanisms of virtually all

living things). Although very small amounts of these micronutrients are required in the human body, MicroNutrient-Deficiency (MND) can lead to health impacts as deaths if left untreated. The most common deficiencies in the human body are vitamin A, D, folic acid, iron, iodine and zinc. However, there are several other MND disorders (Bailey, 2015; Fao, 2016; West, 2012).

Unfortunately, there are no biomarkers available for all micronutrients or existing biomarkers are not practicable/feasible for widespread evaluation or use in the clinical environment (Bailey, 2015). In this way, Brazilian pharmaceutical laboratories have made efforts to launch several concentrations of vitamin D in the market to act in the public health area, specifically MND.

## 2. Method

This is a descriptive study involving data mining in bibliographical references in indexed scientific databases such as SCOPUS, Medline (PubMed) and official portal websites as IMS Health (<http://www.imshealth.com/>), Food and Agriculture Organization of the United Nations (<http://www.fao.org/home/en/>) and National Health Surveillance Agency (ANVISA-Brazilian term, <http://www.portal.anvisa.gov.br/>). In order to identify the state of the art of the subject in question, searches were carried out in the databases indexed with the following terms: adult, biotin, birth, child, chrome, deficiency, disease, essential, folate, folic acid, food, hidden hunger, infant, innovation, iodine, iron, micronutrient, mineral, nutrient, nutrition, old, vitamin D, pregnant, pregnancy.

## 3. Results and Discussions

### 3.1 *The Hidden Hunger*

Historically, hunger has been one of the greatest woes of humankind. About 30 million die in China between 1958 and 1961 and 4 million in India in 1943. In this sense, continues to plague sub-Saharan Africa. However, even with this scenario, far fewer people are hungry today than in the past due to the adoption of mechanization, agrochemicals and agricultural techniques to obtain high crop yields during the last 50 years. Thus, the average per capita calories consumed in the developing world jumped from around 2,000 Kcal to over 2,700 Kcal (Muthayya et al., 2013; Shekhar, 2013).

However, there is one type of malnutrition that continues to devastate many populations: hidden hunger which is the invisible deficiency in the diet of essential vitamins and minerals. Although supplements and fortified foods are helping to address this problem they are expensive and sometimes impractical. An alternative strategy is to encourage farmers to switch to basic crops especially planted with improved micronutrient levels. So, such biofortified varieties could yield much more than cultivation on micronutrient-poor soils (Shekhar, 2013; Muthayya, 2013).

Hidden hunger compromises several stages of the metabolic process, impacting mainly on the immune system and the physical and mental development of the individual. It occurs to economic, geographic and/or educational reasons, the individual has access to a basic diet that is not diversified and is usually deficient in several micronutrients with the number of families affected being even more significant than

those affected by protein-energy malnutrition. It should be noted, pregnant women, infants and children are the populations most vulnerable to micronutrient deficiency and consequently suffer the worst adverse effects (Black, 2013; Tulchinsky, 2010).

Hidden hunger is present in every country in the world even the richest. Hidden hunger and obesity are not mutually exclusive. The hierarchy of food prices is such that foods with high energy density, composed of refined grains, added sugars, or fats have become the least expensive sources of energy in the concentrated diet. Not surprisingly, diets high in sugars and fats are cheaper than prudent diets based on lean meats, fish, fresh vegetables and fruits. The more nutrient-rich foods not only cost more but the price difference between foods that are energy dense versus nutrient-rich continues to grow. Thus, populations in developed countries are becoming malnourished even though they are overfed (Biesalski, 2013).

### *3.2 Micronutrient Supplementation*

In the 1980s, infant mortality in northern Sumatra caused by vitamin A deficiency was reduced by 1/3 of the previous data at the cost of 4 cents per micronutrient capsule. In this sense, other ways of attenuating MND were implemented such as increasing the frequency of supplementation through fortified foods. Thus, the United Nations Children's Fund (UNICEF) distributes between 400 and 600 million vitamin A capsules annually (Shekhar, 2013).

