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Evaluation of Validation Plans and Validation Activities in Iranian Pharmaceutical Industries

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ABSTRACT

One of the main elements for fulfilling Good Manufacturing Practice (GMP) requirements is validation performance. Therefore, those pharmaceutical factories trying to synchronize cGMP compliance should fulfill validation requirements. With accepting Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) standards by Iran Food and Drug Administration (FDA), pharmaceutical factories are required to perform such a validation. Despite the gap existing between production conditions and PIC/S standards, pharmacy factories are extremely rushing for their quality improvement. In this study, 84 factories were checked for having validation master plan (VMP), in their company. Then, a complete checklist was provided by checking WHO, PIC/S, and FDA guidelines of all VMP requirements. Those pharmaceutical factories, which have VMP or are providing it, have put in three categories. The first group performed validation project on their own. The second group got help from an Iranian adviser, and the third group performed it with foreign adviser company assistance. The results of these three categories are quantified and compared with each other by one-way ANOVA test. About 60 factories of 84 answered the initial questionnaire. About 26 factories of the same number introduced themselves for having VMP, and seven factories were providing it. Comparing these three categories, the second and third groups with $P < 0.05$ do not differ from each other very much statistically. With respect to quality of their VMP, the first group with $P > 0.05$ is very different from the two other groups, while it has a lower average from them.

Keywords: *Master Validation Plan, Iranian Pharmaceutical Industries, PIC/s, cGMP, FDA, VMP*

1. Introduction

At first validation was introduced to improve certainty of production quality, and this was done through as excessive tests and documents. Not enough recognition was resulted to an incorrect process for validation chosen by some pharmaceutical factories. Hence, legislator organs started to publish guidelines to show the factories of pharmaceutical production, the road map and required recommendations. With the publication of these guidelines, the main elements of validation and performance sequence of each stage and the way of its performance were specified [1].

At the time of rising of a subject like validation in pharmaceutical industries, following challenges have been considered such as charges resulted from performing it, how to manage the project, nurturing expert staffs in this field, and keeping scientific information up to dated according to scientific growth [1-3].

In the case of validation management subject, some issues such as spacious validation operating area, the influence of various factors on it, duplication possibility, qualitative assessment of some parts, not considering some charges, unavailability of equipment's for validation process performance, etc. are introduced [4].

Validation master plan (VMP) sensationally helps the validation project management [3]. For some issues as aligning superior managers view, supplying organizational budget, cooperation of all groups for their share in the validation process, correct and logical sequence of activities, time scheduling, processes description, standard operating procedures (SOPs) requirement, validation lifecycle, revalidation, planning staff education, and required documentations are provided in VMP [5].

In addition to introduced issues, with the spread of operation range over time, and joining of computer validation, material qualification to it. Also, change in view of validation from a retrospective to prospective matter that has led to the strength of risk analysis in this science, attention to validation has been transformed into one of the key points in designing production sites of pharmaceutical preparations [6,7]. All of these factors resulted in validation project management into a critical and delicate matter.

In Iran, synchronous to pharmaceutical production system and also acceptance of Good Manufacturing Practice (GMP) Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) as an acceptable standard for pharmaceutical productions on behalf of Drug and Food Department, pharmaceutical factories pay an increasing attention to production condition improvement and synchronization with these standards [8].

As for many pharmaceutical production centers in the country, nearly 110 productive factories, and the variety among their productions, chemical, recombinant, herbal and bestial, a general estimation of validation conditions and recognition of these centers strengths and weaknesses are prerequisites for the right management of this issue.

As it is known that the first stage in the validation is designing a correct VMP [9]. According to the importance of VMP in performance, validation management, and documentation, pharmaceutical companies VMP evaluation is the main priorities of this study.

2. Experimental

At first, for estimating general approach of human finished product factories in the field of validation, an initial validation questionnaire, which is mentioned in annex 1, was given to authorities of 84 factories to answer the introduced questions. After a 2-week period, phone-calls were made to persuade the technical authorities to make sure to answer the questionnaire. The obtained data was analyzed via Excel Software and transformed into a diagram. Thereafter, the checklist, which is mentioned in annex 2, was sent to those factories introducing themselves for having VMP.

