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Article

Application of HACCP for development of quality risk management in a water purification system

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The present work reports the implementation of the Hazard Analysis Critical Control Point (HACCP) methodology to analyze the water purification system of a pharmaceutical site, in order to assure the system quality and prevent failures. As a matter of fact, the use of HACCP for development and implementation of Quality Risk Management (QRM) is not usual in pharmaceutical plants and it is applied here to improve the performance of the water purification system of a polymerization pilot plant used to manufacture pharmaceutical grade polymer microparticles. Critical Control Points (CCP) were determined with the aid of a decision tree and questions were made to characterize whether identified hazards constitute actual CCPs and should be monitored. When deviations were detected, corrective actions were performed and action plans were used for following-up and implementation of corrective actions. Finally, microbiological and physicochemical parameters were analyzed and the obtained results were regarded as appropriate. Therefore, it is shown that HACCP constitutes an effective tool for identification of hazards, establishment of corrective actions and monitoring of the critical control points that impact the process and the quality of the final pharmaceutical product most significantly.

Keywords: Quality. Pharmaceutical industry. Purified water. Risk. HACCP.

INTRODUCTION

Several techniques can be used for risk assessment, either alone or in combination with other techniques (Faisal, Khan, Abassi, 1998; Tixier *et al*., 2002; Reniers *et al*., 2007; Marhavilas, Koulouriotis, 2008). In all cases, the selected technique (or combination of techniques) should allow the effective analysis of the studied process and the resulting evaluation should be safe enough to support the decision-making process regarding the product quality (WHO, 2013). Particularly, the Product Quality Research Institute (PQRI), whose primary objective is to generate research data on the quality and development of pharmaceuticals for submission to regulatory authorities, reported in 2008 the main methodologies currently used by pharmaceutical industries for risk assessment, highlighting that the selection of the most appropriate methodology depends on the degree of risk that can be accepted by the organization (Reddy *et al*., 2014; Who, 2013). According to this report, the most often used techniques for qualitative analysis are Process Control Charts and FMEA (Failure Modes and Effects Analysis) (Frank *et al*., 2008). Particularly, the FMEA procedure can be expanded to FMECA (Failure Mode, Effects and Criticality Analysis) when the risk assessment is provided by the Risk Priority Number (RPN) (Peeters,

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Basten, Tinga, 2018), since PQRI does not impose a quantitative technique for the pharmaceutical industries.

As a whole, risk assessment should be conducted by appropriate techniques that can describe and identify the degree of risk, ensuring the product quality management. Many techniques have been proposed since the 1970's with these purposes, including the ones reported by Faisal, Khan & Abbasi (1998), Tixier *et al*. (2002), Reniers *et al*. (2007), Marhavilas & Koulouriotis (2008) and Faisal, Rathnayaka & Ahmed (2015), which described qualitative and quantitative procedures for risk assessment that can be used independently or in association with other techniques.

Hazard Analysis and Critical Control Point (HACCP) is a risk assessment technique that has been applied mainly in the food supply chain (WHO, 2013; Scipioni *et al*., 2002). For this reason, in 2005 the International Organization for Standardization (ISO) issued the ISO 22000, which incorporated HACCP into food safety management systems (Psomas, Kafetzopoulos, 2015, Hurst, 2013). Additionally, in 2010 the Association of Normalization Mercosur (ANM) established HACCP requirements within the food chain. For the pharmaceutical industry, the Quality Risk Management guideline ICH Q9 indicates that HACCP can be used as a tool for risk assessment. Currently, HACCP principles have being expanded to automotive, chemical, and aviation industries (WHO, 2013).

The hazards that affect the quality of pharmaceutical products are monitored with help of Good Manufacturing Practices (GMP), as required by regulatory agencies. In this case, HACCP can be implemented as a complementary procedure, used to identify and perform the control of chemical, physical or biological agents that can affect the final product quality and the operations that affect the product manufacture (WHO, 2013). The successful implementation of the method can normally be achieved through application of the seven basic HACCP principles (Wallace *et al*., 2014; Trafialek, Kolanowski, 2014; WHO, 2013), as described below.

The first principle is the main pillar and can be stated as identifying, analyzing and understanding the hazard. When one fails to apply this principle, due to lack of knowledge or use of inadequate risk analysis methods, the HACCP becomes inefficient, as well reported in the food industry (Wallace *et al*., 2014). As a matter of fact, appropriate training of the technical team on the HACCP procedures and overall understanding of the process constitute critical issues to reach the success of this step.

The second principle regards the determination of the Critical Control Points (CCP), which can be defined as any place, process, person or operation procedure that can generate an unacceptable risk to the final product quality. If the risk is not known and monitored, it can exert direct impact on the process control and can become a critical process control point. Once CCPs are defined, the main goals and boundaries of control routines can also be defined (Chemat, Hoaru, 2004).

