An Application of QFD for Production Start-up of a Generic Drug in a Government-Owned Pharmaceutical Institution

Lin Chih Cheng, Leonel Del Rey de Melo Filho,

Silvia Satiko Onoyama, Bruno F. P. Coelho

(NTQI – Center for Quality and Innovation Technology, Department of Production Engineering, Federal University of Minas Gerais, Brazil)

Abstract: The aim of this article is to present a case of QFD applied to transition from laboratory scale to preparation for production in industrial scale of a generic drug – amoxicillin – in a government owned pharmaceutical institution. This QFD application had two dimensions: work organization and QD deployment process. In the first dimension, a multifunctional team involving the various functional areas of the company was formed, and it was divided into four working fronts. In the second dimension, the team initiated the construction of a conceptual model of positive quality deployment. This construction work was divided into two stages: the first covered up to the final product capsule and the second covered the packaging process. Subsequently, the tables and matrices were filled up for use in generation of standards. This project contributed to early detection of problems related to product, process and raw material. Another contribution of this work is the construction of a conceptual model for developing generic drugs, which can be adapted and utilized in future projects.

Key Words: QFD, product development, generic drugs, conceptual model, work organization.

摘要：本文阐述了 QFD 的应用由实验室规模到工业中的生产规模过渡的一个例子——以公有制药机构中普通药物阿莫西林生产为例。QFD 在本例的应用中包括了两个维度：一个是工作组织还有一个是 QFD 展开的过程。在前一个维度中，包含着各种功能性部门的多功能团队形成了，并将它划分成了四个工作部门。在第二个维度中，团队开始构架积极的质量拓展概念模型，这部分工作分为两个阶段：一个是最终产品的生产，另一个是包装过程。然后，将表格和矩阵填好备用，以用作标准。这个工作能够在早期就发现产品、过程和原材料中出现的种种问题。同时，这个工程中的生产普通药物的概念模型还能够在今后的项目中得到改造和利用。

关键字：QFD，生产开发，普通药物，概念模型，工作组织

1. Introduction

The Economic Commission for Latin America and Caribbean (CEPAL) presented, in 1987, a classification of evolution of a country's pharmaceutical industry according to its capability of

executing one or more links of the chain of activities presented in Figure 1 (Palmira Filho and Pan, 2003).

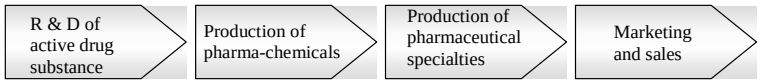


Figure 1– Classification of evolution stages of pharmaceutical industry
Source: Palmeira Filho and Pan, 2003.

In general, developed countries are in the first stage. They have sufficient technology and resources for developing an innovative drug. These countries also participate in other stages due to consumer demands from their population. Countries that have less available resource and technology are in other stages.

In Brazil, there is still little development of active drug substances, however, there is a great demand for large quantity of generic drugs to supply the Unified Health System (SUS) for free distribution of medicines by the government through hospitals and health units spread around the country (Policastri, 2003). There, the pharmaceutical industry concentrates in two final stages: production of pharmaceutical specialties and marketing and sale. The law of generic drugs (Lei 9.787/99) was created in 1999 with the objective of improving the access of population to medicines. Figure 2 shows the growth of generic drug production in Brazil.

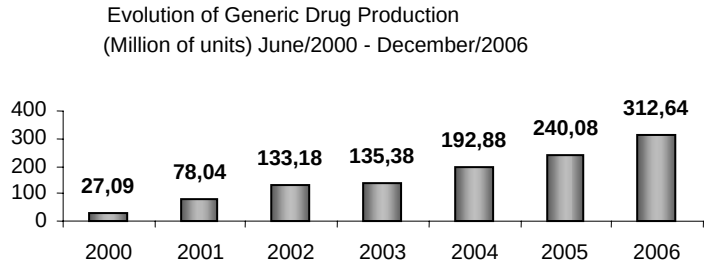


Figure 2 – Evolution of generic drug production in Brazil.
Source: Anvisa

Since the expiration of some drug patents and the passing of laws for generic drugs, official laboratories (federal and state government laboratories) have made large investments that have contributed to the increase of generic drug production. The state government of Minas Gerais, for instance, has made available resources for building new manufacturing units in FUNED (the state official laboratory), for the production of generic antibiotics. This investment enabled a greater medicine distribution to the needy population. However, few works have been published on the development of generic drugs in the world, despite its social and economic relevance

