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Optimizing liquid chromatography analysis scheduling in pharmaceutical quality control

– Case study on schedule optimization to improve LC throughput in a QC laboratory

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Master's Thesis | Abstract

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Optimizing liquid chromatography analysis scheduling in pharmaceutical quality control

- Case study on schedule optimization to improve LC throughput in a QC laboratory

This study, commissioned by a Finnish pharmaceutical company, investigates the efficiency of liquid chromatography (LC) analysis in raw material quality control. LC was identified as a major bottleneck due to complexity and resource constraints, affecting lead time and operational performance. The objective was to reduce lead time and improve equipment utilization while ensuring regulatory compliance. A mixed-method case study applying Lean principles and the DMAIC framework was conducted, including process mapping, cycle time analysis, and interview for LC analysts. Results revealed scheduling delays and underutilization of equipment. Implementing Lean tools and DMAIC steps reduced lead times and optimized resource allocation. Findings indicate that Lean and DMAIC methodologies can significantly enhance LC efficiency and provide a foundation for broader process optimization initiatives.

Keywords:

Lean, high-performance liquid chromatography, right time delivery, lead time, scheduling process, pharmaceutical and chemical quality control

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Nestekromatografisten analyysien aikataulutuksen optimointi lääketeollisuudessa

- Tapaustutkimus aikataulutuksen optimoinnista LC-analyysien läpimenoajan parantamiseksi laadunvalvonnassa

Tämä tutkimus, jonka toimeksiantajana on suomalainen lääkeyhtiö, tarkastelee nestekromatografia-analyysien (LC) tehokkuutta raaka-aineiden laadunvalvonnassa. LC tunnistettiin merkittäväksi pullonkaulaksi sen monimutkaisuuden ja resurssirajoitteiden vuoksi, mikä vaikuttaa läpimenoaikoihin ja toiminnan suorituskykyyn. Tavoitteena oli lyhentää läpimenoaikoja ja parantaa laitteiden käyttöastetta säädösten noudattamisen ohella. Tutkimus toteutettiin monimenetelmällisenä tapaustutkimuksena soveltaen Lean-periaatteita ja DMAIC-menetelmää. Aineistonkeruu sisälsi prosessikuvauksen, läpimenoaikojen analyysin ja haastattelun LC analyysien suorittajille tehottomuuksien tunnistamiseksi ja tietoon perustuvien parannusten ehdottamiseksi. Tulokset paljastivat kriittisiä pullonkauloja LC-työnkulussa, kuten aikatauluviiveitä ja laitteiden vajaakäyttöä. Lean-työkalujen ja DMAIC-vaiheiden käyttöönotto johti läpimenoaikojen lyhentymiseen ja resurssien käytön optimointiin. Tutkimus osoittaa, että Lean- ja DMAIC-menetelmät voivat merkittävästi parantaa LC:n tehokkuutta lääkealan laadunvalvonnassa ja toimia perustana laajemmille prosessien optimointihankkeille.

Avainsanat:

Lean, korkean suorituskyvyn nestekromatografia, oikea-aikainen toimitus, läpimenoaika, aikataulutusprosessi, lääkinnällinen ja kemiallinen laadunvalvonta

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Used abbreviations or glossary

AI	Artificial intelligence
API	Active pharmaceutical ingredient
Analyte	The component of a sample to be analyzed (“Analyte”, 2025)
Column	A tube packed with stationary phase used to separate components of a mixture.
CQC	Chemical quality control
DAD	Diode array detector, UV-Vis detector
DMAIC	Structured problem-solving and process improvement methodology used in Lean Six Sigma (Define, Measure, Analyze, Improve and Control).
ERP	Enterprise resource planning
Fimea	Finnish Medicine Agency
FLD	Fluorescence detector
Eluent	Liquid mobile phase, also referred as solvent
GMP	Good manufacturing practices
Gradient	A differential ratio, the change in the quantity of e.g., liquid mobile phases. (“Gradient”, 2025)
Isocratic	A single solvent or a mixture of solvents used as the mobile phase throughout.
HPLC	High-performance liquid chromatography
KPI	Key performance indicator
LC	Liquid chromatography, a separation method for components that are dissolved in liquid solutions. (Ahmed et al., 2023)

Lean	Continuous improvement method, which concentrates on reducing waste in operations. (Tarantino, 2022)
Mobile phase	A moving phase, which interacts with stationary phase in a defined direction. (“Mobile phase”, 2025)
OTD	On time delivery
Ph. Eur.	European Pharmacopoeia, the official collection of standards that defines the quality requirements for medicines and raw materials in the European region.
QC	Quality control
RID or RI	Refractive index detector
Six Sigma	Framework for solving problems in existing processes (Tarantino, 2022)
SOP	Standard operating procedure
Stationary phase	Nonmoving phase, that interacts with analytes to enable their separation (“Stationary phase”, 2025)
UHPLC	Ultra-high-performance liquid chromatography
USP	United States Pharmacopeia, the official collection of standards that defines the quality requirements for medicines and raw materials in the United States.
VWD	Variable wavelength detector, UV-Vis detector
WI	Working instruction
WIP	Work in process

1 Introduction

The thesis commissioner, Orion Pharma, is a Finnish company operating in the pharmaceutical industry. The company has a broad portfolio that includes different kinds of medical and non-medical products. It operates several manufacturing sites in Finland, including subsidiary sites. Because of the wide variety of final products, the number of raw materials used is also extensive. This thesis focuses on chemical quality control laboratory, where more than 700 raw materials are analyzed each year, resulting in thousands of individual batches.

According to the company's strategy, the goal is to improve the efficiency of its operations. One potential way to achieve this is by shortening throughput times in analysis, which directly increases productivity. These goals have been incorporated into each employee's personal annual objectives for 2025. However, the pharmaceutical industry is governed by strict regulations and laws that control all operations, including quality control and analytical methods. In the quality control (QC) of raw materials, liquid chromatography (LC) analysis has been identified as a bottleneck due to its methodological complexity and the time required for system and sample preparation, as well as analysis itself. Additionally, there are limited amounts of equipment and personnel resources.

The aim of this thesis is to identify waste and enhance the efficiency of performing LC analysis by planning for shorter throughput times. Another goal is to increase the utilization rate of LC equipment. Pharmacopeias and other regulations specify the methods used for each pharmaceutical substance. Due to regulatory complexity, modifying pharmacopoeia methods is not within the scope of this thesis. Instead, the focus is on enhancing operational efficiency in LC analysis through Lean Six Sigma principles, while adhering to existing validated methods. The study is a mixed-method case study, which aims to improve efficiency in the quality control laboratory by using both qualitative and quantitative methods. DMAIC process, a Lean Six Sigma problem solving method, is also utilized.

The following research questions support the aims of this thesis by addressing key aspects of planning efficiency, resource optimization, and waste reduction in liquid chromatography analysis:

1. Can lead times in liquid chromatography (LC) analysis be effectively reduced by minimizing operational waste and enhancing planning efficiency?
2. Can resource allocation (instrument and personnel) be optimized to minimize downtime, enhance throughput, and ensure continued compliance with regulatory standards in LC analysis scheduling?

This thesis is conducted as a collaborative effort between two authors, each contributing from their respective areas of expertise in pharmaceutical industry. Sini Korkka has expertise in quality control, particularly in raw material analysis and schedule planning. Salla Vuolamo specializes in high-liquid chromatography (HPLC), analytical methods and quality control practices and processes.

Spelling and grammar corrections in this document were made with the assistance of Microsoft Copilot (Microsoft, 2025)

2 Quality management and continuous improvement in the pharmaceutical industry

Quality management and continuous improvement are closely interconnected concepts. Continuous improvement methodologies include the use of quality tools. The most significant continuous improvement methodologies are statistical process control, total quality management, Lean, and Six Sigma (Laman, 2022).

2.1 Continuous improvement and Lean Six Sigma methods

The Lean philosophy was invented in the 1960’s in Japan. It is developed from Toyota Production System (TPS), and it is a method for continuous improvement which concentrates on identifying and reducing any waste on processes. Lean consists of various tools for maximizing customer value and minimizing waste which together enhance sustainability (Bicheno & Holweg, 2023; Tarantino, 2022).

The history of Six Sigma leans back to the 1980’s and Motorola. Six Sigma offers a structured approach to improving existing processes by solving problems through targeted projects. The key focus in Six Sigma is customers, but also financial efficiency and safety issues by reducing defects and improving quality. Customer focus is also known as VOC, which means voice of customer (International Organization of Standardization, 2011; Tarantino, 2022).

Since Lean and Six Sigma methods support and complement each other, these methods are often used together to perform continuous improvement actions. Industry 4.0 is the more recent concept for continuous improvement. Due to global competition and the evolution of customer needs continuous improvement is currently developing to Industry 5.0, Smart Technologies and Smart Quality Management (Khoshsepehr et al., 2025; Tarantino, 2022).

2.1.1 DMAIC

One of Six Sigma tools is DMAIC, which is often being used for a Six Sigma project for an existing process. The steps of DMAIC are Define, Measure, Analyze, Improve, and Control, which can be seen in Figure 1. In the Define phase shortcomings are named, and the problem is defined. Also, the customer is determined which is the key focus of the Six Sigma approach. The customer can also be internal, for example the next organization in the process. The purpose of Measure phase is to make a data collection plan, evaluate the data collected from various sources, and measure the problem. In the Measure phase success is also defined. There are various measures for defining the problem. One of those measures is On Time Delivery (OTD) which describes the percentage of how many orders are delivered within the target time (International Organization of Standardization, 2011; Tarantino, 2022).

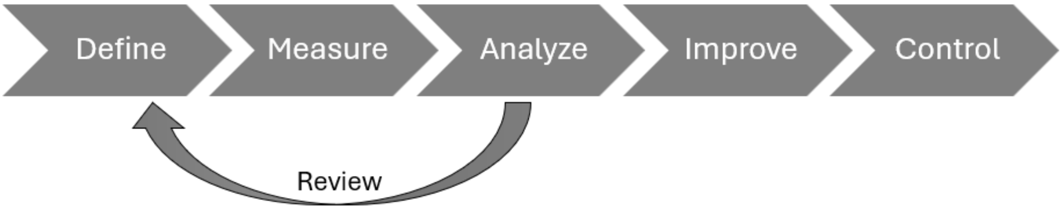


Figure 1. DMAIC process.

The Analyzing phase includes most of the work. The aim is to identify the root causes. The findings of this phase can lead to re-defining of the problem, and it is required to repeat the first three phases until the problem definition is stable. It is important to identify the bottlenecks, and it can be done using detailed processes or value stream maps. Value stream map (VSM) is a flowchart, where process is defined with boxes and arrows with additional information of the process steps (Laman, 2022). One easy option for defining a bottleneck is to compare the actual work time to the whole duration of the process. The difference between those two factors implicates the size of the bottleneck. In the analyzing phase also the improvement opportunities are prioritized (International Organization of Standardization, 2011; Tarantino, 2022).

Improvement phase is for establishing an improvement to the process. This phase includes testing and implementing the potential solutions. Various tools can be used in this phase, such as brainstorming or Failure Mode and Effects Analysis (FMEA). The last phase is the Control phase. It is for determining the effectiveness of the solution and this is the most challenging phase because it requires resources to monitor improvement actions. However, all the five steps need to be followed to achieve successful project. Controlling should be done continuously after the project (International Organization of Standardization, 2011; Tarantino, 2022).

2.1.2 5S

One of the Lean tools is 5S, which means Japanese words*: seiri, seiton, seiso seiketsu*, and *shitsuke*. They can be translated to English: sort, straighten, shine, standardize, and sustain. All these are helpful for optimizing the work area, which reduces waste. Sorting is done to remove all the unnecessary things so that just the necessary ones are kept. Straightening means that every item, tool and equipment has its own place, and the places are marked so everything can be found easily. Shine means keeping the work area in order. Standardizing means that work is done in a specific order every time. The last one “sustain” combines all the previous four together and incorporates them in a daily work life. (Laman, 2022)

5S is an important Lean tool creating a foundation for all improvement acts. (Laman, 2022) It is defined as one of the basic tools in a Lean system. 5S helps to create a well-organized workplace which “enables Lean culture in the organization”. The most important thing about implementing 5S is the commitment of the management and employees. Training is also essential to make the 5S effective. (Vinodh, 2022)

2.1.3 Visual control

Visual control is based on marking and identification of locations for tools, inventory, and safety equipment. It also consists of necessary information people need to maintain their tasks (Laman, 2022). Visual control is a remarkably effective Lean tool which enables employees to outline the overall picture of operations. It can also help to recognize the bottlenecks (Vinodh, 2022). Visual control contains for example trend charts, schedules and problems which are displayed on the wall (Siaudzionis Filho et al., 2018). Visual control is most effective when it is as simple as possible and maintained by hand instead of IT solutions. Avoiding IT-based visual controls is justified since when controlling them by hand the visual controls are near, accessible for everyone, easy to modify and inexpensive to maintain. IT solutions can be available only for a few, they are expensive and can offer old information if not updated on time (Mann, 2014).

2.1.4 Standardized work

Standardized work is one part of 5S and the basis for continuous improvement. It has the aim that each task is performed the same way every time. The key is to engage the people to follow the standardized work instructions and involve them in creating those instructions. When work is standardized, it helps to improve efficiency by reducing cycle time and reaching more consistent quality (Bicheno & Holweg, 2023; Laman, 2022). Although standardized work sounds stable and permanent, as a Lean tool it should be changing over time, since in continuous improvement things are continuously changing (Fredendall & Thürer, 2016).

2.1.5 Waste

In Lean philosophy, waste is defined as any activity or material which is used for producing a product or a service without adding any value. Another definition for waste is any action “that does not affect form, fit, or functionality” (Bicheno & Holweg, 2023). One example of waste is rework. Waste is categorized into seven or eight types, which are overproduction, waiting, motion, transport, over- or no value-processing, inventory, defects, and skills (Bicheno & Holweg, 2023; Laman, 2022).

Overproduction is the most markable waste. Overproduction is performing too much, too early or just in case. It complicates the steady flow of the process. The second most markable waste is waiting, which is also affecting the steady flow. Waste of motion can occur due to layout or human. Motion waste is also a health and safety issue, and it can be repeated multiple times per day without noticing. The waste of transport includes any movement of material. It cannot be fully removed but can be continuously reduced. Excess transport also increases the risk of damage. Transport is also connected to communication. If interacting groups are placed far away from each other, communication is suffering and can cause inadequate quality. The waste of over- or no value processing can be challenging to recognize. It is an action which is done due to, for example, another waste, waiting. Something must be done for a product or service because of waiting for the next step of the process. The waste of excess inventory is a cost for business and can reduce quality and productivity, and there is a risk of obsolescence. Waste of defects is increasing costs and the later the defect is noticed the higher the costs are. Skills, or lost creativity, is the last type of waste and it includes the difficulty to suggest new improvement ideas and implementing them due to inflexible, standardized organizational structures (Bicheno & Holweg, 2023; Laman, 2022).

2.2 Quality control in pharmaceutical industry

Quality management is one crucial part of GMP, and it is extremely important in the pharmaceutical industry. The pharmaceutical products are intended to affect the body system of a patient, so it is crucial to ensure that the products meet their specifications, are safe to use and delivered to patients at right time and with the required quality. If products do not meet their specifications, they can endanger patient safety. Pharmaceutical companies and authorities are obliged to monitor the safety, quality, and effectiveness of products also after the medicine has been brought to the market (Botet, 2015; Jain et al., 2022; Orion Pharma, -c).

Quality control is an essential part of quality management in the pharmaceutical industry. Finnish medicine law obliges that “the product meets the Pharmacopoeia or other similar manufacturing, and quality requirements set for it” (Lääkelaki 21§, 1987/395). It means that all materials and products are being sampled and tested against their specifications with Pharmacopoeia methods. In addition, environmental samples and stability of products must be monitored. All these actions must be documented and reviewed by a second person. This is ensured and controlled by Finnish Medicine Acency, Fimea. Fimea is part of the EU’s marketing authorization network (Botet, 2015; Fimea, n.d.-c). Fimea also monitors that the company complies with Good Manufacturing Practises (GMP). GMP encompasses guidelines and protocols used in the production and quality control of pharmaceuticals to guarantee that the products comply with all established production standards (Fimea, n.d.-a).

Pharmaceutical manufacturing process is described in Figure 2. Quality is controlled before and after production. Before production all raw materials and packaging materials are sampled and analyzed against specifications before approval decision. All these actions are also documented. This phase is highlighted with red circle in Figure 2. After production and packaging the final products are also sampled and analyzed to ensure the required quality.

