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Short communication

Consistency of FMEA used in the validation of analytical procedures

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ABSTRACT

In order to explore the consistency of the outcome of a Failure Mode and Effects Analysis (FMEA) in the validation of analytical procedures, an FMEA was carried out by two different teams. The two teams applied two separate FMEAs to a High Performance Liquid Chromatography–Diode Array Detection–Mass Spectrometry (HPLC–DAD–MS) analytical procedure used in the quality control of medicines. Each team was free to define their own ranking scales for the probability of severity (*S*), occurrence (*O*), and detection (*D*) of failure modes. We calculated Risk Priority Numbers (RPNs) and we identified the failure modes above the 90th percentile of RPN values as failure modes needing urgent corrective action; failure modes falling between the 75th and 90th percentile of RPN values were identified as failure modes needing necessary corrective action, respectively. Team 1 and Team 2 identified five and six failure modes needing urgent corrective action respectively, with two being commonly identified. Of the failure modes needing necessary corrective actions, about a third were commonly identified by both teams. These results show inconsistency in the outcome of the FMEA. To improve consistency, we recommend that FMEA is always carried out under the supervision of an experienced FMEA-facilitator and that the FMEA team has at least two members with competence in the analytical method to be validated. However, the FMEAs of both teams contained valuable information that was not identified by the other team, indicating that this inconsistency is not always a drawback.

1. Introduction

Our laboratory carries out analysis on suspected illegal medicines in order to detect pharmaceutical crime. As the results of these analyses are used in court, the reliability of our results is of utmost importance. The usual way of testing an analytical procedure for reliability is to perform an analytical validation. This analytical validation covers accuracy, precision, reproducibility, repeatability, intermediate precision, specificity, detection limit, quantification limit and linearity, taking all technical and instrumental parameters into account [1]. However, according to Kieffer [2], "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". Risk analysis therefore has considerable added value in analytical validation, to assess failures due to human error. FMEA is a risk analysis tool often used to assess such failures.

The use of FMEA in the development of analytical processes was previously described by Borman et al. [3]. A proposed analytical procedure was subjected to FMEA, whereby the outcome enables high risks to be controlled or eliminated. Dejaegher et al. [4] applied FMEA to the HPLC of a drug substance to identify the most important factors affecting the capability of the assay. FMEA was also applied in a clinical laboratory to identify and estimate the risks of failure of some analytical processes. Capunzo et al. [5], and Van Leeuwen et al. [6] demonstrated the potential of FMEA to identify human risk factors in a Near-Infrared (NIR) analytical procedure, enabling an improvement in the reliability of the outcome of that procedure through relatively simple interventions.

However, FMEA is always based on subjective judgements. So, it is important to know the consistency of an FMEA in order to determine the value of its outcome. No literature was found on this aspect.

In order to study the consistency of the outcome of an FMEA when used in the validation of analytical procedures, we subjected a High Performance Liquid Chromatography–Diode Array Detection–Mass Spectrometry (HPLC–DAD–MS) analytical procedure used in our laboratory to FMEAs by two different teams. We then compared the putative failures of process elements with the highest risks identified by both teams.

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Table 1
Process steps defined by Team 1 and Team 2.

Step	Description
1	Verification & validation of equipment by technician
2	Preparing sample(s) and reference substances by technician
3	Performing measurements of sample(s) and reference substances by technician
4	Processing measurement results by technician
5	Interpretation of measurement results by technician
6	Verification of identity of pharmaceutical substance by technician
7	Quantitative determination of pharmaceutical substance
8	Reporting measurement results by technician to HPLC–DAD–MS expert
9	Review of the technicians report by HPLC–DAD–MS expert
10	Conclusions of examination by HPLC–DAD–MS expert
11	*Discussion of measurement results and conclusions of examination by HPLC–DAD–MS expert and head of the department*
12	*Drafting of result of examination letter by HPLC–DAD–MS expert and discussion of letter with head of department*
13	Signing result of examination letter by head of the department
14	Archiving dossier by HPLC–DAD–MS expert

Steps in italic (11 and 12) were exclusively defined by Team 2.

