

Guide for 21 CFR part 11 on NucleoView™ NC-200™

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Introduction

Scope

Title 21 of the Code of Federal Regulations Part 11 (21 CFR part 11) defines the criteria under which electronic records and electronic signatures are considered trustworthy, reliable, and equivalent to paper records.

This document is written for IT and QA professionals and describes the NucleoView™ NC-200™ features relevant for setting up a 21 CFR part 11 compliant setup with the NucleoCounter® NC-200™.

The white paper *NucleoCounter® NC-200™, NucleoView™ NC-200™ Software and Code of Federal Regulation 21 Part 11; Electronic Records, Electronic Signatures (21 CFR Part 11) (994-0208)* outlines how ChemoMetec addresses relevant parts of 21 CFR part 11.

The NucleoCounter® NC-200™ '21 CFR Part 11 module' requires a specific license that can be purchased by contacting your local sales representative.

Activating '21 CFR part 11 mode' will block NucleoView™ NC-200™ functionalities that could violate '21 CFR part 11' guidelines. Enabling '21 CFR part 11 mode' in itself, will not ensure compliance with the 21 CFR part 11 guidelines.

The NucleoCounter® NC-200™ and NucleoView™ NC-200™ systems are intended for research use only and are not approved for diagnostic or therapeutic use. Persons and organizations using the NucleoCounter® NC-200™ and NucleoView™ NC-200™, hereafter referred to as 'client', are responsible for the configuration, qualification, and validation activities required for their application.

The NucleoView™ NC-200™ data files will not automatically be secure on the local workstation drive in '21 CFR part 11 mode'. Strategies for securing local data files are provided in this document, but it is the client's sole responsibility to configure and validate the integrity of the NucleoCounter® NC-200™ system operating in '21CFRp11 mode'. The configuration of IT systems outside NucleoView™ NC-200™ is not supported by Chemometec.

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 the use of electronic records and electronic signatures as equal to paper records with handwritten signatures. The NucleoView™ NC-200™ application can be set into a restricted mode (hereafter referred to as 21 CFR Part 11 mode), which prevents operators from violating the 21 CFR Part 11 regulations via the NucleoView™ NC-200™ application itself. Consequently, it is possible to achieve compliance on a computer system that is already 21 CFR Part

11 compatible. The 21 CFR Part 11 regulations can only be applied when the NucleoCounter® NC-200™ and the NucleoView™ NC-200™ software are a closed system.

Setting up NucleoView™ NC-200™

Access rights and operator rights in NucleoView™ NC-200™ are controlled by three user groups, defined in Windows Active Directory.

Setting up '21 CFR part 11 mode' consists of the following steps:

1. Assign users to predefined user groups in Windows Active Directory
2. Activate '21 CFR part 11 mode'
3. Configure NucleoView™ User Permission
4. Secure local NucleoView™ files

Assign users to predefined User groups.

Three user groups must be created and should be named (case sensitive):

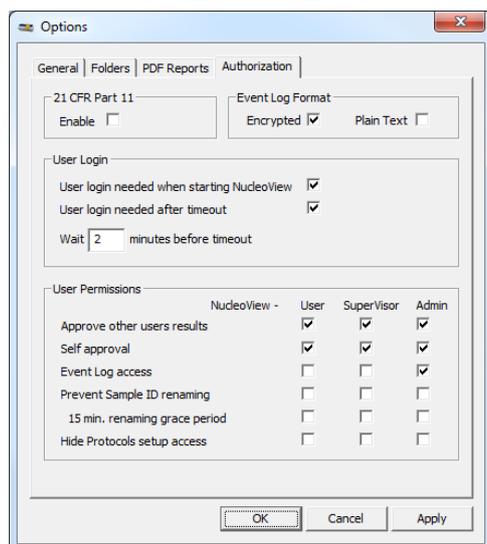
- NucleoViewUser
- NucleoViewSuperVisor
- NucleoViewAdmin

Users logging in to NucleoView™ NC-200™ in '21 CFR part 11 mode' must belong to a user group for NucleoView™ NC-200™ to launch. The NucleoViewAdmin users have full rights in the NucleoView™ NC-200™ application and can disable '21 CFR Part 11 mode', breaking the 21 CFR Part 11 compliance. The NucleoViewSuperVisor and NucleoViewUser groups have restricted user rights in NucleoView™ NC-200™. The rights of each user group are summarized in the 'User level restrictions' section.

