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OPTIMIZING BLOOD COLLECTION SYSTEMS: ISSUES AND SOLUTIONS FOR LABORATORIES AND MANUFACTURERS

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Abstract

Background: The pre-analytical phase is the most vulnerable to errors in laboratory testing, with blood collection tube (BCT) components—including tube materials, additives, separators, and closures—serving as a significant source of interference that can compromise test accuracy. This review examines the impact of these components on clinical assays and proposes collaborative solutions for laboratories and manufacturers.

Methods: A comprehensive analysis of current literature was conducted to identify documented interferences caused by BCT components across various clinical applications, including therapeutic drug monitoring (TDM), coagulation testing, hormone immunoassays, and specialized testing for biomarkers and trace elements.

Results: Key issues identified include the adsorption of lipophilic analytes onto plastic surfaces and gel separators, leading to falsely decreased concentrations in TDM; leaching of stopper components (e.g., plasticizers, magnesium) causing interference in immunoassays and coagulation tests; and variable performance of clot activators affecting electrolyte and hormone measurements. Innovations such as chemically modified plastics, mechanical separators, and hybrid tubes offer promising solutions by reducing analyte adsorption and improving sample integrity. The lack of global standardization and the commodity-driven market pose significant challenges to the adoption of improved technologies.

Conclusions: Optimizing blood collection systems is critical for diagnostic accuracy. Clinical laboratories must implement rigorous tube validation and standardized procedures, while manufacturers should enhance material disclosure and pursue collaborative innovation. A concerted effort from all stakeholders is essential to mitigate pre-analytical errors, improve the reliability of laboratory results, and enhance patient

INTRODUCTION

The integrity of clinical laboratory testing results depends significantly on the quality of blood specimens and the collection devices used to obtain them. Despite technological advancements in analytical methodologies, the pre-analytical phase—which includes patient preparation, specimen collection, handling, and processing—remains the most vulnerable to errors, accounting for up to 70% of laboratory errors (John et al., 2025). Blood collection tubes (BCTs) serve as the critical interface between patients and laboratory testing systems, making their design, materials, and components essential for ensuring accurate and reliable test results.

The financial impact of poor specimen quality and pre-analytical errors is substantial, with an estimated cost of $1,200 per bed annually in acute care settings (Green, 2013). These costs arise from the need for recollection, retesting, delayed diagnoses, and potential patient harm from incorrect clinical decisions based on erroneous results. As healthcare systems worldwide face increasing pressure to improve efficiency while maintaining quality, optimizing blood collection systems represents a significant opportunity to enhance diagnostic accuracy and patient care.

This article examines the complex interactions between blood collection devices and laboratory testing, identifying key issues affecting test accuracy and proposing solutions for both clinical laboratories and manufacturers. By understanding the various components of blood collection systems—from tube materials and additives to mechanical separators and stopper compositions—laboratories and manufacturers can collaborate to mitigate interferences and improve the reliability of clinical testing.

Blood Collection Tube Components and Their Impact on Testing

Tube Materials: From Glass to Plastic

Historically, glass was the preferred material for blood collection tubes due to its inert properties and excellent barrier characteristics against gas exchange. However, safety concerns related to breakage and handling led to a transition toward plastic materials, primarily polyethylene terephthalate (PET). This shift introduced new challenges, as plastic surfaces can interact with blood components and analytes in ways that glass does not (Bowen & Remaley, 2014).

Plastic tubes may release additives into blood specimens, including plasticizers, surfactants, and lubricants used in manufacturing. These substances can interfere with various assays, particularly those measuring lipophilic compounds or drugs. Additionally, the hydrophobic nature of plastic surfaces can promote protein adsorption, potentially altering the concentration of critical analytes in the sample (Kim et al., 2015).

Recent innovations have addressed some of these issues through the development of hybrid tubes that combine glass-like properties with plastic safety features. Weikart et al. (2020) described hybrid blood collection tubes that integrate the best attributes of both materials, providing enhanced safety with improved shelf life and reduced chemical interferences. Another approach involves chemical modification of plastic surfaces to transform them from hydrophobic to hydrophilic, reducing protein adsorption and improving compatibility with various assays (Bowen et al., 2016; Dil et al., 2018).

Additives: Anticoagulants and Clot Activators

Blood collection tubes contain various additives depending on the intended testing applications. These additives fall into two main categories: anticoagulants (used in plasma tubes) and clot activators (used in serum tubes).

