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Quality assurance in Belgium

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Summary. - Clinical laboratories in Belgium working within the social security system require to be licenced. Internal quality control and participation in external quality assessment (EQA) belong to the licencing conditions. The evolution of the Belgian EQAS is outlined, including a performance evolution over the last ten years. Halving of interlaboratory CVs is observed for most clinical chemistry and immunoassay analytes. Improvement is less spectacular for haematological analytes and is missing for coagulation analytes. Using the results of EQAS 1989-1991 the mean overall method interlaboratory CVs could be estimated. Using data from a commercial internal quality control program for clinical chemistry and a request in 145 laboratories, current intralaboratory CVs are estimated.

Key words: legislation, internal quality control, external quality assessment.

Riassunto *(Il sistema di garanzia di qualità in Belgio)*. - In Belgio i laboratori clinici che operano nell'ambito del sistema della protezione sociale debbono essere autorizzati per legge. L'attuazione di un programma di controllo di qualità interno e la partecipazione a schemi di valutazione esterna di qualità sono requisiti indispensabili per la concessione dell'autorizzazione da parte del governo. In questo articolo viene messa in evidenza l'evoluzione del sistema belga per la valutazione esterna di qualità negli ultimi dieci anni, anche in riferimento all'evoluzione di capacità ed efficienza dei laboratori. Per la maggior parte delle analisi chimico cliniche ed immunometriche si è verificata una riduzione del 50% dei CV interlaboratori. Il miglioramento è meno vistoso per le analisi ematologiche e praticamente inesistente per le analisi in coagulazione. Si riporta una stima dei CV interlaboratori, sulla totalità dei metodi, corrispondenti alla media dei risultati dello schema di valutazione esterna di qualità dal 1989 al 1991. In un'indagine estesa a 145 laboratori, utilizzando i risultati di un programma commerciale per il controllo di qualità interno in chimica clinica, sono stati stimati anche i valori attuali dei CV intralaboratori.

Parole chiave: legislazione, controllo di qualità interno, valutazione esterna di qualità.

Introduction

Since 1978 [1], the reimbursement of laboratory tests, carried out within the scope of the social security system is conditioned by a licence, accorded by the Minister of Health. The conditions of the licence include amongst others:

1. The disposal of a sufficient number of qualified staff members.
2. The disposal of appropriate room facilities, equipment, reagents and scientific documentation needed for the analyses and the sample collection.
3. A system of internal quality control.
4. Mandatory participation in all the programs of external quality assessment (EQA). [2] in these groups of analyses carried out on a routine basis in the laboratory.

These conditions were specified in a ministerial decree [3], but after the reform of the first 1978 licence decree in 1989, and in 1993 [4, 5] the Commission for clinical biology proposed more stringent conditions. These new requirements will be integrated in a quality manual framework for clinical laboratories based on the European EN 45001 standard [6] and, although no decision actually is taken for official laboratory accreditation, clinical laboratories will be obliged in a near future to write their own quality manual and to implement it according to the instructions set out in the official quality manual framework.

In addition to the requirements of the EN 45001 standard, more stringent requirements are foreseen for laboratory supervision and for implementation of an adequate system of internal quality control specified in each of the three main disciplines of clinical pathology (1: clinical chemistry and immunoassays, 2: haematology including coagulation and immunology and 3: microbiology/ serology/parasitology).

External quality assessment in Belgium: evolution

Situation before 1979

Before 1979, external quality assessment (EQA) in Belgium was performed on a voluntary basis and was organized by professional societies. These programs were followed by about 80% of the biologists, but there was a very small response in laboratories of general practitioners and specialists.

The organizational aspects were entrusted to different university laboratories experienced in a particular field

of clinical laboratory sciences and accredited as supervisors by the Ministry of Health [2].

The whole system was based on a relation of confidence between controllers and controlled laboratories. There was also a free choice of supervisor on a one year basis (this typical Belgian policy took into account language and philosophical balances).

As this system was set up in a spirit of sanctioning repeated poor performances, only a limited number of analyses was checked with a high frequency.