The third principle of HACCP is the establishment of critical limits for the CCP (WHO, 2013), which must be specified and controlled on a scientific basis (WHO, 2013, Trafialek, Kolanowski, 2014). The SPC (Statistical Process Control) technique is recommended as an effective tool to indicate when a CCP is below or above its pre-established critical limits (Lim, Antony, Albliwi, 2014; Hurst, 2013). For the identification of Critical Control Points (CCP), the Codex Alimentarus guide indicates the execution of actions that form a decision tree and aim to determine whether the identified hazards indeed constitute CCPs. The decision tree proposes of a logical sequence of questions about the normal process operations, which requires a common-sense approach of the executor and access to the technical data in order to be answered properly. The decision tree constitutes a complementary tool and should be performed for all identified hazards (Bryan, 1996; Codex Alimentarius Commission, 2003). For the decision tree to be used effectively, it is imperative that the four basic sequential questions be interpreted correctly (Codex Alimentarius Commission, 2003):

- Q1: Are there preventive measures for the hazard in question?
- Q2: Is this step specifically designed to eliminate or reduce the probability of occurrence to an acceptable level?

- Q3: Can identified hazard contamination occur in excess reaching an acceptable level or will it increase reaching an unacceptable level?
- Q4: Will the subsequent step eliminate or reduce the probability of occurrence of the hazard to an acceptable level?

Monitoring constitutes the fourth principle of HACCP (WHO, 2013). The CCP monitoring is valid if the process is under control. When the process is not controlled, adjustments and actions must be taken to ensure control of the CCP. Then, the development of corrective actions constitutes the fifth principle of HACPP (Codex Alimentarius Commission, 2003). These actions should be developed in advance, during the HACCP plan, and should also ensure that the CCP can remain within the pre-established limits (Trafialek, Kolanowski, 2014; Chemat, Hoarau, 2004).

The procedures associated with the sixth principle aim to verify whether the HACCP system is working effectively (Codex Alimentarius Commission, 2003). These procedures may include audits of HACCP systems already implemented (Trafialek, Kolanowski, 2014), periodic monitoring of CCP values and evaluation of available records as objective evidences. If the results obtained during the comprehensive verification of the HACPP system identify deficiencies, the multidisciplinary team should modify the current HACCP plan (WHO, 2013).

The seventh and last principle of the HACCP methodology is the preparation of the documentation, which characterizes the implementation of the methodology. The documentation guarantees the accurate and efficient implementation of the HACCP and can be used as a source of objective evidences. Documentation should include CCP monitoring records, corrective action plans, verification, scheduling, identified risks and observed deviations. The documentation must be periodically reviewed in order to be always up-to-date and available as data sources and queries for the technical team (Hallen *et al*., 2015; WHO, 2013).

The integration of HACCP with FMEA is common in the food industry to ensure the final product quality (Scipioni *et al*., 2002) and as an audit tool for the implemented HACCP system (Trafialek, Kolanowski, 2014). While HACCP constitutes a tool for prevention and follow-up, the FMEA tools can be used for inspection (Moran *et al*., 2017).

Although the application of HACCP is consolidated in the food industry, HACCP implementations in the pharmaceutical field are rare. Despite that, the use of HACCP in pharmaceutical plants is promising, can be focused on total quality management, and can provide faster and accurate actions and inspections. In particular, water purification systems are present in most pharmaceutical processes, aiming to remove physicochemical, biological and microbial impurities from process water streams through a number of purification operations, so that the water can be suitable for pharmaceutical use or human consumption according to the specifications of the pertinent regulations (Brasil, 2016b; Brasil, 2011). For this reason, in the present work the HACCP tool is applied for the first time to develop a QRM for the water purification process of a pharmaceutical site. As expected for HACPP implementations, the seven principles of HACCP and the respective decision tree are analyzed, and microbiological and chemical parameters are examined in accordance with the Brazilian legislation, in order to illustrate the effectiveness of the HACPP procedures applied for design of the analyzed water purification system.

MATERIAL AND METHODS

Proposed HACCP procedure

The main HACCP steps and procedures are schematically illustrated in Figure 1. The HACCP study was started with the process flowchart design and the Critical Control Points (CCPs) were determined. For the determination of CCPs the decision tree was used (Codex Alimentarius Commission, 2003). After the identification of CCPs, critical limits must be established for each CCP and the analysed process must be monitored continuously to ensure that it is under appropriate control and corrective actions performed in case of deviation. In this step, audits and monitoring are common procedures. When the audits or monitoring indicate any deviation, corrective actions are immediately taken, which are extremely important

and essential for the quality management implementation. The last step is to verify the compliance to the critical limits. The HACCP program must be documented, therefore validations, critical limits, procedures tests and other evaluations should be part of the HACCP documentation. In addition, these data must be accessible at any time and be easy to add changes to it (Scipioni *et al*., 2002, Moran *et al*., 2017).

The EngePol pilot plant has capacity to produce up to 200 kg per batch of polymer micro- or nanoparticles for pharmaceutical use. The plant can be used to carry out suspension, emulsion and miniemulsion (Fonseca *et al*., 2013) polymerizations, allowing the *in-situ* encapsulation of chemicals into different polymer materials.

The processes implemented to produce purified water and the respective uses of the water are extremely important for the pharmaceutical industry, since purified water is utilized in all sections of the plant, from product manufacture to cleaning of sites and equipment. As a matter of fact, Brazilian regulations describe in detail the general requirements for the water quality intended for pharmaceutical use (Brasil, 2010).