Anticoagulants such as EDTA, heparin, and sodium citrate prevent blood clotting through different mechanisms. EDTA chelates calcium ions essential for coagulation, making it suitable for hematology testing. Heparin activates antithrombin III to inhibit thrombin formation and is preferred for many chemistry tests. Sodium citrate sequesters calcium ions and is used primarily for coagulation studies. Each anticoagulant can potentially interfere with specific assays, necessitating careful selection based on the intended testing (Lima-Oliveira et al., 2021).

The concentration and formulation of anticoagulants must be precisely controlled to prevent adverse effects on test results. For instance, excessive EDTA can cause erythrocyte shrinkage, affecting hematological parameters, while inadequate anticoagulation may lead to microclot formation. The blood-to-anticoagulant ratio must be maintained within specified ranges to ensure accurate results, particularly for coagulation testing where improper filling of sodium citrate tubes can significantly impact results (Winter et al., 2023).

Clot activators, typically silica particles or thrombin-based compounds, accelerate the coagulation process in serum tubes. While these additives expedite sample processing by reducing clotting time, they can potentially interfere with certain analytes. For example, silica-based clot activators have been shown to interfere with serum lithium measurements in some analytical platforms (Sahu et al., 2023; Naznin et al., 2015; Ikkurthi et al., 2018). Thrombin-based activators may cause degradation of certain peptide hormones, such as parathyroid hormone, potentially leading to falsely decreased results (La'ulu et al., 2014).

Separators: Gel vs. Mechanical Barriers

Separator components in blood collection tubes facilitate the physical separation of serum or plasma from cellular elements after centrifugation. Two primary types exist: gel separators and mechanical separators.

Gel separators, composed of thixotropic materials typically based on polyester or acrylic polymers, form a physical barrier between the cellular and liquid phases during centrifugation due to their intermediate density. While widely used, gel separators can absorb lipophilic drugs and analytes, potentially causing falsely decreased concentrations in stored samples (Wollmann et al., 2019; Garza et al., 2023). This absorption is particularly problematic for therapeutic drug monitoring, where accurate quantification is critical for patient management.

Studies have demonstrated significant differences in drug concentrations measured in gel separator tubes compared to standard tubes without gel, especially for highly lipophilic compounds like antipsychotics, antidepressants, and certain anticonvulsants (Peck Palmer & Dasgupta, 2021; Tokudome et al., 2023). Additionally, gel barriers may occasionally fail to form properly despite appropriate centrifugation, leading to continued contact between cells and serum/plasma and potential interference with test results (Allard & Bowen, 2021).

Mechanical separators, introduced more recently, utilize physical devices made of inert materials to separate plasma or serum from cellular components. The BD Barricor™ tube, which employs a mechanical separator instead of a gel barrier, has shown promising results for various applications, including therapeutic drug monitoring, clinical chemistry, and biobanking (Arslan et al., 2017; Morosyuk et al., 2020; Knutti et al., 2022).

Multiple studies have demonstrated that mechanical separator tubes reduce analyte adsorption compared to gel tubes, providing more stable drug and hormone concentrations during storage (Schrapp et al., 2019; Hegstad et al., 2020). Additionally, mechanical separators may provide more consistent barrier formation and cleaner samples with less cellular contamination, potentially improving test precision for critical analytes like cardiac troponin (Cembrowski et al., 2023).

Tube Closures: Stoppers and Their Components

Tube closures, typically rubber or elastomeric stoppers, present another potential source of interference in blood testing. Traditional stoppers contain various compounds, including plasticizers, lubricants, and release agents that can leach into specimens and interfere with assays.

Historically, significant interferences have been documented with stopper components. Tris(2-butoxyethyl) phosphate (TBEP), a plasticizer used in some stoppers, was shown to displace drugs from protein binding sites, altering free drug concentrations (Borgå et al., 1977; Pike et al., 1981; Shah et al., 1982; Devine, 1984). More recently, magnesium contamination from certain stoppers has been implicated in prothrombin time testing errors (van den Besselaar et al., 2001, 2005, 2014).

Other stopper-related contaminants include isobutylene, which can interfere with toxicology testing (Kosecki et al., 2021), and glycerol-based lubricants that may affect lipid measurements (Baum, 1968; Chowdhury et al., 1971). These examples highlight the importance of understanding stopper composition and potential interferences when interpreting test results.

Manufacturers have responded to these challenges by developing alternative stopper formulations with reduced leachables and improved compatibility with sensitive assays. However, the complex nature of elastomeric materials means that complete elimination of all potential interferences remains challenging, necessitating ongoing vigilance from both manufacturers and clinical laboratories.