All user accounts that need to operate the NucleoView™ NC-200™ application need the Windows security policy '*Impersonate a client after authentication*' enabled. It is recommended to enable this option for the three groups NucleoViewAdmin, NucleoViewSuperVisor, and NucleoViewUser, using Active Directory.

Configuration

The NucleoView™ NC-200™ user group permissions are configured under the 'Options' dialog box (Tools -> Options -> Authorization).



21 CFR Part 11

Enabling and disabling '21 CFR part 11 mode' in NucleoView™ NC-200™ is restricted to the NucleoViewAdmin user group.

Event Log Format

NucleoView™ NC-200™ can store the event log as an encrypted file format and/or a plain text format. The encrypted format serves as an authoritative audit trail and can be authenticated (see 'Event Log'). The plain text format is relevant when importing event log data to data management systems.

User Log In

User login needed when starting NucleoView. Enabling this option will require users to enter username and password upon launching NucleoView™ NC-200™. Only users belonging to the NucleoViewAdmin, NucleoViewSuperVisor or NucleoViewUser group can log into the application when running in 21 CFR part 11 mode. If this option is not checked, NucleoView™ NC-200™ will automatically assign the recorded events to the user ID used to log into Windows.

User login needed after timeout. After a configurable period of inactivity, the user will be prompted with a log-in screen and is required to enter username and password to continue operating NucleoView™ NC-200™.

User Permissions

Approve other users results. Define which user groups are authorized to approve recorded data using the Approve function. (see 'Data Approval')

Allow self approval. Define which user groups are authorized to approve data recorded by themselves.

Event Log access. Define which user groups are authorized to view the 'Event Log' files using the 'Event Log Viewer'.

Prevent Sample ID renaming. Define which user groups are authorized to rename recorded samples ID. The .cm and .cmpp-file name is also changed when the sample ID is changed.

15 min renaming grace period. Define which user groups are authorized to rename recorded samples ID within 15 minutes of recording the sample.

Hide Protocol Setup Access. Define which user groups that have access to the Hide Protocols Function. (see 'Hide Protocols').

User level restrictions

Enabling '21 CFR part 11 mode' restricts several features of the NucleoView™ NC-200™ software and gives different rights to the three user groups. Table 1 below lists the restrictions imposed on NucleoView™ NC 200™ under '21 CFR part 11 mode' and outlines how this applies to the different user groups. Some user policies can be configurable (see 'Configuration of User Rights').

NucleoView™ NC-200™ Software Function	Normal mode	21 CFR part 11 mode.			
	Other	Other	NucleoViewUser	NucleoViewSuperVisor	NucleoViewAdmin
Access to NucleoView™ NC-200™	Yes	No	Yes	Yes	Yes
Access to Event Log	Optional	-	Optional	Optional	Optional
Enable/Disable 21 CFR part 11	Yes a)	-	No	No	Yes
Change configurations in <i>Options</i> (Files save destinations, Log-In requirements, approval configuration, PDF Report configuration)	Yes	-	No	No	Yes
Data approval	Optional	-	Optional	Optional	Optional
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	Yes b)	-	No	No	No
Run unlocked Protocol Adaptation	Yes	-	No	No	No
Unlocked adapted protocols hidden in <i>Protocol selection</i> dialog	No	-	Yes	Yes	Yes
Locked adapted protocols hidden in <i>Protocol selection</i> 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-200™	Yes	-	No	No	No
Change sample ID	Optional	-	Optional	Optional	Optional
Hide/Show Protocols	Optional	-	Optional	Optional	Optional

Table 1. User restrictions in '21 CFR part 11 mode' and at different users group levels. a) Users part of the NucleoViewAdmin group can enable/disable 21 CFR part 11 mode on NucleoView™ NC-200™ installations with a valid 21 CFR Part 11 license. b) Only the user that locked the adapted protocol can overwrite it.

File types and data storage locations

Data storage location

The 'NucleoView Data Folder' refers to the location where NucleoView .cm, .cmpp and .log files are stored. The default folder is the Public folder on the local drive, allowing all users to access the same data. The 'NucleoView Data Folder' can be changed to a different local folder, or network drives from the options dialog (see Table 2).

