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Risk Analysis and Annual Training Program Definition

by Luca Falce

This article presents an example of risk analysis.

Risk analysis is a technique used in all areas of the pharmaceutical industry; however, its major use is associated within the field of validation (equipment, machinery, utilities, cleaning), program inspections definition (audits) and design/maintenance.

This article presents an example of risk analysis associated with quality assurance and an annual training program conducted by an Italian pharmaceutical company with the objective of reducing deviations linked to human error.

Introduction

According to regulatory authorities,[1-2] risk analysis is a technique which could be applied in the pharmaceutical industry; however, examples where this methodology is used in areas other than technical ones are not easily found. This in part lies with the origins of the instruments used, and equally with the difficulty in the application of these concepts to situations related to factors of human behavior.

In the following case, the risk analysis technique has been applied to a variety of human behaviors. The application of this technique is related to the desire of the company's Board to follow authority expectation in order to solve a recurrent problem and to both update and increase the knowledge of company personnel. In concert with the approval of the 2010 Final Quality Report (January 2011), it was decided to create a study group to analyze deviations and to try to reverse the already present trends that indicate that the human factors are a frequent cause for deviations).

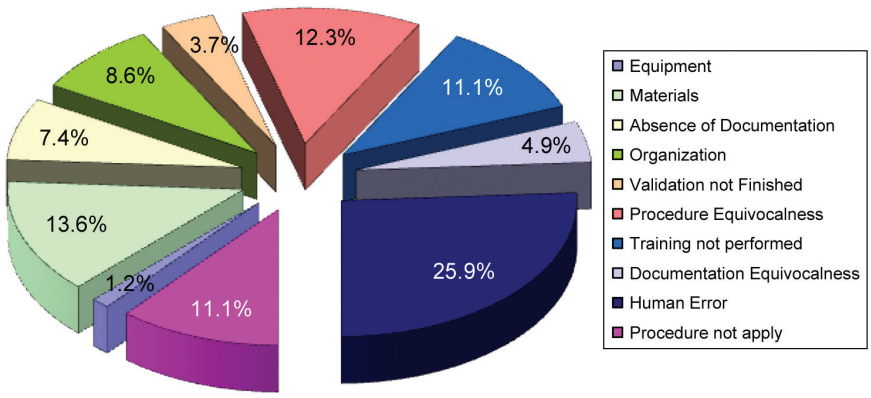

Figure 1. Deviations 2009.

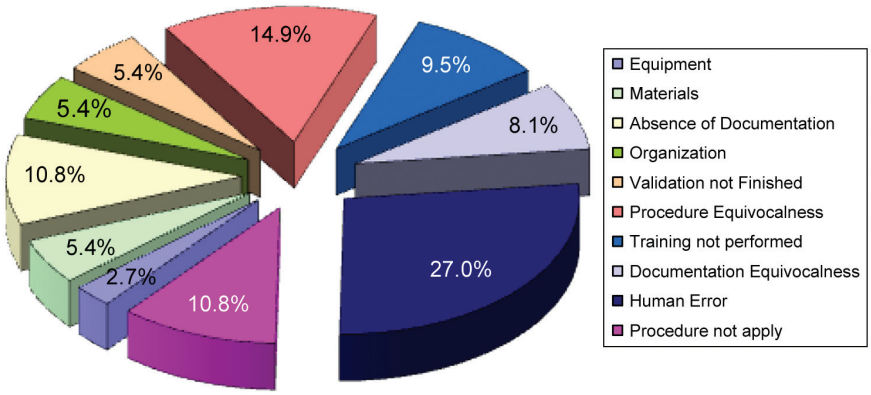

Figure 2. Deviations 2010.

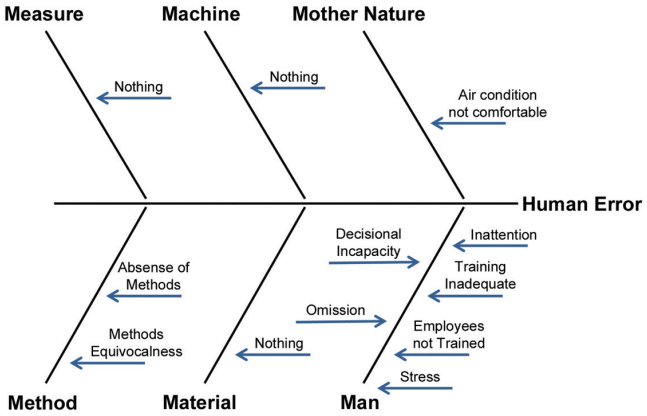

Figure 3. Ishikawa diagram.

