Best Practice Manual (BPM) for controlled drug analysis

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1. AIMS

This Best Practice Manual (BPM) aims to provide a framework for analytical methods, procedures, quality principles, training processes and approaches to the forensic analysis of controlled drugs.

This BPM can be used by member laboratories of ENFSI and other forensic science laboratories to establish and maintain working practices in the field of controlled drug analysis to maximise the quality of the information obtained and deliver robust results. The use of consistent methodology and the production of more comparable results will facilitate interchange of data between laboratories.

The BPM provides guidance for the examination and analysis of controlled drugs.

The term BPM does not imply that the practices laid out in this manual are the only acceptable practices for the examination of suspected controlled drugs.

All examples given in this BPM are informative. The lists in this BPM are not in any preferential order.

2. SCOPE

This BPM is aimed for experts in the field and assumes prior knowledge in the discipline. The manual addresses the laboratory work as it is covered in ISO/IEC 17025 [1] and ILAC/G19 [2]. It is not a standard operating procedure and addresses the requirements of judicial systems in general terms only.

This BPM is limited to qualitative and quantitative analysis of materials submitted by law enforcement personnel. This document does not include mobile laboratories, field testing, clandestine laboratories, trace sample analysis, toxicological analysis and comparison/profiling analysis. This BPM does not cover court performance or expert witness testimony.

3. DEFINITIONS AND TERMS

See Appendix A for the glossary.

4. RESOURCES

4.1. Personnel

The laboratory staff performing drug analyses shall have basic knowledge of drugs, drug analysis processes and methods, related legislation, a quality management system (QMS) and health and safety issues. The competence of the staff shall be maintained [3]. Any new staff member shall be trained to perform their duties at the forensic laboratory according to a plan. All training of the staff shall be documented.
In many laboratories, staff can be divided into different categories due to their allotted tasks. Depending on the tasks performed, there can be different knowledge requirements. For example, staff performing instrumental analysis shall have knowledge of the methods used as well as being aware of the limitations and possibilities in using different analytical techniques.

Tasks can include:

- handling drug analysis cases
- performing drug analysis by methods used within the organisation
- writing reports
- checking reports
- developing methods
- supervising/coaching staff
- contact person for customers
- maintaining laboratory equipment and instruments
- managing quality system
- validating instruments and methods
- etc.

Due to variations in the size of different laboratories and variability within different laboratory systems, absolute standardisation of practitioner competence cannot be achieved. It is also accepted that individuals may be responsible for more than one of the defined tasks.

4.2. Equipment

The equipment used at the laboratory shall be routinely monitored to ensure that its stated function is maintained. The manufacturer's operation manual and other relevant documentation, such as the laboratory´s quality documents, for each piece of equipment should be readily available.
The monitoring of instrument performance shall include the use of blanks, reference materials (RM), control samples and calibration standards, where applicable.

Below is a list of equipment that may be used (not exhaustive);

- Gas Chromatography (GC)
- Mass Spectrometry (MS)
- Infrared Spectroscopy (IR)
- Liquid Chromatography (LC)
- Nuclear Magnetic Resonance (NMR)
- Capillary Electrophoresis (CE)
- Thin Layer Chromatography (TLC)
- Other spectroscopic and chromatographic equipment
- Freezers
- Balances
- Pipettes.

Registration of above mentioned critical instruments are required according to the standard ISO 17025 [1]

4.2.1. Pipettes and balances

Pipettes, volumetric equipment and balances have influence on the precision of the analytical results. The equipment shall routinely be checked to ensure correct performance [4]. The results of the performance checks have to meet predefined criteria and shall be documented. Example for quantitative determination:

- pipettes and volumetric equipment, performance may be checked periodically or quarterly.
- balances, performance control using a defined weight before use.

4.2.2. Freezers and refrigerators

Freezers and refrigerators shall be routinely checked for consistent temperature when this is a defined storage condition. The working ranges have to meet defined criteria and shall be documented. Document the control measures, alarms with pre-set limits on the freezers/refrigerators or monitor using thermometers with an accepted precision.

4.3. Reference materials

Drug reference materials (RM) are an essential requirement for ensuring the validity of test results/measurements. See chapter 7.1.

4.4. Accommodation and environmental conditions

The laboratory should have specific separate storage spaces for seized materials, reference materials, glassware, solvents, reagents and waste. Seized material as well as reference materials shall be stored in locked locations outside working hours. Access to these locations is restricted to authorised personnel. Items, which require storage in a cold environment, shall be kept in a refrigerator or a freezer, depending on the required temperature. Other laboratory equipment and protective clothing should be kept in places specifically appointed for their storage.

The laboratory spaces shall have ventilated areas such as fume cupboards. A normal room temperature should be maintained throughout the year, especially in areas where equipment is sensitive to temperature changes.

4.5. Chemicals and reagents

Chemicals and reagents used in routine drug testing should be free from interfering substances and of an appropriate grade (typically, same grade as used for the validation studies) for the tests performed. The origin of the chemicals and reagents shall be documented. The laboratory shall have documented procedures for reagent and solvent preparation. Chemical and reagent containers shall be properly labelled with identity, expiry date and safety information.

5. METHODS

5.1. Peer review

Requirements when analysing seized drugs are sampling, identification, quantification and analytical techniques. Reported results should be reviewed/double checked by a second competent person (see section 12 for more information). Retrieval mechanisms for any data used to determine a result is necessary.

5.2. Sampling of seized drugs

Sampling is the first step in drug analysis. The Drug Working Group (DWG) has established guidelines for sampling of seized drugs for qualitative and quantitative analysis. Laboratories shall adhere to the ENFSI relevant guideline(s) unless important reasons require otherwise (e.g. legal requirements, national sampling plans), [5,6,7,8]

5.3. Identification of controlled drugs

In routine drug analysis the question to be answered is 'Is a controlled drug present in the submitted material?' To meet the customer's request the expert can choose between a number of analytical techniques. Each technique has its advantages and limitations. DWG encourages laboratories to establish analytical schemes, which are based on different methods. Different, in this context, means that the principle of the techniques used shall be independent from each other. A well-designed analytical scheme is the recommended procedure to ensure a drug is unambiguously identified.

Analytical techniques can be arranged in three categories A, B, and C according to their selectivity (from A to C in descending selectivity), [9] see table 1.

Table 1 Categorisation of analytical techniques [9]

Category A (Selectivity through structural information)	**Category B** (Selectivity through chemical and physical characteristics)	**Category C** (Selectivity through general or class information)
Mass Spectrometry	Gas Chromatography	Colour Tests
Infrared Spectroscopy	Liquid Chromatography	Fluorescence Spectroscopy
Nuclear Magnetic Resonance	Capillary Electrophoresis	Pharmaceutical Identifiers
Raman Spectroscopy	Thin Layer Chromatography	Melting Point
X-ray Diffractometry	Ion Mobility Spectrometry	Immunoassay
	Ultraviolet Spectroscopy	
	Supercritical Fluid Chromatography	
	Microcrystalline tests	
	Macroscopic Examination Microscopic Examination (cannabis only)	

For the reliable routine identification of drugs DWG recommends that laboratories adhere to the following minimum standards:

When a category A technique is incorporated into an analytical scheme, at least one other technique (from either category A, B or C) shall be used.

When a category A technique is not used, at least two independent techniques from category B and one from category B or C shall be employed.

Hyphenated techniques (e.g. gas chromatography-mass spectrometry, liquid chromatography-diode array ultraviolet spectroscopy) will be only considered as separate techniques if the results from each technique fulfil the criteria for positive results.

Thin layer chromatography accounts as a category B technique only when both R_f value/distance from baseline and additional colour detection is applied after separation. If only one of these detection methods is employed, it is considered to be a category C technique.

Examples:

Identification of cannabis;

- Macroscopic or microscopic examination (category B), thin layer chromatography (category B) and colour test (category C).
  Use at least three of these.

Identification of cocaine;

- Gas chromatography-mass spectrometry (GC-MS) with retention time check (category B and category A) or
- Gas chromatography-mass spectrometry (GC-MS) without retention time check (GC no category, MS category A) and colour test (category C).

The results of each examination shall be documented appropriately.

These recommendations are minimum standards for the identification of commonly seized drugs. It should be noted that the results obtained may not yet be sufficient to clearly identify substances that have not yet been characterised and for which comparative data are not available. This may happen, when encountering new psychotropic substances (NPS) or isomers of existing controlled substances. In such cases, it is up to the individual laboratory/drug analyst to determine which additional analytical technique(s) may be necessary to identify the substance in question.

The classification of a technique may be lower, if the sample, analyte or mode of operation decreases its level of selectivity. Examples of decreasing levels of selectivity may include:

- an infrared spectroscopy technique applied to a mixture which produces a combined spectrum;
- a mass spectrometry technique which only produces molecular weight information.

5.4. Quantification of controlled drugs

Analytical procedures for quantification shall be scientifically valid. The necessary scope of validation of routinely performed determinations is presented in chapter 6. In routine drug determination, the recommendations on calibration in chapter 5.4.1.2 shall be followed. In quantification, the procedures shall be monitored by means of quality assurance (see chapter 7).

5.5. Analytical techniques

Use and requirements for the detection or quantification of drugs are described in more detail for those analytical techniques which are most often applied in member laboratories.

5.5.1. Gas Chromatography (GC) and Liquid Chromatography (LC)

GC and LC analyses (with non-mass selective detection) are usually not performed as a screening analysis but as a target analysis for the quantification of a drug. It is important to achieve narrow and symmetric chromatographic peaks with high resolution and reproducible peak areas or area ratios.

