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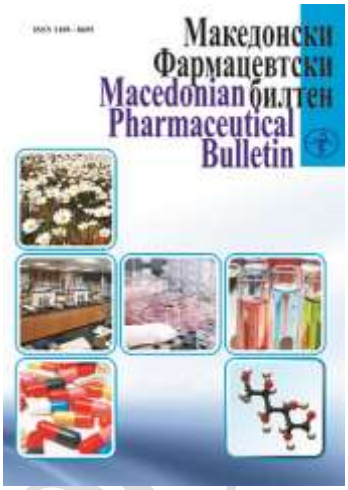

Title: Functional risk assessment as part of the validation in the implementation of chromatography data system

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Functional risk assessment as part of the validation in the implementation of chromatography data system

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Abstract

A Chromatography Data System (CDS) is a complex software that can be configured to the specific needs of the user's business process. As such it falls into the Good Automated Manufacturing Practice (GAMP) 5 Category 4 – Configured Products. The validation process is planned and follows along the phases proposed by GAMP 5 for configured products.

The Risk assessment stage of the CDS validation process is to carry out a risk assessment of each function of the User Requirements Specification (URS) determined on if the function is regulatory risk critical or not. The functional risk assessment is made according to the method-Failure Mode and Effects Analysis (FMEA).

The Overall Risk resulting from the Risk Assessment has identified all potential failures requiring mitigating actions/controls. Mitigating actions and testing controls during the PQ phase is implemented.

The final Overall Risk after implementation of Mitigating actions and testing controls during the PQ phase is not more than Medium.

Keywords: chromatography data system, validation of the CDS Software, risk assessment, laboratory data integrity

Introduction

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The integrity of laboratory data is crucial for audits and regulatory inspections. Compromised data impacts a manufacturer's bottom line and threatens the availability of therapeutic medicines. The industry is facing great pressure to produce pharmaceuticals at low cost while adhering to the highest safety and data integrity expectations. To meet the challenging demands of quality-driven, internal inspectors and safety-driven, government regulators, manufacturers are turning to innovative Information Technology (IT) infrastructures (ISPE's Annual meeting, 2014). One of the aims of data governance should not be a way to keep the regulators happy, but to ensure the survival and growth of organizations (McDowall, 2016; McDowall, 2017). So, from the perspectives of regulatory compliance and practical use of the system, a networked Chromatography Data System (CDS) solution is the only option that should be considered for regulated laboratories (McDowall and Burgess, 2015). CDS is vital for efficient and reliable operation of any modern chromatography laboratory – it must manage all the analytical processes from instrument control, to raw data storage and processing, right through to generating the final results. CDS using validated reports and calculations should be classified as Good Automated Manufacturing Practice (GAMP) category 4. This means that all commercial CDS software's are required to have configurations to acquire data from the chromatography instruments from different vendors, which are connected into the CDS, and to control those instruments. Therefore, the objectives regarding the life cycle and the validation of the CDS should be based on GAMP "V model" (GAMP 4, 2001).

The aim of this paper will be the Functional Risk Assessment as part of the validation, planned for implementation of the CDS (McDowall, 2006) which is setup at laboratories at drug manufacturing industry. CDS is based on Chromeleon™ Chromatography Data System (CDS) software from vendor Thermo Scientific™ (thermofisher.com). It will be used by the Research and Development (R&D), Quality Control (QC) and Quality Assurance (QA) departments for their chromatographic analyses and any required reporting or evaluation of obtained data.

The objective of the Functional Risk Assessment is to evaluate requirements as defined in the User Requirements Specification regarding their GMP risks and to identify mitigating actions or other controls to be established to reduce the risk identified.

Validation of the CDS Software

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Life cycle approach to validation of the CDS Software

The CDS based on Chromeleon Software will be used within a GMP regulated environment and as such it falling under the regulatory requirements (EudraLex, 2011; FDA, 2003; FDA, 2016; MHRA, 2015; MHRA, 2018; OMCL, 2018; WHO, 2016) and industry guidelines and standards (GAMP, 2005; GAMP, 2005; GAMP, 2012a; GAMP, 2012b; GAMP, 2017). The R&D, QC and QA departments are able to connect to this central infrastructure via the corporate network locally or remotely. They operate their Chromatographic instruments via Instrument PC (IPC) computers but also have workstations as separate access points to the system. QA is provided with access to the relevant data also via workstations. There are two environments maintained, one for test and one for production use. Both environments have their own Chromeleon Sofware installed.

To complete a System Life Cycle phase, it is required to have the phase related documents in an approved state. Based on the classification of the CDS as Configured Product (GAMP 5 Category 4) the following Life Cycle Approach has been chosen:

1. *Planning Phase*

During the planning Phase a CDS, Chromeleon has been selected based on the URS Project Documentation software system implementation. The Project has been planned and a Project Organization has been setup. The Planning Phase will be concluded by approving the systems Validation Plan.

2. *Specification Phase*

During the Specification Phase a User Requirements Specification is being produced detailing the general CDS user requirements as well as more specific implementation requirements resulting from the laboratory business processes. The URS Project Documentation software system implementation, used during the Software Selection process will serve as basis of Validation Plan.

A Risk Assessment of the planned systems functions will then be carried out based on the user requirements.