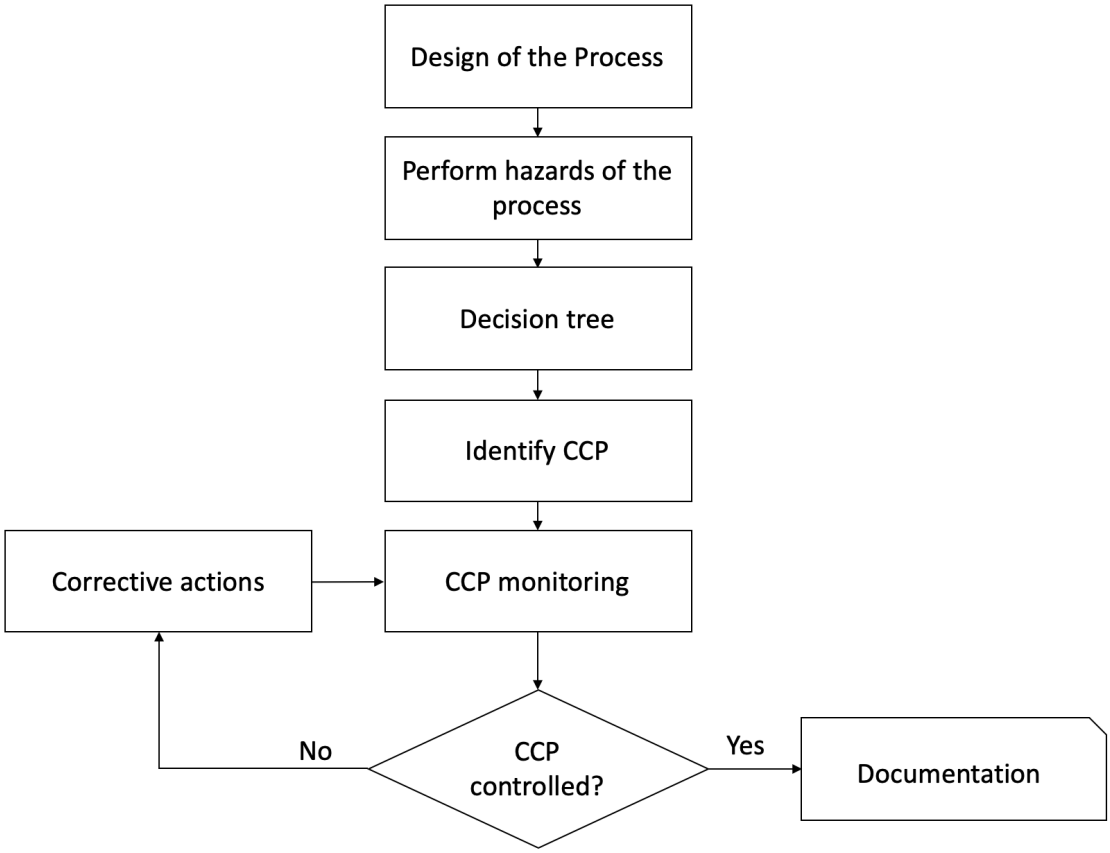
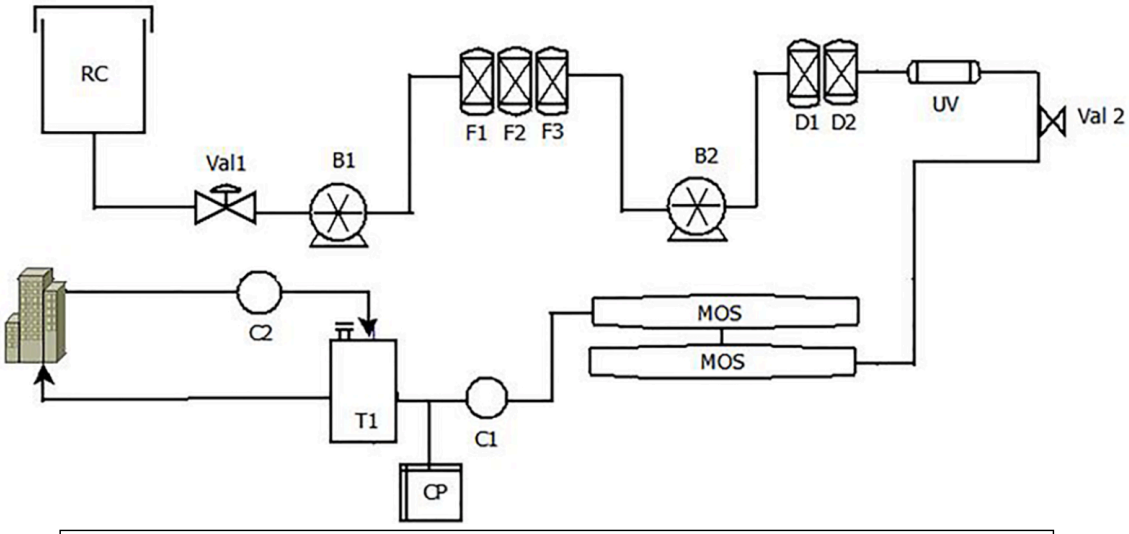


FIGURE 1 - Schematic representation of the main steps of the HACCP procedure for a pharmaceutical plant pilot.

