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Guidelines for Accreditation of Swiss Medical Laboratories Performing Nucleic Acid-Based Diagnostic Procedures

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I. Preface

These guidelines are based on the work of the ad hoc working group of the sector committee for laboratory medicine of the Swiss Accreditation Service (SAS).

These guidelines describe the particularities and requirements in the field of nucleic acid-based (molecular genetics) diagnostics, and are based in most parts on the references referred to in chapter 2. These guidelines can only be used jointly with these references. Requirements mentioned explicitly in the standard ISO/IEC 17025: 2005 and ISO 15189: 2007 and applicable without further changes in the field of laboratory medicine are not mentioned in this document in full length. Therefore, in these particular points the guidelines refer to the corresponding documents. The guideline is updated mainly by adding the actual standards.

SAS replaced the old references in the guidelines by those of the new accreditation standards ISO/IEC 17025 and ISO 15189; also an update of legislation requirements was done. Compared to the initial version of the guideline of June 2004 there are no changes in the basic genetics requirements for accreditation. This guideline is only issued in English.

These guidelines provide a harmonised basis for the assessment of testing laboratories in the field of nucleic acid-based diagnostics. The quality management system (QM-system) of the laboratory shall contain acceptable solutions for all critical points. At the same time, these guidelines together with appropriate check lists may give to the personnel of the medical laboratory helpful hints and guidance for the development of their own adequate QM-system. These guidelines do not utterly cover all aspects of nucleic acid-based diagnostics. During a visit, the extent of conformity between the stated requirements and the actual, practical situation will be assessed.
If elements of the standard ISO/IEC 17025 and/or ISO 15189, parts of it or explicitly stated requirements in these guidelines are not considered in the QM-system of the testing laboratory, corrective actions or measures need to be taken by the medical laboratory in order to obtain or maintain accreditation.

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II Guidelines for Accreditation of Swiss Laboratories performing nucleic acid-based diagnostic procedures

1. Scope

The scope of these guidelines is assessment of nucleic acid-based diagnostic methods in the field of clinical chemistry, haematology, immunology, molecular genetics, virology and microbiology.

A laboratory working with nucleic acid-based diagnostic procedures may work in any of the above-mentioned fields with a broad variety of samples. Only the techniques mentioned beforehand are covered by these guidelines.

Any method for detection, identification, characterisation and quantification of nucleic acids in any kind of sample is the subject of these guidelines independent of the type of nucleic acid-based molecular diagnostic procedure applied.

2. References

General requirements for the competence of testing and calibration laboratories, ISO/IEC 17025: 2005; referred to as **ISO 17025**.

Medical laboratories — Particular requirements for quality and competence, ISO 15189: 2007; referred to as **ISO 15189.**

Molecular Diagnostic Methods for Infectious Diseases: Approved Guideline, NCCLS, Vol. 15 No. 22 (1995); referred to as the **NCCLS** document.

Serodiagnostik von Infektions- und Immunkrankheiten, Teil 60: Polymerasekettenreaktion (PCR), standard DIN 58967-60 (1995); referred to as **DIN 58967**.

American College of Medical Genetics: Standards and Guidelines for Clinical Genetics Laboratories; 2nd Edition 1999; referred to as **AmCollege**.

Cumitech 31: Verification and Validation of Procedures in the Clinical Microbiology Laboratory, American Society for Microbiology (ASM), 1997; referred to as **Cumitech 31**.

Botschaft zum Bundesgesetz und Bundesgesetz über genetische Untersuchungen beim Menschen vom 8. Oktober 2004 (**GUMG**) SR 810.12.

Verordnung vom 14. Februar 2007 über genetische Untersuchungen beim Menschen (GUMV) SR 810.122.1, see also current changes in the text of the legislation; referred to as **Gene-Lex.**

Verordnung über den Umgang mit Organismen in geschlossenen Systemen (Einschliessungsverordnung, ESV) vom 1.11.1999, SR 814.912; referred to as **ESV directives**.

SUVA-Richtlinie über die Verhütung von Berufskrankheiten in diagnostisch mikrobiologischen Laboratorien, 1995; referred to as **SUVA directives**.