The detection of a drug by GC and LC is achieved by the comparison of the absolute retention time (RT) or relative retention time (RRT) of the analyte to an internal standard (IS). Accepted deviations of the RT or RRT for qualitative methods are given in table 2:

Table 2 Acceptable deviation of chromatographic techniques

Chromatographic technique	**Acceptable deviation**	
	Δ RT[1]	**Δ RRT[2]**
GC	± 2%	± 1%
LC	± 5 %	± 2.5%

[1] Retention time of a drug in comparison to a drug reference material measured under comparable conditions.

[2] Retention time of a drug relative to an internal standard in comparison to a drug reference material.

When using GC for quantitative analyses, the internal standard (IS) method is the method of choice. The concentration of the IS should be sufficient and not too high. The IS shall not be present in the sample, have sufficient long-term stability (also in solution) and should be chromatographically separated from other substances in the sample.

For LC the internal standard and/or the external standard method can be used.

5.5.1.1. System check

To ensure that the GC or LC system is fit for purpose a control sample shall be analysed prior to analysing test/case samples. The control sample must be a sample with a known composition. IS can also be used for monitoring the operation of an instrument. The results have to meet the laboratories criteria and shall be documented.

5.5.1.2. Calibration

There are two general approaches for calibration.

Approach 1

Calibrate with a new curve each time a quantitative determination is performed.

At least three calibrator solutions should be used to cover the relevant concentration range. The concentration of the calibrators shall be within the working range determined during the validation (see chapter 6). A zero value or 'forced to zero' is not recommended for the calculation of the calibration curve. Criteria shall be established for the acceptance of the calibration data.

Approach 2

Make a calibration curve which is to be used for a longer timescale.
At least five calibrator solutions should be used covering the relevant concentration range. A zero value or ' forced to zero' is not recommended for the calculation of the calibration curve. Criteria shall be established for the acceptance of the calibration data.

Control samples are used for verifying the calibration. It is recommended that the reference material used for control samples is from a different lot/manufacturer than the reference material used for calibration purposes. The control sample could also be prepared from seized material (see chapter 7.1). A new calibration is required when the quality controls limits no longer meet the defined acceptance criteria for the control chart.

5.5.2. Mass Spectrometry (MS)

MS is usually performed in combination with a chromatographic separation technique (GC or LC). It can be used as a qualitative/confirmation method or for quantification.

5.5.2.1. System check

To ensure that the MS system works properly, the following parameters, mass axis, resolution and sensitivity shall be checked and adjusted if necessary, for example by tuning. For screening methods a mixture of substances with different chromatographic properties should be used and should include an early and late eluter. The sensitivity of the mass spectrometer can also be checked with this mixture. The results have to meet defined criteria and shall be documented.

5.5.2.2. Ionisation techniques

The electron ionisation (EI) is the most commonly used ionisation technique when analysing organic substances using GC-MS. For specific substances, the use of chemical ionisation (CI) may be beneficial in either negative or positive mode (NCI or PCI).
The most common types of ionisation for LC-MS are electrospray ionisation (ESI) and atmospheric pressure chemical ionisation (APCI). When using LC-MS, particular attention should be paid to matrix effects by which the analyte's signal can be suppressed or increased.

5.5.2.3. Detection criteria

The detection of drugs by mass spectrometry is possible by full scan MS or selected ion mode (selected ion monitoring (SIM) or multiple reaction monitoring (MRM)). A signal is considered to be recognised (and thus usable for a mass spectral interpretation) when the characteristic fragment ions have a signal to noise ratio equal to or greater than 3:1.

5.5.2.3.1. Full Scan GC-MS Detection

When full scan GC-MS spectra are recorded, molecular ion, characteristic adducts of the molecular ion and/or characteristic fragment ions and isotope ions should be present. These should reflect the ones displayed in the reference spectrum. Low intensity fragment ions in the high mass regions should also be noted, as they may allow the molecular ion to be identified (important for EI) and isobaric compounds to be distinguished. The occurrence of significant additional ions, which appear in the full scan spectrum and are not present in the reference spectrum, should be considered and if possible, explained. The co-elution of matrix components may contribute additional ions to the full scan spectrum.
If a computer-assisted library search is performed, suggested hits shall be tested for plausibility. When background subtraction or deconvolution is used, the raw spectral data shall be retrievable.

5.5.2.3.2. Selected Ion Monitoring (SIM)

If selected ion monitoring is performed, at least three characteristic ions per analyte with a corresponding acceptable signal-noise ratio (see chapter 5.4.2.3) shall be detected. Only in exceptional cases the detection may be carried out with two ions. Exceptional cases shall be justified and documented in the case file. The selected ions should preferably represent the entire molecule and not exclusively originate from the same fragment of the molecule. Preferably, the molecular ion should be one of the selected ion masses.
The intensity ratio of the selected ions is an important criterion for the identification of the analyte. The relative ion intensities (peak area or peak height ratios) should reflect those of a reference material. They are expressed as percentage of intensity (peak area or peak height) of the most intense ion (= 100%) or transition. Accepted variations for quadrupole mass spectrometers are given in table 3.

Table 3 Acceptable variations for quadrupole mass spectrometers [10]

Ion Intensity (relative)	**GC-EI-MS (relative [2])**	**GC-CI-MS, GC-MS^n, LC-MS, LC-MS^n [1] (relative [2])**
> 50%	20%	20%
> 20-50%	20%	25%
> 10-20%	25%	30%
≤ 10%	50%	50%

[1] n > 1
[2] Referred to the value of relative ion intensity

In the case of major deviations, the analysis may be repeated or justified and documented in the case files, as to why a higher variation of a single mass can be tolerated. A possible plausibility check would be, for example, the presence of decomposition products, by-products or when the results of other analytical methods are considered.

5.5.2.3.3. MS^n with Full Scan Detection

All characteristic ions of a reference spectrum shall be present in the measured mass spectrum. Exceptional cases shall be justified and documented in the case file. The occurrence of additional ions, which are missing in the reference spectrum, should be considered and if possible explained, co-elution of matrix components may contribute. When using a computer assisted database search, potential hits shall be tested for plausibility. When background subtraction or deconvolution is used, the raw spectral data shall be retrievable.

5.5.2.3.4. Detection with several fragmentation reactions

The detection of two mass transitions in the multiple reaction monitoring (MRM) mode is considered to be sufficient for the identification provided that the relative fragmentation intensities are in the accepted range (see table 3).
The precursor ion (e.g. the pseudo molecular ion) can be identical, provided that the productions are sufficiently different (different characteristic fragmentations). In the case of major variations in ion intensity ratios, the analysis shall be repeated or explained why a higher deviation of a single mass can be tolerated. A possible plausibility reason could be the presence of decomposition products, by-products or when the results of other analytical methods are considered.

5.5.3. Infrared Spectroscopy (IR)

IR spectroscopy is mainly applied for the identification of drugs and the detection of isomers (note, enantiomers cannot be distinguished). IR is used to lesser extent for quantitative analysis.

5.5.3.1. System check

To ensure that the IR system works properly specific parameters shall be checked regularly, such as wavenumber resolution, wavenumber accuracy and signal to noise ratio. This can be achieved by a software check (auto check) or by measurement of an appropriate control sample. The results have to meet defined criteria (e.g. manufacturer's specifications) and shall be documented.

5.5.3.2. Detection criteria

For pure substances all of the characteristic signals in the reference spectrum should be present in the sample. The occurrence of any significant additional signals, which are not displayed in the reference spectrum, should be considered and if possible, explained.

A drug in a mixture is considered to be present when characteristic absorption bands are displayed in the IR spectrum, position and intensity match with a library spectrum and no strong absorption bands are missing. Suggested hits of a library search shall be tested for plausibility. When spectrum-processing such as baseline correction, smoothing, standardisation or subtraction is used; the raw spectral data shall be retrievable. The laboratory should establish acceptance criteria for the variation of band position or match factor.

5.5.4. Thin Layer Chromatography (TLC)

TLC is a fast method for separating and detecting drugs in mixtures. To ensure reproducible work, it is necessary to run a reference material together with the samples on each plate because several factors affect the separation. These factors are difficult to control. The salt form of a compound or matrix effects may have an impact on the shape of a spot and the R_f value (e.g. cocaine base and cocaine hydrochloride). The sample quantities used should be similar and the analyte shall be stable in the mobile phase.

Usually, the developed plate is evaluated under ultraviolet light and then the plate is sprayed with a reagent solution by which classes of substances can be differentiated. Some spray reagents are suitable for multiple drug types.

Table 4 Examples of spray reagent

Cannabinoids	Fast blue B salt
Nitrogen containing organic compounds (opiates, cocaine)	Acidified Potassium iodoplatinate
Amphetamine (Phenylethylamines)	Ninhydrin and Dansylchloride
LSD and hallucinogenic mushrooms (containing an indole moiety)	Dimethylaminobenzaldehyde and Iron(III) chloride/concentrated HCl (Van Urk reagent)

Each visualisation step shall be documented, for example by scanning or preferably by a digital camera.

5.5.4.1. Detection criteria

Spots from case samples correspond to a spot of a drug reference material when the colour is comparable and the distance from the starting point is similar. The latter condition can be fulfilled when all spots can be arranged within an imaginary rectangular framework or using R_f values.

6. VALIDATION AND ESTIMATION OF UNCERTAINTY OF MEASUREMENT

6.1. Validation

For the general requirements of a validation process, the reader is specifically referred to the ENFSI document “Guidelines for the Single Laboratory Validation of Instrumental and Human Based Methods in Forensic Science” [11], especially section 3, Instrumental-based methods.

In this manual, validation focuses on instrumental validation as well as qualitative and quantitative analysis of seized controlled substances, for example, analysis of powders, tablets, herbal materials and liquids. This manual does not extend to the validation of methods used for drug-impregnated textiles, biological analyses, trace sample analysis, profiling, doping substances and pharmaceuticals.

