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TOTAL QUALITY MANAGEMENT IN THE BIOPHARMACEUTICAL INDUSTRY: "PLANNING AND DEVELOPMENT OF QUALITY FUNCTION DEPLOYMENT (QFD) FOR THE RESEARCH AND DEVELOPMENT OF PRODUCT AND PROCESSES OF HUMAN PLASMA DERIVATE PRODUCTS"

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ABSTRACT

In the industrial sector, the work of the research and development departments is related both to the processes performed and to the products to be marketed, and it includes everything from the design and development of a new product to the redesign or development of the process of production. Therefore, response time represents a key point in the structure of the company, provided that the response is fast and effective. Besides, the quality of the development and design is not limited to the benefits of the product. Quality Function Deployment (QFD) for Pharmaceutical Products Research and Development appears as an important tool that allows us to face the design or modification of a product or process according to customer's needs, and to their expectations about the product quality requirements. In this work we deal with the development of a plasma derived product, on the basis of QFD rules. The application of QFD fulfilled the proposed objectives. QFD added simplicity and reliability to the production as well security and highly competitive costs to both, the product development and the final product itself. QFD was supplemented with Good Manufacturing Practices (GMP), and it also proved to be highly applicable in the pharmaceutical industry even in the case that certification for a quality system is not pursued.

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Keywords: QFD, Biopharmaceuticals, Quality Management, Human Plasma Products

1. INTRODUCTION

1.1. Research and Development in the Pharmaceutical Industry

In the industrial sector, the work of the Research and Development Departments (R&D Departments) is related to the processes and products to be marketed, and it includes everything from the design and development of a new product to the redesign or development of the process of production.

Pharmaceutical products, like other industrial products, have a life cycle that begins with the development of an idea and culminates when the product is obsolete, and its redesign, discontinuation, or removal from the market is decided (FERRÉ, 1990).

One of the objectives of R&D Departments is to extend the mean lifetime of a product by improving its design, with parallel development of a substitute for the moment when the product is removed from the market (BATES; COLS, 1988).

Therefore, response time represents a key point inside the structure of the company, provided that the response is fast and effective. Besides, the quality of the development and design is not limited to the features of the product but the following should also be taken into account (GRAHAM; ENGLUND RANDALL, 1999; RICO, 1995; NICHOLS, 1994):

- Simplicity and reliability of the production process
- Safety and accessibility for maintenance and handling of the product
- Quality and lack of defects during the product estimated mean lifetime

At the same time, it is necessary to work at competitive costs during the development process and in obtaining the final product. It is known that cost decreases considerably along time as the development of the product progresses towards production scale-up, and the production process is optimized in a cycle of continuous improvement (SPERY; COLS, 1999; TRHOM, 1990).

Thus, another objective of an industrial R&D Department is defined as the improvement of products and processes with a view to reducing costs and increasing

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net profit margins (TINGSTAD, 1990; GORSKY; NIELSEN, 1992; TINGSTAD; 1994).

In sum, the plans of an industrial R&D Department include two main groups:

a) Design of new products and processes.

b) Maintenance and improvement of existing products and processes.

1.2. QFD for Pharmaceutical Products Research and Development:

The central focus of QFD establishes that one of the keys to achieve continuous improvement is that internal and external customers get involved as early as possible in the process of development of a product (MIZUNO; YOJI, 1994; SULLIVAN,1986; AKAO, 1972).

Quality Function Deployment is a practice used to design processes in response to the needs of the customers, and it translates what customers want into what the organization produces. It allows an organization to prioritize customer needs, to find innovative responses for those needs, and to improve processes for maximum effectiveness. QFD is a practice that leads to process improvements which allow an organization to surpass its customers' expectations (SULLIVAN,1986; AKAO, 1972).

In the development and improvement of pharmaceutical products, external customer needs and requirements are reflected in reliability, effectiveness and security of the medication, while internal customers will demand speed, security and low costs. (CLARCK; FUJIMOTO, 1991; BECKELL, 1989; SOWREY, 1987; RICO, 1996; OVIEDO, 2002)

2. METHODOLOGY

2.1. QFD for the Research and Development of Human Plasma Derived Pharmaceutical Products (Model of Application Developed):

In this work we put forward that the development and application of a quality system in R&D laboratories result in efficiency and effectiveness gain for the manufacture of the product under research. We stated that quality flaws of this process are to be found in the planning and programming stages of R&D projects and that such flaw include excessive time demanded by the development process as well as low attachment to normalized registration systems, among others.

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For the implementation of a quality system in R&D groups, we consider that QFD can become an appropriate tool that contributes to planning and execution of R&D projects. In order to prove this, we carried out the development of a new product, applying QFD.

2.1.1. QFD Methodology Flow:

In our work we apply the four basic phases in the methodology of Deployment of quality functions, this occurs throughout the process of product development (SINGGIH; COLS, 2013; LOWE, 2001; AKAO, 1990; COHEN, 1995).

During each phase, we prepare one or more matrices to help plan and communicate the critical planning and design information of the selected product and process in our case.

The applied QFD methodology flow is represented below, where each phase or matrix, that we developed represents a specific aspect of the product's requirements. The relationships between the elements were evaluated for each phase. Only the most important aspects of each phase were implemented in the following matrix.

Phase 1, Product Planning, incinerating the construction of the house of quality with information from the marketing department. Phase 1 documents customer requirements, warranty data, competitive opportunities, product measurements, competitive product measures and the technical capacity of the organization to meet the requirements of each client.

Obtaining good customer data in Phase 1 was critical to the success of the entire QFD process.

Phase 2, product design: this phase included the development work of the pharmaceutical product in the Research and Development department. In this phase of product design, creativity and innovative ideas related to the product were expressed. The concepts of the product were created during this phase and its specifications are defined and documented. The clearances that are determined to be most important to meet the client's needs were then implemented in the process planning during Phase 3.

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
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Phase 3, Planning of processes: process planning is developed following the design and supported the assistance of manufacturing engineering. During the planning of the process, the production flow diagrams, the critical quantities and the process parameters (or reference values) were determined. These are documented in the matrix.

Phase 4, Process control: Finally, the production planning was determined, performance indicators are created to monitor the production process, the maintenance schedules and the training of the operators. In addition, in this phase the flow of decisions about which process represents the greatest risk was determined and fixed and controls are implemented to prevent and avoid failures. The controls executed by the quality control department are established.

2.1.2. Method of Production and Quality System:

The method used is the purification of the plasmatic proteins by means of alcoholic fractionation, which is known as the Cohn – Oncley Method. (COHN et al., 1946; CURLING, 1983).

The production, quality control and process controls are carried out as prescribed by GMP, GLP (OMS, 1994; IRAM-ISO 9000:2000; IRAM-ISO 9001:2000; Disposición ANMAT Nº 2819/2004) and other normative regulations (Farmacopea Nacional Argentina 7°, 2003, 5° Real Farmacopea Española, 2015).

2.1.3. Selection of an application project for QFD:

Within the Pharmaceutical Industry, the alternatives for the development of products and processes can be divided into:

1. A new product, existing or not in the market, and completely different from the range of products existing in the company up to that moment.
2. A new product, existing or not in the market, and within the range of products already existing in the company.