The first consequence of the imposition of a EQA system resulted in a spontaneous relinquishing of the licence demand by a large number of general practitioners, conscious of the bad performance of their analyses. Also a lot of obsolete kits were withdrawn from the market.

For a small number of laboratories, the licence was cancelled as a result of repeated poor performance of analyses. Therefore the criterion of more than 2 consecutive results outside ± 3 SD for the same parameter was considered.

This system gave complete satisfaction, neither to the health authorities, nor to the participants. Some groups of participants were rather small and consequently the statistical treatment and interpretation were difficult. As participants were not allowed any mistake without risks of loss of licence, samples of EQA were treated very carefully and in a completely different way from patient samples.

Finally EQA gave only an idea of the theoretically possible quality that could be obtained in laboratories.

Reform of the EQA system

In 1987 the Commission of clinical biology created a working group to prepare a reform of the licence decree of 1978.

Recommendations were formulated related to the licence procedure, the procedure of appeal in case of licence withdrawal and a new system of EQA based on the following philosophy :

a) EQA should emphasize educational aspects. In this system the laboratory head can allow the EQA samples to be treated as normal routine samples without risks of licence withdrawal. In this way, EQA gives a more realistic impression of quality under routine conditions rather than the best possible quality that could be obtained in a laboratory.

b) EQA should be extended to a broad panel of analytes e.g. those analytes whose determination is problematic. Secondarily, EQA provides a tool to evaluate quality of kits and reagents on the local market.

c) Regrouping of the different controllers in an unique and national system of EQA.

d) More implication of laboratories in the practical concept of EQA and redefinition of the tasks of university laboratories.

