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External quality assessment programs in Lombardy, Italy

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Summary. - In Italy, although a national decree (DPCM of 10/2/84) established that quality control programs involving clinical laboratories should be carried out on a regional basis, external quality assessment schemes (EQAS) are actually run only in some regions. Among these is Lombardy, where an EQAS in clinical chemistry concerning 20 analytes was set up in 1986, and where at present EQA programs (for clinical chemistry, haematology and coagulation) compulsory for both private and public laboratories, are under way. This was made possible by both regional laws and the constant care shown by the regional Committee on pathology department system (Comitato Regionale per l'Ordinamento dei Servizi di Patologia, CROSP). The participation in the schemes (including control material supply) is free of charge. The identity of participants is known only to officers in charge of quality control and analytical results are therefore managed anonymously. Consequently EQAS carried out in Lombardy are not exacting or punitive. In the EQAS for clinical chemistry the following analytes are considered: glucose, urea, proteins, albumin, chloride, sodium, potassium, total calcium, inorganic phosphate, iron, urate, creatinine, cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine phosphokinase, gamma glutamyl transferase and alkaline phosphatase. In the EQAS for haematology and coagulation the tests are: a) leukocytes, erythrocytes, haemoglobin, haematocrit, mean cell (erythrocyte) volume, platelets; b) prothrombin time, activated partial thromboplastin time, fibrinogen and antithrombin III. The general organization of the schemes, the statistical procedures adopted for the analysis of data, and some of the results obtained in the three EQA programs are reported in detail in the present article.

Key words: quality control, clinical chemistry, haematology, coagulation, external quality assessment schemes.

Riassunto *(Programmi di valutazione esterna di qualità in Lombardia).* - Nonostante il controllo di qualità per i laboratori di analisi cliniche sia previsto dal DPCM del 10/2/84, sono poche le regioni che applicano un controllo di qualità esterno nei servizi diagnostici di laboratorio. La regione Lombardia, fin dal 1986 ha istituito il controllo di qualità esterno in chimica clinica su 20 analiti. Attualmente sono operativi schemi di valutazione esterna della qualità (VEQ) nel campo della chimica clinica della ematologia e della coagulazione. La partecipazione ai programmi è obbligatoria per i laboratori sia pubblici che privati. Tutto ciò è stato reso possibile sia dalla legislazione regionale in materia sia dal costante impegno dimostrato anche in questo settore dal Comitato Regionale per l'Ordinamento dei Servizi di Patologia (CROSP). La partecipazione ai programmi è gratuita e l'identità dei partecipanti è nota solo ai funzionari addetti ai programmi stessi. I risultati sono elaborati in forma anonima e l'impostazione del programma non è né fiscale né punitiva. Nello schema di VEQ per la chimica clinica vengono considerati i seguenti analiti: glucosio, urea, proteine totali, albumina, cloruro, sodio, potassio, calcio totale, fosfato inorganico, ferro, urato, creatinina, colesterolo, trigliceridi, aspartatoaminotransferasi, alanina aminotransferasi, lattato deidrogenasi, gamma glutamiltransferasi, creatinfosfochinasi e fosfatasi alcalina. Negli schemi di VEQ per l'ematologia e la coagulazione vengono considerati rispettivamente: a) leucociti, eritrociti, emoglobina, ematocrito, volume cellulare (eritrocitario) medio e piastrine; b) tempo di protrombina, tempo di tromboplastina parziale attivato, fibrinogeno e antitrombina III. L'organizzazione generale dei programmi, le procedure statistiche adottate per analizzare i dati e alcuni dei risultati ottenuti nei tre programmi di VEQ sono riportati in dettaglio nel presente articolo.

Parole chiave: controllo di qualità, chimica clinica, ematologia, coagulazione, schemi di valutazione esterna della qualità.

Introduction

Although according to the decree of the President of the Council of Ministers passed on 10 February 1984 [1] quality control programs involving clinical laboratories should be carried out in Italy on a regional basis, external quality assessment schemes (EQAS) are actually run only in some regions. Among these is Lombardy, where an EQAS in clinical chemistry concerning 20 parameters was set up in 1986, and where a third program is currently under way. This was made possible by both regional laws on clinical chemistry laboratories and the constant care shown, also in this critical field, by the regional Committee on pathology department system (Comitato Regionale per l'Ordinamento dei Servizi di Patologia, CROSP), a technical body founded by Lombardy regional government.