In this work, QFD was aimed at the development of a product that is within the existing range of products, considering two new alternatives:

a) Development of a product already existing in the market (generic), manufactured using similar processes and procedures as those already existing at the industrial plant.

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b) Development of new product, already existing in the market, using a process of production different from the process currently used at the plant.

Our development of QFD was oriented towards an already existing product, using production methods installed at the plant.

For the Development of QFD, the reengineering and re-launching of a completely renewed product which had been discontinued in our laboratory (IgG anti-D) was selected. This product exists in the market and its process of production does not differ much from the process used for the manufacture of the range of products already existing in the company.

3. DEPLOYMENT THE CASE OF STUDY

3.1. Description of the Product:

Immunoglobulin – Anti-D (Rho) is a biological generic medication. Its pharmacological action consists in neutralizing D Antigens (Ag) present in the membrane of human red cells (HRC).

The medication is made from human plasma coming from healthy donors, mostly Rh- women sensitized during pregnancy. In fewer cases, plasma is obtained from sensitizations occurred as a result of blood transfusions or programmed and controlled immunizations.

The use of this medication is mainly directed to prevent the Hemolytic Disease of the New Born (HDNB).

3.2. Need for the Product:

It is estimated that 60.000 annual doses of anti-D are needed in the Argentine Republic for the prevention of HDNB. According to National Law Nº 23674/89, it is obligatory to satisfy that annual requirement, which demands a productive effort in accordance with the above mentioned need.

3.3. Market for the product:

This product presents the following market values:

- In the city of Córdoba, the product annual sale rate reaches about 1000 units, which can be potentially increased by 30-40% through a greater supply of low-cost, high-quality products.

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
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- In Argentina, 1699 units of the product are sold monthly, distributed in dosage forms of 250 and 330 ug of anti-D antibodies/ml. Foreign and private laboratories that market imported products occupy 94,97% of this market.

Patients can acquire the product, if prescribed by a doctor, in pharmacies that buy it from wholesale pharmacy distributors. Public and private hospitals also purchase the product, through bidding procedures.

The market value of the product is of about U$S15 per dose of 250 mg/ml, and of about U$S 21 per dose of 330 mg/ml. These values correspond to prices of the medication in pharmacies.

3.4. Determination of the Customer Requirements:

As a first step, prior to the beginning of the development of QFD, the product internal and external customers were defined.

The internal customer is someone to whom the R&D department should transfer the results of its work, and the external customer is someone that receives the final pharmaceutical product form. External customers can be categorized as follows:

a) Primary Customer, who buys the product from the laboratory, and who is represented by medical care units, wholesale pharmacy distributors and pharmacies.

b) Secondary Customer, who prescribes the medication, and who is represented by the physician.

c) Tertiary Customer, represented by the patient, for whom the pharmaceutical product is prescribed.

In a study on customer needs we found that some needs are common to all external customers while others are specific of each one of them.

Customer needs were determined through interviews and a structured survey that allowed us to define the customer satisfaction index in relation to our product and to the products of other companies, and also to determine the quality and non-quality parameters perceived by the customer. The following aspects were also determined: causes of quality deficits, internal aspects that could cause bottlenecks on the way to the goal of satisfying customer quality requirements, and the internal

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
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perception with regard to the quality of the development project.

The objectives of this work are oriented fundamentally to determine an administration and quality management methodology applicable to R&D groups. The main customer is represented by the sectors that receive findings and developments in order to transform them into products. Therefore, QFD is considered to be applicable to any research project that provides a result for a determined receiver.

Accordingly, during the development of the model we put particular emphasis on internal customer requirements. This did not mean to disregard external customers who are considered in the global quality development process for every R&D project and pharmaceutical product scale-up. When considering internal customers, we determined that they are the first receivers of R&D work in an industrial laboratory. In the case of university research laboratories, the first receiver becomes an external customer.

Data were processed statistically in order to determine our priorities and the components of the QFD matrix.

The most striking internal customers' requirements and expectations, especially those which must be necessarily satisfied, were identified in the analysis. Among them, apart from those considered basic, the following were weighted:

- Greater emphasis on project management.
- Integration of the development projects into the quality system (*do it well from the start*).
- Management of development costs (time, results, equipment, etc.).
- Efficiency in project management, with an improved planning/results relationship.
- Greater interaction with internal customers, such as Quality Control and Production.
- Greater speed in development transfer for development scale-up.
- Transfer in accord with production manuals, standard operational procedures and work manuals at the moment of scaling up.

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- Greater participation in the stage of final adjustment of the development process.
- Decrease in the percentage of post transfer and post scale-up adjustments.

In order to determine which of the above mentioned items were essential, they were evaluated through a Pareto diagram, which showed the results displayed in Table 1, Figure 1 and Figure 2.

Table 1: Internal customer requirements values

Requirements	Order	Value	%	Accumulated %
Project Management	1	36	31.30	31.30
% Post Transfer Adjust	2	27	23.48	54.78
Transfer Time	3	22	19.13	73.91
R&D Costs	4	20	17.39	91.30
Interaction with other Depts.	5	7	6.09	97.39
SOPs and Manuals	6	3	2.61	100
TOTAL		115	100	

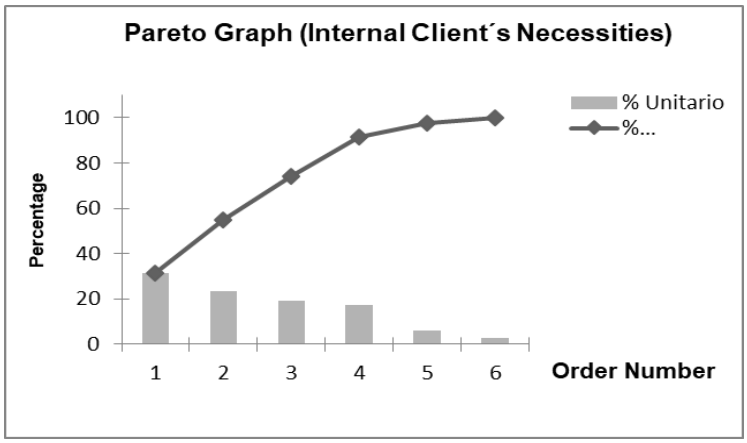

Figure 1: Weighted Internal Customer Requirements

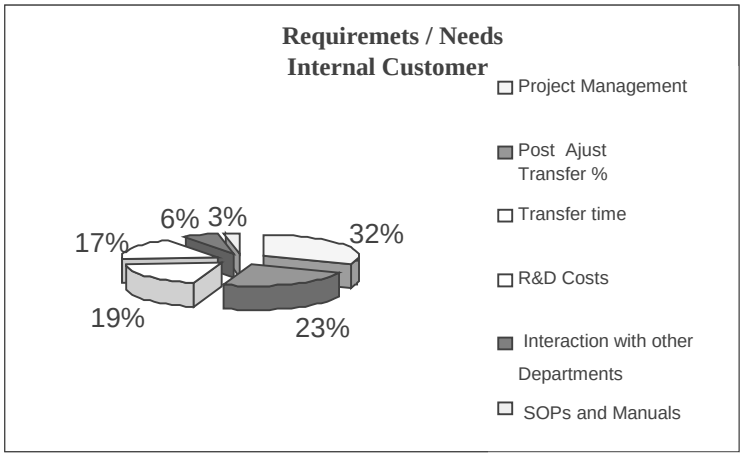

Figure 2: Percentage Distribution of Internal Customer Requirements

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
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Regarding the external customer, it was observed that the most important requirements were reflected in the need for products with adequate market availability and supply, at low cost, and with more potent formulations and stability. Other needs were related to the intravenous form of the product and to the possibility of adjusting the doses according to the degree of sensitization of the patient.

