1 Aim

This document is for medical laboratories that use the Valab® expert system for computer aided biological validation. It provides the medical laboratory with information from the manufacturer, the VALAB company, concerning the use of Valab® in an accredited medical laboratory.

This document serves as a complement to the document "Qualification of Valab® by the Medical Laboratory" (**RD5**) which comprises a guide for qualifying the use of Valab® in the laboratory and performing the control of the system in terms of monitoring, maintenance and traceability of modifications.

For more details on the use of Valab® and on the description of its interface with the LIS, please refer respectively to the Valab® User Manual (**RD6**) and Valab® Developer Manual (**RD7**) provided with Valab®.

- Contents -

The VALAB Company is certified ISO 9001 by:

2 References

2.1 Document change history

Version	Date	Modification description	Author(s)	Modified pages
1/G	1/05/2018	Updated document for version 14 of Valab®. Updated list of Reference documents. Updated Valab® user references. Various minor corrections and updates.	JP. Rogari	§2.3, §3.2, §3.3, §4.1, §4.2.1, §4.2.2, §4.3, §5, §6.3, §7.2.4, §7.2.7, §7.3.1, §7.5, §7.8.
2/A	10/13/2020	Updated document for version 15 of Valab®. Updated list of Reference documents. Updated Valab® user references. Updated Valab® development cycle Relocation of the risk analysis example into the "Qualification of Valab® by the Medical Laboratory" Updated links to the VALAB website Updated VALAB logo.	JP. Rogari	§1, §2.2, §2.3, §4.3, §5, §8, §9.

2.2 Valab® web site www.valab.com

Click the following link to find the current version of this document on the Downloads page of the Valab® web site www.valab.com.

2.3 Reference documents

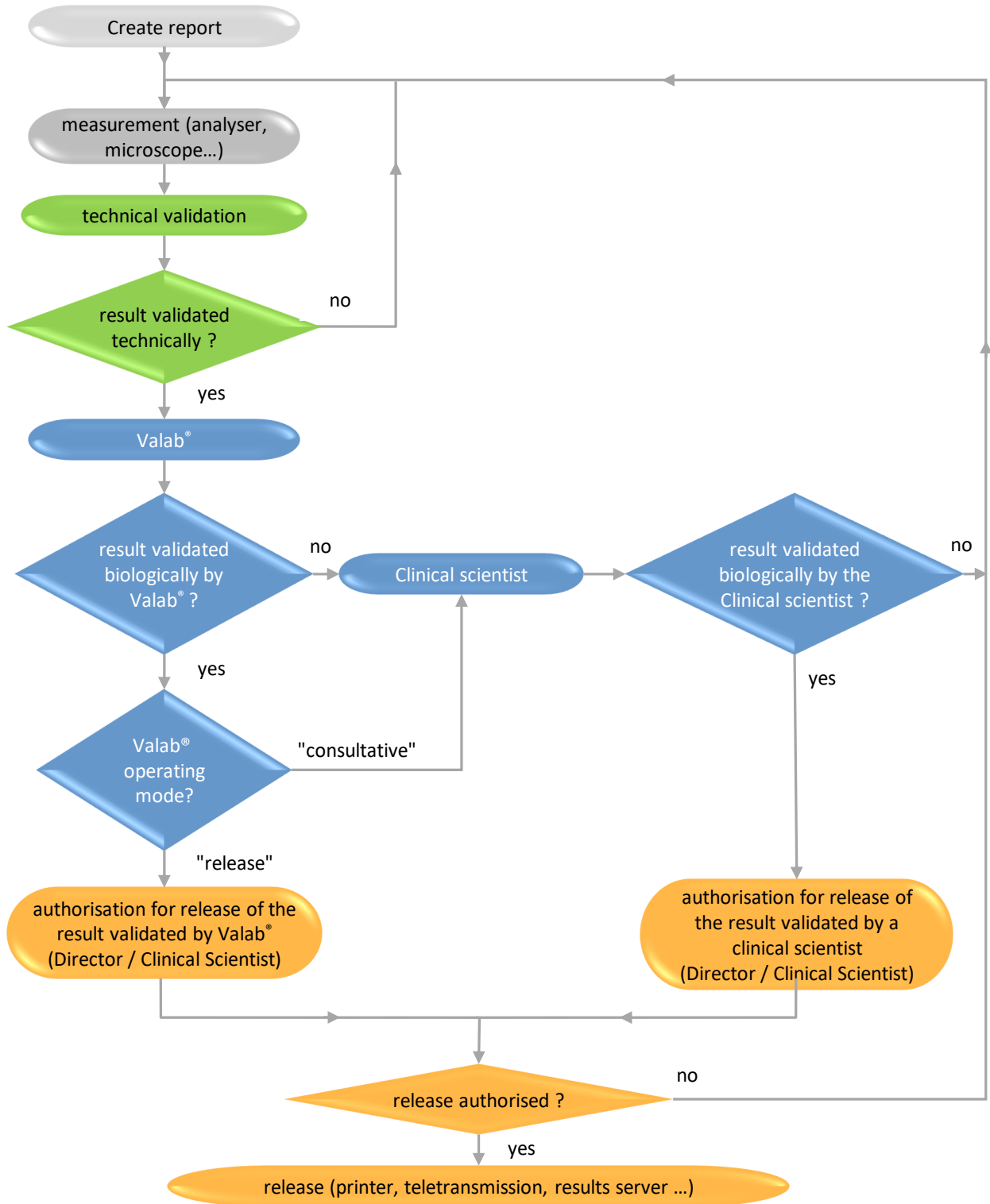|	
RD1	Medical laboratories - Requirements for quality and competence ● ISO 15189
RD2	Guide for the Correct Execution of Tests ● GBEA 2
RD3	Reference document for the accreditation of medical laboratories aimed at clinical scientists and editors of software for medical laboratories ● SFIL / Accreditation reference document
RD4	Recommendations for the accreditation of medical laboratories - Volume 2 ● SFBC / Annales de Biologie Clinique / Volume 70 / special supplement n°1
RD5	Qualification of Valab® by the Medical Laboratory (available at www.valab.com) ● VAL-ACC-09
RD6	Valab® User Manual (provided in Valab® "DOC" subdirectory) ● VAL-MU-XX
RD7	Valab® Developer Manual (provided in Valab® "DOC" subdirectory) ● VAL-MU-XX
RD8	Valab® - Backup and Restore (available at www.valab.com) ● VAL-MU-42
RD9	Manuel Qualité VALAB (Valab Quality Manual - only available in French) (available at www.valab.com) ● VAL-MQ-01
RD10	Privacy policity of the VALAB company (available at www.valab.com) ● VALAB
RD11	Accreditation requirements according to standard NF EN ISO 15189 ● Cofrac / SH REF 02
RD12	Accreditation technical guide for medical laboratories ● Cofrac / SH GTA 01
RD13	Accreditation technical guide to assess the IT systems in medical biology ● Cofrac / SH GTA 02
RD14	Articles L.6211-1 and following of the French Code of Public Health ● CSP
RD15	Articles L.5221-1 and following of the French Code of Public Health ● CSP
RD16	General data protection regulation ● Regulation (UE) 2016/679

