Article Commentary | Commentary

The Reliability-Quality Relationship for Quality Systems and Quality Risk Management

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Abstract

Engineering reliability typically refers to the probability that a system, or any of its components, will perform a required function for a stated period of time and under specified operating conditions. As such, reliability is inextricably linked with time-dependent quality concepts, such as maintaining a state of control and predicting the chances of losses from failures for quality risk management. Two popular current good manufacturing practice (cGMP) and quality risk management tools, failure mode and effects analysis (FMEA) and root cause analysis (RCA) are examples of engineering reliability evaluations that link reliability with quality and risk. Current concepts in pharmaceutical quality and quality management systems call for more predictive systems for maintaining quality; yet, the current pharmaceutical manufacturing literature and guidelines are curiously silent on engineering quality. This commentary discusses the meaning of engineering reliability while linking the concept to quality systems and quality risk management. The essay also discusses the difference between engineering reliability and statistical (assay) reliability.

LAY ABSTRACT: The assurance of quality in a pharmaceutical product is no longer measured only “after the fact” of manufacturing. Rather, concepts of quality systems and quality risk management call for designing quality assurance into all stages of the pharmaceutical product life cycle. Interestingly, most assays for quality are essentially static and inform product quality over the life cycle only by being repeated over time. Engineering process reliability is the fundamental concept that is meant to *anticipate* quality failures over the life cycle of the product. Reliability is a well-developed theory and practice for other types of manufactured products and manufacturing processes. Thus, it is well known to be an appropriate index of manufactured product quality. This essay discusses the meaning of reliability and its linkages with quality systems and quality risk management.

Reliability **Quality risk management** **Quality systems** **Risk assessment**

Introduction

Principles of reliability engineering are seldom mentioned in the pharmaceutical manufacturing sciences literature. Even the quality guidelines from the International Conference on the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are silent on reliability. Rather, quality principles in ICH guidelines are focused on variation reduction techniques and manufacturing process control to prevent the manufacture of poor quality products. These principles support the three main objectives of quality systems in ICH Q10,

- To achieve product realization
- To establish a state of control
- To facilitate continual improvement (**1**)

Although the need to address quality throughout the pharmaceutical life cycle is well understood and accepted in the pharmaceutical manufacturing environment, the role of reliability principles and reliability engineering in predicting a state of process control and facilitating continual improvements is either not generally understood or assumed to be common knowledge. Reliability principles are fundamental to understanding the impacts that each piece of equipment individually and each process step can have collectively on the state of manufacturing control, process validation, and quality risk management. The primary focus of this commentary is to discuss the relationships among product quality, process control, and quality risk management with *engineering reliability* for the product manufacturing system. The commentary concludes with potential benefits from including more explicit reliability principles in a concept of quality throughout the pharmaceutical life cycle.

A more robust and predictive view of pharmaceutical manufacturing quality has evolved in recent decades from industry and regulatory collaborations on defining quality management systems and developing quality risk management tools. Classical quality control approaches in which quality is “controlled” using ex post verification of product specifications are being replaced with more predictive and process analytical controls for manufacturing product quality using *quality by design* principles. It is widely accepted that well-characterized *systems approaches* quality management systems are vital to assuring product quality over the entire pharmaceutical life cycle. The old notion that pharmaceutical quality is a static, end-of-the-line label has been replaced with modern manufacturing concepts of building in quality throughout the product life cycle.

The idea that a product is only as good as ingredients provides only a partial view of a product quality spectrum. Pharmaceutical product quality depends on ingredients in the product's formulation; the manufacturing that combines, assembles, and dispenses dosage forms or active pharmaceutical ingredients (APIs); the facility/facilities that support the manufacturing; the mode of transport of the product; the wholesaler who sells it; and the workforce involved at each stage of the process. Within this context, the international tripartite guidelines are silent about the important role reliability analysis has in predicting failures in processes, equipment, and human operators. Reliability

of either the equipment or the process has only an implicit role in supporting product quality (1–5). Although U.S. Food and Drug Administration (FDA) guidance does not mention reliability directly, some principles for process validation are closely related and, in practice, might be likely to be derived reliability analyses, including root cause analysis (6). In a system-based view, measurements of quality parameters are not focused on a single point but an entire system, made up of interrelated components and processes whose overall quality depends, in turn, on interrelated component and process reliability.

Finally, reliability and risk are conceptually linked and can be fully quantitative for risk management purposes. In fact, there are whole chapters and texts focused on the quantitative linkages (7–9). The popular risk assessment tool called *failure mode and effects analysis* (FMEA) is one example of quality risk management tools that, in fact, are at the interface between risk and reliability assessments (e.g., 10, 11). Root cause analysis—commonly discussed as a part of current good manufacturing practices (cGMPs)—is also considered to be a reliability analysis tool as it is particularly important in human reliability analysis against standard operating procedures (SOPs) (14).