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The questions of this checklist were based on the following guidelines and references:

- Food and Drug Administration (FDA) guidance for industry-process validation: General principles and practices, January 2011
- PIC/S recommendations on VMP installation and operational qualification: Non-sterile process validation, cleaning-validation
- A WHO guide to GMP requirements part 2: Validation
- Syed Imtiaz Haider, Pharmaceutical master validation plan: The ultimate guide to FDA, GMP, and good laboratory practice compliance
- VMP templates, existing on the internet, such as ISPE validation, etc.

Pharmaceutical factories are divided into the three below categories and compared with each other:

1.Factories performing their validation project on their own (specified by number 1-10 in the first horizontal row of table 2)

2.Factories getting help from Iranian advisers to perform the validation project (specified by number 11-15 in the first horizontal row of table 2)

3.Factories getting help from foreign adviser companies to perform the validation project (specified by number 16-19 in the first horizontal row of table 2).

The questions of the checklist have a hidden rating, which is modified with experts' opinion assistance. Factories are rated separately, and rates of each category are compared with each other with one-way analysis of variance (ANOVA) (Table 4).

3. Results and Discussion

It is summarized in table 1 how to answer the initial questionnaire, annex 1. Table 1 shows the factories answers to the below question.

Have you designed the VMP for your validation management? (Question 1, Annex 1).

As you see in table 1, 60 of 84 companies have answered the initial questionnaire. Each of the five answering the questionnaire among biotechnology companies has VMP. This fact indicates the significance of the validation where biotechnology companies were giving the highest priorities in preparation of such a VMP. None of the four herbaceous companies answering the initial questionnaire have launched validation. About 21 have VMP, and 7 are providing it among 51 chemical pharmaceutical companies.

At a glance, pharmaceutical companies appropriate to their pharmaceutical production are very different in performing validation (Table 1).

Factories answered the below question like this (Figure 1):

- Do adviser groups help you in VMP designing and validation performance?

The performance way of validation in pharmaceutical companies is shown in figure 1. About 27.4% of 60 companies that have answered the initial questionnaire performed validation project on their own from which 10 companies have answered the checklist (Table 2). It is noticeable that none of the companies deputes the validation project to foreign companies thoroughly. About 15.1% of 60 companies performed it with foreign adviser companies' assistance. About 4 of these 9 companies have answered the checklist (Table 2), and 4 of them got help from an Iranian adviser.

About 26 factories introduced themselves to have VMP in table 1. About 19 of them have answered the checklist. According to the checklist of annex 2, the questions are divided into 19 different sections. These sections are shown in the first vertical row of table 2. As for experts' opinion, a coefficient is given to each of these sections, which are shown in the second vertical row of table 2.

After obtaining the general score of companies, each company of these three categories, group one specified by number 1-10 in the first horizontal row of table 2, group two specified by number 11-15, group two specified by number 16-19, are compared with each other by ANOVA in terms of the obtained general score. Factories 10 and 12 which are specified with a star in Table 2 are known as out layer in their total prominence. Table 3 shows the ANOVA test of the groups of factories. The significant number is less than the critical value that set at 0.05, show there are significant differences among obtained total prominence mean of each group. Therefore, in order to recognize that among which groups there are differences in total prominence, the post-hoc test has been done (Table 4).

Table 1. Evaluation of whether pharmaceutical factories have validation master plan

Kind of factories	Factories providing VMP, now	Factories that do not have VMP	Factories that have VMP	All factories response initial questionnaire	All factories that initial questionnaire send them
Chemical	7	23	21	51	68
Herbaceous	0	4	0	4	8
Biotechnology	0	0	5	5	8
All factories	7	27	26	60	84

