



Next generation toolbox for greener pharmaceuticals design
and manufacturing towards reduced environmental impact

D2.3-Report on the design and specifications of the ENVIROMED sensors

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Executive Summary

The aim of this document is to describe the activities of Task 2.4 as part of WP2, that are related to the definition of the systems requirements specifications and their conceptual designs.

The document provides a high-level description of the three proposed pharmaceuticals monitoring technologies that will be developed in the ENVIROMED project, namely the Wastewater Spectroscopic Analyser, the Online-Inline Liquid Monitoring Analyser, and the Surface Inspection Analyser. It also describes the tailored-designed laser sources, based on the Quantum Cascade Laser (QCL) technology, that will be delivered to support the above-mentioned monitoring technologies.

The document proceeds with the presentation of the technical and functional requirements of the pharmaceuticals monitoring technologies, based also on requirements collected in previous tasks T2.1, T2.2 (presented in D2.1), and requirements related to the use cases (WP5 & WP7) of the three monitoring technologies.

Finally, the document describes the conceptual designs of subsystems and modules of the three monitoring technologies, based on the defined system requirements specifications.

The systems requirements specifications and conceptual designs presented in this document set the basis for the development of the systems under WP4.

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List of Acronyms

Table 1: Acronyms and abbreviations

Term	Definition
ATR	Attenuated Total Reflection
ADE	Allowable Daily Exposure
CBZ	Carbamazepine
DF	Diclofenac
EC	External Cavity
EC-QCL	External Cavity - Quantum Cascade Laser
EMA	European Medicines Agency
EU	European Union
HCTZ	Hydrochlorothiazide
IEEE	Institute of Electrical and Electronics Engineers
IR	Infrared
LMA	Liquid Monitoring Analyser
MCT	Mercury Cadmium Telluride
MCU	Main Control Unit
Mid-IR	Mid Infrared
MIP	Molecular Imprinted Polymer
MIRLS	Mid-IR Laser Sources
MP	Metoprolol
NIR	Near Infrared
PC	polarisation control unit
PDE	Permitted Daily Exposure
PM-IRRAS	Polarization Modulated Infrared Reflection Absorption Spectroscopic System
ppm	Part Per Million
QCL	Quantum Cascade Laser
SIA	Surface Inspection Analyser
SPE	Solid Phase Extraction
Std	Standard
USB	Universal Serial Bus
UV	Ultraviolet
Vis	Visible

WP	Work Package
WSA	Wastewater Spectroscopic Analyser
WW	Wastewater
WWT	Wastewater Treatment
WWTP	Wastewater Treatment Plant

1 Introduction

This deliverable aims to describe the systems requirements specifications, with an initial conceptual design of each monitoring technology with the subsystems' concepts. Initially a high-level description of the different proposed technologies is provided, allowing to the reader for a smooth transition to the system requirements and concept of each technology. Three are the proposed monitoring technologies (Figure 1.) for pharmaceuticals:

- Wastewater Spectroscopic Analyser (WSA) linked to Task 4.2
- Online - Inline Liquid Monitoring Analyser (LMA) linked to Task 4.3
- Surface Inspection Analyser (SIA) linked to Task 4.4

These monitoring technologies will use custom mid-IR laser sources (MIRLS) that will be designed and fabricated under Task 4.1 (Figure 1). Moreover, each technology will undergo laboratory testing and validation within Task 4.5, and validation in real conditions during WP5 and WP7. The following Chapter 2 describes in brief, each of the proposed monitoring technologies and their usage, while Chapters 3 and 4 provide their technical requirements specifications and conceptual designs, respectively. These are based on requirements collected in previous tasks T2.1 and T2.2 (presented in D2.1), and on requirements related to the use cases of the three monitoring technologies as seen in WP5 and WP7 (Figure 1).

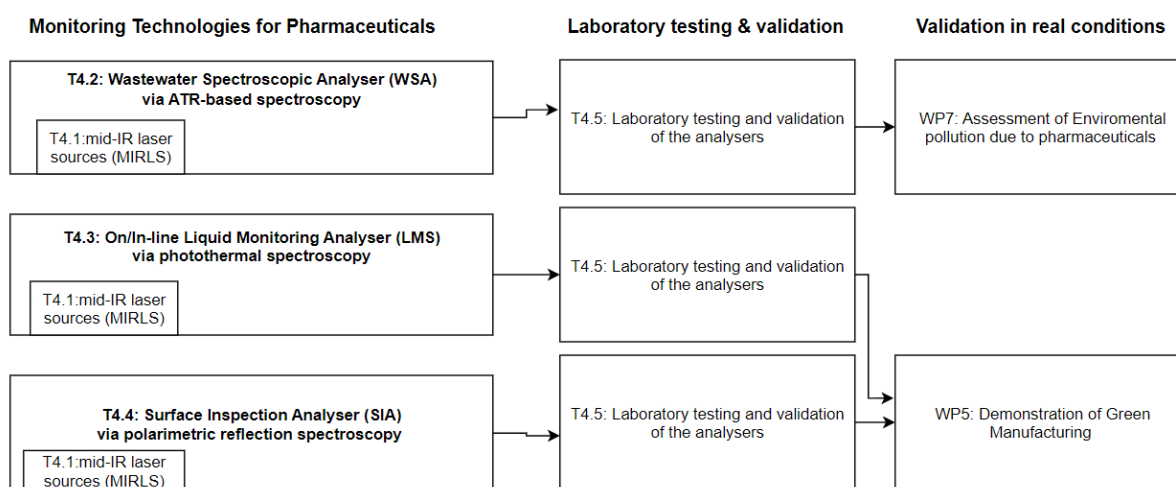


Figure 1. The three monitoring technologies for pharmaceuticals and their validation planning

1.1 Structure

This document is structured as follows:

- Chapter 1: Introduction
- Chapter 2: High level description of the monitoring technologies
- Chapter 3: Systems Requirements Specifications
- Chapter 4: Architecture and Conceptual Designs of the monitoring technologies
- Chapter 5: Conclusions

2 High level description of the monitoring technologies

This chapter provides a high-level description of the three proposed pharmaceuticals monitoring technologies and highlights the purpose of their use.

2.1 Wastewater Spectroscopic Analyser (WSA)

The Wastewater Spectroscopic Analyser will be responsible for the near-real time **monitoring of pharmaceuticals micropollutants in wastewater** and will be used in monitoring campaigns to better understand micropollutants environmental impact. The analyser monitoring technology will rely on mid-IR spectroscopic sensing of high sensitivity, with the usage of molecular imprinted polymers (MIPs) that offer high selectivity to the targeted micropollutants, and on Attenuated Total Reflection (ATR)-based sensing. The WSA (to be developed by UULM & CyRIC) targets to provide a fully automated analysis procedure. Automation most likely will include sample preparation and filtration, since wastewater may include particles that have to be filtered out. In total, two analysers will be needed for the pilots' studies (WP7), a) at MITERA clinical facilities and b) at WWTP monitoring (EYDAP).

The Wastewater Spectroscopic Analyser will consist of the following main units/modules/subsystem as shown in the block diagram below: a) the Spectroscopic Subsystem, b) the Sample Preparation Subsystem, c) the Main Control Unit, and d) the Power Management Module.

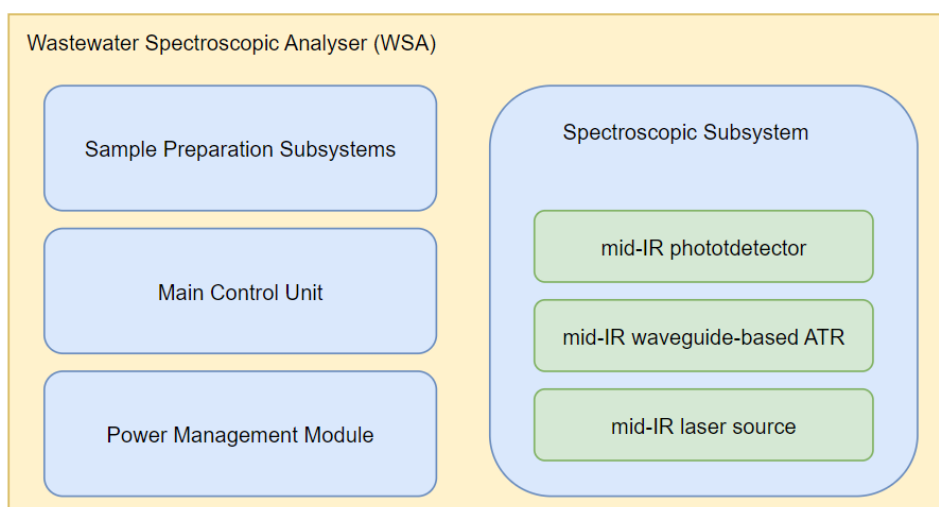


Figure 2. Wastewater Spectroscopic Analyser (WSA) block diagram

The Spectroscopic Subsystem will be responsible for the sensing of complex pharmaceutical pollutants and their metabolites in wastewater, by combining mid-IR lasers (QCLs) for increasing the signal-to-noise ratio of the measurement, and the high sensitivity of mid-IR spectroscopy, with MIPs that renders the sensing of high selectivity. For the implementation of such a sensing scheme, Attenuated Total Reflection (ATR) configuration will be used, where the IR reflected light on the ATR waveguide surface creates an evanescent field in the liquid with an effective depth of penetration up to few tens of micrometres, that enables the interaction of the beam with the liquid and further with the analytes under detection. **The Sample Preparation Subsystem** will be responsible to collect wastewater from the field and drive a small amount of this on the ATR surface to be analysed optically. Sample preparation also involves sample filtration, analyte enrichment, and handling of other substances for cleaning

and maintenance. **The Main Control Unit** will be responsible to control the Sample Preparation Module by driving several hydraulic valves and pumps, and also will be responsible to drive the mid-IR laser sources of the Spectroscopic Subsystem, and record and process the measurement from the photodetector. **The Power Management Module** will handle the power supply of all the above modules.

2.2 Online - Inline Liquid Monitoring Analyser (LMA)

The Online - Inline Liquid Monitoring Analyser will be used **to obtain real time information on the chemical composition (purity) of liquids found in pharmaceutical reactors during cleaning / rinsing steps**. The obtained data can be further used for process control optimisation (e.g., reduction of rinsing chemicals and cycles, etc.). The developed LMA technology will rely on photothermal spectroscopy and take advantage of high-power quantum cascade laser technology to ensure necessary sensitivity for impurity detection at ppm level.