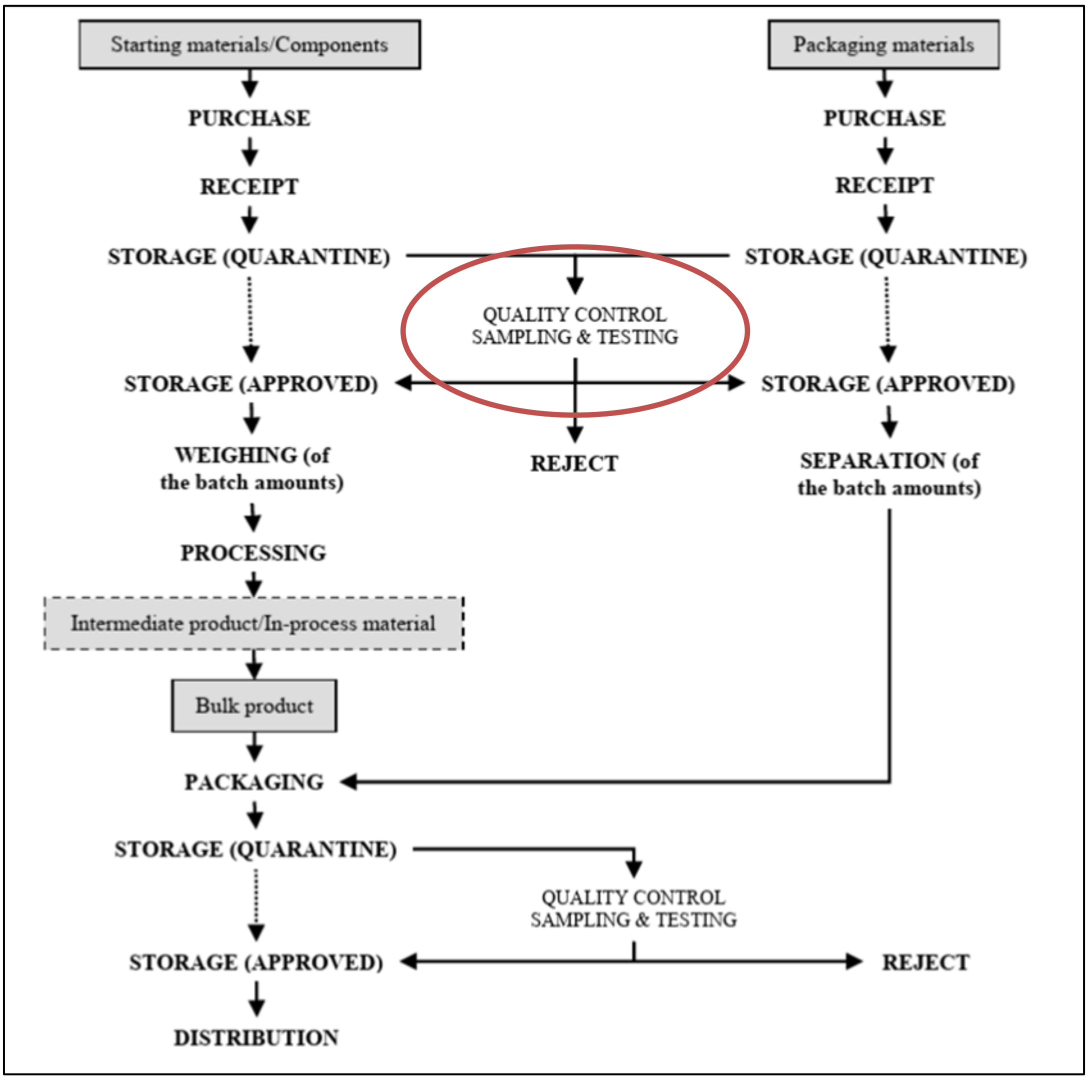


Figure 2. Pharmaceutical manufacturing process (Botet, 2015).

If any deficiencies are identified in any stage of quality control, the raw material, packaging material or final product is rejected and disposed.

2.2.1 Regulations and guidelines

The pharmaceutical industry is a strongly regulated business. GMP guidelines are the most important among national and international laws. GMP is the world-wide standard for pharmaceutical manufacturing, and it includes both human and veterinary drug products. The main principles are maintained by other documents published by authorities or national and international organizations. (Botet, 2015). In Finland Fimea is the authority which supervise the entire life cycle of medicinal products. Operations are guided by national laws, EU legislation and administrative regulations and guidelines. These include Medicines Act (395/1987), Decree on Medicines (693/1987), Finnish Medicines Agency (Fimea), Regulations and EU Regulations and Directives, including EU Guidelines to Good Manufacturing (GMP) (European Medicines Agency, n.d.; Fimea, n.d.-b). In addition, there is also Pharma Industry Finland Code of Ethics (Pharma Industry Finland, n.d.).

In Finland there is obligatory storage system for medicines, which prevents shortages and helps to ensure patient safety by requiring safety storages for certain medicines from manufacturers, importers, health care units and National Institute for Health and Welfare. The system is regulated by the Act on Obligatory Storing of Medicines 979/2008, and it has been in use since 1984, but its significance has increased due to increasing global supply chain issues which cause medicine shortages. One of the major reasons for increasing supply chain interruptions was COVID-19 pandemic due to workforce shortages and lockdowns although these challenges have been present already before the pandemic (Mohan et al., 2024; *Obligatory Storing of Medicines*, n.d.; Ravela et al., 2025).

2.2.2 Documentation

Documentation is crucial in quality management in pharmaceutical industry. GMP and ISO 13485 -standard for medical devices have guidelines for documentation. One part of documentation is instructions and procedures for processes and operations. Creating, updating and removing instructions has its own process and it is also controlled by reviewing. Control of documents is essential, since they are the foundation of quality management systems. Training is also an essential part of instructions (Botet, 2015; Skipper, 2015). According to ISO 13485, standard for medical devices, quality management system must include “all documents, including records, determined by the organization to be necessary to ensure the effective planning, operation, and control of its processes” (International Organization of Standardization, 2016).

General method for controlling instructions is to divide them into standard operating procedures (SOP) and working instructions (WI). Standard operating procedure is an approved mid-level document which describes a specific method or process, and it should be followed every time the instructed operation is performed. A flowchart is usually included in SOP. Working instruction (WI) is a low-level document which is more specific than SOP. WI provides step-by-step instructions for performing the process described in SOP related to the same process. Several WI’s can be related to one SOP where each WI describes one step of the process flowchart (Medicines and Healthcare Products Regulatory Agency, 2017; Skipper, 2015).

2.3 Modern quality management and continuous improvement in pharmaceutical quality control

Modern quality management is based on continuous improvement. It is also an essential part of ICH guidelines on a Pharmaceutical Quality System and ISO standards related to quality, including ISO 13485. Improvement of the quality management system includes corrective and preventive actions for eliminating defects for maintaining the effectiveness of the quality management system (Botet, 2015; International Organization of Standardization, 2016; McDermott et al., 2022).

Due to strict regulations and ensuring patient safety, continuous improvement has been implemented later in pharmaceutical industry than in other industries. It has led to the current state where Lean tools are still infrequently implemented in quality control in pharmaceutical industry, although they are important for improving operational efficiency with better procedures and more precise parameter control, as well as reducing variability. Improvement activities also support improving the quality and service level but also reducing costs (Botet, 2015; Lestari & Subroto, 2022).

In laboratory environment, Lean activities concentrate on testing products or materials as efficiently as possible. Improving efficiency relies on lowering costs and throughput times by minimizing the need for resources and materials. Implementing Lean tools can also enhance the right-first-time rate which releases the resources from rework and investigations. The challenge in laboratory is the complexity and variability of samples. The design of laboratory layout has also a markable impact on effective use of labor, minimizing waste and supporting the usage of 5S. One possibility to achieve improvement in workflow in laboratory is reorganization of the process with reordering the work assignments and fostering collaboration (Letelier et al., 2021; Lestari & Subroto, 2022).

Key performance indicators (KPI) are important for measuring the performance of organization and improvement activities. KPIs are measurable values that show the performance of a process, product, system, or function. Measuring with KPIs is reliable due to their static and stability. KPIs are used for estimating the success of organizations and setting the goals. They are effective tool to present the strategic goals understandably for employees particularly when visualized with colors (Laman, 2022; Trincă, 2020).

Building a culture of continuous improvement, all members of an organization must actively engage in development efforts since it improves the organization’s ability to create and deliver value. Implementing this requires ongoing training. Training is essential because it enhances awareness in daily operations, creates a shared understanding of process management, equips teams with Lean tools, and promotes a mindset of continuous improvement into routine work practices (International Organization of Standardization, 2018; Orion Pharma personal communication, November 13, 2024).

Continuous improvement also involves implementing new innovations that provide solutions for managing future challenges. The pharmaceutical industry faces tightening regulations which complicate the implementation of new technologies but increases the capability of remaining competitive when succeeded. The industry also faces rising research and development costs, and patent expirations, alongside growing and ageing population. (United Nations Department For Economic And Social Affairs, 2025). Modern technologies like data analytics, machine learning, and Artificial Intelligence (AI) could be used to achieve all the requirements and give promising solutions to meet evolving demands. Maturity model (MM) is one approach to strengthen quality systems and fosters continuous improvement in quality management (Cubo, C. et al., 2021; Destro & Barolo, 2022; Mohan et al., 2024).

At the same time, pharmaceutical companies are expected to reduce the cost of medicines for consumers and adopt more sustainable manufacturing practices, while managing rising raw material costs, inflation, and supply chain disruptions. The integration of new technologies not only presents regulatory challenges, such as adapting methods to pharmacopeial standards, but also adds pressure to maintain affordability and operational efficiency. (Dufva & Rekola, 2023, pp.17– 33 and 55–67) Adapting automation and robot-assisted QC applications in pharmaceutical industry has been an ongoing process withing the framework of Industry 4.0, where digital technologies are being implemented into manufacturing and industrial operations. (Papavasileiou, Michalos, & Makris, 2025) However, implementation remains challenging due to strict regulations, while other industries are already moving toward Industry 5.0, which emphasizes patent-oriented and integration of advanced technologies, aligning with Smart Quality Management (SQM) principles. (Love, 2023; Khoshsepehr et al., 2025)

3 High-performance liquid chromatography

Liquid chromatography (LC) is a widely used separation method in analytical laboratories for identifying, measuring, and separating chemical mixtures and their components (solutes) that are dissolved in liquid solutions. (Ahmed et al., 2023; Ahmed, 2024; Fanali et al., 2013) The method is based on a physical separation process in which the components of a mixture are distributed between two phases: a stationary phase (a nonmoving phase), and a mobile phase that flows through it. (Ahmed et al., 2023; “Stationary phase”, 2025) Introduced in the mid-1900s, LC has gradually evolved, alongside other chromatographic techniques and modes, into modern form known as high-performance liquid chromatography (HPLC). (Ahmed et al., 2023)

Based on the guidelines of the European and the US Pharmacopeia, liquid chromatography is one of the most extensively applied analytical quantitative techniques in pharmaceutical quality control. (Dispas et al., 2022) It is essential for ensuring the purity, consistency, and overall quality of drug substances, as well as for identifying impurities in active pharmaceutical ingredients (APIs). (“Liquid chromatography”, 2025) HPLC method is widely accepted because of its analytical versatility across wide range of investigated compounds, its superior separation performance combined with sensitive detection, and its ability to deliver precise and consistently reproducible quantitative results. (Dong, 2019, pp. 2–4)

3.1 Principles of HPLC and UHPLC

In HPLC, the mobile phase, a liquid solution containing fine components, is pumped at high pressure through packed and closed column containing the stationary phase, enabling efficient analysis and separation of complex mixtures, into their individual components. (Harris, 2010; Fanali et al., 2013) The system consists of a pumping system, autosampler with an injector, high pressure column units, detector, and data acquisition system, as shown in

Figure 3 (Ahmed et al., 2023; European Directorate for the Quality of Medicines & HealthCare, 2025). The pumping system drives the liquid mobile phase through chromatographic column, into which a sample containing various analytes is injected. The stationary phase separates the analytes based on their interactions with the flowing mobile phase, releasing them at different times from the column. As the analytes travel through the system, each elutes at a specific time, known as retention time (T_R). These analytes are detected then by their physiochemical properties (e.g., fluorescence, UV-absorption, or molecular mass), generating electrical signals that are converted by the data acquisition system into a graphical output known as a chromatogram (Moldoveanu & David, 2012, pp. 12–14).

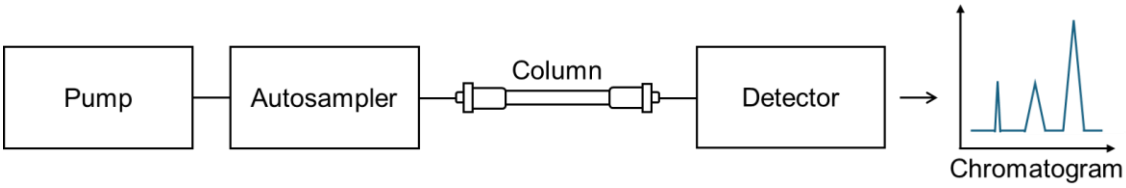


Figure 3. The liquid chromatography system.

HPLC encompasses various separation modes, which are defined by the nature of the stationary phase and the separation mechanism. Furthermore, adjustable parameters of the mobile phase, such as polarity, flow rate, and pH, as well as environmental factors related to the stationary phase, including temperature settings and detector configuration, significantly influence the efficiency and outcome of the separation process (Ahmed, 2024).

While HPLC has become an essential technique for the separation and analysis of multi-component systems, the increasing demand for higher throughput, improved resolution and faster analysis times has driven the development of more advanced chromatographic tools. (Xu, 2013) Ultra-high-performance liquid chromatography (UHPLC, also known as µHPLC) is an advanced mode of HPLC that was developed in the early 2000s. It shares similar chromatographic principles and process with conventional HPLC, (Atta-Ur-Rahman et al., 2018) but the main difference is that UHPLC uses smaller stationary phase particles in its columns. The use of smaller particles makes the separation process faster and increases the sensitivity and precision of the analysis but also requires the use of higher pressures. (Naushad et al., 2014) Although UHPLC can provide more efficient analysis, it is not always possible to switch between these chromatographic methods in pharmaceutical industry, because the Pharmacopoeias and other regulatory guidelines specify which analytical techniques, HPLC or UHPLC, must be used for certain analyses. (United States Pharmacopeia, 2024)

3.1.1 Mobile and stationary phases in LC

The main modes for mobile phases in LC are normal-phase, reversed-phase, ion-exchange, ion-pair, size-exclusion, and chiral chromatography. Each mode utilizes different types of mobile phases (eluents) and stationary phases, depending on the nature of the substances or components being separated (Ramis-Ramos & García-Álvarez-Coque, 2013, pp. 196–215). Table 1 summarizes the principal modes, detailing the characteristics of mobile and stationary phases used as the basis for separation of the analytes.

Table 1. Overview of the main modes of HPLC and their typical mobile phases, stationary phases, and common applications. (Ramis-Ramos & García-Álvarez-Coque, 2013, pp. 196–215)

Chromatography Mode	**Mobile Phase Description**	**Stationary Phase Type**	**Typical Application / Analytes**
Normal-phase (NPC)	Non-polar / moderately polar organic solvents (e.g., hexane, methanol)	Polar (e.g., silica)	Separation of polar compounds
Reversed-phase (RPC)	Polar: Water or aqueous buffer combined organic solvents (e.g., methanol),	Non-polar (e.g., C18, C8)	Separation of non-polar to moderately polar compounds

Ion-exchange (IEC)	Aqueous buffer solutions with varying ionic strength and pH	Ion-exchange resin	Separation of ionic species (e.g., amino acids, proteins, nucleotides)
Ion-pair	Aqueous-organic mixtures containing ion-pairing reagents (e.g., alkyl sulfonates)	Typically reversed-phase	Separation of ionic and highly polar compound
Size-exclusion (SEC-GPC)	Mobile phase selected according to sample properties; can be aqueous or organic	Porous gel	Separation based on molecular size (polymers, proteins)
Chiral chromatography	Similar to normal- or reversed-phase, sometimes with chiral additives	Chiral stationary phase	Separation of enantiomers

Organic solvents, such as methanol, acetonitrile, ethanol, hexane and chloroform, are frequently used in both normal-phase and reverse-phase LC, with the choice depending on the polarity requirements of the analytes. Aqueous solutions, including water or water with buffers (e.g., phosphate, acetate, and citrate buffers), and mixtures of organic solvents with aqueous solutions, are essential for reversed-phase and ion-exchange chromatography analyses. These mixed mobile phases (aqueous-organic) are the most common mobile phase types used in reverse-phase HPLC. Ion-exchange chromatography also widely utilizes buffer solutions with controlled pH and ionic strength. Additionally, additives and modifiers such as ion-pairing reagents, salts, chiral selectors, acids, and bases are used in ion-pair and chiral chromatography to enhance separation of specific analytes, enable chiral separations, or adjust selectivity (Ramis-Ramos & García-Álvarez-Coque, 2013, pp. 196–215).

Both HPLC and UHPLC utilize two main elution techniques: isocratic and gradient elution. These techniques are based on the elution strength, which refers to its ability to separate solutes retained on the stationary phase (Ramis-

Ramos & García-Álvarez-Coque, 2013, pp. 196–215). In isocratic elution, a single solvent or constant mixture of solvents (referred to as mobile phase A) is used throughout the chromatographic analysis run (Corradini, 2010; Harris, 2010). This elution is suitable, when components can be separated effectively under constant elution strength (Harris, 2010; Ramis-Ramos & García-Álvarez-Coque, 2013, pp. 196–215). If a single solvent is not enough for the separation process, gradient elution is employed. In this technique, a second solvent (mobile phase B), typically with higher elution strength, is gradually increased to the system. The continuous change in the composition ratio between mobile phase A and mobile phase B increases the elution strength over time, thereby enhancing interactions with the stationary phase (Harris, 2010; Ramis-Ramos & García-Álvarez-Coque, 2013, pp. 196–215). Gradient elution can be performed with up to four different solvents (mobile phases A, B, C, and D) (Agilent Technologies, 2015).

For successful liquid chromatography analysis, the system requires proper equilibration between the mobile phase and the stationary phase (Riekkola, 2017, pp. 84–85). The equilibration time primarily depends on the column. According to Riekkola (2017), the stationary phase is generally considered equilibrated after 20 column volumes of eluent through the column. Increasing the flow rate can reduce the total equilibration time. For example, a column with dimensions of 50 mm x 4.6 mm (column volume: 0.58 mL) and a flow rate of 1.0 mL/min requires approximately 12 minutes to equilibrate. In contrast, a column with dimensions of 250 mm x 4.6 mm (column volume: 2.91 mL) at the same flow rate requires about 58 minutes for equilibration (Riekkola, 2017, pp. 84–85).

3.1.2 Pump systems

The pump, solvent delivery system, drives constant flow of mobile phase(s) through the liquid chromatography system. This movement is quantified as the volumetric flow rate (U), usually expressed in millimeters per minute (mL/min). To achieve efficient separation, the pump must produce high pressure to overcome the significant resistance caused by the tightly packed stationary phase in the column (Moldoveanu & David, 2012, pp. 31–38). UHPLC systems can withstand higher pressures, up to 1000 bar, while HPLC operates usually at pressures of 70 – 400 bar (Harris, 2010). Also, the flow rate in UHPLC analysis is typically form 0.2 – 1.0 mL/min due to high pressure, whereas in HPLC it is usually 1 – 2 mL/min (Agilent Technologies, n.d.-a).