Directive 98/79/EC of the European Parliament and of the council of 27 October 1998 on in vitro diagnostic medical devices, Official Journal of the European Communities, 7.12.98, L331/1; see also current Swiss legislation in the field of medical devices; referred to as **IVD**.
NOTE: The in-vitro Medical Devices Directive (IVD Directive) sets a framework for the regulation of in-vitro diagnostic tests in the EU. Issued in 1998, the directive came into force in 2003 in all member states. Since then, some issues have arisen with the directive which have particular relevance for genetic testing. Switzerland linkes to the EU directive in her national legislation.

QUALAB: Schweizerische Kommission für Qualitätssicherung im medizinischen Labor, Konzept für die Qualitätssicherung, see http://www.famh.ch; referred to as **QUALAB**.

J. den Dunnen and S.E. Antonarakis, Human Genetics, Nomenclature for the description of human sequence variations, Vol. 109: 121-124, 2001; referred to as **HumGenet**.

Swiss Society of Medical Genetics: Best practice guidelines on reporting in molecular genetic diagnostic laboratories in Switzerland, Reporting Guidelines DNA, V1/2003, see http://www.ssgm.ch; referred to as **reporting guidelines DNA**.

Standard checklist for the accreditation of medical laboratories according to ISO/IEC 17025: 2005 respectively ISO 15189: 2007, document no. 320.dw, edition December 2008, rev. 02; referred to as **320.d** and **320f.**

3. Terms and definitions

Specific definitions are given within this text. More general definitions are used according to the **NCCLS** document.

Abbreviations are summarised in a separate list at the end of this document.

Numbers in rectangular brackets in chapters 4 and 5 of the document refer to the corresponding paragraphs of the standard **[ISO/IEC 17025 / ISO 15189]**.

References in round brackets give additional information for laboratories performing nucleic acid-based techniques about the treated paragraph of the standard (**ISO 17025 / ISO 15189)** or to additional information in **other documents**. The referred documents are listed in chapter 2 of the document (see above) and shall be consulted in order to fulfill or understand the particular paragraph of the standard **ISO/IEC 17025** respectively **ISO 15189**.

4. Management Requirements

4.1 Organization / Organization and management [4.1 / 4.1]

[4.1.1 - 4.1.4 / 4.1.1 – 4.1.4]

No additional interpretation of the clauses for medical laboratories performing nucleic acid-based techniques is necessary.

[4.1.5 / 4.1.5] Laboratories]

In general, the management, the head of the laboratory or one of the technical personnel shall possess the FAMH title in human genetics or at least, the addendum ”DNA/RNA Diagnostik” in the actually holding FAMH title, an equivalent document or certificate accepted by the Swiss

Federal Authority SFOPH. Additionally, his/her deputy should possess the same qualification (see **GUMG** or updated documents of the legislation for additional requirements).

Confidentiality shall be assured at any time like in other medical investigations. The integrity of electronically stored data shall be guaranteed.

Responsibilities, competences and interactions among personnel are regulated. Each person shall qualify by a sufficiently specialised education for the task he/she fulfils according to the requirements of chapter 11 and 12 of the **NCCLS** document defining the technical basis. The responsible personnel shall guarantee that the requirements of the **QUALAB** and the federal public health authorities (such as the Federal Department of Health and Swissmedic) are fulfilled.

A quality manager with distinct responsibilities and appropriate education shall be designated.

4.2 Management system / Quality management system [4.2 / 4.2]

[4.2.1 / 4.2.1, 4.2.2] (Gene-Lex, SUVA directives, ESV directives)

A management system shall be implemented and structured according to the requirements of the standard **ISO/IEC 17025 / ISO 15189** like in other medical diagnostic domains.
A member of the management shall know the relevant regulations and be in charge of their implementation. In particular, the requirements of the referred laws or directives have to be enforced.

[4.2.2 / 4.2.3]

The handling of genetically modified material requires authorization from Swiss Federal Authority SAEFL. The permit to handle genetically modified material shall be presented during assessment.

[4.2.3 - 4.2.4 / 4.12]

No additional interpretation of the clauses for medical laboratories performing nucleic acid-based techniques is necessary.