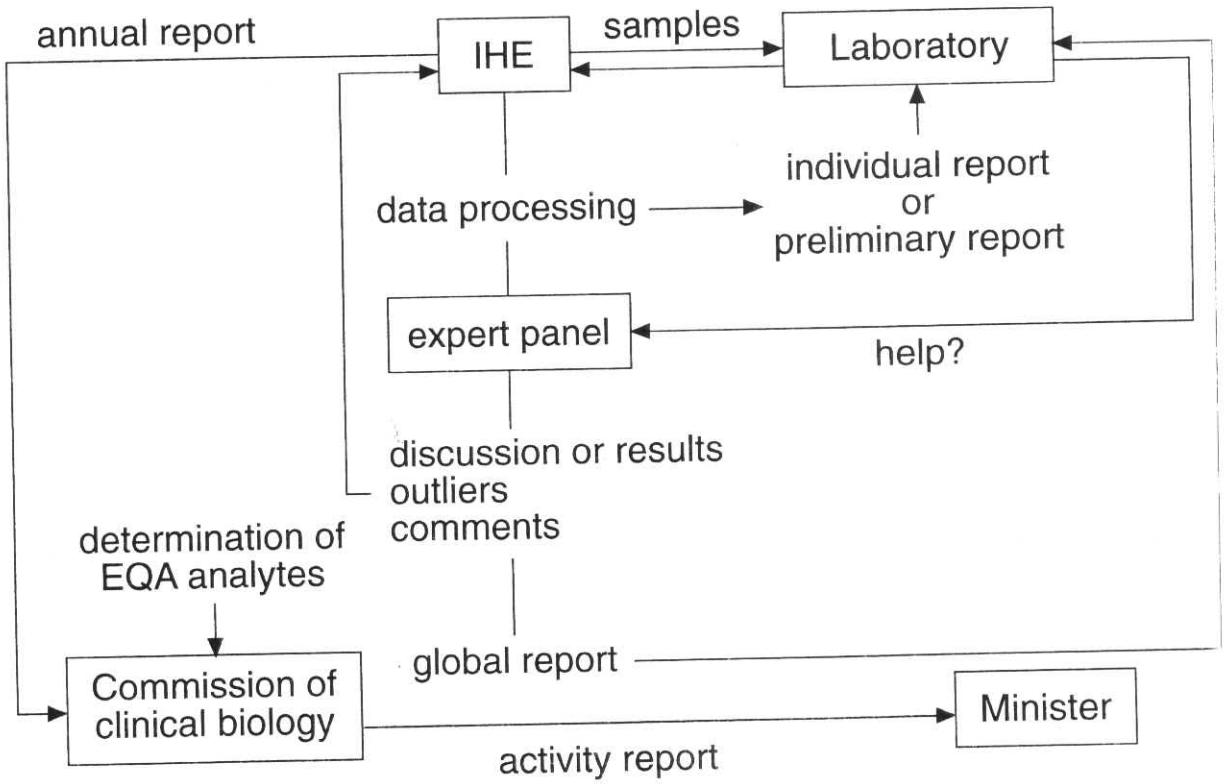


Fig. 1. - EQA partners interaction.

These recommendations were implemented in two new decrees related to the licence and the EQA organization. Recently a third revision was performed in 1993 [4, 5].

Participation in EQA remains mandatory as a condition of the licence but it is no longer possible to sanction a laboratory exclusively based on poor results in EQA. Poor performers are contacted in order to ascertain the reason of this by inspection *in situ*. Based on an inspection report the licence can be withdrawn because of serious errors in the performance of analyses after consultation of the Commission of clinical biology.

Current system of EQA

In the current Belgian EQA, three organisations collaborate:

1) The Commission of clinical biology is an advisory body for all problems related to clinical pathology. The advice is given on aspects requested by the Minister or on the initiative of the Commission itself.

The advice includes criteria for according a licence and for refusal, suspension, withdrawal and non renewal of the licence.

Table 1. - Review of analytes in the Belgian EQAS 1994

Scheme	no. of participants	Quantities	no. of samples/surveys fees/year
		Mandatory schemes	
Clinical chemistry	560	Glucose, urea, urate, ALT, amylase, LD, GGT, Cl, Na, K, Ca, Mg, iron, cholesterol, creatinine, triglycerides, IgA, IgG, Tot., protein, CRP	8/4 6000 B.F. (143 ECU)
Drug monotoring	280	Digoxin, theophylline	8/4 600 B.F. (143 ECU)
Immunoassays	250	Cortisol, progesterone, TSH, ferritin, hCG, hFSH, IgE, Vit. B_{12}	
Haematology	600	RBC, WBC, Hb, PCV, MCV, platelets, reticulocytes, blood smears	10/3 4500 B.F. (108 ECU)
Coagulation	435	PT, APTT, thrombotest, fibrinogen, fibrinogen degradation products	9/3 4500 B.F. (108 ECU)
Immunology	455	ABO/Rh, irregular antibodies, crossmatching tests, ANA, rheuma serology	18/3 4500 B.F. (108 ECU)
Microbiology	390	Identification and susceptibility tests	12/3 4500 B.F. (108 ECU)
Infectious serology	300	HIV, syphilis, ASLO, rubella	10/3 4500 B.F (108 ECU)
Parasitology	350	Parasites in blood and faeces	6/3 4500 B.F. (108 ECU)
		Voluntary schemes	
Allergy (*)	88	IgE tot, 12 specific IgE	36/6 6000 B.F. (142 ECU)
Alcohol	175	Ethanol	10/2 3000 B.F. (71 ECU)

(*) Multi-national program

2) Annual *ad hoc* committees of experts are chosen within a board, nominated by the Minister. These committees are composed of experts in a particular field of clinical pathology, both professionals and academics.

These committees are concerned with the practical organization of EQA:

- determination of sample specifications;
- choice of the statistical evaluation system;
- choice of the samples;
- presentation of answer forms;
- presentation of comments in a final report after each survey;
- answering questions of participants in relation with specific problems.

3) The section of clinical biology of the Institute of Hygiene and Epidemiology. This national institute is the central laboratory of the Ministry of Health. It is active in a variety of disciplines such as microbiology, environment, pharmaceuticals, foodstuffs, epidemiology, toxicology and clinical pathology. In all these fields, the institute plays an important role in the Belgian international scientific relations.

