NucleoView™ NC-250™ 21 CFR part 11 Guide

Contents

Introduction

This document describes the functionalities of the 21 CFR part 11 module of NucleoView™ NC-250™.

21 CFR part 11 compliance requires the implementation and validation of IT system platforms as well as procedural and administrative control systems. Activation of 21 CFR part 11 in NucleoView™ NC-250™ introduces features and restrictions to the graphical user interface of NucleoView™ NC-250™, in order to support implementation of 21 CFR part 11. **Activation of 21 CFR part 11 in ™ NC-250™ in itself does not confer compliance with the 21 CFR part 11 guidelines.**

Background

The US regulatory agency Food and Drug Administration (FDA) 21 Code of Federal Regulation 21 Part 11; Electronic Records, Electronic Signatures (21 CFR Part 11) came into effect on August 20th 1997.
In short, the 21 CFR Part 11 defines the FDA acceptance criteria for use of electronic records and electronic signatures as equal to paper records with handwritten signatures.

The NucleoView™ NC-250™ application can be set into a restricted mode (hereafter referred to as 21 CFR Part 11 mode), so the user via the NucleoView™ NC-250™ application itself can not violate the 21 CFR Part 11 regulations. This means that on a computer system that is 21 CFR Part 11 compatible, it is possible to keep the compliancy even after installation and use of the NucleoView™ NC-250™ application. The 21 CFR Part 11 regulations can only be applied when the NucleoCounter® NC-250™ and the NucleoView™ NC-250™ software are a closed system.

Guidelines on how ChemoMetec addresses relevant parts of 21 CFR part 11 is outlined in the following white paper:
NucleoCounter® NC-250™, NucleoView™ NC-250™ Software and Code of Federal Regulation 21 Part 11; Electronic Records, Electronic Signatures (21 CFR Part 11) (994-0271)

Note that operating NucleoView™ NC-250™ in 21 CFR Part 11 mode requires a specific license that can be purchased by contacting your local sales representative.

Implementation

When 21 CFR Part 11 mode is activated in NucleoView™ NC-250™, several features of the software become restricted, such as post-processing of data and modification of cell counting protocols. These restrictions make the 21 CFR Part 11 mode in NucleoView™ NC-250™ less suited for laboratory environments where flexibility of the software is required, such as R&D and process development. The 21 CFR part 11 module is mostly relevant for laboratories using in-house validated cell counting protocols and where the flexibility of the NucleoView™ NC-250™ software is a potential risk for unwanted parameter changes.

NucleoView™ NC-250™ features that are restricted by enabling 21 CFR part 11 mode are outlined in the 'Restrictions and user rights summary' section.

Activation of 21 CFR part 11 in NucleoView™ NC-250™ in itself does not secure the local data files. The user need to set up IT systems to secure data by storing the NucleoView™ NC-250™ file in a server and/or use 3rd party software to restrict user access to NucleoView™ NC-250™ data files stored locally.

Defining user groups using Windows Active Directory

Access to and rights within NucleoView™ NC-250™ is controlled by three user groups that needs to be defined using Windows Active Directory. The groups must be named NucleoViewAdmin, NucleoViewSuperVisor and NucleoViewUser (case sensitive). Any user logging on to NucleoView™ NC-250™ application while in 21 CFR part 11 mode must belong to one of these groups in order to gain access. The audit trail is maintained by recording the action of the specific user. Note that users belonging to the NucleoViewSuperVisor and NucleoViewUser groups should not have Windows admin rights, to prevent them from designating themselves to the NucleoViewAdmin group.

