Opinion Paper

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Guidance in the application of quality management in the field of chromatography in routine medical laboratories – EFLM Committee: Accreditation and ISO/CEN Standards point of view

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Abstract

Background: Chromatographic separation has become a critical analytical technique in routine laboratory medicine. Although several documents address standardisation in chromatography, they largely focus on industrial and pharmaceutical applications. Routine medical laboratories remain underserved, creating a need for guidance tailored to their specific context. This paper aims to provide technical guidance on applying ISO 15189:2022 requirements to chromatographic methods, ensuring quality and risk management across all laboratory phases.

Content: Building on previous work of the European Federation of Laboratory Medicine Committee on Accreditation and ISO/CEN Standards, we reviewed ISO 15189:2022 requirements and interpreted them in relation to chromatographic procedures. Key vulnerabilities inherent to chromatography – such as sample preparation variability, column performance drift, and detector calibration – were identified and mapped to relevant quality and competence clauses.

Summary and Outlook: The guidance highlights chromatography-specific risks and proposes structured verification,

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documentation, and risk management strategies. It addresses pre-analytical, analytical, and post-analytical phases, emphasizing traceability, method verification, and result of release. Special consideration is given to laboratory-developed tests using chromatographic techniques, aligning them with European *in vitro* diagnostic regulation. By contextualising ISO 15189:2022 within the technical realities of chromatography, this paper provides laboratories and auditors with practical tools to safeguard quality, reduce uncertainty, and ensure reliable patient results. The proposed framework advances regulatory harmonisation and supports the routine implementation of chromatography in medical laboratories.

Keywords: ISO 15189:2022; chromatographic methods; quality and risk management; clinical laboratory standardisation; laboratory-developed tests

Introduction

Over time, the method of chromatographic separation was significantly optimised, and this analytical technique was increasingly recognised as important for use under routine laboratory conditions, so that the need for guidance in the field of chromatography grew increasingly. There are several published documents that point to the importance of standardisation in chromatography [1–6]. These documents mainly refer to the field of research in industry or pharmacy. As far as laboratory medicine and routine laboratories are concerned, this area is still very sparsely populated and opens the door for progress in regulation.

As far as the guidance on methods and procedures in a routine medical laboratory is concerned, the state of the art in laboratory procedures is covered and achieved by the ISO 15189 standard [7]. This standard is an important tool for both laboratories and auditors to assess and maintain laboratory quality and the necessary risk management at all stages of the laboratory process, also to ensure high quality production of laboratory-developed tests for own use that fulfil the requirements of the European Regulation on *in vitro* diagnostic medical devices [8, 9]. However, the standard focuses on a high-level risk-based approach and refrains from technique dependent requirements and recommendations. Although the intent to prevent overprescription by the standard is very useful, this also creates the need for other documents to provide instructions and recommendations to prevent loss of quality due to lack of knowledge of technique dependent vulnerabilities. This is especially true for highly complex analytical techniques such as chromatography [10]. This paper aims to provide technical guidance on how the requirements in the ISO 15189 standard should be applied to chromatographic techniques, covering the complete process from pre-until post-analysis, but also respecting the ISO 5649:2024 [11]. As it is impossible to provide detailed instructions on all aspects of all possible applications of chromatographic techniques, this guidance focuses on the identification of the specific aspects in all laboratory phases that deserve special attestation for chromatographic techniques.

Previous work of our Committee on method verification, result release and documentation of metrological traceability also applies to chromatographic procedures [12–15]. However, these documents did not contain detailed information that is essential for the correct application of these previous instructions for chromatographic methods. The content of this paper focuses on the specific requirements for the correct performance of chromatographic methods and on the management and prevention of risks that ultimately lead to uncertainty in the issued laboratory result.

The main objective of this paper is to emphasise quality and risk management to avoid unintentional errors in the field of chromatography in routine laboratories. In this context, the Committee on Accreditation and ISO/CEN Standards (C: A/ISO) of the European Federation of Laboratory Medicine (EFLM) has addressed the requirements of ISO 15189:2022 and supported laboratories to implement them correctly also for chromatographic methods to facilitate daily routine work and related challenges.

Review and interpretation of individual requirements of ISO 15189:2022 in connection with chromatographic methods

In contrast to other routine methods, chromatographic systems have a complex architecture but are used in medical laboratories on an equal footing with other *in vitro* diagnostic (IVD) devices. In addition, real-time chromatographic techniques can be implemented as laboratory-developed tests (LDTs). Therefore, the use of these techniques in accordance with quality and competence requirements in medical laboratories is an essential prerequisite for properly regulated testing with these methods [8, 9].