(Prasnikar e Skerlj, 2006). In addition, QFD applications in this type of industry and product are scarce (Carnevalli e Miguel, 2007).

2. The Company and the Objective of Intervention

FUNED decided to develop the generic drug Amoxicillin in capsule for production in a new antibiotic manufacturing unit. In the recent past, according to the company's CEO, the time between the start of laboratory development of a generic drug and its distribution to SUS was very long, of about two years. This was mainly due to problems related to meeting required specifications of the product during large scale production. In order to avoid the repetition of this problem, the CEO settled a partnership with NTQI (Center for Quality and Innovation Technology of the Department of Production Engineering of Federal University of Minas Gerais). It was then decided that QFD method would be used with the following objective: to assure the quality of a new generic product, amoxicillin, in the stage of preparation for industrial production - scale-up.

3. Work Organization

After defining the scope of the project, a multifunctional team was formed; it involved the areas of Production (Pro), Pharmaceutical Compounding (Pha), Quality Control (QC), Quality Assurance (QA), and Industrial Production Management. It was expected that this multifunctional team would facilitate the synergy among the actors of the organization, and thus contribute to the early detection of problems and lead to a successful project.

The industrial director, together with other area managers, defined the team and the leader of the project. The leader, a supervisor of the liquid line, was given the responsibility of managing the new unit. She and four operators were released from their previous functions to work full-time in this project and in activities related to the new unit. Figure 3 represents the structure of work organization and the type of multifunctional team (Clark and Wheelwright, 1993).

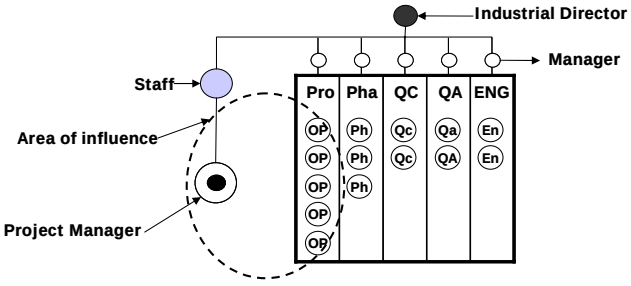


Figure 3 – Structure of work organization. Source: Project Report – FUNED and NTQI

This structure can be classified as an intersection of functional with light-weight type because, except for the leader and the four operators, the remaining participants were not released from their functional areas to work full-time in the project, and, the leader did not have the power over human and financial resources. The team was divided into four working fronts: (a) product, (b) control parameters, (c) packaging, and (d) standards.

The phase of project planning was carried out by the researchers from NTQI together with the project team. The team and the area managers went through training sessions on QFD method. The working sessions were weekly and divided between work fronts, and were mediated by the researchers. The project began in November 2005 and ended in June 2007.

The “product” front was constituted by: two pharmacists from the Division of Pharmaceutical Compounding and Biotechnological Development; the Head of Service of Physical-Chemical Control from the Division of Quality Control; a pharmacist from the Unit of Quality Assurance; and, the leader of the project. During the meetings, the work team (a) developed and revised the conceptual model; (b) questioned about quality characteristics and specifications of final product, intermediary products and raw materials; and (c) analyzed cause-effect relationships, when elaborating and filling tables and matrices.

The “control parameters” front was constituted by the person responsible for the regulatory issues, the Head of Service of Packaging Material Control, and five production operators. Their aim was to build the conceptual model for the packaging process, tables and matrices. In order to improve the range of specifications of packaging material, the “packaging” front generated a work on the improvement of specification of aluminum tape, with revision of inspection plans. This intended to assure the quality since raw material and to make a full potential practice of a company partnership policy with suppliers.