Reliability and Quality

According to Ebeling (12), engineering reliability is “the probability that a component or system will perform a required function for a given period of time when used under stated operating conditions.” ICH guidelines define quality as “the suitability of either a drug substance or drug product for its intended use.” This term includes such attributes as the “identity, strength, and purity” (13) and “the degree to which a set of inherent properties of a product, system, or process fulfills requirements” (4). The fact that a system degrades over time and system degradation can affect the quality portends the notion that reliability is intertwined with quality. For example, Ebeling noted that “a poor-quality product will likely have poor reliability, and a high-quality product will have a high reliability … . Reliability may be viewed as the quality of the product's operational performance over time, and as such it extends quality into the time domain” (12).

Reliability and quality are inextricably linked concepts. Both concepts involve performance of a product, process, component, or systems in terms of meeting user requirements or expectations. The key difference between engineering reliability and quality, per se, is that engineering reliability concerns meeting requirements *as a function of time* over the life cycle of the product, component, or process life cycle while quality concerns meeting requirements either at *defined points in the life cycle* or independently of time from the overall life cycle perspective. An understanding of systems-based manufacturing relies on understanding concepts of both reliability and quality. Understanding the different aspects to reliability enhances a quality professional's ability to define problems clearly when, for example, seeking root causes of defects and failures in the manufacturing environment.

Basic Reliability Concepts

By definition, reliability is the probability that a product, a system, or a process will perform its intended function(s) under specified conditions for a specific period of time. The primary objective of any reliability analysis is twofold. First, in order to prevent and minimize failures of the system or process, we need a clear understanding of how and why failures occur. Second, in order to maximize system performance and efficiently utilize resources to keep the system functioning, it is also important to know how often these failures occur, and to be able to predict levels of reliability in different phases of a system or process life cycle, as depicted in **Figure 1**. In the light of these analyses, the decision maker would be able to improve system or process reliability by removing failure causes in an optimal way (**7**).

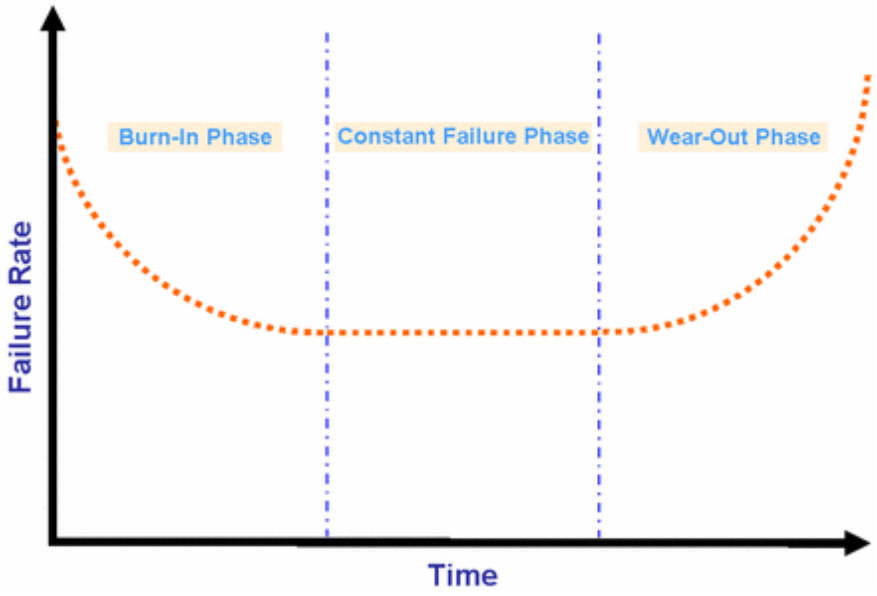

Figure 1

The bathtub curve of failure rate as a function of time. The failure rate, a probability of failures per unit time, is initially high for new equipment or a new process. The failure rate decreases to a constant failure rate driven by random events. As equipment wears out, the failure rate typically increases during a wear-out phase.

The time-dependent concept of engineering reliability generally builds from a *bathtub curve* depiction of the *rate of component failures* with respect to time (**Figure 1**). The failure rate—the probability of failure per unit time—typically declines during a *burn-in* phase and progresses to a relatively stable *constant failure phase* and finally increases over the *wear-out* phase over the life cycle of the equipment or process.

