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Quality Assurance Status in Iranian Pharmaceutical Industry: A Survey

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ABSTRACT

Introduction: Critical role of quality assurance (QA) system in the pharmaceutical industry could affect on product quality, market development, customer satisfaction, and other element of a successful drug company.

Purpose of the Study: The main aim of this study is to evaluate of QA system, the relevant factors to the good manufacturing practice principles and detection of gap between knowledge and implementation of QA indices by their managers in pharmaceutical companies of Iran.

Method: This study contains designing a validated questionnaire with the expert panel and completing it in the pilot and final phases.

Results: This study have shown that there is a gap between knowledge of QA seniors and their practice in all categories of QA indices. Furthermore, it has been shown that measurement category has maximum gap. Moreover, machinery has minimum gap between all categories.

Conclusion: The status of QA managers' knowledge is appropriate, but implementation of QA indices in Iranian pharmaceutical industry is not appropriate.

Keywords: *Quality assurance, good manufacturing practice, Iran, pharmaceutical industry*

1. Introduction

Quality assurance (QA) is a general concept that covering everything which affect directly or indirectly on product quality [1,2]. Within the pharmaceutical organization, the approach to quality is defined by the quality policy, which sets out the governance of the organization with respect to quality [2]. The body that ensures that the quality policy is achieved throughout the organization is the QA function, thus ensure that the finished products are of a consist quality standard [1].

Good manufacturing practice (GMP) as a tool that could help QA system to surveillance on consistency of product quality. It has been presented by some regulation organizations and guidelines like Code of Federal Regulation, Pharmaceutical Inspection Co-operation Scheme (PIC/S), World Health Organization (WHO) guideline, and International Conference of Harmonization. These guidelines have been kept up date by their organization. They are main sources for pharmaceutical companies and their QA systems to improve the quality of products [1,2].

QA plays a central and influential role within the operations of the pharmaceutical industry. This multi-facet function spans its influence over the total operations by defining standards and regulations that govern the highly sensitive pharmaceutical industry [1].

QA department is responsible for releasing a product (via finished or intermediate) and approving or rejecting all products and materials, such as starting materials, packaging and labeling materials, in-process materials, product containers, bulk, and finished products [3].

The common misconception is to think that QA and quality control (QC) are the same when describing product or service management. Quality is synonyms with agreed high levels of excellence of product or service offering in line with the quality policy. QA compares the products and services against the set standards, whilst QC ensures that the said subjects are within the agreed specification and targets [4].

The quality journey has evolved significantly since its humble beginning in the 13th century guilds in medieval Europe. Six hundred years later, this approach to consistent production through deliberate inspection, was incorporated into industrial revolution in Great Britain. The positive approach and attitudes to have quality in the early part of 20th century was demonstrated by the fact that quality processes existed within the arena of manufacturing.

It took significant defining point in the world history, mainly, the second war to ensuring that the quality conscious rebuilding Japanese industries were in direct competition with United States mass production industries. The sense of competition through quality lead to American pioneers Joseph Juaran and Edward Demings modified the Japanese approach and obsession to inspection by concentrating on improving management processes for the American industrial sectors. In mid-1970s, the improving Japanese products superior consistent quality meant that the concept of total quality management (TQM) was successfully introduced with the US, significantly improving quality production, whereas the TQM process faded away toward the end of the 20th century, the concept has subsequently evolved to encompass many other private and public sector areas [5,6].

The Iranian pharmaceutical market has been regulated through the governmental institutions, which has been based on a law that has passed by the parliament in 1955. In the recent years, there is an additional pressure to introduce measures to improve the overall quality (via QA and system) which has to be balanced against the challenges of lowering the overall costs [7].

Critical role of QA in the pharmaceutical industry is the main reason to develop this study. This paper aims to provide insight into the approach and attitudes of the QA managers within the selected pharmaceutical companies in Iran to have quality and identify the gaps between theory and practice.

2. Method

This is a cross-sectional study, which uses situational analysis to find out the gap between the actual situation and what should be established about QA system. This questionnaire is based on a study. Thus, design and development an effective questionnaire is the most important step in this research.

A valid and reliable questionnaire helps well to collect of information about knowledge, attitudes, opinions, behaviors, etc. [8]. Review of literature, guidelines and findings the indices of QA are the inception for designing the questionnaire. However, transforming this

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information into the pertinent and correct questions needs enough knowledge of the subject matter. According to the policy of Iranian Ministry of Health (MOH) and emphasis of it on PIC/S guideline, preparation of this questionnaire is done with a focus on stated guideline. In addition, due to the situation of Iranian pharmaceutical industry and conformity with WHO policies, this guideline has been also used in designing of the questionnaire.