Methods and instruments used shall be fit for purpose. Qualitative and quantitative methods which will undergo accreditation according to ISO/EIC 17025 shall be validated beforehand. It is recommended that all frequently used methods and instruments are validated before taken into use. When methods already in use are changed or changes are made to instruments, verification has to be performed to ensure that the outcome of the method/instrumental analysis has not been affected in a negative way.

The primary purpose of developing a new method will most often be to solve an analytical problem or that the proposed method will give equal or better results than the former one. A new method could also aim to find other benefits such as improved environmental and/or health conditions.

When introducing a new routine method to the laboratory it is necessary to validate the method. A method already in use may also be re-validated in order to meet quality standards. The concept of validation is to check that test methods yield results that are fit for their intended purpose.

The validation process starts with preparation of a validation plan. Before validation commences, a method and an initial standard operating procedure (SOP) needs to be developed. The complexity of the validation process can be broken down into smaller parts and don´t have to be over-burdensome for laboratories to follow. Examples of validation plans for qualitative and quantitative drug analyses are presented in Appendix B.

Different countries may have defined requirements on reporting limits for either qualitative or quantitative analyses. Any such requirements shall be included in the validation plans and the necessary experiments performed.

In this BPM, qualitative and quantitative validation procedures are discussed separately. However, the following parameters may be used as the basis for other method validations as well. Instrument verification is described subsequently, see chapter 6.8.

6.2. Definitions of validation parameters

Table 5 Definitions

Validation parameter	Definition
Selectivity	The capability of the method to detect or quantify the analyte(s) of interest, whether pure or in a mixture.
Linearity	Defines the ability of the method to obtain test results proportional to the concentration of the analyte.
Working range	The concentration of the analyte shall fall between the lower and upper limits of quantification. Within the working range linearity, trueness and precision (repeatability and intermediate precision) shall be acceptable.
Limit of detection (LOD)	The lowest concentration of an analyte in a sample that can be detected but not necessarily quantitated under the stated conditions of the test. LOD is defined by the most sensitive analytical technique employed within an analytical scheme (see chapter 5).
Limit of quantitation (LOQ)	The lowest concentration of an analyte in a sample that can be determined with acceptable trueness and precision (repeatability and intermediate precision) under the stated conditions of the test.
Repeatability	The closeness of the agreement between the results of successive measurements of an analyte within a sample carried out under the same conditions. The repeatability conditions are: same sample, same method, same instrument, same operator, same laboratory.
Intermediate precision	The closeness of the agreement between the results of successive measurements of an analyte within a sample carried out under the same conditions. The intermediate precision conditions are: same sample, same method, different instruments and/or operators, same laboratory, carried out over a longer period of time.
Reproducibility	The closeness of the agreement between the results of successive measurements of an analyte within a sample carried out under the same conditions. The reproducibility conditions are: same sample, same method, different laboratories, carried out over a longer period of time.
Trueness	The closeness of agreement between the average values obtained from a large series of test results and an accepted reference value.
Robustness	The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.
Measurement uncertainty	An estimation of the contribution of errors to the method result.

6.3. General

6.3.1. Sampling

There are different ways of sampling. In exceptional cases, the sampling procedure may be determined in consultation with the customer or law enforcement personnel. A number of sampling methods, from arbitrary methods to methods with a statistical background are included in the DWG sampling guidelines [5,6,7,8]. Laboratories shall adhere to the sampling guidelines unless important reasons require otherwise (e.g. national sampling plans or legal requirements).

6.3.2. Sample extraction

The method's SOP typically deals with the sample extraction. The result of the sample extraction can be affected by many factors, for example differences in matrix of the material requiring extraction, solubility and/or pH-differences.
For qualitative analysis the yield of the sample extraction needs to be sufficient enough to generate a signal in the analysis.
For quantitative analysis the efficiency of the sample extraction must be determined.

Validation of sample extraction procedures may include:

- usage of a solvent free from interfering substances
- efficiency and grade of solvent utilised
- extraction time
- pH
- sample extraction efficiency.

6.3.3. Analytical methods

For all methods precision (repeatability and intermediate precision), matrix/substrate effects and robustness are important parameters. For quantitative determinations, these may be monitored using a control chart.

6.3.4. Validation parameters

Sample in this section is defined as a target drug in a typical matrix, see table 6.

Table 6 Validation parameters (minimum requirements)

Validation parameter	**How to determine.** Note: the following examples are suggestions only	**Qualitative method**	**Quantitative method**
Selectivity	MS (qualitative method). Perform the test on a sample and obtain a signal with the characteristic mass spectrum above the detection limit. Then perform the test on common adulterants and diluents and obtain different mass spectra. LC (quantitative method). Achieve baseline separation of the analyte(s). If not achieved, consider and explain why result is usable.	X	X

Validation parameter	**How to determine.** Note: the following examples are suggestions only	**Qualitative method**	**Quantitative method**
Linearity	Use an appropriate number of concentration levels (minimum of 5 levels) of the target analyte and use a statistical test. Calculate correlation coefficient r or coefficient of determination r^2. Ideally, r shall be greater than 0.99 or r^2 > 0.98.		X
Working range	Take the LOQ for the lower limit and take the highest concentration level from the linearity study within the linear range.		X
Limit of detection (LOD)	Example 1. Measure a signal to noise ratio greater than three for an analyte in a sample. Example 2. Calculate the LOD by extrapolation of the regression data from the calibration curve. Note 1: LOD can be performed for individual substances or classes of substances. Note 2: LOD is determined using the most sensitive method in any analytical scheme.	X	X
Limit of quantitation (LOQ)	Example 1. Measure a signal to noise ratio greater than ten for an analyte in a sample and ensure the response is consistent. Example 2. Calculate the LOQ by extrapolation of the regression data from the calibration curve.		X
Repeatability (one instrument, one operator)	Analyse an appropriate number of separate weighings from the same sample and for quantitative analysis calculate the standard deviation.		X
Intermediate precision (one or more instruments/ operators over a period of time)	Analyse an appropriate number of separate weighings from the same sample and calculate the standard deviation.		X

Validation parameter	**How to determine.** Note: the following examples are suggestions only	**Qualitative method**	**Quantitative method**
Trueness	Example 1. Compare the test result with other independent analytical methods. Example 2. Compare the test result with PT value. Example 3. Use control chart data from known reference materials. Example 4. Determine the recovery of analyte(s) in spiked samples (within matrix if possible).		X
Robustness	Consider the effect of changing analytical and/or environmental parameters to the test result such as temperature, pH-value, sample preparation, extraction time, matrix etc.		X
Measurement uncertainty (MU)	See examples in Appendix E.		X

6.4. Qualitative methods

A qualitative analytical scheme shall confirm if the sample analysed contains controlled substance(s).
LOD is one parameter to be determined in a qualitative method. Where more than one analytical qualitative technique is employed, the most sensitive technique within the analytical scheme is used to determine the LOD. For example, LC-DAD, LC-MS, GC-FID, GC-MS have lower LOD's than IR and NMR.

The measurement of LOD may be determined for an individual target substance. LOD may also be determined as a general measurement for a class of substances using one representative substance from that class.

Appendix B contains examples of validation plans. The validation report includes the results of the validation measurements.

6.5. Quantitative methods

A quantitative method shall determine the amount of controlled substance(s) in the sample analysed. To ensure the validity of the method, validation parameters in table 6 shall be considered in a validation plan.

If a quantitative method has been in use for some time prior to commencing validation that shows it is a robust method, relevant existing data for any validation parameter outlined above should be included in the validation plan and may be referred to in the validation report. Proficiency test results can be used for trueness and robustness of an existing method requiring validation.

Control samples may be inserted in a control chart for repeatability and intermediate precision determination.

Appendix B contains examples of validation plans. The validation report includes the results of the validation measurements.

It is recommended that a validation timetable be compiled so that data required can be generated from the same validation experiments in order to save time.
An example of a timetable is given, see Appendix C.

6.6. Validation report

An evaluation is made of each experiment and the validation experimental results are summarised in the validation report. A conclusion is made if the method is fit for purpose and if there are any limitations to be aware of. When a method is validated a formal record is signed and dated by responsible technical staff and/or management to give acceptance that the method can be used in casework. A final SOP is drawn up after completion of the validation process.

6.7. Implementation

Any laboratory staff that will use the validated method shall be informed and trained prior to using the method. The validated method shall be recorded as the current laboratory method to be used for its specified purpose.

6.8. Instrument verification

Examples of instrument verifications are presented in Appendix D.

6.8.1. Changes to an existing instrument

Verification shall be performed to show that changes made to an existing instrument have not affected the performance. This can simply be done by running the commonly used control samples.
Examples: column changes, solvent gradient change, changes of instrument parameters such as flow, detector response, etc.

6.8.2. New instrument

If a new instrument is purchased that is similar or of a newer version of existing instruments within the laboratory, instrument verification shall be performed. The vendor shall demonstrate that the new instrument performs as specified by the manufacturer and the laboratory shall verify that it also meets the requirements of the analytical methods to be used. This can simply be done by running the commonly used control samples.

6.9. Measurement Uncertainty (MU)

MU for qualitative and quantitative analysis will be addressed separately (see Appendix E).

6.9.1. Qualitative analysis

For qualitative analysis MU estimation is not applicable. However, factors that may affect the result should be considered.
From the validation, LOD and selectivity are the parameters that show the limits of the analytical technique used. For example, a drug below detection limit will not give a positive result.

The laboratory should have documented procedures on how to deal with such a negative result. Examples would be to repeat the analysis with a different analytical technique with a lower LOD, increase the concentration of the analytical sample or increase the analytical sample size.

6.9.2. Quantitative analysis

Results of quantitative analyses are accompanied by a range of uncertainties and an estimation of the MU is required. The standard ISO/IEC 17025 [1] requires the laboratory to identify the significant components which contribute to MU and to evaluate them.