Performed Activities

Preliminary Analysis

The working group was comprised of quality assurance personnel who ran the deviations and training and occasionally, depending on the needs/issues) by staff from various departments. The first activity was to re-check deviations identified as resulting from human errors.

It was decided to use an Ishikawa diagram as seen in Figure 3 to highlight the possible causes for deviations. The results were analyzed with respect to the applicability of a logic tool similar to Fault Tree Analysis (FTA), i.e., the same concept but no reference to the actual technique. At the end of this analysis, some cases were considered by the group as significant with the situation as seen in Table A.

This analysis showed the need to review the documentation by including:

- Photos
- Symbols
- Diagrams of processes
- Flow charts
- Checklists

In order to improve memory skills, learning and decision capability of the operator, the changes led to the addition of some organizational devices to make the work easier, i.e., coding/identification by color of parts and formats, dedicated equipment or similar but used for different products, etc. Examples are:

- Color identification of piping depending on the type of product (diluents – white color, analgesic – yellow color) and position identification depending on the technical parameters (diameter/length; tube 1, tube 2, etc.) as seen in Figure 4.

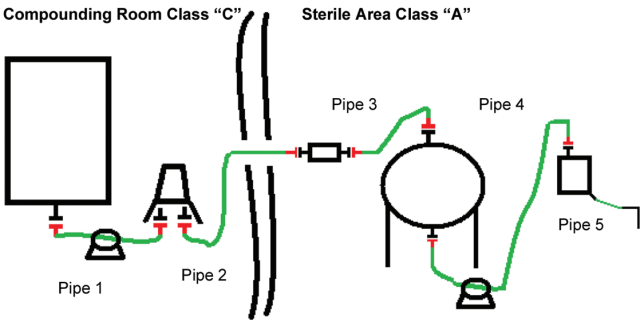

Figure 4. Tube set-up flow diagram.

Cause	Applicability	Explanation/Reason	Action
Air condition not comfortable	No	Air condition system works with the following set point: • 40 % < RH% < 60% • 19 < T < 23 °C	Nothing
Absence of methods/Manuals	Yes	In some case documents are missing because at the beginning they were considered not necessary	Issuing of documentation
Methods equivocalness	Yes	Some manuals are too specific or written by technician people so that not all steps are described.	Revision of manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.
Stress	No	Type of work and working rate cannot considered like an alienating job	Nothing
Employees not trained	Yes	Due to increased work some people were put on the line without an adequate training.	Revision of training procedure to clarify minimum request for each department
Training inadequate	Yes	Job rotation without appropriate know-how to cover unplanned absences	Revision of training procedure to clarify minimum request for each department
Omission	Yes	People know the procedures but are not able to put in practice their knowledge and so operate by guess.	Revision of internal manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.
Decisional Incapacity	Yes	People know the procedures but are not able to put in place their knowledge and so when necessary don't decide how to manage the situation.	Revision of manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.
Inattention	Yes	In some situation people are not concentrated in their work and so they are not able to understand what happens or how to manage the situation.	Emphasize the value of the work. Modify the plant by adding, where possible, acoustics and visible signals to highlight dangerous situations. Revision of manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.

Table A. Cause analysis/applicability/action.

- Changing operational description of sequences with added details and graphics/images:
  - Before – Press the start button and follow the instructions that appear from time to time on the display.
  - After – Hold for at least 3" the start button (the green button) as seen in Figure 5.

Figure 5. Start button.

After the system has completed its initial tests, "cycle ready" will appear on the display, press again the green button until you hear the gasket lock after the pumping up with compressed air.

Failure Modes, Effects, and Criticality Analysis (FMECA) and Classification of Training Chapters

In addition to these activities, it was necessary to change the theoretical and practical training plan by customizing it to be common for all functions.

Through the use of the FMECA technique,[3] for all the different functions, each chapter constituting the annual training plan was analyzed using:

A. GMP standards (such as general SOP training – change controls – deviations)

B. Dressing and behavior in the pharmaceutical plant

C. Dressing and behavior in the class "D" and "C"

D. Dressing in class "A" and "B"

E. Behavior in class "A" and "B"

F. Drawing up and correction of documentation

G. Use of equipment/machineries/tools

H. Cleaning of equipment/machineries/tools

I. Activity execution

Among these, some were selected to perform and other to postpone until the next evaluation.

Before starting the assessment, Severity (S), Detection (D), Activity Impact (A) and Probability/frequency (P) scales were defined - *Tables B, C, and D.*

The definition of scale led to several compromises between group but in the end customized scales specifically created for the work were chosen as customization became necessary to make the judgments as objectively as possible.