Preparing the questionnaire is done by the corporation of some experts (n = 3) of the industry and university. The size of expert group used in the questionnaire survey is variable [9]. There are a number of same studies in which the expert panel has been quite small [10].

Selecting samples were the initial step in this project. Selection of these samples (n = 17) is based on some criteria such as type of the products, ownership situation, size of companies, etc. However, all the companies which have been investigated in this study have been a manufacturer of finished products. It must be said that three companies of this study sample did not answer to the questionnaire, and the response rate in this study was 82%.

The pilot study has been implemented in the 1-year period (2009-2010) in five pharmaceutical companies. In this phase, interviewing with QA managers, filling the questionnaire and taking their advice about questionnaire helps us to modify the questionnaire.

The next step of this study has been the validation of the questionnaire with using an expert panel. In the expert panel, some skillful persons (n = 3) who were working in the pharmaceutical industry, judged about correction and efficiency of the questionnaire. After implementation of the pilot phase and using the expert panel, the questionnaire finalized. However, the final version of the questionnaire is almost similar with the first version. The final version of questionnaire contains 99 interval/ratio scale (0-5) question about the importance and performance of QA indices. After modification and validation of questionnaire, final phase of fulfilling of the questionnaire has been done in a period of 2-years (2011-2012). In this phase, the questionnaire filled in the remained companies (n = 9). Finally, all data, which have been collected in this research, analyzed. At last, we could find out situation of knowledge, behavior and find present gap between these factors.

3. Results and Discussion

Reporting the result of this study is based on the "cause and effect diagram" (6M) which has been categorized all questions in six groups. "Manpower" category (human resources and organizational structure). "Machinery" category (equipment and technology). "Milieu" category (environment). "Material" category (active pharmaceutical substances and finished products). "Method" category. "Measurement" category (self-inspection, validation, qualification, and analytical methods).

It has been shown in table 1, part of human resources and organizational structure (manpower categories), in 64% of cases, a significant gap between knowledge of QA seniors and their practice has been detected. However, it sounds that implementation of QA/QC independency, standard operation procedure (SOP) for visitors and personnel training in Iranian pharmaceutical company are appropriate. The status of other elements of this category is not well-enough.

The results obtained from some issues like job description, on-the-job training, availability of quality manual for personnel, SOPs for limiting access to premises, physical examination before employment, compliance of personnel clothing to GMP and access control system for warehouses shown that there is a significant gap between knowledge and practice in this areas. In addition, the biggest gap in this category is related to "A system for access control of warehouses" and "SOP" for access control to premises". Thus, it could be expressed that there is not an appropriate access control system for all of the premises in Iranian pharmaceutical industry.

One of the issues in this area is the training of personnel hygiene, GMP principles for all personnel and the training of the technical staffs. The average of the importance of each statement was 4.92 and the average of the amount of its implementation was 4.35, which has shown significant gap between knowledge and implementation of the issue. There is also a need for designing retraining courses in pharmaceutical company according to the average of importance and implementation through the evaluation process that have been giving out the company for the proposition (4.78 and 3.71, respectively). In comparison with significance level of 0.26 that shows a gap between knowledge and level of implementation in this issue.

Table 1. Average of knowledge and implementation and significance level of manpower category indices; confidence interval = 95%

Manpower category indices	Number of companies	Mean	Standard deviation	Significant	NC type	RPN
Job description						
Importance	14	4.8571	0.53452	0.318	M	0.212
Implementation		4.0714	1.07161			
QA independency						
Importance	14	4.7857	0.57893	0.000	-	0
Implementation		4.3571	1.15073			
SOP for access control to premises						
Importance	14	4.7857	0.42582	0.534	N	0.177
Implementation		4.0714	1.20667			
System for access control of warehouses						
Importance	14	4.7143	0.61125	0.594	N	0.198
Implementation		3.3571	1.15073			
Availability of quality manual for personnel						
Importance	14	4.7143	0.61125	0.382	N	0.127
Implementation		4.4286	0.85163			
Physical examination before employment						
Importance	14	4.6429	0.49725	0.488	C	0.488
Implementation		3.5000	1.91150			
Personnel clothing complying with GMP						
Importance	14	4.9286	0.26726	0.447	C	0.447
Implementation		4.5000	0.65044			
SOP for visitors						
Importance	14	4.2857	1.13873	0.003	-	0
Implementation		3.7857	1.18831			
Personnel training						
Importance	14	4.9286	0.26726	0.019	-	0
Implementation		4.3571	0.63332			
On-the-job training						
Importance	14	4.7857	0.42582	0.262	M	0.174
Implementation		3.7143	1.20439			
QC independency						
Importance	14	4.9279	0.26707	0.000	-	0
Implementation		4.9286	0.26726			