2.4 Acronyms

Acronyms	Meaning
LIS	Laboratory Information System
ML	Medical Laboratory
MMI	Man-machine interface
QMS	Quality Management System
RCV	Reference Change Value
RD	Reference Document
See	Refers to

3 Reminder of the Valab® integration into the Medical laboratory

3.1 Functional integration overview

The following overview shows the functional integration of Valab® in the laboratory process for the validation of patient test results.

Create report

measurement (analyser, microscope…)

technical validation

result validated technically ?   no

yes

Valab®

result validated biologically by Valab® ?   no   Clinical scientist   result validated biologically by the Clinical scientist ?   no

yes   "consultative"

Valab® operating mode?   yes

"release"

authorisation for release of the result validated by Valab® (Director / Clinical Scientist)

authorisation for release of the result validated by a clinical scientist (Director / Clinical Scientist)

release authorised ?   no

yes

release (printer, teletransmission, results server …)

Colour code :   Technical Validation   Biological Validation   Release Authorisation

3.2 General introduction

3.2.1 Functionality

Valab® is a computer-aided biological validation tool. It assists the clinical scientist with the systematic review of results, their assessment in conformity with available clinical information about the patient, and authorisation for their release. Valab® acts as a filter which identifies any incoherent reports and/or reports containing alerts or critical values for which the intervention of the clinical scientist represents a true biological and medical added value before authorisation for release, if applicable.

The main objectives of the tool are to improve the safety, reproducibility, quality and turnaround times for results. Moreover, in the context of a medical laboratory with several clinical scientists, the Valab® software tool allows to standardise the act of validation and to assess the practice of biological validation by consensualising the different clinical scientists around the use of a single tool.

In all cases, it is important to indicate that all the medical test results released by the medical laboratory are done so under the responsibility of the clinical scientist, including those verified with the help of the Valab® computer aided validation software. In this respect, all the results reports issued by the medical laboratory are assumed to have been validated by the clinical scientist and must bear his/her signature (first name, surname and signature configured in the LIS). Inscriptions of the form "validated by expert system" are not acceptable.

3.2.2 Means of control

As a complement to the present document, the VALAB company provides its users with a guide for the "Qualification of Valab® by the Medical Laboratory" (**RD5**).

This guide provides an approach and a set of example procedures allowing to set up the control of the use of the tool. The recommendations concern in particular the customisation of the parameter settings, the initial qualification, re-qualification after modification, continuous monitoring, the keeping of records, the impact on the QMS documentation of the medical laboratory, and user training.

3.2.3 Advice and expertise

The VALAB company accompanies the user with its expertise during the period of customisation and initial qualification, and afterwards through a maintenance agreement:

- analysis of the statistical indicators with regard to the autoverification of each test
- proposals for parameter setting modifications to the Valab® key contact clinical scientists
- assistance through remote maintenance

3.2.4 Integrated operation

The connection with the LIS and integration of the expertise results of each test on the biological validation screens of the LIS exists for many laboratory information systems, without changing the work habits of the laboratory.

