Journal of Pharmaceutical and Biomedical Analysis 50 (2009) 1085–1087

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

Risk analysis by FMEA as an element of analytical validation

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ARTICLE INFO

Article history:
Received 6 April 2009
Accepted 28 June 2009
Available online 7 July 2009

Keywords:
Near-Infrared spectroscopy
Analytical validation
FMEA
Risk analysis
Human factor

ABSTRACT

We subjected a Near-Infrared (NIR) analytical procedure used for screening drugs on authenticity to a Failure Mode and Effects Analysis (FMEA), including technical risks as well as risks related to human failure. An FMEA team broke down the NIR analytical method into process steps and identified possible failure modes for each step. Each failure mode was ranked on estimated frequency of occurrence (O), probability that the failure would remain undetected later in the process (D) and severity (S), each on a scale of 1–10. Human errors turned out to be the most common cause of failure modes. Failure risks were calculated by Risk Priority Numbers (RPNs) = O × D × S. Failure modes with the highest RPN scores were subjected to corrective actions and the FMEA was repeated, showing reductions in RPN scores and resulting in improvement indices up to 5.0. We recommend risk analysis as an addition to the usual analytical validation, as the FMEA enabled us to detect previously unidentified risks.

1. Introduction

Analytical procedures must provide reliable results. To ensure the reliability of analytical procedures, e.g. those used in the quality control of registered drugs, it is essential to validate the analytical procedures [1]. This analytical validation covers technical and instrumental aspects. For example, the International Conference on Harmonisation (ICH) Guideline requires validation with respect to Accuracy, Precision, Repeatability, Intermediate Precision, Specificity, Detection Limit, Quantitation Limit, Linearity and Range [1]. In the European Union, the validation of Near-Infrared Spectroscopy (NIR) is described in a separate regulatory document [2], which focuses on technical and instrumental aspects.

However, the reliability of an analytical procedure does not depend solely on technical and instrumental aspects. On the contrary, Kieffer [3] argues that: "Frequently the steps in the process which involve human intervention are the weak links in the process (...) Quite often in validation work the human element is ignored while mechanical and technological aspects are studied in great detail". In the regulated pharmaceutical industry, this discrepancy might originate from the fact that technical and instrumental aspects are covered by the Registration Dossier whereas human aspects are covered by Good Manufacturing Practice.

Risk analysis can bridge that gap, but up to now few results have been presented in which the human factor is fully taken into account. Cogdill et al. [4] introduced risk analysis into the development of a NIR analytical procedure, but no practical results were included. Dejaegher et al. [5] used Failure Mode and Effects Analysis (FMEA) in combination with other tools to study the reliability of a High Performance Liquid Chromatography (HPLC) analytical procedure, but did not explicitly discuss the human factor. Borman et al. [6] performed FMEA to identify important risks of a NIR analytical procedure for the monitoring of drying. However, only minor attention is paid to the human element as a risk factor. Capunzo et al. [7] applied also FMEA, to a clinical laboratory process. The authors mention the human factor and conclude FMEA to have a high improvement potential.

In our Official Medicines Control Laboratory we use a NIR analytical method for screening drugs on authenticity. In addition to the technical validation of our NIR analytical method, we applied risk analysis to our method using FMEA, taking into account human factors.

2. Materials and methods

The FMEA was performed according to the principles laid down in *The FMEA Pocket Handbook* [8]. The FMEA was performed by a team of four people with different competences: a NIR expert, a senior technician, an expert in Quality Assurance with experience in

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doi:10.1016/j.jpba.2009.06.049

Table 1
Process steps of NIR analysis.

	Process step[a]
1	Receipt of order and sample(s) by secretary
2	Transfer of order to head of department
3	Examination of order by the head of the department and assignment of examination to NIR expert
4	Registration of the sample(s)
5	Drafting examination plan by NIR expert
6	Review and authorization of examination plan by head of department
7	Meeting between NIR expert, technician and head of department on examination plan
8	Collecting of sample(s) by technician
9	Verification & validation of equipment by technician
10	Preparing sample(s) by technician
11	Performing measurements by technician
12	Processing of measurement results by technician
13	Interpretation of measurement results by technician
14	Reporting measurement results by technician to NIR expert
15	Review of the technicians report by NIR expert
16	Conclusions of examination by NIR expert
17	Discussion of measurement results and conclusions of examination by NIR expert and head of the department
18	Drafting of result of examination letter by NIR expert and discussion of letter with head of the department
19	Signing result of examination letter by head of the department and sending letter to the commissioner of examination
20	Archiving dossier by NIR expert

[a] Steps not subjected to FMEA indicated in grey.

laboratory quality systems and HACCP, and a senior pharmacist who mainly participates in the review of the chemical–pharmaceutical part of registration files. The participants of the team all attended a one-day course on FMEA and the FMEA itself was planned within four months.

First, the team visited the facilities with NIR equipment. Thereafter, the team broke down the analytical method in single process steps (see Table 1). Some of the steps were very general and not directly related to the NIR analytical method. These steps were consequently excluded from the FMEA and are indicated by grey shading in Table 1.

Subsequently, failure modes were identified for each of the remaining steps. Each failure mode was then ranked by its estimated frequency of occurrence (O), its probability that the failure would remain undetected (D) and its severity (S), each on a scale of 1–10. A high number represents a high risk. Ranking was performed by a consensus decision of the team.

For each identified failure mode, the RPN was calculated by multiplying the rankings for O, D and S. Consequently, the highest RPN that was theoretically possible became 1000 ($10 \times 10 \times 10$) and the lowest theoretically possible RPN became 1. We reviewed the results of the FMEA and corrective actions were undertaken with respect to the six failure modes with the highest RPN scores. FMEA was repeated and the improvement index of the corrective action calculated, being the quotient of RPN before and after the corrective action.