4.3 Document control [4.3 / 4.3]

[4.3.1 - 4.3.3 / 4.3.1 – 4.3.2] (Gene-Lex)

No additional interpretation of the clauses for medical laboratories performing nucleic acid-based techniques is necessary.

4.4 Review of requests, tenders and contracts / Review of contracts [4.4 / 4.4]

[4.4.1 - 4.4.3 / 4.4.1 – 4.4.3] (IVD, ESV directives)

Analysis of genetically modified material shall be performed according to the requirements of the **Gene-Lex** and the corresponding project shall be acknowledged by the designated ethical committee in charge of the study, evaluation or new development if necessary. In general, CE marked diagnostics (IVD) shall be used for analysis of health relevant parameters of patients. For scientific studies also diagnostics (IVD) without CE marking may be applied.

[4.4.5 / 4.4.5]
Laboratory specific methods shall be developed according to the requirements of the **IVD** if appropriate in terms of use of the system. Methods developed in-house and being used or distributed on a commercial basis need to comply to the **IVD**, in particular where a pre-market approval is necessary.
NOTE: To prove analytic and clinical validity the test's intended clinical purpose shall be known. It is necessary to provide data on both analytic and clinical validity (although for clinical validity it may be sufficient to cite the existing scientific literature).

Projects involving genes of human or animal origin shall fulfil the requirements of the **ESV directives**.

4.5 Sub-contracting of tests / Examination by referral laboratories [4.5 / 4.5]

No additional interpretation of the clause for laboratories performing nucleic acid-based techniques is necessary. Accredited laboratories should be preferred. Distinct business relationships shall be maintained and quality of performed services shall be checked and rated regularly. If possible, the number of subcontractors should be kept as low as possible.

4.6 Purchasing services and supplies / External services and supplies [4.6 / 4.6]

No additional interpretation of the clause for laboratories performing nucleic acid-based techniques is necessary. Certified suppliers (e.g. according to ISO 9001, ISO 13485) or accredited subcontractors (e.g. according to the standards of the series 15000 and 17000) for services and supplies should be preferred. Distinct business relationships shall be maintained and quality of performed services shall be checked and rated regularly.

4.7 Service to the customer / Advisory services [4.7 / 4.7] (Gene-Lex)

The requirements of the standard **ISO/IEC 17025 / ISO 15189** shall be fulfilled.
For example a Vademecum, a list or a catalogue, either in print or as web-site based document should be available to clients giving at least indication of test methods, pre- and post analytical procedures and subcontracting activities.
NOTE: Adequate information of the patient about the possible consequences of genetic analyses shall be performed (in first place) by the medical doctor. The medical laboratory shall be aware that such an advice of the patient is necessary by law. Some situation may demand this advice by the medical laboratory, especially in those cases where the samples are taken in the laboratory.

4.8 Complaints / Resolution of complaints [4.8 / 4.8]

No additional interpretation of the clause for medical laboratories performing nucleic acid-based techniques is necessary.

4.9 Control of nonconforming testing work / Identification and control of nonconformities [4.9 / 4.9]

The requirements of the standard **ISO/IEC 17025** / ISO 15189 shall be fulfilled. False results have to be recalled in writing, commented and corrected immediately.

NOTE: Procedures to guarantee the correct treatment of nonconforming testing work are a very important part of the quality management system. Nonconforming examinations or activities occur in many different areas and can be identified in many different ways, including clinician complaints, quality control indications, instrument calibrations, checking of consumable materi-

als, staff comments, reporting and certificate checking, laboratory management reviews, and internal and external audits.

4.10 Improvement / Continual improvement [4.10 / 4.12]

No additional interpretation of the clause for medical laboratories performing nucleic acid-based techniques is necessary.

4.11 Corrective action [4.11 / 4.10]

No additional interpretation of the clause for medical laboratories performing nucleic acid-based techniques is necessary.

4.12 Preventive action [4.12 / 4.11]

Polymerase chain reactions (PCR) and any other amplification reactions are often prone to contaminations. In order to avoid or to be able to detect any potential contamination, appropriate controls and conditions shall be considered, including:

- contamination controls
- sufficient space allowing clear separation of the different steps
- environmental aspects
- appropriate equipment
- controlled workflow
- risk assessment

As soon as a contamination becomes evident, reporting of any results shall be stopped until the source of the contamination has been properly identified and eliminated.