The results of the Pareto diagram, designed to show the degree of importance of each one of these requirements, can be seen in table 2, Figure 3 and Figure 4.

Table 2: External customer requirements values

Requirement/Need	Order	Value	%	Accumulated %
Market supply	1	411	35.55	31.30
Low Costs	2	221	19.12	54.67
More Potency	3	202	17.47	72.15
Expiration Date	4	202	17.47	89.62
Intravenous form	5	80	6.92	96.54
Multi Doses	6	40	3.46	100
TOTAL		1156	100.00	

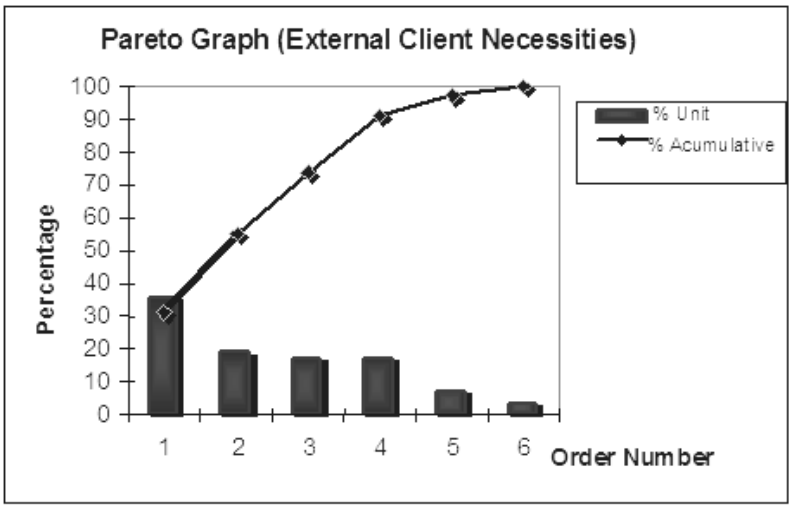

Figure 3.Weighted External Customer Requirements

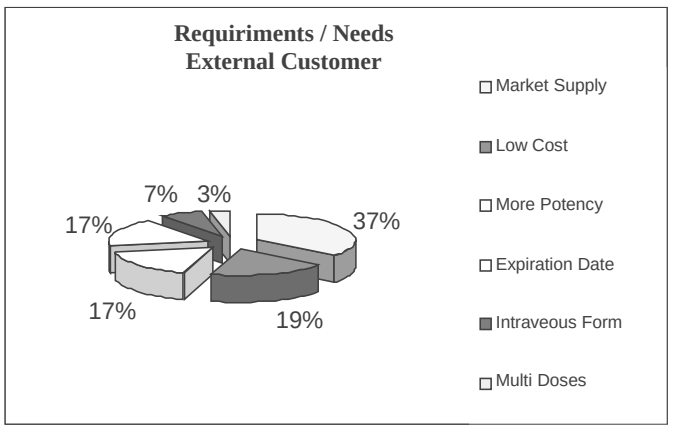

Figure 4: Percentage Distributions of External Customer Requirements

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
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A spiderweb interrelationship digraph (Figure 5) was used in order to identify the points in common between both results. It was observed that the main interaction points were related to the cost and time of development, that is, to the planning process and to good project management.

This analysis facilitated the stratification and selection of needs and it allowed building the QFD matrixes. Figure 4 presents a practical scheme of the QFD applied.

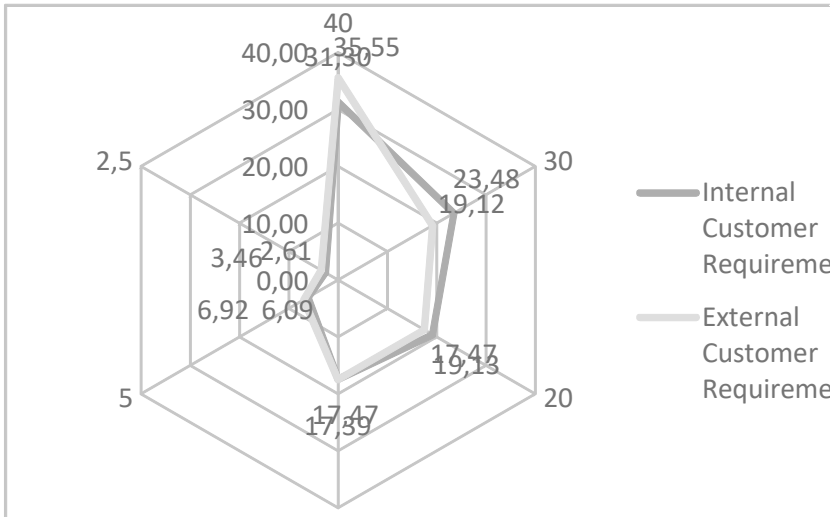

Figure 5: Internal vs. External Customer Interrelationship Diagraph (spider web)

Once the matrixes were completed, we advanced in the development of the project, the control parameters were determined for each stage, and the project improvement indicators were defined. During the realization of the project, the inspection points of the process were defined, the techniques and control trials used were optimized and validated, and the critical parameters of the production process were adjusted.

After de product development was finished, the standard operative procedures (SOP) involved in the production process of the new product, its manufacturing manual and the engineering design process were written, for the subsequent scale-up process.

4. RESULTS AND EVALUATION OF THE APPLICATION OF QFD IN A PROCESS OF RESEARCH AND DEVELOPMENT

A traditional point of view considers a product R&D from the market and marketing perspectives; however, it should be taken into account that the development of a new medical product requires a minimum of five years from the

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
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beginning of the development until the product is obtained. With the application of QFD we plan to reduce that time and achieve a sustained increase in quality.

In our case, one of the most important customer requirements was related to efficient and effective R&D project planning and to appropriate decision-making for the project evaluation.

Within that framework, the results obtained are ordered under the following titles:

a) Project Planning

b) Evaluation of the QFD results

4.1. Project Planning:

For efficient project planning, the application of five governing points was determined, whose execution represents a considerable improvement in the quality of the development of a new medicine.

a) The R&D Manager, the Product Development Chief, or the Researcher must carry out the project planning process as if acting on behalf of the Company Direction, that is to say, they must assume the management role from a global perspective, as from the moment the new idea is conceived.

b) The project planning process should attain a balance between the conflicting interests and requirements of a company on the path of quality, and some conservative management practices applied when the production, marketing, sales, finances and quality areas are involved.

c) The planning process should contain the definition of pre-requirements for the development process and the definition of the product to be obtained from the said process.

d) The project planning process should generate the creation of a *New Project Committee*, composed by the following members and areas of the company: Researchers, Plant Managers, Technical Direction, Marketing, Quality, and Executive Directors. The creation of the committee should allow a global vision of external and fundamentally of internal customer requirements.

