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Design Standards and Regulatory Alignment for Vascular Access Devices in the United States: A Review of Design Control Requirements, Compliance Frameworks, And Opportunities for Scalable Safety-Driven Design Advancement

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ABSTRACT

Background: Vascular access devices (VADs) are ubiquitous in U.S. hospitals but carry risks of infection and thrombosis. U.S. regulations (FDA's 21 CFR 820 and the new QMSR/ISO 13485 framework) mandate stringent design controls, yet their impact on clinical outcomes is unclear.

Objective: To synthesize regulatory, engineering, and clinical evidence on VAD design and performance in the U.S. context and identify factors that enable or hinder safety-driven innovation.

Methods: A narrative review of recent U.S.-focused literature was conducted, including FDA and CDC guidelines, regulatory notices, systematic reviews, randomized controlled trials, observational cohort studies, and quality improvement studies. Sources of literature included PubMed, Scopus, Google Scholar, and FDA/CDC publications from January 2010 to December 2025, with emphasis on evidence quality and applicability to U.S. practice. Key findings from the user's manuscript were integrated and compared with this evidence.

Results: The U.S. VAD regulatory framework (21 CFR 820, QMSR) incorporates international standards like ISO 13485, emphasizing design controls and risk management. However, high-quality studies do not consistently show that compliance with these processes alone reduces complications. In contrast, implementation of evidence-based insertion/maintenance bundles dramatically reduces central line-associated bloodstream infection (CLABSI) rates. Human factor gaps remain; FDA guidance stresses user-centered design to prevent use errors. Overall, evidence suggests that institutional practices (training, sterile technique, line care) often outweigh marginal design changes.

Conclusions: Current U.S. device regulations provide a necessary framework but are insufficient by themselves to ensure safer VAD outcomes. We infer that integrating human-factors engineering, real-world outcome monitoring, and rigorous training is essential. Regulatory evolution (e.g., the QMSR's 2026 implementation) should tie approval and post-market surveillance to clinical performance.

KEYWORDS: Vascular access devices; FDA Quality Management System Regulation; CLABSI; Human factors engineering

1 .0 INTRODUCTION

Vascular access devices (VADs), including peripherally inserted central catheters (PICCs), non-tunneled central venous catheters (CVCs), tunneled catheters, and implantable venous access ports, are among the most frequently used invasive devices in clinical practice. They play a central role in the delivery of medications, parenteral nutrition, hemodynamic monitoring, and renal replacement therapy across both acute and ambulatory care settings (Elangovan et al., 2024). Despite their widespread clinical utility, their use is associated with a substantial and well-documented burden of complications. Central line-associated bloodstream infection (CLABSI) remains one of the most serious healthcare-associated infections in the United States, with an attributable mortality risk ranging from 12% to 25% and an estimated cost exceeding $46,000 per episode (Toor et al., 2022; Zimlichman et al., 2013). Catheter-related thrombosis (CRT), which arises from endothelial injury, altered blood flow, and hypercoagulability, as described in Virchow's triad, affects approximately 5% to 18% of patients, depending on device type and clinical context (Chopra et al., 2014; Wall et al., 2016). In addition, catheter occlusion contributes independently to device failure and interruption of therapy (Girardi et al., 2025; Ullman et al., 2015). Taken together, these complications represent a significant clinical and economic burden and highlight the importance of critically examining the systems that govern VAD safety.

The regulatory framework for VADs in the United States has historically been grounded in the Food and Drug Administration's (FDA) Quality System Regulation (QSR), codified at 21 CFR Part 820. This framework establishes current good manufacturing practice requirements and includes structured design controls under Section 820.30 (U.S. Food and Drug Administration, 2024d). In February 2024, the FDA issued a final rule establishing the Quality Management System Regulation (QMSR), which took effect on February 2, 2026. The QMSR amends 21 CFR Part 820 by incorporating ISO 13485:2016 by reference, thereby aligning domestic regulatory requirements with internationally recognized quality management standards (U.S. Food and Drug Administration, 2024e). In addition, the QMSR integrates risk management principles consistent with ISO 14971:2019 across the total product lifecycle, extending regulatory expectations from initial design through post-market surveillance

(International Organization for Standardization[ISO], 2019; U.S. Food and Drug Administration, 2024e). In principle, these frameworks position safety as an attribute that can be systematically engineered into medical devices through structured design and risk management processes.

However, despite this well-developed regulatory architecture, the extent to which compliance with design control frameworks leads to measurable improvements in patient outcomes remains insufficiently understood. Empirical evidence directly linking specific VAD design features or regulatory design control processes to reductions in complications is limited. A systematic review and meta-analysis by Slaughter et al. (2020) reported no statistically significant association between catheter material or structural design and the incidence of thrombosis, occlusion, or catheter-related bloodstream infection. Similarly, available evidence suggests that complication rates such as CLABSI and CRT are more strongly influenced by insertion technique, adherence to care bundles, and patient-specific risk factors than by device design characteristics alone (Balsorano et al., 2020; Elangovan et al., 2024). These findings point to a disconnect between the theoretical intent of regulatory design controls and the complex, multifactorial determinants of clinical outcomes.

This disconnect raises an important question about the effectiveness of current regulatory paradigms: whether process-oriented design control frameworks are sufficiently aligned with real-world drivers of patient safety. This narrative review, therefore, aims to synthesize the regulatory, engineering, and clinical evidence relevant to VAD design and safety in the United States, identify gaps between regulatory intent and real-world clinical outcomes, and inform more outcome-oriented approaches to device design and evaluation.