The envisioned LMA instrument will consist of the following main units as shown in the block diagram below:

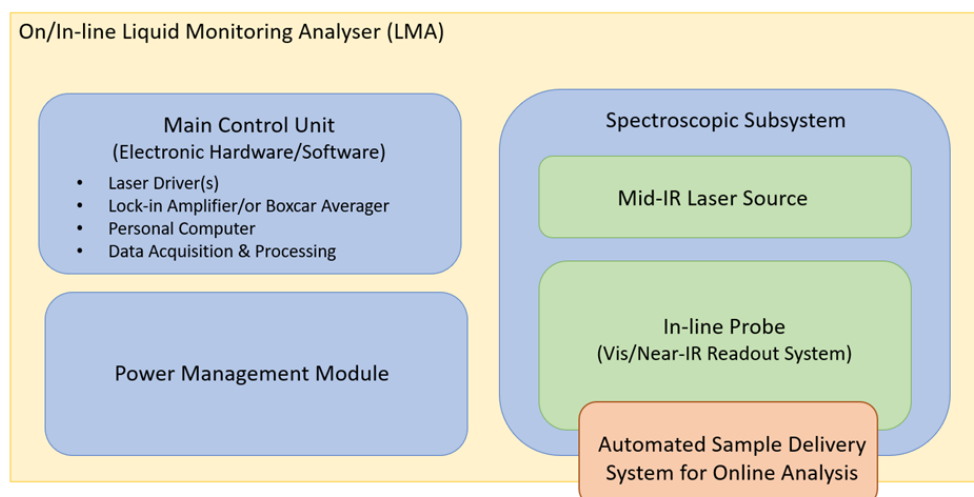


Figure 3. On/In-line Liquid Monitoring Analyser (LMA) block diagram

The Spectroscopic Subsystem will consist of a) a custom tunable quantum cascade laser source (ALPES) and b) a custom designed in-line probe with an integrated Vis/NIR-based optical readout system (TUW).

The mid-IR laser source will be designed to emit in spectral ranges tailored to IR absorption features of the target analytes (impurities) defined by PFIZER and NOVO.

The Vis/NIR-based optical readout system integrated in the in-line probe will measure photothermal response of the liquid sample upon absorption of pulsed mid-IR laser radiation. In this context, temperature induced refractive index changes (proportional to the analyte's concentration) will be measured either by interferometry or by measuring the changes in the probe laser beam propagation after being totally internally reflected from the liquid sample. Thus, the readout system encapsulated in the in-line probe will be comprised of a Vis/NIR laser source, a matched Vis/NIR photodetector and intermediate optical components, e.g., benchtop optics/fibres and/or waveguide optics, for detection of the photothermal signal arising from the

IR absorption. Exact components and their configuration will be defined in the course of the Task 4.3.

The Automated Sample Delivery System for Online Analysis serves as an interface between the spectroscopic subsystem and the process stream (reactor) under investigation. This subsystem can be discarded if the verified LMA technology allows for conversion to the in-line measurements (a spectroscopic probe inserted directly in the reactor).

The Main Control Unit combines the necessary electronic hardware and software to control the elements of the spectroscopic subsystem. It will include components such as pump/probe laser driver(s), lock-in amplifier/boxcar averager, probe temperature control, etc. The aim of this control unit is to a) provide optimised operating parameters to the spectroscopic subsystem (inputs), b) process the acquired spectral data, and c) return qualitative and quantitative information about the liquid composition (outputs). A control software to perform these tasks will be implemented in LabVIEW/MATLAB/or Python. **The Power Management Module** should allow for continuous operation of the LMA instrument during its measurement cycles through a grid supply and/or an integrated battery.

2.3 Surface Inspection Analyser (SIA)

The Surface Inspection Analyser (SIA) will be applied to probe surfaces of pharmaceutical production vessels for potentially remaining substances. The obtained data can facilitate decisions on whether additional rinsing cycles are necessary or redundant, enabling more efficient rinsing and reducing usage of chemicals. The SIA will consist of the following main units/modules/subsystem as shown in the block diagram below: a) the Spectroscopic Subsystem, b) the Optical Measurement Head, c) the Main Control Unit, and d) the Power Management Module.

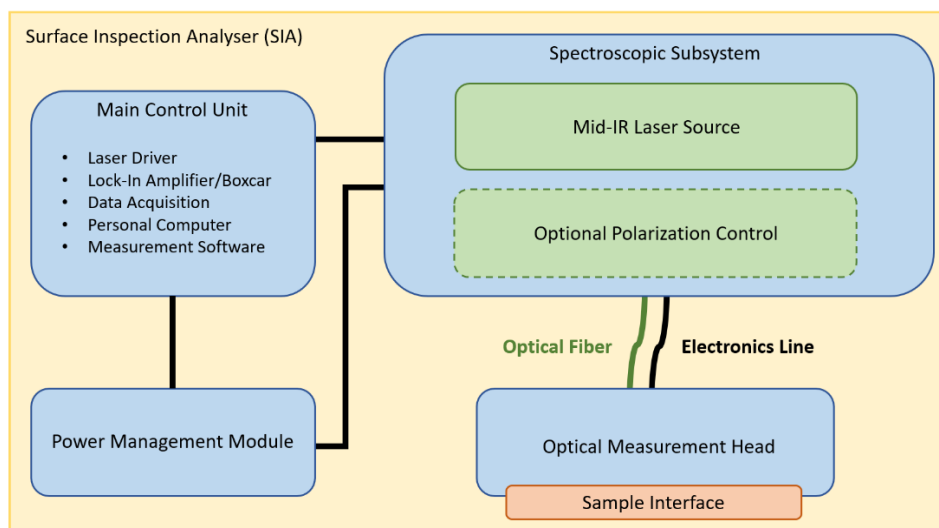


Figure 4. Surface Inspection Analyser (SIA) block diagram

The centrepiece of the developed technology is a designated **Spectroscopic Subsystem** comprising a custom tunable QCL as mid-IR source and an optional device for polarisation control. The tunable QCL will be provided by ALPES and tailored to emit in absorption regimes of target substances defined by PFIZER and NOVO. The emission of the

Spectroscopic Subsystem is guided to an **Optical Measurement Head** via flexible optical fibres for the mid-IR spectral range. While only flexibly connected to the Spectroscopic Subsystem, the Optical Measurement Head provides the interface to the sample surface. The Spectroscopic Subsystem is controlled by a **Main Control Unit** consisting of laser driver, lock-in amplifier, or boxcar averager for signal pre-processing, a data acquisition device connected to a personal computer and a measurement software to control the developed instrument. The electronic power for the respective components is supplied by a **Power Management Module**.

2.4 Mid-IR Laser Sources (MIRLS)

Tailored-designed laser sources emitting in the mid-IR will be delivered, based on the Quantum Cascade Laser (QCL) technology, to support the monitoring technologies described in the previous sections. QCL is an advanced laser system that allows the implementation of robust diode laser systems, tailored to emit in the mid-IR window of the spectrum, namely in the 4 – 12 μm region. Partner ALPES excels in the QCL technology. Within ENVIROMED, ALPES will design and deliver tailored QCL sources emitting in the designated spectral windows needed to detect the analytes of choice for the three use cases. The inputs of the EC-QCL module(s) regards its control of over the selected wavelength of the emitted light, as well as other factor of its operation (e.g., duty cycle), while the output regards the collimated laser beam through an aperture. The laser beam is to be coupled with the main sensor module(s).

The main requirements specifications to be achieved by the novel laser source are:

- Exact spectral windows of the emitted mid-IR laser
- Power per wavelength required
- Beam profile of the emitted laser beam that enables the optimised coupling with the sensing unit
- Control of the laser source by means of a simple interface that defines the specific emission wavelength
- Robustness of the EC-QCL aiming its maintenance-free operation in the field with the need for often recalibration.

3 Systems Requirements Specifications (SyRS)

This chapter describes the system requirements specifications as a follow up of T2.1 and T2.2. The systems' requirements specifications of each proposed technology are defined and presented according to the IEEE Std 1233¹. Specifically, each of the following subsections is referring to a specific technology and the requirements of each system are provided in a Table that indicates for each system's requirements the following:

- a) The id of each requirement,
- b) the source of the requirement (i.e., user, technical community, environment, use case),
- c) type of the requirement (i.e., reliability, availability, maintainability, performance, etc.),
- d) priority (i.e., high, medium, low), and
- e) description of the requirement in terms of the requested capability and its relevant conditions and constraints.

According to the IEEE Std 1233:

Capabilities are the fundamental requirements of the system and represent the features or functions of the system needed or desired by the end user.

Conditions are measurable qualitative or quantitative characteristics that are stipulated for a capability. They further qualify a capability that is needed and provide attributes that permit a capability to be formulated and stated in a manner that can be validated and verified.

Constraints are requirements that are imposed on the solution by circumstance, force, or compulsion. Constraints limit absolutely the options open to a designer of a solution by imposing immovable boundaries and limits.

Concerning the type of each requirement, they were categorised based on the following types, according to the IEEE Std 1233:

- Input (e.g., receive EDI data)
- Output (e.g., export a particular format)
- Reliability (e.g., mean time to failure)
- Availability (e.g., expected hours of operation)
- Maintainability (e.g., ease with which components can be replaced)
- Performance (e.g., response time)
- Accessibility (e.g., different navigation paths for novice and experienced users)
- Environmental (e.g., dust levels to tolerate, temp. range, humidity range, in(out)door)
- Ergonomic (e.g., use of particular colours to reduce eye strain)
- Safety (e.g., below specified limits for electrical magnetic radiation)
- Security (e.g., limits to physical, functional, or data access)
- Facility requirements (e.g., use of domestic electrical current)
- Transportability (e.g., weight limits for portability)
- Training (e.g., includes tutorials or computer-based training)
- Documentation (e.g., on-line help facility)

¹ *IEEE Guide for Developing System Requirements Specifications*, IEEE Std 1233, sponsored by the Software Engineering Standards Committee of the IEEE Computer Society.