The CSV and PDF files can be saved to independent folders.

NucleoView NC-200™ file type	Default Save location	Folder location configurable
Image files (.cm)	<i>C:\Users\Public\Documents\ChemoMetec\NucleoView NC-200\results</i>	Yes. >Options>Folders> 'CM Files'
Post Processing file (.cmpp)	<i>C:\Users\Public\Documents\ChemoMetec\NucleoView NC-200\results</i>	
Event log file (.log and .logx)	<i>C:\Users\Public\Documents\ChemoMetec\NucleoView NC-200\result</i>	
CSV export files (.csv)	<i>C:\Users\Public\Documents\ChemoMetec\NucleoView NC-200\results\csv</i>	Yes. >Options>Folders> 'CSV Files'
PDF reports (.pdf)	<i>C:\Users\Public\Documents\ChemoMetec\NucleoView NC-200\results\pdf</i>	Yes. >Options> 'PDF Report'

Table 2. Default save location for NucleoView NC-200 files

When changing the file storage location in the options dialog, checking the 'All users' box will change the file location for all users. If left unchecked the file location will only be applied to the user logged into NucleoView™ NC-200™.

File Types

A detailed description of each file type is listed below.

Image files (*.cm)

Image files produced by NucleoView™ NC-200™ 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 .cm-extension and are named based on data recording sequence and the string entered into the sample ID field `yyyymmdd-####-c-<user definedID>.cm`

It is not possible to overwrite image files within the NucleoView™ NC-200™ system. Image files in the 'NucleoView Data Folder', in a directory named: (yyyymmdd).

Changing the sample ID (*Data Folders and Files* -> *Right click file* -> *Properties* -> *Sample ID*) will change the file name of the corresponding .cm-file and the .cmpp-file. Once the ID has been changed, a red dot will appear next to the image file in the *Image File Browser* dialog. The previous ID will be stored in the image file along with the new sample ID and will be visible when exporting the data. Changing the sample ID will be recorded in the event log.

Right for changing the sample ID can be disabled (see 'Configuration of User Rights').

Post Processing file (*.cmpp)

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). Post-processing and overwriting the *.cmpp file is not possible in '21 CFR part 11 mode'.

Event Log Files (.log and .logx)

Log files with the “.logx” extension are encrypted, whereas “.log” are plain text files. (see 'Event log' section)

CSV files (*.csv)

Data can automatically be stored as CSV file. One CSV-file will be generated for each run and have the same name as the .cm-file. Storing data as CSV-files are enabled under options:

Multiple data files can be exported into a single CSV-file using the *Report Generator* function (see the *NucleoView™ NC-200™ Software User's Guide* (991-3003) for details).

PDF reports

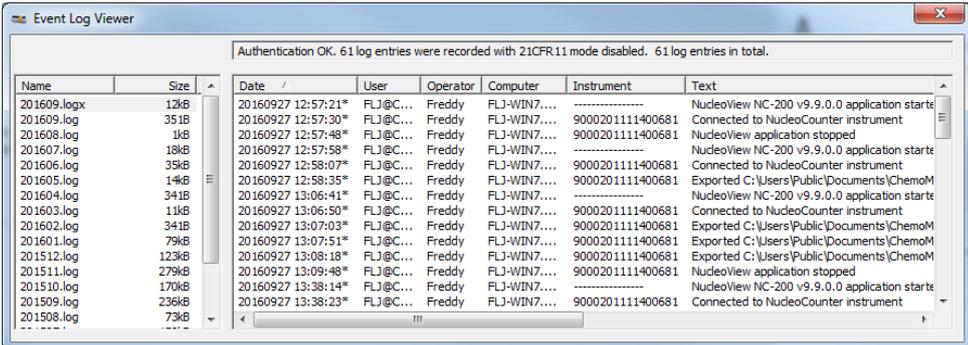
Data can automatically be saved to a PDF report summarizing the cell counting results. The PDF storage location report save destination, and PDF report elements (image preview, scatter plots, etc.) can be configured under:

Tools -> *Options* -> *PDF reports* -> *Auto Generated *.PDF files*

NucleoView™ NC-200™ functionalities

Event log

User activity within NucleoView™ NC-200™ is recorded in the event log files, which may serve as an audit trail. The event logs can be inspected in the *Event Log Viewer* via *View -> Event Logs*. Access to the 'Event Log Viewer' can be restricted to certain user groups (see 'Configuration of User Rights').



