



An efficient design framework for developing and demonstrating high reliability in an autoinjector for medical drug delivery

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Abstract

Greater product reliability is required by the U.S. Food and Drug Administration (FDA) for medical devices designed especially for emergency-use drug delivery systems such as autoinjectors (AIs; EpiPens). To achieve high levels of reliability, manufacturers are implementing design frameworks and their associated methods, which leverage design outcome prediction approaches such as Design for Six Sigma (DFSS) in lieu of the ‘Build, Test, Fix’ (BTF) frameworks that are widely used in the medical device industry. In this context, these two design frameworks, which are currently used by design teams and fit this purpose, are analyzed in the present study. The objective of this study is to compare the frameworks relative to their ability to yield suitably reliable designs and to understand whether changes can be made to these methodologies to improve the time and cost of meeting these high standards. For this purpose, a fundamental shift in how fault tree analysis (FTA) is used to model failures is leveraged to drive the system reliability level to the design targets meeting the mandates of the FDA. The results show the study design outcome prediction framework decreased the time needed to converge on device reliability targets on average by 61% from lead design concept selection to fault model verification in the intervention vs. the control study groups. The findings of this study may contribute to the use of tight mapping of critical parameters to the fault model to develop highly reliability medical device products.

Keywords Autoinjectors · Medical device · Product reliability · Design frameworks · Device design

1 Introduction

A diverse global user population relies on the life-saving delivery of medicaments from autoinjectors (AIs) within minutes of their exposure to symptom-producing triggers. In a study conducted between 2001 and 2005 (Nowak and Macias 2014) for the U.S. alone, it was estimated that every 6 min in hospital emergency departments or in 1,015,000 (14%) out of a total of 7,075,000 emergency department visits made by individuals, patients presented with acute allergic reactions related to food. In a 2014 Canadian study, anaphylaxis accounted for up to 0.26% of overall hospital admissions where a prescribed epinephrine AI was administered in more than half of moderate-to-severe cases (Turner

et al. 2020). National military defense organizations across the world, such as the U.S. Department of War (DOW), depend on medical countermeasures (MCMs) delivered through AIs to treat chemical warfare agent (CWA) exposures.

These life-saving devices have been demanded to be highly reliable by the U.S. Food and Drug Administration (FDA) (US Food and Drug Administration 2020), meaning that a failure rate of not more than one device per 100,000 devices produced is acceptable. This translates into a device system-level reliability that must be at least 99.999% with a confidence level of 95%. The system-level functional responses, Essential Drug Delivery Outputs (EDDO's) like activation force, delivered drug volume, drug delivery time, and extended needle length must be at least 99.99% with a confidence level of 95%.

Despite the wealth of innovation and the large market potential of AIs, design teams are struggling to satisfy new regulatory requirements for emergency-use injectors and parenteral drug delivery systems. The design of highly reliable autoinjectors relies heavily on engineering-technical

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reliability validation techniques of physics-based design functions. The combination of these two aspects of the design problem is unique and requires a new design approach. Teams are looking to engage design frameworks that are well-matched with processing and optimizing these design functions and can drive the design to high reliability.

The design teams of manufacturers use design frameworks and their associated methods to develop designs that meet the users' needs and regulatory requirements (Yang 2007). The design frameworks determine the steps of the design progression, whereas their applied methods determine the measures and effects of the design. Classically defined design methods like Nadler's ten step design method (Nadler 1967) have advanced into approaches and tools such as need finding, storyboarding, brainstorming, systematic design, axiomatic design or TRIZ to support the design team and the designer's new working style. Cross argued that the notion of design methodologies needs to better match the realities of contemporary design practice (Cross 2018). Based on his and others' argument, today's design methods may be better characterized as design processes.

Design outcome prediction approaches such as Design for Six Sigma (DFSS) and reactive approaches such as 'Build, Test, Fix' (BTF), serving in some cases as design processes, are widely used in the medical device industry to develop products. When used as a process, these framework-supported approaches or design processes meet the definition of design methods (Cross 2018). More will be said about design frameworks and methods in the next section.

A gap exists regarding medical device development frameworks and design processes that can provide design teams with strategies for quickly and efficiently iterating product designs and driving them to converge to highly reliable performance levels. The traditional BTF approach works in well-known design spaces and technologies associated with product line extension efforts. Predictive frameworks add value to investigations of unknown design spaces, akin to highly reliable designs. These unknown design spaces may incorporate product technologies that are more revolutionary than evolutionary like a novel drug lyophilization scheme. They provide design teams with tools to understand which design parameters are critical to product performance and how stressful conditions (noise) impact product performance. However, they fall short in providing strong strategies to drive reliability to high levels. If the BTF framework is used in a case with unknown design spaces, it inefficiently masks the sources of the design failures and tends to thwart the team's ability to quickly find and resolve them. This inefficiency, as well as wastefulness, has been well documented by practitioners and those representing U.S. government acquisition procedures and

transactions (Tang 2009), Wasson (2012). This results in project timelines being driven to the right, increasing development costs. The BTF framework, likewise, falls short in terms of providing strategies to meet the rapid reliability convergence needs of teams. The specific effectiveness differences and shortcomings between predictive and reactive frameworks will be highlighted later in the next section.

This research was conducted to investigate if rigorous design outcome prediction frameworks can achieve the high levels of reliability that these design teams require. The causal study addresses the general research aim of determining if there is a framework for applying design outcome prediction design processes that are more effective, are less expensive, and take less time to reach product reliability targets than the industry-accepted and highly used BTF design framework. Specifically, the primary aim is to compare two reliability models of emergency-use AIs for drug delivery. One uses component critical-to-quality (CTQ) dimensions and stack-up tolerances contributing to the basic events in an FTA, as recommended by the FDA. The second model uses design outcome prediction processes to obtain baseline and optimized critical parameters. The model goal is to find parameters that are robust against noise such as device aging, shock, shipping, vibration, environmental factors like temperature extremes and cyclic changes, altitude and pressure effects, and air particulates (dust/ sand).

2 Perspectives from the literature

The design of products and goods impacts everyone's life every day by improving our health, our wellbeing, and quality of life. We have high expectations that the designs of the product we choose to use will meet our needs. To better understand product designs and consider their propensity to succeed or fail, there is value and utility in examining how the product design process has evolved and is practiced today.