3.2.5 Conclusion

Valab® provides a solution to perform, under the responsibility of the clinical scientist and in conformity with regulatory, legal and normative requirements (**RD1**, **RD2**, **RD11**), the systematic review of all the results before their release. This approach also offers the possibility to approach biological validation using consistent and uniform criteria in the context of technical platforms and multi-site laboratories.

3.3 Regulatory, legal and normative context

The biological validation activity must consider the current and upcoming regulatory, legal and standard requirements. They blend in with the broader context of quality, the good practices of the profession and the laboratories accreditation. The corresponding reference documents are:

- ISO standard 15189 (**RD1**): "Medical laboratories - Requirements for quality and competence"
- The Guide for the Correct Execution of Tests (**RD2**)
- Cofrac document SH REF 02 (**RD11**): "Accreditation requirements according to standard NF EN ISO 15189"

Analysis of these texts converges in the idea that the validation and authorisation for release of results is an intellectual, systematic and efficient act under the responsibility of the clinical scientist:

- validation must consider the coherence of all the data known for the patient
- validation must be exhaustive and allow the review of all the results, normal and abnormal
- validation must make use of innovation to improve the efficiency of the medical laboratory

4 History and method of initial qualification of Valab®'s expert kernel

4.1 History

▪ In 1986 the Valab® project was initiated in the Clinical Chemistry Medical Laboratory of Rangueil University Hospital, Toulouse, France, as a prototype for Biochemistry. The knowledge representation model came from research work. Information technology allows to reproduce the logic, complexity and combinatory power of human reasoning by weighting each piece of information considered during the verification process.

▪ From 1989 the EREMS company developed and marketed the Valab® product in the context of a technology transfer initiative supported by the ANVAR (French Agency for Innovation). The evolution of Valab® continued to benefit from a partnership with the Toulouse Hospitals for the development of new applications in Hematology, Blood Gases, and Coagulation. Valab® became a registered trademark in 1990.

▪ In 1992, the CNEH (French National Centre for Hospital Expertise, Paris, France) performed a multi-centre assessment confirming the validity of the autoverification results provided by the Valab® expert kernel (TEP / ANVAR procedure, see section "4.2 - Initial qualification of the expert kernel by the manufacturer").

▪ In 1999 the CNEH performed a multi-centre assessment confirming the organisational and financial benefits for the medical laboratory to be obtained by using Valab® (procedure ACE-GBM / ANVAR).

▪ In 2004 the VALAB department of the EREMS company became independent in the shape of the VALAB company which now develops, markets and maintains the Valab® product. The VALAB company was certified ISO 9001 in 2004 for the design, development, marketing, installation, training and after-sales service of expert systems and software in the field of computer-aided validation of test results in ML.

4.2 Initial qualification of the expert kernel by the manufacturer

A methodology for validation of the expert kernel was defined right from the first versions of Valab®, the validation phase representing a mandatory stage to guarantee the reliability and safety of any operational system. This methodology was used in particular during the multi-centre study carried out in 1992 by the CNEH (TEP / ANVAR procedure). This investigation allowed to confront the expertise results provided by Valab® with those provided by the clinical scientists of five user sites on a pool of around 300 patient reports per site (i.e. a total of 1500 reports), and confirmed the validity of the expertise results provided by the expert kernel of Valab®

4.2.1 Methodology

The guiding principle was to evaluate the performance of the expert system with quantitative criteria by using a prospective protocol based on the comparison of the Valab® expertise results versus those of the clinical scientists.

The methodology takes its inspiration from the epidemiological assessment methods of screening tests, widely used in medicine. Valab® is therefore considered to be a system capable of performing a test of the coherency of results.

Biological validation determines the acceptability of a result or a set of results which are either validated or blocked. This Boolean nature allows to assimilate Valab® autoverification to a screening test of the reports requiring human intervention for their validation. The test is positive when the report is blocked, negative when it is validated. In this way the following equivalences are considered:

▪ V(+): True Positive   Report rightly blocked
▪ V(-): True Negative   Report rightly validated
▪ F(+): False Positive   Report wrongly blocked
▪ F(-): False Negative   Report wrongly validated

The interpretation of the performance of the test is obtained after adding up the numbers present in each response class [V(+), V(-), F(+), F(-)] by calculating the assessment criteria of the screening methods: sensitivity, specificity, positive and negative predictive values. These different epidemiological criteria correspond to the following definitions:

▪ Sensitivity: % of the reports to be blocked for which the test is positive = $(V+) / [(V+) + (F-)]$
▪ Specificity: % of the reports to be validated for which the test is negative = $(V-) / [(V-) + (F+)]$
▪ Positive predictive value: % of the reports to be blocked among the positive tests = $(V+) / [(V+) + (F+)]$
▪ Negative predictive value: % of the reports to be validated among the negative tests = $(V-) / [(V-) + (F-)]$

4.2.2 Protocol

The assessment is based on the verification of a pool of reports submitted in parallel for validation by the clinical scientists and by Valab®. The theoretical assessment phase begins with the creation of a significant and representative sample (e.g. 500 patients' reports).

