MOLECULAR DEVICES

WHITE PAPER

GxP regulated industry assessments of microplate readers

This document outlines references to 21 CFR Parts 58, 211 and 820 and EudraLex Annex 15 to assess the implementation of Molecular Devices microplate readers in regulated environments.

21 CFR Part 58 Overview

Title 21 CFR Part 58 prescribes Good Laboratory Practice (GLP) guidance in the conduct of nonclinical laboratory studies that support applications for research permits for products regulated by the FDA that may include drugs, biologics, and medical devices for human use.

21 CFR Part 211 Overview

Title 21 CFR Part 211 prescribes Good Manufacturing Practice (GMP) guidance for finished pharmaceuticals.

21 CFR Part 820 Overview

Title 21 CFR Part 820 covers quality systems for medical devices by outlining Good Manufacturing Practices (GMP) regulations governing methods used in the design, manufacture, packaging, labeling, storage, installation and servicing of all finished devices intended for human use. These regulations are designed to ensure medical devices are safe, effective, and in compliance with the Federal Food, Drug, and Cosmetic Act.

Part 820 is applicable to manufacturers of medical devices sold in the United States, and foreign manufacturers who import their products for distribution in the United States.

Molecular Devices products maintain the label, “For Research Use Only”, as they are not medical devices intended to diagnose a disease or other condition.

EU GMP Annex 15 Overview

Annex 15 describes the principles of qualification and validation applicable to equipment, facilities, utilities, and processes used for the manufacture of medicinal products. It is a GMP requirement for manufacturers to control the critical aspects of their operations through qualification and validation throughout the lifecycle of their business processes and products.

Whose responsibility is it to validate the system?

A regulated customer, or those that manufacture food or drugs for human consumption are required to comply to regulations. Molecular Devices does not manufacture food or drugs, therefore is not subject to FDA regulatory requirements but can ensure their customers achieve their compliance to 21 CFR Parts 58, 211, and 820 and EudraLex Annex 15.

Annex 11 mentions a process owner, system owner, qualified person, and IT. On the customer side, it is the ‘system owner’ (usually IT management) or the ‘business process owner’ (usually lab managers) who interface with IT are ultimately responsible for validation. A validation team should be representative of multiple stakeholders.

- Quality Assurance (QA) ensures a thorough review to verify local corporate quality standards are met.
- Department heads are vital, as they provide the business case and resources for validation.

Impact of compliance vs. non-compliance

Costs to validate multiple computerized systems can be significant and efforts must be carefully planned to identify resources and procurement and project expenses. Some organizations may enlist third parties to design and execute computerized system validation, but the responsibility for the validation effort and maintaining a compliant validated system cannot be delegated and remains with the regulated customer per regulations in 21 CFR Parts 58.63 and 820.70 and Annex 15.

Public record of judgements against pharmaceutical or independent/contract labs show that the cost of non-compliance is significant (can be in the millions of dollars) for lost productivity and revenue, costs for rework, and reputation with investors and customers.

The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government.

It is divided into 50 titles that represent broad areas subject to Federal regulation.

Title 21 of the CFR is reserved for rules regulated by the Food and Drug Administration (Dept. of Health and Human Services), the Drug Enforcement Administration (Dept. of Justice) and the Office of National Drug Control Policy.

- **Part 58** – Good Laboratory Practices for Non-Clinical Laboratory Studies
- **Part 211** – Current Good Manufacturing Practice for Finished Pharmaceuticals
- **Part 820** – Quality System Regulation

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Medicinal Products – Quality, Safety and Efficacy

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use.

The GMP Guide is presented in three parts and supplemented with annexes that represent broad areas subject to Federal regulation.

- **Part 1** – Basic Requirements for Medicinal Products
  - **Chapter 3** – Premise and Equipment
  - **Chapter 4** – Documentation
- **Annex 15** – Qualification and validation

Table 1: Assessment of 21 CFR Part 58 Compliance for Plate Reader Validation & Maintenance.