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e) The project planning process should generate awareness that beginning and defining a project for a new medication or for a new production process represents only one instant in the planning process as a whole. During the project planning process, the project director should maintain an innovative vision of customer requirements. Besides, the director must ensure that all the contents related to quality as well as the commitment of all the members of the organization are taken into account for the development and successful realization of the project.

In this part of the work we will not go into detail on how and when the above mentioned points should be applied. Instead, we will simply analyze how the project planning process and the quality function deployment influenced the development of the project. In the chapter referred to project planning, a detailed explanation of how to execute the planning process is provided. Planning involved an analysis of the environment and of strengths and weaknesses of the project (Figure 6). Subsequently, a strategic action plan was determined for the development of the project.

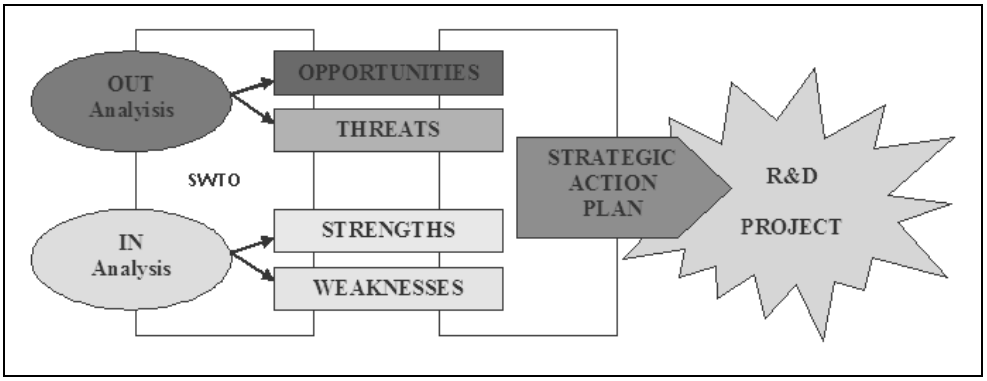

Figure 6: Scheme of the SWTO Analysis for the R&D Project

The project was then structured in five stages that in turn are composed by a group of activities representing the development of the project. The finalization of each stage signals a point of control and of decision making where the continuity or the end of the project is decided.

Stages 1, 2 and 3 are the lengthiest ones and they represent the greatest investment in the development of the project. It was decided that Stage 1, Evaluation and Selection of the Project, would last longer than in previous projects. This constituted an important aspect for making decisions at the beginning of and during the research and development project (Figure 7).

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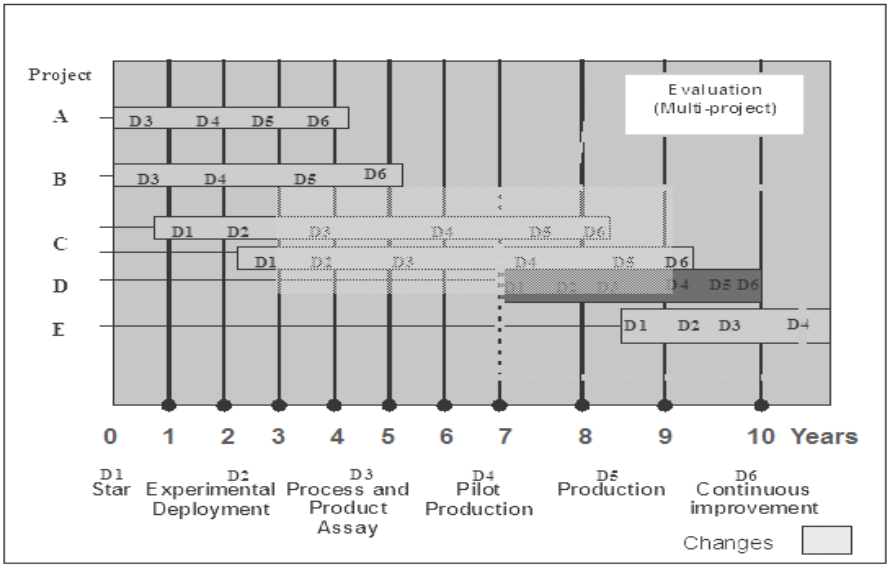

Figure 7: Evaluation of multi-project implications along the three-year development study: case study project (⋆), other simultaneous projects (⋆).

Another aspect considered was the development, quality and investment costs, which were reduced by 18% in relation to the initial projection and by 30% as compared with previous projects (Figure 8).

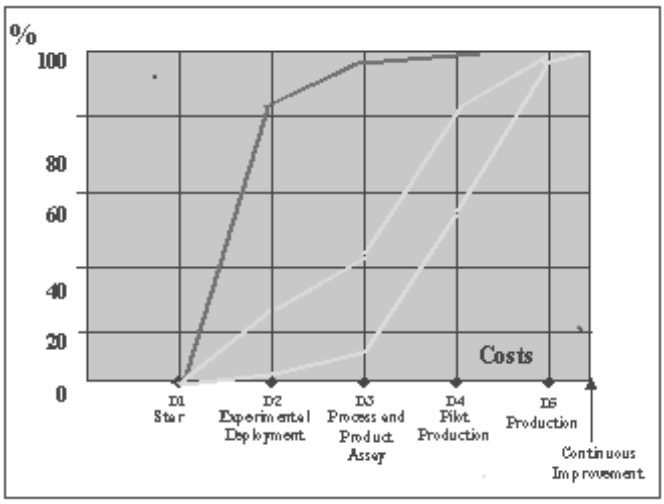

Figure 8: Project Costs vs. Project Investment, (---) Planned Costs, (---) Actual Costs (QFD-based Project) and Costs of other Project (---).

A staggered schedule of activities as well as the participation and involvement of different departments of the company allowed interaction with existing projects and optimization of the employment of resources through the evaluation of multi-project implications (Figure 7) (ALLEN, 1994).

This allowed the company to generate an interactive planning process and almost constant revision of existing projects so as to avoid and eliminate limitations that might otherwise stay out of control.

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In this way, the developers and personnel in charge of other projects did not have to wait until their respective projects were finished in order to become involved in the planning of a new one. Otherwise, the result would have been insufficient project planning.

Planning implied taking into account assumptions about needs, such as the following:

- Volumes: They refer to the capacity of the plant to process and to obtain the new product, the degree of automation of the process, the materials that can be used in product development and design and for the corresponding process, the design of new components, and the cost of application of the technologies adopted.
- This practice was beneficial from the perspective of team work, as all the departments involved in the project were consulted for consensus decision making in order to advance, obtain results, and fulfill the objectives. The result was that experimental development planning work was carried out on the basis of realistic volume estimations and that the work was adjusted to the capacity and infrastructure of the company. This impacted significantly on the investment and on the reduction of the development costs (Figure 8).
- Another planning aspect involved legal aspects: all legislation related to the project was gathered and it was specially taken into account during the evaluation, approval and start-up stages. This work facilitated the task of stage five, related to the final development of the complete Quality Assurance and Regulatory Documentation required for the official registration of the new medicinal product developed.

On the basis of the organization of specific activities for each department participating in the project, parallel lines of work were generated so that the responsibility for the execution of the project did not lie entirely on the Research and Development Department (Figure 7).