A Functional Specification will be produced, covering any functionality used that is not covered by the Chromeleon Standard Documentation.

The planned Configuration of the System will then be described in a Configuration Specification.

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The Specification Phase can be concluded once all the related documents have been approved. An additional formal design review is not planned to be executed as a mandatory task.

3. Installation and Configuration Phase

During this phase the system will be installed and configured as described in the Specification Phase.

To conclude this phase, the verification documents required in the next phase need to be available in approved versions.

4. Verification Phase

4.1. Installation Qualification

The Installation will be verified via an Installation Qualification making use of Chromeleon Standard Documentation where possible.

4.2. Operational Qualification

The Operational Qualification can be started once Installation Qualification has been completed and documented in an approved Installation Qualification Report.

The correct configuration of the system and the covering of the user requirements will be verified in this phase. Functional/Black-Box testing is deemed sufficient for that purpose. The depth of the testing will be based on the results of the Risk Analysis and will include positive, negative and limit testing as required. Where possible testing will follow the business processes and related procedures.

It is not the goal of this verification to test standard Chromeleon functionality.

5. Validation Completion Acceptance Criteria

The Validation is completed once the Validation Report has been approved. To allow acceptance of the validation it is required that all validation phases have been completed successfully including the required documentation.

In case of open issues, they have to be assessed as part of the validation report and a plan has to be provided how, when and by whom they will be resolved and how follow up will be guaranteed.

A release of the system is possible only when all issues deemed relevant for the correct functioning of the system have been resolved or robust workarounds have been defined.

6. System Release

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The System will be released for production use by a separate formal step after validation is completed, initial users and support personnel have been trained and the validation system has been prepared to be used as production system.

Further Rollout of the system will be planned and followed up in separate Rollout Plans.

The objectives regarding the life cycle and the validation of the CDS should be based on GAMP "V model" (DeSpautz et al., 2008). As shown in the figure 1 (with the green division line), there is a division between the user of the CDS software and the supplier of the CDS software. The left-hand side of the V represents the design stages of the CDS software, the bottom is the software installation stage and the right-hand side of the V represents the testing stages of the life cycle.

Fig. 1

This V model is used to generate the validation deliverables during the CDS development life cycle and the documents that are produced during the CDS development life cycle are presented in Table 1. The key validation deliverable, the Functional Risk Assessment will be discussed in more detail in the next sections. Taken together all of these documents will provide the validation package to support the system release declaration that the chromatography data system is fit for purpose, validated and released for production use.

Table 1

Risk Assessment Approach to validation of the CDS Software

The chosen risk assessment approach (FDA, 2006; ICH, 2005; WHO, 2013) aims to establish controls such that the combination of severity, probability and detectability of failures is reduced to an acceptable level, with:

- Severity possible impact of failure, as shown in Table 2;
- Probability likelihood of the failure to happen, as shown in Table 3;
- Detectability likelihood of the failure to be detected timely, as shown in Table 4.

The following definitions will apply throughout this functional risk assessment:

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Table 2

Table 3

Table 4

Each potential failure is assessed in 2 steps:

1. Severity of impact on patient safety, product quality and data integrity against Probability of the failure to happen resulting in a Risk Class, as shown on Figure 2.

2. Risk Class against Detectability (likelihood of detection) resulting in an Overall Risk, as shown on Figure 3.

Fig. 2

Fig. 3

The Overall Risk resulting from the Risk Assessment is used to identify potential failures requiring mitigating actions/controls to be implemented.

These actions/controls are typically aimed at:

- eliminating risk through process or system redesign
- reducing the overall risk by reducing the probability of a failure occurring
- reducing the overall risk by increasing the in-process detectability of the failure

Mitigating actions should be defined where possible even when the Overall Risk is already at an acceptable level.

The final Overall Risk after implementation of mitigation actions/controls should be no more than Medium.

Results and discussion

The Risk assessment stage of the CDS validation process is to carry out a risk assessment of each function of the User Requirements Specification (URS) determined on if the function is regulatory risk critical or not. The tables from the URS and the Functional specification have additional columns added to, in order to evaluate the regulatory risk. The functional risk

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assessment following the Failure Mode and Effects Analysis (FMEA) method (Stamatis, 2003; Spectroscopy Editors, 2006) will be executed based on the requirements described in the URS. The risk assessment has focused on the identification of functions with impact on patient safety, product quality and data integrity and specifically to identify any areas of high risk requiring additional controls. It has also been a goal of the risk assessment to allow a more risk focused functional testing.

The risk assessment outlined here is to take only those functions related to functional requirements that are classified as critical and consider them for testing in the performance qualification phase (PQ) of the validation. In this way, requirements are prioritized and classified for risk and the most critical one can be traced to the PQ test script.

The Overall Risk resulting from the Risk Assessment has identified all potential failures requiring mitigating actions/controls. Mitigating actions and testing controls during the PQ phase should be implemented.

Mitigating actions has not been defined where the Overall Risk is already at an acceptable level. The final Overall Risk after implementation of Mitigating actions and testing controls during the PQ phase is not more than Medium.