- External interfaces (e.g., support for industry standard communication mode/format)
- Testing (e.g., support for remote diagnostics)
- Quality provisions (e.g., minimum required calibration intervals)
- Policy and regulatory (e.g., environmental protection agency policies)
- Compatibility to existing systems
- Standards and technical policies (e.g., products to conform to ASME codes)
- Growth capacity (e.g., will support an additional number of users)
- Installation (e.g., ability to put a new system into service)
- Price
- Durability

3.1 Wastewater Spectroscopic Analyser requirements

The following table provides in detail the WSA requirements:

Table 2: WSA requirements specifications

Req. ID	Source	Req. Type	Priority	Description of requirement
SyREQ_1.1	EU WWT directive ² , D2.1	Performance, Regulatory	High	<p>Capability: the system should be able to measure up to 4 pharmaceutical micropollutants (analytes) that fall into the updated directives for WWT and should be regularly measured. These are:</p> <p>Diclofenac (DF), Carbamazepine (CBZ), Metoprolol (MP), Hydrochlorothiazide (HCTZ)</p> <p>Condition:</p> <p>Targeted concentration range to be measured: ng/L-ug/L.</p> <p>Note: The final range will depend on the enrichment process and the performance of the final spectroscopic analyser.</p>
SyREQ_1.2	EU WWT directive, Use case:	Performance, Regulatory	High	<p>Capability: the system should be able to measure a wide range of micropollutant</p>

² [Proposal for a revised Urban Wastewater Treatment Directive \(europa.eu\)](http://europa.eu)

Req. ID	Source	Req. Type	Priority	Description of requirement
	WWTP Psyttalia (EYDAP)			concentrations (at least 80% difference in concentration). Condition: WWT facility should remove from the effluent water, the 80% of micropollutants found in the influent water.
SyREQ_1.3	Use case: Clinical wastewater facilities (MITERA)	Performance	Low	Capability: the system should withstand 24/7 operation and monitor WW for a total of 12 months. Condition: sampling frequency at least once per month and ideally once per day. Constraint: high dependency on exchangeable parts that need maintenance.
SyREQ_1.4	Technical community, user	Accessibility, Facility requirements	Medium	Capability: the system should be able to send online the analysis' measurements and/or results. Constraint: only Wi-Fi network available at the pilot sites.
SyREQ_1.5	Use cases	Facility requirements	High	Capability: the system should be power supplied via the grid. Constraint: ~220V _{AC} , 50 Hz
SyREQ_1.6	Technical community	Performance	Low	Capability: the system should be able to control/check the inlet-water sampling temperature. Condition: stable sample temperature at $\pm 2^{\circ}\text{C}$ Constraint: temperature range: 15 – 30°C. Note: The average temperature of the water sample in the 2 pilot sites is 15-30°C
SyREQ_1.7	Technical community	Performance, Quality provisions	High	Capability: the system should be able to run analyte enrichment (sample

Req. ID	Source	Req. Type	Priority	Description of requirement
				<p>preconcentration) that involves also sample elution.</p> <p>Condition: targeted analytes recovery >80%</p> <p>Constraint: a) use molecular imprinted polymers (MIP) in a solid phase extraction (SPE) cartridge as the filter, b) low flow rate through filter cartridge to allow some time for the sample (analytes) to interact with the MIP (0,5-4 mL/min, <5bar), c) each analyte needs its specialised MIP cartridge and maybe different elution agent (i.e ethanol, methanol), d) stable sample temperature at 15 – 25°C±2°C, e) air-free filter cartridge</p>
SyREQ_1.8	Technical community, SyREQ_1.7, SyREQ_1.3	Maintainability	High	<p>Capability: the system should be able to regenerate the MIP cartridges and reuse these for another analysis.</p> <p>Condition: a) targeted regeneration cycles >10 times, b) targeted regeneration duration <3 hours.</p> <p>Constraint: regeneration solvent depends on the MIP and the analyte</p>
SyREQ_1.9	Use case EYDAP, technical community	Performance, Quality provisions, Maintainability	Medium	<p>Capability: the system should be able to run pre-filtering of the WW collected from the side, before the SPE (i.e., ~0.7um filter³).</p> <p>Note: Sewage is pre-treated just for removal of grit, heavy solids and large debris (EYDAP).</p> <p>Constraint: facilitate automatic filter exchange</p>
SyREQ_1.10	Technical community,	Performance	High	<p>Capability: the system should use (ALPES) mid-IR laser</p>

³ Batt AL, Kostich MS, Lazorchak JM. Analysis of ecologically relevant pharmaceuticals in wastewater and surface water using selective solid-phase extraction and UPLC– MS/MS. Analytical chemistry. 2008 Jul 1;80(13):5021-30.

Req. ID	Source	Req. Type	Priority	Description of requirement
	SyREQ_1			sources targeting the absorption bands of the analytes under detection. Constraint: a) optical power at around >20mW (pulsed), b) ALPES lasers should be controlled via Ethernet, not USB, c) emitting within the spectral range $1700\text{ cm}^{-1} - 700\text{ cm}^{-1}$, where the chosen analytes have significant absorption peaks.
SyREQ_1.11	Technical community	Performance	High	Capability: the system should be able to drive the sample, after the enrichment, on the sensing area of the ATR waveguide for a static or continuous measurement. Condition: sample quantity on the ATR ~100 μL up to 1 mL. Constraint: a) usage of microfluidic configuration (flow cell) in combination with small pipes ~1-6 mm inner diameter, b) bubble free.
SyREQ_1.12	Use cases, SyREQ_1.7	Accessibility, Facility requirements, Input	High	Capability: the system should be able to collect WW sample from the field. Condition: a) some tens to hundreds of liters of water samples for efficient sample enrichment, b) water collection via water pressure regulation and/or via water pumping. Constraint: a) sample quantity is highly related to the sample enrichment process, b) valves & tubing should be stainless-steel to avoid accumulation of analytes.
SyREQ_1.13	Use cases, SyREQ_1.7	Availability	Medium	Capability: the system should be able to provide near-real time results. Condition: after some hours from the sample collection time. Constraint: analysis duration is highly related to the sample enrichment and elution process.

Req. ID	Source	Req. Type	Priority	Description of requirement
SyREQ_1.14	Technical community	Performance	High	<p>Capability: the system should run an optical analysis described in the following: the laser source is instructed to emit at specific wavelengths and sweep the spectral coverage available. The parameters to control are current, wavelength and duty cycle. For each emission wavelength, a value from the MCT photodetector is to be recorded, allowing to finally construct the full absorption spectrum on which chemometrics are to be applied.</p> <p>Condition: fully automated procedure is targeted.</p>
SyREQ_1.15	Technical community, SyREQ_1.14	Performance	High	<p>Capability: the system should record the voltage signal from MCT photodetector amplifier.</p> <p>Condition: MCU voltage reading requirements: voltage range based on amplifier output, 16–24-bit voltage resolution, ~50 kS/s sampling rate.</p>

3.2 Online - Inline Liquid Monitoring Analyser requirements

The following table provides in detail the LMA requirements:

Table 3: LMA requirements specifications

Req. ID	Source	Req. Type	Priority	Description of requirement
SyREQ_2.1	Use case (PFIZER)	Performance, Regulatory	High	<p>Capability: The LMA analyser should be able to demonstrate the advantages of mid-IR detection and be able to measure weakly UV absorbing molecules like i.e., alcohols in a <u>weakly IR absorbing solvent</u>.</p> <p>Water in organic solvents (i.e.. methanol) is chosen as a model sample system. Alternative model: ethanol (analyte) in methanol (solvent). The other solvents of interest are: acetone, isopropanol, tetrahydrofuran, and water.</p>

Req. ID	Source	Req. Type	Priority	Description of requirement
				Condition: Demonstrating the sensitivities below 100 ppm, ideally matching the EMA Guideline ⁴ EU ADE/PDE calculations.
SyREQ_2.2	Use case (NOVO)	Performance	High	Capability: The LMA analyser should be able to demonstrate the advantages of mid-IR detection of being able to measure weakly UV absorbing molecules like e.g., alcohols in a <u>strongly IR absorbing solvent</u> , such as water. As a model sample system: SDS (analyte) in water (solvent). The other analytes of interest: H ₃ PO ₄ , NaOH, CIP100. Condition: Total organic carbon concentration levels as low as possible, ideally reaching 0.5 ppm.
SyREQ_2.3	User, Technical community	Input, Performance	Medium	Capability: the sample for analysis should be taken on route to waste in a 1-2" pipe (fast loop) using a low-pressure liquid handling unit for transfer to the LMA. Condition: required sample quantity in the liquid flow cell/sensing area below 1 mL. Constraint: maximum sample flow rate on the sensing area below 1 mL/min during measurement.
SyREQ_2.4	Use case	Performance	Medium	Capability: the LMA should be able to provide near-real time results during the measurement sequence (i.e., cleaning process). Condition: response time should be in the range of milliseconds/seconds (excluding the sample transfer to the sensing area of the LMA). Total response time <3 mins.