This implied that different aspects of the development process progressed simultaneously: while experimental tests were conducted, Plant Engineering solved the requirements for equipment and infrastructure, or Quality Management advanced in the preparation of the necessary documentation. This allowed the company to

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
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reduce development time by 35%, (we had said that a pharmaceutical development requires at least five years to be completed), with the corresponding reduction in arising expenses (Figure 9).

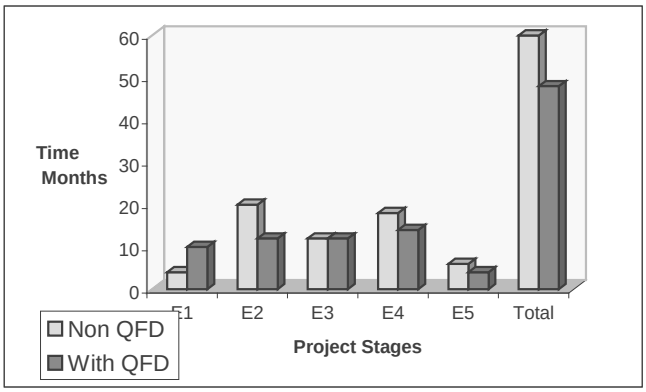

Figure 9: R&D Project Deployment Time

Planning and the employment of quality tools generated joint tasks, consensus decision making, and integration of teams generally acting in a stratified manner. The most important result is not -as it could be presupposed- economic profit, but the cultural and educational transformation achieved by using this method of working.

Early knowledge of internal and external customer requirements allowed the developers of the project to value needs and demands, to determine quality standards, and to make the necessary changes in the original plans of the project in order to respond to customer requirements according to actual transfer and production possibilities. In other words, in the pharmaceutical industry a new idea is actually good only if it can be materialized into a quality product made at low cost production.

One of the planning keys was to translate the requirements into the product specifications, in an economical way. QFD represents a good tool that allows the company to ensure, in a structured way, that what began as a customer requirement is considered all along the development process and is transferred to production in the most economical way possible, always assuring the maximum quality standard.

4.2. Evaluation of the Results of the QFD:

As we said before, QFD means transferring the customer opinion to the product. We also assert that the essence of planning a new project is to define the orientation towards the customer so that researchers and technologists can

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
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transform that orientation into a technical tool for quality and high profitability production.

In our hypothesis we put forward that it was possible to achieve that requirement by using QFD for the development of a medicine.

Planning work brought about an action plan that is summarized in the following five points:

- New QFD Development
- Determination and elimination of bottlenecks
- Development of the new product
- Putting the process under control
- Production and sales

Quality Function Deployment was completed as explained before. In order to evaluate the results and to confirm the validity of the hypotheses formulated, the following were defined as quality indicators:

(A) Time of realization of the development

(B) Percentage of delays in the development

(C) Investment

(D) Costs

(E) Percentage of reprocess and secondary developments subsequent to transfer

(F) On the basis of market trends, compliance with quality requirements

(G) Positioning in the market

(H) Competitiveness.

(I) Number of scientific publications derived from the development of the product

In spite of the forecasts, in the course of the experimental development there appeared some bottlenecks that represented a constraint for the execution of the proposed objectives. Those restrictions were often related to:

a) Delays in the provision of equipment, reagents and drugs coming from abroad which was due to the economic situation and bureaucratic problems of the

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
DOI: 10.14807/ijmp.v9i3.751

country, related to customs procedures that exceeded any previous planning. Besides, insufficient equipment had to be shared among other simultaneous projects (situation that had been taken into account in the multiproject analysis) as well as with other sectors such as Quality Control.

b) Excessive wear and fatigue in some equipment, which caused delays for repairs and corrective maintenance.

c) Modification of experiments and reagents as a result of experimental development, which originated the need to buy new drugs and equipment.

It is normal that experimental and research work result in changes in the original plans leading to the need to find new and different ways to achieve the objectives, which may give origin to new needs with the consequent delays in the predetermined terms. It is normal and preferable for this to happen at this stage of the development and not at later stages; in fact, this type of modifications makes the measures taken at the moment of a new product transfer and scale-up more reliable.

Regarding bottlenecks, the first task was to determine their causes in order to eliminate them. In some cases, such as those related to experimental work, the causes were not eliminated completely since they were inherent in the research and product development work. However, a solution was sought for those causes related to equipment maintenance and repair, which consisted in an equipment validation program and a preventive maintenance plan.

In order to avoid stopping the development of the project and generating major delays, the decision was made to carry on with the project, and continue dealing with the constraints until their causes could be eliminated. For that purpose, in some cases drug and reagent stocks and work shifts were rearranged in accordance with the activities plan for each project in course.

The results allowed the evaluation of the behavior of the quality indicators considering two aspects, related to:

I. Management and Internal Customer Requirements

II. The Product, Market Positioning and External Customer Requirements

Time of Development: The development of products belonging to the same family took between 6 and 7 years to be completed, while with the application of

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
DOI: 10.14807/ijmp.v9i3.751

QFD that time decreased to 4 years, which meant 35% less time. Figure 7 shows the time required for the development of a process in which QFD was not applied, compared with our process, in which QFD was applied.

The most important difference is centered on stage 1, and during the planning process time. This allowed the company to execute more efficiently the research and development stages and also to reduce time in the final stages of the project.

Delays: Although with the application of QFD and process planning it was not possible to avoid delays completely, their final incidence on the transfer from the product development to production scale decreased. Figure 10 details the corresponding reduction percentages.

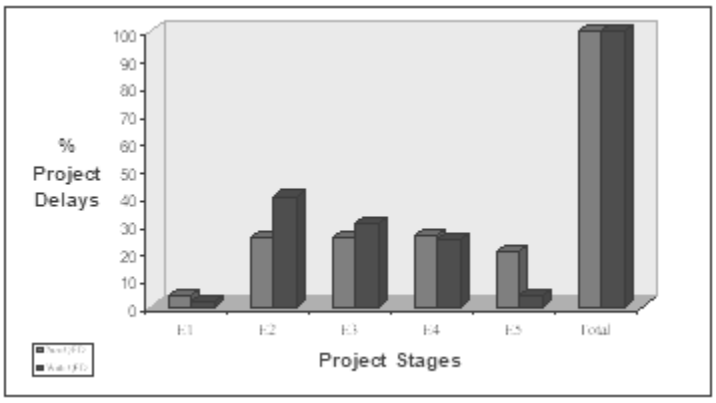

Figure10: R&D Project Delays

Development Investment: With the use of QFD we considerably modified the development investment model, as we distributed the budget so that the greatest portion was assigned to the initial stages. The decrease in expenditure or non-quality costs allowed the company to make a total investment that resulted slightly smaller than the estimate, thus improving the project profit (table 3).