Name	Size	Date	User	Operator	Computer	Instrument	Text
201609.logx	12kB	20160927 12:57:21*	FLJ@C...	Freddy	FLJ-WIN7...	-----	NucleoView NC-200 v9.9.0.0 application start
201609.log	351B	20160927 12:57:30*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Connected to NucleoCounter instrument
201608.log	1kB	20160927 12:57:48*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	NucleoView application stopped
201607.log	18kB	20160927 12:57:58*	FLJ@C...	Freddy	FLJ-WIN7...	-----	NucleoView NC-200 v9.9.0.0 application start
201606.log	35kB	20160927 12:58:07*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Connected to NucleoCounter instrument
201605.log	14kB	20160927 12:58:35*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Exported C:\Users\Public\Documents\ChemoM
201604.log	341B	20160927 13:06:41*	FLJ@C...	Freddy	FLJ-WIN7...	-----	NucleoView NC-200 v9.9.0.0 application start
201603.log	11kB	20160927 13:06:50*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Connected to NucleoCounter instrument
201602.log	341B	20160927 13:07:03*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Exported C:\Users\Public\Documents\ChemoM
201601.log	79kB	20160927 13:07:51*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Exported C:\Users\Public\Documents\ChemoM
201512.log	123kB	20160927 13:08:18*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Exported C:\Users\Public\Documents\ChemoM
201511.log	279kB	20160927 13:09:48*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	NucleoView application stopped
201510.log	170kB	20160927 13:38:14*	FLJ@C...	Freddy	FLJ-WIN7...	-----	NucleoView NC-200 v9.9.0.0 application start
201509.log	236kB	20160927 13:38:23*	FLJ@C...	Freddy	FLJ-WIN7...	9000201111400681	Connected to NucleoCounter instrument
201508.log	73kB						

The left panel shows the list of existing event log files in the 'NucleoView Data Folder'. One event log file is created for each month. The event log file can be exported by right-clicking the selected file and selecting *Export to csv...* or *Create and Show PDF Report...*

NucleoView™ NC-200™ can generate two different 'Event Log' types, (see 'Configuration of User Rights'):

- Event Log files with the ".logx" extension are encrypted, and checksum protected and can be authenticated by the *Event Log Viewer*.
- Event Log files with extension ".log" are plain text files. This file type is un-encrypted and cannot be authenticated.

The top panel shows the authentication status, and the number of log entries for the currently selected log file.

The right panels lists the events recorded during NucleoCounter® NC-200™ and NucleoView™ NC-200™ operation. Each column can be sorted in ascending or descending order, and contain the following information:

- The *date*-column contains the time stamp. An asterisk (*) indicates that the event was not recorded in '21 CFR part 11 mode'.
- The *User*-column lists the username. If 'User log-in during NucleoView startup' is disabled (see 'Configuration' section, the UserID used to log in to Windows will be logged.
- The *Operator*-column lists the value *Operator* field entered before protocol execution. In '21 CFR part 11 mode' it is recommended to ignore this field, as the *Operator* entry is not tied to a specific user.
- The *Computer*-column. The name of the workstation and network.

- The *Instrument*-column. The serial number of the instrument connected to the workstation.
- The *Text*-column. The description of the recorded event.

Data Approval

The Approval function allows recorded data to be reviewed and signed by a second user. The approval right can be defined at three user groups levels (see 'Configuration of User Rights').

Data files are approved by right-clicking the data point in the 'Data folder and files section' followed by "Approve...". Approving data will change the .cm file size and data.