The procedure then consists in carrying out a blind validation of the reports of the sample, by Valab® and by the clinical scientists participating in the study. In order to recreate the natural work conditions of the clinical scientist, the reports are verified sequentially and individually: in series of 100 at a time, without knowing the response either of the other experts or of Valab. The data is collected from individual response notebooks. The exploitation of all this data consists in making a synthesis for each report verified, by bringing together the information contained in each individual response notebook. The experiment shows that around 20% of the reports do not receive a unanimous assessment. The establishment of a reference response for the verification of each report is obtained when the response is unanimous. For the other reports, a consensus meeting is organised to determine the reference response.

The interpretation of this assessment protocol is based on the comparison of the performance obtained by Valab® and by the clinical scientists. For this, the confrontation of all the responses of each individual notebook with that of the reference notebook allows to add up the number present in each response class [V(+), V(-), F(+), F(-)] for each of the participants, the clinical scientists and Valab®.

The final stage consists in calculating the assessment criteria of the screening methods: sensitivity, specificity, positive and negative predictive values. The global performance of Valab® must be evaluated by the scores obtained for the different numerical criteria in comparison with the clinical scientists.

As the consequences of a validation error can be serious in the case of an inappropriate validation (false negative), the obtention by Valab® of a better score for sensitivity testifies to a low rate of false negatives, therefore putting safety first.

4.2.3 Interpretation

Without being exhaustive, the epidemiological approach offers the possibility of assessing the performance of a test through quantitative criteria. The pertinence of this protocol resides on the one hand in the assimilation of the biological validation to a test situation, on the other hand in the implementation of a prospective and comparative procedure between the Valab® system and the clinical scientists.

Several protocols of this nature have now been conducted and published by the VALAB company, by the laboratories using Valab®, and also by the CNEH. The results obtained have always met the requirements of reliability and safety by demonstrating excellent performance in terms of sensitivity. This demonstrates the capability of the Valab® computer-aided validation tool to not validate reports wrongly.

4.3 Conclusion

The initial validation of Valab® in collaboration with users gave rise, in France, to two multi-centre assessments by the CNEH (TEP / ANVAR procedure in 1992 and ACE-GBM / ANVAR procedure in 1999).

Using Valab® has given rise to many publications in congresses and scientific journals with reviewing committees (see section "8.2 - Bibliography and press articles on Valab®").

Using the Valab® computer-aided validation system in 2020 represents the state of the art in the light of the following data:

- Over 30 years developing, maintaining and commercialising
- Over 350 multi-site structures using Valab® in France, Europe and French-speaking Africa
- All the medial laboratories / legal entities users in France are accredited (ISO 15189)
- Over 600,000 patient reports autoverified every day
- International distributors

The industrial qualification of successive versions of the Valab® software (see section "5 - Development cycle and qualification of each version of Valab®") is subjected to a full test plan in conformity with the requirements of our QMS. It integrates in particular, for each version and incrementally, the notions of:

- The utilisation of a methodology inspired from the Agile Scrum method
- Unitary and integration tests
- System tests
- Non-regression testing
- Verification matrix

5 Development cycle and qualification of each version of Valab®

In conformity with the description of the VALAB company's Research and Development process, each new version of Valab® is developed according to a method inspired from the Agile Scrum method.

This method guarantees the control of the development process for each new version of the product. The average development cycle duration for a major version of Valab® is 24 months.

The following paragraphs describe the main steps in this development cycle.

5.1 Specification

The specification of each new version of Valab® is defined in a specification document specific to each version. This document is organised by topics / specification categories (user interface, functionality, protocol, verification expertise, bug corrections, architecture...). It takes into account the following factors:

- The problems detected by users and recorded in problem reports
- The results of satisfaction surveys conducted with our customers
- The result of the monitoring of regulatory, legal and normative changes and technical and technological advances
- The Internal and external ideas for product improvements

Each specification is identified by a unique identifier which is then included in the traceability matrix for system tests (see section "5.5.3 - System tests").

5.2 Planning

The developing of the Valab® next versions planning is formalised into a RoadMap document along with the definition of the chosen delivery dates.

Once the content of a version is specified, the estimated delivery date is reexamined each time a sprint ends according to the speed of the development team and what remains to be done.

According to the calculation result, the version content may be increased or decreased (along with an update of the specifications). Decision can be made of modifying the chosen date of the version release.

5.3 Initialisation

The initialisation (or design) stage allows to study the architecture to be implemented for the new version of Valab® in order to meet the specifications and the schedule of the new version.

The design takes the form of several version-specific analysis documents.

The general architecture of the software is created in UML (Unified Modeling Language).

5.4 Realisation

The realisation (or coding) stage is carried out using the documents from the initialisation phase, in conformity with the procedures of the Research and Development process of the VALAB company (coding rules, software configuration management procedure, development procedure, software design and coding).