Since the mid-twentieth century, food fortification has been accepted and used by food processors whose goal is to enhance nutritional value and correct or prevent nutritional deficiencies (Boen et al., 2007). In Brazil, the regulation took place by CNNPA Resolution 12 of 1978 and Minister Order (Portaria-Brazilian term) n°31 of January 13, 1998. The fortified food is that which in 100 mL or 100 g of the product ready for consumption contain at least 15% of Dietary Reference Intakes (DRI) in the case of liquids and 30% of DRI in the case of solids. According to the Technical Regulation of Complementary Nutrition Information (MS, 1978), the food is considered fortified/enriched and declared on the label "high content" or "rich" (Vellozo, 2010).

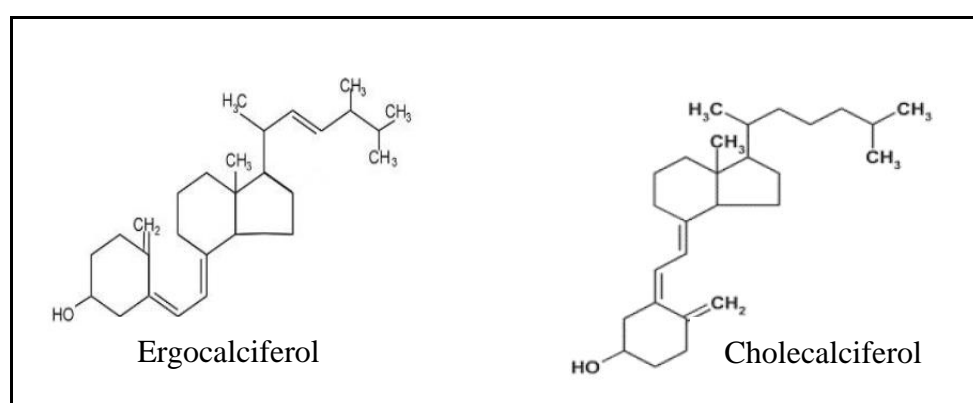
According to Boonen (2007), vitamin D supplements of at least 800 IU/day may be useful in reducing bone loss and fracture rates in the elderly. For the preservation of bone health, one should consume from 1,000 to 1,200 mg per day of calcium through diet and/or supplements (Boonen, 2007). The Brazilian Society of Endocrinology and Metabolism (SBEM), recommends that people with osteoporosis and increased risk of fractures use vitamin D supplements in daily doses between 1,000 and 2,000 IU required to maintain concentrations of 25 (OH-) D ratio was above 30 ng/mL, with respect to the full benefits of preventing secondary hyperparathyroidism, decreased risk of falls, and improved bone densitometry (SBEM, 2014).

Vitamins are a group of organic compounds necessary for the normal physiological function of living organisms and which cannot be synthesized-produced-in adequate amounts by these organisms and therefore need to be obtained from external sources (Lieberman, 1990).

Scientific knowledge about the importance of vitamins only occurred at the beginning of the 20th century

when beriberi disease was associated with vitamin B1 deficiency and pellagra due to lack of vitamin B3. In the 21st century, all vitamins are produced on an industrial scale in chemical and pharmaceutical companies, either by synthesis, semi-synthetic or by fermentation (Philippsborn, 2007).

The main source of vitamins is diet, so, the feeding. However, some vitamins are obtained in other ways such as Vitamin D which is synthesized by the skin when it is exposed to ultraviolet radiation from sunlight. The main sources of vitamin D are ultraviolet-B (UVB), cod liver oil, mackerel, pink salmon, tuna, milk, sardines, liver steak, egg yolk, cheese and mushroom. Figure 1 shows the essential organic compounds and vitamin D nutrients are Ergocalciferol (D2) and cholecalciferol (D3) (Hendler, 2008; Mahan, 2012).