C: Critical non-conformity; M: Major non-conformity; N: Minor non-conformity; QA: Quality assurance; RPN: risk priority number; NC: Non-conformity
SOP: Standard operation procedure; QC: Quality control

Table 2. Average of knowledge and implementation and significance level of machinery category indices; confidence interval = 95%

Machinery category indices	Number of companies	Mean	Standard deviation	Significant	NC type	RPN
Using compatible lubricant with product						
Importance	14	4.7857	0.42582	0.685	M	0.456
Implementation		4.2143	0.97496			
Compatibility of equipment surface with product						
Importance	14	4.6429	0.63332	0.005	-	0
Implementation		3.7143	1.13873			
Equipment log book						
Importance	14	4.7143	0.46881	0.522	N	0.174
Implementation		4.0000	0.87706			
Efficient HVAC system						
Importance	14	4.7857	0.42582	0.480	C	0.480
Implementation		3.4286	1.50457			
Preventive maintenance						
Importance	14	4.6429	0.63332	0.786	M	0.524
Implementation		3.0000	1.51911			
Electronic system backup						
Importance	14	4.8571	0.36314	0.284	N	0.094
Implementation		3.3571	1.86495			
Equipment ID code						
Importance	14	4.5714	0.75593	0.916	N	0.305
Implementation		3.5714	1.39859			
Dust reduction system						
Importance	14	4.8571	0.36314	0.612	M	0.408
Implementation		3.4286	1.22250			
Air-lock system						
Importance	14	4.7857	0.42582	0.036	-	0
Implementation		4.0000	0.96077			
GMP compatible sampling tools						
Importance	14	4.7857	0.42582	0.014	-	0
Implementation		4.4286	0.64621			
Filling and sealing of finally sterilized parenteral in class A with background class C (at least)						
Importance	8	4.8750	0.35355	0.017	-	0
Implementation		4.5000	0.75593			
Filling and sealing of parenteral with aseptic process in class A with background class B						
Importance	8	4.8750	0.35355	0.033	-	0
Implementation		4.3750	0.74402			

C: Critical non-conformity; M: Major non-conformity; N: Minor non-conformity; RPN: Risk priority number; NC: Non-conformity; HVAC: Heating ventilating and air conditioning
GMP: Good manufacturing practice, ID: Identification

There are some grades of similarities in the result of this part to the study [11] which has been performed the knowledge of pharmacists and drug sellers by a questionnaire in Pakistan that has been based on a survey. This study has shown that most of the drug sellers have not appropriate information about prescriptions and storage conditions of medications.

It has been demonstrated that a significant gap between knowledge of QA seniors and their practice existed in 58.4% of machinery category cases (Table 2) (equipment and technology). It means that there is a gap between knowledge and practice in some issues. Using compatible lubricant with product, equipment log book, designing an efficient heating ventilating and air conditioning, preventive maintenance (PM), electronic system backup, equipment identification (ID) code and dust reduction system are examples of this issue. Also, there is not a significant gap between knowledge and implementation in some issues like compatibility of equipment surface with GMP, filling and sealing of finally sterilized and aseptic process products, air-lock system and GMP compatible sampling tools. It must be said that, maximum gap between knowledge and practice in machinery category was detected in “equipment ID code” and “PM”. Thus, it could be said that the gap between knowledge and practice of machinery issues are not caused by lack of appropriate equipment and technology. Also, it could be refer to the absence of some documents such as equipment ID code and schedule for maintenance of them.

This issue for environment (Milieu category) was 66.6% (Table 3). Furthermore, a gap has been shown (64.3% of cases) in active pharmaceutical substances and finished products issues (material category) (Table 4).

The existent gap in milieu category has been rooted in some issues like flow of material, personnel and process, designing of production area which is easily cleanable. GMP compatibility of premises surface, consideration to prevention of cross-contamination in weighing area, Environmental monitoring for production area, separation of QC labs from the production area, protection of biological and microbiological labs, pest-control system and using high efficiency particulate air (HEPA) filters in the exhaust of the hazardous product lines. In addition, Iranian pharmaceutical companies have worst practice in “protection of biological, microbiological labs” and “environmental monitoring for production area”. Also, defects in “environmental monitoring for production area” could be caused by lack of appropriate technology; the weak practice in the issue of “protection of biological and microbiological labs” mostly might refer to shortage of sufficient area for appropriate separation of them.