2.0 METHODS

A structured literature search was conducted in PubMed, Scopus, and Google Scholar, covering publications from January 2010 to December 2025. Foundational regulatory and standards documents published before this period were included where necessary to provide context for current frameworks. Search terms were developed across four key domains: device types and clinical context (“vascular access devices,” “central venous catheters,” “peripherally inserted central catheters”), clinical outcomes (“CLABSI,” “catheter-related thrombosis,” “catheter occlusion”), regulatory frameworks (“FDA Quality System Regulation,” “QMSR,” “ISO 13485,” “ISO 14971”), and lifecycle and engineering concepts (“design controls,” “risk management,” “post-market surveillance,” “total product lifecycle”). These terms were applied in various combinations to capture both domain-specific and cross-disciplinary literature. Representative combinations included: “vascular access devices AND CLABSI,” “central venous catheters AND FDA Quality System Regulation,” “PICC AND catheter-related thrombosis,” “ISO 13485 AND design controls,” “ISO 14971 AND risk management AND medical devices,” “post-market surveillance AND QMSR,” “vascular access devices AND human factors engineering,” “catheter occlusion AND total product lifecycle,” and “CLABSI AND catheter-related thrombosis AND design controls.” Literature materials were screened for inclusion based on their relevance to one or more of four thematic areas: regulatory frameworks governing VAD design and manufacture; engineering and design control principles; clinical outcomes associated with VAD use; and evidence gaps linking design processes to patient safety outcomes. Peer-reviewed articles, systematic reviews, and meta-analyses were prioritised, along with official regulatory and standards documents. Other relevant sources included FDA guidance documents, Federal Register publications, and surveillance data from the Centers for Disease Control and Prevention (CDC) and its National Healthcare Safety Network (NHSN). Sources that were commercial, promotional, or lacked an evidence base were excluded. No formal systematic review methodology or meta-analysis was undertaken, as the goal was to bring together evidence from different fields rather than calculate pooled estimates. The literature was reviewed thematically, focusing on how findings from regulatory, engineering, and clinical domains relate to each other and where the most important gaps lie.

3.0 REGULATORY AND DESIGN CONTROL FRAMEWORKS GOVERNING VASCULAR ACCESS DEVICES IN THE UNITED STATES

FDA Quality System Regulation and Design Controls

The regulatory foundation for medical device quality in the United States is established under 21 CFR Part 820, the Quality System Regulation (QSR), which defines current good manufacturing practice (CGMP) requirements applicable to the design, manufacture, and distribution of finished devices (U.S. Food and Drug Administration, 2024d). Vascular access devices (VADs) are predominantly classified as Class II devices subject to premarket notification under Section 510(k) of the Federal Food, Drug, and Cosmetic Act and are therefore required to comply with QSR provisions, including design controls under Section 820.30 (U.S Food and Drug Administration, 2022). Section 820.30 requires manufacturers to establish and maintain structured procedures governing device design to ensure that specified requirements are consistently met (U.S Food and Drug Administration, 2022). The design control framework includes design planning, design inputs, design outputs, design review, verification, validation, design transfer, and change control, all of which are documented within the Design History File (DHF), which serves as the formal record of design activities (Kinsel, 2012; U.S Food and Drug Administration, 2022; U.S. Food and Drug Administration, 2024d). Within this framework, a critical distinction exists between design verification, which confirms that design outputs meet specified inputs, and design validation, which demonstrates that the final device satisfies user needs and intended use. These represent distinct evidentiary requirements and are central to regulatory compliance (U.S Food and Drug Administration, 2022). Importantly, the QSR is fundamentally process-oriented, specifying how design activities must be conducted and documented rather than prescribing specific technical solutions (Lowery et al., 1996; U.S Food and Drug Administration, 2022). While this structure promotes traceability, consistency, and procedural rigor, it introduces an inherent limitation. Compliance with design control requirements ensures that design processes are systematically executed, but it does not guarantee that the resulting device will achieve optimal clinical performance (Donabedian, 1988; Kramer et al., 2012). In practice, manufacturers may demonstrate full regulatory compliance while variability in patient outcomes persists, particularly for VADs, where complication and failure rates are influenced by clinical context and healthcare processes (Marsh et al., 2024; Teja et al., 2024; U.S. Food and Drug Administration, 2018b). This distinction between process assurance and outcome effectiveness is central to understanding the role and limitations of regulatory design controls within the broader device safety landscape (Donabedian, 1988; Kramer et al., 2012).

Transition to the Quality Management System Regulation (QMSR)

On February 2, 2024, the U.S. Food and Drug Administration (FDA) issued a final rule in the Federal Register (89 FR 7496) establishing the Quality Management System Regulation (QMSR), which became effective on February 2, 2026 (U.S. Food and Drug Administration, 2024e). The QMSR amends 21 CFR Part 820 by incorporating ISO 13485:2016, Medical Devices: Quality Management Systems Requirements for Regulatory Purposes, thereby aligning U.S. quality system requirements with internationally recognized standards while retaining FDA-specific provisions necessary for statutory consistency (U.S. Food and Drug Administration, 2024e). This transition reflects a broader policy emphasis on regulatory harmonization and global convergence. ISO 13485 already underpins medical device regulation in multiple jurisdictions and forms the basis of the Medical Device Single Audit Program (MDSAP), which facilitates a unified approach to quality system auditing across participating regulatory authorities (International Organization for Standardization [ISO], 2016; U.S. Food and Drug Administration, 2024a, 2025b). By incorporating ISO 13485, the QMSR is intended to reduce duplicative compliance burdens for manufacturers operating across international markets and to promote greater consistency in regulatory expectations. From a structural perspective, the QMSR replaces much of the prescriptive language of the QSR with requirements incorporated by reference from ISO 13485 (U.S. Food and Drug Administration, 2026). While documentation constructs are consolidated under the Medical Device File (MDF), the underlying obligation to maintain comprehensive and traceable design and production records remains substantively unchanged (U.S. Food and Drug Administration, 2026). A notable development within the QMSR framework is the more explicit and integrated application of risk management principles throughout the quality system, extending expectations beyond premarket design activities to encompass the full device lifecycle (International Organization for Standardization [ISO], 2016; International Organization for Standardization[ISO], 2019; U.S. Food and Drug Administration, 2024d). However, while the transition to QMSR represents a significant advancement in regulatory harmonization and lifecycle integration, it does not fully resolve the challenge of linking regulatory compliance to measurable patient outcomes (Damkjær et al., 2025; U.S. Food and Drug Administration, 2024a). The increased emphasis on risk management introduces a more proactive and systematic framework, yet risk assessments remain dependent on available data, which may not adequately reflect real-world clinical variability (U.S. Food and Drug Administration, 2024e, 2025c). As a result, the extent to which QMSR will translate into improved patient-centred safety outcomes will depend not only on regulatory alignment but also on the quality, completeness, and effective use of post-market evidence (Burns et al., 2023; Damkjær et al., 2025; U.S. Food and Drug Administration, 2023b, 2025c).