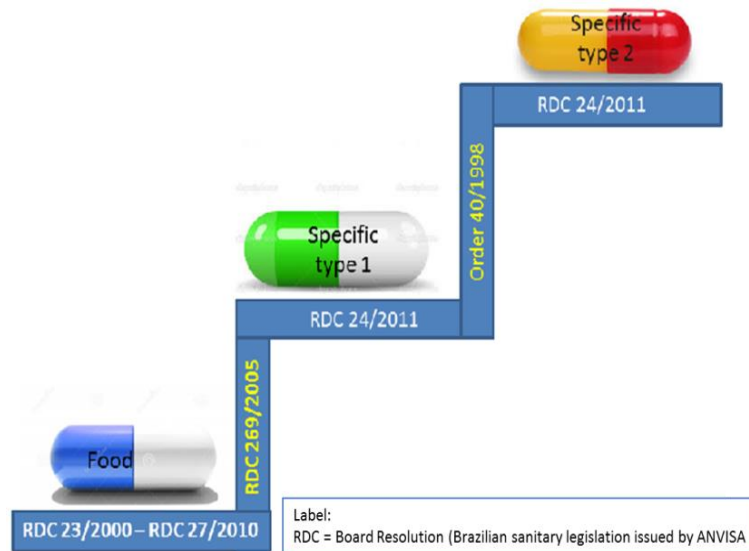
**Figure 1. Chemical Structure of Vitamin D**

According to Lips (2006), a clinical trial in 18 countries involving more than 2,600 women with osteoporosis revealed that 64% of them had vitamin D deficiency. However, vitamin D deficiency may also be associated with increased risk of cancer, autoimmune diseases, hypertension, and infectious diseases (Holick, 2008).

### 3.3 Vitamin D in Brazil

Even in tropical countries where the sunlight is constant such as Brazil with an average annual temperature of 28 °C in the North and 20 °C in the South of the country, a large part of the population has MND. Regions with low latitude (10 °S), even with tropical humid climate and predominant sunlight, the state of Recife, presents women with vitamin D deficiency in postmenopausal. The prevalence of vitamin D deficiency increases significantly with age. It finds in 30% of women between 50 and 60 years of age and in more than 80% in women with 80 years of age (Bandeira, 2006). In the state of São Paulo, Brazil, 250 elderly people with a mean age of 79 years showed 57% with plasma levels of vitamin D below the recommended limit (Saraiva, 2005).

In Brazil, in order to obtain a license to market food supplements, they must meet a series of requirements described in specific legislation managed by ANVISA such as shown in Figure 2.



**Figure 2. Synthesis of Brazilian Sanitary Legislation for Micronutrients**

Considering MND scenario in Brazil and the knowledge of the essentiality of the vitamin D for bone formation and maintenance, the national pharmaceutical laboratories have been striving for a disruptive innovation in vitamin D. Considered as disruptive innovation on the grounds that these laboratories introduced in the pharmaceutical market a new prescription form for vitamin D. So, they created a new market for Vitamin Supplements and/or Pharmaceutical Minerals (VSPM). As too much sun exposure is counteracted by the Brazilian Society of Dermatology (SBD), due to the risk of skin cancer, this fact has generated a market environment even more conducive to the incremental and/or disruptive innovations of vitamin D.

In May 2010, the pharmaceutical laboratory Hypermarcas launched the first VSPM of vitamin D isolated in the Brazilian market: Addera D3®, in the form of drops, registered in ANVISA as a specific drug, reaching sales of around US\$ 1 million in its first year of launching. Subsequently, revenues reached approximately US\$ 5 million, US\$ 8 million and US\$ 13 million in 2011, 2012 and 2013, respectively.

In 2011, the multinational pharmaceutical laboratory Sanofi with a strong presence around vaccines and medicines R & D, decided to enter in this MND market launching the Depura® containing 200 IU per drop and containing lemon flavor. This fact is a differential in relation to Addera D3. Depura sales reached about US\$ 2.3 million in 2011 and exceeded sales of Addera D3 in the following years. Sales in 2012 and 2013 were recorded at approximately US\$ 8.4 million and US\$ 17.2 million, respectively.

Following this fact, there were new releases of vitamin D on the market, namely:

- Maxxi D3®, launched in 2011 by the national laboratory Myralis with concentration limited to 200 IU and without flavor.
- Vitersol D®, launched in 2011 by the national laboratory Marjan. It was the first vitamin D isolated in the form of soft capsules also in the concentration of 200 IU. Sales reached about US\$ 3.5 million in 2014.