In material category; there was a significant gap between QA seniors’ knowledge and their practice in some issues such as QA approval for reprocess and rework, SOP’s for sampling, determination of storage condition on sample labels, prevention of sample mix-up, performing ID test for all containers of starting materials, cleaning containers’ surface before enter to the warehouses, control and monitoring of material storage condition, separation storage area of narcotics and flammable material in warehouses and distribution of product through authorized companies. Also, it has been demonstrated that implementation of “performing ID test for all containers of starting materials” and “prevention of samples mix-up” are the worst cases in this category. Notwithstanding, “performing ID test for all containers of starting materials” is the obvious GMP principle, because of financial cost, there is not appropriate practice in this issue in Iranian pharmaceutical industry.

As it has shown in table 5, issues of “method”, in 66.6% of cases, there was a significant difference between knowledge and practice of QA seniors. Existing gaps in implementation of quality management tools could be affected product quality. This weakness could be seen in

trend analysis and product quality review (one of the item that having a high gap), corrective and preventive actions (CAPA) and change control management (Table 5).

Some of the relevant issues to the documentation like preparing of batch processing records and unavailability of obsolete documents have not been properly implemented in Iranian pharmaceutical market. Also, there was not significant gap between QA seniors' knowledge and their practice in the other elements of documentation (Table 5).

Customer complaint handling and using of an appropriate recall system are very important issues for customer satisfaction and improving of company credit in different industry, product recall system with the average importance of 4.92 and average implementation of 4.00 for companies (significance level = 1) in this study, shows a high gap (maximum gap in this category) between knowledge and implementation. It was shown in a 6-year period study [12] in China (2002-2008), 29 cases of product recall from different fields of industry (food, pharmaceuticals, electronics, and automobile). Also, it has been shown that Chinese companies in the food industry experienced more severe reactions from their recall announcements, while companies in the automobile industry experienced a less severe reaction. It is important to consider the concern of product recall in the pharmaceutical industry.

Another noticeable issue in this part is, considering authority for contract giver to audit contract acceptor facilities. The result revealed average importance of 4.21 and average implementation of 3.42 for companies (significance level of 0.016), which has not shown gap between knowledge and implementation. Besides, it has been demonstrated that there is a significant gap (biggest gap in this category) between knowledge and practice of QA managers in the definition of responsibility in contract manufacturing and providing sufficient documentation to prove eligibility for contract manufacturing companies.

There is also a study in Finland which demonstrated to prepare a tool (a valid questionnaire) by Delphi method for inspection of contract acceptor [13].

Table 3. Average of knowledge and implementation and significance level of Milieu category indices; confidence interval = 95%

Milieu category indices	Number of companies	Mean	Standard deviation	Significant	NC type	RPN
Flow of material, personnel and process						
Importance	14	4.6429	0.63332	0.277	M	0.184
Implementation		3.7143	0.61125			
Designing production area which is easily cleanable						
Importance	14	4.8571	0.36314	0.125	M	0.083
Implementation		3.6429	0.63332			
Designing production area which is preventing cross-contamination						
Importance	14	4.9993	0.00267	0.010	-	0
Implementation		3.5000	0.65044			
GMP compatibility of premises surfaces						
Importance	14	4.7857	0.42582	0.252	M	0.168
Implementation		3.8571	0.86444			
Considering prevention of cross-contamination in weighing area						
Importance	14	4.7857	0.42582	0.138	C	0.138
Implementation		4.5000	0.65044			
Environmental monitoring for production area						
Importance	14	4.6429	0.49725	0.506	N	0.168
Implementation		4.2857	1.13873			
Separation of ancillary places from production, QC and warehousing area						
Importance	14	4.5714	0.64621	0.017	-	0
Implementation		3.5714	1.22250			
Separation of QC labs from production area						
Importance	14	4.7143	0.46881	0.185	M	0.123
Implementation		4.0714	0.99725			
Protection of biological and microbiological labs						
Importance	14	4.9993	0.00267	0.735	M	0.490
Implementation		4.2857	0.82542			
Container and area labeling in warehouses						
Importance	14	4.5000	1.58114	0.003	-	0
Implementation		4.0000	1.69967			
Separate laundry with suitable facilities						
Importance	14	4.7778	0.44096	0.044	-	0
Implementation		4.1111	0.92796			
Pest-control system						
Importance	14	4.7857	0.42582	0.476	M	0.317
Implementation		3.7143	0.99449			
Compatibility of drain design with GMP						
Importance	14	4.9286	0.26726	0.080	M	0.053
Implementation		4.4286	0.85163			
Separation of premises and HVAC system for sensitizing and hazardous products						
Importance	9	4.8571	0.36314	0.000	-	0
Implementation		4.7143	0.61125			
Using HEPA filters in the exhaust of the sensitizing and hazardous product lines						
Importance	10	4.9286	0.26726	0.282	C	0.282
Implementation		4.0714	0.99725			

C: Critical non-conformity; M: Major non-conformity; N: Minor non-conformity; RPN: Risk priority number; NC: Non-conformity; GMP: Good manufacturing practice
QC: Quality control; HVAC: Heating ventilating and air conditioning; HEPA: High efficiency particulate air

Yield calculation for processes, considering time limitation and preventing of gang-printing are other issues which have been observed that there is a gap between knowing and applying of them in Iranian pharmaceutical industry. Moreover, it has been observed that "yield calculation for process" have high gap in this categories.