Table 5

Conclusion

The Functional Risk Assessment as part of the validation process for the CDS implementation has been completed. The requirements as defined in the User Requirements Specification have been evaluated regarding their GMP risks and mitigating actions or other controls has been identified. The final scope of the validation process has been completed. The objectives of this validation process were to have a GMP compliant CDS in place which can be easily expanded to include more users, instruments; laboratories and sites while maintaining its compliant state. All validation phases have been completed successfully including the required documentation.

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References

DeSpautz, J., Kovacs, K.S., Werling, G., 2008. GAMP Standards for validation of automated systems. Available at: https://www.academia.edu/39999095/GAMP_Standards_For_Validation_Of_Automated_Systems_Strategies_to_validate_automated_systems_while_balancing_internal_and_external_demands_Whats_GAMP.

European Commission Health and Consumers Directorate-General, Eudralex, 2011. The rules governing medicinal products in the European Union, Volume 4: Good manufacturing practice, Medicinal products for human and veterinary use, Part I and Annexes specifically - Annex 11 - Computerized systems. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/annex11_01-2011_en.pdf.

Food and Drug Administration (FDA), 21 Code ofFederal Regulations (CFR) Part 11, 2003 (up-to-date version eCFR). Part 210 Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; General, Part 211 Current good manufacturing practice for finished pharmaceuticals. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1.

Food and Drug Administration (FDA), 2006. Guidance for industry: Q9 Quality risk management. Available at: https://www.fda.gov/media/71543/download.

Food and Drug Administration (FDA), 2016. Guidance for industry: Data integrity and compliance with cGMP. Available at: https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf.

*Corresponding author email: mivanoska1@alkaloid.com.mk

Good Automated Manufacturing Practice (GAMP), 2001. Guidelines version 4. International society for pharmaceutical engineering (ISPE), Tampa, Florida.

Good Automated Manufacturing Practice (GAMP), 2005. Good practice guide: Validation of laboratory computerized systems. International society for pharmaceutical engineering (ISPE).

Good Automated Manufacturing Practice (GAMP) 5, 2008. Good practice guide: A risk-based approach to compliant GxP computerized systems. International society for pharmaceutical engineering (ISPE).

Good Automated Manufacturing Practice (GAMP), 2012a. Good Practice Guide: A risk-based approach to GxP compliant laboratory computerized systems.International society for pharmaceutical engineering (ISPE).

Good Automated Manufacturing Practice (GAMP), 2012b. Good Practice Guide: A Risk-Based Approach to testing of GxP Systems.International society for pharmaceutical engineering (ISPE).

Good Automated Manufacturing Practice (GAMP), 2017. Good Practice Guide: Records and Data Integrity.International society for pharmaceutical engineering (ISPE).

International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH), 2005. Harmonised Tripartite Guideline: Quality Risk Management Q9. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf.

McDowall, R.D., 2006. A practical and cost effective risk assessment for the validation of commercial laboratory computerized systems. Applied Clinical Trials. Available at: https://alfresco.ubm-us.net.

McDowall, R.D., Burgess, C., 2015. The ideal chromatography data system for a regulated laboratory, Part II: System architecture requirements. LCGC North America 33(10), 782-785. Available at: http://www.chromatographyonline.com/ideal-chromatography-data-system-regulated-laboratory-part-ii-system-architecture-requirements.

McDowall, R.D., 2016. Validation of chromatography data systems: Ensuring data integrity, meeting business and regulatory requirements, second ed. Royal Society of Chemistry, Cambridge.

*Corresponding author email: mivanoska1@alkaloid.com.mk

McDowall, R.D., 2017. Understanding data governance, Part II. Spectroscopy, 32(4), 12–18.

Medicines and Healthcare products Regulatory Agency (MHRA), 2015. GMP Data integrity definitions and guidance for industry. Available at: http://www.spectroscopyonline.com/understanding-data-governance-part-ii.

Medicines and Healthcare products' Regulatory Agency (MHRA), 2018. GXP Data integrity guidance and definitions. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf.

Official Medicines Control Laboratory (OMCL) Guideline, 2018. Validation of computerized systems, PA/PH/OMCL (08) 69 R7. Available at: https://www.edqm.eu/sites/default/files/guidelines-omcl-computerised_systems-core_document-march2018.pdf.

Stamatis, D.H., 2003. Failure mode and effect analysis. FMEA from theory to execution, 2nd ed. Milwaukee, American Society for Quality, Quality Press.

Spectroscopy Editors, 2006. Validation of spectrometry software: Risk analysis methodologies for commercial spectrometer software. Spectroscopy, 21(7). Available at: http://www.spectroscopyonline.com/validation-spectrometry-software-risk-analysis-methodologies-commercial-spectrometer-software?id=&sk=&date=&%0A%09%09%09&pageID=2.

World Health Organization (WHO), 2013.Technical report series, Guidelines on quality risk management, 981, Annex 2. Available at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf.

World Health Organization (WHO), 2016. Technical report series, Guidance on good data and records management practices, 996, Annex 5. Available at: https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf.

ISPE's Annual meeting, 2014. Making the information systems connection, Available at: https://ispe.org/pharmaceutical-engineering/ispeak/making-information-systems-connection-ispes-annual-meeting.

*Corresponding author email: mivanoska1@alkaloid.com.mk

Product literature, Brochures, eBooks, Technical notes, White papers, 2018. Available at: https://www.thermofisher.com/chromeleon.