The genesis and history of design frameworks and methodologies are central to extending the usefulness of the current frameworks as new development tools and strategies emerge to help guide our efforts (Yang 2007). Additionally, included in this discussion are perspectives concerning the genesis and relatively brief history of fault tree analysis (FTA) due to the role it plays in helping teams drive product reliability levels to their targets. Our examination is restricted to the topic of designing highly reliable medical device products and technology along with the design frameworks, methods, and fault models used to achieve these designs. The historical perspective starts by defining design frameworks.

2.1 Design frameworks

A design framework describes a strategy for developing highly reliable AIs. A product development framework can be defined as a structured process comprising a series of stages or phases, decision points, and supporting tools and methodologies, which guide an organization through the tasks required to convert a market opportunity and customer needs into a commercialized product (Ulrich and Eppinger 2016). Frameworks such as waterfall development, circular product design, generalized margin design, concurrent engineering, axiomatic design for systems, Stage-Gate[®], V-Model, BTF and DFSS exemplify these systematic models. They help teams manage complexity, facilitate communication, and optimize the value of products throughout the development lifecycle (Otto 2003; Cooper 2008). The employed design frameworks and development methods have significant impacts on the performance of a product. Often, if a product does not work properly, takes too long to bring to market, or ends up costing too much, it is the result of a poor design process (Ullman 2010, Cooper 2008).

Design frameworks have the following further characteristics.

1. They create the basic structures that provide support and focus for directing the design process.
2. Frameworks often advocate a set of principles or a particular ethos, or they expound a philosophical position, within which a collection of methods, approaches, tools, or patterns are framed (Knight and Jefsioutine 2006).
3. They have the flexibility to support and guide a wide range of development activities, including product ideation, design analysis, decision-making, manufacturing process development, and multidisciplinary team interactions.
4. Unlike design methods and models, they tend to be broad and encompass wider application areas.

Many design frameworks and their associated design processes are present. However, for the specific case of developing highly reliable AIs, the few approaches that have gained significant traction with design teams typically first emerged in industry as best practices, then were taught in schools and universities, and subsequently were adopted back into industry by design organizations for product development purposes (Yang 2007). The current thinking about product development frameworks heavily favors two types of design frameworks, the BTF design framework where the design is well known and analytical frameworks such as DFSS, which carefully analyze designs via modelling and testing to optimize them (Schenkelberg 2023). While the BTF approach facilitates the early exploration of

failure mechanisms, the analytical approaches of DFSS help design teams quickly gain functional capabilities early in the development process through the optimization of critical parameters. There are downsides to both the BTF and the DFSS analytical approaches. Specifically, there is the risk that with each change cycle, the performance and/or reliability of the target device may improve or degrade for the BTF approach. The analytical approaches need more analysis of subsystems and subassemblies upfront in both the concept and development phases before a complete system is built.

Figure 1 shows how the design team continues in multiple cycles of building system-level prototypes, testing them, then fixing problems (BTF) until the design satisfies the imposed product requirements. It is difficult for them, within these cycles, to determine which critical design or manufacturing process parameters contribute to testing failures. Typically, teams using this framework need four to six BTF cycles, with multiple months required per cycle, to satisfy the input requirements (King 2010).

Cyclic testing rounds result in delays as teams work to discover the sources of failures, pushing project timelines to the right and increasing project costs.

A survey of costs of DOW initiated nerve agent AI development projects was conducted that occurred between 1990 and 2019 using a BTF framework and cyclical testing rounds. The project expenditure rate incurring during the BTF development cycles varied between approximately \$US 50,000 and \$US 200,000 per month. As design flaws remained undetected and system-level prototypes built and tested, the time required to find and resolve these flaws varied between four and 10 months per cycle.

The cost of mitigating undetected design flaws ranged between \$210,000 and \$2,070,000 per cycle. Satisfying the reliability requirements imposed by the FDA via the BTF framework is difficult and sometimes impossible. One company spent 13 years working to satisfy their AI input requirements using BTF and was not successful.

A fundamental shift from BTF was needed to produce designs that met the stringent reliability requirements of the FDA. A novel adaptation of the design outcome prediction methods of DFSS was developed and applied, which has helped manufacturing design teams successfully create highly reliable AI designs. Known as the Improved Product Reliability Development Framework (IPRDF), this framework provides a way for design team members to accurately predict and quickly improve the capabilities and reliability levels of their designs via the microdesign iterations shown in Fig. 2. As probability of failure data is generated as part of the microdesign iterations, this information is close mapped back to corresponding failure events in the FTA. DOEs used in the microdesign iterations can integrate noise factors like