Reference to 21 CFR Part 58 Subpart D – Equipment	Molecular Devices Products/Services	End User Operations
§58.61 – Equipment design Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.	IQ/OQ services ensure computerized systems (plate reader and software entity) are performing within specification. PM/OQ services performed at regular intervals promote ongoing reliability and confirm performance against specification.	It is the end user responsibility to validate and qualify computerized systems (plate reader and software entity) into their regulated environment.
§58.63 – Maintenance and calibration of equipment (a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.		It is the end user responsibility to develop business process and procedures to support computerized system applications in their regulated environment.
(b) The written standard operating procedures shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation.	IQ/OQ services ensure computerized systems (plate reader and software entity) are performing within specification. SOPs for plate reader maintenance and use of SpectraTest® Validation Plates are available.	It is the end user responsibility to govern these activities in an SOP for plate reader maintenance and calibration.
(a) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of nonroutine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.	PM/OQ services performed at regular intervals promote ongoing reliability and confirm performance against specification. A completed report is provided to the customer at the completion of the PM/OQ service.	It is the end user responsibility to maintain written records of maintenance, testing, and calibration activities.

Table 2: Assessment of 21 CFR Part 211 Compliance for Plate Reader Validation & Maintenance.

Reference to 21 CFR Part 211	Molecular Devices Products/Services	End User Operations
§211.160 – General requirements (b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include: (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.	Certified Field Service Engineers (FSEs) provide IQ/OQ or PM/OQ services for plate readers.	It is the end user responsibility to develop business process and procedures to support computerized system applications in their regulated environment.
§211.194 – Laboratory Records (d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by §211.160(b)(4).	Certified Field Service Engineers (FSEs) provide reports after IQ/OQ or PM/OQ services performed on plate readers.	It is the end user responsibility to develop business process and procedures to support maintenance records as required.

Table 3: Assessment of 21 CFR Part 820 Compliance for Plate Reader Validation & Maintenance.

Reference to 21 CFR Part 820 Subpart G – Production and Process Controls	Molecular Devices Products/Services	End User Operations
§820.70 – Production and Process Controls (g) Equipment. Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use.	PM/OQ services ensure instruments are performing within specification at regular intervals, at a minimum, once annually.	It is the end user responsibility to validate and qualify computerized systems (plate reader and software entity) into their regulated environment.
(1) Maintenance schedule. Each manufacturer shall establish and maintain schedules for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities, including the date and individual(s) performing the maintenance activities, shall be documented.		It is the end user responsibility to establish internal programs that manage instrument maintenance and instrument verification.
(2) Inspection. Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual(s) conducting the inspections, shall be documented.		It is the end user responsibility to inspect their internal equipment maintenance schedules.
(3) Adjustment. Each manufacturer shall ensure that any inherent limitations or allowable tolerances are visibly posted on or near equipment requiring periodic adjustments or are readily available to personnel performing these adjustments.	Software validation services are provided that could include automated processes.	It is the end user responsibility to validate and qualify automated processes in their regulated environment.
(i) Automated processes. When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.		

Reference to 21 CFR Part 820 Subpart G – Production and Process Controls	Molecular Devices Products/Services	End User Operations
§820.72 – Inspection, measuring, and test equipment (a) Control of inspection, measuring, and test equipment—Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained.	IQ/OQ and/or PM/OQ services and SpectraTest Validation Plates ensure instruments are performing within specification traceable to NIST and NMI standards. A completed report is provided to the customer at the completion of the IQ/OQ or PM/OQ service.	It is the end user responsibility to validate and qualify computerized systems (plate reader and software entity) into their regulated environment.
(b) Calibration—Calibration procedures shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented.		It is the end user responsibility to calibrate equipment and maintain records in their regulated environment.
(1) Calibration standards—Calibration standards used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.		
(2) Calibration records—The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date shall be documented. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.		

Table 4: Assessment of EudraLex Volume 4 (Part 1) Compliance for Plate Reader Validation & Maintenance.

Reference to EudraLex Volume 4 Part 1 – Basic Requirements for Medicinal Products	Molecular Devices Products/Services	End User Operations
Chapter 3 – Premises and Equipment 3.41 Measuring, weighing, recording, and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.	IQ/OQ and/or PM/OQ services and SpectraTest Validation Plates ensure instruments are performing within specification traceable to NIST and NMI standards. A completed report is provided to the customer at the completion of the IQ/OQ or PM/OQ service.	It is the end user responsibility to develop business process and procedures to support computerized system applications in their regulated environment.
3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.	Not applicable.	
Chapter 4 – Documentation 4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples: • Validation and qualification of processes, equipment and systems • Equipment assembly and calibration	IQ/OQ of SoftMax® Pro GxP Data Acquisition and Analysis Software. IQ/OQ and/or PM/OQ services ensure instruments are performing within specification traceable to NIST and NMI standards.	