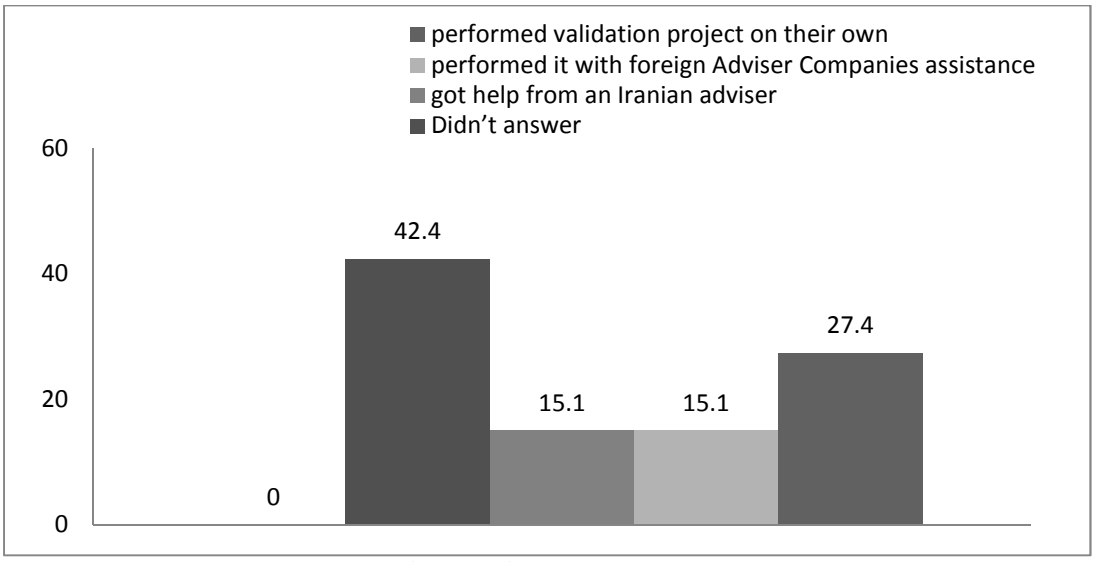

Figure 1. Performance of validation master plan by advisers

Table 2. Result of validation master plan elements investigation in pharmaceutical factories answered the checklist

	Coefficient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10***	**11**	**12***	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**Mean of response**	**Mean of response (%)**
Introduction	3	7/11	5/11	7/11	11/11	7/11	5/11	4/11	4/11	9/11	11/11	9/11	0/11	10/11	10/11	6/11	10/11	9/11	9/11	11/11	7.6/11	69
Facility and equipment description / validation	2	7/10	5/10	10/10	9/10	7/10	6/10	6/10	5/10	9/10	10/10	4/10	0/10	10/10	10/10	6/10	9/10	8/10	8/10	8/10	7.2/10	72
Building description / validation	2	3/4	1/4	1/4	4/4	0/4	0/4	2/4	0/4	1/4	4/4	3/4	0/4	4/4	4/4	2/4	3/4	1/4	3/4	3/4	2.1/4	52.5
Design and drawing description	2	4/4	1/4	1/4	4/4	0/4	2/4	1/4	3/4	2/4	4/4	3/4	0/4	3/4	4/4	3/4	4/4	4/4	4/4	4/4	2.7/4	67.5
Process qualification and validation	3	7/9	5/9	8/9	8/9	5/9	3/9	3/9	5/8	3/8	9/9	5/9	1/9	4/9	3/9	7/9	8/9	7/9	7/9	8/8	5.6/4	62.2
QC laboratory validation	2	1/2	2/2	1/2	2/2	2/2	2/2	2/2	0/2	2/2	2/2	2/2	1/2	0/2	2/2	2/2	2/2	2/2	2/2	2/2	1.6/2	80
Computer system validation	1	0/6	3/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	6/6	2/6	1/6	2/6	4/6	1/6	2/4	2/6	0/6	0/6	1.2/6	20
Cleaning validation	3	1/2	3/3	1/3	2/3	1/3	3/3	1/1	2/3	1/1	3/3	3/3	0/3	1/3	3/3	3/3	3/3	3/3	3/3	3/3	2.2/3	36.6
Standard operation procedures	3	4/4	4/4	4/4	4/4	4/4	4/4	2/4	4/4	2/4	4/4	4/4	1/3	4/4	4/4	4/4	3/4	4/4	4/4	4/4	3.6/4	90
Calibration	3	4/4	4/4	3/4	4/4	2/4	2/4	2/4	1/4	3/4	4/4	4/4	0/4	3/4	0/4	1/4	3/4	3/4	4/4	4/4	2.7/4	67.5
Preventive maintenance	2	2/3	3/3	3/3	3/3	1/3	3/3	0/3	2/3	0/3	3/3	1/3	0/3	3/3	2/3	1/3	2/3	3/3	3/3	3/3	2/3	67
Revalidation	2	0/3	1/3	3/3	2/3	2/3	3/3	0/3	0/3	2/3	3/3	2/3	0/3	2/3	3/3	0/3	2/3	3/3	3/3	3/3	1.8/3	60
Change control	3	0/6	0/6	1/6	1/6	3/6	1/6	0/6	3/6	5/5	6/6	3/6	0/6	4/6	4/6	1/6	5/6	5/6	5/6	6/6	2.8/6	46.7
Staff training	3	1/2	2/2	2/2	2/2	2/2	2/2	0/2	2/2	½	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	1.8/2	90
Costumer complaint	1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	100
Auditing	2	3/3	0/3	1/3	2/3	0/3	0/3	0/3	3/3	0/3	3/3	2/3	0/3	3/3	0/3	3/3	2/3	3/3	3/3	3/3	1.6/3	53.3
Report	3	2/6	3/6	2/6	1/6	4/6	5/6	0/6	0/6	0/6	5/6	0/6	0/6	6/6	6/6	3/6	4/6	6/6	6/6	3/6	2.9/6	48.3
Validation schedule	2	2/3	0/3	3/3	2/3	2/3	3/3	0/3	2/3	0/3	3/3	3/3	0/3	3/3	3/3	2/3	3/3	3/3	3/3	3/3	2.1/3	70
References	3	2/3	3/3	1/3	2/3	1/3	3/3	0/3	0/3	1/3	3/3	3/3	0/3	3/3	3/3	0/3	1/3	2/3	3/3	1/3	1.7/3	56.6
Sum	4	22.8	27.7	28	34.5	24.3	30	13.8	20.7	23.5	44.5	33.0	6.5	38.2	35.7	26.5	36.8	38.9	41.4	39	*****	****