⁴ [EMA Guideline on Dedicated Facilities and Exposure Limits for Cleaning Validation](#)

Req. ID	Source	Req. Type	Priority	Description of requirement
SyREQ_2.5	User, use case	Availability, Input	Medium	<p>Capability: the LMA should withstand 24/7 operation</p> <p>Condition: sampling frequency several times per day; provide external trigger to activate measurement sequence</p>
SyREQ_2.6	Technical community	Performance	High	<p>Capability: the system should be able to control the temperature of a sampled liquid to match the temperature of the sensing area.</p> <p>Condition: stable temperature of the sample/probe interface within 1°C. Note: typical temperature of analysed liquids 20-80 °C</p>
SyREQ_2.7	Technical community	Performance	High	<p>Capability: the LMA should provide selectivity towards different impurities (inherent with mid-IR detection).</p>
SyREQ_2.8	Technical community	Performance	High	<p>Capability: the LMA should work as follows: the pump laser is instructed to emit at specific wavelengths and/or tune through the available spectral range inducing a photothermal effect in the sample. The pump laser's parameters to control are wavelength, modulation frequency, duty cycle. For each emission wavelength, a value from the probe photodetector is recorded, allowing to construct the full absorption spectrum on which qualitative and quantitative analysis is performed.</p> <p>Condition: fully automated procedure is targeted.</p>
SyREQ_2.9	Technical community	Performance	High	<p>Capability: the LMA should demodulate the probe photodetector signal at pump laser modulation frequency.</p> <p>Condition: pump laser modulation frequency should be within 20 – 300 Hz range</p> <p>Constraint: modulation frequency is bound to the signal strength (i.e., sensitivity).</p>

Req. ID	Source	Req. Type	Priority	Description of requirement
SyREQ_2.10	Technical community	Performance	High	<p>Capability: the LMA should use mid-IR laser source(s) (ALPES) targeting the absorption band(s) of the analytes under investigation.</p> <p>Condition: a) optical power > 100 mW peak power, b) emitting in the spectral range(s) 950 – 1250 & 1500-1700 cm⁻¹, where the analytes (impurities) have significant absorption peaks, c) operating mode: pulsed (500ns – 1 μs pulse width), train of short pulses within 50% duty cycle to achieve low modulation frequencies.</p>
SyREQ_2.11	User, Use cases	Facility requirements, Safety	High	<p>Capability: the system should be power supplied via the grid (or integrated battery).</p> <p>Constraint: ~220V_{AC}, 50 Hz.</p>
SyREQ_2.12	User, Use cases	Transportability	Low	<p>Capability: the LMA should be mobile.</p>
SyREQ_2.13	User, Use cases	Facility requirements	Medium	<p>Capability: the LMA should be operational under laboratory conditions 20 to 25°C.</p>
SyREQ_2.14	User, Use cases	Output	High	<p>Capability: the analyser should display measurement indicators, such as e.g., pass/fail/warning/concentration level.</p>

3.3 Surface Inspection Analyser requirements

The following table provides in detail the SIA requirements:

Table 4: SIA requirements specifications

Req. ID	Source	Req. Type	Priority	Description of requirement
SyREQ_3.1	Use cases	Performance, Quality provisions	High	<p>Capability: The SIA should be able to detect insulin and ibuprofen on steel surfaces of production vessels in pharmaceutical industry.</p> <p>Condition: The SIA should be able to measure insulin concentrations of 0.5 μg/cm² or lower and ibuprofen</p>

Req. ID	Source	Req. Type	Priority	Description of requirement
				concentrations of 0.1 µg/cm ² or lower.
SyREQ_3.2	Use cases	Transportability	Medium	<p>Capability: The SIA should be manually operatable by a single person.</p> <p>Condition: The SIA should be comfortable to carry.</p>
SyREQ_3.3	Use cases	Performance	Low	<p>Capability: Spectra of the surface under investigation should be acquirable in point and shoot measurements.</p> <p>Condition: The operator should be able to investigate areas up to 10×10 cm² of the surface.</p> <p>Note: The spot size is not important as contamination is expected to be distributed homogenously within 10×10 cm².</p>
SyREQ_3.4	Use cases	Performance, Availability	Medium	<p>Capability: The SIA should allow measurements of large areas in reasonable time frames.</p> <p>Constraint: The acquisition time of the SIA should be < 10 s.</p>
SyREQ_3.5	Use cases	Performance, Accessibility	High	<p>Capability: The SIA should be able to measure at hard-to-reach areas.</p> <p>Condition: The SIA should include exchangeable measurement heads for different types of surfaces (curvature, diameter, etc.).</p> <p>Constraint: The diameter of at least one of the exchangeable measurement heads should not be larger than 3 inches.</p>
SyREQ_3.6	Use cases	Performance, Accessibility	High	<p>Capability: The SIA should be able to measure 10 cm</p>

Req. ID	Source	Req. Type	Priority	Description of requirement
				<p>inside pipes with a diameter of 3 inches.</p> <p>Condition: The exchangeable measurement heads should be connected to the spectroscopic subsystem by an optical guide such as fibers or light pipes.</p> <p>Constraint: The length of the optical guide should be 10 cm at least.</p>
SyREQ_3.7	Use cases	Performance	Medium	<p>Capability: During spectral acquisition, the SIA should be in a stable position.</p> <p>Condition: The SIA should be in direct contact with the surface under investigation. Note: At least 2 exchangeable sample interfaces with different curvatures should be available for the measurement heads.</p>
SyREQ_3.8	Use cases	Performance	High	<p>Capability: The SIA should be able to detect remaining substances on the most common surfaces of production vessels in pharmaceutical manufacturing.</p> <p>Condition: The SIA should be able to measure stainless-steel surfaces (316L) with finish 7 or higher.</p>
SyREQ_3.9	Use cases	Maintainability, Environmental	Medium	<p>Capability: The SIA should be operatable in class B environment.</p> <p>Condition: The SIA should be cleanable to fulfil the requirements for class B environments.</p>
SyREQ_3.10	Use cases	Availability, Facility requirements	Medium	<p>Capability: The SIA should be operatable without additional power supply.</p>

Req. ID	Source	Req. Type	Priority	Description of requirement
				<p>Condition: The SIA should be battery powered.</p> <p>Constraint: The battery should enable 1 hour of measurement time.</p>
SyREQ_3.11	Use case	Output	High	<p>Capability: The SIA should be fully controllable by the operator. Indicators for correct measurements should be available. Acquired spectra should be named and saved with time stamps.</p> <p>Condition: The SIA should be operated via a graphical user interface.</p>
SyREQ_3.12	Technical community	Performance	High	<p>Capability: the SIA should use mid-IR laser source(s) (ALPES) targeting the absorption band(s) of the analytes under investigation.</p> <p>Condition: a) average optical power of >15mW (3 chips), b) emitting in the spectral range(s): prioritized chip#1 1605 – 1810 cm⁻¹ & chip#2 805 – 1100 cm⁻¹, where the analytes (ibuprofen and insulin) have significant absorption peaks, c) operating mode: pulsed, c) a fiber coupling module option is preferred, d) scan rate on the scale of tens milliseconds (>50 Hz rate), e) pulse repetition rate >100 kHz, f) system with no water cooling required.</p>

3.4 Mid-IR laser sources requirements

The following table provides the MIRLS requirements as sources from the monitoring technologies requirements:

Table 5: MIRLS requirements specifications

Req. ID	Source	Req. Type	Priority	Description of requirement
SyREQ_4.1	SyREQ_1.10	Output	High	Capability: mid-IR laser source should emit within the spectral range $1700\text{ cm}^{-1} - 700\text{ cm}^{-1}$ with an optical power around $>20\text{mW}$, where the chosen analytes, targeted by WSA, have significant absorption peaks.
SyREQ_4.2	SyREQ_2.10	Output	High	Capability: the mid-IR laser source(s) (ALPES) should target the absorption band(s) of the analytes under investigation by the LMA. Condition: a) optical power $> 100\text{ mW}$ peak power, b) emitting in the spectral range(s) $950 - 1250$ and $1500-1700\text{ cm}^{-1}$, where the analytes (impurities) have significant absorption peaks, c) operating mode: pulsed ($500\text{ns} - 1\text{ }\mu\text{s}$ pulse width), train of short pulses within 50% duty cycle to achieve low modulation frequencies.
SyREQ_4.3	SyREQ_3.12	Output	High	Capability: the SIA should use mid-IR laser source(s) (ALPES) targeting the absorption band(s) of the analytes under investigation. Condition: a) average optical power of $>15\text{mW}$ (3 chips), b) emitting in the spectral range(s): prioritised chip#1 $1605 - 1810\text{ cm}^{-1}$ & chip#2 $805 - 1100\text{ cm}^{-1}$, where the analytes (ibuprofen and insulin) have significant absorption peaks, c) operating mode: pulsed, c) a fiber coupling module option is preferred, d) scan rate on the scale of tens milliseconds ($>50\text{ Hz}$ rate), e) pulse repetition rate $>100\text{ kHz}$, f) system with no water cooling required.

4 Architecture-Conceptual Design of the monitoring technologies

This chapter describes the conceptual designs of subsystems and modules of the three monitoring technologies as well as of the Mid-IR laser sources, based on the defined system requirements specifications.

4.1 Wastewater Spectroscopic Analyser conceptual design

The conceptual designs of the subsystems/modules/units of the WSA are provided below.

The following figure presents conceptual designs of the spectroscopic subsystem. The flow-cell integrates either a silver halide (AgX) fiberoptic waveguide (non-tapered or tapered) or a single-mode thin-film semiconductor waveguide (MIRA-guide; GaAs/AlGaAs), as schematically shown in Figure 5(a) and (b). A detailed view of the sensing area at the AgX fiber is given in Figure 5(b). The IR beam propagates by total internal reflection along the AgX fiber and interacts with analyte molecules at the surface of the fiber via evanescent field absorption. The analyte molecules are detected within the penetration depth (i.e., few micrometers) of the exponentially decaying evanescent field. A prior MIP/SPE process will enrich the analyte molecules within the sample, before this reaching the sensing area. Optionally and as a backup plan, the waveguide surface may be coated with an additional polymer membrane that can be used for enrichment. The hydrophobic polymer only enriches hydrophobic analytes (i.e., pollutants), which interact with the generated evanescent field⁵.