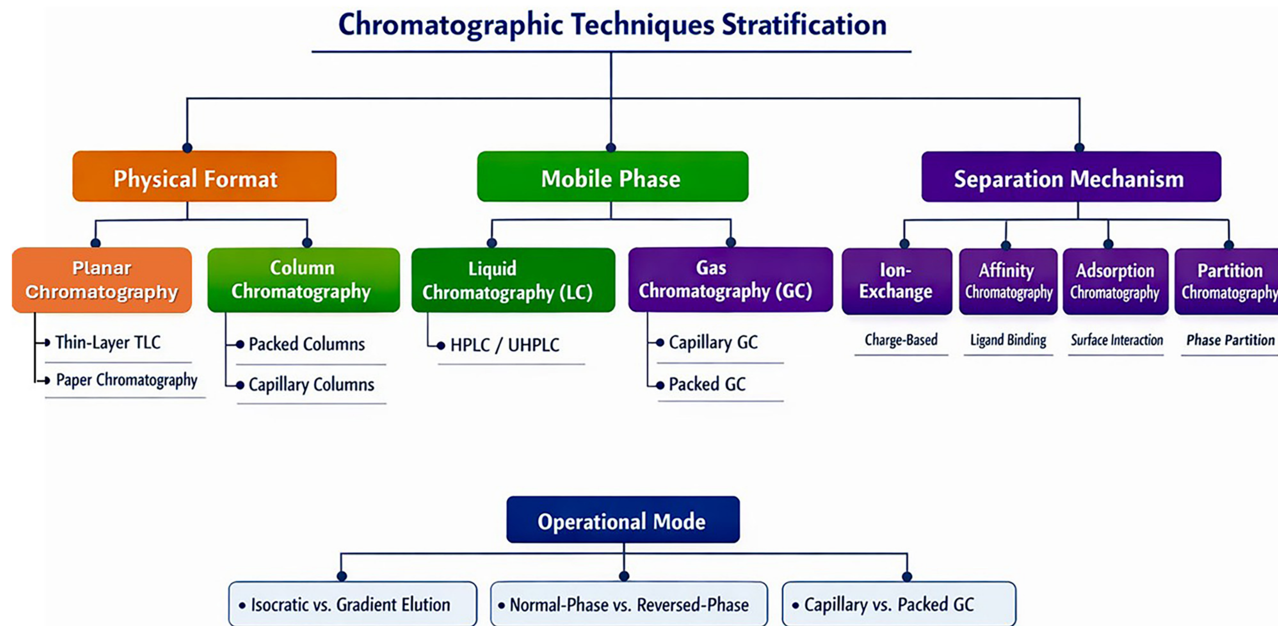

Figure 1: Graphical presentation of chromatographic techniques stratification.

There are different types of chromatography with their specific analytical properties that should be considered when implementing requirements related to chromatographic techniques in medical laboratories (Figure 1).

These properties depend on the specificity and quantity of the analyte as well as on the components of the chromatographic systems. Several main types of chromatography are widely used in the medical field (Table 1) [5, 16–19].

Table 1: Main types of chromatography methods and their application in laboratory medicine.

Types of chromatography techniques	Applications in laboratory medicine
Liquid chromatography	Tumor markers (catecholamines, metanephrines, vanillylmandelic acid, serotonin, 5-hydroxyindoleacetic acid); drugs of abuse; amino acids panel Hormones (thyroid hormones, steroid hormones, cortisol and metabolites, catecholamines/biogenic amines); Vitamins (vit B complex, vit D metabolites, vit A, vit C, vit E, vit K) Proteomics, oxidative-stress biomarkers, metabolomics and lipidomics, therapeutic drug monitoring
Gas chromatography	Therapeutic drug monitoring, drugs of abuse, amino acids, microbiome testing, steroid hormone analysis, fatty-acid analysis
Thin-layer chromatography	Amino acids panel, sugars
Other chromatography types	Therapeutic drug monitoring, drugs of abuse, proteomics, metabolomics and lipidomics

General requirements

Laboratories using chromatographic methods should assess and monitor the risks that could compromise impartiality and confidentiality. It is not uncommon for laboratories to use chromatographic systems to act as referral laboratories. The decision to select and implement the components of the chromatographic system is the responsibility of the referral laboratory itself and the detailed knowledge of its laboratory professionals. Documents are available to assist end users in validating chromatographic procedures and specific system components [3, 11, 20, 21]. Nevertheless, if it is an IVDR method, it should be validated by the manufacturer, and the validation data will be described in the instructions for use. In this case, the laboratory should verify the validation data in the context of its settings, according to available documentation.

Laboratories using chromatographic methods are required to apply and fulfil the patient-related requirements of ISO 15189:2022 [7]. The focus of the laboratory determination, regardless of the method or technique used, is on a clear and understandable result and supporting patient care as the ultimate goal. The requirements of the standards in relation to the patient broaden the horizon of two-way communication. It is therefore important that patients are familiar with the laboratory's capabilities when it comes to chromatographic techniques or the capacities of individual components and measurement procedures. It is the responsibility of the laboratory to provide its users with

understandable information about the complexity of the entire laboratory investigation [5].

Structural and governance requirements

Laboratories using chromatographic methods are encouraged to have responsible, qualified, and competent personnel to implement a quality management system specifically in the area of these complex tests. Regardless of whether the chromatographic determination is performed in a government laboratory of any level of health care or in a private laboratory, the final product of the analysis, the laboratory result and the entire laboratory report are legally valid documents. According to the latest version of the standard, every single step of the analysis, from sample collection to counselling, should be comprehensively described [7, 22]. This corresponds to the requirements of good laboratory practice and the purpose of the laboratory as a central service in the healthcare sector.

Chromatographic methods are complex analytical procedures and in the case of "in-house" developed tests are subject to LDT regulations [10]. Since LDTs continue to play a crucial role in meeting unmet medical needs, the regulatory requirements for LDTs should be clearly defined. The EFLM Task Force on European Regulatory Affairs and the EFLM Committee on Quality and Regulation have pointed out the undesirable side effects of the intended transparency of in-house diagnostics under the EU IVDR [9]. The global regulatory framework for LDTs is diverse [4, 23]. This may require additional consideration in situations where Research Use Only (RUO) products are used as IVD components. Additionally, this is intended to express the responsibility and self-confidence of authorities and specialised/laboratory personnel in the processing of chromatographic methods. This is clearly recognised in ISO 15189:2022 and reference is made to risk management at every step of the entire laboratory process to avoid hazards [8]. This ensures that the laboratory's objectives and strategies are focused on both laboratory and patient safety.