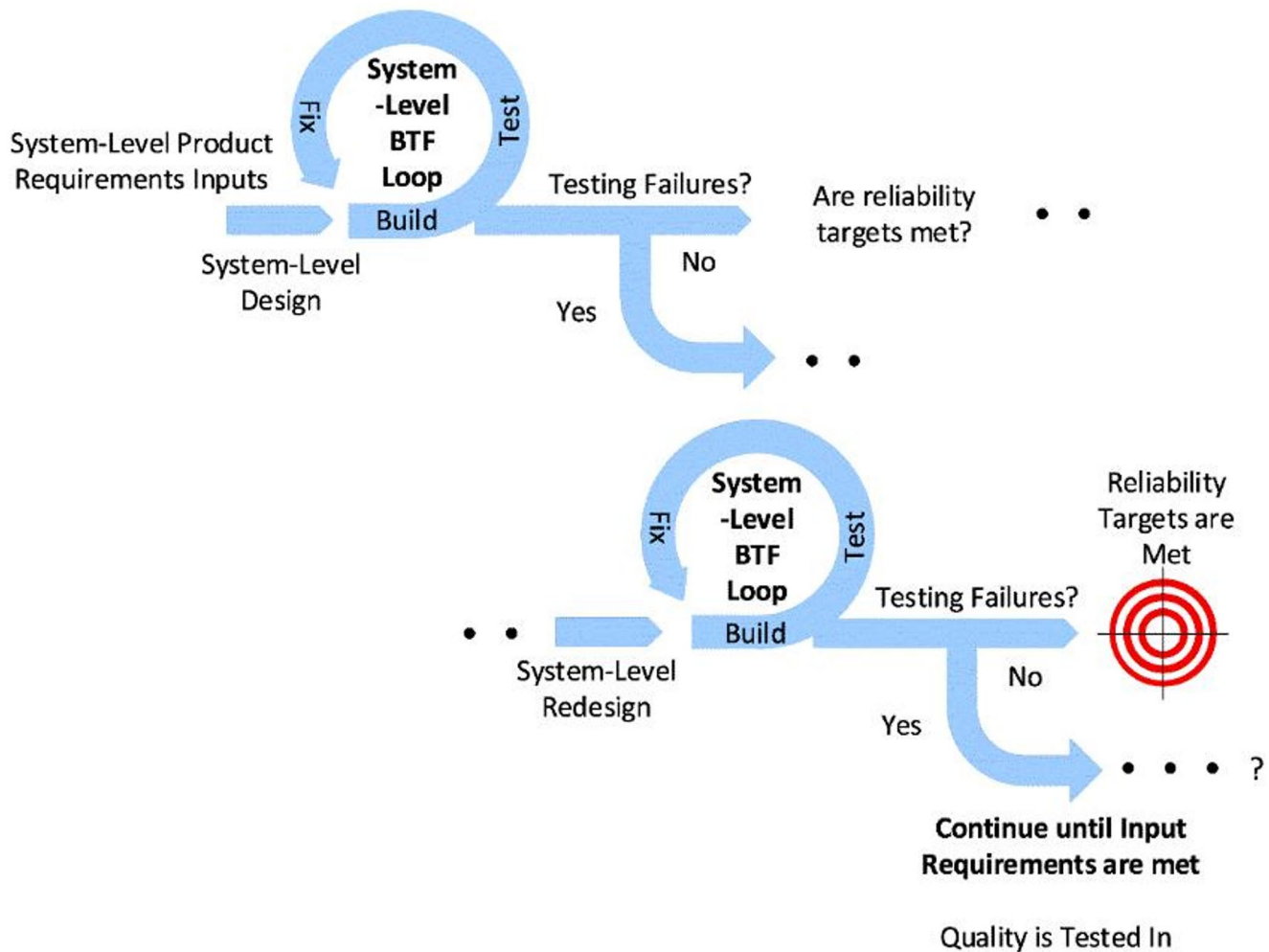


Fig. 1 The BTF product development framework

aging, shock, effects of shipping and others into the experiments to provide estimates of failure.

Customer needs (requirements) drive the identification of device functions and their control parameters via systems engineering (SE) and quality function deployment analyses implemented at all design levels. These and other assessments typically include voice-of-customer (VOC) long-range assessments, function diagrams, FAST diagrams, houses of quality, preliminary risk assessments, systems requirements, analytical and empirical models (ideal functions), patent trend impact analyses, and patent strategies resulting in the identification of the critical functions and parameters of the device and their target function capabilities. Preliminary and revised design failure modes, effects analysis (dFMEA) and process FMEA (pFMEA), along with houses of quality and risk analyses, help identify the critical functions of designs and map them to FTAs.

The teams predicted with relatively good accuracy how reliable a product design was as it was being designed. Such

a case occurs when design teams use the results derived from designed experiments to iteratively update their FTA and identify design improvement opportunities. A team uses a prioritized list of candidate critical parameters that are associated with the critical functions of their design to achieve rapid sublevel reliability improvements.

Microdesign iterations facilitate the optimization of the candidate critical parameters as needed at the design sub-levels (Wynn and Eckert 2017). The IPRDF improvement features a tight coupling paradigm involving DFSS processes, risk assessment, and risk management by iteratively updating the FTA of the target design with failure probabilities taken from critical parameter designs of experiments (DOEs) and other types of testing. The close mapping of critical functions to the fault model or FTA of interest shown in Fig. 3 provides the iterative pathway that is necessary for the execution of microdesign iterations to improve the impact of the critical parameter on function capabilities. The probability of failure is substituted directly from DOE

Fig. 2 Improved product reliability development framework

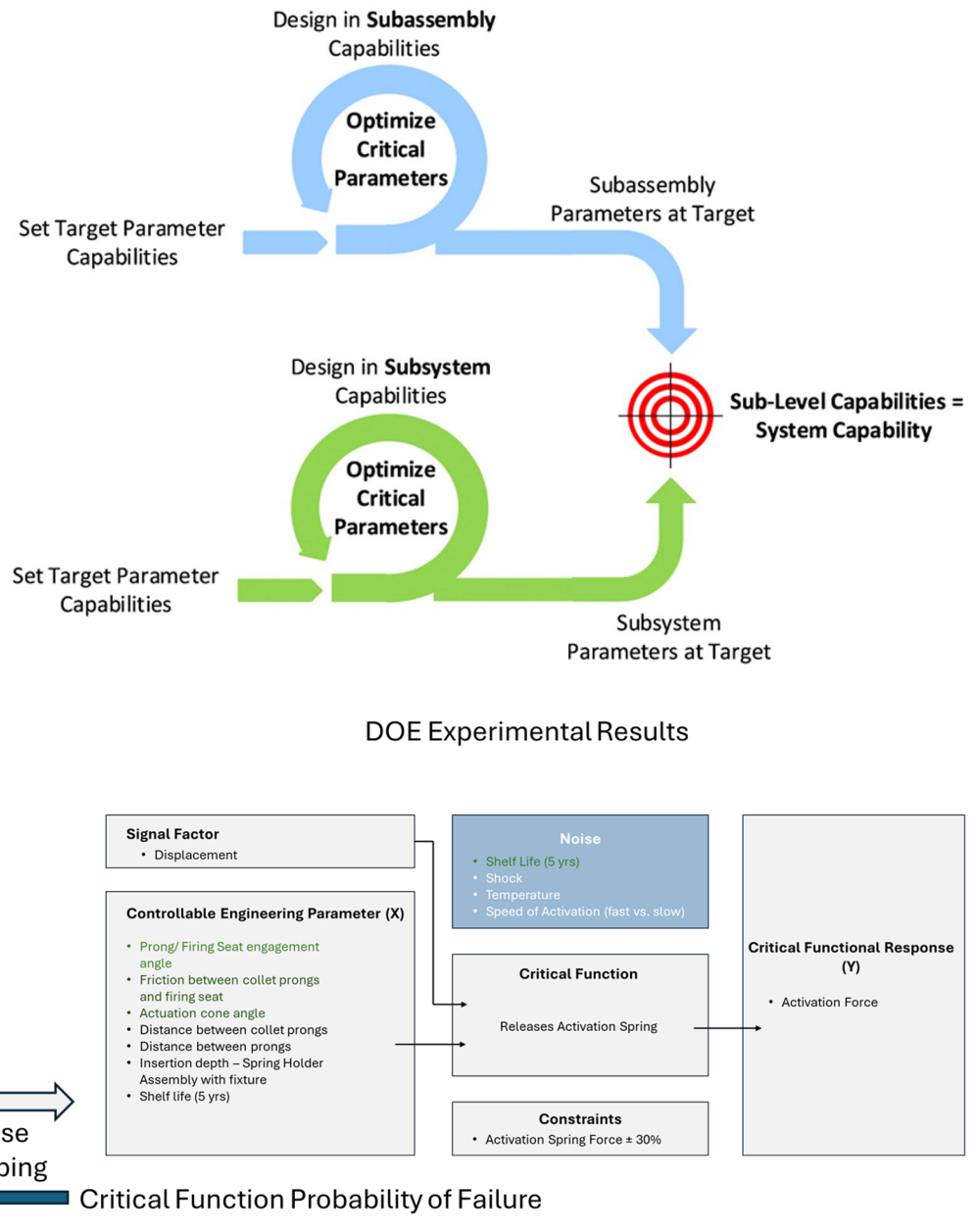


Fig. 3 Close mapping of the critical function to an underdeveloped intermediate event