The “standards” front, constituted by the team leader and the operators, was responsible for developing production standards, which was done through the analysis of the content explicated by matrices and conceptual models.

4. QD deployment process

The objective of this project was to assure the quality of a new product in the stage of preparation for industrial production (transition from laboratory scale to industrial scale). Therefore, the development team decided that a more elaborated conceptual model was needed, because it was important to establish all necessary contributing factors (Cheng and Melo Filho,

2007). For more details on Objectives vs. Conceptual Model, see guide for intervention in Cheng (2003). The construction of conceptual model was divided in two stages: the first one examined the production process up to the final product capsule, and the second one focused on the packaging process. The team built the production flows in inverted direction, starting from the desired effects: (I) capsule in accordance with the generic drug specification, and (II) blisters (packed capsules) in conformance with the specification (see Figures 4 and 5). Because the product was a generic drug with pre-established technical specifications, it wasn't necessary to build the Quality Matrix.

After defining the main set of contributing factors, a table of QD deployment was linked to each item. For the definition of matrices, the team carried out an effect-cause analysis, starting from the table of quality characteristics of final products, in inverted direction of production flow. To establish the sequence of matrices in the conceptual models, the team followed the same logic by defining, in inverted direction of production flow, the intersections between matrices. Figures 4 and 5 show the rationale used for building the models. Finally, the conceptual models were constructed according to the effect-cause relationship defined previously. Figures 6 and 7 show these models.

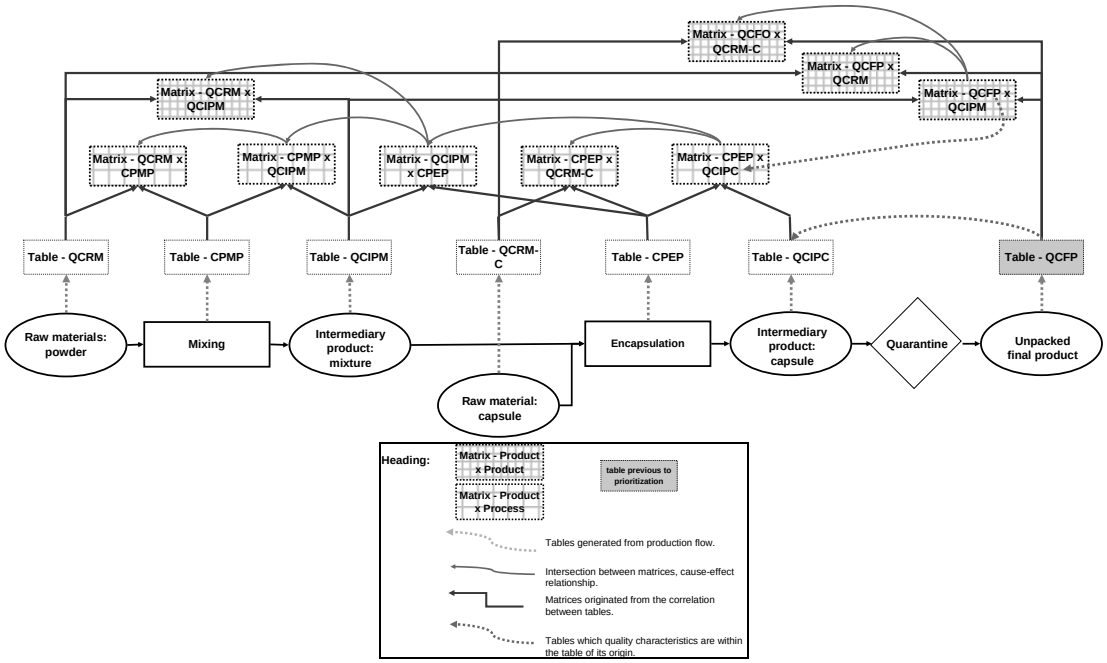
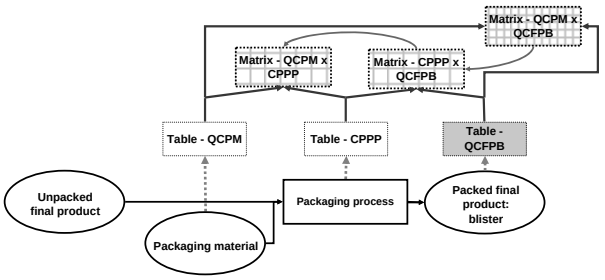