LC pumps differ from each other by their flow delivery mechanisms. A Single-piston reciprocating pump uses one plunger to generate flow, resulting in a pulsating flow that is less stable and can be seen as fluctuations in the chromatogram. This makes it less suitable for high-precision HPLC applications. In contrast, dual-piston reciprocating pumps use two pistons to produce a more stable and continuous flow. This design is more commonly used in both HPLC and UHPLC systems due to its improved consistency (Moldoveanu & David, 2012, pp. 31–38). In addition, the incorporation of advanced mixing systems in dual-piston pumps enables effective implementation of gradient elution (Moldoveanu & David, 2012, pp. 31–38).

In parallel with flow delivery mechanisms, modern liquid chromatography pumps can also be categorized as isocratic, binary and quaternary pump types (Agilent Technologies, n.d.-a). A Binary pump module consists of two identical pump applications (both usually dual-piston pumps) integrated into one LC unit, which allows high-pressure mixing of two solvents to form binary gradients (Agilent Technologies, 2013a). Quaternary pump enables mixing of up to four solvents to create quaternary gradients (Agilent Technologies, 2013b; Agilent Technologies, 2015). Based on Agilent Technologies manual, the isocratic pump delivers one constant solvent composition, while the quaternary pump mixes different solvents before pumping (Agilent Technologies, n.d.-b). Each pump type and mixing system is designed for specific chromatographic applications, ensuring efficient and optimized analytical performance (Agilent Technologies, n.d.-a).

3.1.3 Detection methods and LC detectors

In liquid chromatography, the detection of the analytes is based on measuring physiochemical properties that differ from those of the mobile phase, thereby enabling their identification and quantification. The choice of detection method depends on the analyte, the mobile phase and the sensitivity of the detector. It is known that some detectors work best with specific solvents, gradient types, environmental parameters (e.g., temperature) or separation methods. Fluorescence, ultraviolet-visible absorption (UV-Vis), refractive index (RI), and mass spectrometry (MS) are common detection techniques used in LC systems (Moldoveanu & David, 2012, pp. 44–63; United States Pharmacopeia, 2025). For high-precision analysis, the detector must be sensitive, accurate across a wide range of concentrations, stable, and consistent. There are detectors, such as RI detectors, that are designed to detect universally all analytes, while others are compound specific or require specific settings to selectively detect certain compounds. It is also possible to configure modern liquid chromatography system with two different detectors for enhancing analytical performance (Moldoveanu & David, 2012, pp. 44–63).

The pharmacopeias do not prescribe a specific detector type for pharmaceutical methods, but they allow a range of detection techniques, provided the chosen method meets system suitability requirements and it’s properly validated (European Directorate for the Quality of Medicines & HealthCare, 2025; United States Pharmacopeia, 2025). According to the Ph. Eur., UV-Vis detectors are the most used in the pharmaceutical analysis, as many pharmaceutical compounds absorb UV-light (European Directorate for the Quality of Medicines & HealthCare, 2025; Moldoveanu & David, 2012, pp. 44–63).

Variable wavelength (VWD) and diode array (DAD) detectors are types of UV-Vis detectors used in HPLC. VWD measures absorbance primary at one selected wavelength at time, while DAD offers simultaneous measurement across a wide range of wavelengths (Fanali et al., 2013; (Moldoveanu & David, 2012, pp. 44–63). One key difference UV-Vis detectors and refractive index detectors (RID), is that RID is incompatible with gradient elution, whereas DAD and VWD function effectively under gradient conditions. Additionally, RID has a detection limit about 1000 times higher (less sensitive) than UV detectors. The measurement of RI detectors relies on the differences in refractive index between the isocratic mobile phase and the eluent containing the analyte. In addition to UV-Vis and refractive index detectors, fluorescence detectors (FLD) offer enhanced sensitivity for specific analytes. FLD measures light emitted by a compound after excitation, allowing detection of substances that either naturally fluoresce or have been chemically derivatized to do so (Harris, 2010).

3.2 LC applications for the pharmaceutical QC

In pharmaceutical quality control LC plays a critical role in identification, analysis and evaluation of the stability and quality of pharmaceutical products in public health. It ensures the safety, efficacy and integrity of these products throughout the entire production process, from raw materials to the final dosage form to patients (Dispas et al., 2022). The analytical methods used for each pharmaceutical substance are defined by pharmacopeial standards, which are developed in accordance with official regulations and guidelines in collaboration with expert organizations such as World Health Organization (WHO) (World Health Organization, 2025). The pharmacopeia specifies, through monographs, LC method types and parameters, mobile and stationary phases that are used for each pharmaceutical substance. Modifying these methods is often a time-consuming and complex process, involving extensive documentation, method revalidation, and coordination with regulatory authorities (European Directorate for the Quality of Medicines & HealthCare, 2022).

Liquid chromatography analysis is utilized widely in QC laboratories due to its short turnaround time, high method reliability, and sensitivity. Its ability to perform both quantitative and qualitative analysis makes it a versatile tool for various applications (Fanali et al., 2013). In QC, liquid chromatography is used for the identification and quantification of both medical and non-medical components, as well as packing materials, including impurity profiling.

Additionally, LC plays a critical role in cleaning validation by detecting and quantifying residues of cleaning agents, APIs, and unknown compounds on production equipment. This analytical review is essential for ensuring that pharmaceutical production line remains continuously operational when processing new batches, enabling smooth transition between batches and maintaining cleanliness and readiness of equipment (Orion Pharma, personal communication, 2025).

Orion Pharma’s QC laboratories also utilize LC techniques to monitor the chemical stability of substances under different storage and stress conditions, as well as in method validation, development, and transfer activities across laboratory units.

4 Implementation of the new process of liquid chromatographic analysis through schedule planning

The study concentrates on chemical quality control (CQC) of raw materials in Finnish pharmaceutical company, Orion Pharma. The aim of this thesis is to identify waste and enhance the efficiency of performing LC analysis by planning for shorter throughput times. Another goal is to increase the utilization rate of LC equipment. Pharmacopeias and other regulations specify the methods used for each pharmaceutical substance. Due to regulatory complexity, modifying pharmacopeia methods is not within the scope of this thesis. Instead, the focus is on enhancing operational efficiency in LC analysis by using DMAIC process, which is a common method for process improvement projects.

4.1 Define phase

The Finnish pharmaceutical company's, Orion Pharma's, values form the foundation for all operations and guide future strategic decisions. Emphasizing safety, responsibility, and collaboration, the company reflects a people-oriented approach. In process development, the goal is to create added value, strive for top performance, and develop solutions together with customers, ultimately improving quality of life (Orion Pharma, n.d.-b). This study supports these principles by ensuring that the implementation of the new LC process through schedule planning aligns with the company's values, so improvements enhance both efficiency and responsibility.

4.1.1 Problem statement

The commissioner has ambitious strategy for years 2024–2028. Financial objectives include growing net sales with average annual growth rate of 8 % at minimum and growing operating profit faster than net sales. These strategic goals require significant growth (Orion Pharma, n.d.-a). Another target is to reduce the overall costs in organization which CQC is part of.

The high cost of LC equipment, combined with expensive maintenance contracts, represents a major challenge because these systems are vital for analytical operations. The company’s annually conducted internal analysis indicates that the current utilization rate of these instruments is too low relative to their cost, making their use inefficient and not cost-effective. As a result, one to two HPLC systems will be removed from CQC laboratory by the end of the year 2025. In addition, certain types of LC instruments, such as those equipped with VWD or DAD detectors, occasionally create bottlenecks in raw material analysis. The annual goal for the CQC laboratory is to improve throughput time, in alignment with the overall cost-reduction strategy. Both objectives depend on more efficient resource utilization and streamlined processes, which can be influenced through improved work planning. Currently, LC analysis work is standardized based on a three-day planning model defined by a standard timetable. However, the individual phases of the process are not standardized. Furthermore, there are numerous different methods for various raw materials, over 700 raw materials and thousands of methods, yet these variations have never been studied in detail in HPLC methods.

As background information related to the LC equipment, the pharmaceutical company currently operates an instrument base that has evolved over the years through various changes. Until around 2018, the CQC laboratory analyzed not only raw materials but also finished tablet products using LC instruments, whose methods required devices equipped with DAD detectors. After a project, where analysis types were centralized by location, the detector configurations of the instrument base were not reassessed. In addition, cleaning validation tasks in the CQC laboratory must also be performed using LC-DAD instruments to enable spectral data collection. The instrument base has also been influenced by the subsidiary’s historical practice of using only DAD-equipped instruments for method development. The current chromatographic equipment supplier’s LC-DAD systems have been the only detector type capable of measuring two wavelengths simultaneously until approximately 2025. Modern VWD detectors now offer this capability as well, creating new opportunities. This raises questions regarding SOP guidance, as current way of working does not address how LC-VWD could be used for dual-wavelength analysis. Instructions and practices have not kept pace with technological development, which presents an opportunity for process optimization. As standardized knowledge in the CQC laboratory, analysts generally consider LC-VWD systems to be the best detector choice for impurity determinations, where the peaks of the components under investigation are small compared to those in concentration (e.g. assay or identification) methods. The equipment supplier outlines that both modern UV-detectors, VWD and DAD, are at a comparable level in accuracy and performance. However, the developed and validated methods in CQC can be outdated compared to modern devices, which can cause system suitability issues. This thesis also aims to investigate how many methods require a specific detector type and whether the assumptions behind detector selection are outdated or still valid today. Furthermore, the instrument base at the site relevant to this study is shared between the Raw Material team (including cleaning validation), and the Method Implementation and Problem-Solving team (MIPS).

In the CQC laboratory, time measurements of the work steps were previously studied as part of an earlier project focusing on CQC processes. The testing was carried out on the largest products across the entire chemical quality control laboratory. However, due to the diversity of methods, this did not produce desired results within the Raw Material team because of the high variability. One intention was to make work planning in laboratory easier by creating detailed standardized work model templates. However, these templates proved impractical and were never implemented. Nevertheless, the results can still be utilized in process development, for example, in connection with this study.

Standard timetable for LC analysis in CQC

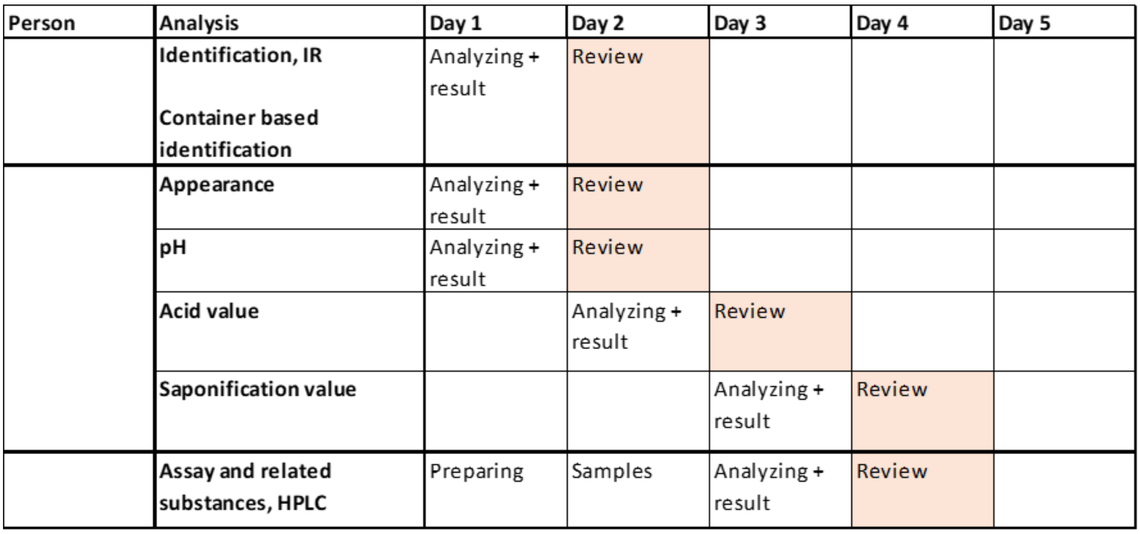
Planning significantly impacts what is done and when in quality control laboratory. CQC involves numerous moving parts, making it extremely challenging to consider all factors. The most important aspect of planning is achieving synergy benefits by combining several batches' analyses. This requires monitoring purchase orders and the arrival of batches from the Enterprise Resource Planning (ERP) system. Effective planning maximizes synergy benefits and minimizes disruptions, chemical usage, and waiting.

Basic principle of planning, which batches are included in next week's schedule plan, is first in, first out (FIFO method). Currently, the flow of incoming batches is somewhat inconsistent, with unexpected changes requiring the prioritization of analyses based on production demands. In addition, raw material CQC is also acting as the subsidiary's outsourcing laboratory for the analysis of its APIs and those batches' analyses must also be prioritized. In addition, the work in process (WIP) rate of raw material CQC has constantly been higher than targeted. It leads to increasing number of urgent needs from production.

Schedule plan for the Raw Materials team is done one week at a time, and currently it is complete manual work with no help of IT solutions, such as laboratory planning software or AI assistance. Quality control planning in raw materials CQC is based on available resources, competence matrix and standard timetables. Standard timetables have been created for every raw material, and they are updated continuously. In the standard timetable the analysis has been divided into sections by four analysis type: infrared spectroscopy, gas chromatography analysis, wet chemistry analysis, and liquid chromatography analysis. The standard timetable estimates the required time and resource needed to perform the analysis of the material. Each raw material has its own standard timetable, and the number and duration of analyses varies a lot depending on the material.

In Table 2 an example of the team's standard timetables is presented. The top box is for infrared spectroscopy identification, the middle box is for wet chemistry analysis, and the bottom box is for liquid chromatography analysis. In the current state there are always three days scheduled for performing the liquid chromatography analysis. The first day is for preparation, the second day is for running the samples and the third day is for analyzing the results. Each analysis includes a final day allocated for reviewing the results and ensuring compliances. Throughout all phases, documentation is performed in real time and in strict adherence to GMP guidelines, ensuring traceability, accountability, and regulatory compliance. The CQC laboratory performs various types of analyses, such as assay, identification, enantiomeric purity, enantiomeric ratio, related substances, organic impurities, and purity, each with different method names. In this thesis, the method names have been grouped into three categories: impurity analysis (including all types of impurity-related tests), assay, and identification.

Table 2. Example of a standard timetable.



Person	Analysis	Day 1	Day 2	Day 3	Day 4	Day 5
	Identification, IR **Container based identification**	Analyzing + result	Review			
	Appearance	Analyzing + result	Review			
	pH	Analyzing + result	Review			
	Acid value		Analyzing + result	Review		
	Saponification value			Analyzing + result	Review	
	Assay and related substances, HPLC	Preparing	Samples	Analyzing + result	Review	

Liquid chromatography analysis is one of the most time-consuming analyses in the CQC laboratory. Figure 4 provides a visual overview of this workflow, illustrating the key steps and their sequence during the analysis process. According to the current process, the first day encompasses the selection and preparation of analytical instrument and the secondary phase, LC column. Instrument methods are configured using a chromatography data system, and run sequences are constructed in alignment with pharmacopeial method requirements and SOPs. Instrument setup also includes the preparation of cleaning and equilibration solutions. The mobile phase planning and preparation are integral to this stage. Estimation and calculation of the required mobile phase and solvent volumes are performed prior to analysis. The process involves retrieving appropriate containers, selecting and collecting reagents, weighing and dissolving them, and typically includes pH adjustment and filtration. Alternatively, the mobile phase preparation may consist solely of mixing pure solvents, depending on the method requirements. Additional solutions required for the analysis are also prepared on the first day. Upon completion, the LC system is typically left to equilibrate overnight to ensure stability for the subsequent analytical phase.

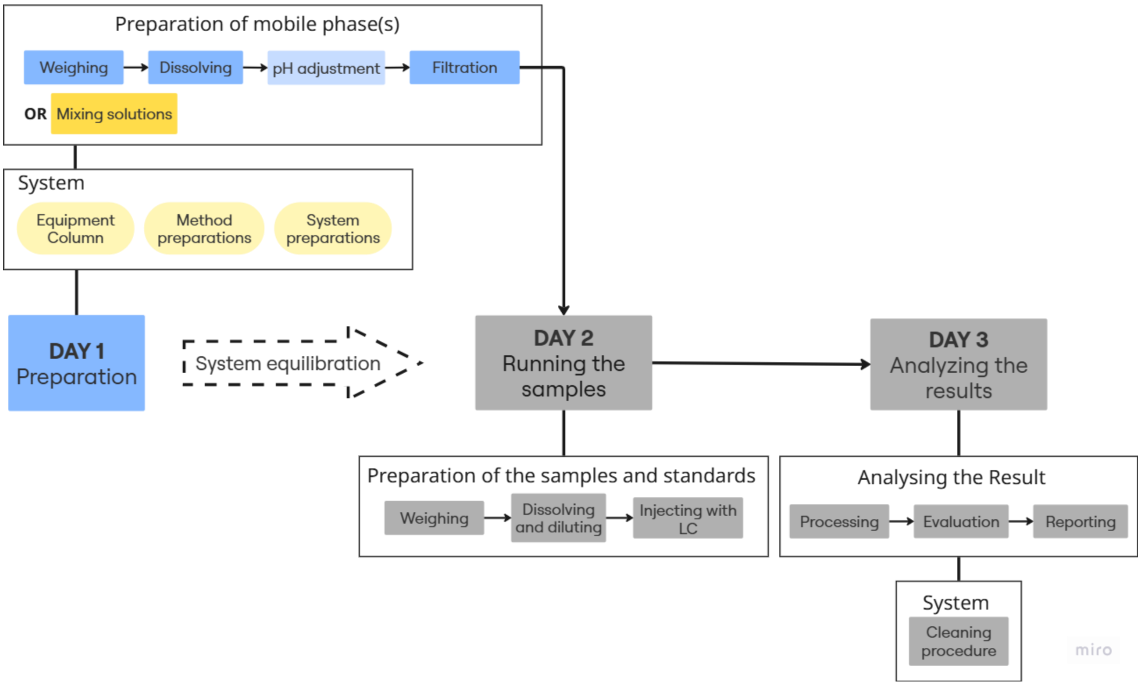


Figure 4. LC analysis process based on the standard timetable.