The regional law (LR) no. 79, passed on 7 June 1980 [2] as "Regulation on the opening and management of laboratories outside hospitals", article 14, states that the laboratories are subject to quality control in order to ascertain their efficiency and reliability. The regional regulation no. 5 of 9 June 1982 [3] regulates both inter- and intra-laboratory quality control in clinical chemistry. The regional council decree, DGR III/29805 [4], of the 30 June 1983, extended mandatory quality controls to public laboratories in order to assure uniformity to all results obtained in this field. With regard to haematology and coagulation, explicit indications of the compulsiveness on quality control were given by the LR no. 65 [5] passed on 30 May 1985, and confirmed by the LR no. 61 of 18 May 1990 [6]. Quality control in hematology was regulated by the regional regulation no. 1 of 13 March 1988 [7]. At present a bill on quality control in immunohaematology has been brought before regional Council.

It is very easy to make quality control compulsory by law, but it is not so easy to apply and manage it. When the first quality control program in clinical chemistry was started, difficulties and misunderstanding arose, mainly because laboratory operators feared an exacting and punitive EQA application. This was gradually overcome, as alarm and worries proved groundless; experts' sense of responsibility proved, yet again, to be the winning card. It should be underlined that quality control was largely applied on a voluntary basis in Lombardy even before it became mandatory: in clinical chemistry it was performed in 79% of public laboratories and in about 75% of private ones.

The goals to achieve, with the cooperation of every participant in the EQAS, were and are as follows:

- to enable all operators to compare their own results with those obtained in other laboratories;
- to gain useful statistical information on the reliability of analytical methods, so as to select the better ones while rejecting the poorer ones;
- to facilitate the choice of effective internal quality control procedure;
- to enable the future use of "recommended methods" at the national level.

Our five year EQA experience in clinical chemistry showed that some of these goals have been achieved. It has to be stressed that a simple recommendation provided by the CROSP on the temperature to be used in measuring enzymatic activities, sent to laboratories by letter in May 1990, has found widespread approval. Now, 95% of laboratories in Lombardy perform all the measurements of serum enzymatic activities at 37°C and report results at the same temperature.

In the three regional EQA programs - for clinical chemistry, hemocytometric determinations, and hemocoagulation tests - the participation (including control material supply) is free of charge.

For the first and second EQA programs in clinical chemistry the contracts for serum supply and data management were assigned to Sclavo Co., while in the third program the contracts were assigned to BIO-RAD laboratories. EQA programs in haematology and coagulation were assigned to Ortho Diagnostics Systems. All firms have taken the necessary steps to avoid any indiscretion concerning participants; should this happen, the contract becomes invalid. In order to ensure the confidentiality of the information a code number was assigned to each laboratory, whose identification is known only to officers in charge of quality control. Analytical results are therefore managed anonymously: thanks to the code system, indiscretion is avoided, as it is impossible to identify individual participants.

EQA programs in clinical chemistry

The first EQA program in clinical chemistry started in June 1986 and ended in October 1988; the second one was started in May 1989 and ended in October 1991. The third program, started in January 1994, will also last two years.

Laboratories participating in the third program (no. = 437) are subdivided as follows: a) 149 hospital laboratories; b) 35 public extra-hospital laboratories (i.e. 184 public institutions); c) 58 private clinics; d) 195 private laboratories (i.e. 253 private institutions).

In the third program the following analytes are to be evaluated: glucose, urea, proteins, albumin, chloride, sodium, potassium, total calcium, inorganic phosphate, iron, urate, creatinine, cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP). Amylase, included in the first program, due to the many different amylase tests in use, which did not allow for a correct statistical evaluation was no further evaluated. In the second program, the analyte albumin was included.

For this third EQA program, four 6 month cycles, allowing a monthly analysis of two samples, have been allotted.

Sera are to be reconstituted and analyzed only on the indicated dates. The results have to be sent to the BIO-RAD laboratories quality control program office by the Saturday following the date of analysis, by registered mail to be charged to the Lombardy region. Results received beyond dead-line are not processed.

As for substrates, values are statistically processed in one or more groups, subdivided according to any analytical procedure used by more than 20 participants. As for enzymes, the values obtained with any method and temperature form a homogeneous group, which is processed when including a number of results suitable for statistical analysis.