Figure 4 – The construction logic of a conceptual model for amoxicillin-capsule.
Source: Project Report – FUNED and NTQI



Heading	
Conceptual Model for Amoxicillin Capsule	
QCFP	Quality characteristic of final product amoxicillin-capsule (characteristics controlled in batches)
QCIPC	Quality characteristic of intermediary product – capsule
CPMP	Control parameter of mixing processes (equipments)
CPEP	Control parameter of encapsulation process
QCRM	Quality characteristic of raw materials (powder)
QCRM-C	Quality characteristic of raw material capsule
ENC	Environmental characteristics
STC	Storage conditions
Conceptual Model for Packed Product – Amoxicillin Blister	
QCFPB	Quality characteristic of packed final product amoxicillin-blister
CPPP	Control parameter for packaging process (equipment)
QCPM	Quality characteristic of packaging materials

Figure 5 – The construction logic of a conceptual model for blister (Amoxicillin – packed capsules).
Source: Project Report – FUNED and NTQI

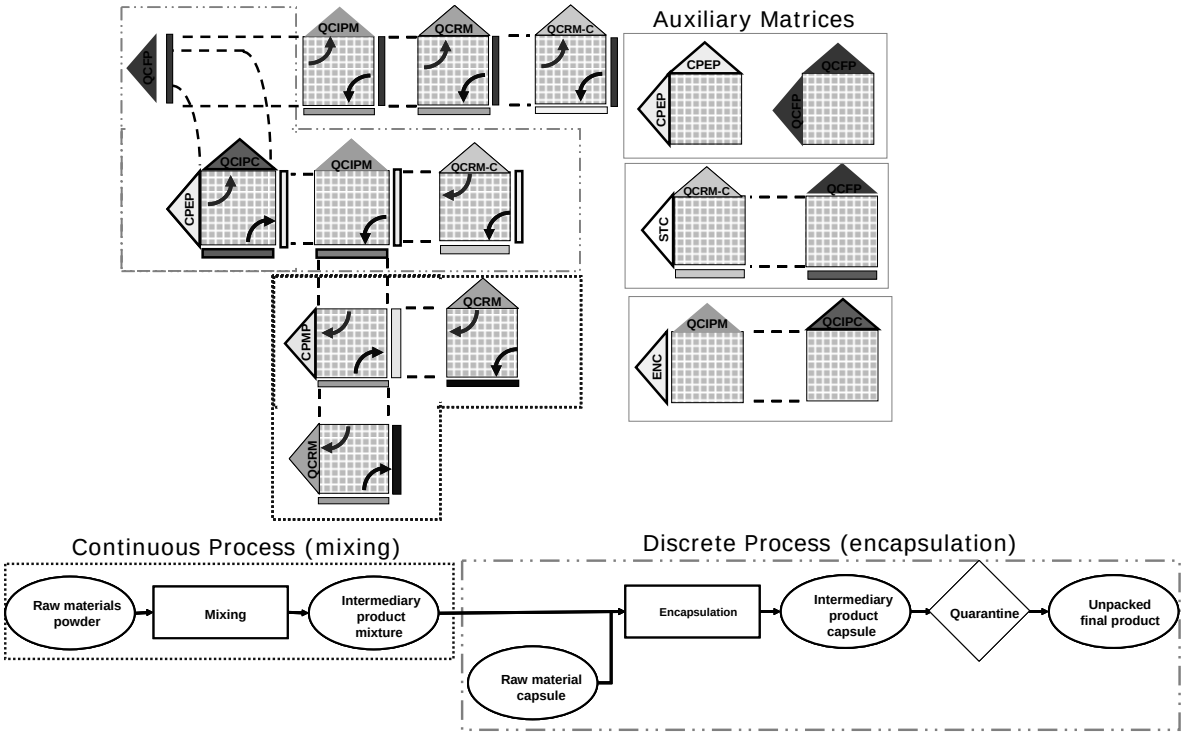


Figure 6 – Conceptual model for Amoxicillin-capsule.
Source: Project Report – FUNED and NTQI

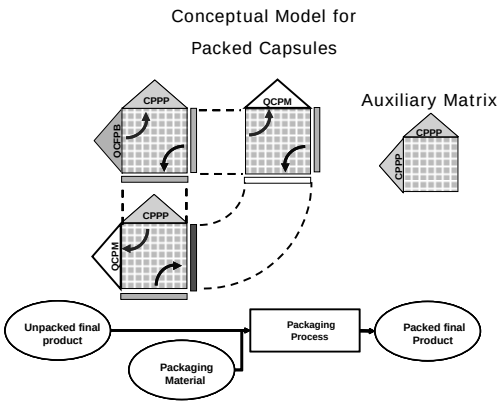


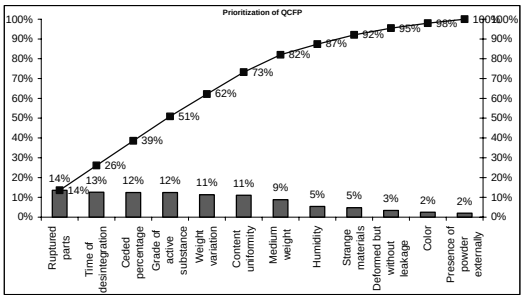
Figure 7 – Conceptual model for blister (Amoxicillin – packed capsules).

Source: Project Report – FUNED and NTQI

The model shown in Figure 6 is divided in two parts. One refers to the continuous process of obtaining Mixture, and another one refers to the discrete process of obtaining Amoxicillin-Capsule in Process (intermediary product – QCIPC) which, after quarantine, is called final product (QCFP). Since the characteristics of the intermediary product capsule are inserted in the quality characteristics of the final product, this table is separated in QCIPC (the triangle QCFP is a table, not a matrix). This distinction was fundamental for establishing cause-effect relationship needed for obtaining the final product, and it facilitated the analysis by the project team.