On the second day, necessary containers for the analysis are collected. Samples and reference standards are weighed and prepared in accordance with the validated method instructions. This phase ensures that all analytical components are ready for execution under controlled conditions. Once prepared, the samples are injected and run using the LC system. System suitability is assessed in parallel with the sample run to confirm compliance with method-specific requirements.

The third day is dedicated to the processing, evaluation, and reporting of analytical results. Simultaneously, cleaning procedures are performed on both the instrument and the LC column to maintain system integrity and readiness for future use. Each analysis day also includes timely documentation in accordance with GMP.

The current planning model is based on a fixed three-day workflow, and most LC analyses have been standardized according to this schedule. However, the actual execution of analyses can vary significantly from this. The duration of an analysis depends on multiple process steps and their characteristics, including mobile phase type and preparation steps, system equilibration time, column properties, sample characteristics (e.g. solubility, handling, and Environment, Health and Safety requirements), run time, and post-run activities such as system cleaning. The current model does not account for these variations, which can affect efficiency and flexibility. In addition, unexpected situations such as deviations, equipment failures, or human errors also have an impact on the completion of the analysis.

4.1.2 Customer and scope

In the pharmaceutical industry, the end customer is a patient, an individual person. While many medicines are available in generic form, the commissioner is the sole global manufacturer of certain drugs. Stock-outs in such medicines can lead to fatal consequences if drugs have not been produced at right time. CQC has a markable role in the whole supply chain, and often the threat of stock-outs leads to the need for quick response for urgent production needs. The internal customers of this study are therefore company’s own production, and the sales of the subsidiary.

The scope of this study is liquid chromatography analysis scheduling and the usage of different device types. Since regulations defines strictly the methods for analysis, they cannot be modified. Performing the analysis is also described in the SOPs at a general level and they need to be followed, but the way of working can be changed within the limits of SOPs. This study concentrates on those ways of working, because it has been noticed that performing the analysis has not been fully standardized and there are differences between working habits, since analyzing in laboratory is handcraft and the work is highly independent. In accordance with the commissioner’s request, planning software is considered out of scope for this study.

4.2 Measure phase

The measure phase was aimed at identifying existing processes and working practices to detect waste and inefficiencies in LC workflows in CQC. It was also aimed at identifying missing information linked to inefficient work planning. This supports continuous improvement and helps in determining which practices are effective and which outcomes are desired. To achieve this, detailed process mapping was employed to simplify the complex liquid chromatographic process and its influencing factors. To understand the overall picture, data collection plan was created, and data was measured to establish a baseline for the change process toward shorter throughput times and improved equipment utilization. In this study, data was collected using both quantitative methods (LC methods, ERP data, and standard timetables) and qualitative methods (survey).

4.2.1 Bottleneck identification in LC process through process mapping

In the current LC analysis process, each analyst performs all work phases independently, which leads to inefficiencies and duplication of effort, as illustrated in Figure 5. Multiple individuals (analyst 1, 2 and n+1) carry out the same core tasks daily, particularly in the preparation of mobile phases. These tasks include retrieving containers (e.g. glassware and accessories), collecting reagents, weighing, and filtering solutions.

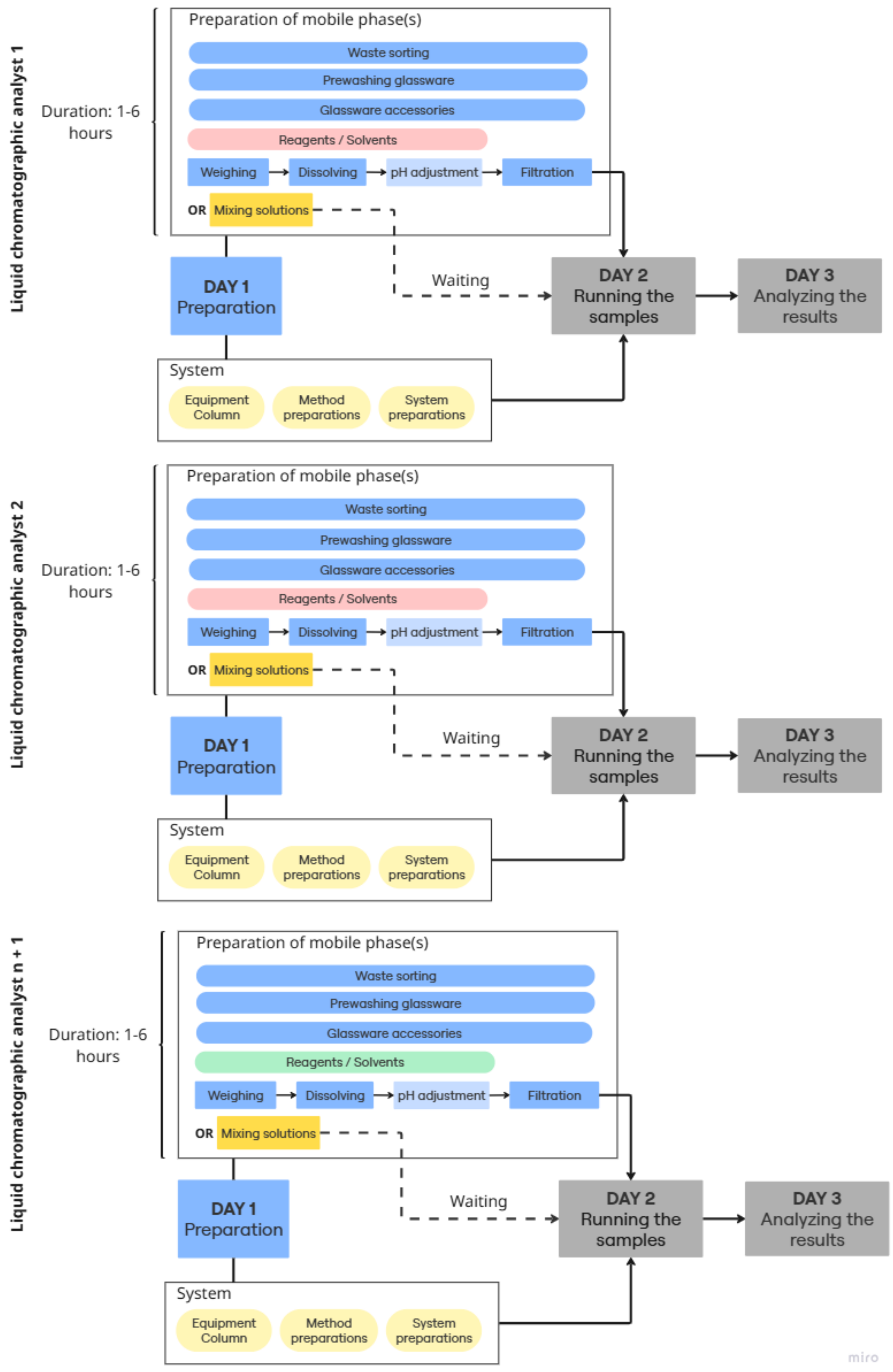


Figure 5. Current state of LC process based on the standard timetable.

Such a decentralized and repetitive approach results in considerable inefficiencies and non-value-adding activities, which conflict with Lean principles. The duplication of tasks leads to unnecessary resource consumption and operational redundancy. These inefficiencies contribute to excessive movement, task switching, and workflow disruptions during the first day of the process, ultimately reducing overall productivity and process effectiveness in the Raw Material team.

Additionally, depending on the method and the time required for mobile phase preparation, the duration can vary significantly. For some analytical methods, mobile phase preparation may take as little as one hour (e.g. simple mixing of pure solvents), whereas for others, the process can extend up to six hours due to more complex requirements. This variability contributes to inefficiencies, that is seen as waiting time and process waste. The more individuals are involved in preparing mobile phases that require only simple solvent mixing, the less efficient the work becomes when evaluated against a standardized timetable.

The current illustration of standard timetable is not sufficient informative or specific to support effective LC analysis schedule planning, as there is remarkable method variation within CQC depending on the analytical procedure. This lack of accuracy in timetables contributes to inefficiencies across multiple stages of the process, leading to delays and ultimately impacting batch throughput times. Also, having one standard timetable for all LC analysts leads to varied working practices, because each person interprets and adjusts it to fit their own tasks and preferences. This contributes to variability in execution despite the consistency in scheduling. Conducting the analysis in less than three days may result in waiting or significant modifications to the weekly schedule, as the analyses are frequently interdependent.

In contrast, days 2 and 3 do not contain similar waste-generating process phases, as the tasks performed during these stages are highly specific and vary depending on the analytical method. This specificity reduces the likelihood of duplicated effort and unnecessary transitions, contributing to a more streamlined workflow. Furthermore, system preparation and method setup, in day 1, are tailored to each individual analysis, which means these activities do not generate waste within the process.

4.2.2 Key Performance Indicators (KPIs)

In the current state the equipment time for LC analysis is approximately 2.5 days. It includes the system preparation on the first day and stabilization of the system overnight. The second day is for running the samples, and on the third day the washing of the equipment takes approximately half a day. Throughput time of the analysis is three days. These times have been presented in Table 3.

Table 3. Equipment and analysis time in the current state.

	Preparation	**Running the samples**	**Analyzing the results + washing the system**	**Sum**
Equipment time (days)	1	1	0.5	2.5
Analysis time (days)	1	1	1.0	3.0

One of the most important KPIs is throughput time of all analyses for the batch in CQC. The target is to improve the throughput time annually, and it is also set for everyone’s personal annual targets. The target median throughput time for 2026 is set to be one day shorter than the realized median throughput time in 2025. Currently, the actual throughput time median from January to October 2025 is 2 days from the target.

Another KPI is on time delivery (OTD), which describes how large number of batches have been analyzed in the target throughput time. The actual OTD from January to October 2025 is 16 % from the target. These numbers prove that improvement measures are needed to achieve the targets.

Throughput times are being calculated for entire number of batches analyzed collectively. Not all materials include LC analysis due to variability in specifications. Furthermore, LC analysis throughput times are not reported separately in the statistics, because no dedicated system currently exists to capture this data.

Table 4 presents a manual calculation of the number of analysts and LC analysis performed, based on planning records from January to June 2025. Week 6 has no statistics due to a strike. In weeks 16, 17, 18, 22 and 25 there was one day as holiday, and therefore work week was only 4 days.

Table 4. LC analysts, and analysis performed in early 2025.

Week/ 2025	**Number of LC analysis (pcs)**	**Number of LC analysts (5 d = 1)**	**Analysis/ analyst/ week**
3	12.63	8.60	1.47
4	12.96	7.30	1.78
5	11.00	6.00	1.83
6	-	-	-
7	10.98	6.40	1.72
8	10.32	5.50	1.88
9	11.31	7.60	1.49
10	10.98	6.20	1.77
11	13.00	6.80	1.91
12	9.32	6.20	1.50
13	10.33	6.20	1.67
14	8.32	4.80	1.73
15	8.00	4.80	1.67
16	6.33	3.60	1.76
17	7.32	3.90	1.88
18	5.66	3.40	1.66
19	8.65	5.80	1.49
20	9.97	6.40	1.56
21	12.97	7.20	1.80
22	5.99	3.40	1.76
23	10.66	6.50	1.64
24	9.64	5.50	1.75
25	8.99	4.80	1.87
Average	9.79	5.77	1.71

In the current state 9.79 LC analysis is performed weekly on average, and there are 5.77 analysts available for the analysis. The ratio of analysis per analyst in one week is 1.71.

4.2.3 Establishing success criteria

Success in this study is defined as improving throughput time of LC analyses through enhanced work efficiency and increasing the utilization rate of LC equipment. If these improvements are achieved, they will enable more optimal use of reagents, resulting in reduced waste and improved environmental sustainability. Another aim was to gather information from the actual throughput times of different types of LC analysis methods and refine them in the standard timetables. More precise standard timetables would enhance the efficiency of QC planning, thereby minimizing analysts' waiting time.

Since most waste and variability from a Lean perspective occur on day 1 of LC analysis, this study focused on examining day 1 activities in detail, particularly mobile phase preparation, to improve efficiency. Figure 6 illustrates the future state of the LC process, in which one analyst prepares as many mobile phases as possible for upcoming analyses for the other analysts. In this scenario, waste is reduced, if similarities in mobile phase preparation or composition are identified in the analyzing phase. Figure 6 presents ideal future state, where one analyst prepares mobile phases for three other analysts beforehand, and they can perform the analysis in two days. Fourth analyst performs an analysis which has been recognized as fast analysis based on the method content, and it is also analyzed in two days. The result is that throughput time for four analyses is 2.25 days on average, while in the current state the throughput time is 3 days per analysis. On the other hand, also the equipment time for one analysis reduces from 2.5 days to 1.5 days.

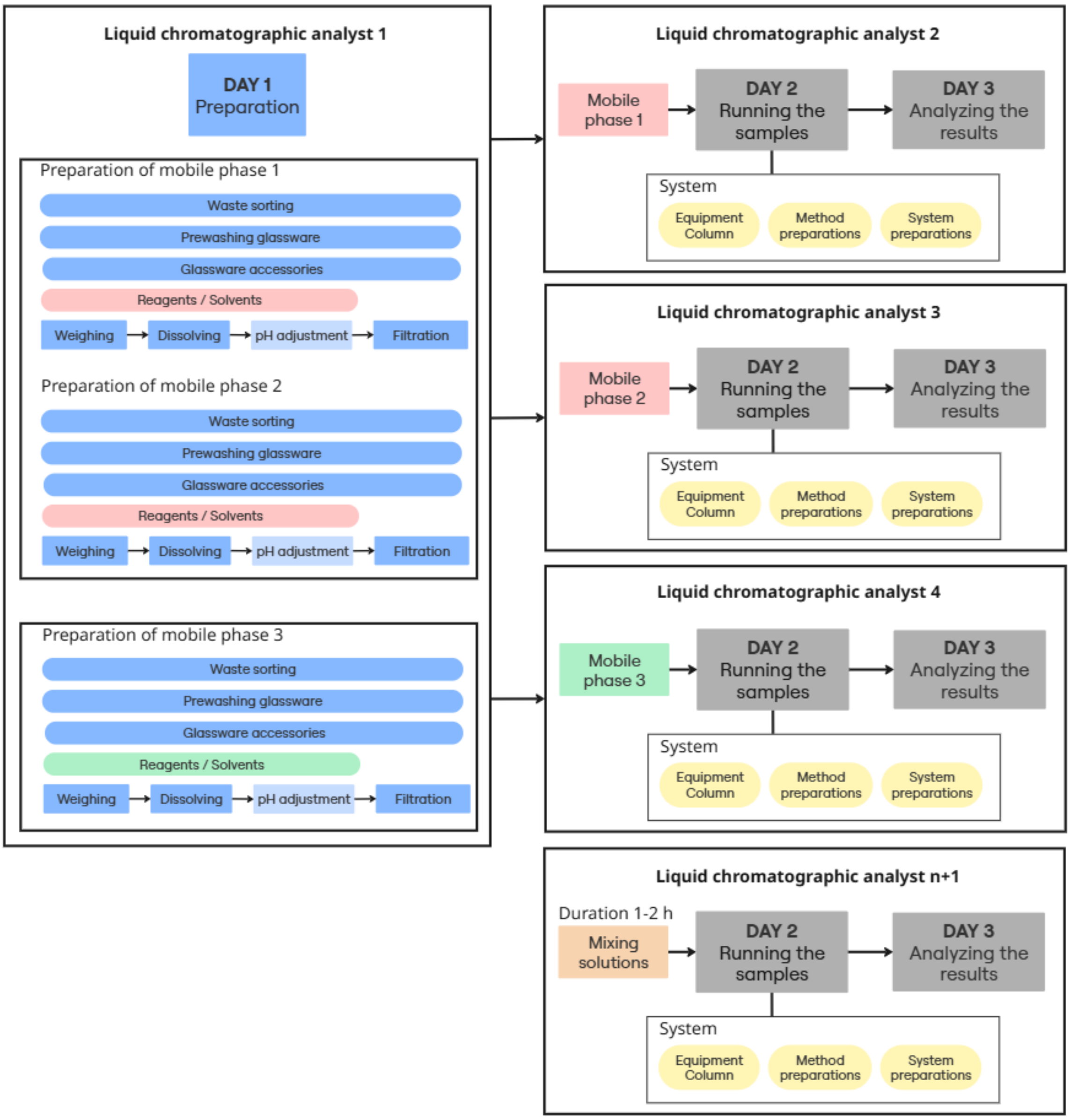


Figure 6. Future state of the LC process.

The study aimed to gather information on whether this type of process could be applicable for performing LC analysis in a QC laboratory and identify different methods and provide visibility into the standard timetable.

4.2.4 Questionnaire

Questionnaire (Appendix 1–9) was created for LC analysts in Raw Material team in CQC. It was sent to 13 recipients. The purpose of the questionnaire was to gather information about common practices and estimate how analysts choose the type of device for different types of analysis. Another purpose was to estimate what is the attitude towards collaboration and whether there is resistance to changing ways of working. The questionnaire included open questions, multiple-choice questions, and questions with a Likert scale. Question 4 opened only if the answer to the previous question was answered as 4 (important) or 5 (very important).

The questions set for the questionnaire were:

1. How long have you been working in a chemical quality control laboratory?
2. Estimate, how long have you been performing the HPLC and UHPLC analysis?
3. How important is it to you that you have prepared the mobile phase solutions for your analysis yourself?
4. Justify why it is important for you to use self-made mobile phase solutions in your work.
5. If the mobile phase solution is made by another person and the preparation has been reviewed, estimate how likely you are to use it in your analysis.
6. Choose what factors affect your choice of device in the analysis (do not take special methods into account in your answer).
7. It is common knowledge that old and new LC equipment models differ from each other. Does this information influence your choice of equipment for assay and impurity analysis?
8. You are choosing the LC II equipment for your assay analysis. The pharmacopoeia or method instructions do not require a specific detector,

and there are no additional instructions in the standard timetable. Which detector type will you choose?