Probability/frequency (P)

With the availability of the list of deviations that occurred over several years, it was decided to consider each working day (220 days/year) as an opportunity for a "deviation possibility" and basing on the average of the last two years. The score percentage was determined by rounding to the next higher number in case of decimal.

Example – Human error deviations injectable department:

- four deviations in 2009 (1 for dressing and behavior in the Class "D" and "C", 1 for dressing in Class "A" and "B", 1 for behavior in Class "A" and "B" and 1 in the execution of the activity)
- three deviations in 2010 (1 for dressing and behavior in Class "D" and "C", 1 for dressing in Class "A" and "B" and 1 for behavior in Class "A" and "B")

Score	Evaluation	Description
1	Nothing	Only bureaucratic activity is necessary to solve the deviation.
2	Low	Operational activity is necessary to solve the deviation
3	Moderate	Material rejection could happen due to the deviation
4	High	Reworking could happen due to the deviation
5	Maximum	Drug product rejection could happen due to the deviation

Table B. Severity (S).

Score	Evaluation	Description
1	Sure	Simultaneous double checks and IPC in stop are in force
2	High	Simultaneous double checks are in force
3	Average	Check list is present at the end of the activity
4	Low	Double checks are present at the end of activity
5	Nothing	No double checks, no check lists and no IPCs

Table C. Detection (D).

Score	Evaluation	Description
1	Nothing	Activity without impact on final product, intermediate, manufacturing materials (API, excipient, packaging)
2	Low	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow
3	Moderate	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow
4	High	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step
5	Maxim	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step

Table D. Activity Impact (A).

Frequency deviation for dressing and behavior in the local Class “D” and “C”:

$1/220 \times 100 = 0.45\%$

After defining the scale of magnitudes, the Risk Priority Number (RPN) has been fixed with a conservative approach as seen in Table F.

After the set of the scale of FMECA and RPN value were used to determine the priority in training, the various departments were analyzed with respect to the chapters of the annual training plan. In order to do this, quality assurance personnel, managers and supervisors of the departments who have analyzed department participated in order to formalize the rules to be followed in allocating scores:

- Microbiology Quality Control (Micro QC) performs in process controls during production in sterile areas
- Chemistry Quality Control (CH QC) follows sampling in non-sterile area
- Warehouse performs the dispensing
- Technical Services (TS) performs the maintenance, calibration and validation

Score	Evaluation	Description
1	Nothing	$0 \leq \% \leq 0.2$
2	Low	$0.2 < \% \leq 0.5$
3	Moderate	$0.5 < \% \leq 2.0$
4	High	$2.0 < \% \leq 10.0$
5	Maxim	$> 10.0\ \%$

Table E. Probability/frequency (P).

RPN	Color	Action
≤ 54		Training can be postponed to the next evaluation waiting for SOP expiry.
54 <		Training has to be performed.

Table F. RPN table decision.

- The calculations of the analysis are to be performed manually on notebook (there is no management information system)
- Cleaning batch record/cleaning modules are in force
- If not applicable, should be scored as a minimum
- All production activities are performed by a team of at least two people

Training Chapters	Impact of Deviation	S	P	Check	R	Activity Impact	A	RPN
GMP standards (such as general SOP Training – Change Controls – Deviations)	Nothing; operator doesn’t perform directly the activity object of these chapters	1	1	Activities are always performed by a supervisor	2	No impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	2
Dressing and behavior in the pharmaceutical plant	Nothing; operator has to change his dressing before getting in contact with any object used for manufacturing	1	1	Colleague check	4	No impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	4
Dressing and behavior in the class “D” and “C”	If the operator doesn’t follow the procedures, it could be necessary to repeat some Operational activities	2	2	Before going inside the rooms a picture to show the correct dressing and a mirror to perform a self-check are present	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	3	36
Dressing in class “A” and “B”	Drug product rejection could happen if the operator doesn’t follow the procedures	5	2	Before going inside the rooms a picture to show the correct dressing and a mirror to perform a self-check are present	3	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	120
Behavior in class “A” and “B”	Drug product rejection could happen if the operator doesn’t follow the procedures	5	2	Colleague check	4	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	200
Documentation design and correction	If the operator doesn’t follow the procedures, it could be necessary to repeat some Operational activities	2	1	Activities are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	2	16
Use equipment/machinery/ tools	Drug product rejection could happen if the operator doesn’t follow the procedures	5	1	Simultaneous double check are in force	2	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	50
Cleaning equipment/ machinery/tools	Drug product rejection could happen if the operator doesn’t follow the procedures	5	1	Cleaning Batch Record/ cleaning modules are in force	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	75
Activity Execution	Drug product rejection could happen if the operator doesn’t follow the procedures	5	2	Simultaneous double check are in force	2	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	100

Table G. Injectable department.

