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The measurements and testing programme of the European Union in the field of biomedical analysis: reference materials and cooperation between European EQAS

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Summary. - About twenty years ago, the European Commission established the BCR (Bureau Communautaire de Référence) programme with the objective of improving the quality of the results of measurements, in order to assist in the establishment of reliable and comparable measurement systems in the EU member states. Its usual procedure consists of collaborative studies - involving preferably laboratories from all member states - in terms of: intercomparisons, research and development and preparation and certification of reference materials when necessary. The aim of the biomedical activities of the programme is to harmonize results obtained from analyses of samples of tissues and biological fluids. In the current programme "measurements and testing" (BCR's successor) emphasis is focused on two categories of activities: 1) feasibility preparation and certification of reference materials (including the appropriate method development when necessary) and 2) collaboration between EU national external quality assessment schemes (EQA).

Key words: reference methods, reference materials, European Union, external quality assessment schemes.

Riassunto *(Il programma "misure e prove" dell'Unione Europea nell'area dell'analisi biomedica: materiali di riferimento e cooperazione tra schemi di valutazione esterna di qualità in Europa).* - Circa venti anni fa la Commissione della Comunità Europea (oggi Unione Europea) istituì il programma "Bureau Communautaire de Référence" (BCR) con l'obiettivo di migliorare la qualità dei risultati delle misure. Lo scopo finale era di definire un sistema di misure che garantisse la comparabilità e l'affidabilità negli stati membri dell'Unione Europea. Il programma prevedeva studi collaborativi fra laboratori - possibilmente di tutti gli stati membri - consistenti in confronti fra misure, preparazione e certificazione di materiali di riferimento, ove necessario. Obiettivo del programma, per quanto riguarda le attività biomediche è l'armonizzazione dei risultati ottenuti da analisi effettuate su campioni di tessuti o di fluidi biologici. Attualmente il programma BCR è stato sostituito dal programma "measurements and testing", nel quale, sempre in campo biomedico, viene dato particolare rilievo a due categorie di attività: 1) studi pilota per l'allestimento e la certificazione di materiali di riferimento, (quando è necessario in tali studi è incluso lo sviluppo di un metodo di analisi adeguato); 2) collaborazione fra stati membri dell'Unione Europea per l'allestimento di schemi nazionali di valutazione esterna di qualità (external quality assessment schemes: EQAS).

Parole chiave: metodi di riferimento, materiali di riferimento, Unione Europea, schemi di valutazione esterna di qualità.

Introduction

About twenty years ago, the European Commission established the Community Bureau of Reference (known by its French initials, BCR) to encourage and support technical collaboration between the laboratories of EU member states in order to eliminate disputes arising from measurements. In this way, the Commission intended to help laboratories in the member states to provide accurate and reliable measurements in those sectors which are vital to the European Union as a whole: trade, agriculture, food, environment, health, consumer protection and competitiveness of European manufacturing industry. By improving the reliability of measurements it is also possible to avoid disputes, which is a very crucial factor in the context of the internal market. This kind of activities is now continued under the measurements and testing programme (M&T).

General objective of the programme

The aim of the programme is and has always been to improve the quality of the results of the measurements, in order to assist in the establishment of reliable and comparable measurement systems in the EU member states.

It contributes to the development of novel methods of measurement and testing and to the improvement of measurement and testing techniques and chemical analyses where these are not sufficiently accurate or precise, by providing the technical support needed (e.g. by estabilishing reference materials when necessary); thus it promotes the exchange and transfer of "know-how".

The outlined general objectives, reflecting the needs on which the member states agreed after negotiations, had been implemented by the Commission as follows:

From 1973 to 1982, under the name of "reference materials and methods", the programme focused mainly on the production of certified reference materials as well as on the respective measurement methods.

In the periods 1983 to 1987 and 1988-1991, under the names of "applied metrology and reference materials" and "applied metrology and chemical analysis" respectively, emphasis was given to method development.

Lastly in the current programme 1992-1994, under the name "measurements and testing", the main activity is to provide support for the competitiveness of the European industry and the development of novel measurement instrumentation.

Means of action

The usual procedure consists essentially in bringing together - for each project - qualified laboratories from the member states, for improving the measurement or analysis in question through collaborative work comprising:

- preliminary interlaboratory studies to define the state-of-the-art (intercomparisons); in some cases the exercise is repeated several times with improvements made at each step, until a satisfactory agreement is reached;
- methodological investigations to identify errors and sources of between laboratory discrepancies, and hopefully to solve them (research and development);
- preparation of reference materials (if required).

Due to the research nature of the programme, prior to being selected, the participating laboratories must have shown proof of scientific and technical excellence and be open to transnational collaboration, in order to foster cohesion throughout in European Union.