An understanding of the reliability curve can help quality managers understand and predict potential risks to product quality, *ex post* in terms of a recognized quality defect, and help the quality managers isolate root causes of failures attributable to system performance. To anticipate quality problems, it is helpful to know where along the reliability curve (in terms of operational hours) the system is operating. For example, for a manufacturing process, pharmaceutical manufacturing companies will likely go through the burn-in phase during process validation activities (**6**). This period is characterized by an initially high, but then decreasing, failure rate as the system becomes operational. This phase of reliability coincides with the demonstration that the system can perform within its specific limits and that the threshold for quality of product can be attained.

The constant failure region is the most stable period for the system and is part of the *continued process verification* phase of the product life cycle (**6**). During the constant failure phase, relatively less failure of the system is expected and the occurrence of failures is dominated by random events as opposed to burn-in adjustments and age-related failures during the wear-out phase. If a large amount of defects or quality issues are discovered during the continued process verification phase, special cause variation might be identified in the system or the actual quality process that is designed for the product. It is highly unlikely that frank defects that arise during this period are connected to a system. However, a common cause variation is an expectation of random events (e.g., **15**).

Finally, during the wear-out failure region there is an increasing rate of failures in the system. These increases in failures are attributed to the aging of the system and its components. The high rates of failure are inevitable once a system reaches this phase.

The understanding of the reliability curve is an asset for proactive quality risk management and for thinking about preventive measures. Each component of a system has a finite life span (hours of operation), and not all of the components are synchronized in terms of life time. Reliability concepts and strategic planning allows for the replacement of components and quality control measures. With each component replaced, the reliability curve resets and a new cycle is initiated for the component.

Contrasting Engineering and Statistical Reliability

Pharmaceutical manufacturing quality professionals and cGMP regulators encounter another important reliability concept: statistical reliability (e.g., **15**, **16**). Statistical reliability typically captures the consistency or reproducibility within a set of measurements or of a particular measuring instrument. Statistical reliability is a crucial concept for manufacturing control laboratories and for understanding detection of quality defects such as contamination. Reliability of a process also appears in quality-by-design (QbD) problems (e.g., **17**) in which models to find optimal design space operating parameters, measured against acceptable limits for critical quality attributes (CQAs), measure specified performance level in terms of statistical reliability. Finally, understanding the reliability bathtub curve concept can help parse sources of uncertainty due to sample, the projection models for failures, and even the concept uncertainty (**18**).

The difference between engineering and statistical reliability is subtle yet important (**Figure 2**). Statistical reliability is often defined as a function of the uncertainty in a set of measurements or the expected uncertainty given a specific measuring device (e.g., spectrometers, high-performance liquid chromatography, near infared, etc.). Of course, both laboratory and real-time physicochemical assays support the monitoring of both QbD and engineering reliability. Statistical and QbD reliability are fundamentally based on assessment and control of random error(s). In contrast, reliability concepts in engineering focus on hazard rates (the proportion of failures per unit time) for each component of the system and, in sophisticated models, the entire system. The differences among statistical, QbD, and engineering reliability are founded in this difference between random error and are evident in the mathematical formalism; however, an elaboration of the formal equations of reliability theory is beyond the scope of this paper and is left to the reader to explore (**8**, **9**, **17**).