Trend analysis and product quality review (one of the item that having a high gap), CAPA, change control management, preparing of batch processing records and unavailability of obsolete documents, have been considered.

As shown in table 6, issue of the "measurement", in 85% of cases, there was a significant difference between knowledge and practice of QA seniors. The result revealed that there is a significant gap between knowledge and implementation of self-inspection, validation principles, calibration and qualification. The significance level in most issues of this category has shown that the major defects are in some relevant issues of validation, calibration, and qualification.

Furthermore, it has been observed that there is a significant gap between knowledge and practice of some issues such as integrity test for HEPA filters during installation, daily verification of balances, analytical method validation, stability study, post marketing surveillance, system suitability, documentation of lab data, monitoring of pharmaceutical water. However, there is not significant gap in others issues of this category, such as, integrity test for sterilized filters, storage condition of samples, lab standards, testing method according to marketing authorization license and reporting of out of the specification to QA unit.

Table 4. Average of knowledge and implementation and significance level of material category indices; confidence interval = 95%

Material category indices	Number of companies	Mean	Standard deviation	Significant	NC type	RPN
Container labeling and identification						
Importance	14	4.9993	0.00267	0.003	-	0
Implementation		4.3571	0.92878			
QA approval for reprocess and rework						
Importance	14	4.9286	0.26726	0.072	M	0.048
Implementation		3.5000	1.45444			
Reprocess complies marketing authorization license						
Importance	14	4.2143	1.80506	0.013	-	0
Implementation		3.0714	1.97929			
SOPs for sampling						
Importance	14	4.6429	0.49725	0.379	M	0.252
Implementation		3.9286	0.99725			
Determination of storage condition on sample labels						
Importance	14	4.7143	0.46881	0.679	M	0.448
Implementation		4.1429	0.77033			
Prevention of samples mix-up						
Importance	14	4.7143	0.61125	0.699	C	0.699
Implementation		4.6429	0.63332			
Performing ID test for all containers of starting materials						
Importance	14	4.7143	0.46881	0.865	M	0.576
Implementation		4.7143	0.46881			
Cleaning containers' surface before enter to the warehouses						
Importance	14	4.9286	0.26726	0.513	N	0.170
Implementation		4.5714	0.64621			
Control and monitoring of material storage condition						
Importance	14	4.7143	0.46881	0.259	M	0.172
Implementation		4.7857	0.57893			
Warehousing comply with FEFO/FIFO systems						
Importance	14	4.5714	0.75593	0.000	-	0
Implementation		4.4286	0.85163			
Separation storage area of narcotics and flammable material in warehouses						
Importance	14	4.8571	0.36314	0.679	M	0.452
Implementation		4.6429	0.49725			
Separation storage area of quarantine and rejected material						
Importance	14	4.8571	0.36314	0.001	-	0
Implementation		4.7857	0.42582			
Separation storage area of waste material according to SOP						
Importance	14	4.5714	0.85163	0.048	-	0
Implementation		3.8571	0.86444			
Distribution of product via authorized companies						
Importance	14	4.8571	0.36314	0.368	M	0.245
Implementation		3.3571	1.39268			

C: Critical non-conformity; M: Major non-conformity; N: Minor non-conformity; RPN: Risk priority number; NC: Non-conformity; QC: Quality control; QA: Quality assurance
SOP: Standard operation procedure; ID: Identification; FEFO: First expired first out; FIFO: First in first out

In this study, we have demonstrated that the level of QA experts' knowledge in all categories is appropriate enough (more than 4 of 5), but some gaps between this level of knowledge and the level of implementation of QA indices was detected. The maximum gap has been observed the category of "measurement" in QA indices. This category includes self-inspection, validation, qualification, and analytical tests although the minimum gap has been detected in the category of "machinery" which contains: equipment and technology. Overall, we demonstrated some gaps between knowledge and implementation of QA indices which could divided into three general types of non-conformities: critical, major, and minor. The study has highlighted 28 cases of high risk non- conformities (28%) to the stated legalizations' within the Iranian pharmaceutical industry.