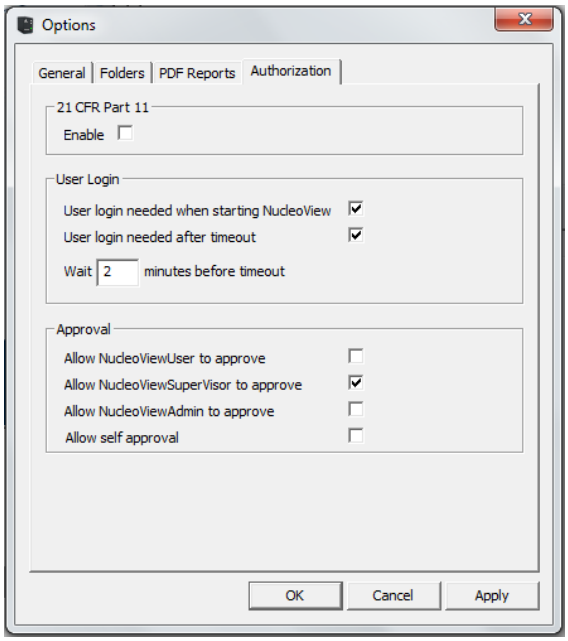
The NucleoViewAdmin users have full rights in the NucleoView™ NC-250™ application and may switch 21 CFR Part 11 mode off, thus breaking the 21 CFR Part 11 compliance. The NucleoViewSuperVisor and NucleoViewUser groups have restricted user rights in NucleoView™ NC-250™. The rights of each user group are summarized in the 'Restrictions and user rights summary' section.

All user accounts that need to operate the NucleoView™ NC-250™ application need the security policy *Impersonate a client after authentication* enabled. It is recommended to enable the *Impersonate a client after authentication* for the three groups NucleoViewAdmin, NucleoViewSuperVisor and NucleoViewUser. Impersonate a client must be enabled to allow a user to log in to NucleoView™ NC-250™ using Active Directory even though the running Windows session is for another user.

Enabling 21 CFR Part 11 in NucleoView™ NC-250™

21 CFR Part 11 mode can be enabled/disabled in the *Authorization* dialog (*Tools -> Options*) shown in the picture below. Once the check box for 21 CFR part 11 is checked, the user will need to successfully enter username and password in an input box, in order to authorize the change of 21 CFR part 11 mode. Only users belonging to the NucleoViewAdmin user group has rights to enable/disable 21 CFR part 11 mode. A 21 CFR part 11 license should be purchased in order to activate NucleoView™ NC-250™ in 21 CFR part 11 mode. The licenses associated with the instrument can be observed under *View -> License File*.

Once 21 CFR part 11 mode has been enabled, only NucleoViewAdmin group users are able to apply changes to the *Options* dialog. Configurable software features in the *Authorization* tab of the *Options* dialog is described below.



User Login

User login needed when starting NucleoView™. Checking this box will require users to enter username and password upon launching NucleoView™ NC-250™. Only users belonging to the NucleoViewAdmin, NucleoViewSuperVisor or NucleoViewUser group are able to log into the application when running in 21 CFR part 11 mode.

Note that the user logging into NucleoView™ NC-250™ does not need to be same user that is logged into Windows. If *User login needed when starting NucleoView™* is not checked, NucleoView™ NC-250™ will automatically record the user who is logged into Windows as the logged in NucleoView™ NC-250™ user.

User login needed after timeout. After a configurable period of inactivity, the user will be prompted with an input box and is required to enter username and password in order to continue operating NucleoView™ NC-

250™. If a different user enters his or her credentials, the application will shut down and restart, logging in as that user.

Approval

Which user groups are allowed to approve image files (which contain the data) can be defined here. It is possible to define whether users should be allowed to self approve. If an image file has been approved, information on the user who approved the data and the time of approval can be found by right clicking the data file and selecting *Properties*. Approval information will also appear in the PDF report.

Adapted protocols

Adapted protocols are derived from the standard protocols. These protocols can be adjusted by:

a) Changing the parameters for when the intensity and size of an event is counted.

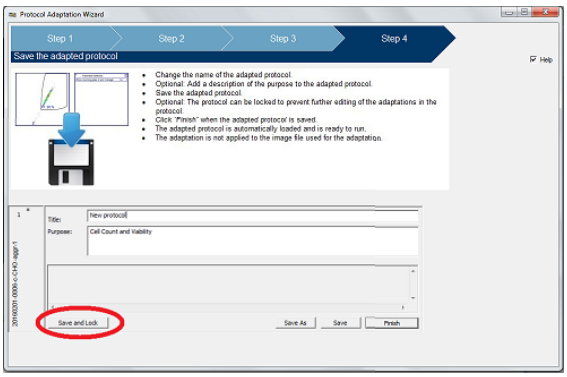
b) Configuring how results are represented with plots and tables.

c) Changing how the cell count is reported in the NucleView NC-250™ main screen (for example displaying live cells/ml instead of total cells/ml).

d) Automatically populate diluent and sample default volumes, in the NucleView NC-250™ main screen.