- Depura Kids®, launched in 2012, Sanofi launched the first isolated vitamin D designed for children in the form of raspberry-flavored drops. The sales of this presentation grew discreetly and continuously year after year and in 2015 reached US\$ 3.8 million.
- Supra D®, launched by O Kley Hertz laboratory. This containing orange flavored in drops. Sales totaled about US\$ 4 million in 2015.
- Vitax D3®, launched in 2013 by Arese laboratory. Presentations in drops and soft capsules with sales of approximately US\$ 300,000 in the first year of launch.
- Desol®, launched by the Apsen laboratory. In drops and with a sweet-milk flavor. Revenue was approximately US\$ 1.5 million from the launch year and in 2015 reached about US\$ 2.2 million.
- Font D® launched in 2013 by the Union Chemical Laboratory in the form of drops. Sales reached about US\$ 2.2 million in 2015.
- Maxxi D3 launched in 2013 by Myralis laboratory. Tutti frutti flavor.
- Dose D® by the laboratory Ach é in the year 2013 containing a version apple-green flavor drops.

The great diversity of products in the form of drops was justified by the physician's flexibility to prescribe high doses of vitamin D (above 1000 IU/day), since the medical practices pointed to treatments of 2000 IU/day where the blood tests Indicated an adequate level of vitamin D in the individual. In this way, doctors sometimes prescribed up to 5000 IU/day—equivalent to 25 drops of the Depura or 200 IU/drop. Thus, two competing pharmaceutical laboratories developed presentations in the form of tablets at high dosages (above the limits established by ordinance No. 40 of 1998). Therefore, they products were classified as type 2 specific medicine. So, getting a new license to market. Now as a medicine and no longer as a supplement.

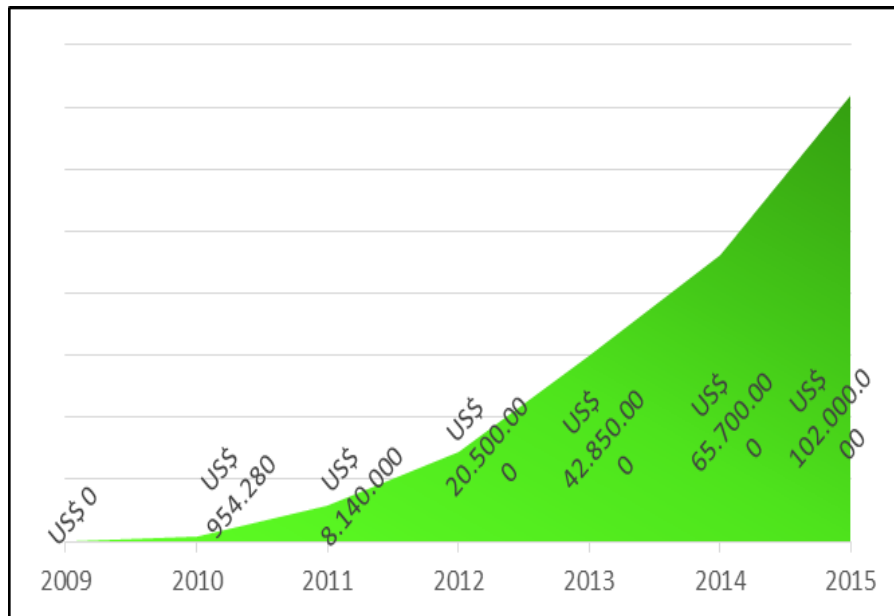
In this new scenario, in 2014, the Myralis laboratory launched D-Prev®, being coated tablets in the concentrations of 1,000 IU, 2,000 IU, 5,000 IU and 7,000 IU per pharmaceutical unit. The brand's sales reached approximately US\$ 1.5 million in the launch year at US\$ 5 million in 2015. Following the groundbreaking wave in 2014, the pioneering lab relaunched Addera D3 with three coated tablet concentrations: 1,000 IU, 7,000 IU and 50,000 IU. The presentations achieved sales of approximately US\$ 10 million and in 2015 reached about US\$ 36 million.