Each laboratory is given a monthly report, showing, for each analyte:

- the result obtained by the laboratory itself;
- the expected value, calculated as "consensus mean";
- the standard deviation (SD) calculated for the values obtained by all laboratories that have assayed the same serum;
- the deviation of the result obtained from the expected value, expressed in SD units (Z score);
- the percent deviation of the result obtained from the expected value;
- the coefficient of variation (CV);
- the number of laboratories that have determined the same analyte;
- the recommended limits;
- the interval containing the mean ± 3 SD;
- a graphic presentation of the Z scores obtained by the laboratory during the program;
- a graphic representation (bar chart) of the results obtained by all laboratories with reference to the mean ± 3 SD limits; the position of the laboratory is indicated.

At the end of each cycle, all laboratories receive the following documentation:

- a summarizing print-out where all the results obtained by the laboratory for each analyte are compared with the expected values; the percentage of results falling within the recommended limits is also calculated;
- a cumulative print-out comparing the results obtained for each analyte by applying the single methods and/or instruments listed in the questionnaires.

A concise monthly print out, showing the results obtained by each laboratory compared with expected values, is prepared for the regional health service.

The CVs obtained for the determination of substrate and enzymes in the second cycle of the second program are reported in Table 1 and 2, respectively.

EQA results have often been used by public laboratories directors as a reason for requesting renewal of equipment from the laboratory administration.

From the point of view of public health, a low score is a serious warning signal: laboratory operators must then be given time and opportunity to improve their performance, and the local authorities must care, the necessary measures set down in the LR 79/80 [2].

EQA programs for haemocytometric determinations

After the positive experience of the EQA programs in clinical chemistry, the regional authorities, through CROSP and the regional health service for quality control, decided to start EQA programs for haemocytometric determinations and for the assays of coagulation parameters.

All laboratories were informed by circular letters in July 1990.

The first EQA program in haematology - started in September 1990 - ended in July 1992; the second program which was started in January 1994 will also last two years.

In brief, in EQA for haemocytometric determinations the same regulations apply, as those in clinical chemistry.

In the second program, 425 laboratories are participating, subdivided as follows: a) 143 hospital laboratories, b) 30 public extra-hospital laboratories (i.e.

Table 1. - CVs for substrates obtained in the second cycle of the second program in clinical chemistry

Glucose	4.1
Urea	5.1
Protein	3.3
Albumin	6.6
Chloride	3.5
Sodium	1.7
Potassium	2.4
Total calcium	4.1
Inorganic phosphate	5.9
Iron	6.8
Urate	7.1
Creatinine (enzymatic method)	10.2
Creatinine (all methods)	7.3
Cholesterol	4.0
Triglycerides	6.6

Table 2. - CVs for enzymes obtained in the second cycle of the second program in clinical chemistry. The percentage of laboratories (% of labs) adopting the most utilized methods is also reported

Analytes	CV	% of labs
AST		
IFCC (without pyridoxal-phosphate)	7.3	38
SCE	7.1	43
all methods	7.5	
ALT		
IFCC (without pyridoxal-phosphate)	6.9	38
SCE	7.8	43
all methods	7.3	
LDH	6.8	
CPK	8.8	
GGT		
L-γ-glutamyl-3-carbossi-4-nitroanilide	5.7	57
L-γ-glutamyl-4-nitroanilide	9.8	42
all methods	7.7	
ALP		
Diethanolamine buffer, p-nitrophenyl phosphate	10.4	85
all methods	12.3	

173 public institutions); c) 57 private clinics, d) 195 private laboratories (i.e. 252 private institutions).

The following tests were chosen: leukocytes counts (WBC), erythrocyte counts (RBC), haemoglobin (Hb), haematocrit (Hct), mean cell (erythrocyte), volume (MCV) and platelet counts (PLT). During the two-year program divided in four/six-months cycles, two samples are distributed every 45 days. The same analytical method used for patients' samples is to be used for EQA samples.

Ortho Diagnostic Systems, the firm running the quality control program in haematology and coagulation on behalf of Lombardy, processes data and sends a report on the results obtained for each test to all laboratories.

The report includes:

- the result obtained by the laboratory itself;
- the "consensus mean";
- the standard deviation (SD) calculated for the values obtained by all laboratories;
- the distance of the result obtained from the expected value, expressed in SD units (Z score);
- the coefficient of variation (CV);
- the recommended limits;
- two Youden plots, which refer, respectively, to the results relative to: a) all the analytical methods and b) only the methods used by the laboratory concerned; in both plots the result obtained by the laboratory is indicated.