Specific Issues in Clinical Applications

Immunoassays and Hormone Testing

Immunoassays are particularly vulnerable to interferences from blood collection tube components due to their reliance on antibody-antigen interactions that can be disrupted by surfactants, plasticizers, and other leachables (Dorokhin et al., 2015). Sex hormone assays, for example, may be affected by both gel separators and tube materials, with studies showing differential stability depending on the collection device used (Hepburn et al., 2016).

Vitamin D testing presents another area where blood collection tubes can significantly impact results. Studies have demonstrated that both tube type and storage temperature can affect 25-hydroxyvitamin D measurements, potentially leading to misclassification of vitamin D status (Yu et al., 2016; Chae et al., 2024). These effects appear to be method-dependent, highlighting the importance of validating specific combinations of collection devices and analytical platforms.

Thyroid hormone testing, particularly free T3 and T4 measurements, has also been shown to be influenced by tube components. Chemically modified tubes with altered surface properties demonstrated improved performance for thyroid hormone testing compared to standard plastic tubes, suggesting that surface interactions play a significant role in these assays (Dil et al., 2018).

Therapeutic Drug Monitoring Therapeutic drug monitoring (TDM) represents a critical area where blood collection tube selection can significantly impact patient care. Many drugs monitored for

therapeutic levels are lipophilic and prone to adsorption onto plastic surfaces or absorption into gel separators.

Multiple studies have documented substantial differences in measured drug concentrations between different tube types. Wollmann et al. (2019) demonstrated significant decreases in serum concentrations of psychoactive drugs stored in gel separator tubes compared to standard tubes. Similarly, Jordan et al. (2022) evaluated different tube types for 11 therapeutic drugs, finding variable effects depending on drug lipophilicity and tube composition.

Shepard and Bliumkin (2023) further highlighted the risk of drug adsorption during prolonged storage of plasma samples in gel separator tubes, with some drugs showing concentration decreases of more than 50%. These findings emphasize the importance of standardizing blood collection protocols for TDM and considering the potential impact of tube selection on result interpretation.

Mechanical separator tubes (e.g., BD Barricor™) have emerged as a potential solution for TDM applications, with studies showing improved recovery and stability for many drugs compared to gel separator tubes (Morosyuk et al., 2020). However, comprehensive validation is necessary for each drug-tube combination to ensure reliable results across different analytical platforms and clinical settings.

Coagulation Testing

Coagulation tests are highly sensitive to pre-analytical variables, including the type of blood collection tube used. Sodium citrate tubes are standard for coagulation testing, but variations in citrate concentration, tube fill volume, and tube components can significantly affect results.

The discovery of magnesium contamination in certain evacuated blood collection tubes and its impact on prothrombin time testing highlighted the subtle ways tube components can influence coagulation results (van den Besselaar et al., 2001, 2005). This contamination caused falsely shortened prothrombin times and reduced international normalized ratios (INRs), potentially leading to inappropriate anticoagulant dosing decisions.

The surface properties of collection tubes also affect coagulation testing through their influence on the activation of the intrinsic coagulation pathway. Blood contact with artificial surfaces triggers the contact activation system, initiating a cascade that can alter test results if not properly controlled (Kuchinka et al., 2021). Tube manufacturers have addressed this issue by optimizing surface treatments and additives to minimize unwanted activation while maintaining proper sample processing.

Specialized Testing: Alzheimer's Biomarkers and Trace Elements

Emerging diagnostic areas present unique challenges for blood collection systems. Alzheimer's disease biomarkers, particularly β-amyloid in cerebrospinal fluid, are highly prone to adsorption onto collection tube surfaces, potentially affecting diagnostic accuracy (Strand et al., 2021; Ladang et al., 2021). The development of specialized collection protocols and tube materials for these applications remains an active area of research.

Trace element analysis represents another specialized area where tube composition can significantly impact results. Yang et al. (2023) demonstrated that certain collection tubes could cause false elevations in antimony measurements, highlighting the importance of tube selection for occupational and environmental exposure assessments. Similarly, lead testing has been affected by collection device issues, as evidenced by recalls of point-of-care testing systems related to blood collection tube compatibility (Mason et al., 2019; Nakata et al., 2021).

Challenges for Clinical Laboratories and Manufacturers

Standardization and Harmonization

The lack of global standardization in blood collection tube components and color coding presents significant challenges for laboratories operating across different regions or using tubes from multiple manufacturers. Simundic et al. (2015) called for harmonization of color coding for blood collection tube closures to reduce the risk of pre-analytical errors related to tube selection.