Resource requirements

The "holy trinity" of laboratory services includes professional and trained staff, carefully selected and reliable equipment, and appropriate and safe premises and environmental conditions. Although chromatography is nicknamed "complex testing", laboratory managers should bear in mind that most of the methods, which are validated in the laboratory as in-house developed tests, can improve the risk-benefit ratio [8]. Users of chromatographic methods should have the scientific and technical expertise and experience required to perform the test [4, 5, 23, 24]. Laboratory personnel performing highly complex tests must undergo additional training, education, and professional development [4].

To implement a chromatography process with respect to the requirements and to properly perform a risk assessment to identify hazards at each stage or task level, we suggest reviewing the individual components of the chromatography system (Table 2) [25, 26].

Standards, controls and reagents in chromatography

In accordance with the requirements of ISO 15189:2022, inventory management and acceptance testing are continuous tasks. The creation, maintenance and control of analytical quality in chromatography is the responsibility of the equipment and reagent manufacturers as well as the individual laboratory [27]. In addition to the equipment, the selection of suitable reagents, certified reference materials, standards and controls, as well as proper reconstitution of lyophilized samples also contributes to the reliability of the test results. The use of an appropriate standard reference material ensures reliable comparison between instrument responses for standards and samples, enabling accurate identification and quantification of analytes in the samples [28]. We suggest some points to consider for the three types of standards in chromatography in terms of proper implementation and use (Table 3).

The external standard serves as a calibration standard with which direct quantification is achieved without correction for sample preparation or injection variations. The internal standard and the surrogate standard are considered important "controllers" of the accuracy and precision of extra analytical and analytical procedures in chromatography [29–31]. An ideal internal standard is an exogenous compound that is absent from the sample matrix. Both standards are used to check the overall recovery of the method and to correct variations in sample preparation, injection volume and detector response. Both are not naturally present in the samples and should be added in the same known amount to both the dilutions of the calibration curve and the test samples. Harmonisation and standardisation in the use of internal standards should be an issue for the standardisation bodies to address.

Table 2: Basic components of the chromatographic system and critical points to be checked.

	Components	Critical item to verify
System components	Stationary phase	Polarity, chemical compatibility, stability, pore size, and selectivity
	Mobile phase	Compatibility with stationary phase and with detection methods, quality/purity of the mobile phase, polarity, analyte solubility, viscosity, volatility, pH range and buffer capacity, chemical stability, cost and availability
	Sample injection system	Injection volume and accuracy, carryover, peak symmetry and contamination, reproducibility and stability, temperature control, material and solvent compatibility, proper loop sizing, injection timing and flow, needle wash and solvent management
	Solvent delivery system	Liquid chromatography (LC)/high pressure LC (HPLC)/Ultra HPLC (UPLC)HPLC: solvent reservoirs, pumps, filters, degassing system, gradient and flow accuracy and precision, pulsation dampers, pressure stability, valves and seals Gas chromatography (GC): gas source(s), mass-flow and pressure stability, detectors for flow stability, leak management
	Column	LC/HPLC/UHPLC: particle size and column efficiency, pore size and surface area, column dimensions, pH and chemical compatibility, temperature stability, gradient compatibility and dead volume sample and solvent compatibility. GC columns: stationary phase/type, film thickness and column dimensions, temperature tolerance, dimension, carrier gas compatibility, stability and bleed, end-capping and deactivation; column/guard column lifecycle management: criteria for end-of-life (pressure, resolution, tailing), change strategy, lot qualification, and requalification after maintenance.
	Detector	"signal-to-noise" ratio, sensitivity, fast response time, linearity, flow rate or temperature, stability and reproducibility, application and reliability in operation, how efficiently the detector couples with the LC system
Analytical performance parameters	Elution efficacy	Resolution – degree of separation between two adjacent peaks in a chromatogram which depends on column efficiency, selectivity – ratio of the retention factors of two peaks, capacity factor – how long a compound is retained by the stationary phase
	Identification and qualitative analysis	Retention time as "fingerprint" for peak identification, comparison retention time of a peak in an unknown sample to the retention time of a known standard, peak purity, spiking with internal standard (highly dependent on the detector used), system consistency
	Quantitative analysis	Calibration methods, the peak area or peak height, are used to relate the concentration of the analyte to the detector's response.

The requirements for calibration of equipment and metrological traceability as specified in the chapter on resource requirements of ISO15189:2022 are also discussed in detail [7, 22]. Additionally, the laboratory should have risk management for situations where calibration is out of control according to ISO15189:2022. The EFLM working group on Accreditation and ISO/CEN standards has discussed how the metrological traceability requirement in ISO15189 should be fulfilled by the medical laboratory and how this should be assessed by the accreditation bodies [15]. This is of particular importance for the interpretation of measurement uncertainty and the achievement of confidence in the measurement results. It should be noted that for routine chromatographic measurements it is important to provide available data on metrological traceability and measurement uncertainty, although this is not an easy challenge for an LDT. Hindering factors can include the lack of external standardisation, the complexity of the analyte, the variability of the method, and limited regulatory oversight. These challenges can be addressed by implementing continuous internal validation and verification [12, 32, 33].