In EQA, the section of clinical biology is involved in the practical organization and the coordination :

- financial management;
- general contacts with participants;
- evaluation of the conformity of samples;
- purchase of samples;
- selection of participating laboratories for each survey in relation with the accorded licence;
- mailing of samples and reports;
- receipt of results;
- preparation of the global annual report;
- research in the field of EQA sample preparation;
- determination of reference method values.

Interactions between participants and EQA organisms is given in Fig. 1.

A review of parameters submitted to the Belgian official EQA scheme 1994 is given in Table 1.

Sequence of official EQA surveys is organized in such a way that participants receive samples ten times a year, once clinical chemistry/drugmonitoring and immunoassays (4 mailings), haematology/coagulation and immunology (3 mailings) and microbiology/ infectious serology and parasitology (3 mailings).

Beside the official EQA voluntary schemes are also run a) for allergens in collaboration with the UK NEQAS (Dr. R. Fifield) (6 mailings) and LWBA (Landelijke Werkgroep Bindingsanalyse, NL), b) for blood alcohol determinations (2 mailings).

The actual budget to EQA is about 0.77‰ of the total budget for clinical pathology tests in the Belgian Social security system (actually 26 billion B.F. = 620 million ECU).

Reports and evaluation

EQA schemes can be separated into those giving numerical results and assessment results (based on interpretation); evaluation is slightly different.

In the schemes with numerical data, an interim report is distributed to the participants at the closing date of the survey; in the other schemes an individual report is prepared, allowing the participant to compare his results for each analyte with those of other participants using the same method or kit.

Table 2. - Overall interlaboratory precision performance in Belgian laboratories (1989-1991)

Quantities	Inter-laboratory CV%
Clinical chemistry	
AST (modified IFCC)	8
ALT (modified IFCC)	9.5
Calcium	4
Chloride	4
Cholesterol	4
Creatinine	6.4
Glucose	4
Iron	15
Potassium	2.5
Sodium	2
Magnesium	8
Triglycerides	7
Urea	5
Uric acid	6.5
IgA	20
IgG	15
Immunoassays	
Chorionic gonadotrophin	24
Cortisol (RIA)	12
Digoxin (RIA)	8
Ferritin	23.5
Folate	20
IgE	19
Progesterone (RIA)	51
Theophylline	10
Thyroid stimulating hormone (RIA methods > 0.5 IU/l)	19
Vitamin B_{12}	12
Haematology	
PCV	4
Haemoglobin	3
RBC	3
WBC	9
Coagulation	
APTT	15
PT	14
Fibrinogen	12

This individual report is confidential. Each survey is closed with a final report distributed to the participants, summarizing the precision performances of all the used methods and kits and containing general written comments.

At the end of a year cycle an annual report is produced with detailed investigations on some specific topics and with an appreciation of methodologies and individual laboratory performances.

For statistical evaluations, a non-parametric method is used, having the advantage of a more realistic approach in the interpretation of the results (in many cases distribution of results is not gaussian) and excluding arbitrary truncation procedures.

In the schemes with interpretative results (immunohaematology, microbiology and morphology) a detailed report is sent to all the participants allowing a critical evaluation of their own results.

At the end of a cycle persistent poor performers are identified. These are laboratories who have at least one error in bloodgroup determination or crossmatching tests, three errors in microbiological identifications and a mean deviation index (mDI)>3 for numerical results, where:

$$mDI = \frac{\Sigma\ DI}{N\ samples} \quad \text{and} \quad DI = \frac{\text{laboratory result-target value}}{SD}$$

Peer group consensus median values are used as target values.

A letter is written to the laboratories who are detected as poor performers, to call attention to the problems and to invite them for further examination.

However, if failure is so severe as to suggest that patient health and safety are jeopardized they are visited as soon as possible.

Other acceptability limits are being discussed and a system of long-term follow-up of laboratory performance based on the variance index scoring system used in the UK [7] is being considered.

