Millipore®
Preparation, Separation,
Filtration & Monitoring Products

Application Note

How to achieve full data integrity for the MAS-100 NT® air sampler

Introduction

The EDM 2020 draft of EU GMP Annex 1 has undergone significant changes to incorporate quality management through the introduction of the contamination control strategy (CCS) concept. Environmental monitoring (EM) is the key process measuring the efficiency of the sum of all measures implemented to minimize the contamination risk in the aseptic manufacturing environment. The draft guidance on data integrity and compliance with cGMP (draft guidance 2016) clarifies the role of data integrity in current good manufacturing practice (cGMP) for drugs, as required in 21 CFR parts 210, 211, and 212.

”For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).”

Requirements for achieving data integrity are listed below:

- § 211.68 (requiring that “backup data are exact and complete,” and “secure from alteration, inadvertent erasures, or loss”)
- § 212.110(b) (requiring that data be “stored to prevent deterioration or loss”)
- §§ 211.100 and 211.160 (requiring that certain activities be “documented at the time of performance” and that laboratory controls be “scientifically sound”)
- § 211.180 (requiring that records be retained as “original records,” “true copies,” or other “accurate reproductions of the original records”)
- §§ 211.188, 211.194, and 212.60(g) (requiring “complete information,” “complete data derived from all tests,” “complete record of all data,” and “complete records of all tests performed”)

Authorities, such as the FDA, expect data to be reliable and accurate. Companies or Pharmaceutical companies must implement meaningful and effective strategies to manage their data integrity risk based on their process understanding and knowledge management of technologies used.

For the microbiological path in environmental monitoring, a rough overview of the required steps is indicated in **figure 1**. Depending on the available IT infrastructure, these steps can be performed manually using paper-based documentation, using digital tools or a hybrid.

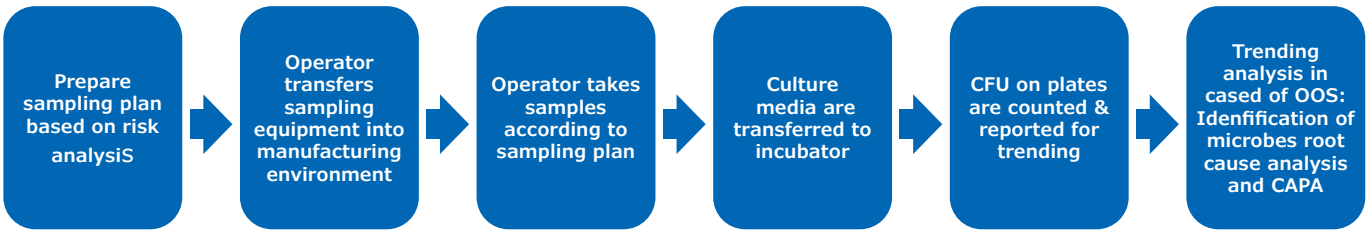


Figure 1: Process steps for Environmental Monitoring (classical microbiological part)

When using air samplers and culture media, it is important to fulfil the requirements for completeness, consistency, and accuracy of data.

The air samplers must be qualified in order to deliver reliable and efficient sampling results. The MAS-100 NT® air sampler provides an accurate flow rate of 100 SLPM ± 2.5%. This is verified on a regular basis by a calibration process. The calibration tool is directly traceable to standards, such as ISO 17025 or NIST. Furthermore, the MAS-100 NT® air sample is validated together with ICR settle plates according to ISO 14698 (now replaced by EN 17141) in European countries for physical and biological efficiency. A d50 of less than 0.8 µm and a biological efficiency of more than 80% is experimentally proven by an external, independent laboratory.

Reducing human error is key to maintaining data integrity. This is achieved by designing an easy to use, with an intuitive interface air sampler.

Compliance

The MAS-100 NT® microbial air sampler is able to achieve full compliance following one of the two methods listed below:

1. Treat the instrument as a simple probe.
2. Integrate the instrument in a 21 CFR part 11 compliant, fully computerized, EM management system.