9. You are choosing the Infinity II equipment for your impurity analysis. The pharmacopoeia or method instructions do not require a specific detector, and there are no additional instructions in the standard timetable. Which detector type will you choose?

4.2.5 Data collection and measure for LC methods

As part of the study, all liquid chromatography methods used in the CQC laboratory were examined in detail for each raw material-product combination and documented using Excel file and standard timetables. Prior to documentation, each method was reviewed for validity in accordance with the relevant SOP, utilizing data retrieved from both the documentation management system and the ERP system.

The methods were analyzed and data collected based on several criteria: the instrument type (HPLC or UHPLC), method category (e.g. assay, identify, impurity analysis, or a combination thereof), mobile phase composition, detector and system pump requirements, analysis type (online or inline requirements), and other method-specific considerations (preparatory steps for used containers or defined system setup procedures). All these factors influence the execution of day 1 analysis according to the standard timetable for LC analysis.

Additionally, Excel documentation included for day 1 relevant factors derived from material-specific standard timetables and safety data sheets (SDS), which had previously been compiled in a separate project to support the work of the QC planner. Furthermore, data retrieved from the ERP system was incorporated to account for factors influencing batch quantity determination. These included whether the material was subject to reduced analytical requirements or full analytical procedures, which directly affect how frequently the material is analyzed in CQC. The documentation also noted whether the raw material was sourced from a subsidiary or the parent company, as this distinction may influence analytical planning and prioritization.

During this study, reference laboratories and comparable practices were examined. However, the commissioning company proved to be globally unique, with no direct equivalent. Whereas most pharmaceutical firms operate with a narrower range of core products, this organization conducts analyses involving more than 700 raw material components. Such breadth distinguishes the company and constitutes one of its strategic advantages. Furthermore, because pharmaceutical laboratories are highly regulated environments, a key challenge was that other studies or published articles could not be utilized in this research.

4.3 Analyze phase

Analyzing phase was divided into two sections. First section was for analyzing the questionnaire results. Questionnaire results gave an understanding of current attitudes towards the possibility for increasing collaboration in performing LC analysis, as well as giving important information on device selection.

The second section was for analyzing the LC methods, which gave numerous new detailed information. This analyzing phase was performed twice due to detected complexity in methods' contents.

4.3.1 Analyzing the questionnaire results

The questionnaire (Appendix 1–9) was conducted in August 2025 with an initial one-week response period, later extended to two weeks to aim for full participation due to the small recipient pool. 12 out of 13 responded, yielding a 92 % response rate.

Questions 1-2 focused on the work experience of LC analysts. One respondent (8 %) had worked in the commissioner's CQC laboratory for less than two years, 50 % for 2–10 years, and 42 % for more than 10 years. Regarding LC analysis experience, 50 % estimated 2–10 years, while the remaining 50 % reported over 10 years. These results suggest that the analysts possess substantial expertise in LC analysis and are likely highly committed to their work. However, experienced personnel may also develop individualized practices within the boundaries of SOPs and WIs, which can vary between individuals.

Questions 3–5 aimed to assess attitudes toward a new collaborative working approach. Questions 3 and 5 used a Likert scale (1 = ‘not important at all,’ 5 = ‘very important’), while Question 4 was open-ended and required a response only if Question 3 was rated as 4 (important) or 5 (very important). Results show that 67 % of respondents considered preparing mobile phases themselves as ‘not important’ or ‘not very important,’ whereas 33 % rated it as ‘important’ or ‘very important.’ Those respondents were asked to justify their answers. Common arguments included concerns about small differences between ways of doing, and the lack of understanding the method instructions when mobile phases are prepared by others, and the need to review preparations made by someone else. Responses to Question 5 indicated a more positive attitude toward collaboration when such reviews occur: 75% stated they would likely use a mobile phase prepared by another person if its preparation had been reviewed.

Questions 6–9 addressed factors influencing device selection for analysis. Figure 4 summarizes these factors. The two most important considerations were the method and detector type: 92 % of respondents select equipment based on method requirements, while 50 % choose a specific detector type (DAD/VWD) even when the method does not specify it. Needle wash type (which is a device-specific feature to enhance cleaning efficiency) was relevant for 33 % of respondents, and 25 % considered either the time since the last maintenance or hot wash, or whether the device was modern or legacy, as influencing their choice.

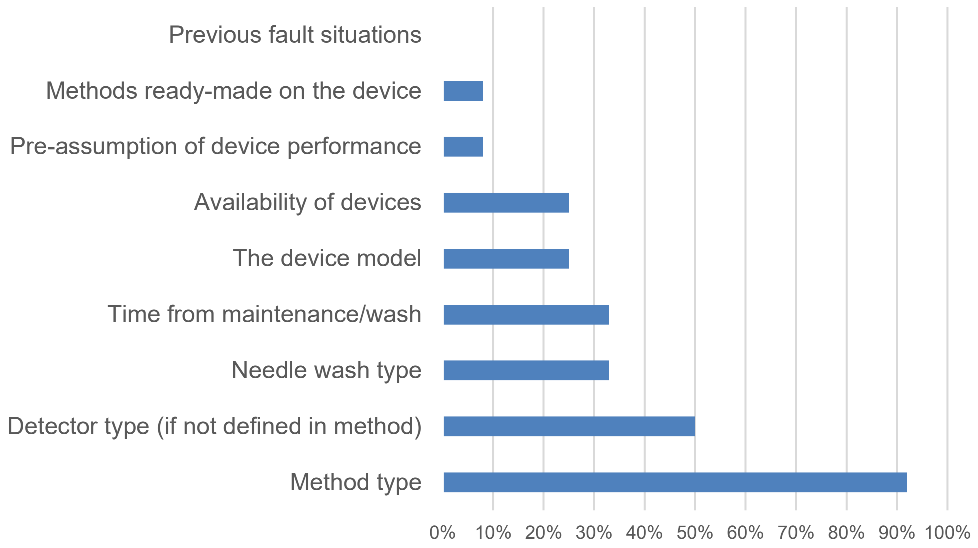


Figure 4. Equipment selection criteria.

Questions 7–9 aimed to gather information on how analysts choose between modern and legacy devices and their preferred detector types for different analyses, given the known differences between older and newer LC systems. Half of respondents stated that the device model does not influence their choice, while 17 % indicated it matters for impurity analysis. Open-ended responses frequently mentioned the needle wash type of device. For assay analysis, 83 % of respondents would use both detector types, whereas 42 % preferred a VWD detector for impurity analysis. Some respondents also noted that they check the history of detector use for the same analysis when making their selection.

The findings indicate that multiple factors influence device selection beyond the method specifications. Therefore, comprehensive guidelines for equipment selection are needed to address rooted practices and misconceptions regarding device performance. Attitudes toward increased collaboration are predominantly positive, despite analysts' extensive experience with established workflows. While some resistance to change persists, it remains limited.

4.3.2 Analyzing the LC methods

After the data from LC methods and standard timetables was collected, it was analyzed manually and sorted based on information about equipment, detector, method type, and mobile phases. It was found that there are 210 raw material components that have one or more LC analytical methods specified in their material specification within the ERP system. Because no previous studies have examined dispersions across different types of analytical methods, and the current workflow in the CQC laboratory is influenced, among other factors, by the choice of method, the methods were divided into different categories.

Analysis of LC systems and detectors in CQC

The aim was to gain more insight into the relationship between assay and identification methods as well as impurity methods. Table 5 illustrates the collected data, which shows that a total of 225 methods were identified, of which 139 were impurity or combined impurity and identification methods, which accounts of over half of all methods (61.8 %). This indicates that impurity control is a key focus in CQC because it helps to ensure raw materials are pure and safe. Assay and identification methods accounted for 26 (11.6 %), and analyses where all are performed together (assay, identification, and impurity) totaled 59 (26.2 %). Although assay and identification analysis tests are important, they are usually performed as part of broader impurity-focused methods rather than as separate analyses. Combining single methods (where possible) saves not only analysis time but also improves the utilization rate of LC equipment. The current situation during this study shows that the reduced number of analyses was 82, which included all types of methods. This represents 36.4 % of all methods, which are analyzed according to annual-based cycle predefined in the ERP system, supporting workload reduction and improved efficiency.

Table 5. Overview of method types applied in the Raw Material team.

		pcs	%	pcs	%
Method types in LC analysis	**Assay**	14	6.2	**26**	**11.6**
	Assay and identification	12	5.3		
	Identification	1	0.4	n/a	n/a
	Identification, impurity	8	3.6	**139**	**61.8**
	Impurity	131	58.2		
	Assay, impurity	33	14.7	**59**	**26.2**
	Assay, identification, impurity	26	11.6		
	Methods, total	225	100.0	n/a	
Reduced analysis, total		**82**	**36.4**		

In this study the mobile phase elution strategies were also examined in relation to mobile phases and equipment selection. Preparing two or more mobile phases takes more time, and QC laboratories often have different types of instruments or instrument modules that may not be suitable without additional testing or validation. For example, the laboratory has LC systems equipped with either binary pumps or quaternary pumps. Binary pump systems are suitable for most current methods (using isocratic or two-phase gradient methods), but quaternary pump systems may not be directly compatible with gradient analyses without method-specific parameter adjustments. Since QC laboratories aim to perform analyses consistently and routinely, extra adjustments can add unnecessary time, and it is not desired. However, investigating these adjustments would enable greater cross-utilization of equipment, reducing bottlenecks between different LC systems. The table below (Table 6) presents the mobile phase elution strategies across different QC methods, showing that 128 methods (56.9 %) use isocratic elution and 97 methods (43.1 %) gradient elution, making the distribution nearly even. Only one raw material method required the use of a quaternary pump system due to its gradient characteristics and validation requirements. To increase the utilization rate of this equipment, testing should be carried out to assess the suitability of different methods for the system.

Table 6. Mobile phase elution strategies and their proportion across methods.

Mobile phase elution strategy	**pcs**	**%**
Isocratic methods	128	56.9
Gradient methods*	97	43.1
*One gradient method utilizing mobile phases A, B, and C.	225	100.0

A detailed examination of the equipment requirements for the methods is provided in Table 7. The table shows that most methods (91.1 %) require HPLC systems with a binary pump, while only few methods need additional configuration such as an organic solvent pump head (3.1 %) or a quaternary pump (0.9 %). UHPLC systems accounts for 4.9 % of the methods. This indicates that most LC analytical workflows in quality control rely on standard HPLC configurations with binary pumps. Specialized pump configurations and systems may create bottlenecks if work planning is not clearly defined. These special requirements have been visualized into the current standard timetables for each material.

Table 7. Overview of LC system types based on method specifications.

LC system type requirements	**pcs**	**%**
HPLC (binary pump)	205	91.1
HPLC (binary pump) with organic solvent pump head	7	3.1
HPLC (quaternary pump)	2	0.9
UHPLC (binary pump), contains UHPLC-FID	11	4.9

As outlined in Section 4.1.1. the Raw Material and MIPS team shares the same LC systems, some of which are also utilized by the Gel and Ointment team for specialized purposes. The laboratory operates with 21 LC systems, primarily with HPLC instruments with UV-based detectors, as presented in Table 8. In addition, the QC laboratory includes the Gel and Ointment team, which operates seven additional LC systems; however, this was excluded from the scope of the thesis. The 21 systems include legacy (I) and modern (II) types, indicating a mix of older and newer technology. Detector distribution includes HPLC-VWD in 8 systems (38.1 %, potentially 42.9 % if quaternary pump systems are configured for binary pump use), HPLC-DAD in 8 systems (38.1 %, potentially 47.6 %), and dual-wavelength detection capability in 10 systems (47.6 %). Legacy systems removal in the end of 2025 will slightly reduce redundancy, so planning for replacements or reconfiguration is essential.

Table 8. LC systems and detector types in QC laboratory.

System and detector type	**pcs**	**%**	**VWD-HPLC**	**DAD-HPLC**	**Dual-wavelength capability**	
HPLC-DAD, I*	1	5		x		
HPLC-VWD, I*	5	25	x			
HPLC-DAD, II	5	25		x	x	
HPLC-DAD/ -RID, II (pure solvents only)	2	10		x	x	
HPLC-VWD, II	3	15	x		x	
HPLC-DAD/ -VWD II, with quaternary pump	1	5	(x)	(x)		
HPLC-DAD II, with quaternary pump	1	5		(x)		
UHPLC-DAD-/ -FLD, II	1	5				
UHPLC-DAD, II	2	10				
Systems, total	**21**	100	**8** (9)	**8** (10)	**10**	**pcs**
			38.1 (42.9)	**38.1** (47.6)	**47.6**	**%**
*Two HPLC, I systems (DAD and VWD) will be removed at the end of 2025.						

Detector-specific requirements in LC methods are relatively uncommon, as shown in Table 9. Out of 225 methods, only 44 (19.6 %) explicitly specify a detector type, while the majority (181 methods, 80.4 %) do not, indicating high flexibility in instrument allocation. Among the methods that do require specific detectors, LC-DAD accounts for 8.0 %, LC-VWD for 4.4 %, LC-RID for 5.8 %, and LC-FLD for only 0.4 %. Dual-wavelength capability is relevant for just two methods (0.9 %), suggesting that while useful, it is not a major driver for scheduling decisions. This distribution reinforces the operational insight that detector-specific constraints are minimal, and resource planning should focus on pump configuration flexibility rather than detector type.

Table 9. Detector type requirements in LC methods.

		pcs	**%**
LC detector type requirement	**Yes***	44	19.6
	No	**181**	80.4
*Includes methods identified through practical work and method requirements.			
LC detector type requirement based on the methods	**LC-DAD**	18	8.0
	LC-VWD	10	4.4
	Dual-wavelength method (LC-DAD/ -VWD)	2	0.9
	LC-RID	13	5.8
	n/a	**181**	80.4
	LC-FLD	1	0.4
	Methods, total	225	100.0

As discussed earlier, enabling quaternary pump systems to function as binary pumps would significantly improve cross-utilization and reduce bottlenecks. Furthermore, the planned removal of two legacy systems in the end of 2025 is unlikely to impact detector coverage, as most methods remain detector neutral.

Analysis of mobile phases in CQC

The original purpose, related to the new LC process, was to identify similar types of mobile phases across methods so that this could be utilized in schedule planning for day 1 mobile phase preparation. However, during the first stage of analysis and data review, it became evident that there were many variations in LC methods due to differences in mobile phase composition that they could not be grouped into a new workflow suitable for work planning. It was found that there were 138 distinct final mobile phases across 225 methods, of which only 44 mobile phases were used as-is in at least in two different methods. This means that 181 methods were found unique, with no overlap in mobile phase composition with other methods. Based on this, standardizing mobile phase preparation in the timetable would not significantly improve LC process efficiency, as the overlap between methods is minimal. For this reason, it had to be revised and redefined the purpose and scope of the study. This reassessment is characteristic of the DMAIC approach, as described in section 2.1.1, and its purpose is to add value to the process requiring improvement while ensuring that the problem definition remains stable.

The scope of the mobile phase study was revised to specify the type of stock solutions used in mobile phases (i.e., the base solution), which were divided into two categories: pure solvents and buffer or ion-pairing reagent solutions. The collected data was also reanalyzed to determine how quickly the analysis and mobile phase preparation could be performed. In other words, analyses were identified that could theoretically be completed faster than the standard timetable, for example, in two days instead of three, based on the method. The criteria for fast analyses in terms of mobile phase preparation were as follows:

- The mobile phase does not contain buffer (i.e., it consists of pure solvents).
- No filtration is required.
- No pH adjustment is needed.

- No pre-treatment is required for the equipment, column, or containers (e.g., ethanol treatment).
- Other steps scheduled for days 2 and 3 can be completed quickly.

Based on the data collected, 45 theoretically fast analyses were identified, either according to the method specifications or from previously executed methods recorded in the chromatographic data system. This accounts for 20 % of all methods. The identified fast analysis methods were coded as fast analysis and incorporated into the standard timetable for each material.

As shown in Table 10, more than half of the analytical LC methods (118, 52.4 %) require mobile phase pH adjustment according to method instructions. A significant amount (100 methods, 44.4 %) does not require any adjustment, while 7 methods (3.1 %) specify pH adjustment only if needed. This indicates that pH adjustment is a common and often time-consuming step in method preparation, representing a critical factor in workflow planning and resource allocation.

Table 10. Mobile phase pH adjustment in analytical LC methods.

Mobile phase pH-adjustments based on method instructions	**pcs**	**%**
Yes	118	52.4
No	100	44.4
If needed	7	3.1
Methods, total	225	100.0

It was found that there are 55 different buffer or ion-pairing reagent based mobile phases across 225 methods (represents 24.4 % of all methods), of which 21 types (9.3 % of all methods) were used in at least in two methods. Table 11 illustrates these variations. The most frequently occurring buffer or ion-pairing reagent bases in the methods were KH_2PO_4 in water (found in 32 different methods, with 23 unique concentrations, meaning 9 were identical) and $NaH_2PO_4 \cdot H_2O$ in water (found in 15 different methods, with 8 unique concentrations, meaning 7 were identical). Although the preparations of these mobile phase stock solutions are labor-intensive, they share the same base composition, with differences primarily in concentration or pH adjustment. Consequently, if raw materials requiring methods with the same mobile phase base are scheduled for analysis concurrently, the preparation process could be streamlined. This would allow the use of identical reagents and standardized weighing and filtration steps, thereby improving overall efficiency in mobile phase preparation. To support laboratory schedule planning, each buffer type was assigned a stock solution code. In total, 18 codes were created, as three stock solutions correspond to methods already paired for efficiency due to their high workload, which cannot be completed by a single analyst within an eight-hour workday. The code was designated as SOL X, where SOL refers to solution and X represents a sequential number. These codes were added to standard timetables.

Table 11. Mobile phase stock solutions and corresponding codes in the LC standard timetable.