Further development

In order to accelerate the communications between the organizers and the participants, the transmission of EQA data will be integrated in an electronic data interchange (EDI) system covering multiple health care communications in Belgium. A national server for medical purposes has recently become into operation and the communication standard used in this system has been developed in the European Euclides project [8] (Euclides = a European standard for clinical laboratory data exchange between independent information systems).

Table 3. - Current intra-laboratory precision performance in Belgian laboratories, expressed as fractiles 0.25, 0.50 and 0.90 (CV_{P25}, CV_{P50} and CV_{P90}) for clinical chemistry quantities (between-series CV for at least 20 consecutive runs). In the last column the overall methods CV obtained in the Wellcome QAP scheme 1991 is given

Quantity	no.	CV_{P25}	CV_{P50}	CV_{P90}	All methods CV QAP 1991
Tot. protein	18	1.0	1.8	3.0	1.9
Phospholipids	10	2.4	2.9	4.6	/
Triglycerides	15	1.9	2.3	4.0	4.5
Tot. cholesterol	17	1.5	3.0	3.9	4.2
Phosphate	17	1.5	2.1	3.8	2.7
Sodium	18	0.7	1.0	1.3	1.4
Magnesium	15	2.3	3.9	6.9	4.3
Potassium	17	1.2	1.5	4.7	1.7
Iron	16	1.2	2.0	3.0	4.1
Chloride	18	1.0	1.4	2.9	1.5
Calcium	17	1.0	2.0	4.2	2.1
Urea	18	2.2	3.0	4.7	3.1
Urate	17	1.5	2.5	4.8	2.8
Glucose	17	1.3	2.1	2.7	2.8
Creatinine	17	2.4	3.0	5.6	2.7
Bilirubin	15	2.0	2.6	9.1	5.6
Lipase	5	4.5	6.0	10.3	/
Lactate dehydrogenase	7	1.9	3.0	6.6	3.5
LAP	4	1.5	2.5	/	/
γ-glutamyl transferase	15	1.7	2.0	4.8	3.2
ALT	18	2.0	3.0	4.5	4.0
AST	18	2.0	3.0	5.5	3.2
Creatine kinase	17	1.4	3.6	7.8	8.6
α-amylase	13	1.0	3.3	4.5	4.5
Alkaline phosphatase	15	2.4	3.0	5.6	3.6

The experimental phase for EQA data transmission was started at the beginning of 1994 and we hope that the system will be operational for all laboratories in 1995.

Follow-up of EQA performances versus time

Follow-up of global EQA results in the course of years has allowed a study of the state of the art performance of methods and the evolution of inter-laboratory variation [9].

For a number of routine analytes in clinical chemistry, hormonology, haematology and coagulation, we compared reproducibility during 3 different periods (1982, 1985 and 1989-1991). Therefore we plotted inter-laboratory CV values versus the overall mean or median values. Some examples are given in Fig. 2 for clinical chemistry (glucose and cholesterol), and immunoassays (cortisol and TSH) and in Fig. 3 for haematology (RBC and WBC) and for coagulation tests (APTT and PT).

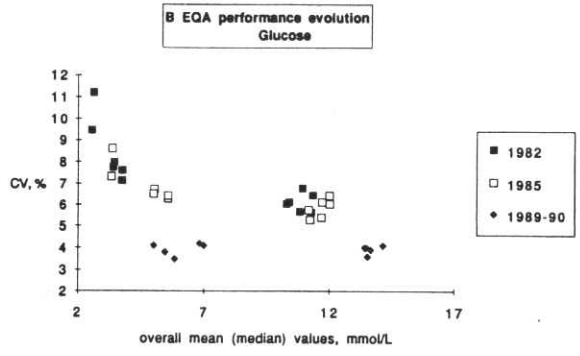
For clinical chemistry analytes CV's have decreased at least half of their initial values in one decade. This improvement of performance is mainly caused by improvement of methods and in particular by general application of automated analyzers.