In the EM workflow, the operation and documentation of active air sampling should follow the ALCOA+ principles, which are also described by the PIC/S Guidance on Good Practices for Data Integrity in regulated GMP/GDP Environments (Draft 3 Nov 2018):

- **Attributable:** "It should be possible to identify the individual or computerized system that performed the recorded task. The need to document who performed the task / function, is in part to demonstrate that the function was performed by trained and qualified personnel. This applies to changes made to records as well: corrections, deletions, changes, etc."
- **Legible:** "All records must be legible – the information must be readable for it to be of any use. …"

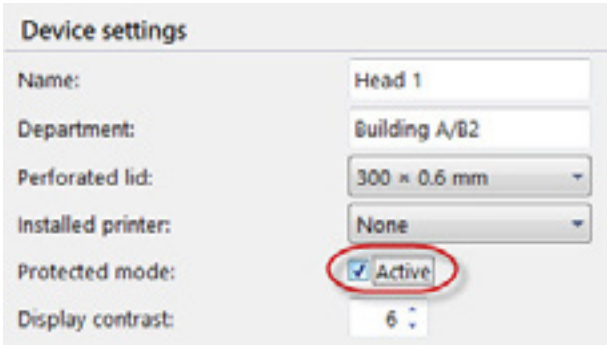
MAS-100 NT® air samplers manufactured by MBV AG, Switzerland. www.mbv.ch

- **Contemporaneous:** "The evidence of actions, events or decisions should be recorded as they take place. …."
- **Original:** "The original record can be described as the first-capture of information, whether recorded on paper (static) or electronically (usually dynamic, depending on the complexity of the system) …."
- **Accurate:** "Ensuring results and records are accurate is achieved through many elements of a robust pharmaceutical quality system. This can be comprised of:
  - equipment-related factors such as qualification, calibration, maintenance, and computer validation.
  - policies and procedures to control actions and behaviors, including data review procedures to verify adherence to procedural requirements.
  - deviation management including root cause analysis, impact assessments and CAPA
  - trained and qualified personnel who understand the importance of following established procedures and documenting their actions and decisions."
- **Complete:** "All information that would be critical to recreating an event is important when trying to understand the event. …"
- **Consistent:** "Good Documentation Practices should be applied throughout any process, without exception, including deviations that may occur during the process. This includes capturing all changes made to data."
- **Enduring:** "Records … need to remain intact and accessible as an indelible/durable record throughout the record retention period."
- **Available:** "Records must be available for review at any time during the required retention period, accessible in a readable format to all applicable personnel who are responsible for their review whether for routine release decisions, investigations, trending, annual reports, audits or inspections"

Treating the MAS-100 NT® air sampler as a simple probe

Environmental monitoring trends are generated by the CFU counts and not the air sampler data. The air sampler, therefore, may act as a simple probe, comparable to a pump, which impacts a defined and precise volume of air on the agar surface. The most important feature for routine use of the air sampler is high accuracy of the flow rate and the precision of the collected volume of air.

In order to avoid any human errors by the operator and to reduce the documentation workload, the MAS-100 NT® air sampler offers the probability to limit the operator action just to a one button-use, meaning loading the plate into the instrument and pressing start for sampling. The sample volume can be fixed in this state. The required configuration to do so is shown in **Figure 2**. Using this protected mode will ease the process to fulfill the ALCOA+ rules indicated above while following all other rules for good documentation practice.



Protected mode: Checkbox <<Active>> Switches the protected mode for the instrument on.

This function blocks manual intervention on the instrument. The only accessible functions on the instrument are now reduced to starting and stopping a sampling, and the user has only read access.

Figure 2: Protection of the MAS-100 NT® air sampler from changing settings by the operator (see software manual of MAS-100 NT®)

Integrate the MAS-100 NT® air samplewith Novatek´s EM software

Frequently, software and hardware interfaces are complicated, require too much user interaction, and in the worst case require more time and verification than manual entry. Additionally, when the equipment manufacturer updates drivers or models, the interface must as well be updated. Novatek International (Montreal, Canada) has market leading interfaces that are standard and use the latest technologies.