The adapted protocols are generated using the *Protocol Adaptation Wizard*, which are described in more detail in the *NucleoView™ NC-250™ Software User's Guide* (991-0252). Adapted protocols cannot be generated while 21 CFR part 11 is enabled.

When 21 CFR part 11 mode is enabled, only locked adapted protocols are viewable in the *Protocol Selection* dialog. Locking adapted protocols can be done in the *Protocol Adaptation Wizard*.

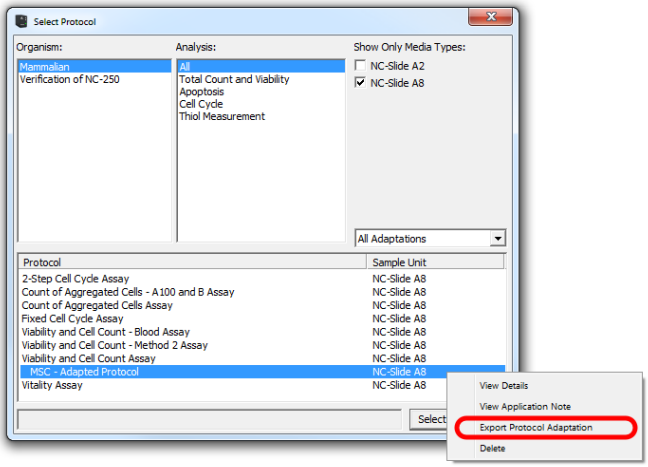


To lock a protocol, click the *Save and Lock* button on the bottom left.

Adapted protocols can be transferred from a NucleoCounter®/NucleoView™ NC-250™ instrument pair to another NucleoCounter®/NucleoView™ NC-250™ instrument to replicate the counting conditions. The

transfer of protocols can only be done by a user in the NucleoViewAdmin user group while 21 CFR part 11 mode is enabled.

Adapted protocols are exported from the *Protocol Selection* dialog.



By right clicking the adapted protocol and selecting *Export Protocol Adaption* the adapted protocol are saved as a *.cmsu or .cmsup file. In 21 CFR part 11 mode all users are able to export an adapted protocol.

Adapted protocols can only be deleted by users belonging to the NucleoViewAdmin group when 21 CFR part mode is enabled.

Exported adapted protocols can be imported into the application by selecting *File -> Import Package...* and choosing the relevant *.cmsu or *.cmsup file. In 21 CFR part 11 mode, only NucleoViewAdmin users can import adapted protocols. Importing an adapted protocol with the same name as any existing adapted protocols , thereby overwriting it, is not possible.

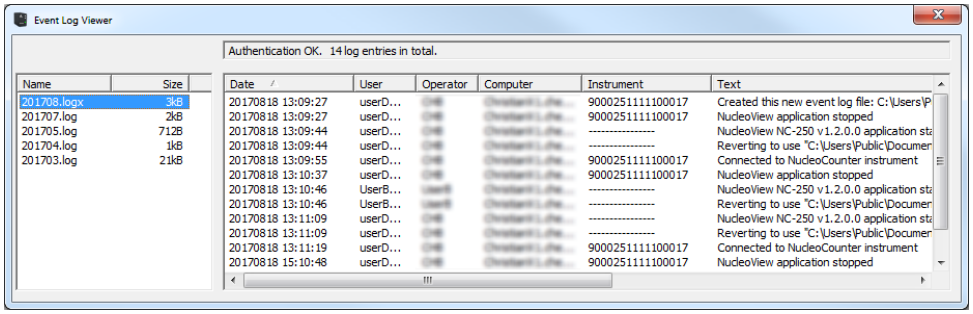
Newly created and imported adapted protocols are saved as *.cmsu or *.cmsup files and are located in the following folder:

C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\scripts\adapted

Event log

User activity within NucleoView™ NC-250™ is recorded in the event log files. Apart from securing that the user cannot tamper with measured results in the NucleoView™ NC-250™ application while in 21 CFR Part 11 mode, all operations changing the functionalities of NucleoView™ NC-250™, all new files created etc. are logged in the event log system. Only the users belonging to the NucleoViewAdmin group are able to view the event log.