Water purification process

The analyzed water purification process is based on double-step Reverse Osmosis (RO) (Brasil, 2016b), as shown in Figure 2. Particularly, purified water is distributed to all rooms (receivement, solution preparation, reaction, purification, storage, shipment) located at the first floor of the pilot plant and the last distribution point is located at the second floor (characterization and quality assurance). Distribution piping and water reservoirs are

made of 316L stainless steel, with low carbon and high corrosion resistance, as required by regulations. In Figure 2, drinking water is stored in the reservoir (RC). The first sampling point (P1) is connected to a pressure valve (Val1) and to a pump (B1) that feeds the purification pre-filters (F1, F2 and F3), where removal of sediments (until 5 mm) particles and chlorine is performed. Subsequently, a second pump (B2) feeds the treated water to two deionizers (D1 and D2) that remove dissolved inorganic salts. The treated water then flows through double-pass reverse osmosis membranes (MOS) after being exposed to ultraviolet light (UV), for sterilization. Finally, the water is transported to the storage tank T1, where conductivity and temperature are monitored at sampling points placed before (C1) and after (C2) the storage tank and the measure made in control painel (CP). The water stored in tank (T1) is kept under continuous recirculation to avoid the formation of stagnant films and the settling of remaining suspended particles. The water quality is also monitored with help of sampling points (P1) placed at the solution preparation room (P2), the reaction room (P3) and the quality control laboratory (P4).



Legend			
RC	Central reservoir	B2	Water pump 2
Val1	Valve 1 – P1	D1	Deionizer 1
B1	Water pump 1	D2	Deionizer 2
F1	Particles filter	Val2	Valve 2
F2	Carbon filter 20	MOS	Reverse osmosis membrane
F3	Granular coal filter	C1	Conductivity meter
UV	Ultraviolet light	C2	Return conductivity meter
T1	Purified water tank	CP	Control panel

FIGURE 2 - Schematic diagram of double pass reverse osmosis water treatment system in a pharmaceutical pilot plant

Hazard identification constitutes the first step of the HACCP procedure; however, this step may be subjective and may depend on the opinions of experts. Therefore, knowing the process is fundamental. In the analyzed case, the main pursued objective is the establishment of biological, chemical and physical parameters that can constitute potential hazards for production of purified water with pharmaceutical grade. A list of potential hazards, shown in Table I, indicates how each hazard may be controlled, based on the

identifiable deviations and respective corrective actions. Questions were formulated to determine whether the identified hazards should be regarded as CCPs. Then, a decision tree was built and applied to monitor the CCP candidates and determine the respective critical limits, as shown in Table II. Subsequently, the limits for several CCP candidates were established in accordance with Table III. Particularly, continuous monitoring of the analyzed system is advised for two main reasons: (1) to understand how the system is working and to evaluate if the obtained results are in accordance with all required parameters; and (2) to provide corrective actions when deviations are detected. The action plan 5W2H (Gil, 2010) should be used to define and implement corrective actions, and to establish necessary responsibilities, costs and procedures (constituting a quality management tool that tracks the activities through a series of questions: "What?", "Who?", "Why?", "Where?", "When?", "How?" and "How much?", as described by Daychoum, 2018). Table III shows some physicochemical and microbiological parameters required for the sampling points P1 to P5. Sampling point P1 was monitored according to the criteria established by the Brazilian Ministry of Health, 2914/2011 and PRC 5/2017 for drinking water (Brasil, 2011; Brasil, 2017). The physicochemical parameter monitored in the distribution system (P1) was pH at 25ºC and the microbiological parameters were total count of mesophilic bacteria pour plate and absence of faecal and total coliforms. The sampling points P2 to P5 followed the criteria determined by the Brazilian Pharmacopoeia (Brasil, 2016b) for purified water as shown in Table III.

The presence of total and fecal coliforms in drinking water was analyzed by incubation for 24 h, using the broth test (Brasil, 2016b). For detection of total coliforms, the Brilliant Green medium (Difco – Sweden) was utilized at 32.5 ºC/24 h in an inverted Duhram tube (Pinto, Kaneko, Pinto, 2010). For detection of fecal coliforms, standard EC Broth (Difco – Sweden) was employed at 44.0 ºC/24 h with an inverted Duhram tube. Soybean Casein broth (Difco – Sweden) and Enterobacteria Enrichment broth (Difco – Sweden) were used to prepare the incubation broth and detect coliforms in purified water (Brasil, 2016b). A plate containing Cetrimide agar (Difco – Sweden) was used to detect the presence of *Pseudomonas aeruginosa*. Colony growth was confirmed by microbial identification tests, gram staining and biochemical tests for *Pseudomonas aeruginosa* and coliforms (Pinto, Kaneko, Pinto, 2010; Brasil, 2016c).

The physicochemical parameters pH and conductivity followed the values established by the Brazilian Pharmacopoeia (2016). The pH of the samples was determined with the aid of a pH meter (MS Tecnopon, MPA-210, Brazil) immediately after sample collection. Conductivity measurements were performed in line using a cell (MS Tecnopon, mCA-100, Brazil) with a constant of 1.0 cm^{-1} (corresponding to 1 cm^3 conductor resistance). Application of the HACCP procedures and the activities for the implementation of the HACCP plan resulted in the regulatory documentation, which can be used as a tool in pharmaceutical industries for monitoring and establishment of measures for risk management (Pinto, Kaneko, Pinto, 2010).