experimental results into an underdeveloped intermediate event in the fault tree analysis. An underdeveloped event in a fault tree analysis is an event that cannot be further broken down due to insufficient information or because it is not significant enough to warrant further analysis. It is typically represented in the fault tree as a basic event that does not require resolution (Vesely 1981). The use of an underdeveloped event, in this case, is not resolved to a CTQ part or assembly dimension that contributes to a basic event as in a bottom-up CTQ FTA. A bottom-up CTQ FTAs utilize the limits of individual components (their dimensions, geometries, material strengths, etc.) to assess the potential of basic

event failure modes. The probabilities of failure mapped to underdeveloped events were obtained through the incorporation of potential failure mechanisms and experimental effects that were not accounted for in the bottom-up CTQ FTA approach. One team found that for a device critical function of activation, the CTQ FTA approach yielded a probability of failure estimate of 2.16×10^{-7} vs. the DOE mapped FTA failure rate of 1.6×10^{-6} . The team judged the latter estimate to be significant. This difference in the two approaches provided the impetus for the design team to continue optimization of the critical parameter in turn improving the device design.

Design engineers can quickly identify design weaknesses in the fault model and then adjust the critical parameter levels to minimize variations and shift the mean values to their specified targets. This results in a design that has greater reliability and robustness.

The target sublevel response variable capabilities (Cp and Cpk) are determined at the start of the design process within the employed design outcome prediction framework to ensure that the product reliability and robustness levels meet user expectations. The default targets obtained from DFSS are $C_p=2$ and $C_{pk}=1.5$. Designs that meet user expectations have capable functions. The critical parameters for controlling these functional device responses are optimized by adjusting their levels to include the manufacturing process parameters.

Sublevel parameters are easier and quicker to optimize than system-level parameters are because they involve fewer interactions with adjacent device functions. The effects of internal and external noise stresses are easier to trace and mitigate throughout the sublevel design (Creveling et al. 2003). The teams found that optimizing the sublevels first results in a system that, when assembled, performs at the required sublevel capability targets. Reliability targets were reached when the corresponding function capability targets were met.

The improved framework goes beyond the current DFSS and SE practices. The novelty of the improved framework in achieving high system-level reliability is the tight mapping of all critical design-level parameters to the fault model. This facilitates microdesign iterations of critical parameter optimizations and design improvements. The IPRDF leverages the failure probabilities that are already present in the critical function DOE results to update the FTA.

2.2 Design methodologies (processes)

Although they are used interchangeably in some cases to describe design frameworks, design methodologies are defined as overarching design approaches that may include sets of philosophies, principles, processes, and techniques. Methodologies concern how strategies are carried out. Modern design methodologies include but are not limited to critical parameter development and management (CPD&M), value engineering, quality function deployment, designing for X (manufacturing, assembly, reliability, etc.), designs of experiments, agile design, lean design, digital- and model-based design, and the physics-of-failure method. These distinctions help further define their differences from frameworks.

1. Design methodologies have evolved through the study of the principles, practices, and procedures of design in

a rather broad and general sense (Cross 1982; Friesen et al. 2005).

2. The distinction that separates a design methodology is its characterization as an approach rather than a structure like design frameworks.
3. Design methodologies began in design science and are used to develop knowledge and verifiable evidence of product performance. According to Cross (1982, 2018), design science, which refers to the body of work that attempts to improve our understanding of design through ‘scientific’ (i.e., systemic and reliable) methods of investigation, embodies the notion of design methodologies.
4. Design frameworks are meant to represent higher levels of design process structures.
5. SE, DFSS, axiomatic design, and BTF, among other popular frameworks, incorporate design methodologies into and as parts of their frameworks.

Both BTF and DFSS approaches can be considered methods or processes depending on how they are used by the design team. Many currently used design methodologies are not noted in literature specifically by name (Cross 2018). While the exact phrase “‘build-test-fix” is not a formal, standalone design methodology, the underlying concept of an iterative test-fix (or test-fix-retest) process is widely recognized and advocated in engineering and design literature outside of software, particularly in areas like product development and quality/reliability engineering. A few papers and books, however, do discuss the BTF approach directly (Tang 2009), (Broemm 2000), (Tang et al. 2018).

The test-fix approach is a core component of several established methodologies:

Iterative design: This general process in design (especially user experience or product design) involves building a version, testing it (often with users), identifying flaws, revising the design (fixing the flaws), and repeating the cycle.

Reliability Growth Testing (e.g., HALT/HASS): In hardware engineering, methods like Highly Accelerated Life Testing (HALT) explicitly use a “test-fix-test” cycle where engineers intentionally stress a product to generate failures early in development to find and “fix” weaknesses, thereby increasing reliability.

DMAIC (Six Sigma): The “Improve” and “Control” phases of the DMAIC (Define, Measure, Analyze, Improve, Control) methodology involve implementing solutions and testing them to ensure they fix the identified problems and hold the gains.

Plan-Do-Check-Act (PDCA) Cycle: This foundational quality management model involves planning a change, doing it (implementing the change/design), checking the

results (testing), and acting to standardize or improve the process, which aligns closely with a test and adjust loop.

In these contexts, the “test-fix” loop is seen as a fundamental, practical approach to problem-solving and quality improvement, rather than a singular, named “design methodology” in itself like Test-Driven Development (TDD) in software.

Today, design methodologies continue to progress and adapt to new challenges and opportunities. Methods in practice become socio-technical systems that depend on the knowledge, skills, and experiences of the design teams using them (Gerriker et al. 2017). Methods that are generated in academic environments tend to evolve into design processes as they are integrated into industry. Design has become an increasingly interdisciplinary field, with designers working in areas such as technology, healthcare, and sustainability. As a result, new design processes that are tailored to the needs of specific industries and contexts are emerging.