Training Chapters	Impact of Deviation	S	P	Check	R	Activity Impact	A	RPN
GMP standards (such as general SOP Training - Change Control - Deviations)	Nothing; operator doesn't perform directly the activity object of these chapters	1	1	Activities are always performed by a supervisor	2	No impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	2
Dressing and behavior in the pharmaceutical plant	Nothing; operator has to change his dressing before getting in touch with any object needed for manufacturing	1	1	Colleague check	4	No impact on final product, intermediate,manufacturing materials (API, excipient, packaging)	1	4
Dressing and behavior in the class "D" and "C"	Reworking activity could happen due to the deviation	4	2	Before going inside the rooms a picture to show the correct dressing and a mirror to perform a self-check are present	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	3	72
Dressing in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Behavior in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Documentation drawing up and correction	If the operator doesn't follow the procedures, it could be necessary to repeat some Operational activities	2	1	Activities are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	2	16
Use equipment/machinery/ tools	Drug product rejection could happen if the operator doesn't follow the procedures	5	1	No other checks are in force	5	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	5	125
Cleaning equipment/ machinery/tools	Drug product rejection could happen if the operator doesn't follow the procedures	5	3	Cleaning Batch Record/ cleaning modules are in force	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	3	135
Activity Execution	Drug product rejection could happen if the operator doesn't follow the procedures	5	1	No other checks are in force	5	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	100

Table H. Warehouse department.

Examples of the assessments for three different departments, made during the meetings, are reported in Tables G, H, and I.

The activities started in January, 2011 and finished in March, 2011. The activities were completed in time to prepare the annual training program and to put into force all the corrective actions linked to the lack of documentation, an raised during the work.

The annual training program was prepared by choosing all the chapters with a score higher than the fixed limit score (54) with no regard to the final number of chapters. If "red zone" chapters were less than 3, green zone chapters with decreasing scores were considered in order to assure that at least three chapters were considered for training purposes.

If training was linked to a document that according to the outcome of the analysis was to be re-issued, the training was

Training Chapters	Impact of Deviation	S	P	Check	R	Activity Impact	A	RPN
GMP standards (such as general SOP Training - Change Control - Deviations)	Drug product rejection could happen if the operator doesn't follow the procedures	5	2	Activities are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	160
Dressing and behavior in the pharmaceutical plant	Only bureaucratic activity is necessary to solve the deviation	1	1	Colleague check	4	Activity without impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	4
Dressing and behavior in the class "D" and "C"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Dressing in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Behavior in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Documentation drawing up and correction	If the operator doesn't follow the procedures, it could be necessary to repeat some Operational activities	2	2	Activities are checked by another operator	4	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	80
Use equipment/machinery/ tools	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Cleaning equipment/ machinery/tools	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Activity Execution	Only bureaucratic activity is necessary to solve the deviation	1	1	Activity are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	16

Table I. Quality Assurance department.

Training Chapters	Injectables	Orals	Packaging	Warehouse	QA	CH CQ	CQ Micro	TS
GMP standards (such as general SOP Training – Change Control – Deviations)	NO	NO	NO	NO	NO*	NO	NO	NO
Dressing and pharmaceutical behavior in the plant	NO	NO	NO	NO	NO	NO	NO	NO
Dressing and behavior in the class "D" and "C"	NO	YES	NO	YES	NO	NO*	NO	NO
Dressing in class "A" and "B"	YES	NO	NO	NO	NO	NO	YES	YES
Behavior in class "A" and "B"	YES	NO	NO	NO	NO	NO	YES	YES
Documentation drawing up and correction	NO	NO	NO	NO	YES	NO	NO	NO
Use equipment/machinery/tools	NO	YES	NO*	YES	NO	NO*	NO	NO
Cleaning equipment/machinery/tools	YES	YES	YES	YES	NO	NO*	NO	NO
Activity Execution	YES	YES	NO*	YES	NO*	YES	YES	NO*
*Training Chapter chosen even if its score was inferior to limit score, in order to reach minimum number.								

Table J. Training plan for 2011.

postponed until the new version was issued.

It is possible to see the final action plan for all plant departments. "Yes" or "No" has been indicated as to which training chapters had to be considered and for which department - *Table J*.

	2009	2010	2011
Equipment	1	2	5
Materials	11	4	4
Absence of Documentation	6	8	5
Organization	7	4	11
Validation not Finished	3	4	5
Procedure Equivocalness	10	11	5
Training not Performed	9	7	8
Documentation Equivocalness	4	6	2
Human Error	21	20	12
Procedure not apply	9	8	6
Total	81	74	63

Table K. Trend deviations for 2009 – 2011.