Process requirements

In accordance with the process requirements, particular emphasis is placed on a risk-based approach in the processes

Table 3: Chromatography standards.

Standards	Items to consider
External	Purity, concentration range, matrix, stability
Internal	Physically and chemically similarity to the analyte of interest, baseline separation, retention time (differing from the rest of the analytes), no interference.
Surrogate	Chemical and physical similarity to the analyte of interest, baseline separation, retention time, and detector response.

for identifying risks of harm to patients and communicating any residual risks to users where necessary [20].

Pre-examination processes consideration

Regarding the “garbage in garbage out” principle, the correctness of the pre-testing phase in the medical laboratory is of decisive importance for the correctness of the test results. Automated pre-analytical systems are available for most standard determination methods in medical laboratories, ensuring a high degree of accuracy in the initial phase of laboratory diagnostics [34]. In chromatography, the preparation of samples for determination is in most cases performed manually. There are some examples of pre-analytical systems coupled with LC or LC-Mass Spectrometry (MS)/MS systems, e.g., for immunosuppressive drug testing [35].

Table 4 lists the most important pre-analytical areas and the critical points to be checked in order to overcome the challenges of pre-analytics in chromatography [35–38].

Table 5 lists the sample preparation steps and the usual sample preparation techniques for chromatography procedures [37–43].

Comprehensive standard operating procedures, appropriate training and strict quality control measures are required to ensure the correctness and proper verification of each key step of the pre-analytical process. It is important not to lose any quantity of the analyte of interest between the different preanalytical steps. Traceability of pipettes/volumetrics is specifically important for sample preparation because chromatography often involves many manual steps, (micro) volumetric uncertainty and correct technique (pipette training) are a greater source of error than in many routine analyses. Through careful management of pre-analytical variables, laboratories can improve the accuracy, reliability, and reproducibility of chromatographic analyses, ultimately ensuring the validity of scientific and clinical conclusions.

Table 4: Key pre-examination areas and proposed critical item to verify in chromatography.

Key pre-examination areas	Proposed critical item to verify
Information for patients and users	Available laboratory tests and sample requirements, test indication/utilization, request form, clinical information, criteria for sample acceptance/rejection
Patient preparation	Fasting state, dietary restrictions, no medication in the last specified period, no intensive physical activity, stress, smoking, etc.
Sample collection	Type and amount of the primary sample (venous blood (serum/plasma), 24-h urine, cerebro spinal fluid (CSF), anti-coagulant/preservative, consumables, body position to avoid stress
Sample handling	Sample labelling, homogenisation, centrifugation
Sample/eluate transportation and storage	Sample/eluate stability, preservatives, environmental conditions, transportation equipment
Matrix effects, interferences management and co-elution risks	Signal-to-noise ratio, usage of surrogate/internal standard, inertness of consumables; structural approach for isobaric compounds, metabolites, and drug interferences, including criteria for flagging and confirmation (alternative transitions, second column, different retention time); ion suppression/enhancement as a routinely monitored risk (especially LC MS/MS) not only during validation, but also monitoring for matrix/population differences.
Stability of calibrators/quality control and patient extracts (processed sample stability)	Storage time in autosampler, freeze-thaw cycles, batch reinjections, and acceptance criteria.
Consumables	Correct storage/handling to avoid contamination (e.g., plasticizers, detergents)

Examination processes consideration

The EFLM Working Group on Accreditation and ISO/CEN Standards (WG-A/ISO) has proposed a guideline for the validation and verification of test procedures according to ISO 15189 [12]. This guideline applies to test procedures in chromatography and supports laboratories in the quality management of complex analytical systems regarding the “intended use” of the test procedures [12]. Laboratories already using validated test methods according to the manufacturer`s instructions should check and confirm the adequacy of verification under their own working conditions [12]. If the laboratory uses an LDT or RUO, or has adapted the manufacturer`s original procedure, the test procedure should be validated [11].

For chromatography procedures, it is important to choose an appropriate data system that enables fully electronic workflows and has features that ensure regulatory compliance, although the software does not necessarily have to be an integral part of the measurement system [44–48]. The ISO 15189:2022 emphasises the importance of control of data and information management [7, 49]. The use of suitable and validated software and hardware ensures the

Table 5: Sample preparation steps and common sample preparation techniques for chromatography procedures and points to check.

Sample preparation steps	Common steps to verify
Homogenisation	Test tube/container inversion before homogenisation
pH adjustment (within the desired range)	Usage of appropriate acids or bases
Purification	Protein, lipids, salts, or other molecules removal/precipitation – specificity of a precipitating agent (e.g., organic solvent, acid, salt) Filtration – suitable pore size of membrane filters
Extraction	Solid phase – specificity of sorbent materials to accommodate different analyte properties Solid phase microextraction – specificity of coated stationary fibre phase Liquid-liquid – organic (extraction) solvent/an aqueous phase ratio
Derivatisation (if required)	Suitability of derivatisation reagents and conditions, adhere to the derivatisation protocol
Sample composition adjustment (into the linear range of the detector)	Concentration – for low analyte concentrations (centrifugation) Dilution – for high analyte concentrations
Solvent compatibility	Usage of HPLC-grade solvents, the mobile phase purity, peak shape and quality, quality of water/gases to prevent contamination, LC MS background (plasticizers, PEG), solvent lot-to-lot effects, gas purity/leakage (GC)
Final sample preparation	Accuracy of transfer of the prepared sample, suitable labelled vials or containers for injection with attention to capping, storage of the prepared samples under appropriate conditions (e.g., refrigeration, protection from light), accurate pipetting taking all the volume, accurate elution on pre-columns, transfer of volume to the final vials

desired analytical properties of the method's performance, prevents unexpected errors, and minimises risks. In addition, regulated management of information systems enables the desired and necessary harmonisation of the technical properties of the test procedure, e.g., for LDT. Of note, software for IVDR methods is "locked" to changes in comparison to software for RUO methods which is "open" to changes.

