Quality by Design
by Mark Shal, Ph.D.

Confronted with the complexity of communicating design or process changes to FDA, and concerns due to delays in obtaining regulatory approvals, some organizations are led to discount weaknesses in design of new or existing products despite objective evidence, and resolve to risky strategies to cope with the situation.

The goal of this paper is to facilitate design and process changes in compliance with the FDA/ISO requirements, and make their communication easier. It is based on the assumption that simplicity leads to less variability, and more communicable evidence. It is significant to realize how less variability leads to more reproducibility, and faster learning and development, as future opportunities can be discriminated against past experiences.

Problems described are typical, and not associated to any single enterprise, or group. Process validation has been treated in an earlier paper (1). The intent of this article is to reduce variations in the product development process, and the amount of time spent in statistical analysis and FMEA while keeping the risks in check.

The typical problems are:

1. Product development processes with insufficient or too many gates
2. Confusing FMEA analysis, more complex than they need to be
3. Statistical methods that are too cumbersome, and at time misleading

The impact of the above is increased complexity, dispersion of resources, delayed projects, and fear of change. The following describes an approach I have used over the years to bring to market three successful families of medical devices (each with a very limited number of post-market failures over their life spans). The methods proposed are applicable both to 510k and PMA submissions or amendments.

1. Product Development

The product development needs a maximum of 4 documented gates in which all functional representatives must be present and give their approvals: 1) design input; 2) design output; 3) limited (clinical) release; and 4) commercial/general release. Although each document will be signed by several managers, to prevent the diffusion of responsibilities, each document has only one owner. A single person who bears full responsibility for well understanding the document, and being able to explain it to others. What happens before the first gate has for aim to qualify a project from a business perspective, and has no regulatory relevance. What happens after the 4th gate is handled through change control, and quality improvement processes. The four gates answer the following questions:

- Gate 1: Is the design input complete, accurate and void of conflicts?

- Gate 2: Does the design output satisfy the requirements of the design input?
- Gate 3: Have processes been validated, and capable of meeting users' requirements?
- Gate 4: Is any adjustment needed in light of the feedback from the limited release?

2. FMEA Analysis

FMEA needs 5 levels of severity going from catastrophic to nuisance. Three of these are health-hazard related, the two others are not. Health hazards are defined by FDA and are death or permanent injury, serious injury requiring medical or surgical intervention, and minor or temporary injuries, reversible without medical or surgical intervention. The other two events are malfunctions or misuses that 1) delay the performance; or 2) are only nuisance.

Occurrences need 5 levels of probabilities going from frequent to highly unlikely. These correspond to the distance from zero of a standard normal distribution (see below for details).

In compliance with ISO 14971:2012, risk is defined as the probability of occurrence multiplied by Severity, and what we consider for our analysis is the risk over the life span of the product. We define 4 levels of risks:

- 4- (X) unacceptable - the only possible action in this case is mitigation
- 3- (M) High - Possible actions are mitigation, or approval at the highest level of the organization (M for Management)
- 2- (PT) Medium - possible actions are mitigation, or approval by the Project Team
- 1- (As is) Low - Benefits overweigh the risks, and the process is accepted as is.

Performance feedback is captured through communications with the sales force, Complaints, and Quality Systems and integrated the in the next design revision. The communication of quality with sales is of extreme significance because it provides early warning feedback, and puts the manufacturer ahead of the troubles.

The table below provides a summary. The letter p represents the designed probability of failure over the life of the product. It is important to note that no failure is designed purposefully, but in practice, at some point in time a ratio is considered negligible. We still fly safely despite 119-185 airplane accidents per year over the past 10 year.