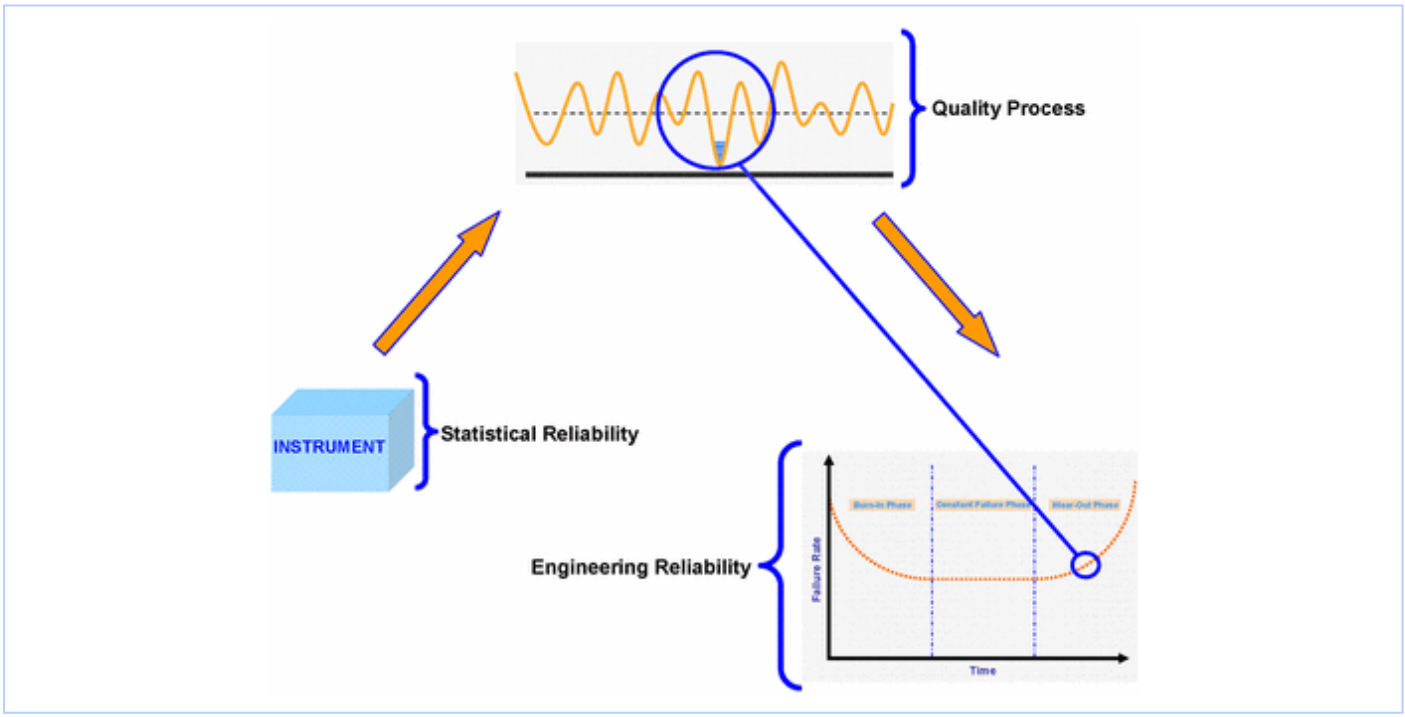

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Figure 2

A conceptual view of the relationship with engineering reliability, statistical reliability, and quality process.

The expectation of reliability in a system can be characterized by asking simple “how” and “why” questions. For example, hypothetical investigation questions might be useful during either FMEA or as part of a corrective and preventative action (CAPA) process (**Table I**). Structured, yet simple, questions about reliability analogous to the

simple three questions for risk assessment (e.g, What might go wrong? What is the likelihood it will go wrong? What are the consequences?) (4) might help interdisciplinary teams to identify risks to component, process, and system reliability. These questions are a short list of examples that quality managers and engineers might consider when evaluating the reliability of a system.

Table I

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Hypothetical Investigation Questions

Question	Example/Reasoning
What is the operational life of the component?	Tablet press is designed to operate for 4500 h.
How long has the component been in operation?	Tablet press is designed to operate for 4500 h; here you're asking how many operational hours have been accumulated. A press working for 1125 h is at 25% of its expected life.
Is the component repairable?	Repairable components need to be verified to ensure that they meet specifications.
	If it is a component that is nonrepairable, substitution of new equipment sets another bathtub curve in motion for the component and the process. It is important to verify and validate that the new component also meets all prior specifications.
Has the component successfully completed the burn-in phase (if it was replaced or repaired)?	Documentation should be provided to demonstrate that the component was successfully tested during the burn-in phase and at what point in time the component started to produce product(s) during the constant failure phase.

Reliability is not only directly related to the current and future states of the system and components, but also by past performance. This time-dependence is the intersection between the statistical process reliability, for example, of control charting and engineering reliability, and is a critical piece when evaluating a system. With this in mind, when evaluating reliability on a full time scale (past, present, future) it is imperative to collect information from maintenance logs, reports, and even SOPs that provide a look into the reliability of the current system. In addition, these sources of information can include CAPAs, equipment cleaning and maintenance documentation, and laboratory records.

The Marriage of Quality and Reliability

The strategy taken by quality managers should be one that approaches the quality inspection with a series of questions as opposed to a checklist of items. Although we talk about the quality of a product coming from a system, it is important to see that quality is only a snapshot of a single point in the system/process. Using this snapshot to gauge the entire production line of the product cannot be done. As an analogy, this would be similar to looking at only one frame of a movie and attempting to infer how good the whole film is.

The checklists of compliance items are critical for ensuring regulatory compliance of specifics. However, reliability is a vital component. Reliability paints an entire picture of the system/process by combining all the snapshots of quality and giving the quality manager a comprehensive story on the compliance of the system.

Reliability and Risk

Reliability is inextricably related to risk (e.g., **8**–**10**). It is generally believed that highly reliable processes lead to fewer losses from failures (i.e., risk) than do poorly reliable processes (e.g., **10**). The losses might be expressed in costs, human health endpoints, or even in Six Sigma manufacturing terms such as a number of failed batches per million opportunities. Tools such as FMEA rank potential failures in terms of a risk priority that might have changing picture of the occurrence probability depending where along a bathtub curve the process is operating.

Conflict of Interest Declaration

The authors declare that they have no competing interests.

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