4.13 Control of Records / Quality and Technical Records [4.13 / 4.13]

No additional interpretation of the clause for medical laboratories performing nucleic acid-based techniques is necessary.

4.14 Internal Audits [4.14 / 4.14]

No additional interpretation of the clause for medical laboratories performing nucleic acid-based techniques is necessary. The internal audits shall specially emphasize to nucleic acid-based diagnostic procedures and practical aspects of laboratory work including quality and contamination control efforts.

4.15 Management Reviews [4.15 / 4.15]

No additional interpretation of the clause for medical laboratories performing nucleic acid-based techniques is necessary. The management review shall specially emphasize to nucleic acid-based diagnostic testing procedures, internal and external quality control schemes as well as educational aspects of personnel.

5. Technical Requirements

5.1 General

Many factors determine the reliability of laboratory testing / medical examinations. The strict avoidance of contaminations is a major issue in the field of nucleic acid-based testing.

5.2 Personnel [5.2 / 5.1]

The requirements for the responsible person as a member of the management of the ¨medical laboratory are defined in chapter 4.1.5 of these guidelines.

The medical laboratory's management defines the minimum levels of qualification and experience necessary for staff members within the laboratory:

- ensuring that the responsible persons (head and deputy of the medical laboratory) possess the required professional title(s) enabling them to be officially in charge of the analyses.
- ensuring that the personnel is experienced and adequately trained for nucleic acid-based testing.
- maintaining the competence of laboratory personnel by monitoring their work performance and verifying technical skills.

Training, effectiveness of it and work experience shall be documented for all members including management of the medical laboratory.

The range and type of duties of laboratory personnel will vary according to the size and scope of the laboratory. However, each laboratory should guarantee:

- for a competent deputy according to the (legal) requirements defined for the person in charge of nucleic acid-based techniques.
- that laboratory technicians possess at least a nationally recognised laboratory technical degree and are experienced in nucleic acid-based techniques.

Nucleic acid-based techniques are a vital part of genetics and all analyses shall meet the **reporting guidelines DNA** of the Swiss Academy of Medical Sciences if appropriate in terms of technique used and applicable laws for work with genetically modified material. All personnel handling samples and performing analysis shall be instructed accordingly. The instruction shall be documented.

5.3 Accommodation and Environmental Conditions [5.3 / 5.2]

Access to the laboratory area is strongly restricted and visits of external persons shall be documented including date, time, name, address and signature of the visitor. In order to minimize any risk of contamination, laboratories are obliged to demonstrate appropriate measures such as:

1) Separation of working areas for each individual step of a nucleic acid-based test procedure. The following four distinct working areas are strongly recommended for:

   a) preparation of reagents
   b) sample handling (e.g. splitting and extraction)
   c) setting up of reactions
   d) amplification and analysis of amplicons.

2) If amplification and analysis are not combined and automated, additional specific safety requirements shall be fulfilled and documented to avoid contamination and proof correct handling.

3) Unidirectional workflow and changing of protective clothing are mandatory. Each particular working area needs its own and specifically labelled (preferentially in different colours) equipment (e.g. pipettes centrifuges, adequate protective clothing, as well as vials, heating blocs etc.).

4) If rooms with different pressures are available, always the highest positive pressure should prevail in the area of nucleic acid extraction and set up of reaction mixtures.

5) Safety procedures shall be carefully defined and documented including the following issues:

   a) Precautions to prevent accidental contamination.
   b) Regulations for protective clothing (e.g. laboratory coats and safety glasses).
   c) Prohibition of eating, drinking, and smoking in the laboratory.
   d) Separate and safe storing of properly labelled:
      - reagents
      - specimen
      - nucleic acid extracts
   e) Any microbiological specimen requiring nucleic acid-based testing shall arrive as straight as possible without previous manipulation and shall be opened exclusively in the PCR sample handling area. Where materials are used for multiple types of testing, separate collection of samples is preferable for splitting. Any splitting shall be performed immediately in the PCR sample handling area only. Samples containing potential infectious agents shall be handled risk adapted according to the applicable laws.
   f) In principle, no splitting is permitted for samples analysed for germ line mutations! However, splitting may exceptionally be permitted if e.g. different extraction procedures are explicitly required for the same sample. Nevertheless, splitting shall always take place in the designated sample handling are only.