Integrated Quality and Risk Management (ISO 13485:2016 and ISO 14971:2019)

ISO 13485:2016 establishes a lifecycle-oriented quality management framework governing the design, development, production, and post-market monitoring of medical devices (International Organization for Standardization [ISO], 2016). Within this framework, design and development processes are required to incorporate regulatory requirements, intended use considerations, and outputs derived from risk management activities (International Organization for Standardization [ISO], 2016). Post-market information, including complaints, adverse events, and surveillance data, is also expected to be systematically collected and integrated into quality system processes such as corrective and preventive action (CAPA), thereby enabling continuous feedback into the design and production system (Bills & Tartal, 2008; International Organization for Standardization [ISO], 2016; U.S. Food and Drug Administration, 2022). ISO 14971:2019 complements this structure by providing a formalized methodology for risk management across the device lifecycle, encompassing hazard identification, risk estimation and evaluation, implementation of risk control measures, and ongoing monitoring of residual risk (International Organization for Standardization[ISO], 2019). The standard emphasizes the continuous and iterative nature of risk management, particularly through requirements for production and post-production information review, which are intended to incorporate real-world performance data into ongoing risk assessment and control processes (International Organization for Standardization, 2020; International Organization for Standardization[ISO], 2019; U.S. Food and Drug Administration, 2022). Overall, ISO 13485 and ISO 14971 establish an integrated framework in which quality management and risk management are interdependent and mutually reinforcing (International Organization for Standardization, 2020; International Organization for Standardization [ISO], 2016; International Organization for Standardization[ISO], 2019). Within this framework, identified hazards are translated into design requirements, risk control measures are subject to verification and validation, and post-market information is used to reassess residual risk and inform potential design modifications (Bills & Tartal, 2008; International Organization for Standardization [ISO], 2016; International Organization for Standardization[ISO], 2019). For vascular access devices, this includes structured consideration of risks such as thrombosis, infection, and occlusion within a traceable and systematically managed design process (Baskin et al., 2009; Grau et al., 2017; O'Grady et al., 2011). However, while this integration provides a coherent and theoretically robust architecture for managing device-related risk, demonstrating translation into measurable improvements in clinical outcomes remains challenging (Timbie et al., 2024; Zuckerman et al., 2011). The effectiveness of risk management processes depends on the accuracy and completeness of hazard identification, the validity of risk estimation, and the extent to which premarket assumptions reflect real-world clinical use (International Organization for Standardization[ISO], 2020; International Organization for Standardization[ISO], 2019; Nolan & McDermott, 2025). In complex clinical environments, where outcomes are influenced by multiple interacting factors, the predictive capacity of structured risk management frameworks may be inherently limited (Nolan & McDermott, 2025; Timbie et al., 2024). This highlights a broader challenge in medical device regulation, namely that even well-established quality and risk management systems may not fully capture the variability and uncertainty associated with real-world device performance (Timbie et al., 2024; Zuckerman et al., 2011).

The Total Product Lifecycle (TPLC) Framework

The Total Product Lifecycle (TPLC) framework reflects the FDA's shift toward continuous, lifecycle-based oversight of medical devices, in which premarket evaluation and post-market surveillance are treated as interconnected components of a unified regulatory system rather than sequential stages (Hausman & Altaie, 2004; U.S. Food and Drug Administration, 2023b, 2024c). This approach is intended to enable ongoing integration of evidence and decision-making across the device lifecycle (U.S. Food and Drug Administration, 2023b, 2024c). Within the TPLC model, post-market data, including adverse event reports, surveillance studies, and real-world evidence, are expected to inform regulatory assessment and support iterative modifications over time (U.S. Food and Drug Administration, 2024c, 2025c). Approaches such as computational modelling and simulation further illustrate how assumptions made during device development may be reassessed using post-market performance information,

when model credibility is established for the relevant context of use (Morrison et al., 2017; U.S. Food and Drug Administration, 2023a). While the framework provides a clear pathway for data-driven design refinement, its effectiveness depends on the availability, quality, and integration of post-market data, as well as the capacity of stakeholders to act on emerging evidence (Timbie et al., 2024; U.S. Food and Drug Administration, 2025c). In practice, limitations such as under-reporting, delayed submissions, data fragmentation across sources, and variability in reporting practices may constrain the reliability of these feedback mechanisms (Everhart et al., 2025; Mishali et al., 2025; U. S. Government Accountability Office, 2025; U.S. Food and Drug Administration, 2025a). As a result, although the infrastructure for lifecycle-based oversight and data linkage is increasingly formalized, its translation into consistent, outcome-linked design evolution may remain uneven where post-market evidence is sparse or difficult to interpret (Timbie et al., 2024; U.S. Food and Drug Administration, 2023b).

4.0 DESIGN AND ENGINEERING CONSIDERATIONS FOR VASCULAR ACCESS DEVICES

Material Selection and Biocompatibility

Polyurethane and silicone remain the dominant polymer materials used in vascular access device construction, each exhibiting distinct mechanical and biological performance characteristics. Polyurethane supports thinner-wall, higher-pressure, and multi-lumen catheter designs, whereas silicone is more compliant and flexible but generally less resistant to mechanical stress (Cohen et al., 2011; Seckold et al., 2015). However, device durability outcomes are influenced not only by material selection but also by overall design configuration, placement conditions, and mechanical loading during use. At the biological interface, material properties influence protein adsorption and subsequent cellular interactions. Adsorbed plasma proteins form a conditioning layer that mediates platelet adhesion, activation of coagulation pathways, and complement responses, which are central mechanisms in catheter-associated thrombosis (Brash et al., 2019; Gorbet & Sefton, 2004). Over time, thrombus and fibrin sheath formation can further facilitate microbial adherence and biofilm development, functionally linking thrombosis and infection as interrelated device failure pathways (Donlan & Costerton, 2002; Esposito et al., 2013). Regulatory evaluation of material biocompatibility is structured around the ISO 10993 framework, which adopts a risk-based approach to biological safety assessment. For blood-contacting devices such as VADs, this includes hemocompatibility testing addressing thrombogenicity, coagulation, platelet response, and haemolysis as part of premarket evaluation (U.S. Food and Drug Administration, 2023c). While these assessments are essential for design verification, it is recognized that in vitro testing conditions may not fully replicate in vivo environments, particularly with respect to blood flow dynamics, shear stress, and patient-specific physiological variability. Accordingly, material selection is treated as a traceable design input within the device quality management system, linked to design outputs, risk controls, and verification and validation processes (International Organization for Standardization [ISO], 2016). However, isolating the independent effect of material choice on clinical outcomes remains challenging. Complication rates such as thrombosis and infection are influenced by multiple interacting factors, including insertion technique, catheter-to-vessel ratio, dwell time, and patient-specific risk profiles (Chopra et al., 2014; O'Grady et al., 2011). As a result, while material optimization is a necessary component of device design, it is unlikely to be sufficient on its own to ensure improved patient-level outcomes.