2.3 Fault tree analysis

FTA is an important facet of this discussion and, as such, deserves attention regarding how this design methodology has evolved and become well suited for being integrally linked with the CPD&M tasks involved in the production of highly reliable designs.

FTA is a systematic, deductive failure analysis method that was first developed in the early 1960s, primarily for conducting safety assessments in the aerospace and nuclear industries. It was initially developed in 1962 by H.A. Watson and A. Mearns at Bell Telephone Laboratories at the request of the U.S. Air Force. The aim was to evaluate the safety of the Minuteman missile launch control system (Aylen 2022). The method provides a systematic approach for identifying the possible failure paths within complex systems via a top-down, logic-based diagram known as a “fault tree.” This approach focuses on resolving an undesired event into its causes.

Its structure make it suitable for regulatory compliance, such as the requirements imposed by the U.S. FDA on medical device manufacturers (US Food and Drug Administration 2020). FTA has advanced considerably since its inception, becoming a vital tool in modern product development processes implemented across multiple sectors, including biomedical engineering and medical device development.

From its beginning, FTA has been able to use the characteristic parameters of the components, subassemblies, and subsystems of a system design as basic events (Vesely et al. 1981). To develop autoinjectors, the FDA recommends utilizing the limits of individual components (their dimensions, geometries, material strengths, etc.) to assess the potential of basic event failure modes. This limits design teams from

quickly settling on reliable autoinjector designs (US Food and Drug Administration 2020) in the concept phase. This method of generating an FTA is referred to in the study as a bottom-up CTQ FTA.

FTA remains a fundamental risk assessment tool, especially in safety-critical systems, including biomedical engineering systems, where it is applied to identify hazards and assure the reliability of devices (Stamatis 2003).

A gap remains in the literature regarding the close mapping from CPD&M parameter results to fault models and the use of fault models as heatmaps to focus on reprioritizing the candidate critical parameters during parameter optimization. Specifically, no studies involve the practice of close mapping and the use of microdesign iterations at the sublevels of systems to quickly drive designs to reliability targets.

3 Study methods

3.1 Study designs

An analytical-experimental study was conducted over a seven-year period starting in April 2018 to determine the ability of a design team to satisfy device reliability requirements and the time needed to reach their design targets based on their use of the IPRDF for parenteral AI drug delivery development projects. The objective of this study was to investigate the time and cost of this product design strategy for developing highly reliable devices. Three medical device design teams worked under the leadership of their respective U.S. and international manufacturers and within the confines of medical device combination product contracts with the Department of the Army to develop five separate products. The results of this prospective study were compared with retrospective data derived from three similar teams and four projects with comparable scopes and constraints that started in July 1987 and ended in December 2024. These retrospective projects serve as a control for the prospective study (IPRDF). The design teams operating during this retrospective (BTF) period used the BTF design framework to develop their products. Both groups of design teams (IPRDF and BTF) used similar engineering tools and analysis methods such as computer aided design (CAD) and computer aided engineering (CAE) techniques like finite element analysis (FEA). Both groups of design teams started their development projects using the BTF design framework until the IPRDF teams learned the design process for the new design framework. Limitations of the study are discussed in Sect. 6.

3.2 Materials

The six analytical-experimental study BTF and IPRDF product design teams were composed of 3 to 5 core individuals comprising primarily engineers, technicians, and designers. Table 1 highlights the composition of each team. They were part of the cross-functional product development team of a manufacturer. The design teams were typically led by principal engineers with ten to fifteen years of product development experience. Only two individuals on the three IPRDF design teams had received various degrees of DFSS training prior to joining these teams. One of the two was a green belt in DFSS. Two of the IPRDF design teams and their manufacturing leaders received a one-week DFSS course taught by a master black belt expert as well as ongoing training and assistance from the government acquisition team's separate DFSS black belt expert. The remaining IPRDF design team received training from the start of the project and throughout its duration from the government acquisition team's DFSS black belt also. Prior to starting these projects, the design staffs of all companies relied exclusively on the BTF framework for their development strategies. None of the individuals in the design teams involved with the retrospective BTF projects were trained in DFSS.

The equipment and calibration methods used to gather data for estimating failure probabilities and critical parameter variable data were similar to those used in industry (Schwartz and Seeger 2012). These measurements were the responses of critical functions associated with the subassemblies, subsystems, and systems. The testing procedures conformed to the design control regulation of the FDA (21 CFR 820.30) and their guidance for AIs and reliability assessments (US Food and Drug Administration 2020).

3.3 Study procedures

The procedure for conducting the analytical-experimental study involves determining the number of days it takes for each autoinjector development design team to achieve a system-level device design reliability of 99.999% with a confidence level of 95%. Intervention was provided to the IPRDF group and not the BTF control group. The intervention involved structuring the Request for Proposal and subsequently the Statement of Project Work for the development project to require the use of a design outcome prediction framework and associated deliverables. The intervention also involved providing training and guidance to design teams in the use of the IPRDF, a design outcome prediction framework. The control group consisted of past autoinjector

Table 1 Comparison of important characteristics among projects

Project number	Product design scope	Design team size and experience level ^c	DFSS training prior to project start	Non-clinical studies – device related
1	New device design ^a	A senior engineer, a designer, and 3 technicians or graduate interns made up the team.	None. BTF used simultaneously while learning DFSS & IPRDF.	None required
2	New device design	A senior engineer, a designer, and 3 technicians or graduate interns.	None. BTF used simultaneously while learning DFSS & IPRDF.	None required
3	New device design	A principal engineer, a design engineer, and 3 technicians or graduate interns. Also used was a design team from component supplier.	None. 1-week DFSS training after one year from project start. BTF is used simultaneously while learning DFSS and IPRDF.	None required
4	New device design	A principal engineer, a design engineer, and 2 technicians or graduate interns. Also used design team from component supplier.	None. 1-week DFSS training after one year from project start. BTF is used simultaneously while learning DFSS and IPRDF.	None required
5	New device design	A principal engineer, a design engineer, and 2 technicians. Also used 2 contracted design firms.	1-week DFSS training at project start. BTF is used simultaneously while learning DFSS and IPRDF.	None required
6	New device design	A PhD scientist, one engineer, and 2 technicians were used.	BTF is used exclusively. No DFSS or IPRDF design processes used.	3 required by FDA
7	Legacy device design change	A senior engineer, a designer, and 2 technicians or interns	BTF is used exclusively. No DFSS or IPRDF design processes used.	None
8	Legacy device design change ^b	A senior engineer, a designer, and 2 technicians or interns	BTF is used exclusively. No DFSS or IPRDF design processes used.	None
9	Legacy device design change	A senior engineer, a designer, and 2 technicians or interns	BTF is used exclusively. No DFSS or IPRDF design processes used.	None

^aA new device design involves starting with a new design concept from the project beginning to meet user needs

^bA legacy device design requires major modifications or changes to an existing design to meet user needs

^cAll design teams meet the Department of Defense's experience requirements

development projects conducted using a BTF design framework as evidenced by the project documentation.