Obtained results are disseminated through publications both in open literature and by the EU Office for Official Publications (EUR reports). Another way of dissemination, which is to a certain extent characteristic of the programme, is the establishment of reference materials. Organization of workshops and training courses complete the spectrum of accompanying measures.

Activities of the biomedical part of the programme

The biomedical part of the programme aims at harmonizing the results obtained from examination of samples of tissues and biological fluids. The assessment of priority of the topics to be studied in depth on a European level takes account among others:

- the clinical importance of the parameter to be measured;
- the frequency and difficulty of the analysis;
- the consequences of false results from the economic and social point of view.

Two major categories of activities are currently running:

1) studies on feasibility, preparation and certification of reference materials (and/or development of the appropriate method). A large range of parameters is covered, such as: electrolytes, proteic and non proteic hormones, enzymes, other proteins, tumour markers, heavy metals, lipids and substrates and autoimmune related substances;

2) collaboration between the organizers of external quality assessment (EQA) schemes operating in health care related fields.

Definition, intended use and illustration of reference materials

According to the guide ISO 30-1981 definition "materials or substances one or more properties of which are sufficiently well established to be used for the calibration of an apparatus, the assessment of a measurement method or for assigning values to materials, are characterized as reference materials" (RM).

Those in which "property value are certified by a technically valid procedure, accompained by or traceable to a certificate, or other documentation which is issued by a certified body, are considered certified reference materials" (CRM).

In conformity with these definitions, the most beneficial approach would be for CRMs to be used by manufacturers of kits, EQAS organizers and reference laboratories. The former would in fact provide routine users with control materials traceable to the CRMs.

For all the following examples (projects), two conditions were initially established: a) definition of the parameters to be quantified or of the property to be measured; b) choice and/or development of the appropriate method(s) to be used.

The first step consists of a feasibility study on a small scale production of a pilot batch including subsequent homogeneity, stability and characterization assessment.

The production of the main batch of the candidate RM and the relevant value assignment then follow, provided the aforementioned properties meet the requirements initially set by the participating experts.

A final report (including every detail of the project) and a certificate of analysis are submitted to the certification Committee assisting the Programme. When approval is obtained, the report and the certificate are officially published and thereafter accompany each dispatch of reference material(s) requested by the respective user(s).

The stocks of reference materials are kept (under appropriate conditions) and distributed by the EU storage laboratory in Geel, Belgium. The long term stability of the stored materials is monitored throughout time. In case of significant degradation of the measured property the material is withdrawn and the users informed in writing.

Table 1 illustrates the certified reference materials prepared up-to-date.

Table 1. - Certified reference materials for biomedical analysis

Haematology		
CRM	**CRM description**	**Intended use**
148	Thromboplastin bovine	calibrator for prothrombin time determinations
149S	Thromboplastin rabbit (second replacement)	calibrator for prothrombin time determinations
165 166 167	Nominal 2 μm latex spheres Nominal 4.8 μm latex spheres Nominal 9.6 μm latex spheres	calibrator for blood cell sizing
522	Haemiglobincyanide	calibrator for measuring haemoglobin
Clinical chemistry		
CRM	**CRM description**	**Intended use**
192 193	Cortisol in human serum (normal) Cortisol in human serum (spiked)	calibrator/control
347 348	Progesterone in human serum (low) Progesterone in human serum (high)	calibrator/control
372 373 374	Thyroxine in human serum (low) Thyroxine in human serum (normal) Thyroxine in human serum (high)	calibrator/control
303 304	Ca, Mg, Li in human serum (normal) Ca, Mg, Li in human serum (path.)	calibrator/control
299	Creatine kinase (CK-BB)	calibrator
319	γ-glutamyltransferase	calibrator
371	Alkaline phosphatase	calibrator
404	Lactate dehydrogenase (LD1)	calibrator
410	Prostatic acid phosphatase	calibrator
426	Alanine aminotransferase	calibrator
393 394	Purified human apolipoprotein (A-I) Purified human apolipoprotein (A-II)	calibrator calibrator
457	Purified human thyroglobulin	calibrator
405	Reference human blood for glycated haemoglobin	control (non certified)
470 470	Reference human serum for 14 proteins Reference human serum for Antichymotrypsin, K-λ light chains	calibrator calibrator in preparation
486	Purified αFoetoprotein	calibrator
Occupational health		
no.	**CRM description**	**Intended use**
194 195 196	Lead and cadmium in blood (low) Lead and cadmium in blood (medium) Lead and cadmium in blood (high)	calibrator/control

Collaboration between European Union EQA schemes

EQA schemes have been in operation for a number of years in the field of measurement and testing related to health care and now-a-days play an undisputed important role. This might be because it is recognized that health care requires top quality, synonym of which - in an analytical context - is high reliability of qualitative and quantitative data: information produced for diagnostic purposes or for the monitoring of the efficiency of a therapy must be reliable since the medical decisions based on it have direct and sometimes even vital consequences for human life.