5.4 Test Methods and Validation of Method / Examination procedures [5.4 / 5.5]

[5.4.1 / 5.5.1 -5.5.3 General]

All technical procedures and methods shall be validated before being applied to routine diagnostics. The head of the laboratory is responsible for adequate validation and shall provide all the necessary means to fulfil the task.

Molecular test methods can be divided into two different classes:

1. Qualitative methods (e.g. nucleic acid amplification, genomic DNA- or c-DNA-sequencing, RFLP)
2. Quantitative detection methods (e.g. real time PCR, Gene-Array)

The specificity of an amplicon shall be confirmed by one or more techniques like e.g. hybridization (such as the so-called Southern Blot), sequencing, and restriction enzyme analysis.

Laboratories offering nucleic acid-based testing are obliged to participate in appropriate external quality control schemes (proficiency testing schemes).

Validation of test methods (depending on the analysis performed) should include at least:

- Specificity (e.g. subtypes of viruses)
- Sensitivity (e.g. minimal residual disease detection in oncology)
- Linearity and precision within the selected range (e.g. for quantitative PCR)
- Reproducibility
- Stability of DNA or RNA in the sample under conditions of the assay
- Ruggedness of the method

Validation studies are conducted by different means:

- By the scientific community in case of standard material or standard methods and officially published.
- By the laboratory itself in case of methods developed in-house or already validated methods, yet significantly modified in-house for specific purposes.

Records of all performed validations shall be safely stored for future reference. In case of rarely used tests, reliable technical performance of test methods shall first be verified by testing of appropriate reference material followed by replicate analysis of the (real) clinical sample(s).

NOTE: By these means the laboratory personnel is expected to regain all necessary skills before they treat clinical samples with rarely used test methods.

[5.4.2 / 5.5.2, 5.4.3] Selection of method]

Whenever indicated, standard methods should be used. A laboratory introducing a new method shall demonstrate and document the performance characteristics of the procedures used. If new commercialized test methods are introduced, the performance characteristics of each procedure shall be verified in the laboratory. If the new commercialized test method replaces a previously used method, the performance of the tests shall always be compared. The selection and performance of test methods shall be fully documented. An official approval of the new test methods prior to use in routine work shall be performed. The parameters on which the decision for approval was taken shall be listed and commented.

[5.4.3 / 5.5] Laboratory-developed methods / Examination procedures

The introduction of test methods developed by the laboratory for its own use shall be a planned activity and shall be assigned to qualified personnel equipped with adequate resources. Plans shall be updated as development proceeds and effective communication amongst all personnel involved shall be ensured.

All in-house methods shall be fully documented and validated in the sense mentioned in chapter 5.4 and 5.5 of the standards, respectively (where relevant requirements of the **IVD** shall be taken into consideration). They shall include procedures for internal and external quality control. Wherever possible, certified reference materials shall be used and regular participation in external quality control measures shall be taken into consideration.

NOTE: In genetics it is not always possible to participate in an appropriate proficiency test (PT) as no external quality control measures are established on national or international level so far. In many cases the recent detected genetic mutations are ~~very~~ seldom and only detectable / confirmable in connection with clinical data. Such a medical laboratory is highly specialized, skilled and works in the particular scientific field together with other centres of excellence for the detected rare or similar diseases. In such a case interlaboratory comparisons may overcome the lack of PT participation.

[5.4.4 / 5.5.7] Non-standard methods]

In most of the cases non-standard methods in the meaning of the standard **ISO/IEC 17025** / **ISO 15189** are used. For further information refer to chapters “Selection of methods” and “Laboratory-developed methods” above.
NOTE: Where commercial test methods (test kits) for the determination of routine parameters are used, which are developed by IVD manufacturer, only CE-marked products shall be used in connection with the treatment of the patient. This is only valid for the analysis of samples of human origin, not for samples originated from animals or other biological material. For the determination of non-coded areas of the DNA (e.g. for forensic DNA trace analysis) the requirement of the IVD directive is not valid and the CE-marking of the product is not necessary, but welcome.