In our study, we have determined the risk priority number (RPN) of risks by failure mode and effect analysis (FMEA) method. In this method, we have calculated the RPN by multiplying the gap between importance and implementation of QA indices (occurrence) to type of non-conformity (severity). Occurrence is a number between zero to one and severity could be: zero (no non-conformity), 0.333 (minor non-conformity), 0.666 (major non-conformity), or one (critical non-conformity). Hence, the result (RPN), could be from zero (the least risk) to one (the highest risk). In this method, we have defined the value of 0.333 as the limits for initiation of measures.

Hence, in the category of "manpower," "physical examination before employment," "personnel clothing complying with GMP" has shown the highest risk.

Table 5. Average of knowledge and implementation and significance level of method category indices; confidence interval = 95%

Method category indices	Number of companies	Mean	Standard deviation	Significant	NC type	RPN
Change control management						
Importance	14	4.9286	0.26726	0.638	M	0.425
Implementation		3.2857	1.48989			
Corrective and preventive actions (CAPA)						
Importance	14	4.5714	0.85163	0.686	M	0.457
Implementation		4.0000	1.51911			
Trend analysis and product quality review (PQR)						
Importance	14	4.5714	0.64621	0.760	M	0.506
Implementation		2.8571	1.51186			
SOP for documentation						
Importance	14	4.9993	0.00267	0.054	M	0.035
Implementation		4.3571	0.74495			
Just last version of documents should be accessible						
Importance	14	4.8571	0.36314	0.206	N	0.068
Implementation		4.3571	1.00821			
Archiving of quality documents in QA						
Importance	14	4.7143	0.61125	0.000	-	0
Implementation		4.0000	1.51911			
SOP for coding system and editing documents						
Importance	14	4.7857	0.57893	0.007	-	0
Implementation		4.7143	0.61125			
Stratifying of documents						
Importance	14	4.5714	1.34246	0.048	-	0
Implementation		4.2857	0.82542			
Appropriate interval between approving and implementing SOPs						
Importance	14	4.3571	1.33631	0.000	-	0
Implementation		3.7857	1.47693			
Batch processing record (BPR)						
Importance	14	4.9993	0.00267	0.190	M	0.126
Implementation		4.6429	0.49725			
SOPs for handle customer complaint						
Importance	14	4.8571	0.36314	1.000	M	0.666
Implementation		4.0000	1.35873			
QA should be responsible for customer complaint						
Importance	14	4.8571	0.36314	0.899	N	0.299
Implementation		4.1429	1.61041			
Activation of recall system after critical defect						
Importance	14	4.9286	0.26726	1.000	C	1
Implementation		4.0000	1.17670			
Responsibility definition of contract giver and contract acceptor						
Importance	14	4.6429	0.63332	1.000	N	0.333
Implementation		4.0000	1.35873			
Permission of audit for contract giver						
Importance	14	4.2143	1.42389	0.016	-	0
Implementation		3.4286	1.69680			
Sufficient document to proof company ability to implement a contract						
Importance	14	4.4286	0.93761	0.145	N	0.048
Implementation		2.9286	1.68543			
SOP for production, packaging and labeling processes						
Importance	14	4.7143	0.46881	0.002	-	0
Implementation		4.5000	0.65044			
Prevention of cross-contamination and mix-up during processes						
Importance	14	4.9286	0.26726	0.019	-	0
Implementation		4.1429	0.53452			
Yield calculation for processes						
Importance	14	4.7143	0.46881	0.947	N	0.315
Implementation		3.7857	1.18831			
Time limitation for processes						
Importance	14	4.1429	1.51186	0.066	N	0.022
Implementation		2.9286	1.73046			
Prevention of gang-printing						
Importance	14	4.7857	0.57893	0.211	M	0.140
Implementation		4.4286	0.85163			

C: Critical non-conformity; M: Major non-conformity; N: Minor non-conformity; RPN: Risk priority number; NC: Non-conformity; SOP: Standard operation procedure
QA: Quality assurance

Table 6. Average of knowledge and implementation and significance level of measurement category indices; confidence interval = 95%