Consistently increasing demand for clinical analysis can only be met because industry has developed very efficient and extremely easy to handle *in vitro* diagnostic tools. Consequently routine laboratories are mainly free to choose between various automated systems or diagnostic kits offered by different manufacturers. The basic analytical procedure itself is predefined and already built into the product, and the "end user" laboratory is neither expected to modify it nor provided with facilities to independently control their performance including the calibration of their apparatus or kits.

In this context EQA schemes help to increase confidence in both the analytical performance of those industrial products and the user's manipulations which are much more difficult to standardize. EQA schemes provide their subscribers with a retrospective overall assessment of both aspects, giving proof of individual success or failure. Since this information is given in comparison with the results obtained from all other participants an end is put to the laboratories' isolation and a measuring community is established.

It is obvious that EQA scheme organizers are in a strategic position to influence both the *in vitro* diagnostic manufacturers on the one hand and the laboratories on the other. To this end the M&T programme undertook efforts to strengthen inter-scheme co-operation. Improved contacts between the schemes operating in the different member states were thought to be first step to ascertain a Community-wide coherent level of the analytical performance related to health care. Such general conditions would be beneficial to European citizens in terms of improved health care and could lead to uniform conditions throughout the single market for service laboratories and the *in vitro* diagnostic industry, both challenges worthwhile to be achieved.

During the last three years M&T made specific efforts to establish well communicating groups of EQA scheme organizers operating in haematology and clinical chemistry. The respective groups reviewed organizational and functional aspects of the various schemes in order to identify divergencies which could give rise to disputes and conflicts with regard to the single market.

One of the major differences identified concerns the definition of evaluation criteria for laboratory performance (for both clinical chemistry and haematology). For a limited number of parameters there are schemes which assess the respective laboratory performance independently of the method used, in contrast to a target value set by the respective reference method procedure. This strategy is not undisputed and the fact that one reference laboratory responsible for setting the common target creates major concern due to the possibility that, in a worse case scenario, one wrong result could bias an entire scheme.

There are a number of other approaches for the definition of the target value, one of which is the establishment of a consensus referee. That can be achieved by the collaboration of a few selected leading laboratories with respect to the analyte concerned. The overall mean calculated from the participants' results (after some corrective measures, e.g. elimination of statistical outliers) represents another widely used target setting technique. Whenever measurement results are strongly method dependent the latter approach is modified and observations per method principle are grouped and separately appreciated.

It is not the intention to give an exhaustive list of procedures used to establish scheme target values; however, it becomes obvious that Europe's characteristic feature also applies for EQA schemes: unity in diversity.

Neverthless it is not desirable that the performance of one specific laboratory would be differently classified by the various operating schemes due to the discrepant target setting techniques applied. Such a situation would not be acceptable neither from a scientific point of view nor with respect to its severe consequences for the single market which allows free movement of services.

First experiences obtained from experiments organized with the respective groups of EQA schemes indicate that the above mentioned scenario is not purely a theoretical possibility. Thus, when the various haematology schemes processed a common set of data consisting of reports of laboratories participating in a routine survey the individual performance classifications turned out to be incompatible.

Another inter-scheme experiment undertaken with the group of scheme organizers in the field of clinical chemistry showed the bizarre situation in which for one chemically well-defined substance different target values are established in function of the various target setting procedures.

These initial inter-scheme collaborations on a Community-wide scale catalized further activities.

The organizers of haematology schemes pioneered the drafting of a commonly agreed "EQA Code of practice" paying the way towards mutual recognition between schemes. The organizers of clinical chemistry schemes have come to a similar conclusion. The setting up of unanimously agreed basic criteria for scheme functioning was the only possibility to ensure compatible judgement of laboratory performance.

Encouraged by the vivid and the constructive across-border collaboration between the scheme organizers so far addressed, there is an intention to broaden this kind of activity including schemes operating in other fields such as clinical microbiology and occupational health.

By fostering the aforementioned activities, the M&T programme and more specifically its biomedical part intends to contribute to the improvement of the quality of health services for EU citizens, by providing the means to achieve better accuracy and reliability of results obtained by medical/clinical laboratories throughout the EU. At the same time an additional goal (to be more emphasized in the programme succeding the current one) is to support and promote the competitiveness of European industry e.g. *in vitro* diagnostic and/or medical device manufacturers, by improvement of the relevant production, quality-control and research and development procedures.

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