At the end of each cycle, Ortho Co. sends the following documentation to each laboratory:

- a print-out summary, where the results obtained by the laboratory for each parameter will be compared with the expected results;
- a print-out showing the results obtained with the single methods and/or instruments listed in the questionnaire;
- a graphic representation (bar chart) of the Z scores obtained for each analyte and each exercise.

Results are, of course, processed anonymously, as they are for clinical chemistry.

After each survey a review print-out is placed at the disposal of Lombardy quality control office.

The CVs obtained for the first two EQA samples (circulated on 26/1/94) examined in the second program are reported in Table 3.

The CV values indicate the good quality of the results obtained so far. We cannot exclude, however, that in some cases the material has been given a preferential treatment, as compared with patients' samples.

Table 3. - CVs for the first two control samples analyzed in the second EQA program for haematology

Tests	Sample A	Sample B
RBC	2.11	2.34
WBC	5.93	6.79
Hb	1.82	2.12
Hct	4.18	4.45
MCV	3.95	4.07
PLT	8.63	8.64

EQA programs for coagulation tests

The first EQA program on coagulation parameters lasted two years as well. There were eight quarterly distributions each consisting of three samples. At present, the second program is being planned.

In the first program, started in October 1990 and ended in June 1992, 433 laboratories participated, subdivided as follows: a) 136 hospital laboratories, b) 31 public extra-hospital laboratories (i.e. 167 public institutions); c) 56 private clinics, d) 210 private laboratories (i.e. 266 private institutions).

The following tests were evaluated: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), antithrombin III (AT III).

Each laboratory is given a summarized print-out every four months including, for each test:

- the values found by the laboratory itself (FV);
- the expected value;
- SD and CV calculated for the values obtained by all laboratories;
- the deviation of the result obtained from the expected value, expressed in SD units (Z score);
- the recommended limits;
- a graphic representation of FVs related to recommended limits.

Youden plots are given for each parameter, taking into account the way of expressing results; thus, for PT three plots are given accounting for expression of results as seconds, activity % and ratio; for APTT, two plots are given (second and ratio); for FIB, one plot (mg/dl); for AT III, several plots according to different data expressions. In preparing the plots, the many reagents and instrumentations used are taken into consideration, in the attempt to subdivide the data into groups, as homogeneous as possible. The Youden plots refer to (a) all reagents and instruments, (b) individual reagents and all instruments, (c) individual reagents and individual instruments. In all cases the result obtained by the laboratory is indicated.

A review report is placed at the disposal of Lombardy quality control office.

The CVs observed for coagulation parameters in the survey of 10/6/92 in the first program are shown in Table 4.

There is an apparently higher imprecision for coagulation tests as compared with clinical chemistry and hematology tests. This is mainly due to the fact that

Table 4. - CVs for three control samples analyzed in the first EQA program for coagulation

Tests	Sample A	Sample B	Sample C
PT (s)	22.43	7.29	22.77
APTT (s)	18.97	22.35	20.22
FIB (mg/dl)	14.18	13.03	13.99
AT III (%)	8.84	10.21	9.61
AT III (mg/dl)	41.34	39.87	43.66

coagulation tests are more affected by analytical variables and have, therefore, not yet achieved optimal standardization levels (particularly in the case of AT III).

Other EQA programs

Besides the quality assessment programs outlined above, other two compulsory EQA programs are run cooperatively with University of Brescia and Presidio Multizonale di Assistenza Ospedaliera (PMAO) Spedali Civili di Brescia:

- the EQA program for private laboratories which are authorized to determine anti-HIV antibodies;
- the EQA program for transfusion centres and transfusion services for the determination of HBsAg, anti-HCV antibodies, and anti-HIV antibodies.

Final remarks

In conclusion, regional authorities of Lombardy, and especially the regional Committee on pathology department system, CROSP, have always considered EQA programs as tools for improving the quality of test results and the performance of diagnostic devices, both in public and private laboratories.

Apart from the undoubted technical and organizational difficulties related to EQA (and also, to a lesser extent, to internal quality control), the main goal is to increase the cooperation among laboratories and between laboratories and local offices, which in my opinion, are facing the task with a good degree of professionalism.

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