The team also felt it was necessary to collect and analyze other information, thus, auxiliary matrices were constructed as shown in Figure 6. It was important to determine (a) the environmental conditions because these affect the QCIPM and QCIPC, and (b) the storage conditions of capsules (raw materials) and encapsulated amoxicillin, because these may be influenced by those conditions.

For the conceptual model of blister (Figure 7), it wasn't important to evaluate the cause-effect relationship between amoxicillin capsule (raw material) and the process of blistering, because only the physical characteristics (length and thickness) would be influenced, these were assured by the quarantine process. In case of non conformity, the capsule would not enter the packaging process. The team also found it was necessary to obtain and analyze other information, thus, auxiliary matrices were built. The question was: if a PCAC were altered, how would other PCAC behave? On the whole, the team elaborated 12 tables and 19 matrices. Figure 8 shows an example of table and matrix.



Level 1	Level 2	Level 3	Level 4	Measure unit	Type of inspection	Direction
Physical characteristics	Appearance	Integrity	Deformed but without leakage/scratched	yes/no	QL	-
			Ruptured parts	yes/no	QL	-
			Strange materials	yes/no	QL	-
			Presence of powder externally	yes/no	QL	-
		Color		C/NC	QL	-
	Peso	Medium weight		mg	QT	↓↑
		Weight variation		%	QT	↓↑
		Time of desintegration		min	QT	↓
Chemical characteristics	Ceded percentage			% V.R. in minutes	QT	↓
	Grade of active substance			% of value in label	QT	↓↑
	Content uniformity			% of V. R. and DPR	QT	↓↑
	Humidity			%	QT	↓