Beyond color coding, the composition and properties of tubes marketed for the same applications can vary significantly between manufacturers and even between different production lots from the same manufacturer. This variability complicates the establishment of standardized pre-analytical protocols and may contribute to inter-laboratory differences in test results for certain analytes (Scheuer et al., 2023).

The International Organization for Standardization (ISO) has developed standards for blood collection tubes (ISO 6710), but these focus primarily on dimensions, additives, and labeling rather than comprehensive performance characteristics and interference testing. More detailed standards that address tube-analyte interactions would benefit both laboratories and manufacturers by providing clear performance expectations and validation requirements.

Regulatory Considerations

Blood collection tubes are classified as medical devices in most regulatory frameworks, requiring appropriate validation and verification before clinical use. However, the regulatory landscape for blood collection tubes has evolved significantly in recent years, with increasing recognition of their potential impact on test results.

Bowen and Adcock (2016) proposed verification and validation processes for clinical laboratories to assess the performance of blood collection tubes in their specific testing environments. These processes include evaluation of tube performance with the laboratory's specific analytical methods, patient populations, and handling procedures.

The regulatory classification of blood collection tubes varies internationally, affecting the level of scrutiny applied during pre-market evaluation. In some regions, tubes are considered lower-risk devices with limited pre-market testing requirements, while in others, they face more rigorous evaluation, particularly when containing novel additives or materials.

Recent regulatory developments related to laboratory-developed tests (LDTs) may also impact how tube-related interferences are addressed, as these tests are typically validated using specific collection systems that may not be generalizable across different tube types (Epstein Becker Green, 2025). Laboratories developing LDTs must carefully consider tube effects during their validation processes to ensure reliable performance in clinical practice.

Innovation Challenges

Developing improved blood collection systems requires balancing multiple, sometimes competing, objectives: chemical inertness, mechanical stability, safety features, ease of use, and compatibility with automated processing systems. Innovations in tube materials, additives, and separators must undergo extensive validation to ensure they do not introduce new interferences while addressing existing limitations.

The economic pressures facing healthcare systems worldwide also influence innovation in this space. Blood collection tubes are often viewed as commodity items, with purchasing decisions driven primarily by cost rather than performance characteristics. This perspective can limit investment in advanced materials and designs that might improve analytical performance but at a higher unit cost.

Moreover, the interconnected nature of pre-analytical systems means that changes to tube design must consider compatibility with existing equipment for specimen collection, transport, centrifugation, and automated processing. Innovations that disrupt these established workflows may face resistance despite potential analytical benefits.

Solutions and Best Practices

For Clinical Laboratories

Comprehensive Tube Validation

Clinical laboratories should implement comprehensive validation protocols for blood collection tubes, particularly when changing tube types or manufacturers. These validations should include:

1. Method comparison studies using patient samples collected in both current and proposed tube types
2. Evaluation of tube performance across the analytical measuring range, including medical decision points
3. Assessment of sample stability under the laboratory's specific storage conditions
4. Monitoring of quality indicators related to pre-analytical factors during implementation

For specialized testing areas like therapeutic drug monitoring, additional validation steps may be necessary, including drug recovery studies and evaluation of potential interferences from tube components (Peck Palmer & Dasgupta, 2021).

Standardized Collection and Processing Procedures

Standardizing blood collection and processing procedures can mitigate some tube-related interferences. Key elements include:

1. Consistent tube fill volumes, particularly for anticoagulant tubes where the blood-to-additive ratio is critical
2. Standardized mixing procedures immediately after collection to ensure proper interaction with additives
3. Uniform centrifugation conditions optimized for the specific tube type and separator system
4. Consistent sample storage conditions and timeframes before analysis

Laboratories should develop detailed procedures that consider the specific requirements of different tube types and communicate these requirements effectively to phlebotomy staff and other healthcare providers involved in specimen collection.

Monitoring and Quality Assurance

Ongoing monitoring of pre-analytical quality indicators can help identify tube-related issues before they significantly impact patient care. Useful indicators include:

1. Hemolysis rates by tube type and collection location
2. Rates of specimen recollection due to inadequate volume or processing issues
3. Delta checks or trend analysis for analytes known to be sensitive to tube interferences
4. Regular verification of critical analytes using reference methods or alternative collection systems

Laboratories should also participate in external quality assessment programs that address pre-analytical variables, sharing information about tube-related issues with professional networks and regulatory authorities when significant problems are identified.