Table 5: Assessment of EudraLex Volume 4 (Annex 15) Compliance for Plate Reader Validation & Maintenance.

Reference to EudraLex Volume 4 Annex 15: Qualification and Validation	Molecular Devices Products/Services	End User Operations
Section 2 – Documentation 2.5 Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).	IQ/OQ services ensure instruments are performing within specification onsite when requested.	It is the end user responsibility to develop business process and procedures to support computerized system applications in their regulated environment.
2.6 Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.	IQ/OQ and/or PM/OQ services and SpectraTest Validation Plates ensure instruments are performing within specification traceable to NIST and NMI standards.	
Section 3 – Qualification Stages for Equipment, Facilities, utilities and Systems 3.1 Qualification activities should consider all stages from initial development of the user requirements specification through to the end of use of the equipment, facility, utility or system. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:	Not applicable.	It is the end user responsibility to develop business process and procedures to support equipment and computerized system applications in their regulated environment.
Factory acceptance testing (FAT) /Site acceptance testing (SAT) 3.4. Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.	SpectraTest Validation Plates are in scope of accreditation to ISO/IEC 17025 and ISO 9001:2015.	
3.5 Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable.	IQ/OQ and/or PM/OQ services and SpectraTest Validation Plates ensure instruments are performing within specification traceable to NIST and NMI standards.	
3.6. Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation.	IQ/OQ services ensure instruments are performing within specification onsite when requested.	It is the end user option to request an IQ/OQ when the plate reader is set up in the lab for a baseline of tests prior to performing PQ.
3.7 FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.	Not applicable.	It is the end user option to use Factory Acceptance Test criteria based on their risk-based approach to validation.
Installation qualification (IQ) 3.8. IQ should be performed on equipment, facilities, utilities, or systems.		It is the end user option to perform IQ on equipment, facilities, utilities, or systems.
3.9. IQ should include, but is not limited to the following: i. Verification of the correct installation of components, instrumentation, equipment ii. Verification of the correct installation against pre-defined criteria iii. Collection and collation of supplier operating and working instructions and maintenance requirements iv. Calibration of instrumentation	IQ/OQ services for software validation and IQ/OQ and PM/OQ services ensure instruments are performing within specification.	It is the end user responsibility to request an IQ/OQ when the plate reader is set up in the lab for a baseline of tests prior to performing their own qualification tests prior to GMP/GLP use.
Operational qualification (OQ) 3.10. OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).		

Reference to EudraLex Volume 4 Annex 15: Qualification and Validation	Molecular Devices Products/Services	End User Operations
3.11. OQ should include but is not limited to the following: i. Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed ii. Tests to confirm upper and lower operating limits, and/or "worst case" conditions	IQ/OQ services for software validation and IQ/OQ and PM/OQ services ensure instruments are performing within specification.	It is the end user responsibility to request an IQ/OQ when the plate reader is set up in the lab for a baseline of tests prior to performing their own qualification tests prior to GMP/GLP use.
3.12. The completion of a successful OQ should allow the finalization of standard operating and cleaning procedures, operator training and preventative maintenance requirements.		
Performance qualification (PQ) 3.13. PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.	Not applicable.	It is the end user responsibility to demonstrate equipment is suitable for use.
3.14. PQ should include, but is not limited to the following: i. Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behavior under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified. ii. Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.		
Section 4 – Re-Qualification 4.1 Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.	IQ/OQ and/or PM/OQ services and SpectraTest Validation Plates ensure instruments are performing within specification traceable to NIST and NMI standards.	
4.2. Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.		

Disclaimer

This document serves as a reference for regulated customers to make independent decisions regarding the use of Molecular Devices microplate readers and Professional Services. This document does not constitute legal or professional advice. Each party should perform adequate diligence based on their internal processes to ensure the product(s) and service(s) align(s) with its intended use and regulatory compliance.

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