Measurement category indices	Number of companies	Mean	Standard deviation	Significant	NC type	RPN
Self-inspection						
Importance	14	4.9286	0.26726	0.420	M	0.28
Implementation		3.9286	1.14114			
Validation master plan (VMP)						
Importance	14	4.8571	0.36314	0.457	N	0.152
Implementation		3.0714	1.81720			
Revalidation						
Importance	14	4.8571	0.36314	0.938	M	0.625
Implementation		1.9286	1.32806			
Process validation						
Importance	14	4.8571	0.36314	0.808	M	0.538
Implementation		2.7143	1.26665			
Computer system validation						
Importance	14	4.2143	0.97496	0.760	M	0.506
Implementation		2.0000	1.75412			
Duration of cleaned equipment validity						
Importance	14	4.5714	0.51355	0.899	M	0.599
Implementation		2.7143	1.13873			
Cleaning validation						
Importance	14	4.8571	0.36314	0.895	M	0.596
Implementation		2.1429	1.56191			
Alert and action limits determination						
Importance	14	4.7857	0.42582	0.729	M	0.486
Implementation		1.6429	1.64584			
Supporting utilities validation						
Importance	14	4.8571	0.36314	0.122	M	0.081
Implementation		2.2143	1.18831			
Appropriate program for equipment calibration						
Importance	14	4.6429	0.49725	0.851	M	0.567
Implementation		2.9286	0.99725			
Design qualification						
Importance	14	4.6429	0.49725	0.611	M	0.407
Implementation		3.0000	1.03775			
Installation qualification						
Importance	14	4.7143	0.46881	0.584	M	0.389
Implementation		3.0714	0.73005			
Operation qualification						
Importance	14	4.7143	0.46881	0.464	M	0.309
Implementation		2.8571	1.09945			
Performance qualification						
Importance	14	4.9993	0.00267	0.455	M	0.303
Implementation		4.5714	0.75593			
Integrity test for HEPA filters during installation						
Importance	14	4.7857	0.42582	0.636	C	0.636
Implementation		4.0000	1.30089			
Integrity test for sterilized filters, before use and immediately after use						
Importance	14	4.4286	1.39859	0.017	-	0
Implementation		3.8571	1.83375			
Daily verification of balances						
Importance	14	4.8571	0.36314	0.138	N	0.046
Implementation		4.8571	0.36314			
Analytical method validation						
Importance	14	4.7143	0.46881	0.273	M	0.182
Implementation		4.3571	0.74495			
Stability study for the first 3 batches						
Importance	13	4.9231	0.27735	0.387	M	0.258
Implementation		3.6154	1.85016			
Post marketing surveillance (PMS)						
Importance	11	4.9091	0.30151	0.753	M	0.502
Implementation		3.6364	1.96330			
Storage condition of samples and lab standards						
Importance	14	4.4286	1.34246	0.001	-	0
Implementation		4.0714	1.49174			
Testing method according to the marketing authorization license						
Importance	14	4.7143	0.82542	0.029	-	0
Implementation		3.8571	1.02711			
System suitability						
Importance	14	4.6429	0.63332	0.319	M	0.212
Implementation		3.3571	1.59842			
Documentation of lab data						
Importance	14	4.8571	0.36314	0.838	N	0.279
Implementation		3.6429	1.00821			
Monitoring of pharmaceutical water						
Importance	14	4.7143	0.46881	0.273	C	0.273
Implementation		4.3571	0.74495			
Out of specification should be reported to QA						
Importance	14	4.5000	0.94054	0.004	-	0
Implementation		4.0000	1.03775			

C: Critical non-conformity; M: Major non-conformity; N: Minor non-conformity; RPN: Risk priority number; NC: Non-conformity; QA: Quality assurance; HEPA: High efficiency particulate air