Other vitamin D releases:

- Doss®, in the year 2014 by Biolab laboratory, a product as coated tablets of 1,000 IU.
- Font-D® by Uni ã Qu ímica laboratory: in the form of soft capsules.
- Detamax D3® by Momenta laboratory: a new version in the form of drops and without flavor.
- Devera® launched in the year 2014 by Takeda laboratory: in the form of drops and honey flavor.
- Tridevit® by Zodiac laboratory: it innovated in the pharmaceutical form and launched the first chewable vitamin D tablet isolated with strawberry flavor.
- Deforce® launched by Zydus laboratory: in chewable form and strawberry flavor.
- Depura® from Sanofi lab: in the year 2015 as 1000 IU.

Figure 3 shows the evolution of the pure vitamin D market consolidated as the largest micronutrient

market in Brazil reaching around US\$ 100 million in sales in 2015.



**Figure 3. Vitamin D—Sales in Brazil**

Source: IMS Health, 2016.

Given this scenario of micronutrients, the national pharmaceutical medium-sized laboratory GROSS, developed efforts to the possibility of a better repositioning in the market of its products such as Adefort drops. This product, having as active principle vitamin D. It was relaunched with a new concept of marketing—totally reworked. The Pharmaceutical laboratory had already license to market in ANVISA, but it opted for its market repositioning rather than launching it a new VSPM (food). It should be noted that the formulation of Adefort Drops consists of the association of three fat soluble vitamins (vitamins A, D and E).

After the implementation of new packaging and distribution to the medical class the product was consolidated along with another vitamin D existing ones. In 2010, the presentation of Adeforte Drops totaled 22,451 units. The following year, in 2011, sales grew by 133%, representing 52,421 units. Already in the year 2012, a total of 130 thousand units and in 2013 about 170 thousand units sold.

Considering this scenario, the GROSS laboratory developed the soft capsule form for the already existing formulation of Adeforte (vitamins A, D and E), but registering as VSPM of pure vitamin D. But, in this way, the concentrations of the soft capsule formulation were adjusted following the RDI limits established by RDC 269/2005 of ANVISA.

Table 1 shows the comparison between the dosages of Adeforte Drops (medicament) and Adeforte Capsules (SVMF) formulations according to the amounts recommendations to ingest of each micronutrient.



**Table 1. Concentration of Adeforte® Formulations**

Micronutrient	Drops	Soft capsules
Vitamin A	10.000 UI/day	600 UI/day (100% IDR)
Vitamin D	800 UI/day	200 UI/day (100% IDR)
Vitamin E	10 UI/day	10 UI/day (100% IDR)

In 2013, the sales of soft capsule form exceeded 13 thousand units which corresponds practically to the presentation in drops. Only capsule version reached sales in the order of US\$ 350,000, US\$ 500,000, US\$ 700,000 and US\$ 1 million from 2013 to 2016 respectively.

This scenario of vitamin success for MND treatment also occurs by other associations with vitamin D. This fact has been observed by market innovation since the launch of Addera D3 from the Sanofi laboratory, mainly the associations of Calcium with vitamin D where its synergistic effect potentiates the absorption of the two substances in the bone mineralization of the human being.

#### 4. Conclusions

There is a worldwide concern with the topic of hidden hunger where the micronutrients inserted in the daily food can contribute to the resolution of the problem. Nevertheless, governmental regulatory actions for the pharmaceutical industries have assisted in the direction of new treatments through specific dosages for both medicaments and the VSPM class, as in the case of Brazil, through its sanitary regulatory agency, ANVISA.

National pharmaceutical Brazilian laboratories have intensified their efforts in the introduction of new pharmaceuticals in the market, given that the lack of micronutrients is still a very present reality in society. It should be noted that many of these deficiencies are not caused by nutritional problems. In this sense, efforts should be made for new studies that enable MND treatment with vitamins and minerals for populations in need.

It is noted that small repositioning in the portfolio of pharmaceutical industries may favor a new opportunity in the pharmaceutical market share of a given region. This is especially interesting for laboratories that have limited financial resources for high R & D investments.

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