[5.4.5 / 4.2.4, 5.5.2] Validation of methods]

Compare chapters [5.4.1 to 5.4.3 / 5.5] of both standards.

[5.4.6 / 5.8.3] Uncertainty of measurements

Standardized or defined control material has to be used during validation procedure in order to estimate uncertainty of measurement. Uncertainty of measurement shall be estimated by means of international acceptable procedures, e.g. given as examples in the guidelines of European co-operation for Accreditation (EA) listed under http://www.european-accreditation.org (e.g. EA-4/17 Traceability of Measuring and Test Equipment to National Standards to assure traceability of classical parameters covered by SI).

5.5 Equipment / Laboratory equipment [5.5 / 5.3]

[5.5.1 / 5.3] General

As part of a quality system, laboratories are required to operate a program for the maintenance and calibration of their equipment. The equipment used in a laboratory performing nucleic acid-based techniques is diverse and will range across a number of different scientific and technical disciplines. In most areas equipment may be categorised into:

a) general service equipment not directly used for measurements, e.g. hot plates, stirrers, centrifuges, non-volumetric glassware, refrigerators, heating ovens
b) small measuring equipment with direct relation to the test result, e.g. thermometers, balances, volumetric glassware, pipettes, pH-meter
c) instruments for measurement and detection systems (e.g. for extraction, amplification, separation, spectral analysis (spectrophotometer))
d) computers and computer networks

[5.5.2 / 5.2.4, 5.3.1-5.3.3] General Service Equipment]

General service equipment (5.5.1a)) will typically be controlled and maintained by regular visual inspection, safety checks and cleaning. Calibrations or performance checks and cleaning are required for equipment settings being involved in the maintenance of the quality of the test or the analytical result (e.g. temperature of a refrigerator or an incubator).

[5.5.3 / 5.3.5] Small Measuring Equipment]

Regular calibration, cleaning and servicing of small measuring equipment (5.5.1b)) shall be performed and documented. The handling of this type of equipment shall be documented if manufacturers’ manuals and documentation are insufficient. To avoid contamination by pipettes, tips with aerosol barrier (filter tips) are recommended.

[5.5.4 / 5.3.3] Measuring Equipment]

Correct use combined with periodic servicing, cleaning and calibration will not necessarily ensure accuracy and reliability of a measuring instrument or detection system (5.5.1c)). Therefore, periodic performance checks as well as assignment of pre-determined limits of acceptability are usually required. The frequency of performance checks shall be determined based on former experiences, type and previous performances of the equipment. All service and maintenance work shall be documented. The use shall be documented, including the action taken in case of system failure.

NOTE: Measuring equipment failing to meet requirements upon routine checking cannot be used for further analyses until repaired, checked and re-admitted for use.

[5.5.5 / 5.3.4] Computers and Computer Networks]

Records shall be maintained of each item of equipment and its software significant to the tests and/or calibrations performed.
Computers and other micro-processors that generate data shall be protected against data loss, unwanted data manipulation and abuse. Safety and integrity of data storage has to be guaranteed according to currently accepted rules.

In general, the requirements in the standards ISO/IEC 17025 and specially in ISO 15189 for record keeping in analogue and digital form are detailed enough. Therefore, no additional interpretation of the clause related to computer systems, automated equipment (computer guided automates), record keeping and IT security for medical laboratories performing nucleic acid-based techniques is necessary.

5.6 Measurement Traceability / Assuring quality of examination procedures [5.6 / 5.6]

[5.6.1 / 5.6.3] General

No additional interpretation of the clause for laboratories performing nucleic acid-based techniques is necessary.

[5.6.2 / 5.6.3] Specific requirements]

No additional interpretation of the clause for laboratories performing nucleic acid-based techniques is necessary.

[5.6.3 / 5.6.3] Reference Materials]

No additional interpretation of the clause for laboratories performing nucleic acid-based techniques is necessary.

NOTE: An absolute quantification cannot be performed without a certified or otherwise characterized reference material. This does not apply to relative quantification.