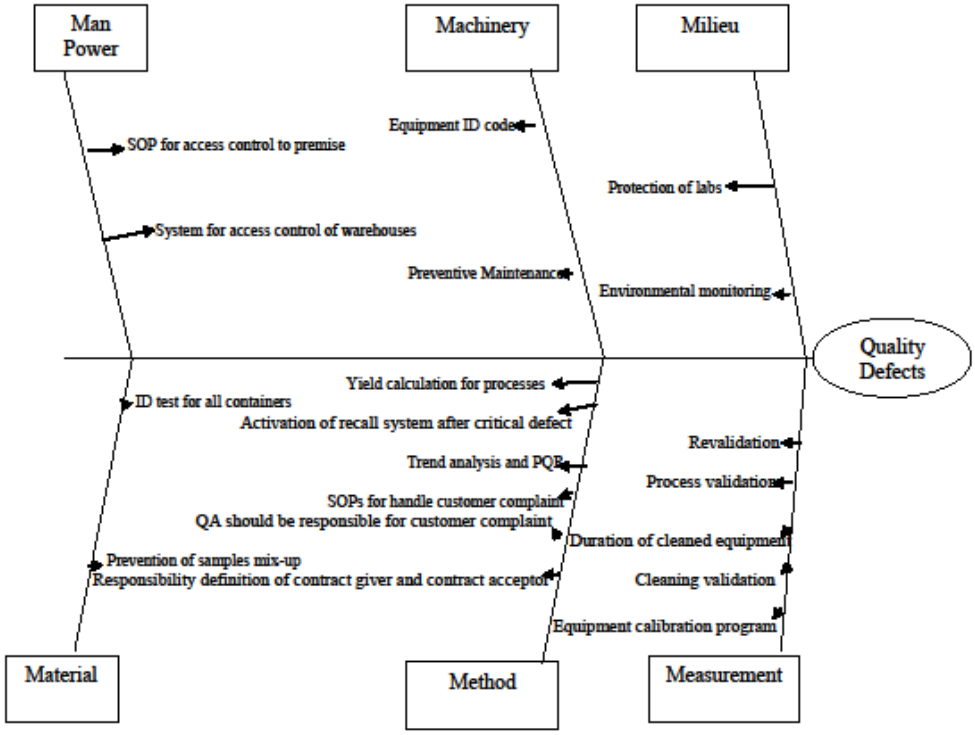

Figure 1. Quality causes and defects diagram

Furthermore, in the category of "Machinery", "Preventive maintenance" has shown the highest risk.

Also, in some issues detected high level of gaps between knowledge and implementation of QA indices. However, the level of importance in these issues may be various. Summary of the highest risks have been shown in figure 1.

The reason of this outcome might refer to this fact that Iranian pharmaceutical industry in last decades has been met the preliminary needs the community by quantity aspect. It brings companies to the next step which is quality phase. Companies are trying to renew old facilities by instructing GMP approved lines and modern machinery and equipment. In fact, very few companies are able to invest high cost for validations, qualifications, and other processes related to the measurement aspects.

Since the level of knowledge in QA managers is appropriate, poor performance could be caused by the absence of other staff of pharmaceutical company. We believe that another important reason for practice weakness is pricing system of Iran MOH, and emphasizing on keeping prices down which neglects investment of companies for quality issues. On the other hand, there is no enough pressure to pharmaceutical companies by Iran MOH for compliance with GMP principles.

4. Conclusion

The status of QA seniors' knowledge in Iranian pharmaceutical companies is in the appropriate level, but due to the absence of staff knowledge, economical situations and lack of a serious reaction from authority body (Iran MOH) to nonconformities of companies, the implementation of QA main indices is not appropriate.

References

(1) McCormick K. Quality (pharmaceutical engineering series). 1st ed. Woburn, MA: Butterworth Heinemann; 2002.

(2) World Health Organization. Quality assurance of pharmaceuticals: a compendium of guidelines and related materials: Geneva, Switzerland: World Health Organization; 1999.

(3) Food and Drug Administration. 21 Code of federal regulations: parts 210 and 211. Silver Spring, MD: Food and Drug Administration; 2000.

(4) Shamoo AE. Quality assurance and regulation. Regul Toxicol Pharmacol 1991; 14(1): 1-2.

(5) Sharma J. An Expedition to quality: a review. The Quality Assurance Journal 2010; 13(1-2): 1-13.

(6) Shah M, Nair S, Wilson M. Quality assurance in Australian higher education: historical and future development. Asia Pacific Education Review 2011; 12(3): 475-83.

(7) Cheraghali AM. Iran pharmaceutical market. Iran J Pharm Res 2006; 5(1): 1-7.

(8) Radhakrishna RB. Tips for developing and testing questionnaires/instruments. Journal of Extension 2007; 45(1): 1-4.

(9) Cantrill J, Sibbald B, Buetow S. The Delphi and nominal group techniques in health services research. Int J Pharm Pract 1996; 4(2): 67-74.

(10) Stewart J, O'Halloran C, Harrigan P, Spencer JA, Barton JR, Singleton SJ. Identifying appropriate tasks for the preregistration year: modified Delphi technique. BMJ 1999; 319(7204): 224-9.

(11) Butt ZA, Gilani AH, Nanan D, Sheikh AL, White F. Quality of pharmacies in Pakistan: a cross-sectional survey. Int J Qual Health Care 2005; 17(4): 307-13.

(12) Zhao X, Lee Y, Ng S, Flynn BB, editors. The impact of product recall announcements on stock market reaction: a study of chinese listed companies. Proceedings of Conference US-China Business Cooperation in the 21st Century: Opportunities and Challenges for Enterpreneurs; 2009 Apr 15-17; Indianapolis and Bloomington, Indiana.

(13) Linna A, Korhonen M, Mannermaa JP, Airaksinen M, Juppo AM. Developing a tool for the preparation of GMP audit of pharmaceutical contract manufacturer. Eur J Pharm Biopharm 2008; 69(2): 786-92.