5.5 Verification and Validation

This paragraph explains how the verification and validation stages are qualifying each new version of Valab®.

5.5.1 Unit tests

The unit tests allow to validate singly / independently each elementary object of the Valab® software architecture. These unit tests are implemented as source code. New unit tests are added with each new version of the product.

Tools allow to "play" the unit tests automatically and at will throughout the coding phase in order to validate the new code as it is developed.

All the unit tests are then re-run at the end of the development cycle, they must be run successfully before the system tests can be executed. The results of the unit tests are then reported in the test reports of the version (see section "5.5.3 - System tests").

5.5.2 Coding review

A coding review is performed at the end of the development cycle, it is recorded in a coding review report.

This review relies in particular on the use of metrics generated by tools for the automatic analysis of code complexity, respect of coding rules, comment inclusion rates, and good practice in relation to the

development language. These metrics are checked throughout the entire coding phase in order to detect any deviations at this level.

5.5.3 System tests

The system tests stage allows to qualify the finished product as it will be delivered to the customer. It is formalised in a test and validation document (test and validation plan)

This document is enhanced with each new version with new tests allowing to qualify the new product functionality. As a complement, the existing tests used for the qualification of previous versions of the product are verified and adapted to any modifications and / or corrections applied to existing product functionality.

The approach of this document is to test each functionality of the finished product by using test scenarios defined in test procedures allowing to validate that the product meets the specifications. This document also includes tests of backward compatibility with previous versions and non-regression tests allowing to ensure that the product has not regressed with regard to previous versions both at the level of verification expertise and on the level of the other functionality of the software.

This document also contains reports indicating the result of each system test and a report indicating the result of the unit tests.

Some of the system tests dealing with the qualification of the "ValabServer" service are automated through its API. Tools allow to "play" these system tests automatically and at will throughout Coding phase in order to validate the new code as it is developed. These automated system tests are "replayed" into the current stage of system tests and integrated into the test and validation document.

As a complement, in order to check that all the specifications of the new version have been tested at system level, a traceability matrix is used which contains the unique identifier of each specification (see section "5.1 - Specification") and the system tests which are associated with it. This ensures that all the specifications have been tested at system level.

When each of the system tests has been played with success or exceptionally accepted by a waiver (with a problem report for minor problems if applicable), the version is considered to be qualified.

5.6 Release of the version

At the end of the development cycle, when all the steps of the cycle have been passed with success, the product is released under the responsibility of the Director of the VALAB company. The Research and Development process of VALAB then makes the qualified version available to the VALAB Order Delivery and Customer Support processes with a view to its release. Afterward the version is considered as in production.

This new version is first of all released to a limited panel of our customers under a maintenance agreement, then progressively to all of our existing customers as well as to new customers.

5.7 Registering the new version source components

At the end of the development cycle, the source components of the new Valab® version (software source code, related documentation, transfer document allowing to regenerate the product deliverables) are registered with a specialised third-party company.

6 Valab® autoverification

6.1 Principle

Valab® is an expert system born out of research in artificial intelligence and knowledge modeling. It does not approach biological autoverification like a classic algorithmic system, but globally and contextually just like a clinical scientist does.

The "intelligent" model at the origin of Valab® consists in implementing all the processes related to the interpretation of a result according to a strategy approaching the logic, complexity and combinatorial nature of human reasoning. The Valab® software allows to weigh up each piece of information taken into account in the verification.

The acceptability of a result depends on a true combinatorial analysis and not on a classification in a pathological model. This last point makes it difficult to provide an exhaustive description of the verification logic because in no way does the result depend on the application of an exclusive rule, on the contrary, it depends on the application of all the applicable rules.

A simple example illustrates this aspect:

Given a patient with the clinical information "hepatitis" and an extremely disturbed ASAT (GOT) result at 800 UI 37°: this information is compatible, and a simple rule allows to model it.

However, adding an ALAT (GPT) with a normal result of 20 UI 37° in the same report makes the overall report incoherent and it is no longer validated.

Only a "combinatorial" approach allows to describe complex models in this way.

The following information categories are used by the Valab® autoverification in the context of a global reasoning strategy for validation:

- Demographics (age, sex)
- Context (prescriber and/or department, emergency, hospitalised)
- Therapeutic and clinical information (medical data)
- Technical information (observation data)
- Inter-parametric correlation (coherence of the results)
- Anteriority and inter-parametric kinetics (variation and kinetics of the results)

The strategy implemented in Valab®, with a global and systematic approach for the validation of each patient report, corresponds to the Quality requirements of the profession. This approach allows to both validate a "normally abnormal" result and block an "abnormally normal" result.

As a computer-aided biological validation system, Valab® represents an intelligent filter at the service of the clinical scientist and brings additional safety and efficiency to the organisation of a medical laboratory. To this end, the implementation and use of such a system participates both in the improvement of the quality of the results returned to the patient and in the accreditation strategy of the laboratory.