The setting or selection of suitable analytical characteristics is closely related to the detector used, which is an essential component of the chromatography system. The correct detector, the eye of the chromatography system, is necessary to ensure reliable and accurate identification and quantification of the analytes when eluting from the chromatography system. There are no special regulations for this area in laboratory medicine. Another important point to consider is that several detectors can be installed in a chromatography device, all of which should be properly evaluated. For general use, there are defined operating conditions for certain detectors provided by the manufacturer. Table 6 summarises the detection methods of chromatographic separation techniques with specific analytical properties [26, 50–52].

Nevertheless, as regulatory requirement and safeguard for data integrity during method development and routine analysis, laboratory should prepare system suitability test (SST) as formal release before each batch: fixed, predefined acceptance criteria (e.g., resolution, tailing factor, retention time window, ion ratios for MS) and what to do in case of failure. This aims to help identify any issues within the system before sample analysis, ensuring that the results are valid and reliable [51, 52].

EFLM Committee: Accreditation and ISO/CEN standards suggest important characteristics of the chromatographic system and detector that should be evaluated. These characteristics have an influence on reliable chromatography measurements.

Adequate sensitivity

An appropriate limit of detection (LOD) and limit of quantification (LOQ) should be established. The most common approach is to use the signal-to-noise ratio (S/N) and a calibration curve. Other steps that should be considered are sample preparation, solvent quality, column selection, instrument optimisation and detector settings. Linearity should also be verified across the working range, including evaluation near the LOD and LOQ using serial dilutions.

Suitable measuring range

The linear range and the reportable range should be evaluated to ensure a reliable and useful detector response over the entire concentration range. The reportable range is a practical range, especially in chromatography, because this information provides a portion of the linear range in which the results are not only linear, but also accurate and precise. The reportable range should include the upper and lower specifications or reporting limits.

Reasonable stability, repeatability and reproducibility

Determine the values of the analyte of interest in prepared standard sample/eluate solutions stored under the

Table 6: Detection methods of the liquid and gas chromatographic separation method.

Detection methods for the liquid chromatography	Characteristics	Sensitivity	Detecting analytes
Ultraviolet-visible absorption detector (UV-vis detector)	High sensitivity, wide linear range, low noise and suitable for gradient elution; measures the absorption of UV or visible light	ng to pg	Broad spectrum of analytes that absorb UV or visible light
Mass spectrometry detector (MS)	Provides information on molecular weight and structure; highly sensitive and selective; suitable for complex mixtures and structure elucidation	fg to ag	Broad spectrum of analytes, proteins, peptides, nucleic acids, redox reactions with various bioorganic molecules
Fluorescence detector (FD)	Highly sensitive and selective detector; detects compounds that fluoresce when excited	pg to fg	Trace analytes that fluoresce naturally or after derivatisation
Differential refractive index detector (RID)	Lower sensitivity compared to a UV detector, is affected by temperature fluctuations; measures changes in the refractive index of the eluent	µg	Some components that cannot be detected by selective detectors, such as polymers, sugars and fats, UV-inactive compounds
Electrochemical detector (ECD)	High sensitivity, selectivity and no need to derivatise the analyte	fmol	Various inorganic and organic anions and cations, metabolites of biological tissues and body fluids, food additives, environmental pollutants, biochemical products, pesticides, pharmaceuticals and medicine; amino acids and neurotransmitters
Chemiluminescence detector (CLD)	Fast and sensitive detector that measures the light emitted by a chemical reaction	µg	Analysing neurotransmitters, drugs, food and the environment
Evaporative light scattering detector (ELSD)	Low sensitivity, no structural information, destructive, non-linear response, high reproducibility, cheap, simple	To ng	Non-UV-active compounds by measuring the scattered light after evaporation; used for lipids, sugars and polymers, surfactants, pharmaceuticals, compounds without chromophores
Charged aerosol detector (CAD)	A response independent of chemical properties, a wide dynamic response range with high sensitivity, good precision for a wide range of analytes and simple and reliable operation	ng	Lipids, proteins, steroids, polymers, carbohydrates, peptides, bile acids and other compounds with weak chromophores, non-volatile and semi-volatile compounds
Detection methods for the gas chromatography	**Characteristics**	**Sensitivity**	**Detecting analytes**
Mass spectrometric detection (GC-MS)	Universal and selective, noise-free detection with low detection limits	fg to ag	Eicosanoids, members of the L-arginine/NO pathway, post-translational modifications, biogenic amines and polyamines, oxidative stress, oxidised and nitrated fatty acids including oleic acid, amino acids
Thermal conductivity detector (TCD)	Universal component of chromatographic system, is used to analyse gases and organic compounds, most often used when sensitivity is not an issue	µg	A wide range of compounds, including permanent gases (such as hydrogen, oxygen, nitrogen and carbon dioxide), light hydrocarbons
Flame ionization detector (FID)	The most popular of all gas chromatography detectors, widely recognised for its unwavering reliability and sensitivity	pg to ng	Primarily recognises organic compounds, not sensitive to inorganic substances
Thermo iconic detector (TID)	Not widely used, sensitive and selective for the presence of compounds with phosphorus or nitrogen atoms	pg	Especially for compounds containing nitrogen and phosphorus
Flame photometric detector (FPD)	High sensitivity and low selectivity	pg	Sulphur and phosphorus compounds, but can also detect organic tin compounds
Electron capture detector	Highly sensitive and selective for the detection of compounds that readily capture electrons	pg to fg	Compounds containing electronegative functional groups such as halogens

recommended conditions and re-analyse them regularly at different time points and evaluate the stability of the peak areas or retention times. Check the precision of the method and the repeatability of the injection. During the run, the batch autosampler should remain stable. Trends or shifts in control charts should be used to track critical parameters