2. Methods

The two teams followed the same FMEA introduction course and performed their FMEA independently according to the international standard for FMEA [7]. Both teams consisted of four members, including an HPLC–DAD–MS-expert, a senior technician and a senior pharmacist, mainly participating in the review of chemical–pharmaceutical part of registration files. However, a different person participated in each team. The fourth member of Team 1 was an expert in Microbiological Risk Assessments for food, while in Team 2 the fourth member was an expert in Quality Assurance with experience in laboratory quality systems and Hazard Analysis and Critical Control Points (HACCP). The members with the same background had a comparable level of experience in their field.

Each team separated the analytical procedure into single steps and subsequently identified failure modes associated with each step, see Table 1. Each team defined scoring scales for severity of that failure mode (S), probability of occurrence (O) and probability of detection of that failure mode (D), see Tables 2–4. From

Table 2
Score scales for severity (S) of failure modes defined by Team 1 and Team 2.

Team 1

Score	Definition
1	No result by disfunctioning of the apparatus or shortage of qualified personnel. This causes reputation damage for the analytical centre and possible loss of a customer
2	A significant higher amount of pharmaceutical substance is reported than present. This may lead to undeserved condemnation of suspected persons as the reported amount has a therapeutic effect whereas the present amount has no effect
3	A significant lower amount of pharmaceutical substance is reported than present. This may lead to a public health risk as the reported amount has no therapeutic effect whereas the present amount has an effect
4	False positive (identity). The sample does not contain the pharmaceutical component of interest however it is reported to the client as detected. This may lead to undeserved condemnation of suspected persons. As other not detected pharmaceutical substances are present this may cause public health risks
5	False negative (identity). The sample contains the pharmaceutical substance of interest without being detected and is therefore not reported to the customer. This can be dangerous for public health

Team 2

Score	Definition
1	Unnoticed; no relevant effect
2	Failure not noticed; little effect
3	Extra effort to produce, no delay
4	Short delay in process
5	Moderate delay in process
6	Long delay in process due to carrying out repairs
7	Rejection of produced products
8	Customer end up with faulty report/product
9	Fail does no longer meet legal rules
10	People can get severely wounded

Table 3
Score scales for frequency of occurence (O) of failure modes defined by Team 1 and Team 2.

Team 1

Score	Definition
1	0–0.001
2	0.001–0.005
3	0.005–0.02
4	0.02–0.1
5	0.1–1

Team 2

Score	Definition
1	Once within 5 years or less than 2 in 10^9
2	Once within 3–5 years or 2 in 10^9
3	Once within 1–3 years or 6 in 10^7
4	Once within a year or 6 in 10^5
5	Once within 6 months–1 year or 1 in 10^4
6	Once within 3 months or 3 in 10^3
7	Once within a month or 1 in 10^2
8	Once within a week or 5 in 10^2
9	Once within 3–4 days or 3 in 10
10	More than once a day or more than 3 in 10

Table 4
Score scales for probability of detection of failure modes (D) defined by Team 1 and Team 2.

Team 1

Score	Definition
1	0.1–1
2	0.02–0.1
3	0.005–0.02
4	0.001–0.005
5	0–0.001

Team 2

Score	Definition
1	The defect is clearly visible or the product is 100% automatically controlled with regularly calibration and maintenance of the control apparatus
2	The product is 100% automatically controlled
3	A qualified SPC process control is used with Cpk > 133[a]
4	SPC[b] process control is used and immediately action is undertaken as thresholds are crossed
5	A form of SPC process control is carried out and the product undergoes a final control off-line
6	The product is 100% manually controlled with a go/no go or some way of failure prevention
7	The product is 100% manually controlled
8	The product is controlled randomly and released based on zero defects
9	The product is controlled randomly and released based on an acceptable quality level
10	The product is not inspected or the defect is not detectable

[a] Cpk = minimum {(upper limit tolerance − nominal value)/(3× standard deviation), (nominal value − lower limit tolerance)/(3× standard deviation)}, representing the extent in which a process produces within tolerance limits. Target value for Cpk: ≥1.33.
[b] SPC = statistical process control.

Table 5
Failure modes leading to urgent corrective actions identified by Team 1 and Team 2.