Projected quality									
Prioritization									
Weight / Importance	3		3	5	1				
	Pharmaceutical equivalence	Bioequivalence	Stability	Bioavailability / Therapeutic effect in patient	Sensorial satisfaction in patient	Absolute weight	Relative weight	Specified values - goal	Globe values 1- lot 06050274
	3		1	0	3	15	3%	yes	
	5		5	5	5	60	14%	no	
	3		3	0	3	21	5%	no	
	1		1	0	3	9	2%	no	
	1		1	0	5	11	2%	C	
	5		3	3	0	39	9%	689	604 mg
	5		3	5	1	50	11%	+- 7,5%	-3,20 - +3,10 %
	5		5	5	1	56	13%	<= 45 min	16 min 7 s
	5		5	5	0	55	12%	> 85% (Q+5) V.R. in 90 min	96,34%
	5		5	5	0	55	12%	90% - 120% V.R	99,43%
	5		3	5	0	49	11%	????	100,13% DPR 0,75
	5		3	0	0	24	5%	max 14,5%	12,66%
						444	100%		

Figure 8 – Table of QCFP amoxicillin-capsule. Source: Project Report – FUNED and NTQI

The table of quality characteristics of final product (Figure 8) was elaborated based on Brazilian, North American, European and Japanese pharmacopoeia; and, it was deployed into physical, chemical, and biological characteristics. During working sessions, the biological characteristics were taken out, because they were not measured batch by batch. The team filled up the measure units, the specified values, and the goal for each characteristic (based on generic drug pharmacopoeia). The criteria used for prioritizing the characteristics of final product were: pharmaceutical equivalence, bioequivalence, stability, expected effect in the final consumer, and sensorial satisfaction of consumer (patient). The team attributed weight to each criterion and, then, gave to the parameters scores of : 5, influence; 3, may influence; 1, has to be considered; 0, no relationship. In order to facilitate the visualization of the importance attributed to each characteristic, the team drew a Pareto graphic as illustrated in Figure 8. To obtain the QCFP, the team deployed the cause-effect relationship as shown in Figure 6 (see, for example, CPEP x QCIPC). The questions asked were: how the control parameters of the encapsulation equipment may interfere with the quality of the intermediary product capsule? And what should be the control limits of CPEP for achieving QCIPC? Figure 9 shows this matrix.