TABLE I - Potential hazards identified during the HACCP analysis of the water purification system

Item	Hazards	Level of Control	Possible Deviation	Corrective actions
1	Physicochemical and microbiological quality control of drinking water	Weekly analyses of physicochemical and microbiological properties of drinking water.	Drinking water is analyzed only after cleaning of the water reservoir.	Assure the weekly physicochemical and microbiological analyses of drinking water.

(continues on the next page...)

TABLE I - Potential hazards identified during the HACCP analysis of the water purification system

Item	Hazards	Level of Control	Possible Deviation	Corrective actions
2	Control of use and exchange of pre-filters (resin filter and activated carbon)	Control of use and exchange of pre-filters (resin filter and activated carbon)	Exchange date of pre-filters and of pressure and leak tests are not reported accordingly.	Establishment of routine operation procedures and documents for control of pre-filters.
3	Control of pH, oxidable substances and conductivity	Daily logs of pH and conductivity of purified water	pH, oxidable substances and conductivity measurements are not reported accordingly.	Establishment of routine operation procedures and documents for control of pH, conductivity and oxidable substances.
4	Time control of the UV lamp	Record and control number of hours of use of the UV lamp	Time of use and control number of the UV lamp are not reported accordingly.	Establishment of routine operation procedures and documents for control of time of use and control number of the UV lamp.
5	Calibration of in-line conductivity meter, thermocouples and temperature indicators	Regulatory	Miscalibration	Implement calibration program for in-line conductivity meter, thermocouples and temperature indicators
6	Microbiological control	Regulatory	The microbiological control is not reported accordingly.	Establishment of routine operation procedures and documents for microbiological control.
7	Control of use and exchange of reverse osmosis membranes	Control of pressure, leakage and water conductivity.	The control of use and exchange of reverse osmosis membranes is not reported accordingly.	Establishment of routine operation procedures and documents for control of use and exchange of reverse osmosis membranes.
8	Control of "Cleaning In Place" procedures	Establish cleaning routine with circulating water between 80-90 ºC	The control of "Cleaning in Place" procedures is not reported accordingly.	Establishment of routine operation procedures and documents for control of "Cleaning in Place" tasks.

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TABLE I - Potential hazards identified during the HACCP analysis of the water purification system

Item	Hazards	Level of Control	Possible Deviation	Corrective actions
9	Calibration of water pump manometers	Regulatory	Miscalibration	Implement calibration program for water pump manometers.

TABLE II - Decision tree of the HACCP plan used to determine CCPs for the analyzed water purification system

Hazards	Q1	Q2	Q3	Q4	CCP
	(Yes/No)	(Yes/No)	(Yes/No)	(Yes/No)	
Physicochemical and microbiological quality control of drinking water	Y	Y	-	-	**CCP1**
Control of use and exchange of pre-filters (resin filter and activated carbon)	N	Y	-	-	**review process**
Control of pH, oxidable substances and conductivity	Y	Y	-	-	**CCP2**
Time control of UV lamp	N	Y	-	-	**review process**
Calibration of in-line conductivity meter, thermocouples and temperature indicators	Y	Y	-	-	**CCP3**
Microbiological control of purified water	Y	Y	-	-	**CCP4**
Control of use and exchange of reverse osmosis membranes	N	Y	-	-	**review process**
Control of "Cleaning in Place"	Y	Y	-	-	**CCP5**
Calibration of water pump manometers	Y	N	-	-	**N**

TABLE III - Microbiological and physicochemical limits for drinking and purified water

Point	Water type	Microbiological Parameters			Physicochemical Parameters	
		TCMB[1]	Coliforms[2]	*P.a*[3]	pH	Conductivity
P1	**Drinking**	≤ 500 CFU/mL	absence	NC[4]	6.0 – 9.5	NC[4]
P2 to P5	**Purified**	≤ 100 CFU/mL	absence	absence	According to steps 1, 2 e 3[5]	≤ 1,3 µS/cm According to steps 1, 2 e 3[5]

1- Stands for "Total Counting of Mesophilic Bacteria pour plate" (TCMB).
2- Includes total and fecal coliforms (*Escherichia coli*).
3- *Pseudomonas aeruginosa* is regarded as the main pathogen of purified water.
4- Stands for "not controlled".
5- Brasil, 2016a

RESULTS AND DISCUSSION

The quality and safety of purified water streams must be ensured to meet the standards of pharmaceutical use, as the water used for preparation of pharmaceuticals, and cleaning of utensils and equipment must be free of chemical and microbiological contaminants. Table I shows the hazards identified in the water purification system, while Table II indicates the CCPs that must be controlled to produce water within the current legislation criteria as shown in Table III (Brasil, 2016a). According to the proposed decision tree model (Codex Alimentarius Commission, 2003; Horchner *et al*., 2006), five CCPs were identified:

CCP1: Physicochemical and microbiological quality control of drinking water;
CCP2: Control of pH, oxidable substances and conductivity values at the sampling points;
CCP3: Calibration of monitoring equipment;
CCP4: Microbiological control of purified water at the sampling points;
CCP5: Control "Cleaning in Place".