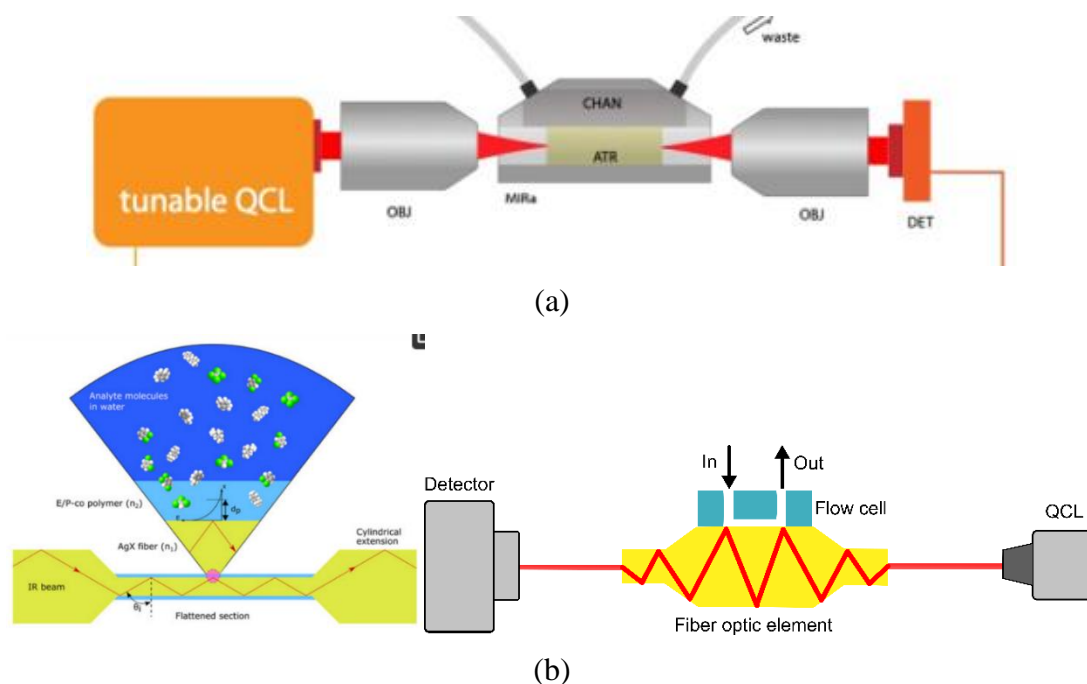
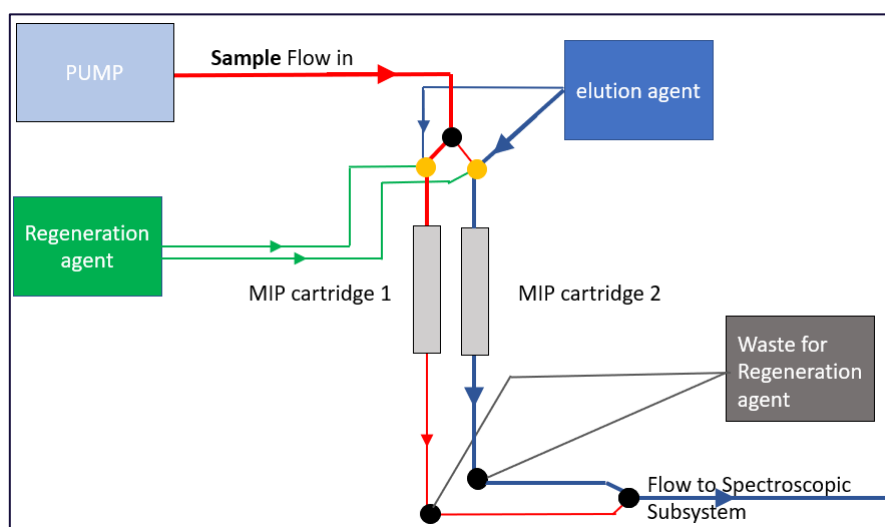
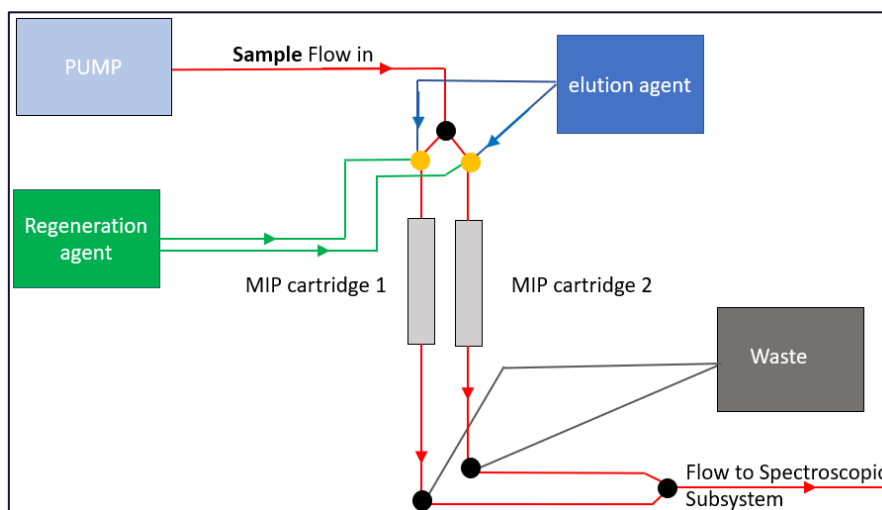


Figure 5. Conceptual design of the spectroscopic subsystem a) using thin-film semiconductor waveguides or b) silver halide fiberoptic waveguides

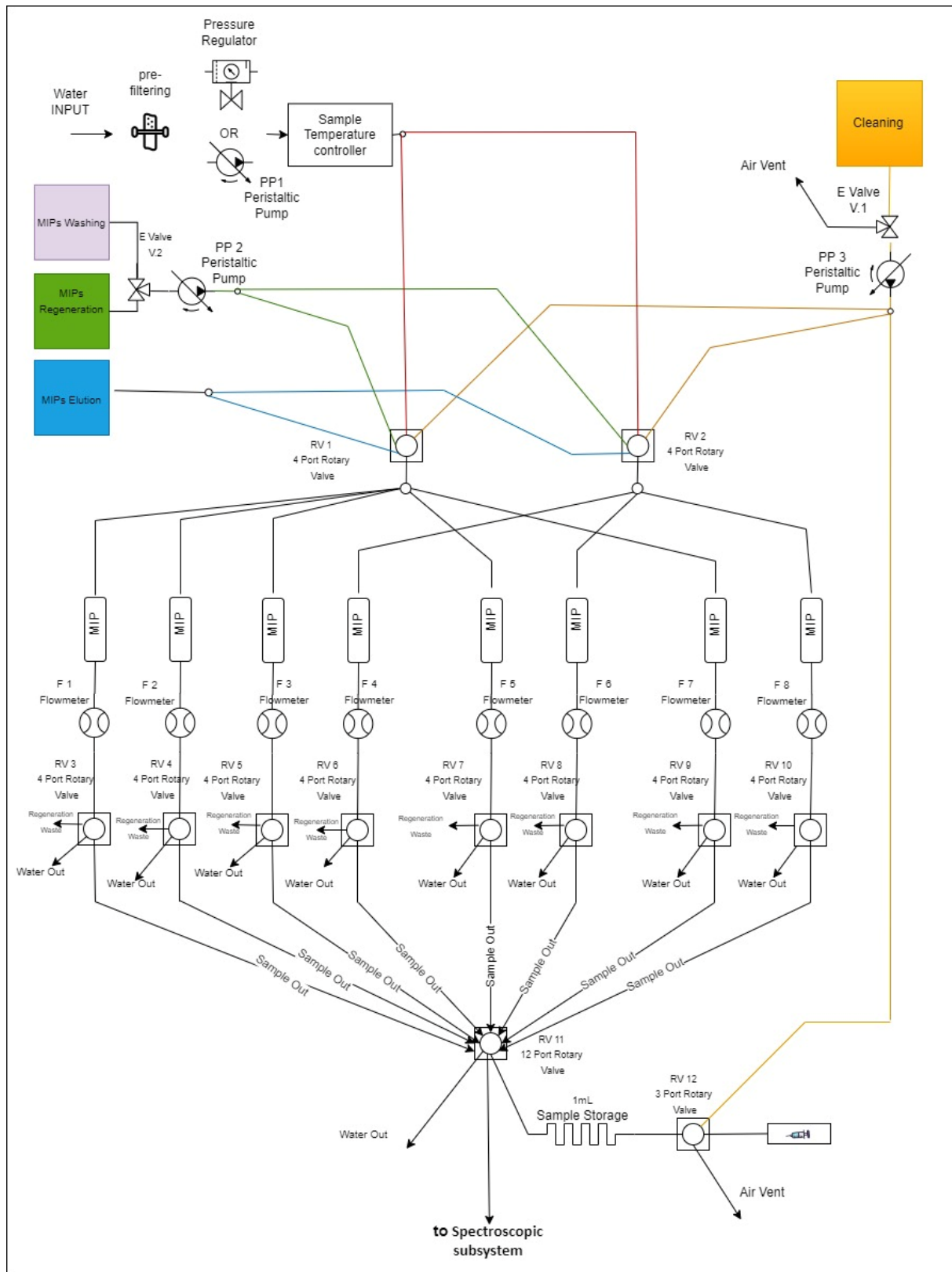
⁵ C. Dettenrieder et al., *Toward the Required Detection Limits for Volatile Organic Constituents in Marine Environments with Infrared Evanescent Field Chemical Sensors*, *Sensors* 2019, 19(17), 3644; DOI:[10.3390/s19173644](https://doi.org/10.3390/s19173644)

Figure 6 presents the general conceptual design (a) and two detailed conceptual designs (b & c) of the Sample Preparation Subsystem of WSA. The general idea as depicted in Figure 6(a), involves water sampling and sample enrichment (preconcentration) via MIP cartridge 1, and then washing of the unbonded molecules and elution of the analytes trapped in the MIP filter, and spectroscopic analysis of the sample, followed by MIP regeneration procedure for preparing the MIP cartridge 1 for another analysis. While MIP cartridge 1 is under elution/regeneration, the MIP cartridge 2 is used in parallel for sample enrichment and in that way the 2 cartridges work alternately. The detailed conceptual designs portrait 8 cartridges to serve the detection of 4 different analytes based on the requirements (SyREQ_1.1).