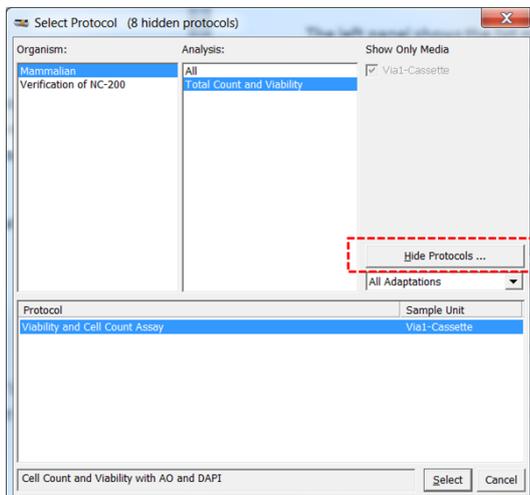
Adapted protocols

Un-locked adapted protocols will not be displayed in the *Protocol Selection* dialog in '21 CFR part 11 mode'. Adapted protocols can be locked with the *Protocol Adaptation Wizard*, on a workstation not running in '21 CFR part 11 mode'.

Adapted protocols can be transferred from one NucleoView™ NC-200™ installation to another, 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.

Hide Protocols

NucleoView™ allows specific protocols to be hidden by a 'Hide Protocol' button in the 'Select Protocol Dialog'. This button is only visible to authorized users.



Data integrity

The data files generated by NucleoView™ NC-200™ are not automatically protected when activating '21 CFR part 11 mode'. Thus, the client should use IT solutions to secure these files (see File Types section).

In the following, three potential strategies for securing the local NucleoView™ data files are presented: a) Secure local files using folder permissions in Windows, b) Secure local files by blocking access to the Windows shell using third party software, c) Securing data by storing NucleoCounter® NC-200™ files on a remote server.

These strategies are only meant as suggestions, and other strategies could be used to secure the data.

Use folder permission to protect local files

Windows can restrict user access to specific local folders on the workstation with NucleoView™ NC-200™ installations.

A service account, hereafter referred to as NC-Host, can be created for each workstation connected to a NucleoCounter NC-200™. When '*User login needed when starting NucleoView*' is enabled, the NucleoView™ NC-200™ process will run with operator User ID, while all other Windows processes will run with the NC-Host ID. Folder access permissions can be used block access to the 'NucleoView Data Folder' for the NC-Host, but not for all other users. By restricting the Windows log-in permission to the NC-Host, the operator cannot manipulate the files in the 'NucleoView Data Folder', while being able to record data with NucleoView™ NC-200™.

Access to the 'NucleoView Data Folder' should not be blocked for the Operator's User ID, or the NucleoView user groups, since this will prevent NucleoView™ NC-200™ from functioning correctly.

If the aforementioned strategy is employed the sequence of instrument operation should be:

- The operator will log on to the NC Host PC using the NC Host ID and password.
- The operator will log in to NucleoView™ NC-200™ using their personal credentials.
- Data is acquired.
- NucleoView™ is closed, or the log-in screen will appear after a fixed amount of time.

Use third-party software to protect local files

Shell replacement software, or kiosk software, can be used to prevent access to Windows files and configuration. Instead of the Windows Explorer shell (start menu, desktop icons, taskbar), the user will see an alternative Shell, that only has icons for the programs the operators is allowed to launch. Access to the Windows file browser is blocked.

There are multiple software products that may be used in combination with NucleoView™ NC-200™. Secure Desktop 10 from Visual Automation is one such solution.

Securing data storing files on a remote server

Remote data storage can be used as a strategy to secure the 'NucleoView Data Folder'. By either a) configuring NucleoView™ to save data on a remote file server, or b) backing up data from the local hard drive to a remote server.

The remote data is considered the authoritative copy of the files and changes to the local files after data acquisition will be ignored, or flagged for investigation.

Terms and Acronyms

Term / Acronym	Description
'NucleoView Data Folder'	Folder that is defined as receiving data recorded by NucleoView
Active Directory	Active Directory (AD) is a Microsoft directory service that among other things are used for authentication of users and computers in a Windows domain network.
'21 CFR part 11 module'	A collection of software functionalities, that are made available to the user after purchasing and installing a '21 CFR part 11 license'
'21 CFR part 11 mode'	NucleoView operated when '21 CFR part 11' are activated (see Configuration Section)

Product Notes

The NucleoCounter® NC-200™ 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-200™ instrument is not considered a Medical Device and was not designed or validated according to 21 CFR Part 820 (GMP for Medical Devices).

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