[ISO 15189, 5.6.5]

Whenever a formal interlaboratory comparison programme is not available, the medical laboratory shall develop a mechanism for determining the acceptability of procedures not otherwise evaluated. Whenever possible, this mechanism shall utilize externally derived challenge materials such as exchange of samples with other laboratories (in most cases legally available clinical samples with distinct diagnosis of the patient). Laboratory management shall monitor the results of this mechanism of interlaboratory comparison and participate in the implementation

and recording of corrective actions. Else no additional interpretation of the clause for laboratories performing nucleic acid-based techniques is necessary.

[ISO 15189, 5.6.6]

For those examinations performed using different procedures or equipment or at different sites, or all these, there shall be a defined mechanism for verifying the comparability of results throughout the clinically appropriate intervals. Such verification shall be performed at defined periods of time appropriate to the characteristics of the procedure or instrument and be recorded. Adequate stable reference material shall be used to perform the comparison.
Reference collections of data which are maintained for identification, comparison or interpretation purposes shall be fully documented and unequivocally identified. Properly identified and controlled reference materials shall always be stored separately from clinical samples.

5.7 Sampling / Pre-examination procedures [5.4 / 5.7]

The selection and collection of sample material are important elements of nucleic acid amplification methods. Laboratories which perform sampling on their premises shall ensure documentation of all procedures for this process and appropriate training of personnel.

NOTE: If sampling is performed by the laboratory it will be a part of assessment of the assessor team of SAS.

5.8 Handling of Samples (NCCLS, DIN 58967, AmCollege)

For sample handling all general and specific rules for preserving stability, safe shipment and prevention of contamination apply.
The traceability of all activities from receipt through preparation, proper analysis, reporting of results, storage to disposal of the sample shall be guaranteed.

5.9 Assuring the Quality of Test and Calibration Results / Assuring Quality of Examination Procedures [5.9 / 5.6]

No additional interpretation of the clause for laboratories performing nucleic acid-based techniques is necessary.

5.10 Reporting the Results (reporting guidelines DNA, Gene-Lex, HumGenet) [5.10 / 5.8]

Reporting of results shall follow the requirements and recommendations of **ISO 17025 / ISO 15189** and also **reporting guidelines DNA** if appropriate in terms of performed analyses.

To get proper identification of the medical laboratory patient, test procedures and presentation of results the report consists at least of:

a) identification of the laboratory performing the tests (including a reference to the corresponding web-site and/or Vademecum, list or laboratory manual if considered to enclose additional information for the medical doctors the reports goes to);
b) patient identifiers (family name, first name, sex, date of birth) and/or identification number;
c) unique sample identification;
d) name and address and/or identification of the submitting medical department or individual authorised medical doctor;
e) date of receipt;
f) date of report, type of report;
g) type of specimen, including date and time of sampling;

h) test principle/technique;
i) presentation of test result(s);
j) where necessary, limitations of test methods should be mentioned in the interpretation;
k) approval by authorized individual(s).

Both standards ISO/IEC 17025 / ISO 15189 also include points to add on a test report, which are not mentioned here in detail. The SAS document **320.d** or **320.f** lists under chapter 9.1 Test Reports all relevant information which is necessary on a test report (the documents can be downloaded under http://www.sas.admin.ch. It may be impractical to explicitly describe in the report all properties of the test methods used. However, the report shall include brief technical details about the test methods used in the analysis (e.g. PCR, RT-PCR, quantitative PCR) and indicate sources of additional actual information (such as e.g. corresponding web-site and/or Vademecum, list or laboratory manual).

NOTE: The STS directory is the official presentation of the scope of accreditation of the medical laboratory and the base of the accreditation decree of SAS.

Every performed analysis listed in the report shall be linked to the respective methodological protocol valid at the point in time.

NOTE: The list of analyses/diagnostic brochure (Vademecum, laboratory manual) of the laboratory can be considered as a source of information in the report if maintained actual and properly cited.

Confidentiality shall be guaranteed at any time including the certainty that only authorized persons receive test results and information independent from the method of transmission (e.g. mail, phone, fax, e-mail by computer). Policy for retention or release of information shall comply with current laws and directives.

Terminology in reports

1. **“Positive”** indicates that a particular substance has been identified in accordance with the laboratory protocols. **“Negative”** (to use the term “not detected” would be preferable instead) indicates that particular substances were absent within the limitations of the test(s) performed.