Finally, the team was asked to evaluate the risk analysis tool, i.e. FMEA, itself.

3. Results

Six sessions of two hours each were needed to perform the FMEA.

In the process steps subjected to FMEA, a total of 31 failure modes were identified, with RPN scores ranging from 12 to 320. Table 2 shows the six failure modes with the highest RPN scores, the corrective actions taken, the RPN after these corrective actions were taken, and the improvement indices.

When evaluating the methodology, a team of a NIR expert and more general pharmaceutical experts was reported to work well, as the interaction between them was of surplus value when identifying possible failure modes. However, only one NIR expert in the team was considered too few; it was felt that at least two NIR experts should be part of the team, in order to facilitate a substantive discussion. Also, the working procedure in which the team had to come to a consensus decision was positively evaluated, as the discussion needed to reach consensus was helpful in identifying possible failure modes. The introductory visit to the facilities and NIR equipment was reported to be important and contributed to a better understanding of the process. The visit provided the opportunity for the more general pharmaceutical experts to ask critical questions about the NIR analytical method. The team reported that if written information had been provided only, this would have been diminished the value of the FMEA.

4. Discussion

Several tools are available for the risk analysis. ICH Q9: QUALITY RISK MANAGEMENT [9] describes FMEA, Failure Mode, Effects and Criticality Analysis (FMECA); Fault Tree Analysis (FTA); Hazard Analysis and Critical Control Points (HACCP); Hazard Operability Analysis (HAZOP); Preliminary Hazard Analysis (PHA) and Risk Ranking and Filtering. We choose FMEA, a tool which, according to ICH Q9, "can be used to prioritize risks and monitor the effectiveness of risk control activities" and also because this tool is commonly used and well documented.

We restricted the risk analysis to the NIR analytical procedure and hence excluded steps common to all analytical procedures in our laboratory (see Table 1). In communicating the results, it is important to restrict the results to the part of the process examined.

In the FMEA tool, we did rank O, D and S on a scale of 1–10. This was an arbitrary decision; other rankings, such as 1–3 or 1–5 would have been also possible. Different ranking scales for O, D and/or S could also have been chosen. A further arbitrary decision was to rank O, D and S through a team consensus. An alternative would have been for each team member to make its own ranking. Lastly, we calculated RPN by multiplying O, D and S. Another option would have been to calculate an RPN with powers of O, D and/or S, for instance, to calculate an RPN with S^2 if S is considered to be of extraordinary importance.

Moreover, the RPN is a result of subjective opinion and it is quite likely that the composition of the team would have influenced the rankings.

Table 2
Risk Priority Numbers (RPNs) of failure modes with highest RPN and RPN after corrective action.

Step[a]	Failure mode	Possible effect	Possible cause	Possible mode of detection	Estimated frequency of occurrence (O)	Estimated frequency of detection (D)	Estimated severity (S)	RPN	Corrective action	RPN after corrective action	Improvement index[b]
10	Mistakenly switching of samples	Wrong result	Inadequate procedure	None	4 (after corrective action: 2)	10	8	320	Number the trays when more than one sample is analyzed	160	2.0
15	Inadequate control by NIR expert	Wrong result	Carelessness	Not timely	4	10 (after corrective action: 3)	8	320	Second control by other NIR expert	96	3.3
12	Lack of experience with chemometrics	Wrong interpretation of result	Incompetence	None	3	10 (after corrective action: 4)	8	240	Second control by NIR expert	96	2.5
18	No qualification of library in letter to commissioner	Wrong interpretation of result	Inadequate communication	None	3	10 (after corrective action: 2)	8	240	Include standard restriction in letter.	48	5.0
9	Wrong measurement parameters of NIR equipment	Unreliable result	Carelessness	Control by NIR expert	4	7 (after corrective action: 3)	8	224	Printing out measurement file	96	2.3
11	Wrong parameters NIR equipment for sample analyzed	Unreliable result	Carelessness	None	3	10 (after corrective action: 2)	5	150	Printing out measurement file	30	5.0

[a] See Table 1 for description of process step.
[b] RPN/RPN after corrective action.

Indeed, FMEA is not an "absolute" method. However, by using the same team and ranking method before and after a corrective action, the RPN before and after that action will be subjected to the same arbitrary parameters, as will be the quotient, i.e. the improvement index of the two RPNs. With this in mind, we shortened the FMEA process, to limit the turnover of team members and to minimise shifts in the ranking methodology.

Working with improvement indices was reported to lead to the uptake of corrective actions of only those failure modes with which the largest improvements can be realised [10]. This pitfall can only partially be circumvented by using an RPN formula that reflects the major risks that need to be avoided.

Despite the drawbacks, in our hands FMEA appeared to be a valuable tool in reaching our objective to identify risks, including those related to human factors. Process steps that were initially neglected or thought uncritical turned out to be of major importance. For example, the preparation of samples (step 10, see Table 2) was not considered as a major risk before performing the FMEA; however, FMEA showed that mistakenly switching samples during the preparation is actually a major risk. Overall, the human factor turned out to be the most important risk factor and these human risks are not directly covered by classical analytical validation. Using FMEA, we were able to improve our NIR analytical method by relatively simple interventions.

We conclude that FMEA is a useful addition to analytical validation, especially when considering the risks of human failure.

Acknowledgements

The authors would like to thank D.W. Groot and F. Bakker for their contribution in carrying out the FMEA.

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