

## Assuring Accuracy, Preventing Fraud

The Critical Role of Validation in Bioanalytical Methods

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# Harmonizing Regulatory Guidelines for Assay Validation

## A Focus on Ligand-Based Assays Using Octet BLI Systems

In the constantly advancing fields of scientific research and pharmaceutical development, the precision and reliability of bioanalytical methods are critical. Kinetic-based assays, particularly those employing **Octet® BLI systems**, have become fundamental due to their ability to provide real-time, label-free analysis of biomolecular interactions. Thorough validation of these assays is crucial, as it ensures data generation that is both accurate and reliable. This level of data integrity is vital for informed decision-making in clinical diagnostics and drug development.

The **validation process for bioanalytical methods** begins with the determination of the standard deviation of the blank, a critical step that lays the foundation for establishing the Detection Limit (DL) and the Quantitation Limit (QL) of the assay. These parameters are vital for defining the sensitivity and precision of the assay, which in turn, influences the reliability of the data obtained.

Another key aspect of assay validation is defining the assay range, which is the span between the lower limit of quantitation (LLOQ) and the upper limit of quantitation (ULOQ). Range can also be established for ligand binding assays and spans the lowest and highest affinity constant (KD) values obtained during assay qualification studies.

The robustness and stability of the assay are equally critical factors. Robustness refers to the assay's resilience to minor, deliberate variations in the testing procedure, while stability indicates the assay's ability to produce consistent results over time and across various conditions. These characteristics are rigorously evaluated during **method development** to confirm that the assay is suitable for real-world application and that the data generated is consistently reliable.

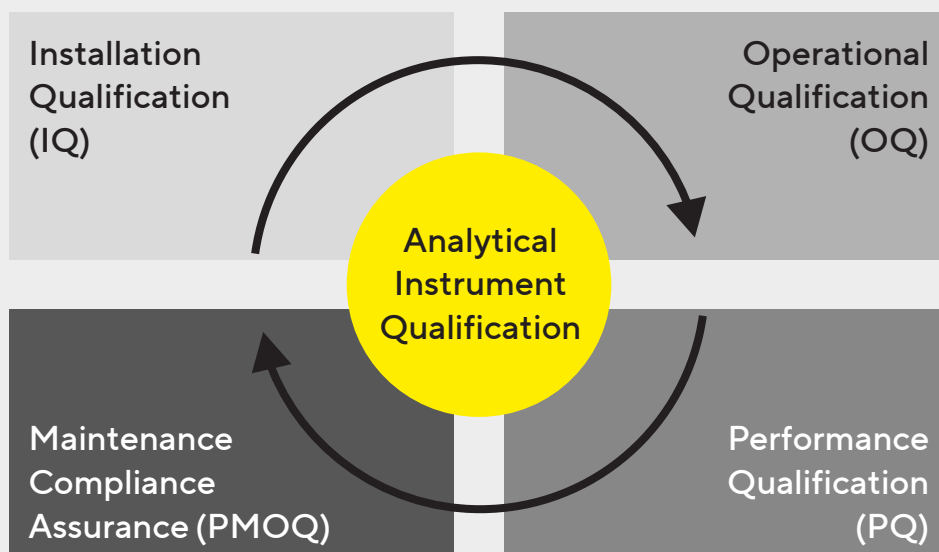
The assay validation process transcends the objective of adhering to regulatory standards; it is fundamentally about confirming that the assays are suitable for their designated purpose. This necessitates adapting the validation process to effectively address the specific requirements and challenges associated with kinetic-based assays.

Furthermore, the validation includes the assessment of the analyte's linear response. Linear regression analysis is performed to establish the correlation between analyte concentration and signal response. Acceptance criteria are set for signal-to-noise ratio, standard deviation of the linear response, and slope, all of which are critical to ensure the precision and accuracy of the assay.

Stability testing forms an integral part of the robustness evaluation, examining the assay's performance over time and under various storage and handling conditions. This testing serves as evidence of the assay's durability and the consistency of the data it produces.