The partnership and co-development agreement between Novatek and Merck KGaA Darmstadt, Germany helped create the first bidirectional interface, fully compliant to CFR-21 part 11, with the MAS-100 NT® microbial air sampler.

Currently there is a strong trend towards full automation of EM sample planning, data analysis and trending. Automation will reduce time required to collect, report and trend the data while complying to data integrity requirements and eliminating the need for paper-based double checks.

MAS-100 NT® sampler integration with Novatek Environmental Monitoring Software provides a completely compliant solution by removing the manipulations from the device and controlling it from the computerized systems with full traceability, user access controls, user rights and time stamps.

Novatek Environmental Monitoring software uploads the sampling protocols to the MAS-100 NT® instrument via a secure bidirectional integration. The operator follows the instructions on the device and takes the samples as per defined Standard Operating Procedures. Once the sampling is completed, the operator connects the MAS-100 NT® sampler into Novatek EM Software and the system automatically downloads the data (sampling start and stop time, date, volume of air, etc.). The operator must provide a reason for any sample that is not taken.

Compliance to requirements of 21 CFR Part 11 and Data integrity when using MAS-100 NT® air sampler with Novatek EM Software are listed below:

DESCRIPTION DATA INTEGRITY & 21 CFR PART 11	NOVATEK EM AND MAS-100 NT® INTEGRATION
11.1 Records to be trustworthy, reliable, and generally Equivalent to paper records.	Once the record is deemed official and approved, it will be blocked and cannot be further modified. User cannot delete other users' data; this is permission controlled and is for administrative users only. Full audit trail for the integration and data transfer.
11.1 E Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA Inspection.	Novatek Software Applications source code and Client System Validation are readily available for inspection by any regulatory authority including but not limited to the FDA.
11.10 (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.	As per the regulations (21 CFR part 11, GAMP 5) and quality requirements the system will be fully validated to assure the quality of the system and the integrity of the records contained within the system
11.10 (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency.	The software hardware is validated to produce complete copies in human readable and electronic forms. All sections can be printed for review.
11.10 (c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.	Once the data is approved and deemed official it cannot be altered except by an authorized person. In the case where data is altered this change is tracked in the system wide audit trails. All changes are logged automatically. Data is maintained throughout the record retention period as per the predicate regulations.