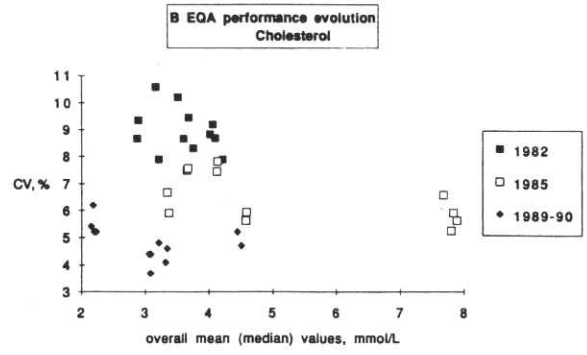
The Belgian EQA evolution clearly distinguishes 3 different precision levels related to the 3 snapshots. It must also be remarked that in 1979 the precision in foreign laboratories was better than the Belgian situation; CV's of 1985 are comparable with those of other countries.

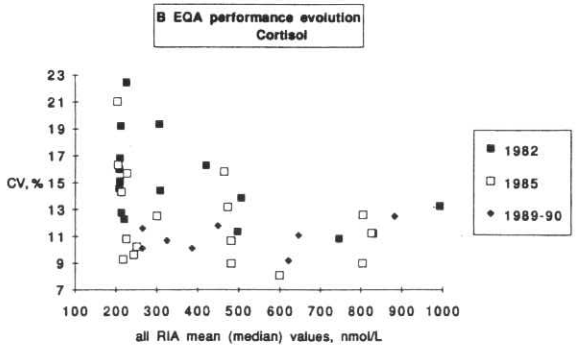
Our investigation in immunoassay performance evolution was limited by the fact that only cortisol and TSH could be followed within the concerned period.

Table 4. - Current intra-laboratory precision performance for immunoassays (between-series CV for at least 20 consecutive runs). For each quantity the fractiles 0.25, 0.51 and 0.90 (CV_{P25}, CV_{P50} and CV_{P90}) of the *normal* control levels were calculated. The CV_{P25} can be considered as an estimator for the state of the art

Quantity	no.	CV_{P25}	CV_{P50}	CV_{P90}	CV range
17-α-OH-progesterone	26	7.0	9.0	13.0	2 - 16
α-foetoprotein (AFP)	49	4.0	6.0	9.0	1 - 33
Aldosterone	25	6.7	9.0	15.0	1 - 22
CA 15-3	9	5.7	7.0	12.6	2 - 13
CA 19-9	14	4.0	5.5	9.8	3 - 17
CA 125	16	6.0	7.5	9.0	4 - 9
Carcinoembryonic antigen (CEA)	57	4.7	6.0	9.0	1 - 10
Chorionic-gonadotrophin (hCG)	54	4.0	6.0	10.1	1 - 15
Cortisol	59	4.2	6.0	10.0	1 - 21
DHEA-sulphate	35	7.0	8.0	13.0	3 - 20
Digoxin	43	5.0	6.0	8.2	1 - 12
Estradiol	60	6.0	8.0	11.0	3 - 19
Estriol, free	16	4.0	5.0	9.9	2 - 20
Estriol, total	12	5.0	7.0	16.6	2 - 25
Ferritin	62	5.0	7.0	11.3	1 - 22
Folate	68	5.5	7.0	12.0	1 - 23
Follicle stimulating hormone (hFSH)	57	5.0	6.0	10.0	2 - 16
Free T3	41	5.0	7.0	11.0	1 - 14
Free T4	40	5.0	7.0	10.0	1 - 14
Gastrin	16	8.0	9.0	12.9	6 - 20
Growth hormone (hGH)	20	5.0	8.0	12.5	5 - 13
Immunoglobulin E (IgE),total	48	4.2	7.0	10.4	1 - 21
Insulin	47	5.0	7.0	13.0	3 - 16
Luteinising hormone (hLH)	56	5.0	6.0	10.9	1 - 13
Parathyroid hormone (PTH), C-terminal	12	6.0	7.0	10.0	5 - 10
Placental lactogen (hPL)	18	4.0	7.0	10.0	3 - 14
Progesterone	60	5.0	7.0	12.5	1 - 17
Prolactin	58	4.0	5.0	11.0	2 - 17
Prostatic specific antigen (PSA)	37	5.0	7.0	11.0	2 - 20
Renin	10	6.0	7.5	14.5	5 - 16
T3 uptake (T3-U)	34	2.0	3.0	7.1	1 - 13
Testosterone	45	5.0	7.0	12.0	2 - 15
Thyroid stimulating hormone (TSH)	65	3.0	4.0	8.0	1 - 21
Thyronine uptake (T-U)	2	/	4.0	/	3 - 5
Thyroxine (T4)	57	4.0	5.0	9.0	2 - 16
Transferrin	12	3.0	3.0	5.3	1 - 6
Triiodothyronine (T3)	59	4.0	6.0	8.0	2 - 10
Vitamin B_{12}	70	5.0	6.5	11.5	2 - 26