(e.g., retention time, peak area, stability of the baseline) over time.

Carryover management

Evaluate carryover as a patient safety risk: maximum carryover criteria, carryover checks (after high sample), cleaning protocol (needle wash/flush), and documentation of decision rules (reanalysis/dilution).

Robustness

Evaluate robustness by intentionally making small changes to critical method parameters and observing the effects on performance (e.g., temperature, mobile phase composition, pH: adjusting the pH of the mobile phase slightly). At normal operating temperature plus/minus a few degrees Celsius, minor fluctuations may occur during routine operations. The stability of the baseline, retention time, resolution, peak area, and peak shape should be consistent within the defined temperature range.

High accuracy

Verify accuracy using reference materials, certified standard samples or interlaboratory comparison to conduct recovery testing or calculate bias. Verify imprecision by evaluating repeatability and reproducibility. Present data as mean, standard deviation and coefficient of variation. After each change, a standard or control sample should be analysed to verify that key performance metrics such as retention time, resolution and peak area remain within the acceptance criteria.

Low noise

Assess the appropriate signal-to-noise (S/N) ratio by establishing a stable baseline. Evaluate peak-to-peak noise by measuring the maximum vertical distance between the highest and lowest points on the baseline across the measurement window. Other steps that should be considered are detector issues, mobile phase issues, temperature fluctuations, column contamination, and physical vibrations.

Short response time at independent flow rate

Check the detector time constantly by reviewing the detector specifications provided by the manufacturer and assessing the peak shape and width to ensure it is narrow. Assess the extra column volume of the system (the volume of all tubing, connections, and detector cells). Check the flow rate of independence by running a standard at different flow rates, compare the peak area – it should remain constant across the different flow rates – and assess the peak height.

Selectivity of the column

Check that the peak shape is symmetrical, check the strength and type of mobile phase by adjusting the ratio of organic solvent to water or changing the organic solvent or adjusting the pH of the mobile phase.

Methods designed or developed in the laboratory, methods used outside their originally intended field of application or validated methods that are subsequently modified should be validated by quantifying the relevant performance characteristics [7, 12].

In accordance with the requirements of ISO 15189, the measurement of uncertainty should be calculated and verified [7]. In chromatographic techniques, various factors can contribute to measurement uncertainty, e.g., sample preparation and handling, chromatographic separation, software tuning, detector response, calibrator traceability, and data analysis. The ISO TS 20914 standard facilitates the use of measurement uncertainty in combination with other sources of variation [22, 53]. For some analytes, data for other sources such as biological variation are not available, so the calculation of analytical performance specification (APS) for chromatography methods may be limited. However, measurement uncertainty for chromatography method should be based on data from method validation and quality control (reproducibility, bias, accuracy from validation/verification, calibration of volumetric equipment and uncertainty of calibrators, etc). For chromatography methods, a top-down approach is more practical, but then working conditions such as temperature, humidity, illumination and airflow should be as little variable as possible, as chromatographic systems are sensitive to frequent changes in environmental conditions.

When evaluating biological reference intervals and clinical decision limits using chromatographic methods, it should be considered that the accuracy and precision of the chromatographic assay directly influence the reliability of the derived reference interval.

To ensure the validity of the test results using the chromatography method, analytical performance of the measurement system should be monitored via internal quality control [7]. In the case of an IVDR method, the laboratory should use the controls provided by the manufacturer or third-party controls. For chromatographic IVDR methods, both are available. In chromatography, analysing a certified reference material (CRM) with known concentrations can

Table 7: Important post-analytical steps and critical points to be observed during chromatography usage.

Key postanalytical steps	Critical points to consider
Data processing and integration	Appropriate baseline correction and peak integration according to peak area or peak height in a unique manner, accurate identification of peaks based on retention time and spectrum
Quantification	Calculation of concentrations using the calibration curves/calibration factors (automatically or manually), correction of dilution or sample preparation factors
Verification and validation of the examination results	Define "alarm" or "critical" intervals/decision limits, repetition, reflex determination, "delta check", "adds on"
Data documentation	Recording chromatograms, calibration data and calculations, keeping detailed records for traceability and audits
Interpretation of results	Determine whether the results meet the acceptance criteria, considering potential interferences or anomalies
Reporting results	Produce clear, complete reports with the necessary explanations, including details of the method, results, units of measurement and validation parameters, as well as restrictions of the method
Clinical-interpretative quality points	Clarity around decision limits, reflex/-confirmation algorithms, report comments (e.g., "interference suspected," "below LOQ"), and consistent policy for reanalysis
Result harmonization between methods/platforms	Policy for method changes (new column, new batch of internal standard), comparison studies, bias evaluation, and communication to clinicians
Data storage and archiving	Secure, long-term storage of raw data and reports to facilitate audits and future reference, and in compliance with the local and European legislation

sometimes be unreliable due to the specificity of the analyte of interest and the method of determination itself [28]. The alternative to controlling the „chromatographic analytical factory system“ is to use an internal reference material using routine samples with predetermined values analysed in each sample batch, provided their stability is documented. The internal reference material consists of a large amount of material that is routinely analysed and prepared in the laboratory. The choice of a suitable matrix ensures the commutability of the material and the reliability of the results.