DESCRIPTION DATA INTEGRITY & 21 CFR PART 11	NOVATEK EM AND MAS-100 NT® INTEGRATION
11.10 (d) Limiting system access to authorized individuals.	Novatek Software has a fully integrated user access management feature which limits access to the system and the MAS-100 NT®. No person without a valid login can access the application.
11.10 (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information	There are audit trail entries made while operators are creating or modifying records using the MAS-100 NT®. Each time data is saved to the database, the name of the user and the date/time stamp is automatically saved to the audit trail for the data in question.
11.10 (f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.	Operation system checks include the transfer of protocol from Novatek EM to MAS-100 NT®. Sampling as per MAS-100 NT® instructions and transfer of data from MAS-100 NT® to Novatek EM securely. Within the Novatek system completing data entry prior to approving data is enforced. Data does not display in certain grids until it is approved. This sequencing of events is inherent throughout the system.
11.10 (g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter the record, or perform the operation at hand.	Only users with active logins and valid passwords can log into the system to access the MAS-100 NT®. The system password must consist of a minimum six characters. After a number of unsuccessful attempts to access the system, the user ID becomes inactive and an email is sent to the administrator urgently and immediately advising of potential tampering. Only the System Administrator can re-activate the user.
11.10 (h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.	The data is tracked to the user who captured it along with the date and time stamp. The authenticity of the data is checked via passwords each time data is saved.
11.10 (l) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.	All personnel will be fully trained to their role in the system. This training will be conducted and documented according to SOP on training.
11.10 (k) Use of appropriate controls over systems documentation including: (1) Adequate controls over the distribution of, access to and use of documentation for system operation and maintenance. (2) Revision and change control procedures to maintain an audit trail that documents time sequenced development and moderation of systems documentation.	System documentation will be stored in a document control/management system. A change control procedure for computerized systems is in place to ensure correct version of the documentation (IQ, OQ and user manual) are used.
11.30 Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt	The ability to control user access via user ID and password is in the Novatek EM software. Critical data such as passwords are encrypted in the database.
11.50 (a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following: (1) The printed name of the signer; (2) The date and time of signature execution; (3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature. 11.50 (b) The items identified above (11.50 (a)) shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record.	In the Novatek EM software MAS-100 NT® integration: (1) The name of person who entered the data is shown on the screen. (2) The date and time of entry is automatically attached to the data. (3) Once reviewed the data will be blocked from further changes by the users. Only the authorized person can change the data. All operations will be logged.
11.70 Electronic signatures and hand-written signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.	In the Novatek EM software MAS-100 NT® integration: The password along with username will ensure that signatures cannot be excised, copied. No two people can have the same username hence there is no possibility of transferring the authority. Once the person leaves the company, his username will be deactivated by the system admin. In addition, after a default time-period the password expires. All electronic signatures are linked to their respective printed records in that the name, date and time and a manual sign offline is included on all reports where required.
11.100 (a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.	In the Novatek EM software MAS-100 NT® integration does not accept two people with the same username.

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11.100 (b)Before an organization establishes assigns, certifies, or otherwise sanction an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual. 11.100 (c)Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system.	In the Novatek EM software MAS-100 NT® integration tracks the ownership of each electronic signature in that all user information is recorded. This information includes First name, Last name, Date of Birth, Employee number, and Date of Hire.
11.200 (a)(1) Electronic signatures that are not based upon biometrics shall: Employ at least two distinct identification components such as an identification code and password.	In the Novatek EM software MAS-100 NT® integration: There is a username and password associated with each person using the software. The username and password make up the two components required to be considered an electronic signature.
11.200 (a)(1)(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual. 11.200 (a)(1)(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all the electronic signature components. Signatures can be used only by their genuine owner.	In the Novatek EM software with MAS-100 NT® integration, at initial login both the username and the password are required to access the system. (Two components) At each subsequent saving of data within the login session, the software asks for the password to verify the authenticity of the person entering the data. (One component) A user cannot enter and save data if a different user opened the program. Upon saving, only the password of the user who opened the application is accepted. Each person enters the software once with a unique username and password. Concurrent sessions are disallowed by the application.
11.200 (a)(3) Electronic signatures that are not based upon biometrics shall: Be administered and executed to ensure that attempted use of an individual’s electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.	In the Novatek EM software, MAS-100 NT® integration is designed such that only the user can know both components of an electronic signature; the username and password.
Controls for identification codes and passwords. (a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	In the Novatek EM software with MAS-100 NT® integration, when a user is added to the system, the system enforces a password change at first logon. Each user has a unique name. The software does not accept two people with the same username. There is a username and password associated with each person using the software.
11.300 (b) Ensuring that identification code and password issuances are periodically checked, recalled or revised (e.g., to cover such events as password aging).	In the Novatek EM software with MAS-100 NT® integration, the password expires within a predefined time limit. The user is requested to enter a new password after the expiration of the password. The same password cannot be used twice.
11.300 (d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, any, as appropriate, to organizational management.	In the Novatek EM software with MAS-100 NT® integration the password consists of an adequate level of complexity. After a number of unsuccessful attempts, the user ID becomes inactive. Only the System Administrator can reactivate the user. An email is triggered to immediately and urgently inform the system administrator of the potential illegal activity.
Following loss management procedures to electronically de-authorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.	In the Novatek EM software with MAS-100 NT® integration any user can be deactivated from the system, ensuring that there is no possibility of unauthorized data entry.

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