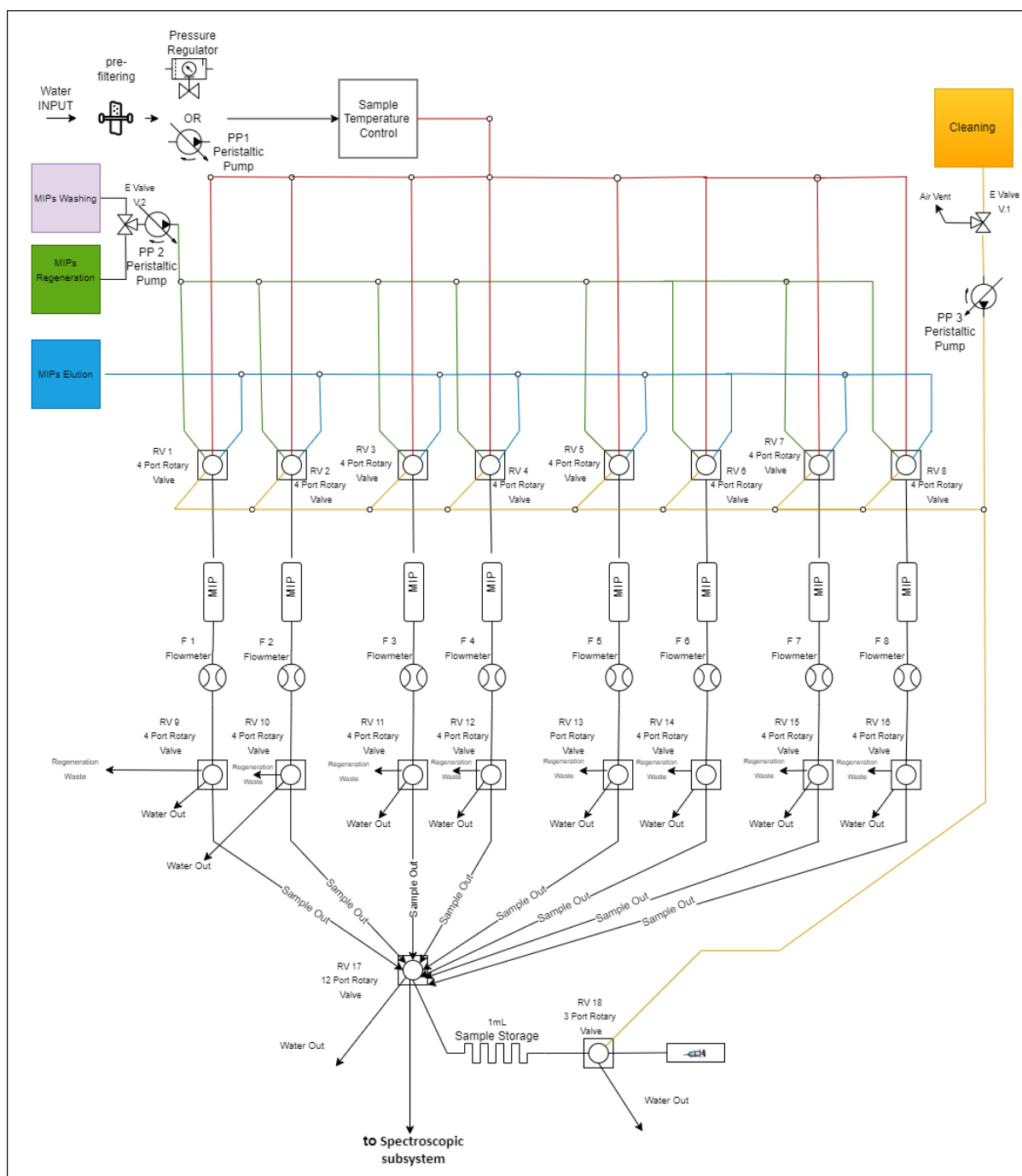
The main differences between the two concepts are that the second one, depicted in Figure 6(c), has the potential to handle different elution and regeneration solution in case it is needed, and the first concept, depicted in Figure 6(b), uses less 4-port rotary valves for reducing the cost and complexity of such configuration. Peristaltic pumps are used in the design for the liquid handling, while a syringe pump is used for driving the sample into the sensing area. Other main features of the sample preparation subsystem as seen in Figure 6(b) and (c) are: a) pre-filtering of the inlet water (potentially with automatic filter exchange mechanism), b) temperature control of the water sample, and c) cleaning procedure for the valves and the tubing.



(a)



(b)



(c)

Figure 6. The general (a) and two detailed conceptual designs (b,c) of Sample Preparation Subsystem

The MCU will be responsible for: a) Controlling the EC-QCL laser, b) Measuring the output of the photodetector after amplification, c) Communicating the results of the analysis wirelessly, d) Controlling the hydraulic parts of the system that include peristaltic pumps, rotary & electric valves, flow meters, syringe pump, pressure sensor (optional), level sensor (optional) and a filter exchange mechanism. Figure 7 presents the connections and interfaces of the MCU with the different parts/modules of the WSA system.

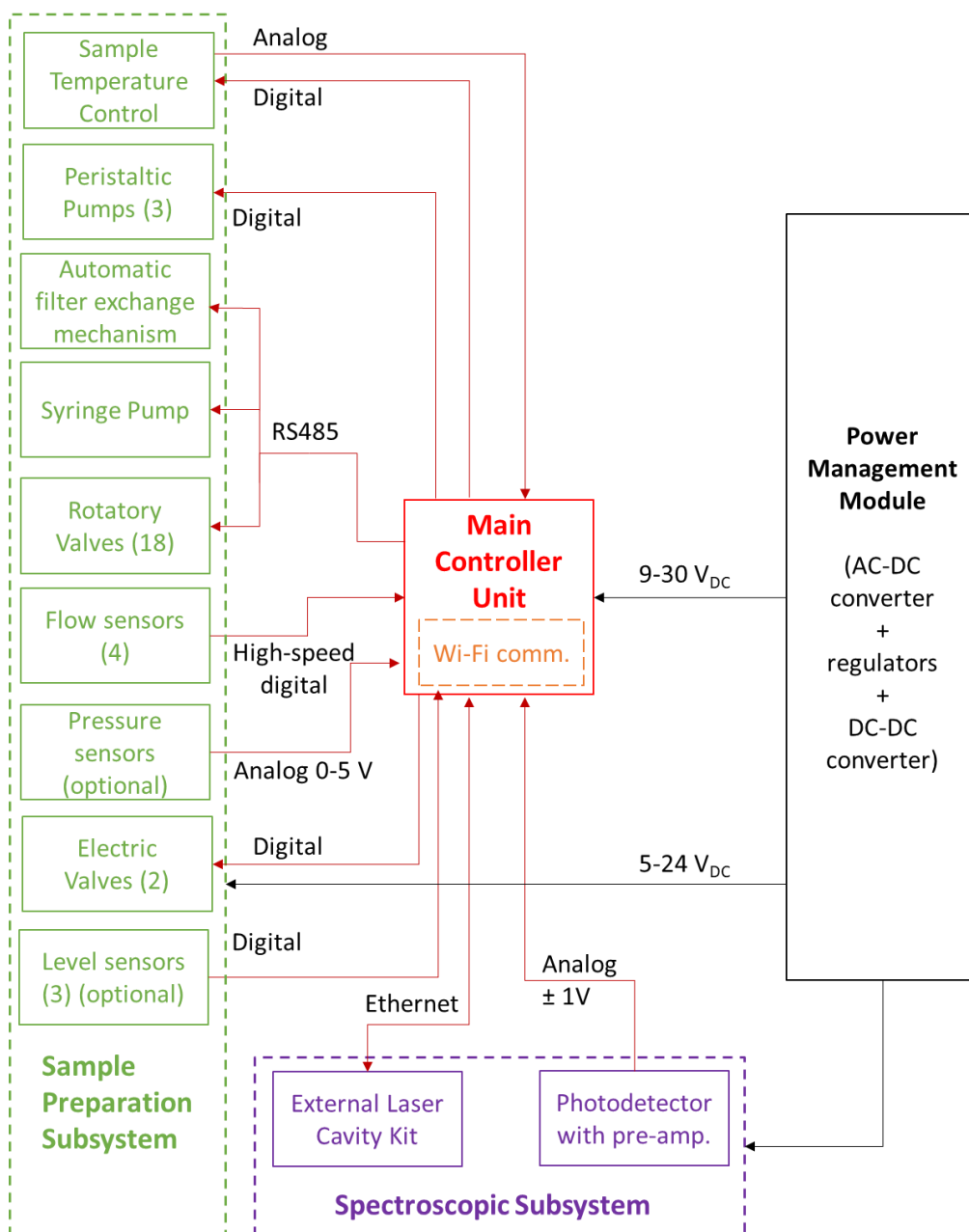


Figure 7. The conceptual design of the Main Control Unit with the Power Management Module

4.2 Online - Inline Liquid Monitoring Analyser conceptual design

The considered conceptual designs of the subsystems/modules/units of the LMA are provided below. Different spectroscopic subsystem configurations will be tested within WP4.3 for their capability to meet the requirements specified in section 3.2 of this deliverable. Finally, the most optimum configuration will be selected for the LMA sensor. All these above configurations are suitable for online analysis. In addition, configuration c) is particularly suitable for inline analysis.

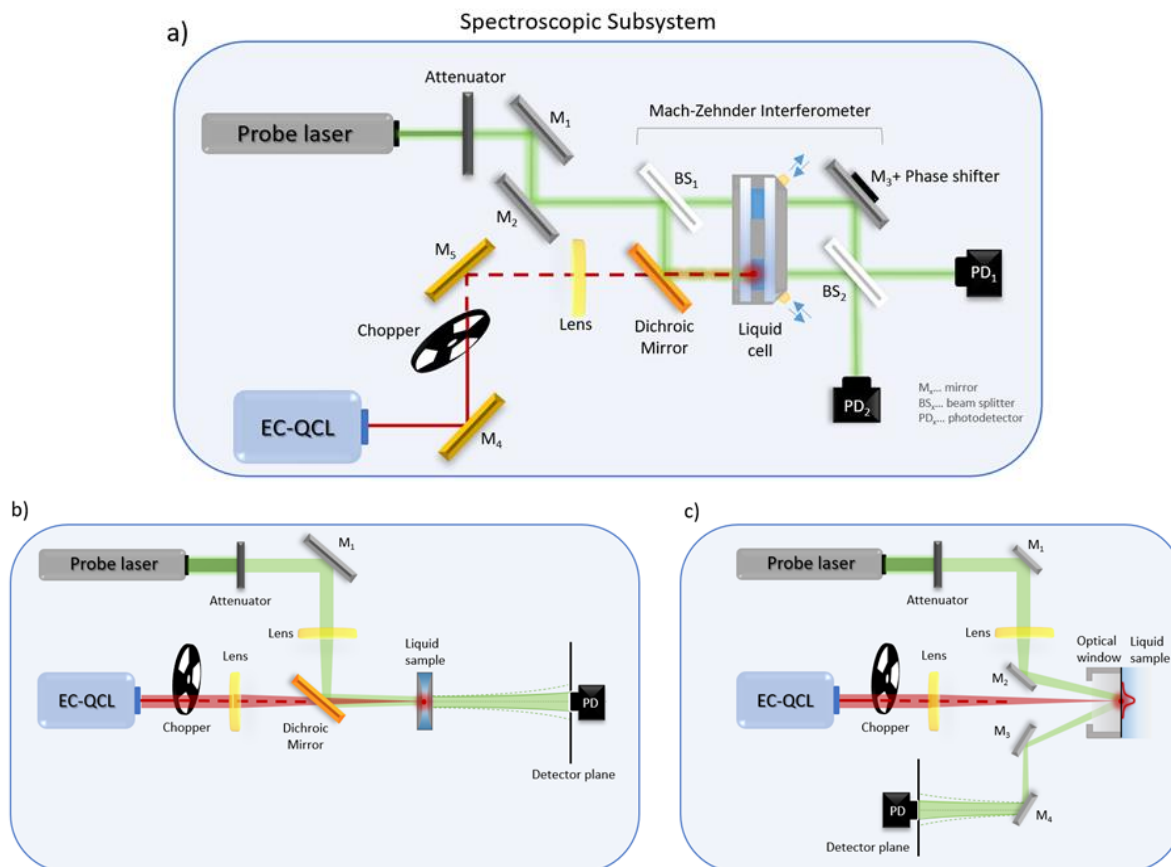


Figure 8. The conceptual design(s) of the spectroscopic subsystem(s) based on (a) photothermal interferometry involving Mach-Zehnder Interferometer, or (b) photothermal lens, or (c) photothermal mirror