Device Geometry and Flow Dynamics

Geometric design parameters, including catheter diameter, lumen number, intravascular length, and the resulting catheter-to-vein ratio, influence local hemodynamics and represent modifiable design variables with plausible links to catheter-related thrombosis. Modelling work has shown that increasing the catheter-to-vein ratio can markedly reduce venous blood flow, providing a mechanistic basis for thrombosis risk associated with larger devices (Nifong & McDevitt, 2011). This reduction in flow is clinically relevant because venous stasis promotes local accumulation of procoagulant factors and favours thrombus formation. Clinical evidence generally supports this relationship, although it remains context-dependent. Larger-diameter and multi-lumen PICCs have been associated with higher rates of symptomatic upper-extremity deep vein thrombosis, while smaller and single-lumen devices tend to carry lower risk (Chopra et al., 2014; Liem et al., 2012). More recent work on catheter-to-vein ratio further suggests that oversized devices relative to vessel calibre are associated with increased thrombosis risk, supporting device downsizing and vein selection as practical mitigation strategies (Sharp et al., 2015, 2021). Catheter tip position is also an important geometric determinant, with placement in the lower superior vena cava or at the Cavo atrial junction associated with more favourable flow conditions and lower thrombotic risk than more proximal positions (Frykholm et al., 2014; Kleidon et al., 2021; Saber et al., 2011). However, the clinical effect of geometry is difficult to isolate from other determinants of thrombosis. Device choice is often driven by treatment intensity, insertion technique, vein size, and patient-specific factors such as malignancy or critical illness, all of which can confound observed associations (Fallouh et al., 2015; Wall et al., 2016). In addition, variation in thrombosis surveillance and outcome ascertainment limits direct comparison across studies and may lead to underestimation of asymptomatic events (Fallouh et al., 2015). Accordingly, current evidence supports catheter geometry as a meaningful contributor to thrombotic risk, but not as an independent or singular causal determinant of clinical outcomes.

Surface Modifications and Antimicrobial Coatings

Surface modification strategies, such as antimicrobial impregnation and antithrombogenic coatings, are employed to reduce infection and biofilm formation at the device-blood interface, aiming to address two primary mechanisms of catheter-related complications: microbial adhesion and thrombus formation. These coatings work by preventing microbial colonization and by altering the blood-material interface to reduce thrombus formation, to prevent infection and thrombosis, two major causes of catheter failure (Donlan & Costerton, 2002; I. I. Raad & Hanna, 2002). While experimental studies provide strong mechanistic support for antimicrobial and antithrombogenic coatings, clinical evidence remains heterogeneous. U.S.-based randomized trials on central venous catheters (CVCs) have shown that antimicrobial coatings, such as chlorhexidine-silver sulfadiazine and minocycline-rifampin, reduce catheter-related bloodstream infections (CLABSI), particularly in high-risk populations (Maki et al., 1997; I. Raad et al., 1997). However, some meta-analyses have found mixed results. A meta-analysis on antimicrobial-coated peripherally inserted central catheters (PICCs) reported a reduction in CLABSI risk but with significant statistical heterogeneity, and further analysis suggested that minocycline-rifampin coatings may offer stronger protection (Kramer et al., 2017; Wu et al., 2023). In contrast, large U.S. cohort studies and retrospective data have demonstrated more limited benefits of antimicrobial coatings. For example, a cohort of 42,562 patients

across 52 U.S. hospitals found no significant association between antimicrobial coatings and reduced CLABSI risk after adjustment for patient and procedural factors (Ullman et al., 2022) Similarly, the benefits of antimicrobial coatings on thrombosis and occlusion remain unclear, with some studies indicating no significant difference compared to standard devices (Ullman et al., 2022). These mixed findings likely reflect differences in study design, patient populations, catheter dwell times, and concurrent infection prevention practices. The current U.S. infection prevention framework, which emphasizes aseptic insertion practices, hand hygiene, and the use of chlorhexidine-alcohol skin antisepsis, may overshadow the marginal benefits of antimicrobial coatings (Centers for Disease Control and Prevention [CDC], 2024a; Pronovost et al., 2006). As a result, antimicrobial coatings should be viewed as an adjunct to a comprehensive infection prevention strategy rather than a standalone solution. In conclusion, the group of studies suggests that while antimicrobial and antithrombogenic coatings are supported by strong mechanistic and in vitro evidence, their clinical benefit, particularly for PICCs, remains uncertain. Their role in infection prevention is likely complementary, contributing to a broader multifactorial infection control strategy that includes proper insertion techniques, maintenance, and timely line removal (Centers for Disease Control and Prevention [CDC], 2024b; Donlan & Costerton, 2002). The lack of large randomized trials specific to PICCs and the residual confounding in observational studies further complicate the interpretation of their efficacy.