The criteria for selection of the IPRDF and BTF projects were that its purpose was to develop an emergency-use injector as a nerve-agent poisoning antidote for the government. It additionally required FDA licensure as an end point and must be a revision to an existing design or a totally new design. The controls for these projects were the adherence to selection and acquisition rules by the project selection committee and the monitoring of project schedule, cost, and deliverables by the acquisition teams.

The procedure for the analytical–experimental study involving the design teams was similar for each of the manufacturers. Manufacturers responded to requests for proposals by the then DOD and Health and Human Services (HHS) acquisition teams to develop a combination product (AI) and submit it to the FDA for approval. A Government selection team vetted each manufacturer proposal using a strict set of selection rules and criteria related to capability, expertise, and experience. The same set of selection rules and criteria applied to the control group. For the IPRDF group, the selected manufacturer received a contract specifying the deliverables, specifically requiring the use of the DFSS CPD&M process and the IPRD design framework. Some design teams and their manufacturer leaders opted for one week of DFSS training during their development processes. Other design teams requested training and assistance from the subject matter expert of the DOD and HHS acquisition teams. In all cases, the teams begin the design process using the BTF framework until they were trained in the use of the IPRDF and DFSS processes. Table 1 shows the important characteristics of each of the study projects.

Note that Project 6 required three FDA mandated clinical studies during the device design phase. These studies did not impact the design or impede the design process. Consequently, the time required for these trials was deducted from the development time.

Much of the intervention for the analytical–experimental study consisted of the DOD subject matter expert meeting with the design team members. In some cases, their third-party design contractors were included in this meeting every two weeks to provide the requested training and answer design and manufacturing process development-related questions. Specific IPRDF training was given to each design team to assist them in planning their design frameworks and methods. The design teams reported their progress in terms of gaining design knowledge about the seven standard DFSS metrics for the critical parameters. This was accomplished at regular intervals so that the acquisition teams could track their progress against the master schedule of the project. The reliability targets of the design teams were met as evidenced by the submission of the FDA Reliability Report or

the completion of FTAs of their system ahead of the device design verification efforts, as outlined in the FDA Guidance for the Reliability of Emergency-Use Injectors (US Food and Drug Administration 2020).

The number of business days, excluding weekends and holidays, needed to reach the reliability target was recorded from time the teams selected a lead concept to the time the system reliability is evidenced by the FTA. Although the IPRD framework can be employed from the start of the device design, in all the projects, the design teams started using BTF.

All design teams were constrained by contracts to meet the design control requirements of the FDA as part of 21 CFR 820.30. All the tests and reports were required to conform to the requirements imposed by the FDA under this regulation. The manufacturer's design deliverables were monitored by the DOD acquisition team.

3.4 Statistical analysis

The days to reliability target data from each study group shown in Table 2 was determined to be normal with a p value of 0.411 and an AD value of 0.399. A two-sample t -test was used to determine there was a statistically significant difference in the means of the two study groups with a p value of 0.008 at a confidence level of 95%. The t -test indicates sample sizes were indeed sufficiently large (together with the results obtained) to detect a significant difference.

The days to reliability results shown in Table 2 that were determined to be normally distributed, were normalized by converting them to Z-Scores. Converted values for the combined study groups range between 1.31 and -1.48 standard deviations about the study group means, indicating that there are no outliers.

4 Results

The analytical–experimental study was conducted to assess whether there was a difference in how long it took the teams to reach their respective reliability goals. The times needed by the three IPRDF design teams engaged in the development of five new product projects were compared with the times it took three BTF design teams engaged in four BTF projects involving similar products. Table 2 shows the five IPRDF projects, the four past DOD BTF projects, the reliability targets of the teams, and the numbers of business days needed to reach the targets.

Projects 1, 2, 3, and 5 used a combination of the BTF framework and the IPRD framework primarily during the Concept Phase as they learned how to use the IPRDF. The Project 4 team used BTF for 3 years before adapting IPRDF

Table 2 Comparison among the numbers of days needed to reach the target reliability level by project and design framework

Project number	Design framework used	Reliability targets	Days needed to reach target
1	BTF/IPRDF ^a	99.999% System ^c , 99.99% EDDOs ^d	523
2	BTF/IPRDF	99.999% System, 99.99% EDDOs	912
3	BTF/IPRDF	99.999% System, 99.99% EDDOs	864
4	BTF/IPRDF	99.999% System, 99.99% EDDOs	1229
5	BTF/IPRDF	99.999% System, 99.99% EDDOs	961
6	BTF ^b	99.5% EDDO	2410
7	BTF	99.9% EDDO	2970
8	BTF	99.91% EDDO	2062
9	BTF	99.5% EDDO	1771

^aBTF/IPRDF is the combined use of the Build, Test, Fix framework and the Improved Product Development Framework by the IPRDF design teams

^bBTF is the Build, Test, Fix framework used by the BTF design team

^cSystem designates the reliability target at the system level determined by the fault tree analysis

^dEDDOs are the essential drug delivery outputs at the system level which were selected by the design team to characterize system performance

strategies. The reliability targets for the IPRDF teams were the FDA's combined requirements for system reliability at 99.999% (confidence level of 95%) and EDDO's of 99.99% (confidence level of 95%) (US Food and Drug Administration 2020). Projects 6 through 9 were not constrained by these requirements. The reliability required by their individual DOD contracts was that of the system's activation force denoted in Table 2 as an EDDO.

Projects 1 through 9 were similar in their scopes and design complexity levels. Projects 1 through 5 yielded higher system-level reliability, as demonstrated through an FTA. The essential drug delivery outputs of these projects, such as their activation forces, delivered doses, delivery times, and extended needle lengths, were determined through a tolerance interval analysis (TIA) as directed by the FDA (US Food and Drug Administration 2020). The reliability levels of Projects 6 through 9 were assessed by TIA, a Monte Carlo simulation, and other appropriate statistical methods.

Figure 4 shows a graphical representation of the performance of the teams in terms of reaching their reliability targets. The reliability target of each project is indicated along the ordinate, and the number of days between the time at which the lead design concept was established and the time at which objective evidence reaching the reliability target was presented is shown on the abscissa. The analysis of these data will be discussed in the next section.