The event logs can be inspected in the *Event Log Viewer* via *View -> Event Logs*. Only members of the NucleoViewAdmin user group can launch the *Event Log Viewer*. A screen shot of the *Event Log Viewer* is shown below.



The left panel shows the list of existing event log files in the image file (*.cm) save destination folder (see 'Image files' section below), with one event log file created for each month.

The top panel will show the authenticity status of the selected log file. Authentication status and number of log entries for the currently selected log file is displayed above the content window. Log files with the “logx” extension, generated by NucleoView™ NC-250™ 1.2.0.0 and later, are encrypted, checksum protected and can be authenticated by the *Event Log Viewer*. Earlier versions of NucleoView™ NC-250™ use log files with extension “log”, which are plain text files that cannot be authenticated by the *Event Log Viewer*.

The right panel will display the content of the log file. Clicking on one of the headers in the right window will sort the content according to the selected column either ascending or descending.

Note that in the date column, some entries may be marked with an asterisk (*). This indicates that the event happened when the NucleoView™ NC-250™ application was not in 21 CFR Part 11 mode.

The *User* column lists the user name at the time of logging the entry.

The *Operator* column lists the content of the *Operator* field in the main window of NucleoView™ NC-250™. In 21 CFR part 11 mode it is recommended to ignore this field, as the text string entered into the *Operator* field is not restricted by the software. Thus, the *Operator* entry is not tied to a specific user.

The event log file can be exported by right clicking the selected file in the left panel. The following options are available:

Select Folder…, to inspect log files in another folder.

Export to csv…, to export the log entries to a tab separated *.csv file.

Create and Show PDF Report…, to create and show a pdf-file report and optionally print it.

The event log files are created by the NucleoView™ NC-250™ application and are stored in the folder defined to be the image files save destination folder, which by default is:

C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results

Changing this folder will create a new .logx or .log file in the new folder destination and all new event log files will be saved in the new folder onwards. It is recommended to backup the event logs.

Data integrity

The image files generated by NucleoView™ NC-250™ should be secured by the user, for example by storing the data on a secure location, or using third party software to limit access and rights of users to folders where data is saved. Note that the save location for result files is configurable; see the 'NucleoView™ NC-250™ files' section below for more information. If third party software is used to block access to the Windows file system, a default printer must be defined for each user on the computer, to prevent the printer selection dialog from granting access to Windows file system. The default printer must not print to a file; it must be a physical printer. However, once installed this printer does not need to be connected to the system.

It is recommended for image files to be stored on the local computer system, since saving image files across a network may prevent data acquisition in situations where the network speeds are low. Instead it is recommended to schedule remote backup of the image files using 3rd party systems.

NucleoView™ NC-250™ files

The table below lists NucleoView™ NC-250™ files that need to be secured together with their default save locations.

NucleoView™ NC-250™ file	Save location
Image files (*.cm)	*C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results**
Post Processing file (*.cmpp)	*C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results**
CSV files	*C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results\csv**
PDF reports	*C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results\pdf**
Adapted protocols	*C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\scripts\adapted*
Event log file (.log and .logx)	*C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results**

*Save location is configurable as described in the relevant sections.

A detailed description of each file type with important information related to 21 CFR part 11 is listed below.