Table 3. The analysis of variance test of the groups of factories

Sourc	Sum of squares	df	Mean square	F	Significant
Between groups	591.347	2	295.674	11.196	0.001
Within groups	369.738	14	26.410		
Total	961.085	16			

Table 4. Post-hoc test

(I) group	(J) group	Mean difference (I-J)	Standard error	Significant	95% Confidence interval	
					Lower bound	Upper bound
1.00	2.00	−8.31667(*)	3.08818	0.043	−16.3993	−0.2340
	3.00	−13.99167(*)	3.08818	0.001	−22.0743	−5.9090
2.00	1.00	8.31667(*)	3.08818	0.043	0.2340	16.3993
	3.00	−5.67500	3.63386	0.294	−15.1858	3.8358
3.00	1.00	13.99167(*)	3.08818	0.001	5.9090	22.0743
	2.00	5.67500	3.63386	0.294	−3.8358	15.1858

*The mean difference is significant at the 0.05 level

The results show that there is a significant difference between the first and second group ($P < 0.05$) and the first and third group ($P < 0.01$) in their prominences. The comparison shows that the second and third groups have a higher total prominence mean than the first group (Table 4).

The results show a clear difference in total prominence among the factories of the first and two other groups. Factories getting help from an adviser, either internal or foreign, have a better condition in designing and performing their VMP. There are not any statistical differences between the second and third group in their prominence. Also, must reflection and verification tests for more assistance in evaluation of validation performance in these groups. It is obvious that the factories of the first group not only spend too much time in staff validation education, but also they have a problem in their final performance result and keep their data up to date. These factories in addition to bearing high charges of buying required equipment for validation and performing validation, they do not get a considerable result.

Companies getting help from advisers to perform validation would not be something more than an administrating agent if they depute the whole affair to external individuals, and would not have independence in this issue over time. Also, the increasing growth of technology does not make the pharmaceutical companies needless of external advisers' assistance. Thus, they will be successful only when they accompany the advisers step by step, and contribute into decision makings, performance, and conclusions.

There is a significant difference in validation activity among the country's pharmaceutical factories, so that in one hand some factories have got a very high total prominence from the checklist and, on the other hand, some even did not have tried to write a VMP. It is noticeable that writing a correct and general VMP is a very effective step toward validation performance [10]. Hence, supervisions in the issue of validation should go through VMP evaluation, in order to assist the factories in validation performance and also prevent them from waste of budget and duplication.

According to the growth of validation, submitting new solutions, and updating former methods, being synchronous with this matter requires spending time and significant charges. On the other hand, daily increasing deterioration of Marketing Certificate Standards has made the pharmaceutical factories looking for making solutions decrease the charges [11].

Many articles have been published in the field of decreasing validation charges methods, which can help us with a more correct and economic validation performance. Getting help from adviser companies trying to make the generic validation science, the right design of VMP, appropriate statistical software, and merging the small production units in large factories are some of these solutions for decreasing validation charges [12,13].