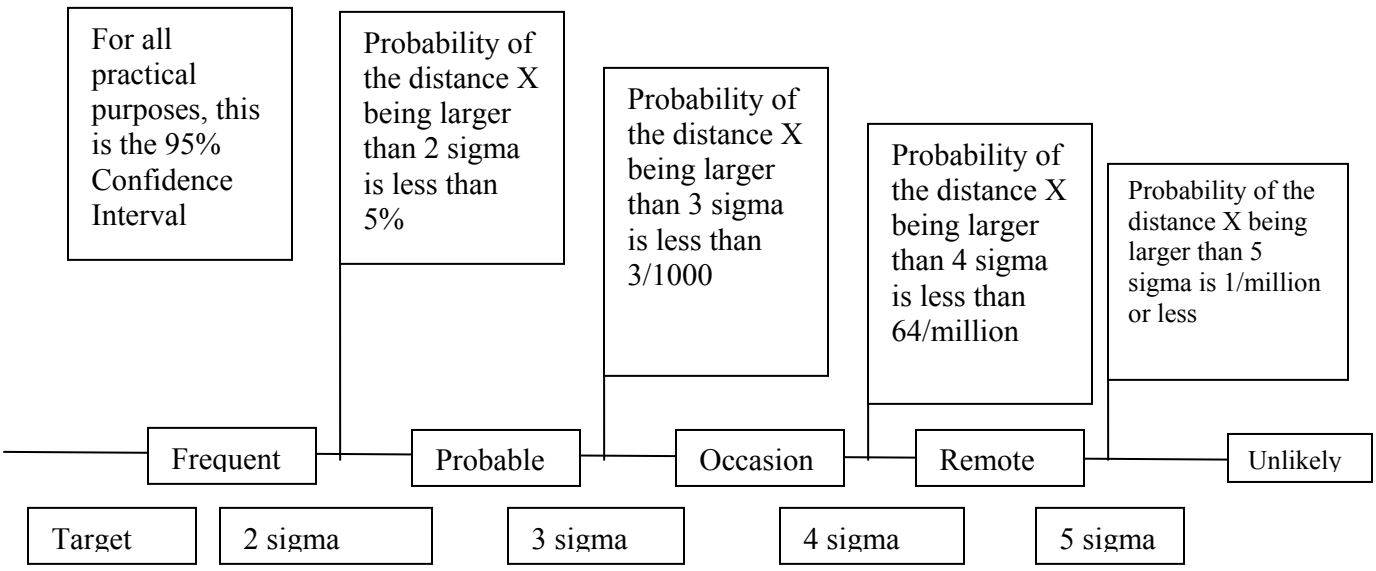
Risk Management/Hazard Analysis Summary

Probability of a failure mode, or expected proportion of a failure mode over the life span of the product	Malfunction or operator error likely to lead minor nuisance	Malfunction or operator error likely to lead to delay but no health hazard	Malfunction or operator error likely to lead to minor injury	Malfunction or operator error likely to lead to serious injury	Malfunction or operator error likely to lead to death or permanent injury
	Negligible	Marginal	Moderate	Critical	Catastrophic

Frequent: p more than 5%	**M**	**X**	**X**	**X**	**X**
Probable: p Between 2.7/1000, and 5%	**PT**	**M**	**X**	**X**	**X**
Occasional: p Between 65/million, and 2.7/1000	**As is**	**PT**	**M**	**X**	**X**
Remote: p Between 1/million and 64/million	**As is**	**As is**	**PT**	**M**	**X**
Unlikely: p less than 1 per million	**As is**	**As is**	**As is**	**PT**	**M**

3. Statistical Analysis

Statistics are thought in terms of distance X from target a key variable (or proportion) is allowed to fall during the life span of the product or process. The unit of the distance is a standard deviation (sigma). For all practical purposes, these permissible failure rates vary from 2 sigma (less than 5/100) to 5 sigma (less than 1/million) failures.



This simple analysis (2) is understandable by all, does not require any software, or table, and will provide consistent results across people, variables, and project.

For example, imagine a system parameter is designed to fail less than 2/1000.
If in 150 trials, we find 1 defective, should we consider this as a random event, and accept the process, or should we reject the process, and seek improvement?

Well, we have a repeat Bernoulli trial with probability 2/1000 of failure for a single trial. If the experiment yields one failure in 150 trials, the sample average is 1/150 or 6.7 failure per thousand. The estimated standard deviation in 150 trials is 3.65 per thousand (3), so the observation is at a distance (6.7-2)/3.65 = 1.28 sigma of the target. As this is less than 2 sigma, we cannot reject randomness (null hypothesis). Now the situation will be completely different if we change the failure to 2/150. In this case, we are at 3.11 sigma distance of the target and we have to reject the process.

It is worth noting that based on the third raw of the risk management table in section 2, accepting 2/1000 failure rate is a valid strategy for events of severity negligible to moderate, but of course not acceptable for events leading to serious injury or death.

One serious consequence of confusing NPD, and FMEA processes, and poor statistical procedures, is that failure modes leading to health-hazards are designed at 2/1000 level, and still accepted despite more than 2/150 failure rates in clinical trials.

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(1) Retrospective Validation, 2013.
(2) Analysis is based on the Central Limit Theorem: a sample's average sigma distance from its population's mean converges in distribution to a standard normal distribution. We are assuming measurement are unbiased so the specified target is the population's mean.
(3) Sqrt(2/1000)(998/1000)/150)

About the author:
Mark Shal offers sixteen (16) years of result-focused experience assuring changes in manufacturing, quality, supply chain, and engineering of medical device are CFR820/ISO 13485/CMDCAS compliant. He has developed, brought to market, and/or CE marked several families of medical devices (Electronic infusion pumps, disposables administration sets, and pain management devices). He has managed the V&V's, changes and transfers of medical device manufacturing tooling and assemblies from US to Mexico, and Thailand. Transfers required validation of molding, extrusion, and sterilization.
His background, combining statistics with QA/RA enables him to extract relevant information from the Quality Records (DHF, DMR, DHR, CAPA, MDR, Complaints, Suppliers performance, NCR's..) to speed up design, validation, submissions, ECO's, mitigation efforts, and manage risk with present and future products.

Mark has a PhD in statistics, a MS in Stochastic Control, and a MS in Engineering Mathematics from the university of Paris VII, Paris France.