Mechanical Performance and Durability

Mechanical properties such as catheter tensile strength, kink resistance, and resistance to flexural fatigue and internal pressures are essential engineering specifications for intravascular catheters. These characteristics, which are subject to formal design verification under FDA and ISO 13485 guidelines (U.S. Food and Drug Administration, 2018b, 2024e), directly impact device longevity and procedural safety. For example, insufficient tensile strength, particularly at body-to-hub attachments, can lead to fractures or separations during use, with potential for intravascular embolization of catheter fragments (Kossoff & Poirier, 1998). Similarly, poor kink resistance can restrict blood flow and lead to device failure in tight anatomical regions (U.S. Food and Drug Administration, 2024b). Regulatory guidance emphasizes mechanical testing under simulated use conditions as a critical component of device validation. These tests, including those for tensile strength, burst pressure, and flexural fatigue tolerance, are intended to ensure that devices perform safely under expected clinical conditions (U.S. Food and Drug Administration, 2023c). Catheter developers typically employ recognized consensus test methods to meet these regulatory requirements and provide objective evidence of device safety (U.S. Food and Drug Administration, 2018a). In the U.S., these tests complement biocompatibility assessments and are considered essential for compliance under both 21 CFR 820 and ISO 13485 (U.S. Food and Drug Administration, 2026). However, while the mechanical performance requirements are necessary for regulatory compliance, their direct correlation with patient-level outcomes such as thrombosis or occlusion remains poorly defined in clinical literature. A large multicentre study of PICC use across Michigan hospitals found complications such as catheter occlusion and deep vein thrombosis, but did not link these outcomes directly to specific bench-measured mechanical properties like catheter stiffness or fatigue endurance (Chopra et al., 2014). Additionally, studies examining catheter design variables, such as larger gauge or multi-lumen devices, indicate that design choices are more often implicated in clinical complications than specific mechanical attributes (Chopra et al., 2014; Itkin et al., 2014). Ultimately, mechanical performance properties should be regarded as necessary safety controls to mitigate predictable failure modes such as kinking, leakage, and fracture. However, they should not be viewed as direct predictors of long-term thrombosis or occlusion risk. Clinical outcomes are influenced by multiple factors, including material design, surface-blood interactions, and patient-specific conditions. Therefore, while robust bench verification is essential for safety assurance, further U.S.-based comparative effectiveness research is needed to better understand how specific mechanical performance characteristics impact clinical outcomes, especially in diverse, real-world settings (Bunch et al., 2023)

Human Factors and Connector Design

Needleless connectors (NCs) and catheter hubs are among the most frequently accessed components of the vascular access system and are correspondingly among the most infection-vulnerable. A systematic review of NC disinfection practices estimated that connector colonization contributes to approximately 50% of post-insertion catheter-related infections, with compliance rates for recommended disinfection protocols reported as low as 10% in observational settings (Moureau & Flynn, 2015). Design characteristics of connectors, including internal fluid pathway geometry, septum configuration, and displacement mechanism, influence both reflux dynamics and susceptibility to intraluminal contamination. A prospective quality improvement study conducted across multiple U.S. hospitals found that connector type influenced occlusion outcomes, with positive displacement devices associated with higher occlusion rates despite concurrent reductions in CLABSI across study groups (Patel et al., 2017). Human factors research further underscores the importance of design-user interaction. A 2024 analysis conducted in U.S. intensive care settings identified physical design features, including packaging complexity, manipulation difficulty, and limited accessibility in high-acuity environments, as barriers to effective disinfection, independent of clinician training or protocol awareness (Drews et al., 2024). These findings highlight that the safety implications of connector design are mediated not only through device performance but also through usability and workflow integration. Within the FDA's human factors guidance and the QMSR framework, such considerations are formally incorporated into design control requirements through usability engineering and use-error risk analysis. For VADs, this represents a critical interface between engineering design and real-world clinical practice, reinforcing the principle that both technical performance and human interaction shape device safety.

5.0 OPPORTUNITIES FOR SCALABLE SAFETY-DRIVEN DESIGN ADVANCEMENT

The preceding sections have established a critical paradox within the U.S. medical device regulatory landscape: while vascular access devices (VADs) are developed within a sophisticated framework encompassing design controls (21 CFR Part 820), quality management systems (ISO 13485), and structured risk management (ISO 14971), the translation of these rigorous processes into measurable improvements in patient outcomes remains inconsistent (Donabedian, 1988; Kramer et al., 2012). This disconnect suggests that current paradigms, though necessary, are insufficient to ensure safety in the complex environments where VADs are utilized. Addressing this gap requires a fundamental reorientation: shifting from a compliance-focused mindset to a safety-driven design culture that systematically integrates real-world evidence, human factors

engineering, and outcome-based accountability throughout the device lifecycle. This is particularly relevant as the FDA transitions to the Quality Management System Regulation (QMSR), which formally incorporates ISO 13485:2016 and emphasizes risk management across the total product lifecycle (U.S. Food and Drug Administration, 2023b). This section identifies five interconnected opportunities for advancing scalable, safety-driven design for VADs in the United States.

Strengthening Post-Market Surveillance Through Mandatory Registry Integration

The Total Product Lifecycle (TPLC) framework remains limited by the fragmented and often delayed nature of post-market data. These limitations are not incidental: they reflect deep structural, economic, and institutional barriers to effective post-market oversight. The GAO has documented that the FDA's nascent active post-market surveillance system, planned since 2021, was still in early stages as of 2024, constrained by limited use of unique device identifiers in electronic health records, funding shortfalls, and the technical complexity of linking device use to patient outcomes at scale (U. S. Government Accountability Office, 2024). A cross-sectional study of the MAUDE database found that nearly one-third of manufacturer adverse event reports were not submitted to the FDA within the required 30-day window, with just three manufacturers and 13 devices accounting for more than half of all late reports, suggesting that delayed reporting is concentrated among a small number of high-volume actors rather than representing a systemic compliance failure (Everhart et al., 2025). The economic disincentive to robust post-market reporting is also well documented: manufacturers face competitive and litigation risks from voluntary disclosure of adverse signals, while the passive reporting architecture of MAUDE places the evidentiary burden on manufacturers who have little structural incentive to accelerate reporting. Furthermore, qualitative analysis reveals that reporting is hindered by the complexity of causality, where responsibility is often shifted between manufacturer design and user technique, and a lack of systemic feedback (Mishali et al., 2025). These barriers explain why the opportunity for registry-integrated surveillance, despite being technically feasible, as demonstrated by the Ellipsys Vascular Access System post-market study and the Society for Vascular Surgery's Vascular Quality Initiative, has not yet been realized for VADs as a device class (Resnic & Normand, 2012; U.S. Food and Drug Administration, 2026). Realising this opportunity will require not only regulatory authority but also alignment of incentives, investment in interoperable health data infrastructure, and the political will to mandate participation.