Table 3: R&D Investment and Costs (U$D)

Stage	R&D Investments vs. Costs					
	QFD-based Project			Non QFD-based Project		
	Investment $	Total Cost $	Non-Q cost$	Planned Inv. $	Total Cost $	Non Q cost $
1	30000	45000	260	15000	10000	2650
2	60000	50000	4100	45000	47000	2350
3	75000	65000	2350	60000	70000	7000
4	75000	50000	2040	75000	60000	6000
5	30000	30000	3200	60000	20000	10000
6	30000	5000	300	45000	113000	84000
Total	300000	245000	12250	300000	320000	112000
%	100	18	5	100	107	23

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
DOI: 10.14807/ijmp.v9i3.751

Assigning more funds to the initial stages allowed the company to carry out trials and the necessary corrections during the experimental development, adjusting the process so that in the transfer and scale-up stages, the investment gradually decreased. This trend becomes apparent when the new project is compared with previous ones, since in general, in those developments the investment would become higher at the final moments, often as the result of an increase in costs derived from corrections and secondary developments subsequent to transfer of development (Figure 11).

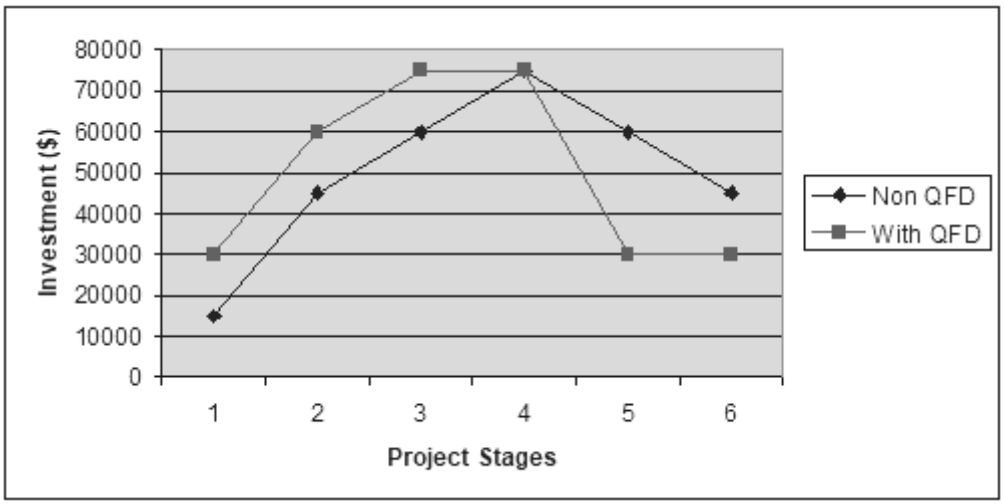

Figure 11: Investment Planning

Multi-project planning, team work, efficiency in the use of equipment and resources, and continuous improvement from the "*do it well from the start"* perspective generated savings in relation to the initial investment forecast. QFD allowed the company to work under quality standards that avoided deviations from the initial objective and unnecessary experimental developments parallel to the main project, which generally respond to matters that draw the attention of the researcher.

Development Costs: An efficient project shows a rise in costs during the initial stages, and a reduction to a minimum amount towards the end of the final stages.

In projects with inefficient planning and poorly defined quality criteria the cost curve was shaped inversely in relation to our proposed project (Figure 6). It showed a rising trend even when the development product had already been totally transferred to production -let us remember reprocess and secondary development necessary for the correction of errors or to lack of foresight. All these costs often responded to incorrect project planning and to non-quality (Figure 12).

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
DOI: 10.14807/ijmp.v9i3.751

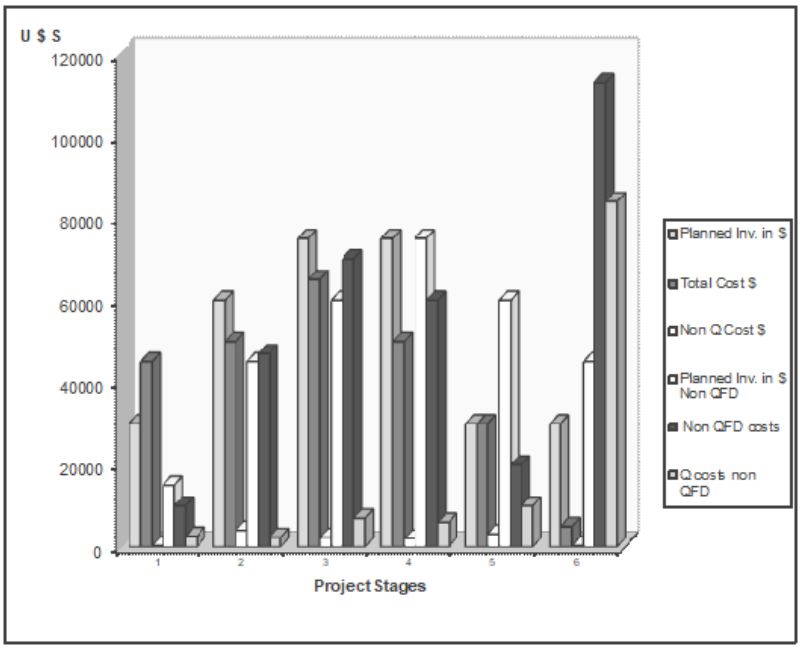

Figure 12: Planned investment vs. project and Non Quality costs.

As of QFD application, efforts were aimed at improving the quality of the development process and of the project administration and management. Besides, more attention was paid to the customer's voice, and the development and experimental works were adjusted to an action plan with finite life and exposed to continuous evaluations for the purpose of making it more efficient (Figure 13).

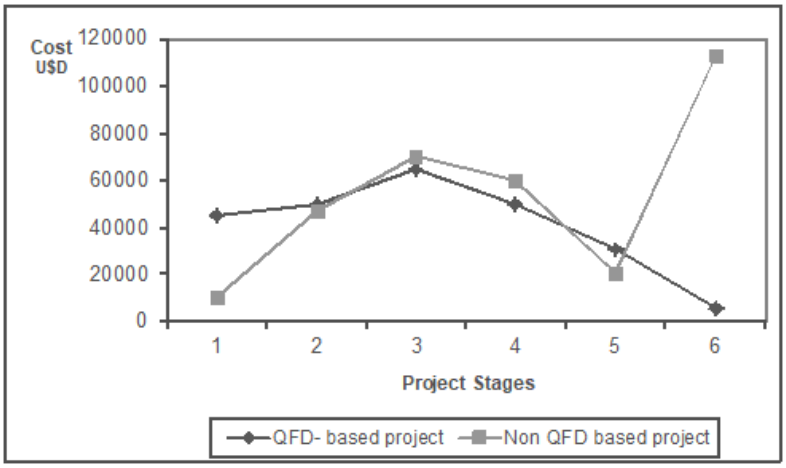

Figure 13. Cost Distribution vs. Project Stages.

This group of actions produces a decrease in the costs, especially on those related to non-quality, and a distribution of expenditure that is close to an ideal distribution (Figure 13).

Reprocess and Secondary Developments subsequent to Transfer: We put forward that one of the non-quality indicators for product development is represented

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
DOI: 10.14807/ijmp.v9i3.751

by the number of corrections made on a complete development project. In fact, this situation illustrates the consequences of lack of planning, managerial deficiencies and inadequate decision making during the course of the project.

We often believe that these corrections are related to technical aspects, but they actually involve all the aspects of the project. Sometimes, poor advice on legal aspects may cause countermarches that delay the definitive launching of the new product. In the case developed a decrease in the percentage of changes was attained because all the necessary corrections were made during the experimental stages so that only final adjustments remained for the transfer and production stages (Figure 14).