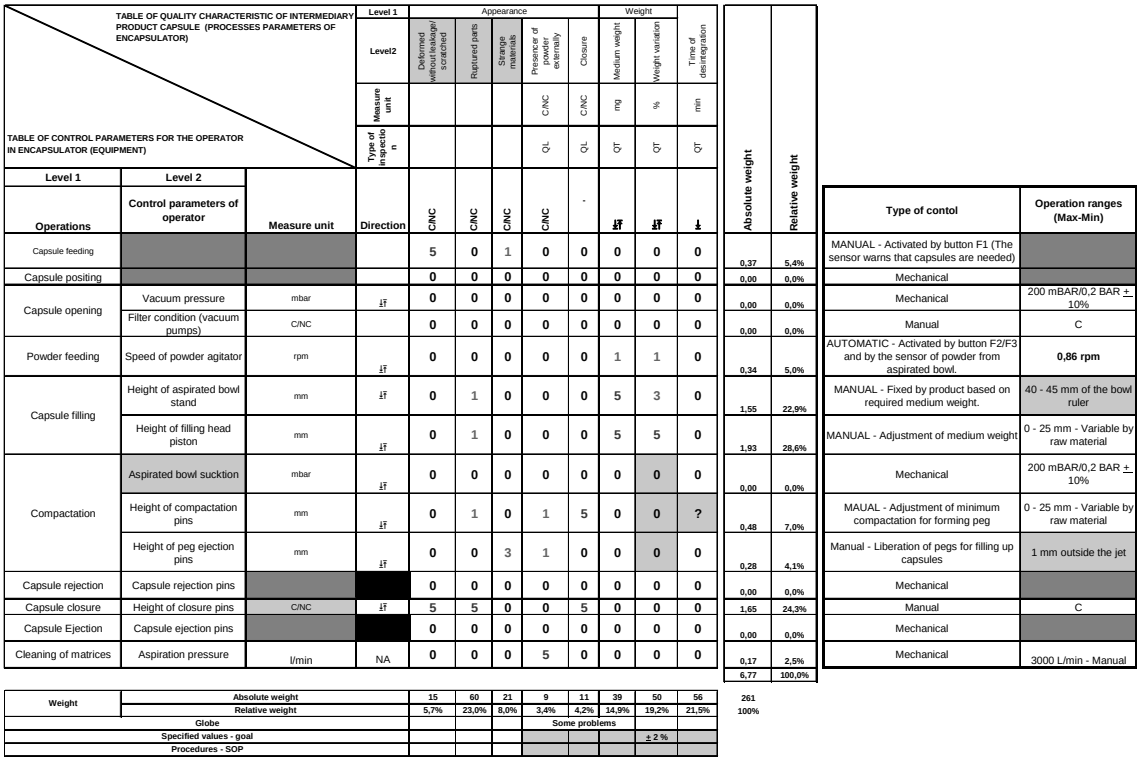


TABLE OF QUALITY CHARACTERISTIC OF INTERMEDIARY PRODUCT CAPSULE (PROCESSES PARAMETERS OF ENCAPSULATOR) / TABLE OF CONTROL PARAMETERS FOR THE OPERATOR IN ENCAPSULATOR (EQUIPMENT)			Level 1	Appearance					Weight			Absolute weight	Relative weight	Type of contol	Operation ranges (Max-Min)
			Level2	Deformed without breakage/ scratched	Ruptured parts	Strange materials	Presence of powder externally	Closure	Medium weight	Weight variation	Time of desintegration				
			Measure unit				C/NC	C/NC	mg	%	min				
			Type of inspection				QL	QL	QT	QT	QT				
Level 1	Level 2														
Operations	Control parameters of operator	Measure unit	Direction	C/NC	C/NC	C/NC	C/NC	-	↓T	↓T	↓				
Capsule feeding				5	0	1	0	0	0	0	0	0,37	5,4%	MANUAL - Activated by button F1 (The sensor warns that capsules are needed)	
Capsule positing				0	0	0	0	0	0	0	0	0,00	0,0%	Mechanical	
Capsule opening	Vacuum pressure	mbar	↓T	0	0	0	0	0	0	0	0	0,00	0,0%	Mechanical	200 mBAR/0,2 BAR ± 10%
	Filter condition (vacuum pumps)	C/NC		0	0	0	0	0	0	0	0	0,00	0,0%	Manual	C
Powder feeding	Speed of powder agitator	rpm	↓T	0	0	0	0	0	1	1	0	0,34	5,0%	AUTOMATIC - Activated by button F2/F3 and by the sensor of powder from aspirated bowl.	**0,86 rpm**
Capsule filling	Height of aspirated bowl stand	mm	↓T	0	1	0	0	0	5	3	0	1,55	22,9%	MANUAL - Fixed by product based on required medium weight.	40 - 45 mm of the bowl ruler
	Height of filling head piston	mm	↓T	0	1	0	0	0	5	5	0	1,93	28,6%	MANUAL - Adjustment of medium weight	0 - 25 mm - Variable by raw material
Compactation	Aspirated bowl sucktion	mbar	↓T	0	0	0	0	0	0	0	0	0,00	0,0%	Mechanical	200 mBAR/0,2 BAR ± 10%
	Height of compactation pins	mm	↓T	0	1	0	1	5	0	0	?	0,48	7,0%	MAUAL - Adjustment of minimum compactation for forming peg	0 - 25 mm - Variable by raw material
	Height of peg ejection pins	mm	↓T	0	0	3	1	0	0	0	0	0,28	4,1%	Manual - Liberation of pegs for filling up capsules	1 mm outside the jet
Capsule rejection	Capsule rejection pins			0	0	0	0	0	0	0	0	0,00	0,0%	Mechanical	
Capsule closure	Height of closure pins	C/NC	↓T	5	5	0	0	5	0	0	0	1,65	24,3%	Manual	C
Capsule Ejection	Capsule ejection pins			0	0	0	0	0	0	0	0	0,00	0,0%	Mechanical	
Cleaning of matrices	Aspiration pressure	l/min	NA	0	0	0	5	0	0	0	0	0,17	2,5%	Mechanical	3000 L/min - Manual
												6,77	100,0%		