We see a great growth of validation and its related branches in scientific terms. Not being synchronous with this growth can lead us to severe retardation in this field. Therefore, creating the required infrastructures can help the country's pharmaceutical production industry in order not to make these gaps greater.

4. Conclusions

The study indicates a significant difference in validation performance among the pharmaceutical factories. Iran FDA should pursue right policies to growth all the factories proportionately to their stage that we get all pharmaceutical factories superior in their consistent quality. It is also considerable that the results of this project need further verification to make a better plan for establishing VMP in Iranian pharmaceutical factories.

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Annex 1

Checking holism on validation performance conditions in pharmaceutical factories of the country

1. Have you designed a VMP for your validation management?
2. Does an advisory group help you in designing VMP and validation performance?

Annex 2

Introduction

	Yes	No
1. Is any foreigner supervisor, from a private company or food and drug administration, assisting your company in keeping VMP correctly and its right performance?		
2. Is there any table on your first page of VMP to specify different editions of your VMP with date and the reason of republication?		
3. Is the reason of validation performance and its goal specified in your VMP introduction?		
4. Is there any organizational chart for general management of validation process in your VMP?		
5. Is the main person who is responsible for validation performance project specified?		
6. Is the validation team determined in your VMP?		
7. Are the responsible persons for each validation processes specified separately in your VMP?		
8. Are the responsible persons for giving reports of each site specified separately?		
9. Are the initial auditors of each site specified separately in your VMP?		
10. Are the responsible persons for audition initial verification of each site specified separately in your VMP?		
11. Is your VMP verified by quality control, production, engineering, R and D, and other associated groups?		
12. Is the validation life cycle determined in your VMP?		

Facility and Equipment Description/Validation

	Yes	No
13. Are general schema of the factory, production different sites, and production rate mentioned in your VMP?		
14. Are production processes and machines used in them determined in your VMP?		
15. Are limited areas of validation performance and machines involved in this project determined in your VMP?		
16. Are the reasons of importing and not importing some machines in validation process of one production line specified in your VMP?		
17. Is the amount of air outflow that is made by HVAC system in different sites of the factory described in your VMP?		
18. Is it described in your VMP that how are consumed materials, such as sterile water, steam, compressed air, electricity, etc., available?		
19. Are the operational tests for consumed materials determined separately in your VMP?		
20. Are the yardsticks of acceptance for verifying correct operation of systems, which produce consumed materials, determined separately in your VMP?		
21. Are qualification tests for operation of machines, which are inclusive in validation project, determined separately in your VMP?		
22. Are acceptance yardsticks for verifying correct operation of machines, which are inclusive in validation project, determined separately in your VMP?		

Building Description/Validaton

	Yes	No
23. Are structure and floor, walls, and ceiling cover in different sites described in your VMP?		
24. Is the amount of components, such as light, temperature, relative moisture, etc. considered in different production sites, determined?		
25. Are cases which should be surveyed in auditing the building determined in your VMP?		
26. Are acceptable criteria for construction equipment's, such as drainage, etc. determined?		

Design and Drawing Description

	Yes	No
27. Does your VMP systematically describe a summary of how equipment's and supporting systems are designed?		
28. Is there any list of designs done for arranging utensils, piping, and HVAC path in your VMP?		
29. Are your designs in accordance to physical features of machines, like size, volume, and number of its users?		
30. Do the users fit with surfaces, glossy packaging of rooms and staff arrangement type in your VMP?		

Process Qualification and Validation

	Yes	No
31. Are the validation types in your VMP? (retrospective, concurrent, prospective)		
32. Do you have qualification matrix for all of the equipment's, supporting and control systems considered in validation in your VMP?		
33. Is the risk analysis done for determining critical parameters and their effects on quality of the product?		
34. Are the variables and response of each point, which should be respectively determined and measured, controlled?		
35. Do you have a verified protocol for the validation of aseptic processes?		
36. Does your VMP determine how the parameters must measurement?		
37. Are the acceptance yardsticks of each parameter considered in production process determined in your VMP?		
38. Are intermediate products features considered in their verification determined in your VMP?		
39. Are final products features considered in their verification, determined in your VMP?		

QC Laboratory Validation

	Yes	No
40. Is there any protocol for controlling the qualification of laboratory equipment's in your VMP?		
41. Do you have a protocol for validation of laboratory processes?		