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Резиме

Проценка на ризик за функционалност како дел од валидација при имплементација на систем за хроматографски податоци

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Клучни зборови: систем за хроматографски податоци, валидација на CDS софтвер, ризик анализа, интегритет на податоци во лабораторија

Систем за хроматографски податоци или CDS е комплексен софтвер кој може да се конфигурира за специфичните потреби на деловниот процес на корисникот. Како таков, спаѓа во GAMP 5 Категорија 4 - Конфигурирани производи. Процесот на валидација е планиран и ги следи фазите предложени од GAMP 5 за конфигурирани производи.

Фазата на проценка на ризикот од процесот на валидација на CDS е да изврши проценка на ризикот за секоја функција од спецификацијата за кориснички барања (URS). Проценката на ризикот за функционалноста е направена по методот Failure Mode and Effects Analysis (FMEA).

Вкупниот ризик кој произлегува од проценката на ризик ги идентификува сите потенцијални пропусти кои бараат корективни активности/контроли. Корективните мерки и контролни тестови се имплементирани за време на PQ фазата.

Конечниот вкупен ризик по спроведувањето на корективните мерки и контролни тестови во текот на PQ фазата не е повеќе од средно ниво.

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Table 1. Validation deliverables for CDS

Validation Deliverable
Chromeleon Documentation - Validation Plan
Chromeleon Documentation - User Requirements Specification
Chromeleon Documentation - Functional Requirements Specification
Chromeleon Documentation - System Design Overview
Chromeleon Documentation - Configuration Specification
Chromeleon Documentation - Functional Risk Assessment
Chromeleon Documentation - Installation Qualification Plan and Protocols
Chromeleon Documentation - Installation Qualification Plan and Protocols (executed) including Installation Summary Report
Chromeleon Documentation - Operational Qualification
Chromeleon Documentation - Operational Qualification (executed) including OQ Summary Report
Chromeleon Documentation - Trace Matrix
Chromeleon Documentation - Validation Report
Chromeleon Documentation - System Release

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Table 2. Severity Levels

Severity Level	Definition
High	Potential severe impact on patient safety and/or product quality
Medium	Potential impact on patient safety and/or product quality and/or major compliance issue
Low	No impact on patient safety and/or product quality and/or minor compliance issue

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Table 3. Probability of Occurrence Level

Probability Level	Definition
High	Likely to occur – more than twice a year
Medium	Likely to occur very rarely - once or twice a year
Low	Unlikely - expected to occur less than once a year

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Table 4. Probability of Detection Levels

Detection Level	Definition
High	Likely to be detected promptly – close to 100% detection expected
Medium	Likely to be detected, maybe slightly delayed – more than 75% detection expected
Low	Potentially to be missed or to be detected with severe delay – less than 75% detection expected

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Table 5. Functional risk assessment for Functional Requirements

Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
UR-XXX	Description of the User Requirement						
FS-YYY	Description of the Functional Specification						
Potential Failure Mode	Description of the potential failure	L/M/H	L/M/H	L/M/H	L/M/H	N/A	L/M/H
Potential Effect	Description of the potential effect						
UR-1	It must be possible to configure and operate the instruments from within the system.						
FS-1	Instruments can be added, removed and configured via the Chromeleon Instrument Configuration Manager. Operation is possible via the Chromeleon Console with ePanel tabs allowing direct monitoring and control options for individual instrument modules.	Low	Low	High	Low	N/A	Low
Potential Failure Mode	Instruments cannot be configured from the system.						
Potential Effect	Data acquisition cannot be performed or instrument cannot be controlled.						
UR-2	It must be possible to monitor instruments.						
FS-2	Instruments can be added, removed and configured via the Chromeleon Instrument Configuration Manager. Operation is possible via the Chromeleon Console allowing direct monitoring and control options for individual instrument modules.	Medium	Low	Medium	Low	N/A	Low
Potential Failure Mode	Instrument cannot be monitored. From within the system.						
Potential Effect	Issue with system will not be noticed timely.						
UR-3	It must be possible to select an instrument to be used for an analysis from within the system.						
FS-3	Instruments to be used for an analysis can be selected e.g. from the Sequence Status Bar.	Low	Low	High	Low	Exemplary testing in OQ -> Detectability = High	Low
Potential Failure Mode	Instrument cannot be selected from within the system.						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
Potential Effect	Data acquisition cannot be performed or instrument cannot be controlled.						
UR-4	It must be possible to define and manage processes for automating laboratory processes related to chromatographic analysis.						
FS-4	Chromeleon is a software package for chromatography instrument control, data acquisition, data management and reporting with: • True Client/server architecture for data acquisition and instrument control • Access to data via a network allowing the sharing of data between different laboratories and/or different company sites • Microsoft style Console and spreadsheet based Report Designer • Instrument control for e.g. HPLC and GC instruments • GLP/GMP and 21 CFR part 11 compliant audit trails/history; documentation of all events and user actions • Proven algorithms for automatic integration of difficult chromatograms • Workflow management via eWorkflows tool • Excel-like spreadsheet Report Designer; custom calculations, formulas and charts • User management for the administration and tuning of user privileges, access rights, etc. Reference: CM-FS Chapter 2, Overview of the System.	Low	Low	High	Low	Exemplary testing in OQ -> Detectability = High	Low
Potential Failure Mode	Chromatographic analysis related laboratory processes cannot be automated.						
Potential Effect	More time is required for laboratory processes.						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
UR-5	It must be possible to support automated method development software solutions (e.g. QbD software)	Medium	Low	Medium	Low	Exemplary testing in OQ ; Communicate with maintenance, IT and external companies involved -> Detectability = Medium	Low
FS-5	Interfaces to other systems are available.						
Potential Failure Mode	No Interface to other systems, e.g. Fusion QbD is available.						
Potential Effect	Data might need to be manually imported to other systems, which could lead to mistakes.						
UR-6	It must be possible to have different processes for different purposes.						
FS-6	Chromeleon is a software package for chromatography instrument control, data acquisition, data management and reporting with: • Access to data via a network allowing the sharing of data between different laboratories and/or different company sites • Instrument control for e.g. HPLC and GC instruments • GLP/GMP and 21 CFR part 11 compliant audit trails/history; documentation of all events and user actions • Proven algorithms for automatic integration of difficult chromatograms • Excel-like spreadsheet Report Designer; custom calculations, formulas and charts • User management for the administration and tuning of user privileges, access rights, etc.	High	Low	Low	High	Exemplary testing in OQ Appropriate training of the users -> Detectability = Medium	Medium
Potential Failure Mode	It is not possible to define different processes for different purposes.						
Potential Effect	The user will have more options increasing the likelihood of mistakes.						
UR-7	It must be possible to define and manage groups of injections as Sequence Template.	High	Low	Medium	Medium	Exemplary testing in OQ -> Detectabili	Medium
FS-7	Sequences Templates can be defined containing						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
	the injection list (groups of injections), the associated items (e.g. Instrument Method(s), Processing Method(s), View Settings, Report Template(s), Spectral Library), the custom variables and the custom formulas.						
Potential Failure Mode	Sequence Templates cannot be defined.						
Potential Effect	Sequences need to be created individually increasing the likelihood of mistakes.						
UR-8	It must be possible to differentiate Sequence Template Status (Draft, Approved).						
FS-8	There is no status assigned by Chromeleon to a Sequence Template. To differentiate between Sequence Templates in different development / approval status a process is defined where the Sequence Templates will be stored in different folders. Key User role will be able to create Sequence Templates in a draft folder and move them after approval to the approved folder.	High	Low	Low	High	Exemplary testing in OQ -> Detectability = Medium	Medium
Potential Failure Mode	It is not possible to differentiate between Draft and Approved Sequence Templates.						
Potential Effect	Analyst might work with Draft Sequence Template.						
UR-9	It must be possible to select a Sequence Template from a group of approved Sequence Templates.						
FS-9	There is no status assigned by Chromeleon to a Sequence Template. To differentiate between Sequence Templates in different development / approval status a process is defined where the Sequence Templates will be stored in different folders. Key User role will be able to create Sequence Templates in a draft folder and move them after approval to the approved folder.	High	Low	Low	High	Exemplary testing in OQ Appropriate training of the users -> Detectability = Medium	Medium
Potential	Sequence Template cannot be selected from a						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
Failure Mode	group of approved Sequence Templates.						
Potential Effect	Analyst might work with Draft Sequence Template.						
UR-10	It must be possible to create and maintain eWorkflows.						
FS-10	An eWorkflow allows to automatically create a Sequence with all required objects and settings. An eWorkflow can be created and maintained using the eWorkflow Editor.	Medium	Low	High	Low	Appropriate training of the users	Low
Potential Failure Mode	eWorkflows cannot be created.						
Potential Effect	The user will have more options increasing the likelihood of mistakes.						
UR-11	It must be possible to provide the analysts with approved eWorkflows.						
FS-11	An eWorkflow is created in status In Development. The eWorkflow can take on different states from In Development -> Ready -> Approved -> Retired. The developer of the eWorkflow is able to move it to a next state or demote it back to the previous state.	Low	Low	High	Low	Appropriate training of the users Appropriate training of system administrators on user privileges	Low
Potential Failure Mode	eWorkflow cannot be moved to Approved state.						
Potential Effect	Analyst might not be able to use an eWorkflow.						
UR-12	When creating a Sequence from a Sequence Template it must be possible to edit the Injection List.						
FS-12	A Sequence Template can be selected from the approved Sequence Template folder and saved as working version of the Sequence to a different folder. The Sequence can then be edited as required, e.g. Injection List, Instrument Method, Processing Method and Report Template.	High	Low	High	Low	Exemplary testing in OQ Appropriate training of the users Appropriate training of system administrators on user privileges -> Probability = Low	Low