For Manufacturers

Improved Disclosure and Documentation

Manufacturers should provide comprehensive information about tube components, potential interferences, and validation data to help laboratories make informed decisions. This information should include:

1. Detailed composition of tube materials, additives, separators, and closures
2. Known interferences with specific analytes or analytical platforms
3. Recommended centrifugation and storage conditions
4. Lot-to-lot consistency data and quality control parameters

Additionally, manufacturers should promptly disclose formulation changes that might affect analytical performance, even when these changes are made to address other issues like improving mechanical properties or manufacturing efficiency.

Collaborative Research and Development

Manufacturers should collaborate with clinical laboratories, professional organizations, and regulatory bodies to develop improved blood collection systems that address current limitations. These collaborations could focus on:

1. Developing standardized protocols for evaluating tube performance across different analytical platforms
2. Creating innovative materials with reduced interference profiles for critical analytes
3. Designing specialized collection systems for emerging biomarkers and analytical technologies
4. Harmonizing tube specifications and performance characteristics across manufacturers

Such collaborations would benefit from structured data sharing and coordinated research efforts to identify priority areas for improvement based on clinical impact and frequency of issues.

Quality Systems and Post-Market Surveillance

Robust quality systems and post-market surveillance are essential for identifying and addressing tube-related issues promptly. Manufacturers should implement:

1. Comprehensive testing protocols that evaluate tube performance under various clinical scenarios
2. Lot release criteria that include interference testing for critical analytes
3. Systematic collection and analysis of user complaints and adverse event reports
4. Regular review of scientific literature for emerging issues related to tube components

Post-market surveillance should include active solicitation of feedback from clinical laboratories about tube performance in routine practice, with mechanisms for rapid investigation and response to reported issues.

Future Directions

Advanced Materials and Surface Technologies

The development of advanced materials and surface technologies offers promising avenues for improving blood collection tube performance. Potential approaches include:

1. Biomimetic surfaces that reduce protein adsorption and cellular activation
2. Self-healing materials that maintain barrier integrity during transport and processing
3. Intelligent polymers that respond to specific conditions to optimize sample preservation
4. Nanotechnology-based surface modifications that enhance compatibility with specific analytes

These technologies could address current limitations related to analyte adsorption, cellular contamination, and barrier integrity, potentially improving the accuracy and reproducibility of laboratory testing.

Integration with Digital Health Systems

The integration of blood collection systems with digital health infrastructure presents opportunities for improved pre-analytical quality and traceability. Future developments might include:

1. Smart tubes with embedded sensors to monitor temperature, time, and handling conditions
2. Automated documentation of collection parameters like fill volume and mixing compliance
3. Integration with electronic health records to link pre-analytical variables with test results
4. Machine learning algorithms to identify patterns in pre-analytical variables that affect specific tests

These digital integrations could enhance the detection of pre-analytical issues and enable more personalized interpretation of test results based on specific collection and handling conditions.

Specialized Systems for Emerging Biomarkers

As precision medicine advances, there is growing demand for specialized blood collection systems optimized for emerging biomarkers and analytical technologies. Future developments might include:

1. Collection systems specifically designed for circulating tumor cells or cell-free DNA
2. Tubes optimized for metabolomic and proteomic analyses with minimal background interference
3. Specialized additives that preserve labile biomarkers during transport and processing
4. Collection systems integrated with point-of-care testing platforms for immediate analysis

The development of these specialized systems will require close collaboration between clinical researchers, diagnostic companies, and tube manufacturers to ensure that collection devices support the specific requirements of emerging biomarkers.

CONCLUSION

Blood collection tubes serve as the critical interface between patients and laboratory testing systems, with significant potential to impact test accuracy and reliability. The complex interactions between tube components and blood constituents can introduce various interferences that affect analytical results, potentially influencing clinical decisions and patient outcomes.

Understanding these interactions requires consideration of multiple factors, including tube materials, additives, separators, and closures, as well as the specific analytical methods and clinical applications involved. Both clinical laboratories and manufacturers have important roles in addressing these challenges through comprehensive validation, standardized procedures, improved disclosure, and collaborative research and development.

As laboratory medicine continues to advance, with increasingly sensitive analytical methods and novel biomarkers, the demands on blood collection systems will grow more complex. Addressing these demands will require continued innovation in materials science, surface technology, and quality management systems, as well as closer integration between collection devices and the broader healthcare ecosystem.

By optimizing blood collection systems through collaborative efforts between laboratories, manufacturers, regulatory bodies, and professional organizations, the healthcare community can reduce pre-analytical variability, enhance analytical accuracy, and ultimately improve patient care through more reliable laboratory testing.

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