Buffer material / ion-pairing reagent stock solution (in mobile phases A and B and C)	**Analytical methods (pcs)**	**Different solution concentrations (pcs)**	**Stock solution code**	**Code added into the standard timetable (x)**
($C_2H_9NaO_5$: TEA: CH_3COOH) in H_2O	2	2	SOL 1	x
(K_3PO_4 x H_2O) in H2O	2	1	n/a	Conducted as paired work
(KH_2PO_4 in H_2O) + ($C_6H_{13}NaO_3S$ in H_2O)	2	1	SOL 2	x
(Na_2HPO_4 x 2 H_2O) in H_2O	3	2	SOL 3	x
($NaC_2H_3O_2$ x 2 H_2O) in H_2O-TEA mixture	2	1	SOL 4	x
($NaC_2H_3O_2$ x 3 H_2O) in H_2O	2	1	SOL 5	x
(NaH_2PO_4 x 2 H_2O) in H_2O	4	3	SOL 6	x
(NaH_2PO_4 x 2 H_2O) in H_2O	4	3	SOL 7	x
(NaH_2PO_4 x H_2O) in H_2O	15	8	SOL 8	x
$(NH_4)_2HPO_4$ in H_2O	3	2	SOL 9	x

$(NH_4)_2SO_4$ in H_2O	3	2	SOL 10	x
$(NH_4)H_2PO_4$ in H_2O	6	5	SOL 11	x
$[(Na_2HPO_4 \times 12\ H_2O)$ in $H_2O]$: MeOH: $(CH_2)_4O$ OR $[(Na_2HPO_4 \times 2H_2O)$ in $H_2O]$ (2L)	2	1	SOL 12	x
$C_{16}H_{37}NO_4S$ in H2O	2	2	SOL 13	x
$C_2H_7NO_2$ in H_2O	6	5	SOL 14	x
K_2HPO_4 in H_2O	3	2	SOL 15	x
KH_2PO_4 in H_2O	32	23	SOL 16	x
$NaC_{12}H_{25}SO_4$ in ($C_2H_4O_2$ in H_2O: MeOH: ACN)	2	1	n/a	Conducted as paired work
NaH_2PO_4 in H_2O	3	3	SOL 17	x
($NaH_2PO_4 \times 2\ H_2O_4$) in H_2O	2	1	n/a	Conducted as paired work
NH_4HCO_2 in H_2O	4	4	SOL 18	x

4.4 Improve phase and pilot testing

Improve phase began with updating the standard timetables based on the findings of the analyzing phase. The SOL X markings were updated next to each applicable method and highlighted in yellow for better visibility. In addition, fast analyses in blue were also added to the standard timetables. In both cases, the assumed duration of the analysis remained at three days, and they are updated to reflect post-test reality. An example of these markings can be seen in Table 12.

Table 12. Example of the updated standard timetable.

Person	Analysis	Day 1	Day 2	Day 3	Day 4	Day 5	
	Related substances (HPLC)	Preparing	Samples	Analyzing + result	Review		SOL 16
	Assay (HPLC)	Preparing	Samples	Analyzing + result	Review		FAST ANALYSIS

Brainstorming was conducted for planning the pilot test. Due to the nature of QC planning where next week's schedule is planned mostly on Thursdays, and large part of the LC analyses are started on Mondays, Friday was chosen to be the most suitable day for preparing the mobile phases for next week. Two volunteers were signed for the mobile phase preparation, and other analysts were guided to the test phase.

Pilot test was conducted in weeks 40–44 in 2025, which led to a test phase of five weeks in total. QC planner prioritized SOL X and fast analyses in every week's schedule during the pilot test when possible. Those analyses with SOL X markings were highlighted with an extra notice on the team's week schedule for increasing the visibility. The person preparing the mobile phases independently checked and planned the preparation of mobile phases. SOL X mobile phases were prioritized, and fast analyses were excluded when preparing mobile phases for each week during pilot test phase.

Pilot test included collecting comments and experiences from analysts in written. Also, they were asked to calculate the actual duration of each analysis during the pilot test. This information was collected on Excel file with information about the analysis type, expected duration and used LC system.

4.5 Control phase

After the pilot test, the new ratio of analyses per analyst in one week was calculated during the pilot test, which can be seen on Table 13. The calculation was made based on planning records so that it could be compared to the calculation from the current state.

Table 13. LC analysts, and analysis performed during the pilot test.

Week /2025	Number of LC analysis (pcs)	Number of LC analysts (5 d = 1)	Analysis/analyst ratio
40	12.33	6.60	1.87
41	9.98	6.00	1.66
42	10.32	5.10	2.02
43	7.99	4.80	1.66
44	12.33	4.80	2.57
Average	10.59	5.46	1.96

During the measure phase, it was determined that in the current state the analysis/analyst ratio was 1.71 on average. In the pilot test the ratio increased to an average of 1.96, representing an improvement of 0.25 units. When turned into percents, the improvement is 15 %. When the average number of analysts is approximately 6 each week, it means that based on the pilot test, it could be possible to perform 1.5 more analyses each week, if the new process is implemented.

For gaining a better understanding of pilot test results, other calculations were made based on the data collected from the analysts during the pilot test. These calculations support the conclusion of the results.

Table 14 presents the whole number of performed LC analyses, how many of them included analysis with ”SOL X” marking, how large share had pre-made mobile phase, and how large share of those were performed faster than in 3 days.

Table 14. Performed “SOL X” analyses during the pilot test.

Week	**Performed analyses (pcs)**	**Analyses with "SOL X" (pcs)**	**Analyses with pre-made "SOL X" mobile phases (pcs)**	**Analyses performed with pre-made mobile phases and with smaller actual duration (pcs)**	**Deviation affected the duration (pcs)**
40	15	8	7	6	1
41	12	3	1	1	0
42	9	1	1	0	1
43	7	2	2	0	1
44	9	4	2	2	0
Sum	52	18	13	9	3

As Table 14 illustrates, total amount of LC analyses was 52 during the pilot test. 18 of 52 LC analyses included “SOL X” marking and 13 of those had pre-made mobile phase. 9 analyses of 13 (70 %) had smaller actual duration due to the pre-made mobile phase. It must be noted that there were also 3 deviations, which have affected negatively to the actual duration due to the investigation and re-analyzing actions.

Table 15 presents the same statistics than Table 14, but for those analyses, which does not have the “SOL X” marking. These analyses have unique mobile phases, and there is not any synergy benefit in preparing the mobile phase. However, these mobile phases can be done beforehand, if there is not any “SOL X” analyses in the schedule plan available. For the analyst it is beneficial to have pre-made mobile phase.

Table 15. Performed LC analyses with pre-made mobile phase during the pilot test.

Week	Performed analyses (pcs)	Analyses with other than "SOL X" pre-made mobile phases (pcs)	Analyses with other than "SOL X" pre-made mobile phases and with smaller actual duration (pcs)	Deviation affected the duration (pcs)
40	15	-	-	0
41	12	-	-	0
42	9	1	0	0
43	7	0	0	0
44	9	2	1	0
Sum	52	3	1	0

Three analyses of 52 total amount had pre-made mobile phase, and 1 of those (33 %) was performed with smaller duration. Since the numbers are small, there is uncertainty in reliability.

Table 16 concerns fast analyses, which were recognized in the analyzing phase. There were performed 9 fast analyses, and 5 of those (56 %) were performed with smaller actual duration.

Table 16. Performed fast analyses during the pilot test.

Week	Performed analyses (pcs)	Fast analyses (pcs)	Fast analyses with smaller actual duration (pcs)	Deviation affected the duration (pcs)
40	15	3	2	0
41	12	2	1	0
42	9	2	0	0
43	7	1	1	0
44	9	1	1	0
Sum	52	9	5	0

All the calculations support the result, that with centralized mobile phase preparation it is possible to shorten the lead times of LC analyses. Due to the comparatively short duration of pilot test, there can be some uncertainty in results. If implemented, the new process should be continuously measured and estimated if it improves efficiency but does not affect negatively on the well-being of personnel. In addition, over a half of the analyses recognized as fast analyses were performed faster than in 3 days. This proves the assumption that standard timetables are not accurate for the LC analyses. The overall result of 52 analyses performed during weeks 40-44 shows that 11 analyses were completed faster than three days, representing approximately 21 % of all analyses.

Pilot test was also for collecting information about device selection. Table 17 presents which detector was chosen for different types of analyses.

Table 17. Detector selection by type of analysis.

Detector		**LC-VWD**			**LC-DAD**		
Week	**Performed analyses without detector requirement (pcs)**	**Assay**	**Impurity**	**Assay and impurity**	**Assay**	**Impurity**	**Assay and impurity**
40	14	1	2	3	2	4	2
41	10	2	4	3	0	1	0
42	6	0	1	1	1	2	1
43	6	2	3	0	0	1	0
44	6	0	3	1	2	0	0
Sum	42	5	13	8	5	8	3
		26			**16**		

During the pilot test 42 analyses of total number of 52 of analyses (81 %) did not require a specific detector. This supports the data collection from LC methods where it was calculated that 80.4 % of LC methods do not have a detector requirement. 26 analyses (62 %) were performed with VWD detectors and 16 analyses (38 %) with DAD detectors. Since there were 5 assay analyses performed with both detectors, the difference occurs in impurity analyses. The results from the pilot testing confirm that practices (LC equipment and detector selection) are aligned with the questionnaire findings, and the selection is based (apart from method requirements) on personal experience (own observations and training at the time) and possible outdated knowledge about device performance and features. Additional training from the instrument supplier and key users is recommended.

Based on the equipment selection results, none of the analysts in the pilot test chose an instrument equipped with a quaternary pump for their analyses. Because the methods did not require this type of pump system, it can be concluded that the analysts consistently favored binary pump systems due to familiarity and perceived reliability.

4.6 Implementation plan

Based on the pilot test results, the commissioner decided to implement the new process of LC analysis. In addition, the result of questionnaire supports this decision with positive attitude towards enhanced collaboration. The planned schedule for implementation is in Q1/2026. The implementation phase requires many issues to be addressed before the new process can be taken into use. First, preparation of mobile phases needs to be standardized with proper instructions. Instructions should include the following steps:

1. Selection and verification of reagents (method-specific)
2. Accurate weighting process and documentation (SOP)
3. Dissolution and mixing procedure
4. pH adjustment steps and requires tools
5. Filtration and labeling requirements

6. Storage conditions and expiry information with reference to the relevant SOP
7. Documentation instructions for the mobile phase preparation steps (e.g. reagent logbook or work execution form)
8. Work inspection process (approval and sign-off)

Secondly, schedule planning will change significantly when the mobile phase preparation needs to be planned to every week's schedule on Fridays. In the pilot test it was recognized that evening shift is recommended for the mobile phase preparation since the scheduling can continue to Friday midday, when there is also the weekly meeting of LC analysts.

One major issue in the implementation is planning the control of the method version changes. Method versions of analyses are constantly updated due to Pharmacopeia updates and continuous improvement. Currently, all the data from the LC methods are collected on Excel file, which requires manual updating if method content has been changed. This new process requires that updating the data is included in change management for streamlined control. Also, the standard timetables need to be updated continuously based on the updated changes to ensure effective schedule planning.

A proposed improvement for controlling the data is to transfer the information into the Laboratory Information Management System (LIMS), which would make data management easier and more reliable. This update should be integrated into the method update process: whenever a method version is changed, LIMS should also be updated with information on analysis execution speed and SOL X details. The system could be also utilized to guide the LC equipment selection during the analysis work planning, provided that enough related data has been collected through separate testing and data-gathering activities.

The most important thing in the implementation phase is comprehensive training of the LC analysts. It must be ensured that everyone is aware of the new process and how it is performed. The instructions must be read and understood by every LC analyst. The possibility of misunderstanding should be minimized by clear instructions. To ensure continuous improvement and full implementation of the process, responsible people should be appointed for this implementation, and continuous improvement should be supported by a structured management process integrated into SOPs. Also, a clear feedback mechanism and regular review meetings should be incorporated into daily operations.

After the issues mentioned have been resolved and the new LC process has been implemented in the Raw Material team, it could be expanded to other teams as well. Work has already started at the site to move this forward, for example in the MIPS team, which is expected to adopt the process during 2026.

5 Conclusions

The aim of the thesis was to optimize the LC schedule planning and improve the throughput times of LC analyses in raw material's chemical quality control laboratory. The study used mixed-method approach with qualitative and quantitative methods.

The research questions were:

1. Can lead times in liquid chromatography (LC) analysis be effectively reduced by minimizing operational waste and enhancing planning efficiency?
2. Can resource allocation (instrument and personnel) be optimized to minimize downtime, enhance lead time, and ensure continued compliance with regulatory standards in LC analysis scheduling?

The study started in April 2025 by collecting data from all current LC methods used in raw material's quality control laboratory. Based on the collected data a new LC process was planned. In August questionnaire was sent to LC analysts to gather information on attitudes towards collaboration, mobile phase preparation and device selection. Questionnaire results were analyzed, and the results supported the planned test phase, where the mobile phase preparation was centralized for one analyst, and fast analyses with easy preparation were conducted as two-day analyses. Standard timetables were updated with markings for SOL X solutions and fast analyses to support schedule planning.

Pilot test lasted 5 weeks during September and October in 2025. After the pilot test, the ratio of analyses per analyst performed was compared to the starting point calculated from the beginning of the year 2025. The result was that 15 % improvement of the ratio of analyses per analyst was reached during the pilot test. The conclusion of this thesis is that throughput times of LC analysis can be reduced by minimizing waste with new ways of planning the LC analyses.

Based on the collected data from analysis methods, questionnaire and feedback information from LC analysts from the pilot test, optimizing resource allocation in LC analysis scheduling requires focusing on pump configuration flexibility rather than detector type. LC systems equipped with quaternary pumps should be enabled as binary pump systems to reduce bottlenecks. In addition, the removal of legacy instruments at the end of 2025 will have little impact in current situation, provided that the workload remains unchanged, because most methods are neutral based. Analysts prefer binary pumps highlight the need for cross-training and dynamic scheduling based on method requirements. Preventive maintenance and clear documentation are essential for compliance and reducing downtime. However, these improvements cannot be achieved with minor changes. They require a dedicated project, further research, and a pilot study to confirm the benefits and ensure successful implementation.

The key challenges are related to updating the information which is needed for the new LC analysis process. Centralized preparation of mobile phases for several analysts require that the instructions and other information related to analyses are constantly up to date. The change management and the responsibilities must be planned carefully to ensure the effectiveness of the new process which may require own project. Another challenge is that schedule planning is possible to do one week ahead at maximum due to the short visibility on production needs. Currently the risk of changes during the week is markable. In addition, the visibility of coming samples is weak making predictability more difficult, which is weakening also effective planning. One challenge is the lack of repeatability of weekly plans due to the large number of different raw materials. There are innumerable number of different combinations of weekly schedule plan which complicate implementing the new LC process with comprehensive instructions.

In future with constantly tightening regulations and cost pressures, planning software will be required for ensuring efficient planning. The complexity of different analyses is a big challenge, and technological solutions could solve the problem of handling vast amounts of information. The device selection could be automated in the planning software system to maximize the device utilization.

The physical environment and facilities have a significant impact on Lean practices. At present, the quality control laboratory layout does not fully support Lean-based LC processes. The facilities require modifications, updates, and maintenance because they are based on old infrastructure. Improving the environment would further enhance efficiency of workflow, reduce waste, and support the implementation of new processes.

The thesis result is likely reliable. An improvement of 15 % based on the pilot test is possible, but it contains some deficiencies. The number of improvement rates does not consider where the improvement has happened. It is possible that the improvement is not entirely caused by the changes in process, but there is also evidence that preparation of mobile phases has had a positive impact on throughput times.

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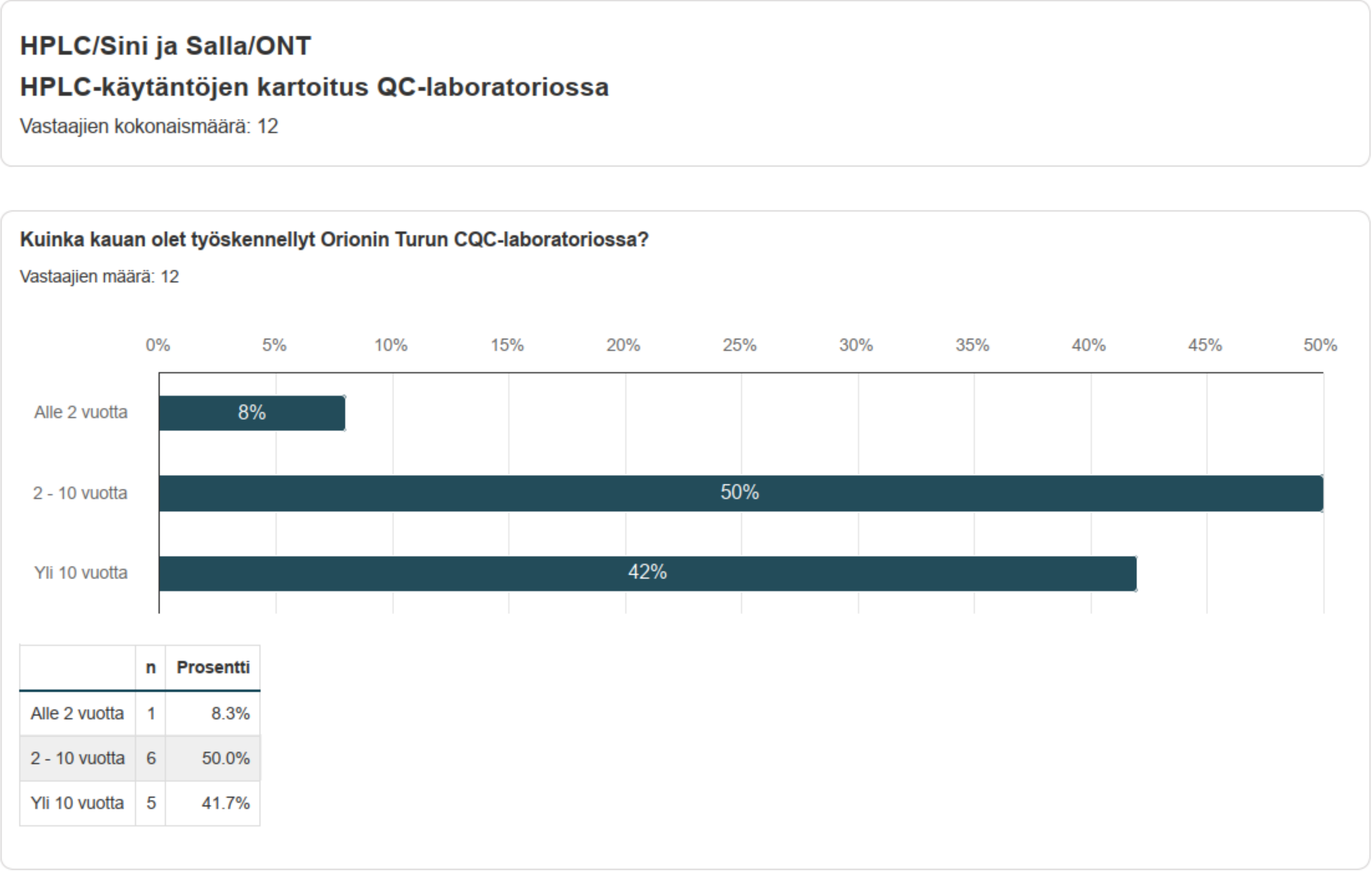
Webropol Survey - Question 1