Quality assurance in chromatography refers to the systematic processes and procedures used to ensure that analytical results are reliable, accurate, and reproducible. The main objectives are to maintain validity of methods, ensure data integrity, and comply with regulations and laboratory standards. The practical way to achieve this is to participate in external quality assessment (EQA) programmes (also referred to as proficiency testing programmes), preferably accredited to ISO/IEC 17043 [54]. For specific techniques such as chromatography, there are possible scenarios that need to be considered to justify participation in external quality assessment (EQA) programmes (also referred to as proficiency testing programmes): use of appropriate CRMs or internal reference materials when appropriate CRMs are not available [55, 56]. Performance assessment and scoring and the impact of a small laboratory population on sample estimates should be considered as well as interlaboratory comparison programmes as an alternative to overcome difficulties. In all cases, the users should be aware of the need for the samples in the EQA programme to be commutable and the consequences for the limitation in the value of the EQA in case the samples are not commutable [7].

Post-examination processes considerations

Postanalytical considerations in chromatography concern the steps taken after data collection to ensure accurate quantification, interpretation, reporting, and utilisation of analytical results. There are some studies that address these postanalytical considerations in chromatography, but not in routine laboratory diagnostics [3, 57–59]. The original term postanalytical refers to the conditioning of the system and column and the preparation for the next chromatographic determination. Indeed, there are some regulatory requirements for data integrity in peak integration, but these are focused on quality control laboratories [6, 60, 61]. Therefore, it is important that the field of chromatography establishes clear guidelines for postanalytical instructions for laboratory personnel working with chromatography in routine medical laboratories. The suggested key post-analytical steps and critical points in chromatography are listed in Table 7 [62].

Effective post-analytical practice is critical to the reliability of chromatography results, adherence to standards and informed decision-making in clinical

laboratories and, consequently, to the right clinical decision for the patient.

Management system requirements

As with all routine laboratory methods, the use of chromatographic techniques requires regular reviews of the laboratory's management system to confirm its ongoing suitability, adequacy, and effectiveness, in line with ISO 15189:2022 [7]. However, due to the relative methodological complexity, in chromatographic techniques the need to define actions for risk mitigation and opportunities for improvement become particularly evident. For monitoring high-risk activities in chromatography-based laboratory testing, quality indicators should be evaluated. An essential management tool to continuously monitor performance, detect early deviations, and guide corrective actions to address risks and opportunities for improvement are **Quality Indicators (QIs)**. According to ISO 15189:2022, laboratories shall establish measurable quality indicators in the pre-analytical, analytical, and post-analytical phases to evaluate their contribution to patient care and to ensure continuous improvement. International recommendations [7] suggest selecting QIs that focus on high-risk and high-volume processes, are measurable from routine data sources and are linked to clear operational targets.

Based on experiences reported in the literature [8, 63–65], the use of QIs allows laboratories to:

- Identify vulnerabilities across the Total Testing Process (TTP): pre-analytical, analytical, and post-analytical phases;
- Quantify process performance and compare it against defined quality specifications or benchmarks;
- Prioritize interventions in areas with the highest probability of error or greatest potential clinical impact;
- Support harmonization of quality management across laboratories, enabling comparability of performance metrics.

Considering the laboratory processing steps in chromatography described above, and the factors that must be addressed to guarantee the suitability of results, a set of QIs is proposed. Each laboratory may choose one or more QIs to apply, with selection guided by the:

- **Criticality** of the test (impact on patient outcomes, urgency, regulatory requirements);
- **Inherent complexity** of the procedure (number of manual steps, operator skills, stability of analytes);
- **Historical occurrence** of errors or non-conformities;
- **Availability** of corrective actions that can realistically mitigate the identified risk.

In Table 8 a set of chromatography-specific QIs aligned with the critical issues described in this manuscript, is proposed. These QIs can be integrated into the laboratory's quality management system, reviewed periodically, and used as a basis for continuous improvement.

Guidance documents for chromatography methods

The development, validation, and performance of chromatography procedures require adherence to established guidelines to ensure accuracy, reproducibility, and regulatory compliance. Several organisations offer comprehensive guidelines tailored to different industries and regulatory frameworks, but the field of laboratory medicine is not fully covered [30, 32, 56, 66]. The scope of chromatographic determination has expanded so that this technique forms a significant part of routine determinations in biochemical and medical laboratories. It is therefore of interest that the relevant guidelines relating to the specific requirements of the medical laboratory take chromatography into account. In Table 9, we provide an overview of the specific requirements for analytical performance specifications required by current standards that are critical in the verification/validation of chromatography procedures [20, 67–70].

Other points that should be part of a guide to ensure stable and efficient chromatographic determination are calibration, maintenance, and suitability of the correct tests and reagents for the chromatographic system and detection type. General parameters for system suitability include retention time, peak symmetry, theoretical plates, and inter-peak resolution. Proper calibration and maintenance are critical to the longevity of the chromatography system. Calibration ensures that the system provides accurate readings, while maintenance prevents problems such as clogging or leaks.