After identification of CCPs and possible deviations, corrective actions can be suggested, as described in Table II. In order to implement the proposed plan as suggested, pre-filters, filters, reverse osmosis membranes and UV lamps were replaced by new ones. Besides, sanitization of water distribution lines was performed at 80ºC for 30 minutes daily, until attainment of the required physicochemical and microbiological parameters after two weeks. Figure 3 and 4 illustrates the evolution of physicochemical process parameters at sampling points after application of corrective actions, indicating that the proposed monitoring procedures were sufficient to guarantee the adequate performances of the analyzed parameters.

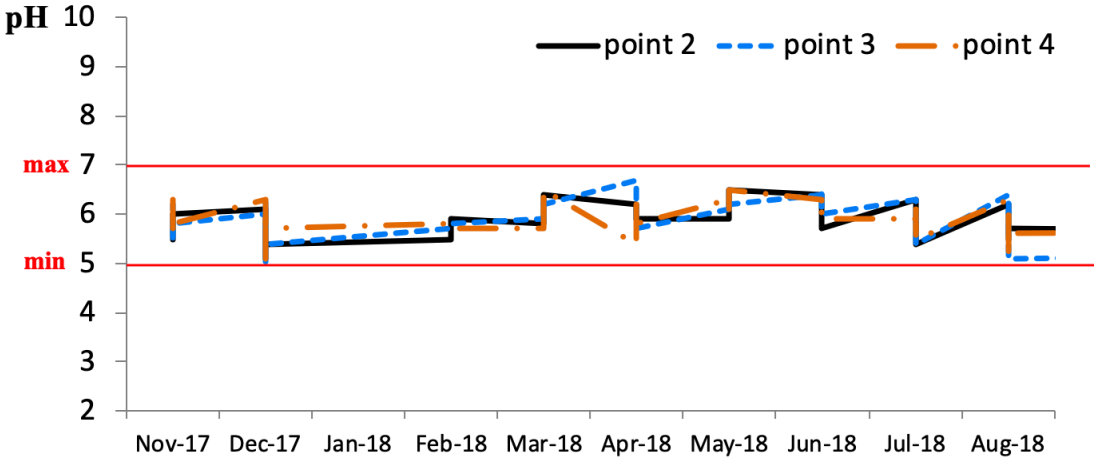

FIGURE 3 - pH Monitoring at sampling points after the application of corrective actions

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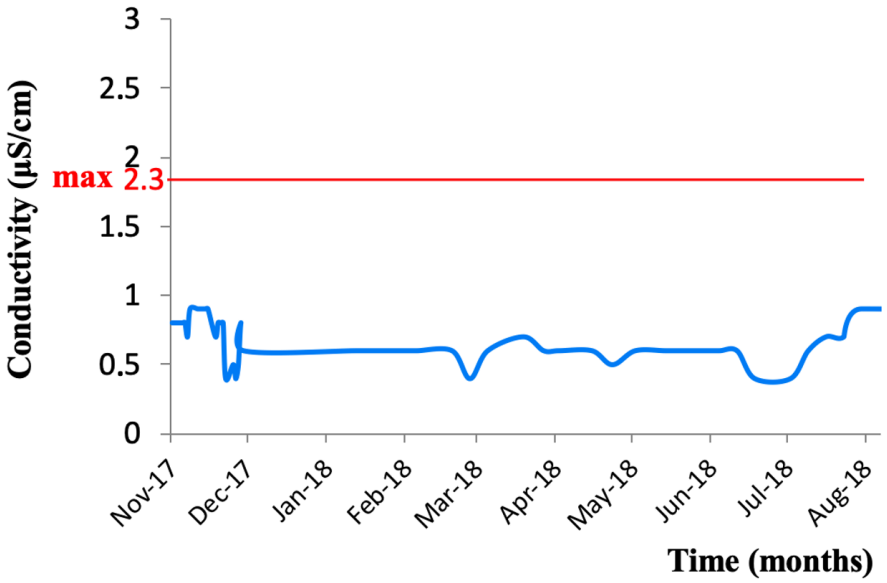

FIGURE 4 - Conductivity monitoring at sampling points after the application of corrective actions

The performance of the water purification system remained appropriate even after the reduction of the sanitization frequency to once-a-week. In the first weeks of operation, undesired bacterial growth was detected at sampling point P3, when counts approached 80 CFU/mL (max. 100 CFU/mL), with detection of Gram-negative bacteria, but not of *Pseudomonas aeruginosa* or coliforms. As the main objective in the treatment of water for pharmaceutical use is microbial control, which consists of biofilm control, sanitization with hot water (80ºC to 85ºC) was an efficient procedure. It was evidenced that, after a sequence of sanitization, the contamination at point P3 was no longer present. This result was expected, since hot water penetrates the biofilm formed on the walls of the purified water treatment system and physically removes it and also promotes the lethality of the microorganisms that colonize it. Thus, after consecutive sanitizations, P3 did not show microbial count.

CCP1 regarded the control of the drinking water. The quality control of drinking water is necessary to monitor the total inorganic and microbial loads to the system, which can accumulate in the pre-filters and lead to recontamination (Damikoukaa, Katsirib, Tziac, 2007). It must be highlighted that very high microbial load was observed in the water purification system in one event, when the external lines that feed water to the plant were manipulated by the fire department for construction of water reservoirs for fire prevention. Due to the proposed procedures, the internal purified water stream remained specified and proper for use.