6.2 Knowledge modeling methodology

The cognitive engineering methodology for knowledge modeling, used to model the Valab® verification expertise, comprises three main steps:

1) Knowledge acquisition:
- Theoretical part: bibliographical research
- Experimental part: observation and analysis of experts (originally, the teams of Pr. P. Valdiguié, Pr. J.X. Corberand and Pr. B. Boneu – Toulouse University Hospital, France) in situ in order to decompose their reasoning into basic rules
2) Modeling:
- This consists in building a software model allowing to exploit the basic rules, previously identified in step 1, and to reproduce the complex reasoning of the expert
3) Qualification:
- This step consists in validating the model obtained in step 2. For more details on the qualification methodology, see section "4.2 - Initial qualification of the expert kernel by the manufacturer"

6.3 Traceability and determinism

An indispensable factor for the ethical acceptability of an expert system concerns its operating reliability and its traceability in the context of accreditation and/or of the GBEA (French Guide for the Good Execution of Laboratory Tests) for obvious reasons of responsibility.

The technical characteristics of the tools at the base of the Valab® application (compilation process and consistency analysis) have allowed to verify the logical coherence of a knowledge base model. The exclusive use of this model allows to guarantee the lack of contradictions between the rules and to automatically generate the algorithmic and deterministic equivalent of an expertise set initially described in the form of rules.

As Valab® is a deterministic system, the decision process is always the same for identical operating conditions (version, parameter settings, correspondence tables, parameter values,...).

Upon a user's request for a problem related to the laboratory's responsibility concerning an autoverification result for a specific report, we apply, in a confidentiality framework, an exceptional procedure.

This procedure allows to reproduce all the elementary reasoning implemented in the decision process, and to provide the user with a comprehensible list of all the rules applied in this particular case.

The Benelux countries were precursors with regard to laboratory accreditation. In 2009, half of the laboratories using Valab® in Benelux were already accredited according to the ISO 15189 (**RD1**) standard: 30 laboratories out of the 60 equipped with Valab®. Here is an example of a procedure set up in October 1996 with the CCKL (Dutch body for the improvement and maintaining of Quality in the health care system):

Certification / accreditation procedure (NL):

⇒ Valab® is a deterministic system,

⇒ Decision process is always the same if environmental conditions are similar (value of parameters, dictionaries, parameter settings...),

⇒ In case of customer's question about the result of expertise on a specific report, we can establish an exceptional procedure as following:

 * Get the number of the Valab® version,
 * Get the complete parameter settings (backup),
 * Get the precise data of the report inside Valab® (file *.ptd),
 * Identify the parameter(s) with the understanding problem to be justified,
 * With this information we are able to produce the whole elementary reasoning used in order to explain the global decision of the system,
 * So our response could be to furnish the list, clearly readable, of all the rules triggered in this case,

⇒ Of course, such a heavy procedure would have to be exceptional, only when there is a responsibility problem for the laboratory (not for the intellectual interest of the biologist).

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7   Implementation and control of Valab®

The operating environment of Valab® benefits from a set of functionality and documentation allowing to meet the requirements for Quality and accreditation in the laboratory.

Additionally, all of the members of staff that use the Valab® software must be trained on how it works and how to use it.

The means of control to put in place may for instance be based in a risk analysis (see the § " Example of risk analysis" of **RD5** "Qualification of Valab® by the Medical Laboratory").

7.1   "Global" Consultative mode

The "Global" Consultative mode, when it is activated, allows to present all the reports verified by Valab® in a validation session of the LIS and systematically imposes the validation of each report by the clinical scientist manually.

This option is activated in particular at the startup of a new site and during the period necessary for the customisation of the parameter settings and the initial qualification of the Valab® autoverification by the medical laboratory (see **RD5** "Qualification of Valab® by the Medical Laboratory").

7.2   Customisation of parameter settings

During the Valab® deployment process, the key contact clinical scientists of the medical laboratory are accompanied by the "biological expertise" Customer Support group of the VALAB company when analysing production data in order to finalise the customisation of the Valab® parameter settings. This phase takes place in several successive work sessions over a sufficient and significant period of activity of the medical laboratory in order to obtain a Valab® operation that is suited to the population, the specifics and the requirements of the medical laboratory.

The following paragraphs describe the main parameters of Valab® that can be customised by the medical laboratory.

7.2.1   Consultative mode specific to one particular test

It is possible to put an individual test in consultative mode ("consultative mode" for a specific test). Reports containing such a test will be verified but they will never be validated by Valab®, and they will be systematically proposed to the clinical scientist in a manual validation session by the LIS.

This option can be activated for example during the connection of a new test to Valab® to allow the medical laboratory to qualify the corresponding autoverification over a given period of time.

7.2.2   Threshold test

Each test can be declared as a threshold test. In this case, a change of state of the test (from "normal" to "abnormal", and inversely) causes the refusal of this test by Valab®. A sub-option enables to cause the rejection only in case of a change in the state of a test from "normal" to "abnormal".

7.2.3   Unit

The units in which each test is sent by the LIS and/or displayed in Valab® are programmable.