Image files (*.cm)

Image files produced by NucleoView™ NC-250™ hold all primary analysis data (picture, counting data, acquisition setting, instrument ID, user ID etc.). These files use a ChemoMetec proprietary file format with the extension cm and are named:

yyyymmdd-####-#-#.cm (year-month-day)-(analysis number)-(chamber number)-(user defined sample ID).cm

It is not possible to overwrite image files within the NucleoView™ NC-250™ system. After acquisition, image files are placed in a directory named yyyymmdd (year-month-day) within the *results* directory. The default location for saving image files is:

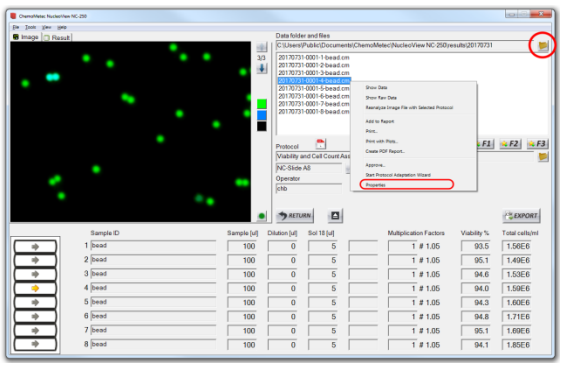
C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results

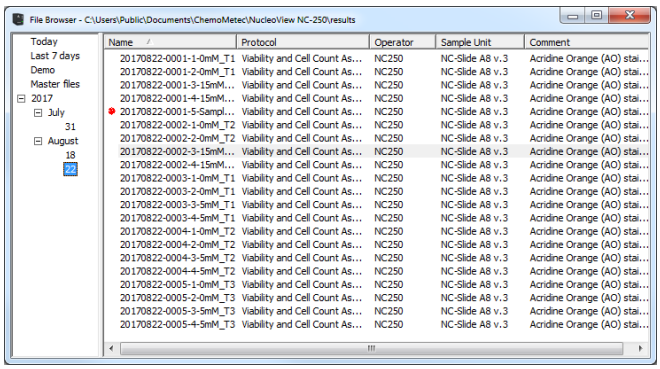
This location may be changed by the user from within NucleoView™ NC-250™ by selecting:

*Tools -> Options -> Folders -> *.CM Files* (press the folder icon to change the save destination)

*.cmpp and event log files will save to the same destination as selected for *.cm files. It is recommended to check the *All users* check box to save data generated by all users to the same location. If this box is not checked, the changed save destination will only apply to the user logged into NucleoView™ NC-250™ when the change was made. In 21 CFR part 11 mode only the NucleoViewAdmin group can change the save destination.

Note that the sample ID of an image file can be changed by right clicking on the image file in NucleoView™ NC-250™ and selecting *Properties* (see red square in the top picture below) -> *Sample ID (see below)*. Once the ID has been changed, a red dot will appear next to the image file in the *Image File Browser* dialog (see below right). The File Browser are opened by clicking the folder icon (see below left, red circle).





Changing the sample ID will change the file name of the corresponding .cm-file and the .cmpp-file. Changing the sample ID will be recorded in the event log. The previous ID will be stored in the image file along with the new sample ID and will be visible when exporting the data.

Post Processing file (*.cmpp)

In NucleoView™ NC-250™ it is possible to perform post processing or modify the analysis of an image file by changing the gates and plots of one row shown in the Plot Manager part of the software (see the *NucleoView™ NC-250™ Software User's Guide* (991-0252) 'Plot Manager' section for more details). The *.cmpp file holds information about the post processed gates and plots for a specific *.cm image file and has the same file name as its corresponding image file (*.cm file). Also the *.cmpp file is placed in the same directory as its corresponding image file. In 21 CFR part 11 mode post processing and overwriting the *.cmpp file is not possible.

CSV files (*.csv)

NucleoView™ NC-250™ can be configured to save the numerical values of the cell counting as a CSV file for every completed run of a protocol. This is done by selecting:

*Tools -> Options -> Folders -> *.CSV Files -> Create CSV results file* (check the box)

It is recommended to check the *All users* check box to save data generated by all users to the same location. If this box is not checked, the changed save destination will only apply to the user logged into NucleoView™ NC-250™ when the change was made. In 21 CFR part 11 mode only NucleoViewAdmin users can change the save destination.

The default save location for CSV files is:

C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results\csv

This location may be changed by the user by opening NucleoView™ NC-250™ and selecting:

*Tools -> Options -> Folders -> *.CSV Files* (press the folder icon to change the save destination)

Bulk data can be exported in CSV format using the *Report Generator* (see the *NucleoView™ NC-250™ Software User's Guide* (991-3003) 'Report Generator' section for more details). In 21 CFR part 11 mode, CSV files cannot be overwritten from within NucleoView™ NC-250™.