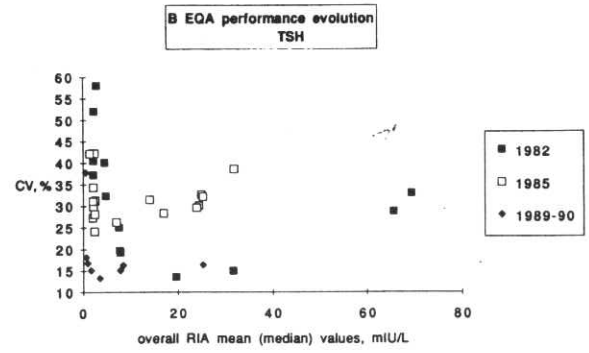
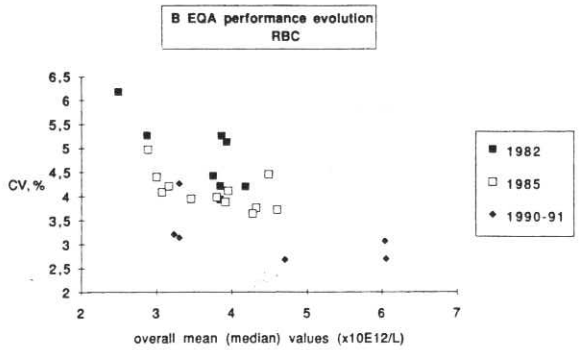
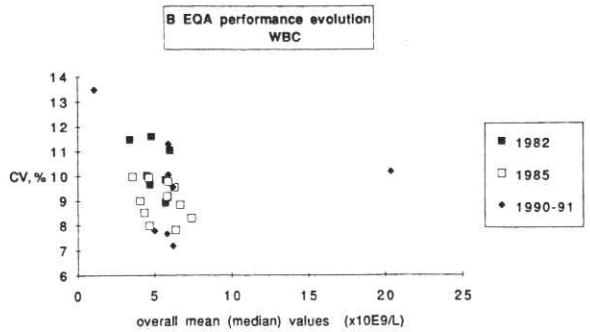
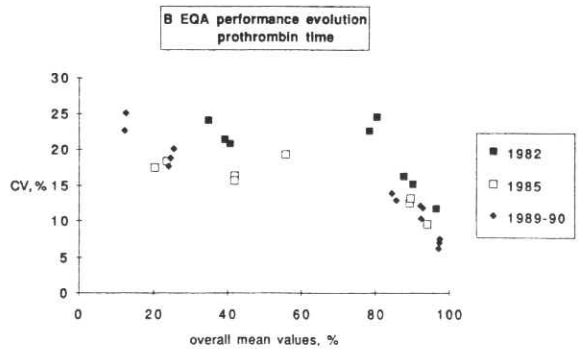


Fig. 2. - Performance evolution assessed in the Belgian EQAS since 1982 for clinical chemistry and immunoassay analytes.