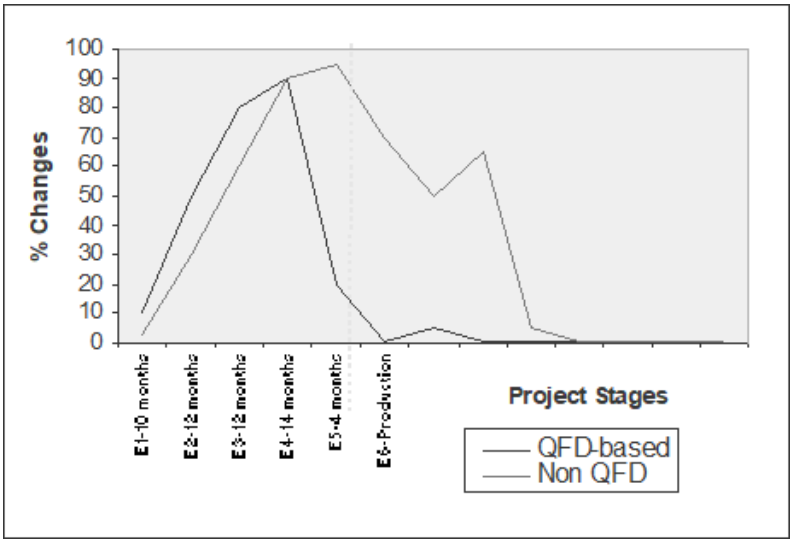

Figure 14. Changes in the project

Quality Requirements: QFD development allowed us to comply with quality requirements and to respond to quality demands. Besides, the market trend for those requirements considered most important was determined through a projection covering 3 to 5 years as from the end of the development. Figure 15 shows the product potency trend and the position occupied by the product developed.

The project allows us to obtain two different potencies of 330 and 250 ug which respond to customer needs, and to compete within the market trend for the coming years. The process of constant feedback and continuous improvement should provide a more potent product by the end of the abovementioned period. For that purpose, a new project is launched, involving new production technologies.

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
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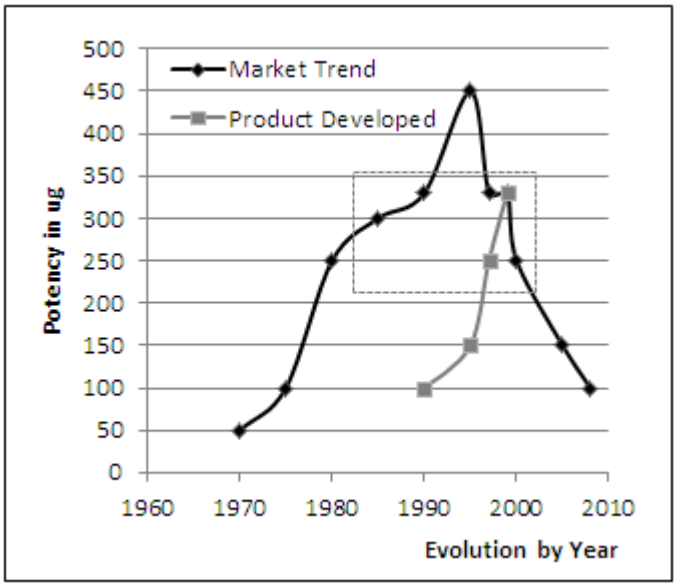

Figure 15: Required Quality: Potency in ug

In relation to potency, the solution volume presented in vials shows a tendency to decrease (Figure 16) as a purer product with greater specific potency is produced. Other aspects that responded to customer requirements were related to the information appearing on the package, packaging type, final price of the product and its availability in the market.

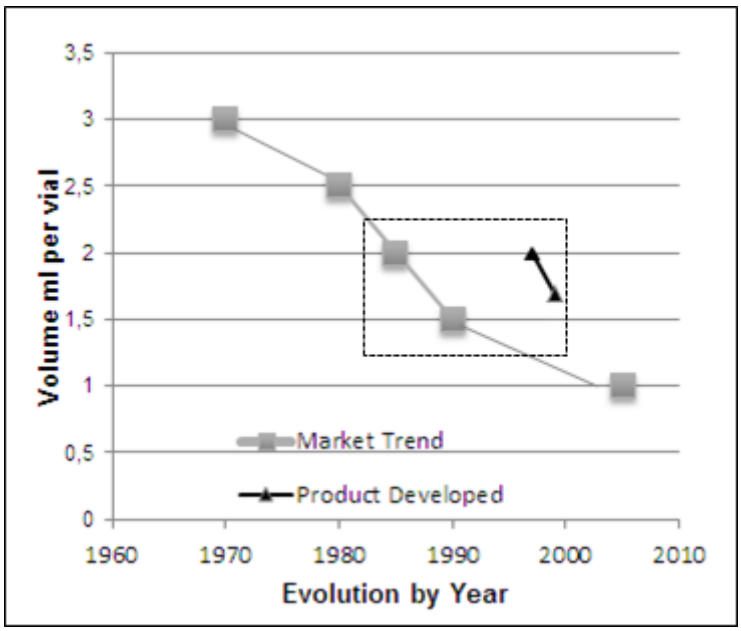

Figure 16: Required Quality: Volume per vial.

Figure 17 (A-B) shows how the said improvements affected the position of the product in the market. Positioning in the Market: Figure 17 shows the product behavior in the market, in terms of quality required by the customer.

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
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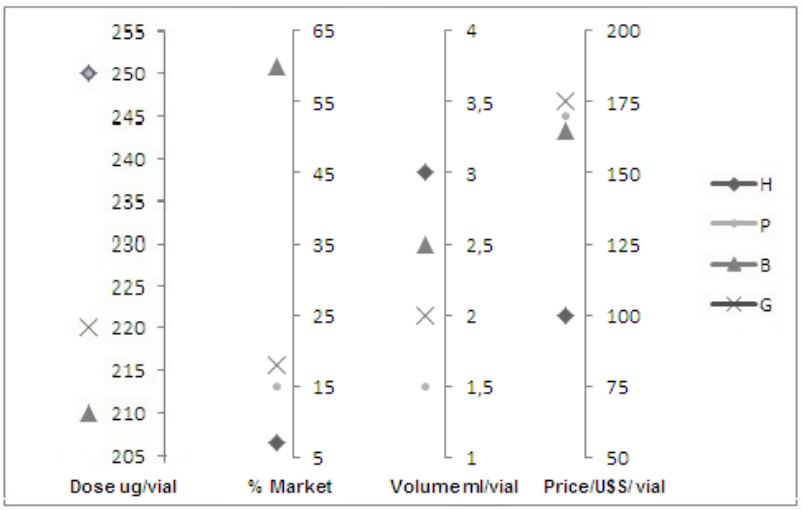

Figure17 (A): Product behavior in the market in terms of the quality required by the customer. Laboratory (H) vs. other Laboratories (B, P, G). Before QFD

Prior to QFD development, a projection was made starting from the product behavior before it was redesigned. The improvement observed in the new product becomes more evident in the growth of the market portion that it occupies and in its quality/price relationship.