PDF reports

NucleoView™ NC-250™ can be configured to automatically save a PDF report summarizing the cell counting results. The PDF report includes the fluorescence micrograph, scatter plots and the numerical cell counting values. NucleoView™ NC-250™ can be configured to automatically save a PDF report after data acquisition by selecting:

*Tools -> Options -> PDF reports -> Auto Generated *.PDF files* (check the *Save* check box)

It is recommended to check the *All users* check box to save all user data to the same location. If this box is not checked, the changed save destination will only apply to the user logged into NucleoView™ NC-250™ when the change was made. In 21 CFR part 11 mode only the NucleoViewAdmin group can change the save destination.

The default folder for saving PDF reports in NucleoView™ NC-250™ is:

C:\Users\Public\Documents\ChemoMetec\NucleoView NC-250\results\pdf

PDF reports can also be manually generated by right clicking an image file in NucleoView™ NC-250™ and selecting *Create PDF Report...* (For more information about creating PDF reports, see the *NucleoView™ NC-250™ Software User's Guide* (991-3003)). In 21 CFR part 11 mode all user groups can create PDF reports, however overwriting PDF files is not allowed.

Restrictions and user rights summary

Enabling 21 CFR part 11 mode restricts several features of the NucleoView™ NC-250™ software and gives different rights to the three user groups. Table 2 below lists the restrictions imposed on NucleoView™ NC-250™ under 21 CFR part 11 mode and outlines how this applies to the different user groups.

NucleoView™ NC-250™ Software Function	**Normal mode**	**21 CFR part 11 enabled.**			
User group	**Other**	**Other**	**NucleoViewUser**	**NucleoViewSuperVisor**	**NucleoViewAdmin**
Access to NucleoView™ NC-250™	Yes	No	Yes	Yes	Yes
Access to logged user actions (event log)	Yes/No*	-	No	No	Yes
Enable/Disable 21 CFR part 11	Yes/No*	-	No	No	Yes
Change configurations in *Options* (Files save destinations, Log-In requirements, approval configuration, PDF Report configuration)	Yes	-	No	No	Yes
Data approval	Yes/No**	-	Yes/No**	Yes/No**	Yes/No**
Create adapted protocol	Yes	-	No	No	No
Export adapted protocol	Yes	-	Yes	Yes	Yes
Delete adapted protocol	Yes	-	No	No	Yes
Import adapted protocol	Yes	-	No	No	Yes
Overwrite locked adapted protocol	No (Yes***)	-	No	No	No
Unlocked adapted protocols hidden in *Protocol selection* dialog	No	-	Yes	Yes	Yes
Locked adapted protocols hidden in *Protocol selection* dialog	No	-	No	No	No
Generate PDF report	Yes	-	Yes	Yes	Yes
Report generator bulk data export (.csv)	Yes	-	Yes	Yes	Yes
Overwrite PDF, .cmpp and .csv files from NucleoView™ NC-250™	Yes	-	No	No	No
Change sample ID	Yes (****)	-	Yes (****)	Yes (****)	Yes (****)

* Only NucleoViewAdmin users can access the event log in normal mode and enable/disable 21 CFR part 11 mode. ** Dependent on configuration (see 'Approval' section within the ' Enabling 21 CFR Part 11 in NucleoView™ NC-250™' chapter, for more details). *** Only the user that locked the adapted protocol can overwrite it. **** Previous ID will be stored along with the new ID and will be visible when exporting the data.

Product Notes

The NucleoCounter® NC-250™ instruments are marked with "NOT FOR USE IN DIAGNOSTIC OR THERAPEUTIC PROCEDURES" to make it clear for customers that our instruments are only validated for research purposes.

The NucleoCounter® NC-250™ instrument is not considered a Medical Device and was not designed or validated according to 21 CFR Part 820 (GMP for Medical Devices).

The NucleoCounter® NC-250™ instruments are widely used in research laboratories. However, many customers have performed their own validation of their NucleoCounter® NC-250™ instrument in order to use it for diagnostic procedures or manufacturing of therapeutic products.

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