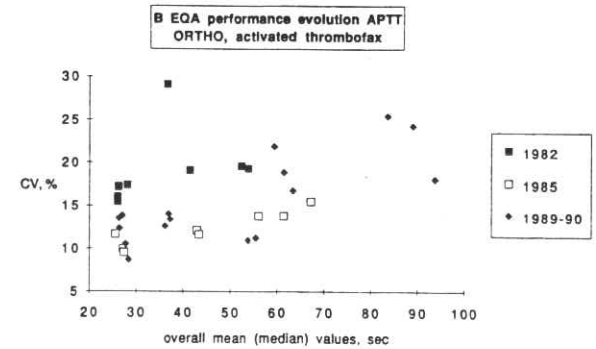


Fig. 3. - Performance evolution assessed in the Belgian EQAS since 1982 for haematology and coagulation analytes.

As shown in Fig. 2, a significant improvement in TSH determinations is observed; for cortisol, however, improvement is less pronounced.

In the haematology schemes, performance improvement is not as spectacular as for clinical chemistry analytes. The overall CV of blood cell counting is rather high in Belgium and must be explained by a relative high number of laboratories using a manual counting technique (13%).

Coagulation analytes show little or no improvement of performance during the observed decade. It is also a fact that little progress was made on automation for these techniques during the same period.

Current precision performance

Interlaboratory precision

Using the results of EQAS 1989-'91, we have estimated the overall methods mean interlaboratory CV's in Belgian clinical laboratories [9], (Table 2).

Intralaboratory precision

In 1992, we collected data on intralaboratory precision performance for clinical chemistry and for immunoassays. The approaches were different in each group: for clinical chemistry we collected data for normal control samples on a group of Belgian participants in a commercial internal quality control scheme; for immunoassays a questionnaire was sent to the first 145 laboratories, having the best performances in EQA cycle 1991 to provide (overall mean deviation index for all analytes and for all surveys between 0.34 and 1.75). We asked them the last available between-series CV's for at least 20 consecutive runs for Lyphochek® level I, II and III (or eventually other controls).

Data were only received from 75 laboratories. The low response rate (51%) once again stresses the importance of having a quality manual with a mandatory method validation and an adequate internal quality control system.

Results of each investigation is given in Tables 3 and 4.

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REFERENCES

1. BELGIUM. 1978. Arrêté royal du 10 Novembre 1978 relatif à l'agrément des laboratoires de biologie clinique par le Ministre de la Santé et de l'Environnement. *Moniteur Belge* du 14/2/1979, pp. 1795-1798.

2. BELGIUM. 1979. Arrêté royal du 1 Août 1979 fixant les règles d'agrément spécial des laboratoires, chargés du contrôle externe de la qualité des analyses de biologie clinique. *Moniteur Belge* du 1/9/1979, pp. 9616-9618.

3. BELGIUM. 1981. Arrêté ministériel du 18 Mars 1981 précisant des conditions à remplir par les laboratoires de biologie clinique afin d'assurer la qualité des analyses. *Moniteur Belge* du 28/4/1981, pp. 5291-5292.

4. BELGIUM. 1993. Arrêté royal du 12 Novembre 1993 relatif à l'agrément des laboratoires de biologie clinique par le Ministre qui a la santé publique dans ses attributions. *Moniteur Belge* du 8/12/1993, pp. 26152-26162.

5. BELGIUM. 1993. Arrêté royal du 16 Novembre 1993 relatif à l'évaluation externe de la qualité des analyses de biologie clinique. *Moniteur Belge* du 8/12/1993, pp. 26162-26164.

6. CEN/CENELEC. 1989. *European standard EN 45001*. The joint European Standards Institution. BIN/IBN, Brussels.

7. BULLOCK, D.G. & WILDE, C.E. 1985. External quality assessment of urinary pregnancy estrogen assay: further experience in the United Kingdom. *Ann. Clin. Biochem.* **22**: 273-282.

8. DUMONT, G. 1991. Commission informatique SFBC. Communications entre ordinateurs: standards de Communication. *Inf. Sci. Biol.* **17**(2): 87-93.

9. LIBEER, J.C. 1993. *External quality assessment in clinical laboratories. European perspectives: today and tomorrow.* University of Antwerp, PHD thesis.