The delivery system is comprised of: (a) a reactor’s waste pipe (fast loop), where the liquids for analysis flow through a large diameter pipe, and b) an analytical loop, where comparably smaller amount of liquid is transferred via a small diameter tubing to the sensing area of the LMA (with the help of i.e., a peristaltic/or a syringe pump). The advantages of such online analysis include: no sample preparation, quick response time, full automation, minimal contamination of process stream, ability to use standards for LMA calibration without interrupting the process.

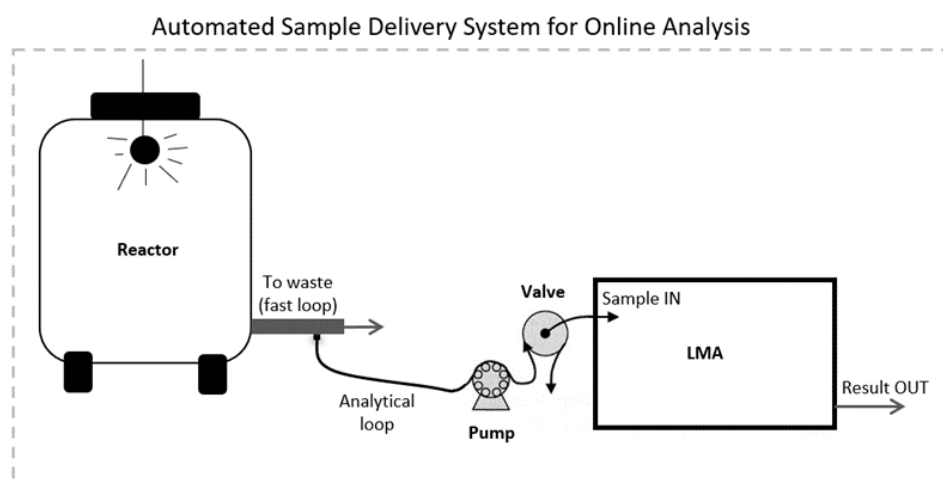


Figure 9. The conceptual design of the Automated Sample Delivery System for Online Analysis

Figure 10 presents in detail the connections and interfaces between the different modules of the LMA, and the MCU & Power Management module.

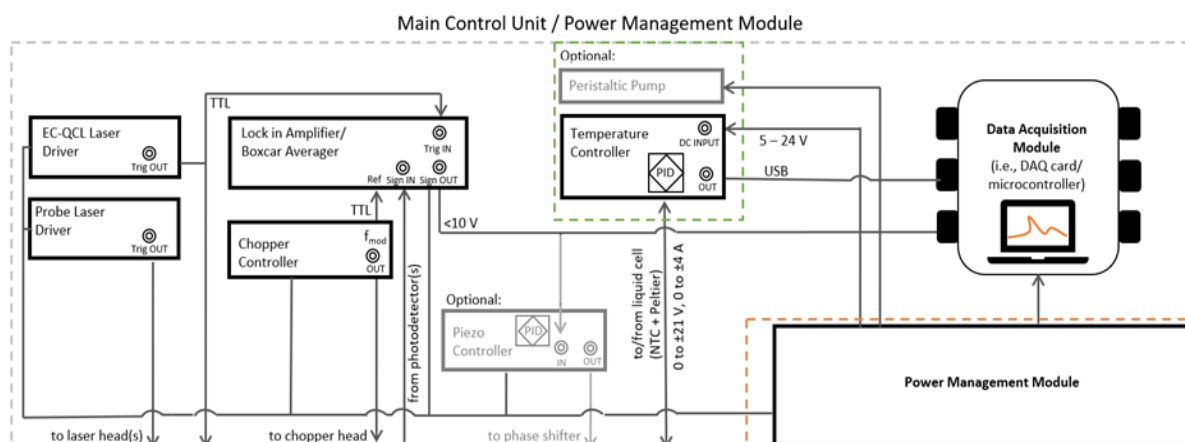


Figure 10. The conceptual design of the Main Control Unit with the Power Management module

4.3 Surface Inspection Analyser conceptual design

In order to address both use cases (NOVO and PFIZER) and achieve the requirements specified in SyRS, the surface analyser possesses two conceptual architectures for the measuring head as well as for the spectroscopic system. The proposed configurations have different key attributes such as sensitivity, speed or simplicity; after versatile system performance characterisation (4 possible architecture combinations) the optimal model will be chosen.

Figure 11 depicts a conceptual design of a polarisation modulated infrared reflection absorption spectroscopic system (PM-IRRAS). The PM-IRRAS system has a higher sensitivity, for this reason a single bounce configuration is used. There are two possible options for the position of the polarisation control unit (PC) indicated with PC1 and PC2 – either in the spectroscopic sub-system or directly integrated into the measurement head (enabling relaxed requirements for polarisation stability).

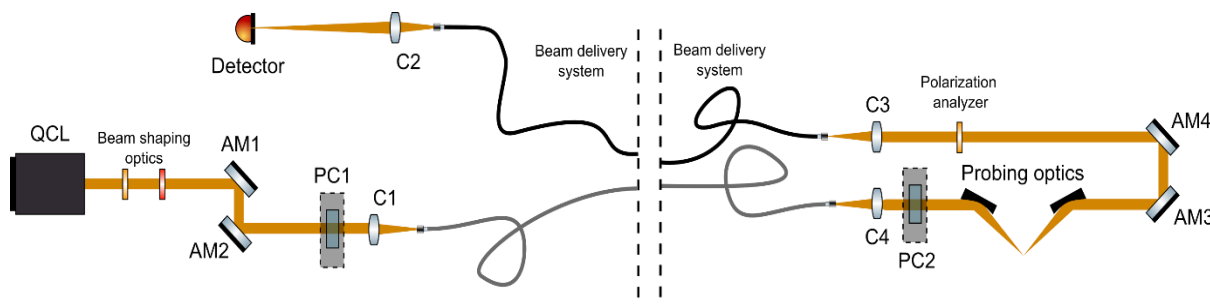


Figure 11. Conceptual design of polarisation modulated infrared reflection absorption spectroscopic system; PC – polarisation controller (two positional options indicated), C1-C4 is beam delivery optics, AM – alignment mirrors, QCL – quantum cascade laser; the spectroscopic sub-system is shown on the left, the measurement head on the right side

Figure 12 displays the second conceptual design of a stationary polarization state infrared reflection absorption spectroscopic system (SP-IRRAS). In this design, low detection limits

can be achieved by using a multiple bounce geometry so that the interaction path length is increased.

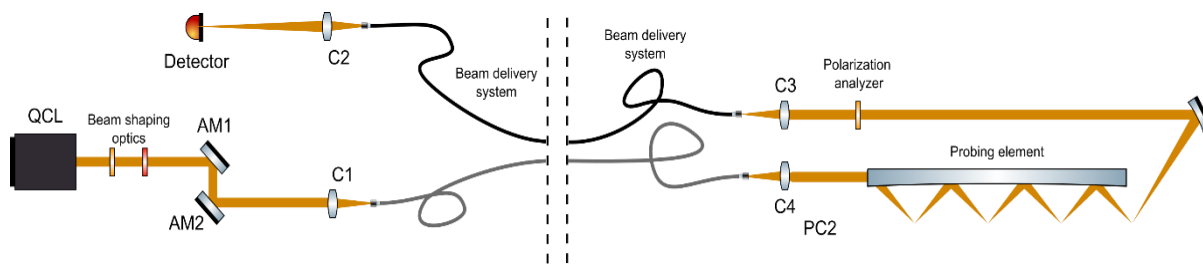


Figure 12. Conceptual design of stationary polarisation infrared reflection absorption spectroscopic system; C1-C4 beam delivery optics, AM – alignment mirrors, QCL – quantum cascade laser; the spectroscopic sub-system is shown on the left, the measurement head on the right side

The configuration is versatile, so that the measuring head of one architecture can be used with a spectroscopic subsystem of another configuration; the only part that has to be adapted in this case is the polarisation controller.

Beam delivery system implies, for instance, fiber optics or articulated laser arms.

Both measurement heads can be designed to match the two use cases requirements, namely NOVO and PFIZER; Figure 13 illustrates corresponding mechanical arrangement of the units.

The measurement heads have adaptable sensor interfaces: in the case of NOVO it is shaped mechanical intermediate adapter of a specified diameter. The measuring head, designed for use with PFIZER, has connectors to adapt to the pipe diameter. The NOVO measuring head should be held in the hand with the handle at the top, and the PFIZER unit should be held along the instrument.