In general, the main uncertainty contributions originate from sampling and random and/or systematic errors. When sampling is done according to the ENFSI guideline [7,8] the contribution of sampling error can be estimated using the results of sampling studies and equations described in the guidelines. However, its contribution to the overall MU is negligible. The remaining random and systematic errors can be evaluated in different ways. Examples for estimating the MU are given in Appendix E.

Additional information can be found in ENFSI guidelines [7,8,11].

7. QUALITY ASSURANCE

7.1. Use of reference materials

The use of reference materials enables the laboratory to demonstrate that the achieved results are reliable.
The laboratories' requirements for the reference material depend on the intended use.

There are different levels of reference material.

- Certified Reference Material (CRM) is delivered with a certificate showing metrological traceability to SI-units combined with measurement uncertainty and expiry date. According to the revised version of ISO/IEC 17025:2017 [1], producers of reference material that follow ISO standard 17034:2016 [12] are competent.
- Reference material (RM) is a homogenous material which has been shown to be stable in accordance with specified criteria.
- In-house reference material can be used when RM is not available. Examples could be dilutions of pure seized drug material, a purified seized drug material, an old reference material which has expired (traceability re-confirmed) etc.

Guidance on the selection and use of reference materials and the production of in-house quality control materials are provided; see [13,14,15].

When preparing an in-house reference material consideration of its intended use is necessary:

- qualitative analysis, used in the control system
- quantitative analysis, used for calibration or as a control sample.

Consideration shall be given to the quantity of substance required, the level of homogeneity and the stability depending on the intended use. When preparing an in-house reference material, it is recommended to prepare a batch big enough for at least one year's use.

If the reference material is to be used for qualitative analysis it is not necessary to know the exact concentration of the controlled drug present. When the in-house reference material is to be used for quantitative analysis the concentration must be known.

There are different ways to validate the concentration of the in-house reference material:

- by comparison to an existing CRM (if obtainable)
- by analysis with a primary method, e.g. NMR
- by analysis with two or more techniques.

For all reference material the laboratory shall have written procedures on how to confirm and reconfirm the validity. Considerations should be given to stability, expiration date and possibilities of their extension and specified storage conditions. The origin of the reference material shall be documented.

All reference materials shall be labelled or have means of recording the following:

- substance name/identity
- date of first opening and initial
- expiry date/date of retesting (when it´s a commercial RM)
- purity/concentration (for quantification).

Reference material shall be stored according to manufacturer's information to ensure stability and shelf life of the material. In-house reference materials are to be stored according to knowledge of the substance chemical properties. This has to be defined by the user. Reference material shall be stored so that any risk for contamination, degradation, affecting stability is minimised.

7.2. Proficiency testing/collaborative exercises

Relevant proficiency tests (PT), collaborative exercises schemes and the frequency of participation should be included in the quality system employed in the laboratory [16]. Frequently available PT include: ENFSI, UNODC, LGC, FTS, CTS, NMIA and national PT. ENFSI member laboratories shall participate in the ENFSI PT programme. Collaborative exercises with other laboratories may also be organised and are encouraged, especially for substances where no current PT is available.

The results of PT shall be evaluated by participating laboratories. Laboratories shall take corrective action if their results deviate by more than three relative standard deviations (RSD) from the PT designated/consensus value. An assessment of the PT results is made in relation to the organisers' reported data (often the stated z-score $\leq \pm 3$ is used). Z-scores can be monitored in a control chart. Deviations from the expected result are assessed and steps are taken to correct any issue which has arisen.

7.3. Quality control

Analytical methods are constructed according to basic scientific principles for obtaining accurate results. Ongoing monitoring of a method and instrument is required to ensure that the determination remains fit for purpose.

Monitoring of the analytical scheme may include the following factors, see table 7.

Table 7 Analytical scheme monitoring

Factor	Example of what to do
Homogeneity of the sample	In quantitative analysis, 2 replicates (weighings) of analytical sample are evaluated to determine the consistency of results. Acceptance limits (which are method dependent) should be defined by the laboratory.
Carry-over	In qualitative analysis, solvent blanks are used to show if carry-over is present. Solvent blanks may be run between different analytical samples. In quantitative analysis, solvent blanks may be used but this is dependent on the method and analytical technique chosen.
Instrument performance	Monitoring by use of control substances which can include standards, samples, matrices etc. The aim is to ensure that the instrument is performing sufficiently to meet the requirements of the application.
Sample preparation	Technique and sample type dependant. Sample preparation may be monitored using control samples, replicate weighings and/or internal standards.
Solvent impurities	Run solvents on instrument to check for interfering impurities.
Identification/quantification	Run control samples and check chromatographic and/or spectral results.

Results of the control samples for routine quantitative determinations should be documented in control charts. Acceptance limits for approval or rejection should be defined.

7.4. Data collection for control, monitoring and trend analysis

Control charts are statistical tools used to evaluate and monitor a quantitative method.
When monitoring a method, it is necessary to analyse control samples of known concentration.
If the performed measurements cover a wide range of concentration levels, it is recommended that at least two control samples at different concentration levels are used.
When using a control chart over a longer period of time you will get knowledge about:

- Precision (from the standard deviation);
- Robustness (sensitivity to changes in temperature, handling etc.);
- Bias (when the control sample used is a certified reference material).

Control charts shall be stored either electronically or in paper form.

7.4.1. Control chart with warning limits

A control chart should include a target value, warning and control limits
See Figure 1 - the upper and lower control limit equals ± 3 s, while the warning limit is equal to ± 2 s. ‘s’ refers to the standard deviation of the method for the individual drug at the relevant level.

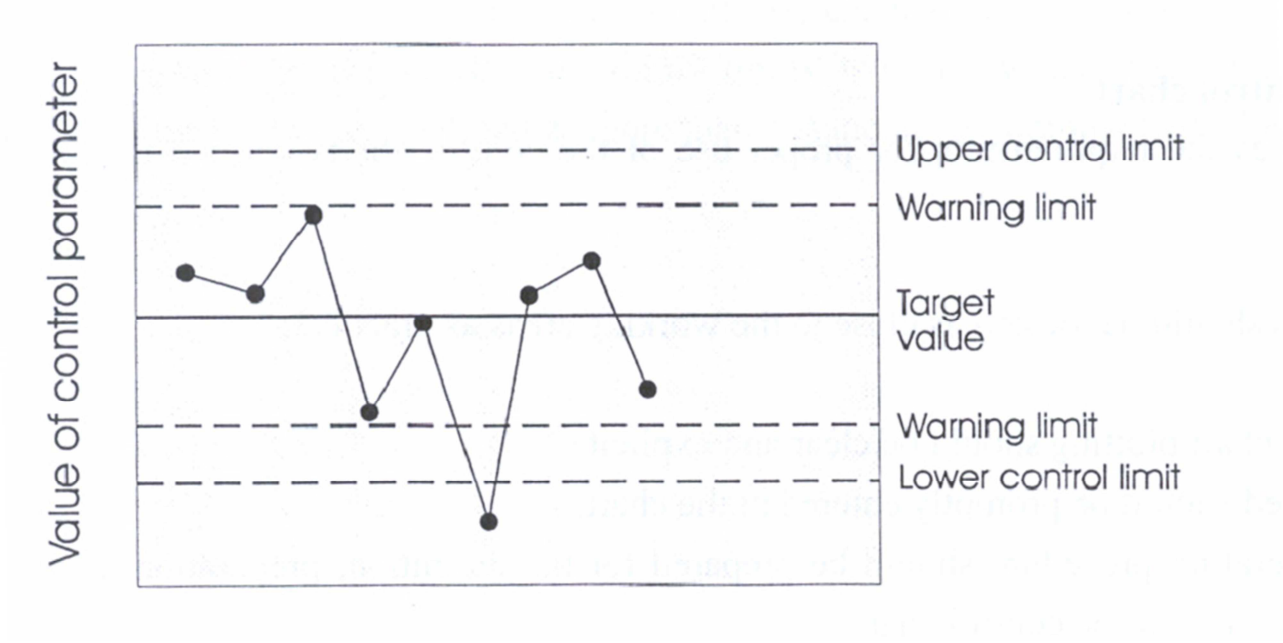

Figure 1 Format of a control chart.

Initially, a control chart may be created using the results from a number of separate quantitative determinations (minimum of 6 [10]) of a control sample. The target value is set from the mean value of the initial quantitative determinations. The control chart limits are then set from the standard deviation as outlined above. After a period of time or after a number of extra determinations, the limits and/or target value may need to be re-evaluated and adjusted, if necessary.

A warning limit of ± 2 s corresponds to approximately 95% confidence level, statistically 1 out of 20 measurements will fall out of this limit (± 1 s: 68%; ± 2 s: 95.4%; ± 3 s: 99.7%). When defined limits are exceeded (outliers above and below warning limits), the follow–up actions defined by individual laboratories should be taken.

The control chart may be used for trend analysis of control samples. Most often, the results will vary above and below from the target value. A trend of results continuously being higher or lower shall be evaluated and follow-up actions defined by individual laboratories should be taken.

7.4.2. Control chart without warning limits

Another possibility to monitor a quantitative method is to run a target value control chart. For this chart type only upper and lower exclusion limits are set. The laboratory defines the exclusion limits, for example a certain precision which has to be achieved (e.g. ± 10% relative). Only when the value is exceeded, actions shall be taken by the laboratory.

8. HANDLING ITEMS

This BPM does not deal with crime scenes. Crime scene investigations are dealt with in the following references [17,18,19,20,21].

A description of the item/sample workflow in the laboratory should be documented and incorporated in the quality management system. The workflow should represent the different stages of items/samples in detail and specify the appropriate procedures and methods for each stage:

Workflow:

Item receipt → Item registration → Sampling and/or sample preparation → Identification of content → Quantification of content (when necessary) → Documenting and reporting of results → Return or disposal of sample.