Weight										
	Absolute weight	15	60	21	9	11	39	50	56	261
	Relative weight	5,7%	23,0%	8,0%	3,4%	4,2%	14,9%	19,2%	21,5%	100%
Globe					Some problems					
Specified values - goal								± 2 %		
Procedures - SOP										

Figure 9 – Matrix QCIPC X CPEP. Source: Project Report – FUNED and NTQI

The team elaborated a set of production standards: three Quality Assurance Standards (Table of QAS for Capsule, Mixture, and Blister); three Technical Standards for Processes (TSP for Encapsulation, Mixing, and Blistering); and, two Control Flowcharts (CF for Control of Capsule Approval and Blister Approval). See an example of standard in Figure 10.

	Quality characteristics		Specification (proportion of non-conformities)	In the beginning of process			When changing PVC bobbin			When changing aluminium bobbin			When there is rupture of PVC			When there is rupture of aluminium			When the machine stops for 10 or over 10 minutes			In the change of shift			In maintenance intervention			When a control parameter of a related equipment is altered			During the process					Related control document
				Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Form of measurement	Size of sample	Record	Frequency	Form of measurement	Size of sample	Record	Who	
Front	Lot number	Correct 1	50 ppm	Visual	1	LVOP																Visual	1	LVOP	Visual	1	LVOP								
		Legible 1	50 ppm	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	30 min	Visual	10	LVOP	Operator	
	Expiration date	Correct 2	50 ppm	Visual	1	LVOP																Visual	1	LVOP	Visual	1	LVOP								
		Legible 2	50 ppm																																	
	Absence of dirt internally		50 ppm																																	
	Presence of all capsules		50 ppm	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	Visual	10	LVOP	30 min	Visual	10	LVOP	perator	

Figure 10 – Table of Quality Assurance for Blister.
Source: Project Report – FUNED and NTQI

This work contributed to the early detection of problems related to product, process, and raw material. Two points can be highlighted: the first was the specification range of raw material characteristic density, which could have jeopardized the capability of compressing the powder in capsules (final product); the second was the quality characteristic humidity of raw material, whose upper specification limit was the same as of final product. This specification did not take into account the possibility of humidity absorption during the manufacturing process.

5. Conclusion

QFD method was applied, in this project, for quality assurance of a generic drug in the stage of pre-production. The method induced a multifunctional integration between different functional areas, which led the members of the company to recognize the importance of cooperation between different sectors in the stage of development. The tacit knowledge of the multifunctional team, when converted into explicit knowledge and organized into matrices showing cause-effect relationship, enabled the construction of a system of standards as a means of transmitting information to shop floor and , thus, contributing to assure the product quality. This system also served as the basis for training operators and, therefore, diminishing the variability in the beginning of production.

The application of QFD method made possible anticipative solution of problems, because it helped to identify, still in the pre-production phase, the cause-effect relationship between contributing factors necessary for obtaining quality characteristics of final product amoxicillin-capsule and quality characteristics of final product amoxicillin-blister.

Finally, this project brought an innovation by building a conceptual model for the development of a generic drug divided into two parts: first, for obtaining amoxicillin capsule; and, second, for packaging. The first was subdivided into continuous process (mixture) and discrete process (encapsulation). It is hoped that this work will contribute to future projects on generic drug development, and help us all to play a positive role in the social and economic development of the world.

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