Computer System Validation

	Yes	No
42. Are computer systems and controlled processes described in your VMP?		
43. Is validation cycle of computer systems determined in your VMP?		
44. Is it determined in your VMP that which computers keep the main data?		
45. Is it determined in your VMP that which computers have controlling role of processes?		
46. Are computer systems checked for giving the appropriate code in the qualification control?		
47. Is the access range of each person to information in accordance to previous projects?		

Cleaning Validation

	Yes	No
48. Is any protocol considered in your VMP for the validation of washing equipment's?		
49. Do you have a verified protocol for your validation of depyrogenation?		
50. Is any protocol considered for validation of utensils sterilization in your VMP?		

Standard Operating Procedures

	Yes	No
51. Do you have a list of standard operating procedures (SOPs) needed for validation in your VMP?		
52. Do you have a standard operating procedure for writing your standard operating procedure?		
53. Does your VMP determine operating procedures writing formats and how they should be referenced?		
54. Are different standard operating procedures determined and verified in your VMP?		

Calibration

	Yes	No
55. Does your VMP contain a standard operating procedure for the state and times of doing calibration?		
56. Is it determined in your VMP that which equipment's are and are not included in the calibration project?		
57. Is the responsibility of doing calibration project specified in your VMP?		
58. Are valid references used in calibration specified in your VMP? (NIST, …)		

Preventive Maintenance

	Yes	No
59. Are preventive maintenance projects planned in your VMP?		
60. Is there any standard operating procedure for preventive maintenance actions?		
61. Do you have a protocol for the process of machines repairing and verification of their accurate operation?		

Revalidation

	Yes	No
62. Is any specific standard operating procedure in relation to the state of doing revalidation determined in your VMP?		
63. Is it determined in your VMP that under which conditions revalidation should be done?		
64. Are specific periods considered for revalidation?		

Change Control

	Yes	No
65. Is a specific protocol determined for change control that may happen in designing, documentation, equipment's and processes?		
66. Imagine that there has occurred an error in one of your processes. Is any specific standard operating procedure designed for removing the reason of this error in your VMP?		
67. Imagine that there has occurred an error in the way of doing a process or a test. Is any project planned for its documentation in your VMP?		
68. Imagine that there has occurred an error in the way of doing a process or a test. Is any specific protocol determined for its management in your VMP?		
69. Imagine that some results are not relevant to your expectations in association to a product feature. Is any specific standard operating procedure determined for managing this error in your VMP?		
70. Is the development cycle used for critical processes, such as sterilization, purging, etc.?		

Staff Training

	Yes	No
71. Do you have a standard operating procedure for continuous evaluating of staff knowledge and confidence toward it?		
72. Is there any codified program for continuous training of staff?		

Costumer Complaint

	Yes	No
73. Do you have a project to observe and check people complaints?		

Auditing

	Yes	No
74. Do you have a validation schedule for operating internal audition in your VMP?		
75. Is there any standard operating procedure for documentation of auditions in your VMP?		
76. Is any standard operating procedure determined for analyzing and checking the audition results, and the state of removing errors and defects in your VMP?		

Report

	Yes	No
77. Have you considered enhanced turn-over package (ETOP) system for easier assessment to the most commonly used engineering documents, such as HVAC, steam system, etc., to classify your documents?		
78. Do you have a standard operating procedure for proper, regular, and separate presentation of the validation protocols?		
79. Have you considered a specific standard operating procedure for a better assessment to documents relevant to a special system?		
80. Is there any operating procedure considered in your VMP to give the final report of validation project?		
81. Is any form considered for giving the final report of validation project in your VMP?		
82. Do you have a certification package requirement for each category of equipment's?		

Validation Schedule

83. When did your VMP record complete?
    - o It completed before beginning the production project.
    - o It started and completed during the performance of production project.
    - o It began before starting the project and was completed during its performance.

	Yes	No
84. Is the priority of each project determined in your VMP?		
85. Is a validation schedule considered for doing different parts of VMP project?		
86. Is a validation schedule determined for giving validation reports?		

References

	Yes	No
87. Do you have a standard operating procedure for the state of page numbering of each document?		
88. Different parts of your VMP have been written based on international, your company national or internal laws. Do you have a standard operating procedure for the state of referencing these cases?		
89. References are given to most of maps, designs, etc. in VMP. Have you considered a standard operating procedure for the state of doing such a work?		