8.1. Items receipt and storage

It is important to be aware of potential hazardous materials, highly potent compounds or chemical, biological, radioactive, nuclear and explosive materials (CBRNE) items that may be present in items submitted.

When items for examination arrive at the laboratory facility, any packaging/bags should be checked for any leaking or possible contamination. It should also be checked that the items received agree with the request description. Any deficiencies should be noted/documented. If necessary the customer should be contacted to clarify discrepancies (e.g. item number or description/item amount not matching). The results of this consultation should be documented.

Items should be stored in a manner that minimises contamination, prevents degradation and damage and maintains sample integrity. The traceability (chain of custody) of items shall be maintained. Items shall be stored securely and only authorised personnel should have access. Different items may require specific storage such as wet plant/fungal material (dry before storage) or lysergide (LSD) (keep in dark), cannabis butter (keep refrigerated) or fresh khat (put in a freezer).

8.2. Items handling

Procedures should ensure that any samples derived from items are not mixed up during analysis. A working strategy of handling only one item at a time is recommended. Items and samples shall be labelled (e.g. with tags, bar codes). Any laboratory generated labelling should follow the sample through the analytical process and documentation so as to ensure traceability (chain of custody).

Item examination and sample handling shall always be carried out on clean surfaces (such as a clean sheet of paper, clean glass slide, evaporating dish, or watch glass) to preserve sample integrity and minimise cross contamination.

All items should be handled according to the requirements of the customer. If problems arise, like insufficient material, it may be necessary to contact the customer before further examination.

After sampling, the item is repackaged (not necessarily in the original packaging material) and stored. The eventual storage, return and/or disposal of the item is dependent on national practice/legislation. Storage, return or disposal shall be documented.

8.3. Handling reference material and control samples

Reference material and control samples shall be in suitable containers, properly labelled and stored. The labelling shall allow reference to information such as substance name, batch number, opening data, expiry date and retesting date.

9. INITIAL ASSESSMENT

Documentation which details the procedure for the receipt of items into the laboratory facility should be available to ensure the following:

- The traceability of the item is recorded and maintained from receipt into the laboratory until its return, storage or disposal.
- Items at the receipt stage should be checked to ensure that they are correctly packaged and all required documentation and labelling is in order. If not in order, the customer should be contacted.
- The analytical tests to be performed are identified and requested.
- The risk of contamination and degradation is assessed and procedures are in place for these factors to be minimised.
- The traceability of sub samples taken from an item is maintained.

10. PRIORITISATION AND SEQUENCE OF EXAMINATIONS

Some items have to be prioritised. Analysis of items may be urgently required by the customer or items may deteriorate quickly, for example fresh khat.

Identification is generally performed prior to quantification unless it is done in parallel.

11. RECONSTRUCTION

Not applicable.

12. EVALUATION AND INTERPRETATION

The key question to answer in qualitative analyses is if there is a controlled drug present. The analytical data is evaluated to determine the presence a controlled drug(s). It is good practice to know the limitations of the methods used in forensic analysis.

Analysis data should be evaluated by an internal risk control technique. Reported results should be reviewed/double-checked by a second competent person, so called `four-eye principle`.

It may be that the first evaluation of instrumental data is performed by a validated computer system. Such information may be subsequently sent to a LIMS system.
The laboratory shall have documented procedures for their peer review process.

Laboratories are encouraged to evaluate negative analytical results and may consider concentrating a sample or utilising an alternative analytical method for further investigation. This is dependent on resources available and will be case dependent.

13. PRESENTATION OF EVIDENCE

The presentation of results for drug identification and quantification is typically done by issuing a certificate of analysis or report. These documents issued by laboratories to the police or the courts shall be objective, accurate and clearly written, meeting the requirements of ISO 17025 and the jurisdictions served.

13.1. Qualitative analysis

It is suggested to include the following in the report [5.] For ISO 17025 accredited laboratories these are requirements. :

- the title of report
- the identity of the laboratory performing the analysis
- a unique case number (on each page)
- name and contact information of customer
- request identification and date of request
- the date of receipt of evidence
- the date of report
- the pages of the report shall be numbered (e.g. 1/3)
- a description of the submitted evidence
- a brief description of the methods and analytical techniques used; in the case of an accredited method, the report should include at least the SOP code
- details of sampling procedure; if the sampling procedure is part of the SOP or a sampling protocol is in place, then it is not necessary to give sampling details in the report
- any deviation from an accredited standard procedure shall be recorded. Either the result or the method used shall be marked as 'non accredited' in the report and the deviation shall be documented
- the results including the quantity of the items (weight, volume, number of tablets, plants etc.); this can be in a tabulated form
- the conclusions to include a statement regarding the identified controlled drug(s) and its/their classification according to the law
- identity and signature (or electronic equivalent) of the analyst or reporting officer.

13.2. Quantitative analysis

The reports issued by laboratories to the police or the courts may include all the elements listed for the qualitative analysis of controlled drugs but the procedures will be different for quantitative analysis. The report shall also include the following [22]:

- quantitative results stated numerically with a meaningful number of decimal points
- the form of the drug (base or salt) on which the calculation is based

Depending on national legislation the uncertainty of the measurement may be stated (e.g. cocaine hydrochloride 31.7% ± 7.3% $_{relative}$, k=2) or a statement given that there is an uncertainty associated with the method. This information shall be available as part of the method validation. The measurement uncertainty can also be given for the equivalent quantity of pure drug (e.g. the powder (net weight 50.0g) contains 15.9g ± 1.2g cocaine hydrochloride, k=2). The measurement uncertainty is most critical in cases where the purity result is close to a legal limit.

13.3. Preliminary reports

A preliminary verbal or written report may be supplied to the customer prior to issuing a final written report**.** Any such communication shall be documented.

14. HEALTH AND SAFETY

Health and safety considerations are important in all aspects and at all stages in the analysis of suspected controlled drugs. Submitted materials may be highly potent/hazardous and this may be unknown at the time of submission. The safe packaging of materials submitted to the laboratory [21], their safe transit and storage while in the laboratory and their packaging for safe return to law enforcement/court personnel shall be considered.

General laboratory safety procedures are the minimum requirement. However, since forensic laboratories deal with many unknown substances, it is recommended that additional safety precautions are taken. Safe working procedures have to be part of quality documents.

14.1. Forensic drugs laboratory facility

- Suitable laboratory accommodation, instrumentation and general appliances (e.g. laboratory benches, safety cabinets, fume-hoods, powder containment units, general laboratory safety equipment, refrigerators, freezers and space to carry out the forensic analysis to the required standard, safely and without contamination).
- Provision of appropriate environmental conditions (e.g. lighting, temperature, humidity, ventilation/air flow) required to facilitate correct performance of examinations or analytical examinations.
- Proportionate protection against any interference with items/samples.
- Storage facilities which prevent loss, deterioration and contamination of items before, during and after analysis prior to their return.
- Facilities for the secure disposal of confidential waste and the safe disposal of hazardous materials.
- Provision of laboratory staff personal protective equipment (PPE) which is appropriate for the potential risks which may be encountered.
- Facilities for the secure disposal of confidential waste and the safe disposal of hazardous materials.

Safety data sheets (SDS) should be collated and available to laboratory staff for chemicals, reagents and reference materials that are purchased from commercial suppliers. It is recognised that many items submitted for examination are unknown in nature and as such present unknown risks. The use of fume hoods, powder containment units or local exhaust ventilation cabinets are recommended to allow safe handling of suspected potent/hazardous items.

14.2. Personal Protective Equipment (PPE)

PPE should be used in the laboratory when working with bulk drug analysis and working with very potent drugs.

14.2.1. Protective clothing

To protect staff from harmful substances the correct use of laboratory coats or single use protective clothing is recommended.

14.2.2. Gloves

The hands are exposed to many substances during a workday. Gloves are therefore an important protective device. Single use gloves (e.g. nitrile gloves) with a good fit are suitable for fine motor (dextrous) work and are the most common gloves type in drug testing laboratories. Thicker gloves, such as laminate gloves, are more resistant for longer duration work or when using concentrated acid or base solutions.

14.2.3. Safety glasses/face protection

Chemicals or particles can cause eye damage. Safety glasses and face shields ensure the protection of face/eyes.

14.2.4. Respiratory protection

Inhalation of harmful substances and materials may cause acute and chronic conditions. For protection against chemical contamination, use a mask with filters (filter mask). There are three main types of filtering masks. All three mask types can protect against particles (e.g. dust, allergens and microorganisms) as well as gasses and vapours.

14.3. Risks when working with potent opioids

Appendix F outlines some concerns specific to fentanyl related compounds.

14.4. Lone working policy

Many forensic drug laboratories have voluntarily introduced a lone working policy to ensure that in the event of staff illness or an incident, a colleague is nearby and quick assistance is available.

14.5. Visitors policy

A visitors policy should be included as part of the quality system. This should outline who can visit the different areas in the laboratory and what visitors should be informed of prior to entering any laboratory area.

15. REFERENCES

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[29] SQS 98 Manual, Kleiner, Joachim, 1998.

16. AMENDMENTS AGAINST PREVIOUS VERSION

Not applicable (first version).