7.2.4   Intervals referred to as "Biological (or clinical) reference interval limits for a man of 25 years of age" and "demographic rules"

Chapter 3.4 of ISO 15189 v2012 standard and chapter 5.7 of Cofrac document SH REF 02 revision 05 define on the one hand *biological reference intervals and clinical decision values* and on the other hand *limits and conditions for the implementation of a strategy* for biological validation using a computer-aided validation software.

Biological reference intervals and clinical decision values (ISO 15189 v2012), commonly referred to as "reference values", correspond to specified interval of the distribution of values taken from a biological reference population. They must be defined, documented and communicated (…) to the users (section 5.5.2). These are the intervals which are shown on the report and allow to situate the result of a test.

In Valab®, the intervals called "Biological (or clinical) reference interval limits for a man of 25 years of age" and the "demographic rules" correspond to a certain extent to the *limits and conditions for the implementation of a strategy* for biological validation using a computer-aided validation software (according to SH REF 02). They are established by the laboratory following customisation of the setup conducted by each medical laboratory during initial qualification and continuous monitoring, in particular by exploiting the statistical data for the laboratory generated by Valab®. In the end, the setup parameters retained correspond to the population, specifics and requirements of the medical laboratory regarding biological validation. The use of these intervals is strictly internal to the medical laboratory.

the ranges defined in Valab fix the limits inside which a result cannot be interpreted as being pathological in the clinical sense, and outside of which it cannot be validated by Valab unless it is justified by another item in the report (values of other tests, pathology, treatment, known previous result, . . .). It is therefore clear that these intervals may be different from the biological reference values indicated on the results report (e.g. Cholesterol).

The "Biological (or clinical) reference interval limits for a man of 25 years of age" and the "demographic rules" retained must be precisely recorded in the laboratory's QMS and all of the clinical scientists must be informed.

Note that the initial settings for the tests provided with Valab® were established when the product was created based on bibliographic research (see the bibliographical references in section "8.1 - Valab® biological bibliography - Extract").

7.2.5 "Expertise" limits for the results without anteriority

"Expertise" limits for the results without anteriority forbid the validation of a test having no anteriority (1 ° realization of this test for the patient or too former anteriority) and a result which is under and beyond a certain value whatever is the coherence of the data.

7.2.6 "Alert" or "critical" limits

The "alert" or "critical" limits prohibit the validation of a test below or above a certain value. Whatever the coherence of the data, they constitute the absolute limits of the field of competence of the system, requiring the mandatory submission of reports with such results to the clinical scientist for validation.

7.2.7 Delta check / RCV

The RCV ("Reference Change Value") is an acceptable variation percentage between the test result and the previous known value (anteriority) for each specific test. The RCV represents an essential component of the interpretation of a variation (analytical and intra-individual variation). It is calculated using the following formula (see the bibliographical references in section "8.1 - Valab® biological bibliography - Extract"):

$$RCV = \sqrt{2} * 1.96 * \sqrt{(reproducibility\ analytical\ CV\%^2 + intra\_individual\ CV\%^2)}$$

The RCV's provided with Valab® can be individually consulted and modified for each test. They have been established on the basis of bibliographic research (see the bibliographical references in section "8.1 - Valab® biological bibliography - Extract").

The actual acceptability of a variation is modulated by the expert analysis of the data contained in the report which generates a dynamic RCV adapted to the clinical situation of the patient.

Valab® proposes to program a maximum validity period for the previous result for each test. If this limit is exceeded, the previous result is ignored by the autoverification.

7.2.8 "Critical" Delta check / RCV

In order to control the effects of the dynamic RCV, the setting of a "critical" maximum delta is also proposed to the user. It introduces the concept of the highest variation above which a result cannot be validated by Valab® and the report will be submitted to the clinical scientist. Different "critical" maximum amplitude values can be defined both for an increase and a decrease. This criterion can be activated or deactivated for each test.

7.2.9 Sensitivity of the autoverification

Setting the sensitivity parameter allows the user to fine-tune the autoverification of each test by acting on the weight of the rules without modifying the internal logic of the system.

There are sensitivity settings for the rules applicable in correlation (for tests without a previous result) and for the rules applicable in anteriority (for tests with a previous result).

Each sensitivity setting can be adjusted (the neutral value is 1) in order to make the system more permissive (value greater than 1) or more restrictive (value less than 1) with regard to the acceptability of a result.

7.2.10 Correspondence tables

Valab®'s correspondence tables allow to match the "symbolic/qualitative" data known by the LIS with the corresponding data in Valab®:

- Table for Prescribers – specialities – departments
- Table for Sexes
- Table for Clinical Information about the patient

- Table for Complementary Information - technical
- Tables for Quantitative tests / alarms or analyser measurement limits
- Tables for Qualitative tests (symbolic tests)

Users enter information into Valab®'s correspondence tables using the data extracted from their LIS.

The "Reject unknown labels" option can be activated independently for each Valab® correspondence table and allows users to set up Valab® so that it "blocks" all of the reports that are sent to it containing "symbolic/qualitative" data that is not identified in its correspondence tables. This allows to ensure that Valab® will not validate reports containing "symbolic/qualitative" data that it does not know sent to it by the LIS.