Team 1					
Step	Failure mode	S	O	D	RPN
Performing measurements of sample(s) and reference substances by technician	Wrong positioning of probe	5	3	4	60
Quantitative determination of pharmaceutical substance	Calculation sheet has been changed in calculation programme	5	2	4	40
Preparing sample(s) and reference substances by technician	Sample inhomogeneous	5	4	2	40
Performing measurements of sample(s) and reference substances by technician	***False setting of electronic pipette***	5	2	4	40
Verification of identity of pharmaceutical substance by technician	***False labelling of sample***	5	2	4	40
Team 2					
Step	Failure mode	*S*	*O*	*D*	RPN
Review of the technician report by HPLC–DAD–MS expert	Inadequate review	8	4	10	320
Performing measurements of sample(s) and reference substances by technician	Wrong pipette	8	3	10	240
Preparing sample(s) and reference substances by technician	Sample inhomogeneous	8	3	10	240
Performing measurements of sample(s) and reference substances by technician	Position of sample probe incorrectly	8	3	10	240
Performing measurements of sample(s) and reference substances by technician	***False setting of electronic pipette***	8	3	10	240
Verification of identity of pharmaceutical substance by technician	***False labelling of sample***	8	3	10	240

Similar failure modes by both teams are shown in bold italic. *S* = severity, *O* = occurrence, *D* = detection, RPN = Risk Priority Number.

the assessments of each team of *S*, *O* and *D*, Risk Priority Numbers (RPNs) were calculated by RPN = $S \times O \times D$. Failure modes above the 90th percentile were defined as failure modes needing urgent corrective actions; failure modes between the 75th and 90th percentile were defined as failure modes needing necessary corrective actions. Afterwards, we compared the failure modes identified by the two teams in both categories.

3. Results

It was noted that in both teams the input of the one HPLC–DAD–MS expert in that team had a major influence on the scores. Team 1 and Team 2 identified a total of 56 and 60 failure modes respectively. Team 1 and Team 2 identified five and six failure modes needing urgent corrective action, respectively, with two being commonly identified. The results of the comparison are shown in Table 5. Note that Team 1 had defined ranking scales for *S*, *O* and *D* from 1 to 5, so the maximum RPN for Team 1 is 125; Team 2 had defined ranking scales for *S*, *O* and *D* scales from 1 to 10, so the maximum RPN for Team 2 is 1000. About one third of the failure modes needing necessary corrective action were commonly identified by both teams (results not shown).

4. Discussion

The outcome of the two FMEAs clearly shows inconsistency. Both the failure modes needing urgent corrective actions and the failure modes needing necessary corrective actions identified by the two teams differ considerably. In particular, two of the four failure modes needing urgent corrective actions of Team 2 were not identified by Team 1.

These differences can be partially explained by the different approach chosen by the teams within the FMEA framework. The general FMEA documentation that was provided to both teams included score tables referring to large scale industrial production processes [8]. Team 2 used these scales without modifications. However, Team 1 decided that these score tables were not useful for an FMEA of an analytical procedure and developed new score tables with their own definitions for the rankings of *S*, *O* and *D*, thereby significantly influencing the values of *S*, *O* and *D*, and consequently the RPN of each failure mode as well as the ranking of these failure modes according to their RPNs. Also, Team 1 based their FMEA on the description of the analytical procedure in its Standard Operating Procedure, whereas Team 2 also visited the laboratory – an approach known as walk-through [3] – and took that visit into consideration when defining their FMEA.

We conclude that the consistency between FMEA outcomes can be improved by developing the skills of a small number of experienced facilitators who can help analysts to use FMEA more effectively and consistently by assisting in the definition of the failure modes and rating of the severity, probability and detectability index. Moreover, the involvement of experienced FMEA facilitators will prove valuable when evaluating the effects of the corrective actions that have been undertaken.

A second possibility to improve the consistency of the outcome of an FMEA of an analytical procedure is to ensure that there is always more than one technical expert in the team, in view of his/her major impact on the scores. At least two technical experts should be included in an FMEA team, to balance out significant individual differences in these crucial judgements.

On the other hand, the inconsistency in the FMEA outcomes does not only indicate a discrepancy in this risk analysis procedure. The FMEAs of both teams contained valuable information that was not identified by the other team. This calls for FMEAs to be sporadically performed by a different team, whereby each team is given the freedom to use a flexible approach.

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