Elevating Human Factors Engineering and Addressing Reasonably Foreseeable Misuse

Designing devices for safe, intuitive use is critical for VADs, yet often neglected. VADs are used in busy, high-stress settings by clinicians of varying experience; mismatches between device design and user expectations can cause serious errors. For instance, complex multi-lumen catheters and a variety of connector types (positive/negative/neutral displacement) demand a precise technique: a single mis-step in the clamping sequence can lead to air embolism (Swayze & James, 2006). In one reported case, a nurse unfamiliar with a new dialysis catheter failed to clamp it before syringe removal, causing a fatal air embolism (Swayze & James, 2006). Observational studies echo this risk: over 50% of nurses initially performed the wrong clamp-flush sequence on positive-pressure connectors until retrained. These examples show that even simple lapses (air in line, port contamination) stem from a design not supporting consistent safe use.

To mitigate use-errors, (Human Factors) HF engineering offers tools: ergonomic handles, clear visual cues, standardized connectors, and thorough usability testing. Regulatory guidance (FDA's HF/usability guidance, IEC 62366) requires manufacturers to demonstrate that design minimizes use-related hazards, but in practice, these have not always been fully applied to VADs. For example, mislabeled or look-alike connectors (flush ports) have led to line misconnection or misconstrued medication administration. Implementation of ISO 80369-7 small-bore connectors for IV/Luer applications is one HF-driven advance: these unique connectors are designed to prevent misconnections, and the FDA notes that adopting ISO 80369 can reduce fatal misconnections (U.S. Food and Drug Administration, 2024f). Yet many VAD systems still employ legacy Luer fittings or mixed connector types, exposing patients to avoidable risk.

Training and procedure design also intersect with HF. AHRQ (The Agency for Healthcare Research and Quality) emphasizes that competency testing for device use is essential, and HF studies show that simulations and checklists dramatically improve outcomes. However, HF has not been systematically leveraged to redesign workflows around VAD use. A full outcome-oriented approach would incorporate HF early: for example, user studies could identify confusing steps in catheter maintenance (e.g., sealing the line) and lead to design fixes (such as auto-closing valves). In practice, FDA premarket reviewers should scrutinize HF validation data for VADs and require corrective design changes if necessary. Hospitals and procurement can demand HF-optimized products. Given that VAD complications often arise at the point of use, investing in HF is an underutilized but powerful lever to improve safety

Reorienting Design Validation Toward Outcome-Based Metrics

Current design control frameworks ensure process compliance, but do not guarantee optimal clinical performance (Donabedian, 1988; Kramer et al., 2012). For VADs, where outcomes are heavily influenced by insertion technique and adherence to care bundles, the link between regulatory compliance and patient safety is attenuated (Balsorano et al., 2020). The Vessel Health and Preservation (VHP) model offers an evidence-based clinical pathway that emphasizes selecting the smallest catheter possible and the healthiest vessel to minimize complications, an approach whose clinical rationale is grounded in evidence linking catheter-to-vein ratio and device size to thrombotic risk (Balsorano et al., 2020; Sharp et al., 2015). A more outcome-oriented regulatory approach would require explicit outcome targets in design inputs and post-market performance confirmation studies that validate pre-market assumptions (Resnic & Normand, 2012). However, achieving these goals is currently challenged by institutional capacity; the U.S. Government Accountability Office has identified significant staffing shortages and high vacancy rates among FDA drug and device inspectors, which may limit the agency's ability to oversee these complex outcome-based transitions effectively (U. S. Government Accountability Office, 2024).

Advancing Next-Generation Materials and Surface Technologies

Surfaces and coatings on vascular catheters have well-defined antimicrobial and antithrombogenic mechanisms, but translating these benefits to patients has been inconsistent. In vitro and animal models show that impregnated coatings (e.g., chlorhexidine-silver, antibiotic, or heparin coatings) can inhibit microbial adhesion and clotting on catheter surfaces (Yoon et al., 2022). Indeed, clinical guidelines cite evidence that chlorhexidine-silver or antibiotic-impregnated catheters reduce bloodstream infections under optimal conditions (Lorente, 2016). However, these

coatings may wear off over time: a recent lab study found that silver/chlorhexidine catheters lost nearly all antibacterial activity after ~48 hours of simulated blood flow (Choi et al., 2017). In short, mechanistic studies suggest these materials work in principle, but durability and context matter. In practice, large studies have shown variable or no benefit from coated catheters. For example, a 2022 cohort of 42,562 hospitalized adults found that neither antimicrobial nor antithrombogenic PICCs significantly reduced infection or thrombosis rates compared to standard lines (Ullman et al., 2022). Likewise, a 2025 randomized trial found no lower incidence of "device failure" (infection, thrombosis, occlusion) with hydrophobic or chlorhexidine-coated PICCs versus standard polyurethane catheters (Ullman et al., 2025). Notably, chlorhexidine-coated PICCs had a higher complication rate (38.6% vs. 21.7% in standard PICCs). These outcomes suggest that real-world factors (patient risk, catheter dwell time, insertion practice) may overwhelm modest surface effects. By contrast, some older meta-analyses of central line trials (not specific to PICCs) did find reductions in infection rates with impregnated catheters (Lorente, 2016). Taken together, evidence supports that advanced surfaces can work, but only when paired with careful implementation; consistent aseptic technique, limited dwell time, and other bundle elements. In line with this, bundles of proven practices remain critical. A key example is a quality-improvement project at a 582-bed hospital, where switching to an antimicrobial/antithrombogenic PICC and enforcing strict insertion checklists and single-lumen criteria cut PICC CLABSI from 1.83 to 0.162 per 1,000 catheter days (a 91.2% reduction) (DeVries & Sleweon, 2021). Importantly, this dramatic drop occurred as part of an integrated bundle - basic measures like full-barrier precautions, chlorhexidine skin prep, and prompt catheter removal were rigorously applied alongside the new catheter (DeVries & Sleweon, 2021). In other words, no catheter technology can replace the fundamentals of catheter care. Landmark ICU trials (e.g., Pronovost's Keystone study) have shown that hand hygiene, barrier precautions, site selection, and removal of unneeded lines can eliminate CLABSIs (Lorente, 2016). Thus, new materials should be viewed as one component within a multifactorial infection-prevention strategy.