HPLC/Sini ja Salla/ONT

HPLC-käytäntöjen kartoitus QC-laboratoriossa

Vastaajien kokonaismäärä: 12

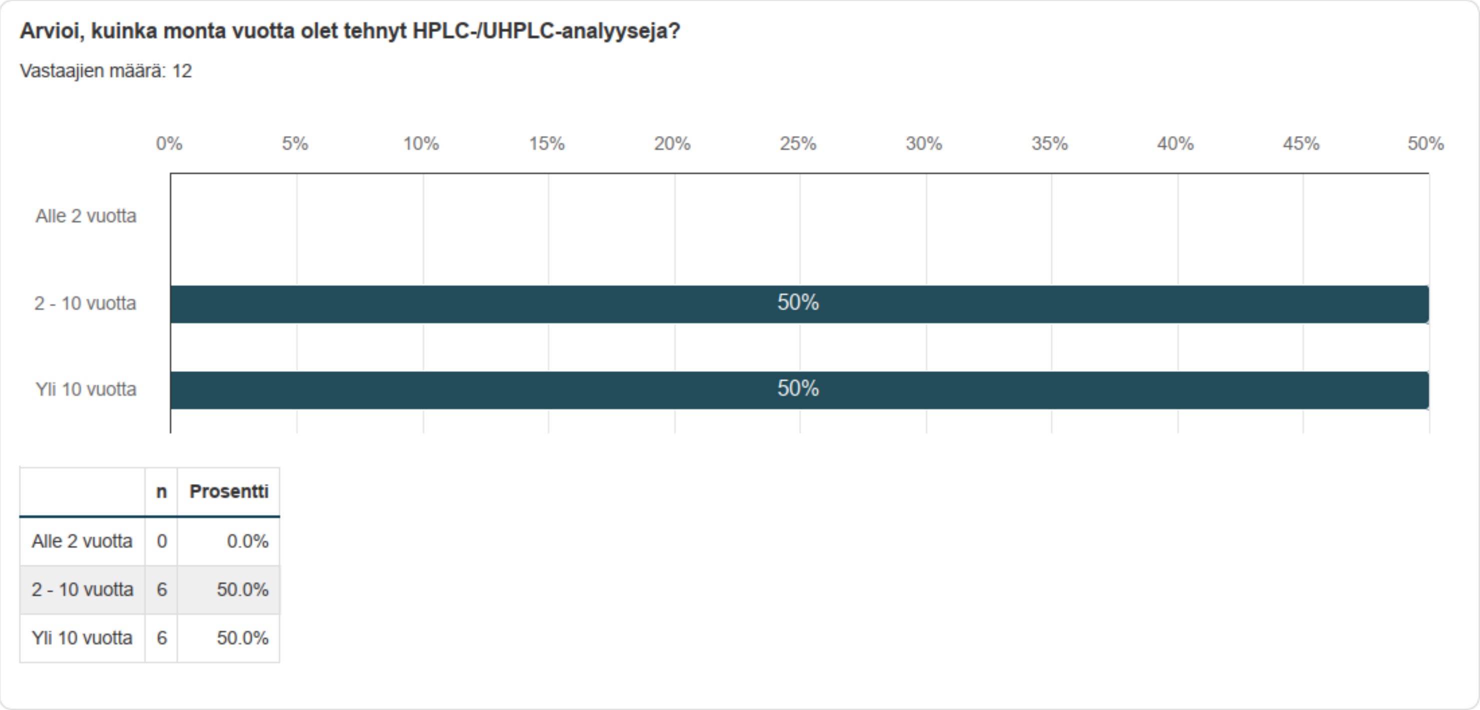
Kuinka kauan olet työskennellyt Orionin Turun CQC-laboratoriossa?

Vastaajien määrä: 12

	n	Prosentti
Alle 2 vuotta	1	8.3%
2 - 10 vuotta	6	50.0%
Yli 10 vuotta	5	41.7%

Appendix 2

Webropol Survey – Question 2

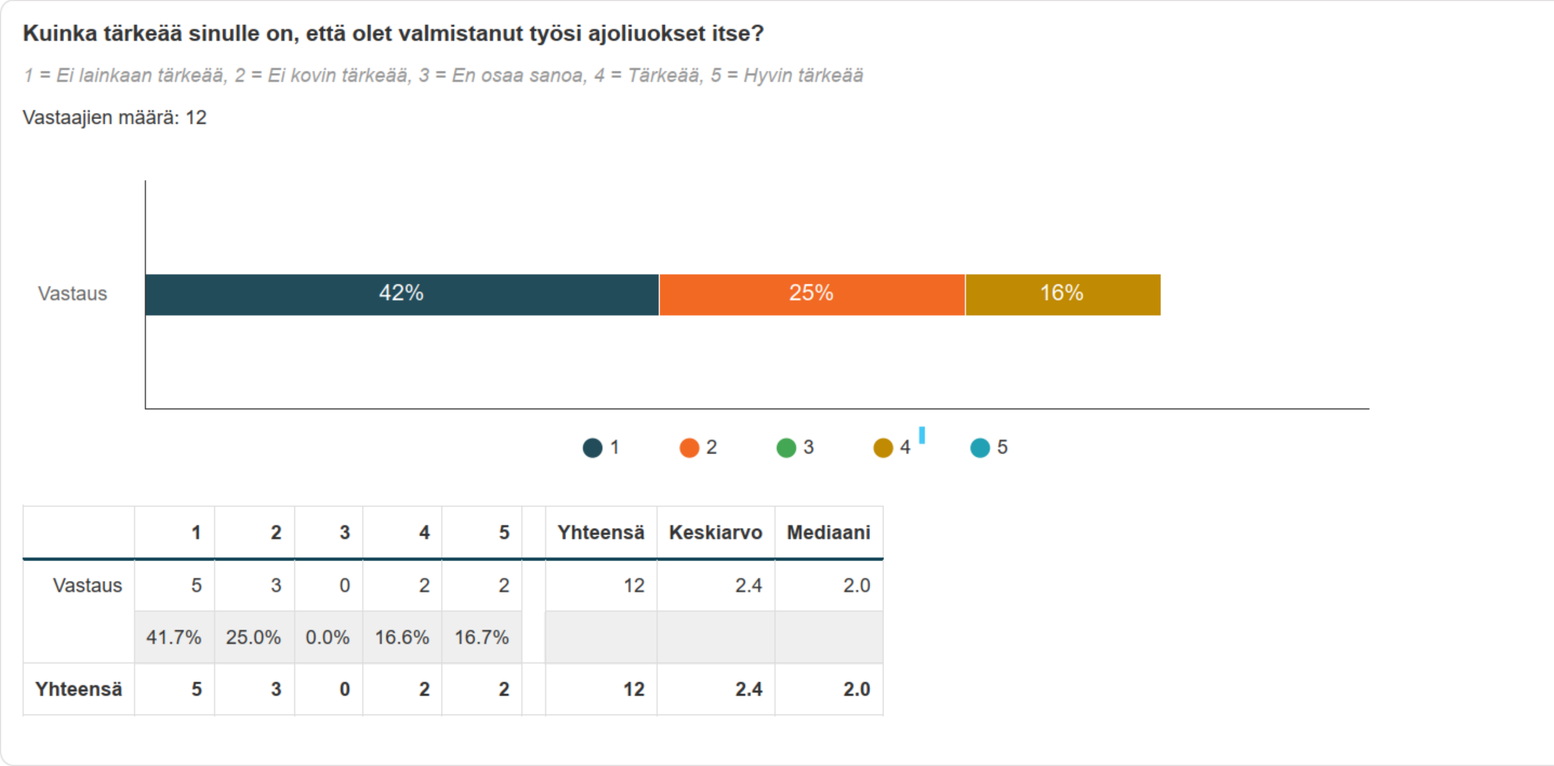


Arvioi, kuinka monta vuotta olet tehnyt HPLC-/UHPLC-analyyseja?

Vastaajien määrä: 12

	n	Prosentti
Alle 2 vuotta	0	0.0%
2 - 10 vuotta	6	50.0%
Yli 10 vuotta	6	50.0%

Webropol Survey – Question 3



Kuinka tärkeää sinulle on, että olet valmistanut työsi ajoliuokset itse?

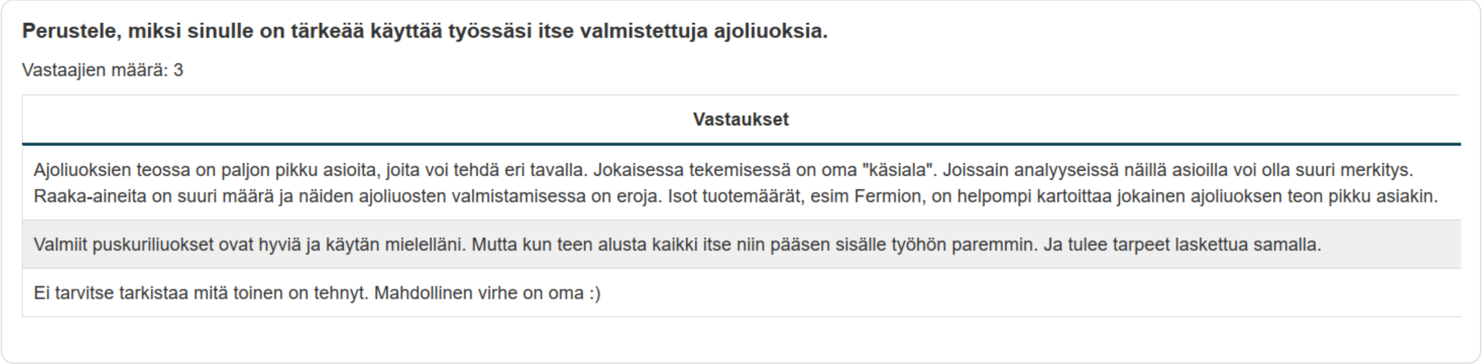
1 = Ei lainkaan tärkeää, 2 = Ei kovin tärkeää, 3 = En osaa sanoa, 4 = Tärkeää, 5 = Hyvin tärkeää

Vastaajien määrä: 12

	1	**2**	**3**	**4**	**5**	**Yhteensä**	**Keskiarvo**	**Mediaani**
Vastaus	5	3	0	2	2	12	2.4	2.0
	41.7%	25.0%	0.0%	16.6%	16.7%			
Yhteensä	**5**	**3**	**0**	**2**	**2**	**12**	**2.4**	**2.0**

Appendix 4

Webropol Survey – Question 4



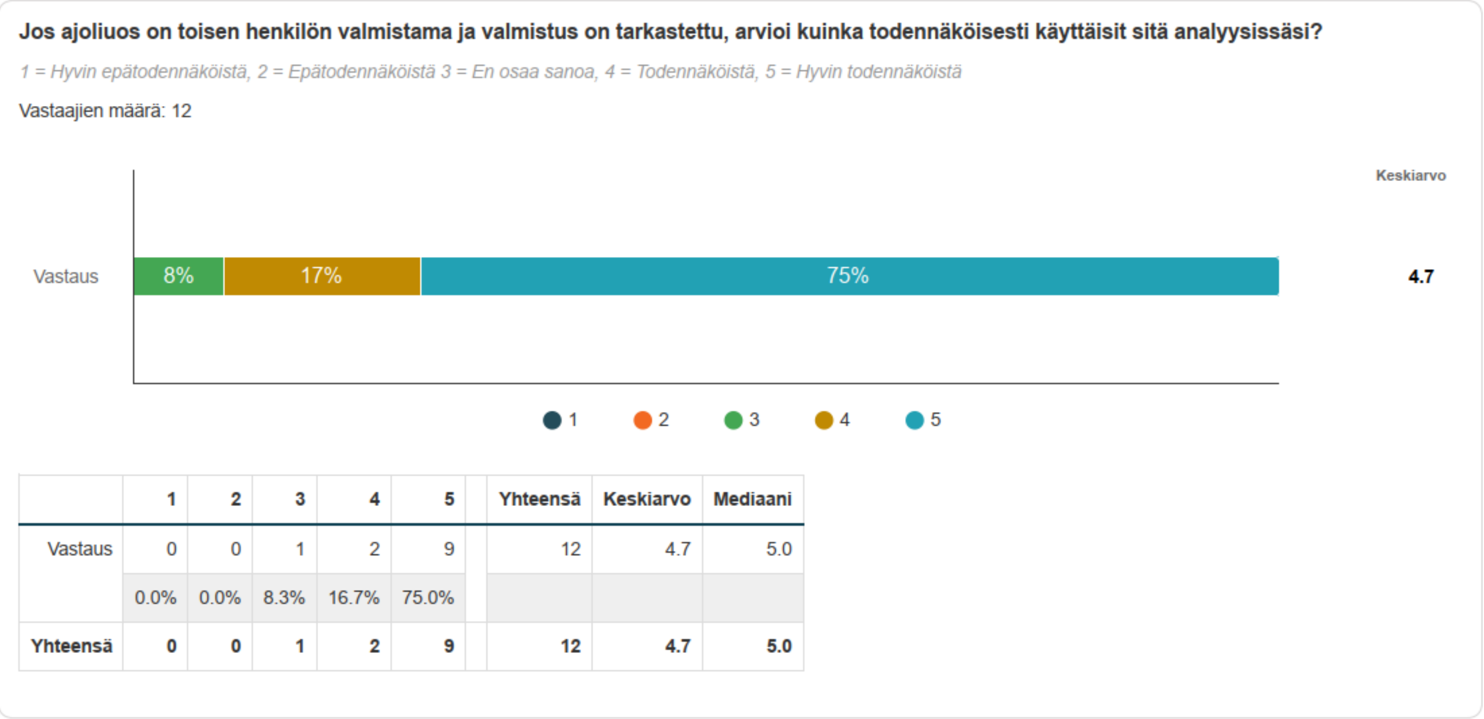
Perustele, miksi sinulle on tärkeää käyttää työssäsi itse valmistettuja ajoliuoksia.

Vastaajien määrä: 3

Vastaukset
Ajoliuoksien teossa on paljon pikku asioita, joita voi tehdä eri tavalla. Jokaisessa tekemisessä on oma "käsiala". Joissain analyyseissä näillä asioilla voi olla suuri merkitys. Raaka-aineita on suuri määrä ja näiden ajoliuosten valmistamisessa on eroja. Isot tuotemäärät, esim Fermion, on helpompi kartoittaa jokainen ajoliuoksen teon pikku asiakin.
Valmiit puskuriliuokset ovat hyviä ja käytän mielelläni. Mutta kun teen alusta kaikki itse niin pääsen sisälle työhön paremmin. Ja tulee tarpeet laskettua samalla.
Ei tarvitse tarkistaa mitä toinen on tehnyt. Mahdollinen virhe on oma :)

Appendix 5

Webropol Survey – Question 5



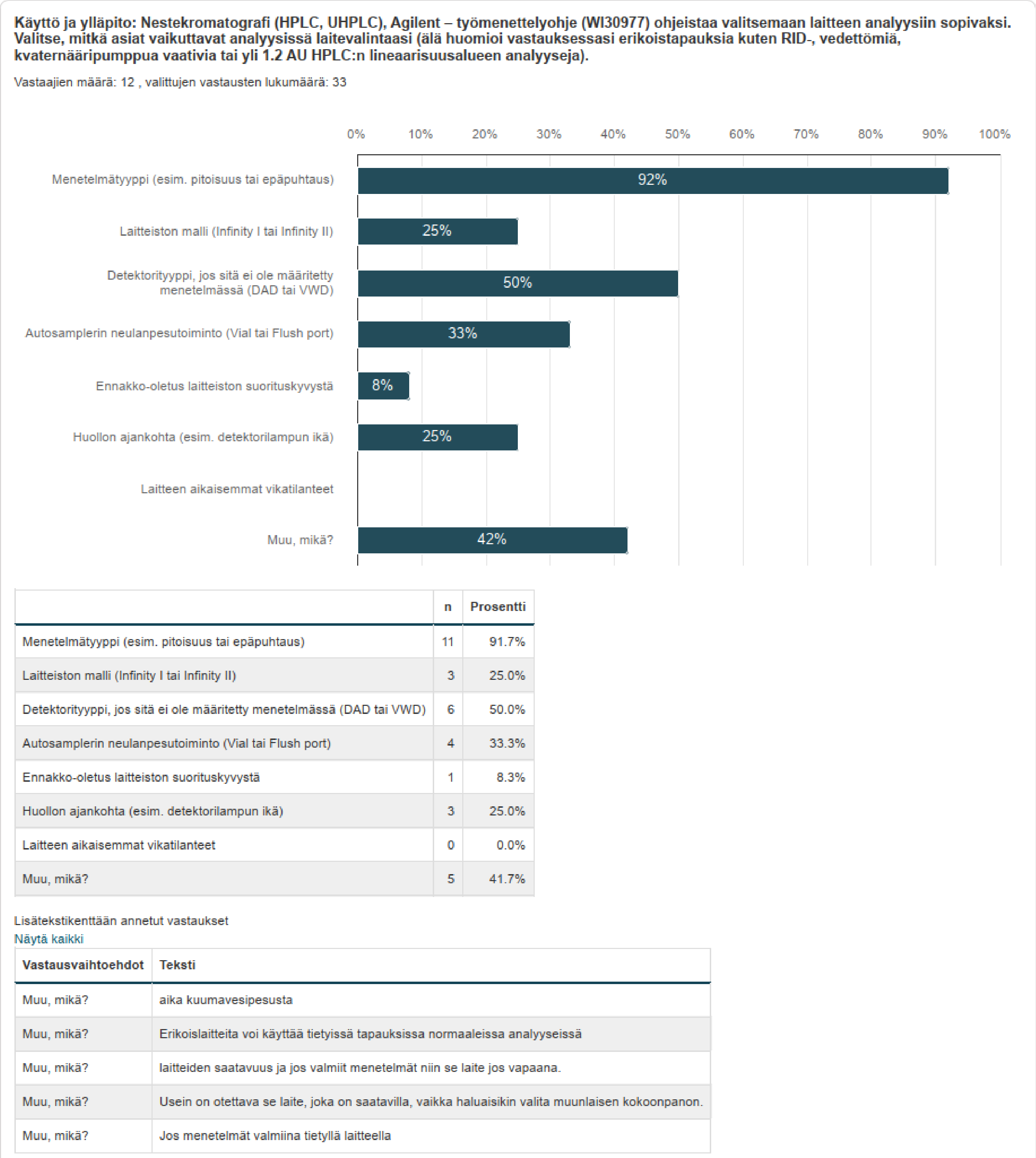
Jos ajoliuos on toisen henkilön valmistama ja valmistus on tarkastettu, arvioi kuinka todennäköisesti käyttäisit sitä analyysissäsi?