5 Discussion

This research was conducted to investigate five AI design projects produced by three IPRDF design teams engaged in developing combination products (AIs for the delivery of nerve agent antidotes) for the then U.S. DOD. These teams met the reliability requirements imposed by the FDA on

their products using a combination of BTF and the IPRD frameworks.

For Department of Defense autoinjector development projects, the IPRDF project timelines were reduced and device reliability was increased by using a design-outcome prediction framework. To achieve high system reliability, the system fault model became an integral tool for use in microdesign iterations. The iterations centered on using the experimental results obtained for the critical functions and focusing the efforts of the design teams on minimizing variations and shifting the mean response values of the critical functions. The teams found that conservative IPRDF failure estimates provided an opportunity to pursue design 'hot spots' that were identified as the fault model was iteratively updated. Close mapping helped them quickly see where critical parameter optimization could improve the sublevel reliability and ultimately the system-level reliability of their designs. The experimental CPD&M results from DOEs captured the mechanical effects of the designs at sublevels that were not captured by the bottom-up CTQ FTA approach. These mechanical effects include among others, actual degrees of freedom of motion, the effects of sliding friction and fitness, and the bending and deformation induced under loads.

The IPRDF facilitated microdesign iterations of the design process by using the close mapping results. As 'hot spots' were identified in the designs by using the fault model, the teams could investigate critical parameter or design changes to improve performance and converge on the critical function capability targets. This allowed the design teams to quickly make the design changes needed and compress their timelines. The IPRDF had a distinct advantage over the BTF design frameworks in terms of microdesign iterations. Important noise conditions such as aging were added to sublevel experiments to aid in the optimization of the critical sublevel parameters.

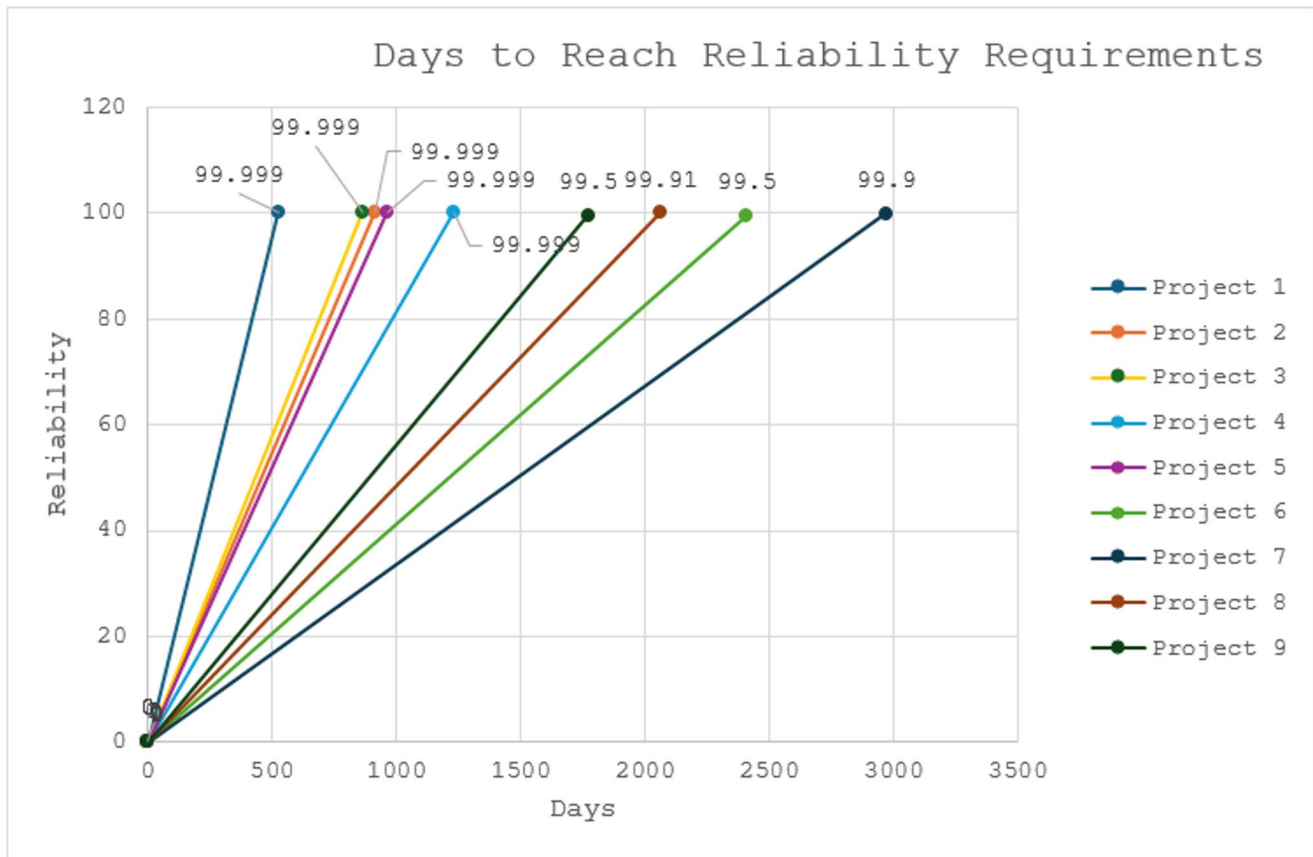


Fig. 4 Project comparison – days needed to reach the reliability targets

The FDA accepts the system-level FTA failure probability estimate of $\leq 1.0 \times 10^{-5}$ in place of testing hundreds of thousands of devices to demonstrate the reliability of emergence-use injectors. The FTA is supported by system-level response variables (EDDOs) such as the activation force, delivered drug volume, extended needle length, and drug delivery time, which meet the FDA's requirement of a probability of failure that is $\leq 1.0 \times 10^{-4}$. (US Food and Drug Administration 2020). Does meeting these design targets, however, translate into tangibly reliable device performance?

One design team provided a very practical demonstration of the design reliability and robustness of their device after reaching the reliability thresholds required by the FDA. The devices were assembled with table-top fixtures using coached untrained operators who ranged from office staff and engineers to individuals visiting the company.

The devices functioned as designed - first time as the untrained operators followed the assembly instructions. This demonstration was successfully repeated hundreds of times. The design was reliable and robust enough to offset the assembly variations imposed by untrained operators, and the devices still operated correctly.