Simultaneously, novel vascular-access technologies are emerging. For instance, the AI-GUIDE robotic ultrasound system (FDA Breakthrough Device, April 2025) uses artificial intelligence to guide clinicians in gaining rapid vascular access under austere, high-stress conditions (Air Force Medical Service, 2026). Similarly, PatenSee's AI-driven optical scanner (FDA Breakthrough, Sept 2025) provides non-contact monitoring of hemodialysis fistulae, aiming to detect stenosis before clinical failure (PatenSee, 2025). These innovations show how sensing and decision-support can be integrated with device design, but they still require rigorous clinical testing to prove real-world benefit.

Given the complex, multifactorial nature of catheter complications, future trials must be carefully designed. Studies should be large and pragmatic, ideally multi-center or cluster-randomized, to balance out local practice variations. They should measure composite endpoints (infection, thrombosis, occlusion, device failure) rather than a single outcome, and stratify or adjust for known confounders (patient comorbidities, insertion site, operator expertise). Crucially, trial protocols must standardize co-interventions (e.g., the use of insertion bundles) so that any device effect is not masked by inconsistent care. Finally, implementation science frameworks (e.g., COM-B model) remind us that device performance depends on user behavior, system factors, and patient context (Fernández-Fernández et al., 2025). In practice, this means embedding new devices in the workflow and possibly pairing them with training or decision-support interventions. By accounting for all these factors, trialists can better isolate the value of a new catheter material or technology and generate evidence that translates into safer vascular care.

Integrating Implementation Science and Behavioral Frameworks

The gap between device design and practice is further addressed by examining provider-level barriers. NIH-funded research has shown that patient concerns, such as fear and worries about cannulation pain, may limit the effectiveness of process-based interventions for vascular access creation (Coventry et al., 2019). If implementation failures, such as inappropriate device selection or patient hesitancy, prevent safety benefits from reaching patients, the return on design investment is diminished regardless of device quality. Understanding why these failures persist requires engagement with implementation science, which identifies multiple interacting levels of barriers: individual clinician knowledge and skill deficits; team-level coordination failures; institutional-level absence of vascular access specialist infrastructure; and system-level misalignment between evidence and reimbursement incentives (Xu et al., 2023). A scoping review by (Takashima et al., 2017) on RCT evidence for central vascular access devices found that only 8% of included trials addressed infection prevention in the post-insertion phase, and fewer than 7% addressed dressing and securement, precisely the maintenance activities where implementation failures are most consequential for patient outcomes. This evidentiary gap means that the behaviours most likely to drive complication rates are also the least well studied, limiting the ability to translate evidence into practice guidelines or device design requirements. Clinical evidence supports structured decision frameworks that contraindicate certain devices based on patient-specific factors, such as avoiding PICCs in dialysis patients to preserve long-term vasculature integrity (Chopra et al., 2014; O'Grady et al., 2011). Addressing the implementation gap requires engaging clinicians and patients in co-design processes, investing in hospital-based vascular access teams as a structural implementation mechanism, and developing decision-support tools as integral components of device development rather than as afterthoughts.

6.0 DISCUSSION

Vascular access devices (VADs) are vital to U.S. healthcare but remain a major source of preventable harm. For example, thousands of U.S. deaths and billions in costs are attributable to central line-associated bloodstream infections (CLABSIs) each year (Haddadin et al., 2026). Findings from this review confirm that existing U.S. regulatory and design frameworks provide rigorous procedural controls (e.g., FDA's 21 CFR 820 quality system rules and upcoming QMSR requirements) (U.S. Food and Drug Administration, 2026), yet translating these into better patient outcomes has been inconsistent. Some studies have shown that variations in catheter materials or geometry alone have not produced a clear clinical benefit (Slaughter et al., 2020). Similarly, antimicrobial catheters confer only modest or context-dependent gains in infection prevention (Wang et al., 2018; Wu et al., 2023). By contrast, strict implementation of evidence-based insertion and maintenance bundles demonstrably cuts infection rates (Fauver et al., 2025). This means that device-specific design changes, without parallel emphasis on human factors and care processes, may offer limited additional value. One can also infer that U.S. agencies and device manufacturers must leverage new regulatory provisions (e.g., the 2024 QMSR aligning with ISO 13485) and advanced surveillance to ensure that design control efforts genuinely improve VAD safety. Where evidence is mixed or incomplete, such as in the case of the uncertain impact of polymer choice on outcomes (Seckold et al., 2015; Slaughter et al., 2020),

clinical decisions should favor safer care through multifaceted strategies. In summary, a more integrated approach combining robust post-market data collection, human-factors-driven design, and proven infection-control practices is needed to link design standards to measurable safety gains.

The table below compares key studies on catheter material and coating differences:

Study (Year)	Device/Setting	Findings
(Seckold et al., 2015)	PICCs (polyurethane vs. silicone)	Polyurethane PICCs had lower rates of infection, thrombus, dislodgement, and catheter rupture than silicone, although overall complication rates were similar.
(Wildgruber et al., 2016)	Implanted CVC ports (PU vs. Si)	Polyurethane catheters were more prone to infections and thrombosis than silicone, whereas silicone had more mechanical failure.
(Slaughter et al., 2020)	CVC materials/designs (various)	No significant effect of material or lumen design on thrombosis or infection risk (RR≈0.98). No difference in occlusion or CRBSI by design.
(Wang et al., 2018)	Central VADs (antimicrobial vs. standard)	Antimicrobial (chlorhexidine/silver or antibiotic-impregnated) CVCs significantly reduced CRBSI rates under bundle conditions (aggregate RR≈0.70).
(Wu et al., 2023)	PICCs (antimicrobial vs. standard)	No statistically significant CLABSI reduction overall with antimicrobial PICCs (RR≈0.67; CI crosses 1). Subgroup analyses suggested benefit with minocycline–rifampin or chlorhexidine coatings.