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
	Additional required information can be entered as well, e.g. sample names, quantities, retention time, batch number.						
Potential Failure Mode	Injection List cannot be edited.						
Potential Effect	Analysis cannot be executed as required.						
UR-13	When creating a Sequence from a Sequence Template it must be possible to edit the Instrument and Processing Method.						
FS-13	A Sequence Template can be selected from the approved Sequence Template folder and saved as working version of the Sequence to a different folder. The Sequence can then be edited as required, e.g. Injection List, Instrument Method, Processing Method and Report Template. Additional required information can be entered as well, e.g. sample names, quantities, retention time, batch number.	High	Low	High	Low	Appropriate training of the users ;Appropriate training of system administrators on user privileges -> Probability = Low	Low
Potential Failure Mode	Instrument and/or Processing Method cannot be edited.						
Potential Effect	Analysis cannot be executed as required.						
UR-14	When creating a Sequence from a Sequence Template it must be possible to edit the Report Template.						
FS-14	A Sequence Template can be selected from the approved Sequence Template folder and saved as working version of the Sequence to a different folder. The Sequence can then be edited as required, e.g. Injection List, Instrument Method, Processing Method and Report Template. Additional required information can be entered as well, e.g. sample names, quantities, retention time, batch number.	Low	Low	High	Low	Appropriate training of the users	Low

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
Potential Failure Mode	Report Template cannot be edited.						
Potential Effect	Analysis cannot be reported as required.						
UR-15	When using Sequence Templates it must be possible to enter additional information, e.g. sample names, quantities, retention time, batch number and/or data to other variables.						
FS-15	A Sequence Template can be selected from the approved Sequence Template folder and saved as working version of the Sequence to a different folder. The Sequence can then be edited as required, e.g. Injection List, Instrument Method, Processing Method and Report Template. Additional required information can be entered as well, e.g. sample names, quantities, retention time, batch number.	Low	Low	High	Low	Appropriate training of the users	Low
Potential Failure Mode	Additional Information cannot be entered.						
Potential Effect	Analysis cannot be reported as required.						
UR-16	It must be possible to run a Sequence.						
FS-16	A Sequence can be selected and started from the Chromeleon Console.						
Potential Failure Mode	Sequence cannot be started from the Chromeleon Console	Low	Low	High	Low	Exemplary testing in OQ -> Probability = Low	Low
Potential Effect	Analysis cannot be executed as required.						
UR-17	It must be possible to check the correctness of and complete the execution of a Sequence.						
FS-17	Execution of a Sequence can be monitored online.	High	Low	High	Low	Exemplary testing in OQ -> Probability = Low	Low

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
Potential Failure Mode	Sequence execution cannot be monitored online.						
Potential Effect	Issues with the execution of the sequence might not be detected timely.						
UR-18	It must be possible to attach additional documentation to a Sequence.						
FS-18	Additional documentation can be added to a Sequence by right-clicking on the Associated Items area and selecting Add Attachment.	Low	Low	High	Low	Appropriate training of the users	Low
Potential Failure Mode	No additional documentation can be added to the sequence.						
Potential Effect	Additional documentation has to be stored and managed at a different place.						
UR-19	It must be possible to make a Sequence Read-Only.						
FS-19	A sequence can be protected by setting it to read-only (e.g. via read-only checkbox on the sequence properties window).	High	Medium	Medium	High	Exemplary testing in OQ -> Probability = Low	Medium
Potential Failure Mode	Sequence cannot be protected by setting it to read-only.						
Potential Effect	Changes to finalized sequence might be applied by mistake.						
UR-20	It must be possible to create a Sequence without using an approved Sequence Template.						
FS-20	A Sequence can be created from the Chromeleon Console via Create Sequence.	Low	Low	High	Low	Exemplary testing in OQ -> Probability = Low	Medium
Potential Failure Mode	Sequence cannot be created without approved Sequence Template.						
Potential Effect	Flexibility is lost as always an approved Sequence Template has to be created first.						
UR-21	It must be possible to edit a Sequence after its starting including Processing Method, Report	High	Low	High	Low	N/A	Low

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
	Template and Instrument Method. It must also be possible to add injections.						
FS-21	A sequence can be controlled and monitored while being executed. Execution can be paused, resumed or stopped completely. Changes can then be applied as required.						
Potential Failure Mode	Sequence cannot be edited after start of execution.						
Potential Effect	Reduced flexibility as short-term changes cannot be applied.						
UR-22	It must be possible to differentiate the Status an Instrument or Processing Method is in (Draft, Approved).						
FS-22	There is no status assigned by Chromeleon to an Instrument- or Processing Method. To differentiate between Methods in different development / approval status a process is defined where the Methods will be stored in different folders. Key User role will be able to create Methods in a draft folder and move them after approval to the approved folder.	High	Low	Low	High	Exemplary testing in OQ -> Detectability = Medium	Medium
Potential Failure Mode	Status of Instrument / Processing Method cannot be differentiated.						
Potential Effect	A method in Draft status might be used.						
UR-23	It must be possible to select/edit a Method from a group of approved Methods. (Instrument / Processing).						
FS-23	There is no status assigned by Chromeleon to an Instrument- or Processing Method. To differentiate between Methods in different development / approval status a process is defined where the Methods will be stored in different folders. Key User role will be able to	Medium	Low	Medium	Medium	Exemplary testing in OQ -> Detectability = Medium	Low