In all nine projects, the design teams started the effort using BTF processes. This provided a close to level playing field to start the comparisons at the selection of the lead concept. It took all three IPRDF teams about a year to become proficient in DFSS and the IPRDF. During that first year, they too continued to use BTF design methodologies. They began seeing positive results from using the IPRDF framework and methods. It took the companies between 1.3 and 1.5 years to achieve their designs and, particularly, their reliability goals after achieving the requisite levels of proficiency.

Learning opportunities begin in the Concept Phase where candidate subassemblies and subsystems can quickly be evaluated for reliable and robust performance. Draft design and process Failure Modes and Effect Analyses along with a draft Fault Tree Analysis were used to guide the team where they needed to focus their efforts. This, in turn, allows the team to make informed choices about what configurations to include in their design and what to not include. When dealing with the requirements of highly reliable design, deep knowledge-in-hand of the design is required at all device levels. Design teams that bypass these opportunities for learning do so at their own peril.

The three IPRDF project teams were able to reach their reliability goals faster when using the IPRDF methods for a portion of their development efforts than the BTF design teams that exclusively used the BTF design framework for design projects with similar scopes. The longer it took the design teams to leverage the IPRDF methods, the longer it took them to reach their reliability targets. The Project 4 IPRDF team is an example of this type of delay. Note that the projects exclusively using BTF took longer to reach lower reliability targets than the IPRDF projects did.

It was assumed that the reliability of the device is zero when the lead concept was selected, when some preliminary reliability work started in the concept phase. For this research, this assumption is reasonable because all the teams were using the BTF framework in the concept phase, during which little or no work was done to assess the reliability of sublevel or system-level critical parameters.

To date, the teams are not fully trained in terms of executing the IPRDF. All of them have adopted these value-adding strategies as part of their design processes.

6 Explicit study limitations

The study has limitations due to the small number of projects available to it and the practicality of accessing the data. The large amount of time, funding, and human resources needed to conduct these projects makes them scarce for generating and collecting this data.

This is a case where randomized controlled trials are not feasible. As a result, bias risk will be higher. The non-randomized study can show treatment effects but have biases that a randomized controlled trial will not. For example, the risk is higher that the individual design teams will add bias. Less controlled conditions leave the generalizability to reflect the real-world scenarios.

In this controlled before-and-after study, the design teams are assigned to the group based on their association with the manufacturer rather than random selection. Where the randomized controlled trial is impractical, this study can be essential in understanding the treatment effect. It is believed, however, that this study can provide valuable insights into the effectiveness of the intervention in these real-world settings.

The IPRDF groups were constrained by FDA requirements to produce a highly reliable product. The BTF groups were constrained by the DOD contract to reach a mandated device reliability which was lower than IPRDF groups.

A bias may be present from the government contracting environment. Rules and requirements of the contracting process remove degrees of study freedom needed for randomization and study rigor. An example is that the acquisition

team cannot tell the manufacturer how to conduct the development project. They can only make recommendations.

Finally, there was inconsistency in the DFSS proficiency among teams. Some teams received consultant led training where other teams used self-study efforts. Augmentation of DFSS learning was provided in all cases by the acquisition team.

7 Conclusions/summary of the key findings

The design outcome prediction framework and methods used in this study for designing AI MCMs were demonstratively effective at producing reliable products, more so than reactive design methods were. To date, no MCM developed by an acquisition team using a BTF framework has been able to reach the level of FDA-required reliability achieved by the IPRDF.

Four key findings underscore the utility and novelty of the IPRDF for achieving high MCM reliability.

7.1 Close mapping provides conservative failure probability estimates

The teams were able to quickly iterate their sublevel designs to increase their critical parameter capability performances to the design targets by directly mapping the failure rates of CPD&M test results to the associated failure events of the FTA using underdeveloped events. They managed priority lists of the critical parameters at the device and manufacturing sublevels, retiring the parameters as they were optimized.

1. The IPRDF yielded more conservative failure rate estimates by incorporating mechanical effects that were not captured by the bottom-up CTQ FTA approach.
2. The IPRDF provided the design teams with a method for quickly identifying ‘hot spots’ in their system fault models and driving them toward capable product performance and the reliability targets.

7.2 Microdesign iterations drove the critical parameters of the critical functions to their design targets

Rapid design changes, informed by close mapping, were carried out at different sublevels in the design to improve the functional capabilities. The designed experiments were used to optimize the functional responses of the devices and drive their performance to the design targets. The reduced scope of the changes needed for the designs in the sublevel microdesign iterations helped the teams move quickly from

one design area to another as improvement needs were identified.

1. Microdesign iteration guided the design teams by reducing the opportunity to bypass dominant effects of the key critical parameters. The prioritized critical parameter candidates list, along with the seven-parameter metrics, helped the teams track their progress in terms of reaching the designated sublevel capability and device reliability targets.
2. The optimized subassembly and subsystem robustness levels directly led to optimal performance capabilities for the functional responses of the systems.

7.3 The noise conditions integrated during the sublevel parameter optimization process improved the failure estimates and sped up the design development procedure

Factors and conditions that cause external and internal noise, such as aging, shocks, and temperature preconditioning, were used within practical limits during the experimentation process to optimize the critical parameters. The subsystems and subassemblies were preconditioned prior to conducting the experiments to incorporate the effects of external and internal noise conditions. Aging had the greatest effect on shifting the mean values and changing the variability exhibited by the functional responses.

Not only did the failure estimates improve, but conducting noise experiments revealed how the noise was traced through and impacted the system.

1. Imposing noise conditions at different sublevels improved the failure rate estimates produced under close mapping.
2. Experiments that incorporated noise conditions early in the design process helped the designs quickly approach the reliability goals.

7.4 The IPRDF saved costs and time

The IPRDF and its associated methods provided the study design teams with a tool to quickly integrate high reliability and strong robustness into their product designs faster than the BTF framework could, saving time and reducing project costs.

1. The IPRDF accelerated the process of obtaining increased design knowledge.
2. Optimizing sublevel critical parameters helped eliminate system-level failures before they occurred.

This study design framework provided a distinct advantage in helping the teams quickly eliminate device failures before the subassemblies and subsystems were assembled and tested at the system level. The IPRDF Study Group took a mean of 1405 (95% CI 624, 2187) less days than BTF Group to reach their target device reliability.

Even with partial implementation, the study design teams found that the IPRDF demonstrated superiority in terms of providing design visibility and knowledge, resulting in opportunities to create better and more reliable products.

Broader applicability of these study results is constrained by existing study limitations. The study evidence points to improved design team performance, but more studies will be needed.

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Declarations

Competing interests The authors declare no competing interests.

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