Although we have presented the main requirements that need to be confirmed for reliable method performance, the additional analytical phases of chromatography in the medical laboratory should also be regulated. Proper sample preparation in chromatography should be part of specific guidelines. Poorly prepared samples can lead to contamination, inaccurate readings, or even damage to the system. Detailed instructions should be provided for sample filtration and dilution, handling of solvents and reagents, and the

Table 8: Example of Quality Indicators for chromatography-based testing.

TTP phase	Critical issues in chromatography	Proposed Quality Indicators (QIs)
Pre-analytical	Sample collection	% Of samples rejected due to inappropriate sample type/container
		% Of samples with wrong anticoagulant/preservative
		% Of samples with insufficient sample volume
		% Of haemolysed (free haemoglobin >0.5 g/L) samples
		% Of clotted samples
		% Of sample with contaminated/degraded/altered analytes
	Sample storage (handling/treatment/transport)	% Of samples with inappropriate storage time
		% Of samples transported within invalidated time/temperature limits/light exposure
	Sample preparation	% Of samples with inefficient extraction
		% Of samples with improper filtration
Analytical	Quality monitoring	% Of quality control samples with unsatisfactory performances
		% Of analytes without EQA/PT
		% Of EQA/PT with unsatisfactory performances
Post-analytical	Data processing and integration	% Of samples with inaccurate identification of peaks based on retention time and spectrum
	Quantification	% Of samples with erroneous calculation of concentration
		% Of chromatograms flagged for re-analysis due to interference
	Reporting results	% Of incomplete reports (method, results, measurement units, validation parameters)
	Documentation concerning data, storage and archiving	% Of incomplete documentation

use of appropriate containers, such as high-quality chromatography vials, to avoid contamination. In addition, after maintenance or updates (after pump seal changes, source cleaning (MS), software updates, column changes, and

Table 9: Specific demands regard to the analytical performance required by the current normative.

Main demands for method performance in chromatography	IVDR/LDT	ICH	USP	ISO
Analytical sensitivity	+	+	+	+
Analytical specificity/selectivity	+	+	+	+
Trueness/accuracy	+	+	+	+
Precision (repeatability/Reproducibility)	+	+	+	+
Limit of detection (LoD)	+	+	+	+
Limit of quantitation (LoQ)	+	+	+	+
Measuring range	+	+	+	+
Reportable range	−	+	+	+
Linearity	+	+	+	+
Reference range/cut-off value	+	−	−	+
Metrological traceability	+	−	−	+
Analytical target profile	−	+	−	−
System suitability testing	+	−	+	−
Allowed adjustments	−	−	+	−
Column characteristics	−	−	+	−
Mobile phase characteristics	−	−	+	−
Flow rate	−	−	+	−

Table 10: Issue to consider when developing guidelines for chromatography in routine medical laboratories.

Method validation	Ensuring validated, reproducible methods is difficult, especially when custom protocols are used.
Standardisation and harmonisation	Lack of standardized protocols can result in variable results, calibration issues, and difficulty in method validation.
Quality control and assurance	Maintaining consistent quality assurance with limited resources.
Data integrity and compliance	Proper handling, storage, and reporting of large and complex data sets generated by chromatographic techniques require robust data management systems that comply with regulations.
Instrument maintenance and calibration	Legacy instruments or outdated software have difficulties supporting modern compliance features like audit trails or electronic signatures.
Staff training and expertise	Misinterpretation of results or improper handling of instruments can lead to non-compliance and diagnostic errors.
Integration with laboratory information systems	Poor integration can lead to data silos, manual errors, and delays in reporting.
Cost and resource allocation	Budget constraints in public or smaller labs limit access to compliant systems. Smaller labs may struggle to afford validated systems or maintain rigorous quality assurance processes.

detector service) it is of interest to define requalification items to be demonstrated.

An action plan for the selection of a chromatography system for routine laboratory purposes would be helpful. In addition to the other points mentioned in this text, due to the specificity of the methodology and technique, it is of interest to pay attention to training and competence, regular evaluation of the analyst's performance, troubleshooting and risk management using standards and guidelines. For this reason, these guidelines are particularly important in the field of laboratory medicine.

Future considerations

120 years ago, chromatography was defined as a new technique for separating the components of complex mixtures [71]. But even today, chromatography remains an open window for regulatory advances to achieve reliable test results under routine conditions. We suggest points that should be considered when developing guidelines for chromatography in routine medical laboratories, but also the challenges when considering them Table 10.

Conclusions

The specific quality management of the total laboratory process in chromatography is an open field for further development. Any method used in a medical laboratory should be selected, verified, validated, and controlled to ensure the reliability of laboratory results, as should complex chromatography techniques. This paper from the EFLM Committee: Accreditation and ISO/CEN Standards highlights the key points that should be considered when implementing a chromatography system. In addition, we encourage routine laboratories to evaluate these specific points related to chromatography when managing laboratory processes. Verification/validation of chromatography techniques and the corresponding risk assessment in medical laboratories should be performed in accordance with ISO 15189:2022. Nevertheless, for specific regulatory requirements, the laboratory may use other available guidelines for chromatography. With this paper, we provide guidance to end users in routine laboratories on what to consider when implementing the requirements of ISO 15189:2022 when handling chromatography methods. This paper could also support assessors in the evaluation of chromatography procedures in routine medical laboratory processes. However, specific guidance should ensure a safe balance between regulation and patient safety.

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