Appendix A Glossary

Term	Definition	Reference
Analytical sample (quantitative)	Last chosen material after homogenisation and mass reduction which will be dissolved for instrument analysis.	[7]
Analytical sample (qualitative)	The material used for analysis.	
Bias	Difference between mean measured value from a large series of test results and an accepted reference value.	[24]
Blank	(i) Material (a sample, or a portion or extract of a sample) known not to contain detectable levels of the analyte(s) sought. Also known as a matrix blank. (ii) A complete analysis conducted using the solvents and reagents only; in the absence of any sample (water may be substituted for the sample, to make the analysis realistic). Also known as a reagent or procedural blank.	[26]
Bulk	The whole amount of material, which has been considered to be associated. In a multiple package seizure the bulk is neither visually nor by other preliminary tests differentiable.	[7]
Certified reference material (CRM)	Reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes its traceability to an accurate realisation of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence.	[13]
Certified value	Assigned value given to a CRM, quantified through a certification process (traceable to SI-unit and with a known uncertainty).	[13]
Coefficient of determination (r^2)	Square of the correlation coefficient r.	[29]
Combined standard uncertainty (u_c)	Standard uncertainty of the result of a measurement when that result is obtained from the values of a number of other quantities, equal to the positive square root of a sum of terms, the terms being the variances or covariance's of these other quantities weighted according to how the measurement result varies with changes in these quantities.	[9]
Consensus value of a PT	The mean value of the results from the participating laboratories without outliers.	[25]
Control sample	Material with known properties analysed in order to evaluate the performance of the test and to ascertain that the data obtained are valid.	[27]

Term	Definition	Reference
Correlation coefficient (r)	$r = \frac{\sum_i (x_i - \bar{x}) * (y_i - \bar{y})}{\sqrt{\sum_i (x_i - \bar{x})^2} * \sqrt{\sum_i (y_i - \bar{y})^2}}$ x_i = Concentration of calibrator i y_i = Measurement value of calibrator i $\bar{x}$ = Mean of calibrator concentrations $\bar{y}$ = Mean of measurement values from calibrators The correlation coefficient r is a measure to evaluate a linear regression (-1 ≤ r ≤ +1).	[29]
Designated value, also known as assigned value, of a PT	The value as provided by the organiser of the PT.	
Detection	The recognition of a drug or class of drugs using an analytical technique.	
Expanded uncertainty (*U*)	Quantity defining an interval about a result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand. NOTES 1. The fraction may be regarded as the coverage probability or level of confidence of the interval. 2. To associate a specific level of confidence with the interval defined by the expanded uncertainty requires explicit or implicit assumptions regarding the probability distribution characterised by the measurement result and its combined standard uncertainty. The level of confidence that may be attributed to this interval can be known only to the extent to which such assumptions can be justified. 3. An expanded uncertainty U is calculated from a combined standard uncertainty u_c and coverage factor *k* using: $U = k \times u_c$	[9]
Four eye principle	Check of analytical results/reports by a second competent person.	
Identification	To determine the identity of a drug using an analytical scheme employing several analytical techniques.	

Term	Definition	Reference
In-house reference material	A reference material made and characterised at the testing laboratory for a defined use.	
Intermediate precision	The closeness of the agreement between the results of successive measurements of an analyte within a sample carried out under the same conditions. The intermediate precision conditions are: same sample, same method, different instruments and/or operators, same laboratory, carried out over a longer period of time.	
Internal standard (IS)	A chemical compound added to the sample test portion or sample extract in a known quantity at a specified stage of the analysis, in order to check the correct execution of (part of) the analytical method. The IS should be chemically stable and/or typically show the same behaviour as the target analyte.	[26]
Item	Object, substance or material that is collected, derived or sampled as part of the forensic process.	[27]
Linearity	Defines the ability of the method to obtain test results proportional to the concentration of analyte. Note: The Linear Range is by inference the range of analyte concentrations over which the method gives test results proportional to the concentration of the analyte.	
Limit of detection (LOD)	The lowest concentration of an analyte in a sample that can be detected but not necessarily quantitated under the stated conditions of the test. LOD is defined by the most sensitive analytical technique employed within an analytical scheme (see chapter 6).	
Limit of quantification (LOQ)	The lowest concentration of an analyte in a sample that can be determined with acceptable trueness and precision (repeatability and intermediate precision) under the stated conditions of the test (see chapter 6).	
Measurement uncertainty (MU)	An estimation of the contribution of errors to the method result.	
Peer review	Evaluation of the reports, examinations, notes, data and findings by others competent in the same field to assess that there is an appropriate and sufficient basis for the conclusions and/or opinions.	[27]
Quality control	Monitoring the results of analytical methods by different means.	
Reference material	Material or substance, one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials.	[13]
Report	Communication of outcomes (e.g. observations, findings, interpretations, conclusions and/or opinions) of the forensic process.	[27]

Term	Definition	Reference
Repeatability	The closeness of the agreement between the results of successive measurements of an analyte within a sample carried out under the same conditions. The repeatability conditions are: same sample, same method, same instrument, same operator, same laboratory.	
Reproducibility	The closeness of the agreement between the results of successive measurements of an analyte within a sample carried out under the same conditions. The reproducibility conditions are: same sample, same method, different laboratories, carried out over a longer period of time.	
R_F value	The ratio of the distance migrated by the sample compared to the distance travelled by the solvent front.	[28]
RMS bias	Contribution of all considered bias. $RMS_{bias} = \sqrt[2]{\frac{\sum bias_i^2}{n}}$	[24]
Robustness	The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.	
Sample	Portion drawn from a whole or population for the purpose of examination/testing, not necessarily representative of the whole.	[27]
Selectivity	The capability of the method to detect or quantify the analyte(s) of interest, whether pure or in a mixture.	
Standard operating procedure (SOP)	Authorised, documented and specified way to carry out a laboratory activity or process.	[27]
Standard uncertainty (u)	Uncertainty of the result of a measurement expressed as a standard deviation.	[9]
Target value	The mean value at the time of determining the limits of the control chart.	
Trueness	The closeness of agreement between the average values obtained from a large series of test results and an accepted reference value.	
u(Cref)	Uncertainty component from the consensus value of a PT or from the certified value of a CRM.	[24]
Working range	The concentration of the analyte shall fall between the lower and upper limits of quantification. Within the working range linearity, trueness and precision (repeatability and intermediate precision) shall be acceptable.	

Term	Definition	Reference
Z-score	$$z = \frac{x_i - \bar{x}}{s}$$ x_i: *Result from participant i* $\bar{x}$: *Mean of* x_i *to* x_n n: *Number of participants* s: *Standard deviation of* $\bar{x}$ The Z-score is a way to compare results from a PT to a normal population. The Z-score tells you how the individual laboratory result compare to all participating laboratories	

Appendix B Examples of validation plans

Appendix B gives examples of validation plans for qualitative and quantitative analyses. These examples are not prescriptive. See chapter 6 for more information.

1. **Example of a template for a qualitative validation plan (depending on client needs).**

Background/Objective
Give a background to the specific needs of the laboratory and what the purpose is for the method to be validated.

Validation Parameters
Parameters listed should be considered in the validation. Describe the experiments to be performed in the validation.

- Selectivity
- Limit of detection (LOD)

Criteria for acceptance
If possible, formulate the criteria for the results acceptable for the stated purpose. These may be adjusted at a later stage during the validation process.
(for example when the method gives equal or better results compared to another specific method or that the method is determined to be fit for purpose).

References
[1] *Author, year, title*

2. **Example of a template for a quantitative validation plan.**

Background/Objective
Give a background to the specific needs of the lab and what the purpose is for the method to be validated

Validation Parameters
Parameters listed should be considered in the validation. Describe the experiments to be performed in the validation. Parameters not appropriate in the validation should be left in the plan and an explanation should be given to why the parameter was excluded.

- Selectivity
- Linearity
- Working Range
- Limit of detection (LOD)
- Limit of quantification (LOQ)
- Repeatability
- Intermediate precision
- Trueness
- Robustness
- Measurement Uncertainty (MU)

Criteria for acceptance
If possible, formulate the criteria for the results acceptable for the stated purpose. These may be adjusted at a later stage during the validation process.
(for example when the method gives equal or better results compared to another specific method or that the method is determined to be fit for purpose).

References
[1] *Author, year, title etc.*

Appendix C Example of a quantitative validation timetable

This is an example of a validation timetable. By planning experiments according to a plan the validation may be performed in an efficient and less time consuming way. Results from the same experiment may be used for different validation parameters. See chapter 6 for more information. These days may extend beyond the executive timetable below and may not be consecutive days:

Day	**Validation parameters**
1	Selectivity
2	Linearity and working range
3,4,5	LOD, LOQ and trueness, repeatability and robustness, (intermediate precision, if multiple operators are used)
Initial control chart data from different operators or instruments	Intermediate precision
6, 7	Evaluation of results and writing a validation plan

Appendix D Examples of instrument verification and report

Example 1. New instrument (e.g. new GC/LC)

This example applies to the purchase of a new instrument (which may be supplied with updated software or hardware) for example a new GC/LC, where a former version of the instrument was in use in the laboratory. The same analytical method is used.
Check selectivity by using a typical case sample or a test mixture/control sample that contain typical target analytes and adulterants. Evaluate results and ensure they are within predefined specifications. Generate a verification report.

If the new instrument will be used for quantitative analysis, perform a modified calibration curve (use at least three calibration levels), check results using control samples. Generate a verification report.

Example 2. Column replacement

This example applies to replacing the same column type in an existing verified GC/LC.
Use the same column type, length and size (may be another lot from same supplier); Check that results delivered from control samples are similar or better than those obtained from the replaced column. Document that results are acceptable in an instrument log book/control chart/simple verification report or similar.

Example of verification report (can apply to examples 1 and 2 above)

Instrument: GC Instrument
Inventory number: xx

Verification of an analytical instrument equal to already existing instrument

☒ Control of delivery by the vendor was performed and accepted xx-xx-xx.
The vendor´s tests have been performed by the service technician with approved results.

☒ Internal controls, specific for the analysis to be performed and specific for the analytical technique used, have been performed by the laboratory analysts and have been approved. The internal controls were analysed xx-xx-xx.
Controls used are specified in the SOP for the specific method.

Digital data is archived in the instrument software and in the intended folder on the computer system.