Results

At the end of 2011, the deviation report showed an improvement in not only in the "human error" field, but also in all the usual deviations areas. The improvement derived from the analysis, which led to a more customized training plan and a different type of internal documentation (manual and procedure user oriented) with direct impact onto working activities as seen in Tables K, L, and Figure 6.

	2009	2010	2011
Equipment	1.2%	2.7%	7.9%
Materials	13.6%	5.4%	6.3%
Absence of Documentation	7.4%	10.8%	7.9%
Organization	8.6%	5.4%	17.5%
Validation not Finished	3.7%	5.4%	7.9%
Procedure Equivocalness	12.3%	14.9%	7.9%
Training not performed	11.1%	9.5%	12.7%
Documentation Equivocalness	4.9%	8.1%	3.2%
Human Error	25.9%	27.0%	19.0%
Procedure not apply	11.1%	10.8%	9.5%

Table L. Trend deviations % for 2009 – 2011.

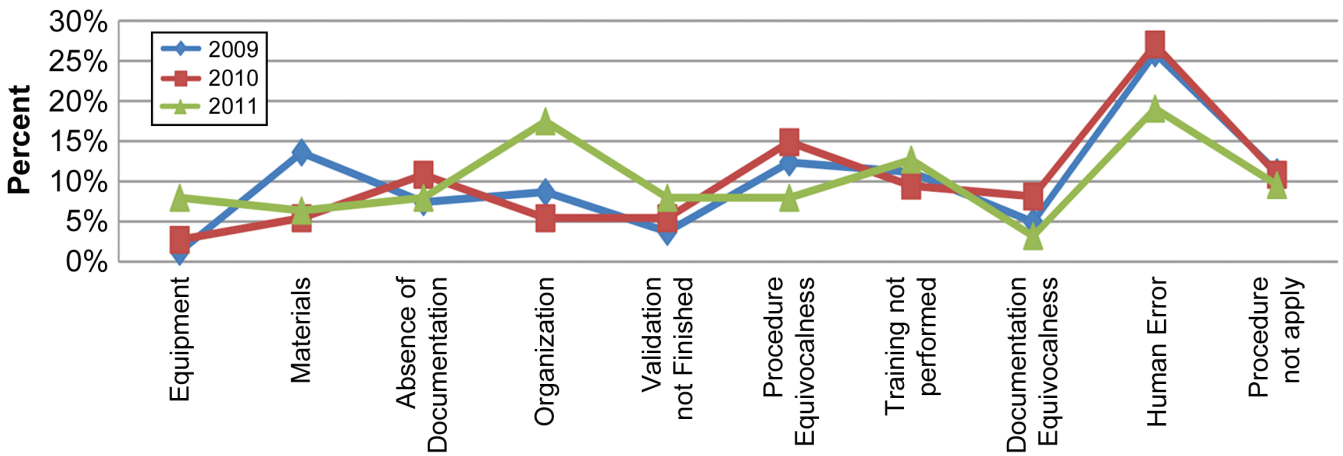

Figure 6. Deviation comparison and trend for 2009 – 2011.

"The improvement derived from the analysis, which led to a more customized training plan and a different type of internal documentation with direct impact onto working activities…

Conclusion

The activities were aimed at increasing the know-how of the risk analysis tools and achieved significant results not only in the main sector (human error – percentage of human error decrease for more than 25% at less than 20%), but also in all of the fields involved in the work.

Together with the reduction of training hours (from minimum of 10 hours to minimum of 4 hours of training for each operator), this shows how it is possible to increase the efficacy and the efficiency of the activities, while preserving the quality by means of tools present in normal working life. At the same time shows, it also demonstrates how it is possible to improve the know-how of the people and improve their efficiency.

References

1. EudraLex Volume 4, Annex 20 "Quality Risk Management."

2. ICH Q9 Quality Risk Management.

3. CEI IEC 812 Analysis Techniques for System Reliability – Procedure for Failure Mode and Effects Analysis.

About the Author

Luca Falce obtained his engineering degree from the Milan Polytechnic in1997; in the same year, he received his professional diploma. He has been in the pharmaceutical field since 1997 with varying technical experience, including validation, quality assurance and production, for both pharmaceutical and engineering companies. He is currently the Production Site Manager in Laboratori Farmaceutici SIT. Speaker in technical courses (QRM – Validation – Water); author of technical articles. He can be reached by email: l.falce@sit-farmaceutici.com.