2. **Mutational** nomenclature strictly follows international guidelines stated in **HumGenet** and references therein. Interpretation of the results to be provided with reporting of the result should be as complete as possible including review of the results in the context of the relevant clinical and family information available as well as the reminder that genetic tests should be accompanied by genetic counselling. However, it is always in the responsibility of the respective laboratory specialist in charge to ensure accordance with laws and directives.

3. For **gene expression profiling** it is recommended that reporting needs to follow the general rules. For a small number of genes, they need to be individually named as well as clearly described whether their expression is repressed or enhanced in a given specimen. Type of specimen and preparative procedures potentially influencing expression shall be described.
   For array techniques, that evaluate hundreds of genes simultaneously is such an approach impractical. In this array technique evaluated gene classes or clusters and their repression

or enhancement should be described and the result interpreted carefully. However, knowing the currently limited experience with the new gene expression profiling interpretation techniques a cautious approach is highly recommended.

4. If **quantitative** analyses of PCR products lack traceability to standards or defined control material, it is recommended to interpret quantitative results in the context of earlier results, preferably performed in the same laboratory with the same test method. Limitations of the performed quantitative test shall be specified in the report.

5. **Units** shall comply with or be in reference to generally established nomenclature used in the field.

Preliminary report

A report may be issued before all studies are completed and the final report has been prepared. This report should have the same identifying information as the final report but be limited to the tests performed to that actual date. It is recommended that any of these written reports reflect confirmed results only according to the laboratory protocols, and that it is clearly stated that they are preliminary report(s).

NOTE: Preliminary (interim) reports shall be clearly marked as such indicating that the results are still preliminary and will be followed by a validated final report.

Revised, supplemental or addendum report

After a final report has been issued, it may be necessary to perform additional tests, requiring an addendum or revised report. Such a report shall always contain the same identifying information as the original report.

Oral reporting

Occasionally, oral reporting may be necessary. In such a situation, the individual receiving the report shall be appropriately identified and the results shall be previously properly validated (e.g. double-checked and released). Elaboration of a corresponding written report is always required.

Corrected report

After the final report has been issued it may become necessary to correct errors, typographical or otherwise, in the original or supplemental reports. In this case the report shall be clearly labelled as corrected. It also shall contain the same identifying information as the original report(s).

Release of reports

There is a directive in the quality management system for the proper release of reports.

Referred tests

Results of tests performed by subcontracted laboratory may be incorporated into the laboratory's final report but shall be clearly indicated as such.

NOTE: Without excessive investigation it should always be possible for the customer of the medical laboratory to know where and by whom the results were generated. That is the result of a subcontracted laboratory or a distinguishable branch office (e.g. an independent profit centre of a company, another site of the laboratory under the same accreditation) and shall remain

identifiable by the customer of the laboratory. An actual list of external laboratories used for sub-contracting or referral shall be maintained.

5.11 Other requirements

Each medical laboratory is aware of Cantonal (state) and/or Federal Regulations that may exceed minimum standards established on the basis of the above guidelines. Therefore, the medical laboratory identifies the relevant laws and ordinances, maintains an actual list of relevant external documents and demonstrates easy access for its staff.

6. Abbreviations

c-DNA	complementary DNA
DNA	Desoxyribonucleic Acid
DIN	Deutsches Institut für Normung
EA	Europaen co-operation for accreditation
ESV	Einschliessungsverordnung / Ordonnance sur l'utilisation confinée (OUC)
FAMH	Foederatio Analyticorum Medicinalium Helveticorum
ISO	International Standard Organization
IT	Information technology
NCCLS	The National Committee for Clinical Laboratory Diagnostics
PCR	Polymerase Chain Reaction
QUALAB	Schweizerische Kommission für Qualitätssicherung im medizinischen Labor / Commission suisse pour l'assurance de qualité dans le laboratoire médical
RFLP:	Restriction Fragment Length Polymorphisms
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAEFL	Swiss Agency for environment, forests and landscape, see also biotech@buwal.admin.ch
SAS	Swiss Accreditation Service
SFOPH	Swiss Federal Office of Public Health
SI	Système internationale (international system) in metrology
SUVA	Schweizerische Unfall-Versicherungs-Anstalt / Caisse nationale suisse d'assurance en cas d'accidents