Appendix E Examples of how to evaluate measurement uncertainty

These examples are not prescriptive.

Estimation of Measurement Uncertainty (MU)

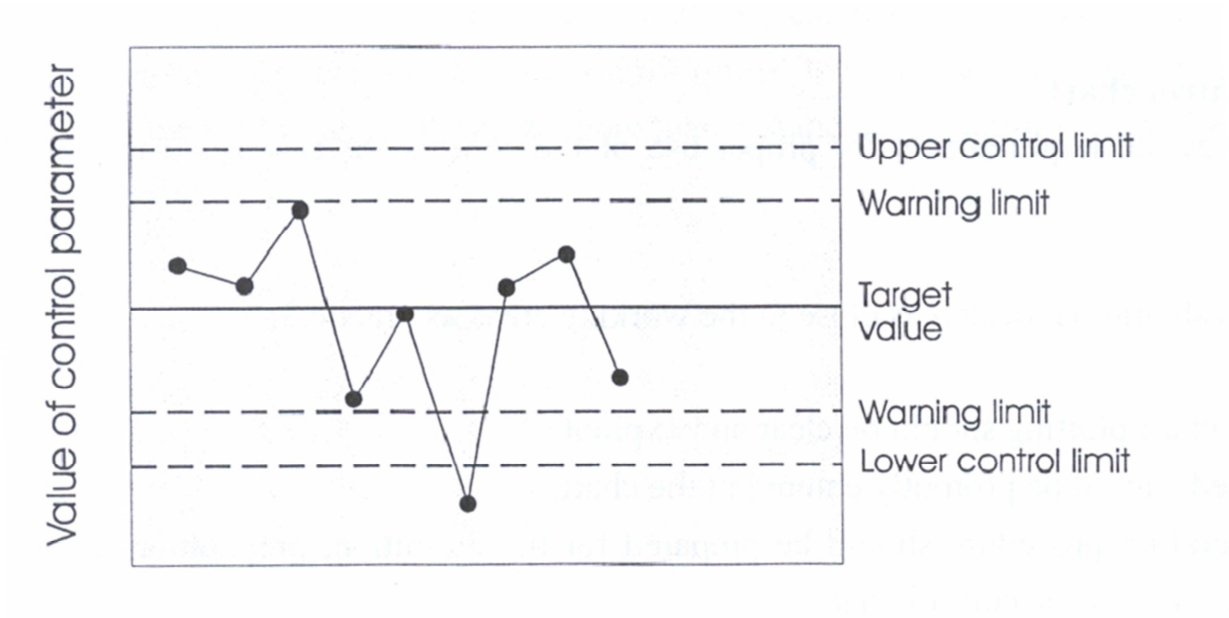
Example 1

How to calculate MU using a control chart [23]

Objective: The laboratory needs to present the measurement uncertainty for a performed quantification of amphetamine to a customer. Quantification of amphetamine is performed with a GC-FID. A five-point calibration curve is established from a reference material. Control samples and case samples are run with duplicate weighings. One set of control samples consisting of a lower and a higher concentration is run in the beginning and the end of each sequence.

The laboratory uses an in-house Excel program for the control chart. The 'target value' is the mean value at the time of determining the limits of the control chart.

See example below:



Two control samples at different concentrations (10.0% and 70.7%) are used for quantification of amphetamine. Both control samples were derived from seizures. The concentrations have been determined previously. The seizures were large and the control samples are robust so they have been used for a couple of years at the laboratory. The control samples are stored in the freezer and are prepared at the same time as the case samples.

In the Excel program for monitoring the control chart, the mean value and standard deviation are continuously calculated.
Measurement uncertainty will be derived from the mean value and standard deviation.

The standard deviation (s) divided by the mean result multiplied by 100 will be the relative standard deviation (RSD). This value multiplied by two (to get approximately 95 % confidence interval) will be the MU. This measurement uncertainty will cover the errors affecting the result except bias.

$$\text{MU} = 2 \text{ x } \left(\frac{s}{\bar{x}}\right) \text{ x } 100$$

In this particular case, the case sample has a value of 59.8%. For the measurement uncertainty calculation, the control sample 70.7% is used, since this is the control sample that is closest in value. The last 60 values are used for the calculation. 60 values cover about one year of analysis.

The mean value for high concentration level control sample during the period was 70.88 %. The standard deviation was 1.19.

$$\text{MU} = 2 \text{ x } \left(\frac{1.19}{70.88}\right) x\ 100 = 3.36\%$$

The laboratory has rules for rounding the uncertainty in a conservative way, so in this case MU is rounded up to 4%. Therefore, the MU for the case sample result at k=2 is:

59.8 x 0.04 = 2.4%

Example 2

The laboratory is requested to determine the average purity of 20 tablets which display similar external characteristics (weight approximately 6 grams) and previously determined to contain MDMA. In this example, measurement uncertainty is calculated using control chart data in combination with proficiency test data using historical proficiency test data collected over several years across an inter laboratory system.

The tablets are homogenised and two samples taken which are analysed by HPLC-DAD. The laboratory uses an in-house reference material for preparation of calibration solutions. The qNMR analysis report states the purity of MDMA Hydrochloride to be 99.4% $_{\text{purity}}$ ± 0.3%$_{\text{purity}}$ (k=2).
In this example, the uncertainty of the reference material will not contribute significantly to the combined measurement uncertainty u_c.

Measurement results of tablets (HPLC-DAD method):
Sample No. 1: 27.6%$_{\text{purity}}$
Sample No. 2: 26.9%$_{\text{purity}}$
Average: 27.3%$_{\text{purity}}$

Sample homogenisation is tested to ensure that the laboratory's homogeneity criteria are met. The laboratory has determined that the purity difference between the two single results must be equal to or less than the control limits from the control chart (± 3 standard deviations = 6,3%$_{\text{relative}}$).

$$\frac{27.6\% - 26.9\%}{27.3\%} * 100 = 2.6\%_{\text{relative}}$$

This value is smaller than the control limits of ± 6.3%$_{relative}$ demonstrating acceptable homogeneity.

Estimating MU [24]:

Step 1: Define control chart limits (R_w)	Control limits are set to ± 6,3%$_{relative}$ (confidence level approximately 99%) R_w = 6,3%$_{relative}$
Step 2: Quantify bias component for each PT event using the difference between laboratory result and consensus value (mean without outliers). In this example u_{cref} is estimated using the consensus values (means without outliers) from a series of PT inter laboratory results.	From proficiency tests over 6 years the bias results were (%$_{relative}$) -5.3, -1.1, +1.7, -6.2, -2.1 and +4.5. The root mean square (RMS) of the bias is $RMS_{bias} = \sqrt[2]{\frac{\sum bias_i^2}{n}}$ $= \sqrt{\frac{-5.3^2 + -1.1^2 + 1.7^2 + -6.2^2 + -2.1^2 + 4.5^2}{6}}$ RMS_{bias} = 4.0%$_{relative}$ The uncertainty of the consensus values is $u_{Cref} = \frac{S_R}{\sqrt{n}}$ S_R : Mean reproducibility standard deviation of six proficiency tests, S_R = 4.5%$_{relative}$ n: Number of proficiency test participants, n = 23 u(C_{ref}) = 4.5/$\sqrt{23}$ = 0.9%$_{relative}$
Step 3: Convert R_w to standard uncertainty u_{Rw} Note: 3 standard deviations (IP) are the set limits of the control chart	Intermediate precision: u_{Rw} = 6.3/3 = 2.1%$_{relative}$

Step 4: Calculate combined standard uncertainty u_c	$u_c = \sqrt{{u_{Rw}}^2 + {u_{bias}}^2}$ $= \sqrt{{u_{RW}}^2 + {RMS_{bias}}^2 + {u_{cref}}^2}$ $= \sqrt{2.1^2 + 4.0^2 + 0.9^2}$ $u_c = 4.6\%_{relative}$
Step 5: Calculate expanded uncertainty, $U = k \times u_c$	$U = 2 \times 4.6\%_{relative} = 9.2\%_{relative}$ (k = 2) (confidence level approximately 95%)
Step 6: Convert U to absolute percent	9.2/100 = 0.092 * experimentally determined mean value $0.092 * 27.3\%_{purity} = 2.5\%_{purity}$
Step 7: Express result	$27.3\%_{purity} \pm 2.5\%_{purity}$ MDMA Hydrochloride (k = 2)

Appendix F Risks when working with potent opioids

In recent years, highly potent substances have become more available in the illicit drug market. One such class of substances are fentanyl related compounds and they are potentially life-threatening if consumed. A significant increase in the danger associated with processing such cases occurs if a powder containing a fentanyl becomes airborne. Some laboratories have a policy of conducting an initial analytical analysis on a small sample of any unknown or suspected powders prior to a full forensic examination. This approach may detect a highly potent substance but it is not fool-proof and may give a false sense of security as poor mixing of a powder may lead to high concentrations in discrete areas of the submitted powder.

When dealing with any unknown suspected material, you and your colleagues' safety should be borne in mind and appropriate safe precautions taken so that exposure to the substance kept to a minimum. The removal of powders from their packaging is typically done to obtain a weight of the powder submitted but in certain circumstances, may not be done due to safety concerns.

It is important that staff in a chemical laboratory work safely (risk management). The following points are important and should be taken into consideration:

- people (skills and behavior)
- procedures/protocols (how to/what if)
- facilities (buildings/PPE).

All unknown powders and solutions may give rise to a risk for laboratory staff. Therefore staff who may encounter for example opioids should be trained to recognize symptoms of opioid intoxication. It is advisable, to have the opioid antidote Naloxon available in the laboratory and trained staff to administer it.