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
	create Methods in a draft folder and move them after approval to the approved folder.						
Potential Failure Mode	It is not possible to select / edit an approved method.						
Potential Effect	A method in Draft status might be used or n approved method cannot be edited						
UR-24	It must be possible to move a Method to another storage location which is part of the system.						
FS-24	A user will be able to move a Method to another storage location as long as the roles privileges and the users access groups permit.						
Potential Failure Mode	Method cannot be moved to another storage location.	Low	Low	High	Low	Execution of IQ on Roles and Access Groups, Exemplary testing in OQ -> Detectability = High	Low
Potential Effect	Methods cannot be shared within the system with different user groups and/ or sites.						
UR-25	It must be possible to copy a Method.						
FS-25	A user will be able to copy a Method as long as the roles privileges and the users access groups permit such action.						
Potential Failure Mode	Method cannot be copied.	Low	Low	High	Low	Execution of IQ on Roles / Privileges, Exemplary testing in OQ -> Probability = Low	Low
Potential Effect	Methods cannot be shared or used as basis for the development of a new method.						
UR-26	It must be possible to use electronic signatures.						
FS-26	Chromeleon supports the use of electronic signatures for Submit, Review and Approve for Sequences.						
Potential Failure Mode	No electronic signatures can be used.	High	Low	Medium	Medium	Execution of IQ on Electronic Signature settings.Exemplary testing in OQ -> Detectability = High	Low
Potential Effect	Required signatures could not be managed by the						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
	system and the data would not be automatically protected against change.						
UR-27	It must be possible to define processes including process steps requiring electronic signatures.	High	Low	Medium	Medium	Execution of IQ on Electronic Signature settings. Exemplary testing in OQ -> Detectability = High	Low
FS-27	Chromeleon allows defining the required signatures as part of the Sequence Properties if Modify Signature Requirements has been granted. By default electronic signatures for Submit, Review and Approve are enabled.						
Potential Failure Mode	It is not possible to define process steps requiring an electronic signature.						
Potential Effect	Required signatures could not be managed by the system and the data would not be automatically protected against change.						
UR-28	It must be possible to lock a Sequence using an electronic signature after an analysis has been completed. (Submit).	High	Low	Medium	Medium	Execution of IQ on Electronic Signature settings. Exemplary testing in OQ -> Detectability = Medium	Medium
FS-28	After a Sequence has been electronically signed, e.g. Submit, the Sequence cannot be modified without revoking the signature first.						
Potential Failure Mode	Sequence data is not automatically protected after Submit signature has been executed.						
Potential Effect	Sequence data could be modified by mistake.						
UR-29	It must be possible to ensure that Submitter, Reviewer and Approver are different users.	High	Low	Medium	Medium	Execution of IQ on Electronic Signature settings.	Medium
FS-29	As a User Database Policies setting it will be defined that Submitter, Reviewer and Approver						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
	have to be different users.						
Potential Failure Mode	Submitter, Reviewer and Approver are not required to be different users Analyst could review / approve his own activities / results.						
Potential Effect							
UR-30	It must be possible to e-sign to complete review.						
FS-30	Chromeleon allows defining the required signatures as part of the Sequence Properties if Modify Signature Requirements has been granted. By default electronic signatures for Submit, Review and Approve are enabled.	High	Low	High	Low	Execution of IQ on Electronic Signature settings. Exemplary testing in OQ -> Probability = Low	Low
Potential Failure Mode	It is not possible to e-sign to complete review.						
Potential Effect	A required signature could be missing.						
UR-31	It must be possible to e-sign to complete approval.						
FS-31	Chromeleon allows defining the required signatures as part of the Sequence Properties if Modify Signature Requirements has been granted. By default electronic signatures for Submit, Review and Approve are enabled.	High	Low	High	Low	Execution of IQ on Electronic Signature settings. Exemplary testing in OQ -> Probability = Low	Low
Potential Failure Mode	It is not possible to e-sign to complete approval.						
Potential Effect	A required signature could be missing.						
UR-32	It must be possible to remove an electronic signature and the associated locked state.						
FS-32	After a Sequence has been electronically signed, e.g. Submit, the Sequence cannot be modified without revoking the signature first.	High	Low	High	Low	Exemplary testing in OQ -> Probability = Low	Low
Potential	It is not possible to remove an electronic						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
Failure Mode	signature.						
Potential Effect	Issues identified in the Review / Approval process could not be corrected.						
UR-33	It must be possible to define and run a Sequence without using formal submit, review and approval steps.						
FS-33	Chromeleon allows defining the required signatures as part of the Sequence Properties if Modify Signature Requirements has been granted. By default electronic signatures for Submit, Review and Approve are enabled.	Medium	Low	High	Low	Exemplary testing in OQ -> Probability = Low	Low
Potential Failure Mode	It is not possible to define and run a Sequence without using formal submit, review and approval steps.						
Potential Effect	Required flexibility would be missing and work could be delayed.						
UR-34	It must be possible to do calculations and statistical evaluations.						
FS-34	Chromeleonis a software package for chromatography instrument control, data acquisition, data management and reporting with: • Access to data via a network allowing the sharing of data between different laboratories and/or different company sites • Microsoft style Console and spreadsheet based Report Designer • Instrument control for e.g. HPLC and GC instruments • GLP/GMP and 21 CFR part 11 compliant audit trails/history; documentation of all events and user actions • Proven algorithms for automatic integration of difficult chromatograms	High	Low	High	Low	N/A	Low