### **Octet® BLI 21 CFR Part 11 Compliance**

Ensuring precision and safeguarding against data manipulation are essential aspects of drug development and quality assurance. The Octet® BLI system from Sartorius is engineered to meet these demands, providing a range of tools and services that support adherence to good practice (GxP) standards. The platform includes installation and operational qualification kits, performance qualification kits, software validation packages, and biosensor validation services, all of which contribute to the integrity and reliability of bioanalytical assays.



A critical component for maintaining data accuracy and security is the Octet® 21 CFR Part 11 Software package, which **aligns with the FDA's 21 CFR Part 11 regulations**. This software suite includes features such as an audit trail, electronic signatures, and robust electronic record-keeping, which are vital for deterring fraud and maintaining data integrity. Sartorius professionals handle the installation to ensure it is implemented correctly.

The Octet® GxP server is instrumental in record compliance, and access to the computer hosting this software is tightly controlled to prevent unauthorized use. The platform's reliability is evidenced by its use in critical quality control processes such as lot release and in-process testing assays, including quantitation, potency assays, impurities testing, and ligand binding assays. Regulatory bodies have acknowledged the precision of the Octet® BLI platform, as evidenced by the inclusion of Octet® BLI data in the approval submissions for several drugs.

#### **FDA Reminds Medical Device Manufacturers to Scrutinize Third-Party-Generated Data**

The validation of assays extends beyond the pursuit of scientific precision; it acts as a safeguard against the risk of fraudulent and unreliable data. In February 2024, the U.S. Food and Drug Administration (FDA) has underscored the importance of this issue, alerting the scientific community to the severe implications that can result from compromised data integrity.

The FDA's advisory serves as a potent reminder for laboratories to maintain the highest standards of integrity and accuracy in their testing procedures. It is a stark warning that the manipulation or falsification of data can lead to severe consequences, such as endangering patient safety, the invalidation of research, and the potential for legal and regulatory action.

To mitigate these risks, the validation process for kinetic-based assays is designed to be comprehensive and transparent. It incorporates stringent checks and balances, including the verification of raw data, the authentication of results, and the implementation of quality control measures throughout the entire lifecycle of the assay. These measures are critical in ensuring that the data generated is not only scientifically robust but also ethically obtained and reported.

The FDA's emphasis on data integrity reinforces the need for a culture of quality in laboratory environments. Such a culture is built upon the principles of good laboratory practices, diligent documentation, and the continuous training of personnel. It is a culture that prioritizes the reproducibility of results and the traceability of data, recognizing that the reliability of laboratory testing is fundamental to both scientific advancement and public trust.

### FDA's Final Rule on Laboratory-Developed Tests

The FDA has issued a final rule to regulate laboratory-developed tests (LDTs) as medical devices, aligning them with the oversight applied to other in vitro diagnostics under the Federal Food, Drug & Cosmetic Act. In the past, LDTs were exempt from FDA review due to their limited use and perceived lower risk. However, given the expanded use of LDTs and their associated higher risks, the FDA has introduced a comprehensive 528-page rule. This rule is intended to gradually eliminate this previous exemption over a period of four years, requiring all diagnostics, including LDTs, to meet the same regulatory standards.



## Conclusion

The harmonization of regulatory guidelines for assay validation, with a particular focus on kinetic-based assays using Octet® BLI systems, is a critical endeavor in the context of scientific research and pharmaceutical development. The comprehensive validation process, which includes establishing detection and quantitation limits, defining assay range, and ensuring robustness and stability, is not just a regulatory requirement but a commitment to scientific integrity and ethical standards. The FDA's recent actions, including the final rule on LDTs and the emphasis on data integrity, serve as evidence to the agency's dedication to patient safety and the reliability of medical devices. Laboratories are now called upon to foster a culture of quality, where good laboratory practices, accurate record-keeping, and continuous training are the norm. As the industry moves forward, the meticulous validation of assays is indispensable for the advancement of science, the protection of public health, and the preservation of trust in medical research and diagnostics.

## Publications and Sources

1. The Impact of IVD Regulations on Manufacturing - Publication | Sartorius
2. Octet® BLI 21 CFR Part 11 Compliance Checklist | Sartorius
3. Fraudulent and Unreliable Laboratory Testing Data in Premarket Submissions: FDA Reminds Medical Device Manufacturers to Scrutinize Third-Party-Generated Data | FDA
4. Federal Register: Medical Devices; Laboratory Developed Tests

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