1 = Hyvin epätodennäköistä, 2 = Epätodennäköistä 3 = En osaa sanoa, 4 = Todennäköistä, 5 = Hyvin todennäköistä

Vastaajien määrä: 12

	1	**2**	**3**	**4**	**5**		**Yhteensä**	**Keskiarvo**	**Mediaani**
Vastaus	0	0	1	2	9		12	4.7	5.0
	0.0%	0.0%	8.3%	16.7%	75.0%				
Yhteensä	**0**	**0**	**1**	**2**	**9**		**12**	**4.7**	**5.0**

Webropol Survey – Question 6



Käyttö ja ylläpito: Nestekromatografi (HPLC, UHPLC), Agilent – työmenettelyohje (WI30977) ohjeistaa valitsemaan laitteen analyysiin sopivaksi. Valitse, mitkä asiat vaikuttavat analyysissä laitevalintaasi (älä huomioi vastauksessasi erikoistapauksia kuten RID-, vedettömiä, kvaternääripumppua vaativia tai yli 1.2 AU HPLC:n lineaarisuusalueen analyyseja).

Vastaajien määrä: 12 , valittujen vastausten lukumäärä: 33

	n	Prosentti
Menetelmätyyppi (esim. pitoisuus tai epäpuhtaus)	11	91.7%
Laitteiston malli (Infinity I tai Infinity II)	3	25.0%
Detektorityyppi, jos sitä ei ole määritetty menetelmässä (DAD tai VWD)	6	50.0%
Autosamplerin neulanpesutoiminto (Vial tai Flush port)	4	33.3%
Ennakko-oletus laitteiston suorituskyvystä	1	8.3%
Huollon ajankohta (esim. detektorilampun ikä)	3	25.0%
Laitteen aikaisemmat vikatilanteet	0	0.0%
Muu, mikä?	5	41.7%

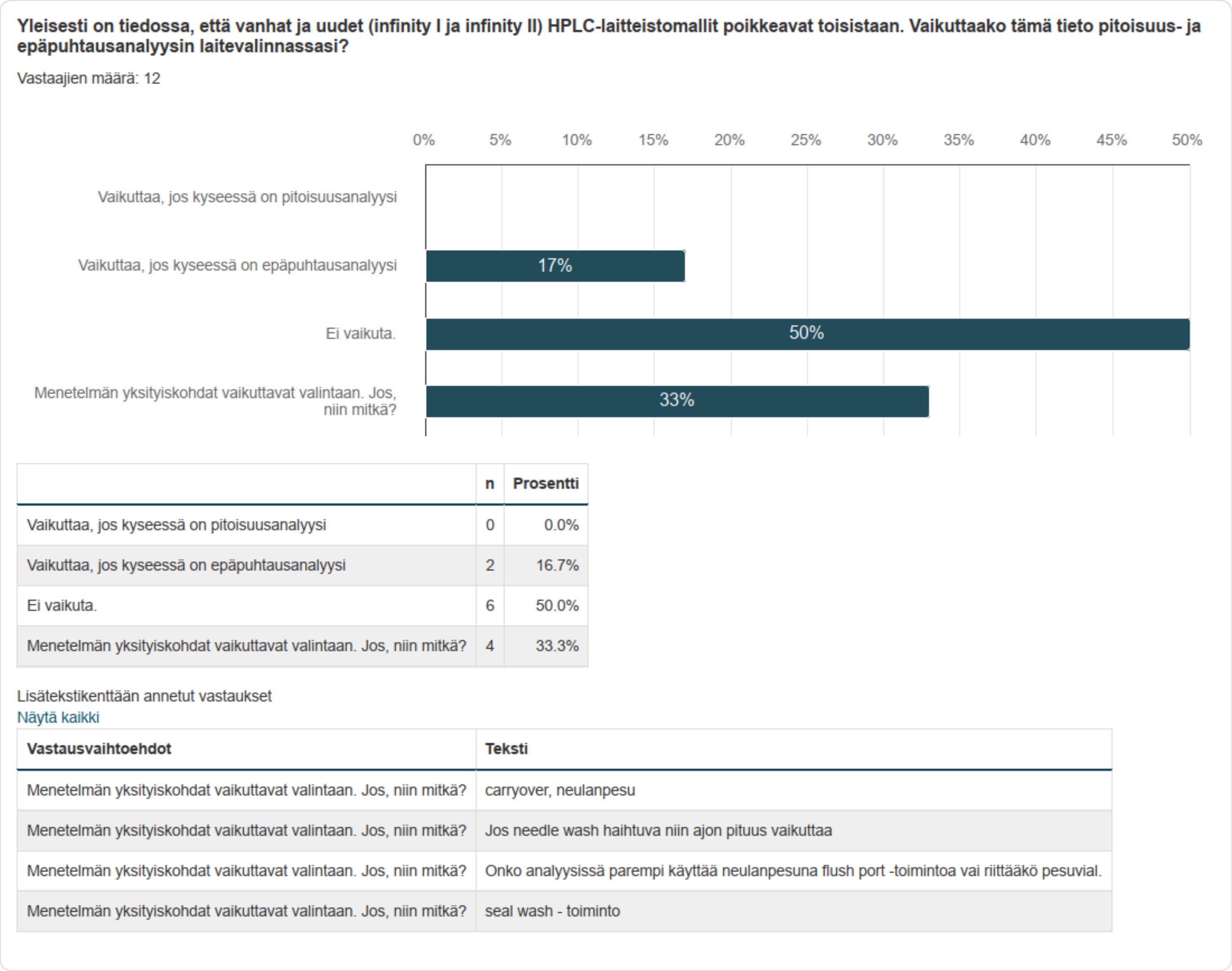
Lisätekstikenttään annetut vastaukset

Näytä kaikki

Vastausvaihtoehdot	Teksti
Muu, mikä?	aika kuumavesipesusta
Muu, mikä?	Erikoislaitteita voi käyttää tietyissä tapauksissa normaaleissa analyyseissä
Muu, mikä?	laitteiden saatavuus ja jos valmiit menetelmät niin se laite jos vapaana.
Muu, mikä?	Usein on otettava se laite, joka on saatavilla, vaikka haluaisikin valita muunlaisen kokoonpanon.
Muu, mikä?	Jos menetelmät valmiina tietyllä laitteella

Appendix 7

Webropol Survey – Question 7



Yleisesti on tiedossa, että vanhat ja uudet (infinity I ja infinity II) HPLC-laitteistomallit poikkeavat toisistaan. Vaikuttaako tämä tieto pitoisuus- ja epäpuhtausanalyysin laitevalinnassasi?

Vastaajien määrä: 12

	n	Prosentti
Vaikuttaa, jos kyseessä on pitoisuusanalyysi	0	0.0%
Vaikuttaa, jos kyseessä on epäpuhtausanalyysi	2	16.7%
Ei vaikuta.	6	50.0%
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	4	33.3%

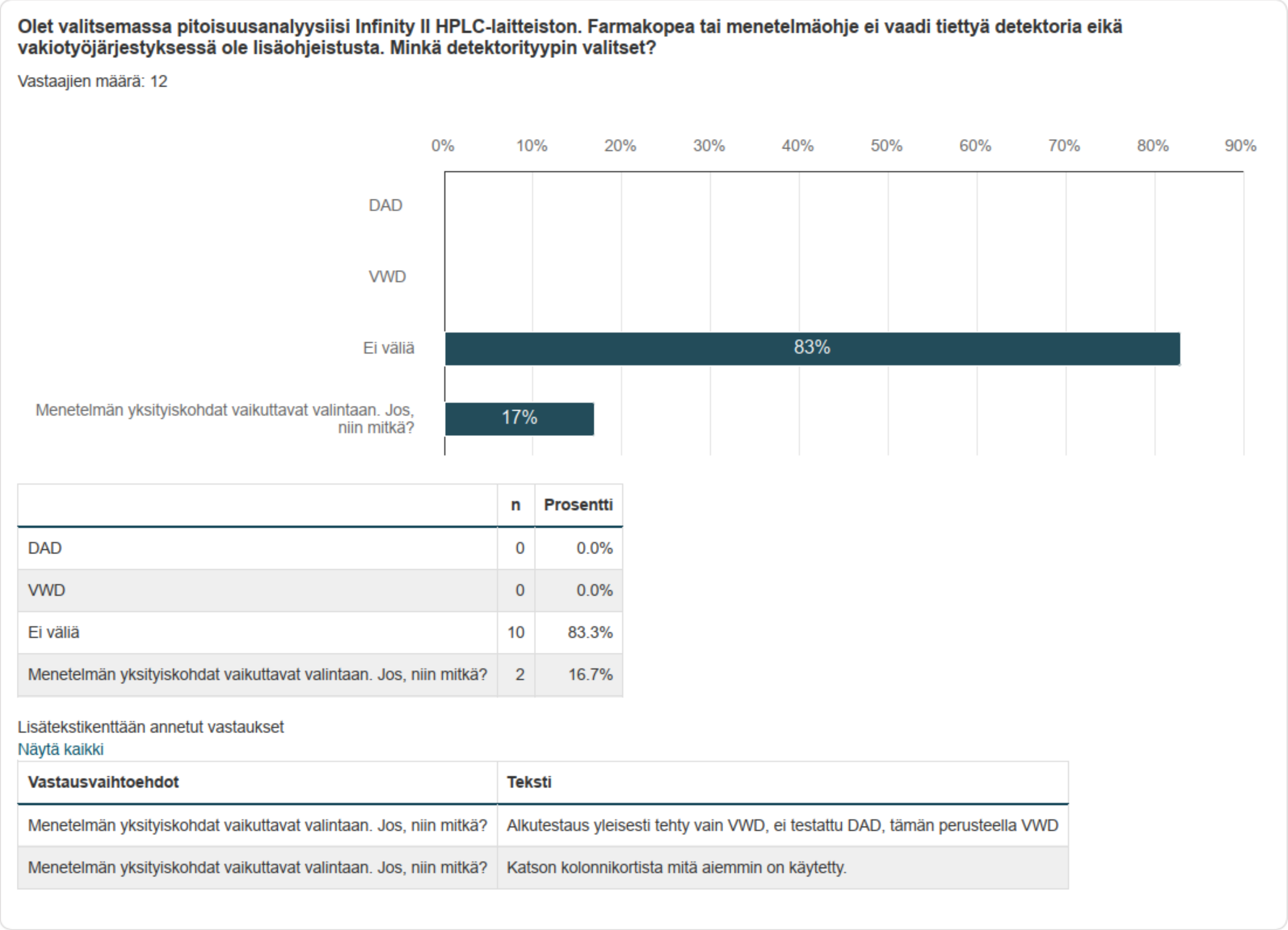
Lisätekstikenttään annetut vastaukset

Näytä kaikki

Vastausvaihtoehdot	Teksti
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	carryover, neulanpesu
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	Jos needle wash haihtuva niin ajon pituus vaikuttaa
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	Onko analyysissä parempi käyttää neulanpesuna flush port -toimintoa vai riittääkö pesuvial.
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	seal wash - toiminto

Appendix 8

Webropol Survey – Question 8



Olet valitsemassa pitoisuusanalyysiisi Infinity II HPLC-laitteiston. Farmakopea tai menetelmäohje ei vaadi tiettyä detektoria eikä vakiotyöjärjestyksessä ole lisäohjeistusta. Minkä detektorityypin valitset?

Vastaajien määrä: 12

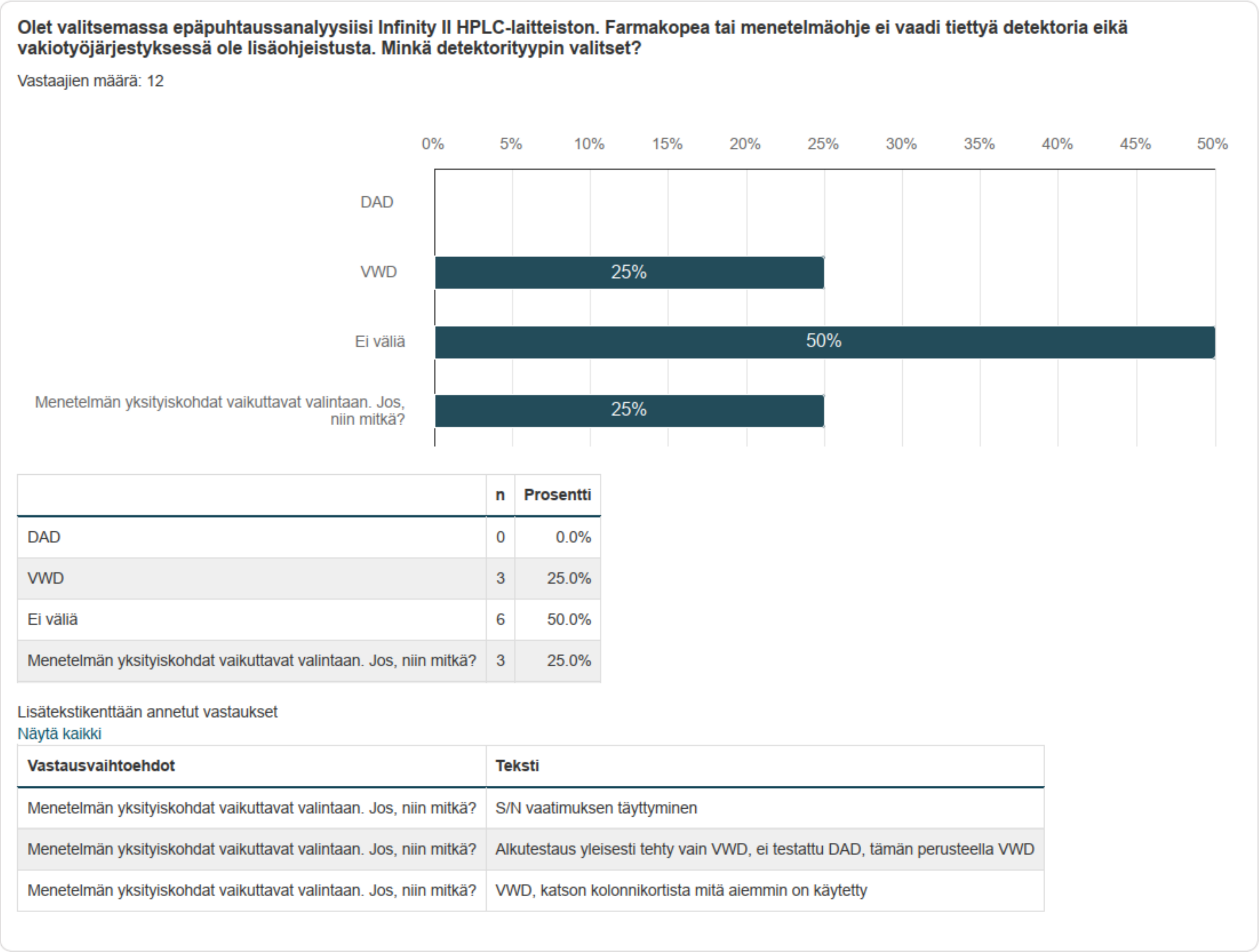
	n	Prosentti
DAD	0	0.0%
VWD	0	0.0%
Ei väliä	10	83.3%
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	2	16.7%

Lisätekstikenttään annetut vastaukset

Näytä kaikki

Vastausvaihtoehdot	Teksti
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	Alkutestaus yleisesti tehty vain VWD, ei testattu DAD, tämän perusteella VWD
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	Katson kolonnikortista mitä aiemmin on käytetty.

Webropol Survey – Question 9



Olet valitsemassa epäpuhtaussanalyysiisi Infinity II HPLC-laitteiston. Farmakopea tai menetelmäohje ei vaadi tiettyä detektoria eikä vakiotyöjärjestyksessä ole lisäohjeistusta. Minkä detektorityypin valitset?

Vastaajien määrä: 12

	n	Prosentti
DAD	0	0.0%
VWD	3	25.0%
Ei väliä	6	50.0%
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	3	25.0%

Lisätekstikenttään annetut vastaukset

Näytä kaikki

Vastausvaihtoehdot	Teksti
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	S/N vaatimuksen täyttyminen
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	Alkutestaus yleisesti tehty vain VWD, ei testattu DAD, tämän perusteella VWD
Menetelmän yksityiskohdat vaikuttavat valintaan. Jos, niin mitkä?	VWD, katson kolonnikortista mitä aiemmin on käytetty