<u>Dermal precautions:</u>
Incidental dermal absorption is less likely to cause opioid toxicity. For routine handling of suspected opioids, nitrile gloves provide sufficient dermal protection. In situations where an enclosed space is potentially heavily contaminated, water-resistant overalls should be worn. Incidental dermal exposures should immediately be washed with water and soap. Alcohol-based hand sanitisers should NOT be used, as they do not wash opioids off the skin and may increase dermal absorption.

<u>Respiratory precautions:</u>
In the circumstance of airborne suspension of powdered or solvated opioids, a properly fitted respirator mask is likely to provide protection. It is essential that protection of eyes and face is used during tasks where there exists the possibility of opioid exposure. If possible use closed fume cupboard.

The opioid antidote, Naloxone should be administered to those with objective signs of hypoventilation or a depressed level of consciousness. It is not to be administered for dizziness and anxiety. If hypoventilation persists following initial Naloxone dose and personnel with advanced airway training are not available, repeat the administration of Naloxone until emergency personnel arrive. Naloxone is available in injection or nasal spray form. Not all countries have access to the antidote due to different law and regulations.

Appendix G Simplify your laboratory work

Informative

This appendix gives examples of how different laboratories within ENFSI have found ways to simplify work, save time, money and give positive contributions to the environment.
The examples are explained in a summarised way and include a reference to the laboratory giving the example. If anyone is interested in finding more information you are encouraged to contact the specific laboratory.

Table of content

1. Quality system

Defined routines

Well defined procedures for handling material to be analysed, sampling, instrumental methods and technical maintenance will save time and have effect on the quality of the work performed. (Armenia, Bulgaria)
Working towards accreditation will per definition lead to defined routines.

Digitalised quality management system

Going from a quality management system based on paper and manual archive to a digital system may save a lot of time and gives a better-defined traceability. Keeping quality documents in an electronic system results in efficient ways to give access to the system, to distribute documents and make changes. (Cyprus)

2. Preparation and batch work

The usage of robots for qualitative sample preparation work and extraction of substances in samples, saves a lot of time. (Sweden, Finland)

The time it takes to get in touch with the customer to find out the real question to be addressed, may impede analysis. Earlier clarification will save time. Develop intake procedures for the questions to be asked at reception. (The Netherlands)

Simpler cases (one to four items, positive result for drugs in instrumental analysis) are sorted out and handled in a fast line with laboratory technicians being specialised in these types of cases. Around 50% of incoming cases are simpler cases which leads to the majority of the cases being completed in 2-4 days. (Sweden)

All instrumental analysis work and maintenance are taken care of by specialised laboratory staff. The case handling is performed by technicians as well as forensic experts, but all

instrumental analyses are performed by technicians and chemists trained for this work. Results are transferred to the technicians/forensic experts who summarise the results, decide if any more analysis needs to be performed and finally do the reporting. Routines and well defined procedures save time, lead to higher quality and more confident and responsible personnel. (Sweden, Denmark)

For similar looking body packs in the same seizure Norway has a routine that is time saving. All packs including the plastic packaging are weighed together (= total gross weight). 5 of the packs (3 packs for cannabis resin) including the plastic packaging are then weighed together (=gross weight of subsamples). The plastic packaging are then removed from these 5 (3) packs, and the content are weighed (=net weight of subsamples). Net weight of the whole seizure is calculated. Sampling for qualitative and quantitative analysis is taken from the sub sample. (Norway)

3. Equipment and instruments

GC-MS is considered adequate for identification of most drugs (retention time and EI spectra). No additional methods are needed. (Finland, Sweden, Poland)

When preparing samples before analysis the usage of dispensers instead of pipettes for solvents is time saving. The solvents are prepared with added internal standard. (The Netherlands)

The frequency of operation qualification of the FT-IR instrument is performed only twice a year. The stability of the instrument allows this frequency. Besides a “daily measurement” (each day when the instrument is used) and alignment (energy optimisation of the IR beam) there is no other control substance measurement performed. The routine gives a time reduction. (Switzerland)

4. Digital efficiency

Using electronic logbooks gives easier access to data, enables search functions and statistical processing of data. (Cyprus)

Balances are connected to the laboratory information management system (LIMS). When weighing samples the weight is automatically transferred from the scale to the digital case file. (Finland, Sweden)

In a well-developed web-based LIMS a lot of time and paper can be saved in combination with quality efficiency and traceability. The system includes case information, safety, quality and training documentation together with communication related to the case. Information from the Police can be directly transferred into the system. Descriptions of items, weights, instrumental analysis results are transferred directly to the LIMS where the statement is automatically created. The system gives very good traceability to adding, checking and accepting results and documents. Quality control charts are also maintained in the system.
The reports are sent out with digital signatures.
Technicians as well as forensic experts take part in writing statements. The process is accredited. (Finland)

For quantitative analysis the peak areas are transferred to the LIMS where calculation of the quantitative result is automatically performed by the system. (Finland)

All cases and samples are labelled with bar codes. Instruments are equipped with bar code readers. This ensures traceability as well as faster handling and secure reading of labels. (Finland, Sweden, the Netherlands)

A quick log report for simple one item cases has been developed for generating automatic reports in the LIMS. (Ireland)

Going to automated LIMS reporting is costly and labour intensive but will in the end save time and raises quality. Reports are sent by e-mails to the customer. (Ireland, Sweden)

Fully integrating balances and instruments with the LIMS is time efficient. Registrations are made and stored electronically. There is also an increased traceability. (Norway).

5. Qualitative analysis

Make a decision of what level of certainty the justice system in your country need. In Cyprus sampling for qualitative analysis using hypergeometric distribution is used. Lowering the proportion of positives in population (k) to 0.75 instead of 0.90 will give a lower number of analyses to be performed. (Cyprus).

Ireland initially reduced its sampling policy from 90% to 75% confidence level and at a later stage from 75% to 50% confidence level. There were no objections from court and it means that fewer samples are analysed for identification purposes (now just 7 samples are analysed for 50% confidence). It is always up to the forensic expert to decide to analyse more. (Ireland)

The hypergeometric tool is used to routinely decide the number of samples to be taken. (Poland).

6. Quantitative analysis

You should be aware of specific needs according to your country's law. If, for example, there is no need for quantification of drug samples where the weight is less than 500 g according to court purposes then there is no need for quantification of lesser amounts. (Cyprus)

Quantification of drugs is performed without previous drying of the samples (Denmark)

Adapting existing methods to changes in the materials analysed will in the end save time. THC levels used to be lower but have increased. Former method was for materials <20%. Changes of calibration and validation of the method made it possible to quantify higher amounts of THC in the first run. (France)

In accordance to the justice system quantification of specified drugs is only performed when the amount exceeds a certain weight. (Finland, Sweden)

Dutch justice system does not require quantification in general. Quantification is only performed in certain cases such as smuggling cases/victim cases/strange matrices. (The Netherlands)

The Swiss laboratory used to start cocaine and heroin calibration for each new series with a six point curve with six separate weighings of reference material over the whole working range. This has successfully been reduced to a four weighing process. Two weighings in the upper range and two in the lower range. The resulting calibration curve was still very satisfying and met all acceptance criteria regarding correlation factor and reproducibility. The result is time and cost reduction. (A further reduction of reference material to two weighings can be considered by dilution of one high and low concentration calibration point sample). (Switzerland)

Changing the type of control chart (statistical with warning limits) to target value type without warning limits has reduced the number of 'out of control instances'. (Germany).

7. Cannabis

Cannabis is analysed by GC-FID for qualitative analysis so as not to contaminate the GC-MS. (Finland)

Cannabis is identified by microscopic and macroscopic examination for specific botanical features and analysis of THC with GC-MS. (Sweden)

Examples of cannabis cultivation, see section 9 “Simplifying sampling”.

8. Solvents and controls

Checking robustness of solvents and stock solutions of reference materials will most likely show that they are stable and the usage of solvents and stock solutions can be prolonged. (Switzerland).

9. Judicial system dependent

Agreements simplifying the analysis work

Adulterants and substances not under control are not analysed unless requested. (The Netherlands).

Disposal

All material not used for analysis is returned to the customer. This gives no material for the laboratory to destroy except for those used in analysis. (Italy)

Most often the whole seizure is sent to the laboratory. Bar codes are used in the disposal routines. Disposal is done in the LIMS and the samples can be traced to the right barrel/bag even after it has been sealed. Disposal is arranged according to routines specified. (Finland, Sweden, Denmark)

Simplifying sampling

Agreements can be made so if there is a large seizure, the Police can contact the laboratory before submitting samples. This makes it possible for the laboratory to sample on site and reduce the amounts of samples since the whole item has been observed and documented. In cases of cannabis cultivations, the Police document the site and send in samples. The remaining material is destroyed according to local routines. (Ireland, Denmark)

The Netherlands do not receive the full amount of the seizure for analysis, just a sample. All received samples already have a barcode that follows the case throughout the analysis process. (The Netherlands)

The Police in Norway are responsible for documenting a cannabis cultivation site by photographing the site, the plants and counting all plants. A sample of five representative plants are dried and sent to the laboratory for analysis. The rest is destroyed according to local routines based on a decision made by the prosecutor involved. (Norway)

10. Cooperation

Using European and international organisations and scientific literature in order to get help and find answers instead of inventing everything on your own is a good way to save time. It is recommended to use ENFSI guidelines, SWGDRUG recommendations and UNODC documentation. (Armenia, Bulgaria, Poland)

Sub-contracting may save time and money when used for analysis that the laboratory does not have the competence for, for example substance structural elucidation. (Finland, Sweden).

11. Websites and help desk

A way of decreasing the number of incoming phone calls can be achieved by giving information on a website on the laboratory's service. Instructions on sampling, submitting of samples, packaging together with information on statistics and current trends can be provided. Usage of a help desk/service telephone enables the transfer of questions to a dedicated phone and saves time for the staff handling cases. (Finland, Sweden)