7.3 Management of user access rights

Access to Valab® is protected by a unique login and password combination for each user account. A user account must be created for each person authorised to have access to Valab®.

7.3.1 Sessions and user accounts

At Valab® startup, no user session is opened in order to avoid unwanted actions. Access to any Valab® functionalities is only possible after the opening of a session. Each access is associated to a user account with a password and customizable rights.

If no action is performed after 5 minutes (default setting), the session is closed automatically.

The sessions and the user accounts also allow to manage the traceability of all the actions made in the configuration of the system.

7.3.2 Different user types

An administrator of the accounts allocates to the various users of Valab® the access profiles to the functionalities (consultation and / or setting rights) adapted to their level of intervention.

7.3.3 Protected functions

All the functionalities are protected in consultation and setting. When a user opens a session he only has access to the functionalities in consultation and /or setting which are adapted to his level of intervention defined by the administrator in his profile access.

7.4 Confidentiality and archiving

An option allows not to display the patients' names from the headers of the reports received from the LIS. In this case, the patient's name is replaced by "…LIS…". On the other hand, only users with a sufficient level access can consult patients' reports expertised by Valab® and the backlog associated to connection exchanges between Valab® and the LIS.

For reasons of traceability and/or use of data in simulation activities, local archiving functions are available for a temporary period (maximum 24 months). They are customisable for a given time period and can be deactivated by the user. The traceability and archiving of the patient reports is ensured elsewhere by the LIS of the medical laboratory and by the implementation of regular backups.

7.5 Traceability of user access and modifications

A logbook allows to keep a history and traceability of all the modifications of parameter settings performed by the user.

The logbook records:

- all the modifications made to the parameter settings
- all of the user logons / logouts
- all of the patient report consultations and their associated trace histories if applicable
- the date, the time of day and the user account from which actions have been performed
- previous values before modification

7.6 Backup and restore

Document **RD8** "Valab® - Backup and Restore", available at www.valab.com, provides all necessary details to set up the backup and restore of Valab® data.

We recommend that you keep a copy of the backups on another site of the medical laboratory (remote backups).

7.7 Activity statistics

The use of Valab® generates a set of statistical indicators for the autoverification results:

- number and percentage of reports validated
- number, percentage and cause of refusal for each test (correlation, anteriority, biological reference intervals or clinical decision values, "alert" or "critical" limits)
- number and percentage of validation for each test

This data is archived to create a history and a database which can be exploited a posteriori and during the entire period of activity of the system.

It allows in particular the implementation of continuous monitoring procedures by watching out for a drift between successive observation periods, for example month by month (see **RD5**).

There are also alarms, with a threshold that can be defined by validation rate and the reason for refusal for each test, to highlight those with a validation or refusal rate that is too high. This helps to customise the fine-tuning of the system by the user.

7.8 Documentation of Valab® and its interfaces

Among the documentation provided with Valab®, there are reference documents to ensure that the user maintains control of the tool and its interfaces and describing the means for monitoring to be implemented:

- User Manual (**RD6**)
- Developer Manual (**RD7**)
- Qualification of Valab® by the Medical Laboratory (**RD5**)

Each new version of Valab® has its own updated User Manual and Developer Manual. Those manuals are available under the "DOC" folder of Valab®.

The User Manual (**RD6**) describes all the functionality of the software that the user needs to know to understand the operation of Valab® and be proficient in its use.

The Developer Manual (**RD7**) presents all the technical characteristics and organisational recommendations to be taken into account by LIS companies to help them develop a connection and integration of Valab® in conformity with our requirements.

The Qualification of Valab® by the Medical Laboratory guide (**RD5**) is provided as an example. It describes the requirements to be implemented by the medical laboratory in order to qualify the integration and initial use of the Valab® software, then to ensure its control in terms of continuous monitoring, maintenance, tracing of modifications and requalification after a modification:

- Qualification of the connection and integration with the LIS
- Initial qualification of the autoverification and customisation of the parameter settings
- Requalification after modification
- Continuous monitoring: activity statistics, sampling of patient reports, pool of typical reports, maintenance
- Impact on the medical laboratory's QMS documentation
- Awareness and training of users

The results and records associated with all the procedures must be kept and archived (in electronic or paper format) as proof by the medical laboratory.

7.9 Training of users

All laboratory personnel who use the Valab® software must be trained on how it works and how to use it. For this purpose, when Valab® is installed, the future key-contact users of the system are trained by an agent of the VALAB company.

The term "user" must be understood in a broad sense, to cover not only the direct users of Valab® (key contact staff authorised to set up, check or otherwise interact with the software), but all the laboratory staff validating reports containing tests connected to Valab®.

Training is recommended both for new users and for existing users when they update to a new major release of Valab®.

8 Bibliography

8.1 Valab® biological bibliography - Extract

Click the following link to consult the Valab® biological bibliography - Extract on the www.valab.com website.

8.2 Bibliography and press articles on Valab®

Click the following link to consult the press articles on Valab® on the www.valab.com website.