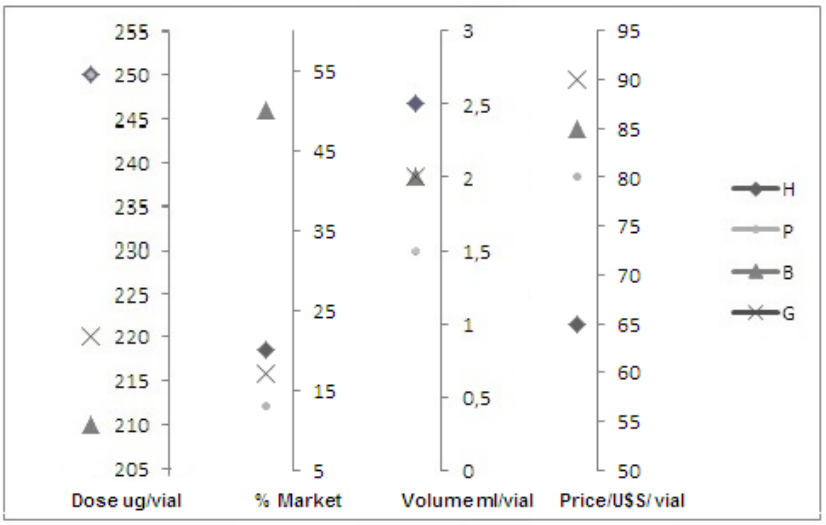

Figure17 (B): Product behavior in the market in terms of the quality required by the customer. Laboratory (H) vs. other Laboratories (B, P, G). After QFD

Competitive evolution of the product: As from the application of QFD to the development of the product, the evolution of the product in relation to competitors' products showed continuous improvement. Figure 18 shows the behavior of the various quality requirements expressing the external customer needs.

INDEPENDENT JOURNAL OF MANAGEMENT & PRODUCTION (IJM&P)
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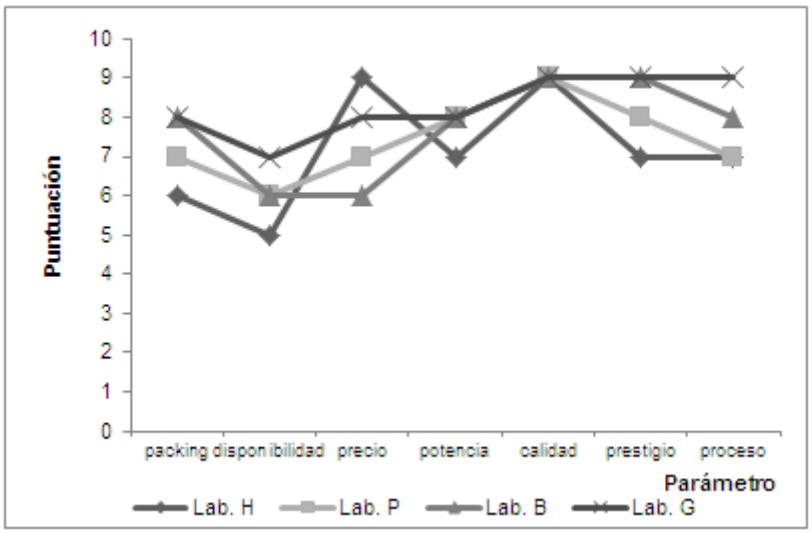

Figure18: Position in the market. QFD-based product (Lab. H) vs. other Laboratories products (B, P, G).

5. FINAL CONSIDERATIONS:

In every research and development process, the possibility of making good decisions is lower at the initial stages of the project, hence the importance of quality planning. Undoubtedly, good planning represents assurance of the product development quality from the beginning itself, and reduction in non-quality costs caused by making wrong decisions (CHENG; DE MELO FILHO, 2010; PRAMOD, 2018).

This idea implies the decision of investing more and better resources in the initial stages of the project, and avoiding expensive correction cycles after the development is finished.

If something that is relatively simple has not yet been appropriately dealt with within the realm of a research and development group, it is due to an incorrect vision of multifunction work, which requires correct project planning.

We can assert that QFD is an appropriate tool for the management of a development project since it allowed us to establish the necessary links between product excellence, internal and external customer needs, and the opportunities existing in a competitive market.

QFD created the need to establish planning mechanisms for research and development projects in the short, medium and long term, in order to avoid

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
DOI: 10.14807/ijmp.v9i3.751

subjective evaluations and decisions made by people wrongly believing to be project management experts.

QFD requires working methods that led to reductions in interdivisional clashes and jealousy as well as in conflicts of power between researchers, product developers, and control, production and marketing technicians. This allowed the execution of projects with collaborative participation of personnel of the most diverse areas and the consequent simplification of planning and control tasks. Besides, QFD made it possible for the personnel to share the responsibilities arising from the project.

The opinion, suppositions or subjective desires of researchers were not mistaken for customer requirements; thus, the satisfaction of customer needs was attained and expressed in the final product. Besides, QFD proved to be applicable to any area of the organization or to any of its processes, culminating in the design of products in accord with customer requirements.

Once the application QFD is finished, it becomes a knowledge tool that may be used for later developments of components or systems specified for other products. This avoids *reinventing the wheel,* so that the transfer of knowledge from project to project is safeguarded and time is saved.

The application of QFD required training and discipline, which helps to attain a cultural change in the research and development process even if such application is not easy when dealing with completely new and creative ideas. In fact, in these cases the most difficult task will be to determine customer requirements (STEFAN SCHURR; ARCIDIACONO, 2011).

We put forward that QFD contributes benefits to the research and development process, mainly for industrial research teams, since it allows them to improve competitiveness along with quality and productivity. The development process acquires the characteristics of orientation towards the customer, efficiency in time-management, orientation to team work, and permanent documentation of the process (YACUZZI; MARTÍN, 2003; GORIYA, 2016).

An organization with total quality management is an organization oriented towards the customer. QFD requires gathering customer input and feedback, information that is translated into a group of customer specific requirements. The

http://www.ijmp.jor.br v. 9, n. 3, July - September 2018
ISSN: 2236-269X
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performances of the organization and of competitor organizations in relation to requirements are carefully studied. This allows the organization to compare itself with competitors with respect to customer needs satisfaction (VONDEREMBSE; RAGHUNATHAN, 1997).

QFD reduces the time of development because it is centered on specific and clearly identified customer requirements. As a result, there is no time waste in developing features that have little or null value for the customer.

QFD is an approach oriented to team work. All decisions are based on consensus and they include thorough brainstorming and discussion. Since all the actions to be taken are identified as parts of the process, individuals can visualize their position within the organization, which fosters team work.

QFD emphasizes the documentation aspect. One of the products of the QFD process is a comprehensive and complete document which gathers all relevant data about all processes and their performance in relation to customer requirements. That document is constantly updated as new information is known and obsolete information is discarded. Updated information on customer requirements and on internal processes is particularly useful when problems arise.

Finally we can assert that with QFD application the proposed objectives were fulfilled. QFD added simplicity and reliability to the production, and security and highly competitive costs not only to the product development but also to the final product. QFD was supplemented with GMP and it proved to be highly applicable in the pharmaceutical industry even in the case that certification for a quality system is not pursued.

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