CCP2 regarded the control of pH, conductivity (µS /cm) and oxidable substances at the sampling points of the purified water circuit. It must be highlighted that these variables remained specified in the whole period considered in the present report. Similar results were obtained for CCP4, which regarded the microbiological control at the sampling points of the purified water circuit.

In order to consider CCP4, which regards the proper calibration of process equipment, a calibration program was implemented, which prevented calibration problems after the beginning of the operation of the proposed HACCP plan. Finally, the "Cleaning in Place" frequency, related to CCP5, was set to one-a-week and led to satisfactory results. As any change in conductivity and pH values may indicate the growth of biofilms inside the water distribution system (Kiskó, Szabó-Szabó, 2011; Macêdo, 2000), extra sanitization procedures may be recommended when

deviations of pH and conductivity values are detected. Nevertheless, during the period considered in the present work, this control action was not necessary.

Casani and Knochel (2002), used HACCP to use reused water in the food industry. The monitoring phase of the HACCP plan, which consists of continuous verification, was considered the initial validation, assessing whether the system is working perfectly or if corrective action was needed. Likewise, we used the CCPs monitoring phase as a validation phase and verified when the CCPs are controlled with reference values below the critical control limits established during the progress of the HACCP plan. Thus, the CCP lower and upper limits could be effectively detected by this procedure, proving the HACCP is an effective tool for monitoring the quality control parameters of the purified water.

HACCP has been applied in a water treatment system in order to guarantee the safety and quality of drinking water (Casani, Knochel, 2002). The HACCP technique was demonstrated by Havelaar (1994) and Damikoukaa and collaborators (2007), for the control of faecal pathogens, bacteria, viruses, protozoa in drinking water in the food industry. The technique proved to be effective in implementing improvements in drinking water treatment systems by imposing barriers through CCP controls to reduce microbial contamination. However, in the pharmaceutical industry, the water suitable for pharmaceutical use for non-sterile products is purified water. The HACCP principles, which were recommended by the World Health Organization (WHO, 2013), applied in the treatment of purified water treatment system had not yet been described in the literature until the present work.

CONCLUSIONS

The present work reported for the first time the implementation of the Hazard Analysis Critical Control Point (HACCP) methodology to analyze the water purification system of a pharmaceutical site, in order to assure the system quality, prevent failures and develop the Quality Risk Management (QRM) procedures of the plant. Critical Control Points (CCP) were determined with the aid of a decision tree and questions were made to characterize whether identified hazards constitute actual CCPs and should be monitored. It was observed that the control of the drinking water quality, the control of the physicochemical parameters (pH, conductivity and oxidizable substances in the purified water stream), the microbiological control, the calibration of in-line instruments and the "Cleaning in Place" policy constitute the main CCPs of the process. Based on the proposed HACCP plan, control actions were developed and implemented and were shown to be sufficient to keep the plant specified during the period considered in the present study. Therefore, it was shown that HACCP constitutes an effective tool for identification of hazards, establishment of corrective actions and monitoring of the critical control points that impact the process and the quality of final pharmaceutical products most significantly.

REFERENCES

Agência Nacional de Vigilância Sanitária (Brasil). Resolução nº 17, de 16 de abril de 2010. Regulamento Técnico de Boas Práticas de Fabricação de Medicamentos. Diário Oficial da União 16 abril 2010; Seção 1.

Allata S, Valero A, Benhadia L. Implementation of traceability and food safety systems (HACCP) under the ISO 22000:2005 Standard In North Africa: The case study of an ice cream company in Algeria. Food Control. 2017;79:239-253.

Brasil. Ministério da Saúde, Agência Nacional de Vigilância Sanitária. Farmacopéia Brasileira. 6ª edição: Condutividade da água [Internet]. Brasília (DF): Ministério da Saúde, 2016a. Available at: < http://portal.anvisa.gov.br/farmacopeia-brasileira>. Accessed on: 20 Sept. 2019.

Brasil. Ministério da Saúde, Agência Nacional de Vigilância Sanitária. Farmacopéia Brasileira. 6ª edição: Água Purificada [Internet]. Brasília (DF): Ministério da Saúde, 2016b. Available at: <http://portal.anvisa.gov.br/farmacopeia-brasileira>. Acessed on: 20 Sept. 2019.

Brasil. Ministério da Saúde, Agência Nacional de Vigilância Sanitária. Farmacopéia Brasileira. 6ª edição: Ensaios Microbiológicos [Internet]. Brasília (DF): Ministério da Saúde, 2016c. Available at: <http://portal.anvisa.gov.br/farmacopeia-brasileira>. Acessed on: 20 Sept. 2019.

Brasil. Ministério da Saúde, Portaria nº 2.914, de 12 de dezembro de 2011 [Internet]. Brasília (DF)**:** Available at: <https://bvsms.saude.gov.br/bvs/saudelegis>. Acessed on: 02 Oct. 2019.

Brasil. Ministério da Saúde, Portaria de Consolidação nº 5, de 28 de setembro de 2017 [Internet]. Brasília (DF): Available at: <http://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prc0005_03_10_2017.html>. Acessed on 02 Oct. 2019.

Bryan FL. Another Decision-Tree Approach for Identification of Critical Control Points. J Food Prot. 1996;59(11):1242-1247.

Casani S, Knochel S. Application of HACCP to water reuse in the food industry. Food Control. 13 2002;13(4-5):315-327.