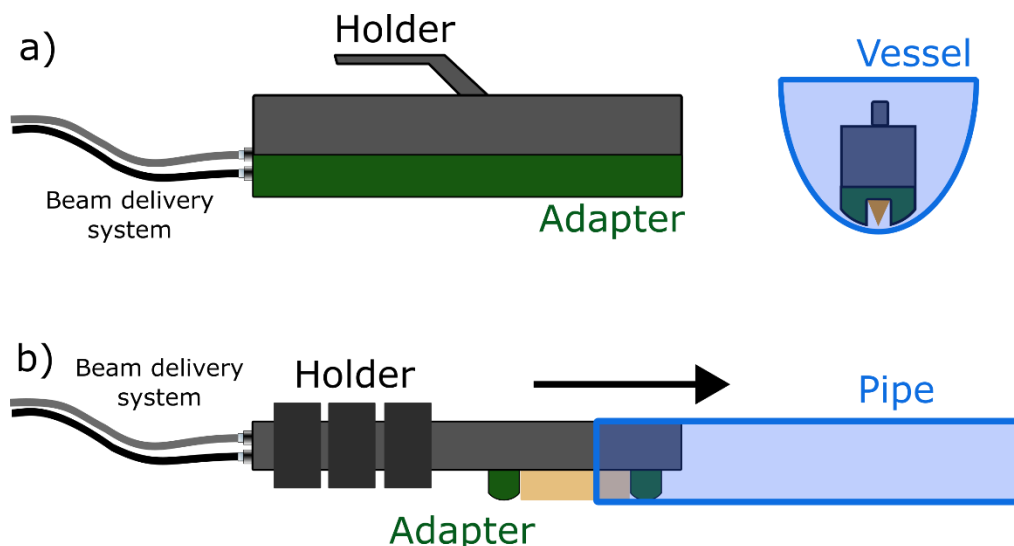


Figure 13. Mechanical arrangement of measurement units for (a) NOVO and (b) PFIZER use cases; the adaptable sensor interfaces (for different vessels/pipes diameters) are shown in green; the scheme illustrates the way the measuring heads are to be operated

The outline of the system architecture - in diagram format - is shown in Figure 14.

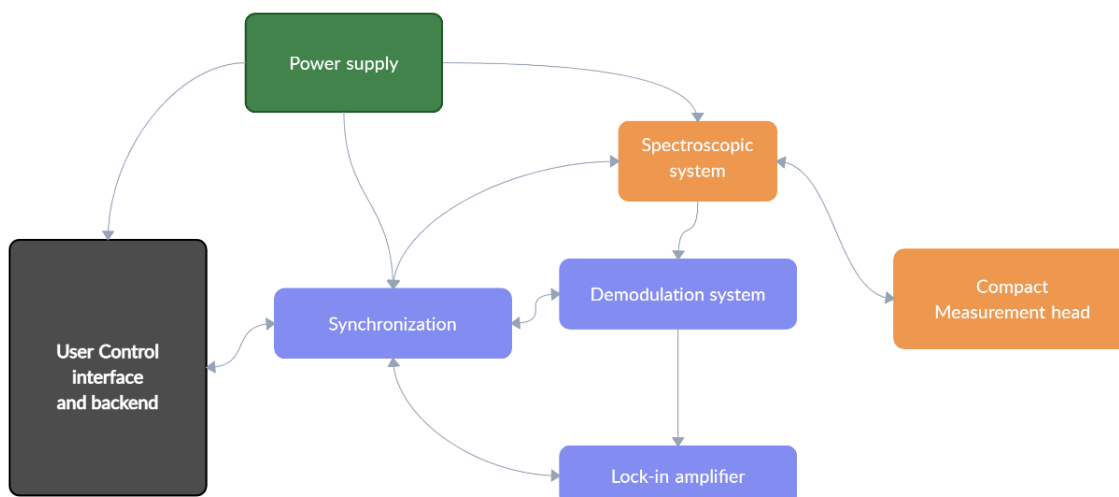


Figure 14. Conceptual design schematic showing the interconnection of electronics, user control/backend interfaces, and optical parts

4.4 Mid-IR laser sources conceptual design

The lasers to be used by the monitoring technologies are based on external cavity quantum cascade lasers (EC-QCLs). The system comprises the QCL broad gain chip mounted on a submount that offers the proper heat dissipation. A TEC component is used to maintain the proper temperature of the chip, typically in the -10°C to 10°C range depending on the laser chip. The TEC component is connected to a TEC driver (to be provided by ALPES), placed within the laser chassis.

The laser chip submount is fixed in position and is aligned to a moving mirror on the backend of the chip. The mirror is placed on a moving stage (a voice coil is currently the stage of choice for ALPES) and is directing the laser beam to a diffraction grating. The system chip-moving mirror-diffraction grating is aligned and forms the so-called external cavity configuration which offers tunability, i.e., the choice of the wavelength of the emitting laser beam. To accomplish tunability, the laser source controller defines:

- The operating voltage and current of the laser chip (via the laser driver)
- The operational temperature (via the TEC driver)
- The specific position (angle) of the moving mirror that enables different wavelengths to be selected (via the voice coil driver).

All sub-modules will be controlled by a single controller based on a Raspberry Pi module, enabling the single control access. For the user or the integrator of the laser source, the system comprises a chassis, typical dimensions being $30 \times 50 \times 12$ cm (L \times W \times H), emitting the laser beam through an aperture. The controller is instructed to emit a specific wavelength at each instance, enabling the sweeping of the emitting wavelengths.

The typical configuration for a single laser EC-QCL is shown next.

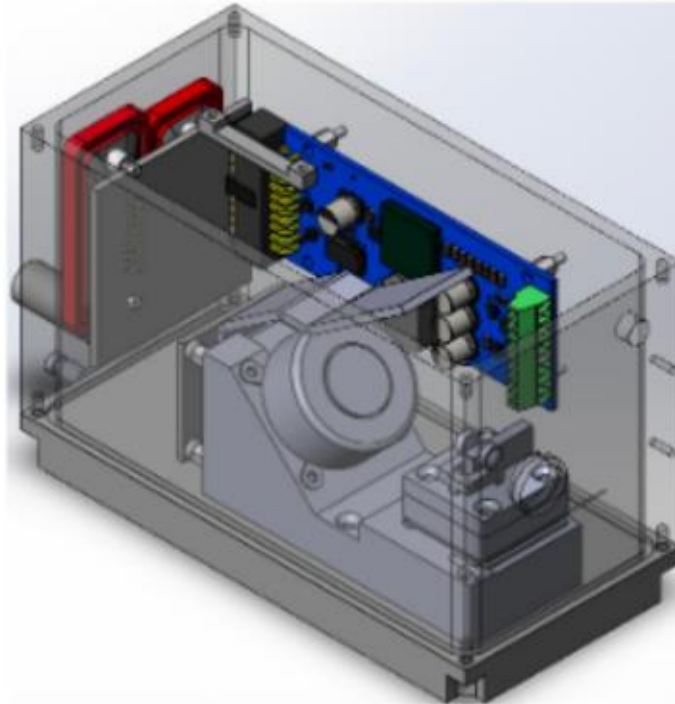


Figure 15. Conceptual design of a single EC-QCL laser

For the purposes of the project, a multiple-EC-QCLs system will be designed. This includes the combination of 2 EC-QCLs in the chassis via an extra alignment mirror. In the latter case, a single controller (Raspberry Pi) controls all EC-QCL modules, delivering a single laser beam at the aperture, as a single laser module is operating at each instant.

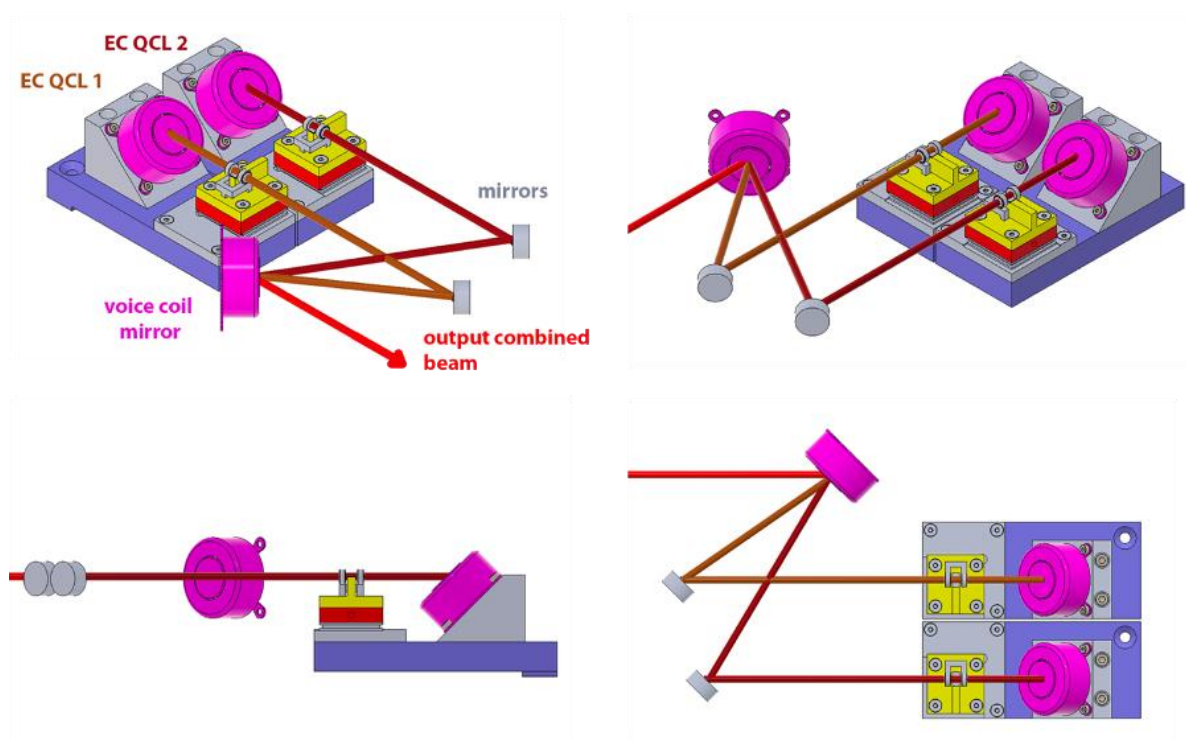


Figure 16. Conceptual design of a multiple EC-QCL system

For the SIA, ALPES will provide a connector for the fiber coupling (pigtailed QCLs). A similar system for single-wavelength emission has been developed by ALPES previously. The concept, shown next, will be expanded for the case of the ENVIROMED tunable lasers using tailored optical elements.



Figure 17. A fiber coupled QCL

5 Conclusions

The elaboration on defining the systems requirements as part of T2.4 (WP2), and the preparation of some important conceptual designs, as presented in this deliverable, is the starting point for the development phase of the three monitoring technologies under WP4.