These data illustrate that while certain catheter modifications can influence infection rates, the overall evidence is mixed: improvements are seen in some trials and subpopulations, but not universally (Slaughter et al., 2020; Wang et al., 2018). Importantly, no large U.S. study has confirmed that mere compliance with design controls or use of a specific material alone translates into better patient outcomes (Slaughter et al., 2020; U.S. Food and Drug Administration, 2026). Instead, the strongest evidence for safety comes from workflow and human factors interventions. For example, comprehensive infection-prevention bundles (ultrasound guidance, maximal barrier precautions, chlorhexidine skin prep, minimal lumens, and rigorous daily review) consistently reduce CLABSI risk (Fauver et al., 2025). A recent implementation at an academic center showed a 37% CLABSI reduction when bundles and accountability tools were applied (Fauver et al., 2025). By contrast, studies adjusting only device characteristics without such system changes have failed to show clear benefits (Slaughter et al., 2020; Wu et al., 2023).

Regulatory authorities recognize this gap. The FDA's Quality System Regulation (soon to be QMSR) mandates formal design controls and risk management (U.S. Food and Drug Administration, 2026), but these require rigorous application. The current QMSR aligns FDA CGMP with ISO 13485, explicitly requiring risk management throughout the product lifecycle (U.S. Food and Drug Administration, 2026). This harmonization should incentivize manufacturers to better link design efforts to risk outcomes. However, the FDA acknowledges that existing regulations focus on process rather than outcomes: a GAO report recently noted that premarket approval rarely demands evidence of improved clinical results. Thus, further alignment (for example, requiring post-market evidence of performance) may be needed. Current post-market surveillance for medical devices in the United States is fragmented, relying heavily on voluntary reporting and siloed registries that limit early signal detection; experts have therefore advocated for mandatory, linked registries and expanded real-world-data collection using NIH- and CMS-supported infrastructures (Manimuthukumar et al., 2025; U.S. Food and Drug Administration, 2021).

From a design standpoint, several insights emerge. Materials and coating evidence: Polyurethane and PTFE catheters have historically shown fewer infections than older materials like PVC (Centers for Disease Control and Prevention [CDC], 2024a), aligning with findings in the table above by Seckold and colleagues. However, as (Slaughter et al., 2020) demonstrate that no single polymer design is definitively safer once modern insertion practices are in place. Antibiotic- or antiseptic-impregnated devices do reduce colonization and CRBSI rates in controlled studies (Wang et al., 2018), but their benefit can be nullified if basic aseptic technique is not optimal (Wu et al., 2023). These results probably suggest that coatings should complement, not replace, fundamental prevention measures. Where the evidence is weak or indirect, such as when the 95% confidence interval for CLABSI reduction with coated PICCs includes no effect, caution is warranted when generalizing efficacy beyond the settings in which the studies were conducted. In cases of mixed findings, stakeholder guidance (e.g., CDC recommending chlorhexidine dressings only when CLABSI rates remain high (Centers for Disease Control and Prevention [CDC], 2024b) is prudent.

Conceptually, catheter size and lumen number affect hemodynamics and complication risk. Smaller-diameter lines may cause more occlusions, and multi-lumen catheters offer convenience but more surface for biofilm. Yet again, no high-level trial has isolated these variables to show

outcome differences independent of use context (Slaughter et al., 2020). This suggests that institutional practices (such as strict line maintenance and flush protocols) likely overwhelm modest design effects. Given this, we infer that changes like universal single-lumen devices or specialized tip designs should be introduced only alongside studies that measure clinical endpoints.

Vascular access device (VAD) systems involve complex user interactions during insertion, access, and maintenance. The FDA's 2016 human factors guidance recommends applying usability engineering principles to minimize use-errors and improve patient safety (U.S. Food and Drug Administration, 2019). Real-world cases demonstrate how device design flaws can lead to serious patient harm. For example, misconnections involving needleless connectors have caused fatal air emboli when clinicians applied familiar techniques to unfamiliar or incompatible devices. Although formal comparative studies of connector designs in the context of infection prevention remain limited, evidence from incident reports and human-factors analyses indicates that misconnections and user error in vascular access device (VAD) use contribute substantially to patient harm. These observations suggest that VAD design should explicitly anticipate how clinicians will use the devices in practice. Standardizing connectors, such as through the ISO 80369 series for small-bore connectors, and improving visual and ergonomic cues may help reduce line-access errors. Training and competency testing, aligned with established accreditation standards for staff education, are also critical. Embedding human factors engineering (HFE) processes into VAD development provides a structured approach to identifying latent hazards before devices enter clinical use (U.S. Food and Drug Administration, 2019). This also suggests that U.S. regulatory bodies treat human factors data as an essential part of VAD submissions, not an afterthought.

Beyond premarket design, real-world data on VAD performance are needed. Currently, U.S. hospitals report CLABSIs to the CDC's NHSN, but linking infections to device models or design features is not routine. We suggest establishing device-specific registries (akin to what CMS does for cardiac implants) to track long-term outcomes. Early identification of design-related problems would allow corrective actions (e.g., design modifications or targeted recalls) before widespread harm occurs. Regulatory agencies could incentivize this by giving feedback to manufacturers based on registry analyses. Until such systems mature, we recommend using existing quality frameworks (e.g., NIH-funded cooperative studies) to measure whether new devices actually lower adverse event rates compared to standard VADs.

7.0 CONCLUSION

In conclusion, our review indicates that while U.S. VAD design standards and evolving regulations (notably the FDA's QMSR and ISO 13485 alignment) establish robust quality controls, there is mixed evidence that these measures alone improve patient outcomes. Rigorous meta-analyses show that differences in catheter material or design do not by themselves reduce infection or thrombosis, whereas strict adherence to insertion and maintenance bundles does dramatically lower CLABSIs. We therefore recommend that regulators and manufacturers shift toward outcome-driven validation: requiring human-factors testing, post-market surveillance of complications by device model, and formal demonstration of clinical benefit. This might include mandated registries or performance data to verify safety improvements. Additionally, device innovation should complement, not replace, proven prevention measures. Research priorities include randomized trials or registries comparing new VAD technologies under U.S. care standards, studies on usability enhancements (connectors, signage, training), and cost-effectiveness analyses of advanced materials. By focusing on practical outcomes and system-level safety, future VAD design can better translate standards into safer care.

AUTHOR'S NOTE

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