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
	• Workflow management via eWorkflows tool • Excel-like spreadsheet Report Designer; custom calculations, formulas and charts • User management for the administration and tuning of user privileges, access rights, etc.						
Potential Failure Mode	It is not possible to do calculations and statistical evaluations as required.						
Potential Effect	Data measured cannot be evaluated, interpreted and reported as required.						
UR-35	It must be possible to use the system for the qualification testing of the equipment.						
FS-35	The built-in Instrument Installation Qualification (IQ) can be used to perform a general function check which tests the connection from the instrument controller to the instrument.	High	Low	High	Low	Qualification of instruments according to supplier recommendations -> Detectability = High	Low
Potential Failure Mode	System cannot be used for qualification testing of the equipment.						
Potential Effect	The built-in Instrument Installation Qualification (IQ) cannot be used.						
UR-36	It must be possible to create Custom Variables for entering information / values or to be used for calculations.						
FS-36	A Custom Variables Editor is available for defining Custom Variables in the Chromeleon Console.	High	Low	High	Low	Execution of IQ on Roles. Exemplary testing in OQ -> Detectability = High	Low
Potential Failure Mode	Custom Variable / Custom Formulas cannot be created.						
Potential Effect	Data measured cannot be evaluated, interpreted and reported as required.						

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
UR-37 FS-37 Potential Failure Mode Potential Effect	It must be possible to monitor processes. A sequence can be monitored in the work area of the Chromeleon Console when the data category bar is selected. Sequence cannot be monitored. Issues with the execution of the sequence might not be detected timely.	High	Low	High	Low	Exemplary testing in OQ -> Probability = Low	Low
UR-38 FS-38 Potential Failure Mode Potential Effect	It must be possible to use standardized templates for procedures, methods, reports. A user will be able to copy a Method/Report as long as the roles privileges and the user's access groups permit such action, e.g. Key User or Maintenance. Sequences and / or methods need to be created for each analysis increasing the potential of Analyst mistakes. Issues with the execution of the sequence might not be detected timely.Validated Report Templates cannot be prepared reducing the evaluation possibilities and increasing the risk to report wrongly calculated data.	High	Low	High	Low	Execution of IQ on Roles ; Validation of reports and custom fields ; Establishing of SOP for Validation of reports and custom fields in CDS Chromeleon. -> Detectability = High	Low
UR-39 FS-39 Potential Failure Mode	It must be possible to use standardized report templates. Reporting can be standardized by utilizing Report Templates. Standardized reports cannot be used during analyses.	Medium	Low	High	Low	Execution of IQ on Roles ; Validation of reports and custom fields ; Establishing of SOP for Validation of reports and custom fields in CDS Chromeleon.	Low

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Number	Description	Severity	Probablity	Detectability	Overall Risk	Mitigating Action / Control	Final Overall Risk
Potential Effect	Issues with the reporting of results might occur.						
UR-40	Sequence variables defining laboratory specific customized values need to be created into the pre-defined sequence templates.						
FS-40	Sequences Templates can be defined containing the injection list (groups of injections), the associated items (e.g. Instrument Method(s), Processing Method(s), View Settings, Report Template(s), Spectral Library), the custom variables and the custom formulas.	High	Low	High	Low	Execution of IQ on Roles ; Validation of reports and custom fields ; Establishing of SOP for Validation of reports and custom fields in CDS Chromeleon. -> Probability = Low	Low
Potential Failure Mode	Sequence custom variables cannot be created.						
Potential Effect	Reporting of the results is compromized.						

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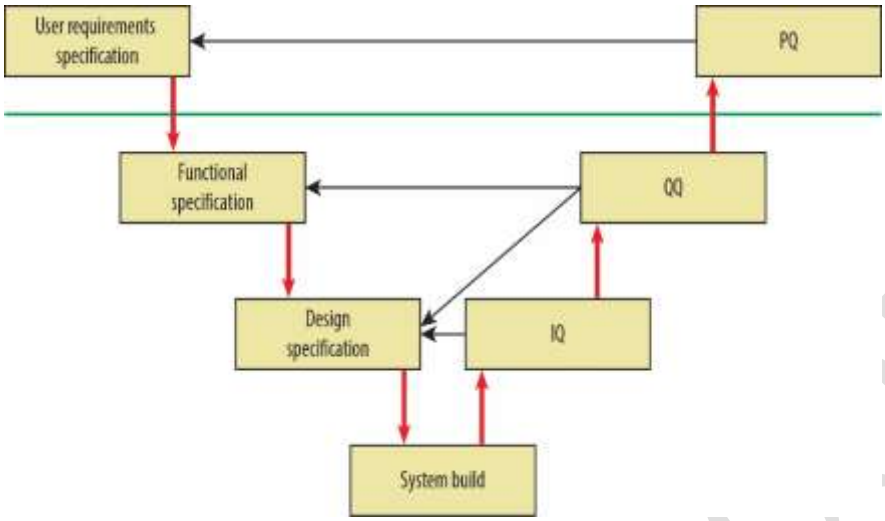

Fig. 1. Chromatography data system development life cycle.

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		Probability		
		Low	Medium	High
Severity	High	2	1	1
	Medium	3	2	1
	Low	3	3	2

Fig. 2. Resulting Risk Class: 1 – High, 2– Medium, 3– Low.

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		Detectability		
		High	Medium	Low
Risk Class	1	2	1	1
	2	3	2	1
	3	3	3	2

Fig. 3. Resulting Overall Risk: 1 – High, 2– Medium, 3– Low.

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