Chemat F, Hoarau N. Hazard analysis and critical control point (HACCP) for an ultrasound food processing operation. Ultrason Sonochem. 2004;11(3-4):257–260.

Damikoukaa I, Katsirib A, Tzic C. Application of HACCP principles in drinking water treatment. Desalination Water Treat. 2007;210(1-3):138-145.

Daychoum M. 40+20 Ferramentas e técnicas de gerenciamento. 7ª edição, Rio de Janeiro, Brasport Livros e Multimídia, Ltda, 2018.

Faisal I, Khan S, Abbasi A. Techniques and methodologies for risk analysis in chemical process industries. J Loss Prev Process Ind. 1998;11(4):261-277.

Faisal I, Rathnayaka S, Ahmed, S. Methods and Models in process safety and risk management: Past, present and future. Process Saf Environ Prot. 2015;98:116-147.

Codex Alimentarius Commission, Hazard Analysis and Critical Control Point (HACCP) System and Guidelines for its Application, Annex to the Recommended International Code of Practice — General Principle of Food Hygiene, Annex to CAC / RCP 1-1969 Rev. 4, 2003. Available at: <http://www.fao.org/fao-who-codexalimentarius/en/>. Accessed at: 25 Sept. 2019.

Frank T, Brooks S, Creekmores R, Hasselbalch B, Murrays K, Obeng K, et al. Quality Risk Management Principles and Industry Case Studies. Pharmaceutical Quality Research Institute Manufacturing Technology Committee. 2008;1-9.

Fonseca LB, Nele M, Volpato NM, Seiceira RC, Pinto JC. Production of PPMA Nanoparticles Loaded with Praziquantel Through "In SituMiniemulsion Polymerization. Macromol React Eng. 2013;7(1):54-63.

Gil, ES. Controle fisico-químico de qualidade de medicamentos. São Paulo, Pharmabooks; 2010.

Hallen RM, Salem MY, Fatahallah FA, Abdelfattah LE. Quality in the pharmaceutical industry – A literature review. Saudi Pharm J. 2015;23(5):463-469.

Havelaar AH. Application of HACCP to drinking water supply. Food Control. 1994;5(3):145-152.

Horchner PM, Brett D, Gormley B, Jenson I, Pointon, AM. HACCP Based Approach to the Derivation of on Farm Food Safety Program for the Australian red meat industry. Food Control. 2006;17(7):497-510.

Hurst WC. Integrating Hazard Analysis Critical Control Point (HACCP) and Statistical Process Control (SPC) for safer nut processing. Woodhead Publishing Limited, Georgia. USA, 2013.

Kiskó G, Szabó-Szabó O. Biofilm removal of Pseudomonas strains using hot water sanitation. Acta Univ Sapientiae, Aliment. 2011;4:69–79.

Lim SAH, Antony J, Albliwi S. Statistics Process Control in the food industry – A systematic review and future research agenda. Trends Food Sci Technol. 2014;37(2):137-151.

Macêdo JAB. Biofilmes bacterianos, uma preocupação da industria farmacêutica. Rev Fármacos Med. 2000;2(7):19-24.

Moran F, Sullivan C, Keener K, Cullen P. Faciliting smart HACCP strategies with Process Analitycal Techonology. Curr Opin Food Sci. 2017;17:94-99.

Marhavilas PK, Koulouriotis DE. A risk-estimation methodological framework using quantitative assessment techniques and real accidents' data: Application in an aluminum extrusion industry. J Loss Prev Process Ind. 2008;21(6):596–603.

Peeters JFW, Basten RJI, Tinga T. Improving failure analysis efficiency by combining FTA and FMEA in a recursive manner. Reliab Eng Syst Safe. 2018;172:36-44.

Pinto, TJA, Kaneko TM, Pinto AF. Controle Biológico de Qualidade de Produtos Farmacêuticos, Correlatos e Cosméticos, São Paulo, Editora Atheneu, 2010.

Psomas EL, Kafetzopoulos DP. HACCP effectiveness between ISO 22000 certified and non-certified dairy companies. Food Control. 2015;53:134-139.

Reddy VV, Gupta NV, Raghunandan hv, Kashyap un. Quality risk management in Pharmaceutical industry: A review. Int J Pharnatech Res. 2014;6(3):908-914.

Reniers GLL, Pauwels N, Audenaert A, Ale BJM, Soudan K. Management of evacuation in case of fire accidents in chemicals industrial areas. J Hazard Mater. 2007;147(1-2):478-487.

Scipioni A, Saccarola G, Centazzo A, Arena F. FMEA methodology design, implementation and integration with HACCP system in a food company. Food Control. 2002;13(8):495–501.

Tixier J, Dusserre G, Salvi O, Gaston D. Review of 62 risk analysis methodologies of industrial plants. J Loss Prev Process Ind. 2002;15(4):291–303.

Trafialek J, Kolanowski W. Application of Failure Mode and Effect Analysis (FMEA) for audit of HACCP system. Food Control. 2014;44:35-44.

Wallace CA, Holyoak L, Powell SC, Dykes FC. HACCP e the difficulty with Hazard Analysis. Food Control. 2014;35(1):233-240.

World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations. Annex 2. WHO guidelines on quality risk management, In: WHO Technical Report Series No. 981; 2013.

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