Ned Tijdschr Klin Chem Labgeneesk 2007; 32: 186-188

EC4: Clinical laboratory globalisation; the EU directives

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The directives of the European Union form the legislation of the European Union. The directives have power of law for the 27 member countries of the EU, however, because of the scale of the EU market, there is a strong influence far beyond the EU borders. Three directives that have large impact on laboratory medicine and the profession of specialist in clinical chemistry and laboratory medicine in Europe and also on a world wide scale are named and their impact treated to some detail. It regards the directive on In Vitro Diagnostic medical devices (IVD) (1), the directive on Recognition of Professional Qualifications (2) and the proposed directive on Services in the Internal Market (3).

IVD directive

The IVD directive requires traceability of reagents and kits to a reference system. In principle traceability is required for category A tests, which include about 80 analytes. A global committee was installed, the Joint Committee on Traceability in Laboratory Medicine (JCTLM), to define reference methods and materials. For several analytes reference methods were defined and for most of these reference materials fit to be used in the reference procedure are available. Among other reference procedures were defined for six serum enzymes.

Commercial tests for serum enzymes should show traceability to these reference procedures. In order to investigate this, an international EC4 study for trueness verification was performed (4), i.e. the assessment of the entity of bias of results obtained by a routine method when compared with the true value, using commutable materials developed in the Calibration 2000 project (5). This study showed that the implementation of traceability in the field of clinical enzymology is still not sufficiently realised. Significant bias for the results obtained by commercial analytical procedures was shown in many cases. Furthermore, when desirable analytical performance criteria based on the biological variation model were applied, inappropriate large between- and, in some cases, within-laboratory variances were noticed.

Trueness verification was also introduced in the Dutch external quality assessment scheme. It assesses the IVD compatibility of methods used and at the same time the individual professional is able to assess the performance of the methods in his or hers laboratory. Commutable materials from the Calibration 2000 project are used throughout. Again the biological variation concept is used in the EQA scheme. Figure 1 shows results for γ-GT. The presently achievable state of the art area is significantly narrower than the Total Allowable Error (TAE) area based on biological variation. A slight positive slope of the line though this laboratory's results is visible. However all results are well within the TAE area, but only partly within the state of the art area, leading to scores of respectively 100% and 59% (purple arrow). The results are also within the area for maximum allowable bias. However, the area which indicates the maximum allowable variation when assessing difference of a result from a previously obtained result, as in monitoring patient data, shows violation.

Directive on recognition of professional qualifications

Through the directive on Recognition of Professional Qualifications specialists in clinical chemistry and laboratory medicine with medical background enjoy automatic recognition in most EU countries via two mentioned specialties: clinical biology and biological chemistry. Pharmacy and science educated specialists, however, are not regulated in the directive and do not enjoy automatic recognition. The directive includes a system of Common Platforms. A Common Platform should provide a simple system for automatic recognition of qualifications of a particular profession between EU countries. EC4 has submitted, as first organisation to do so, a Common Platform to facilitate recognition of specialists in clinical chemistry and laboratory medicine. The requirements in the Common Platform could have global consequences. For the establishment of the Common Platform EC4

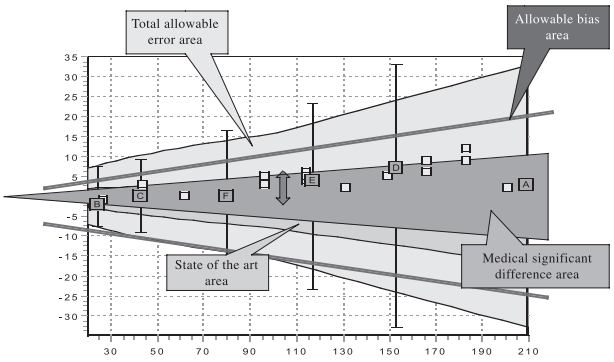

Figure 1. Plot for gamma-GT for a laboratory in a survey of the Dutch NEQAS.

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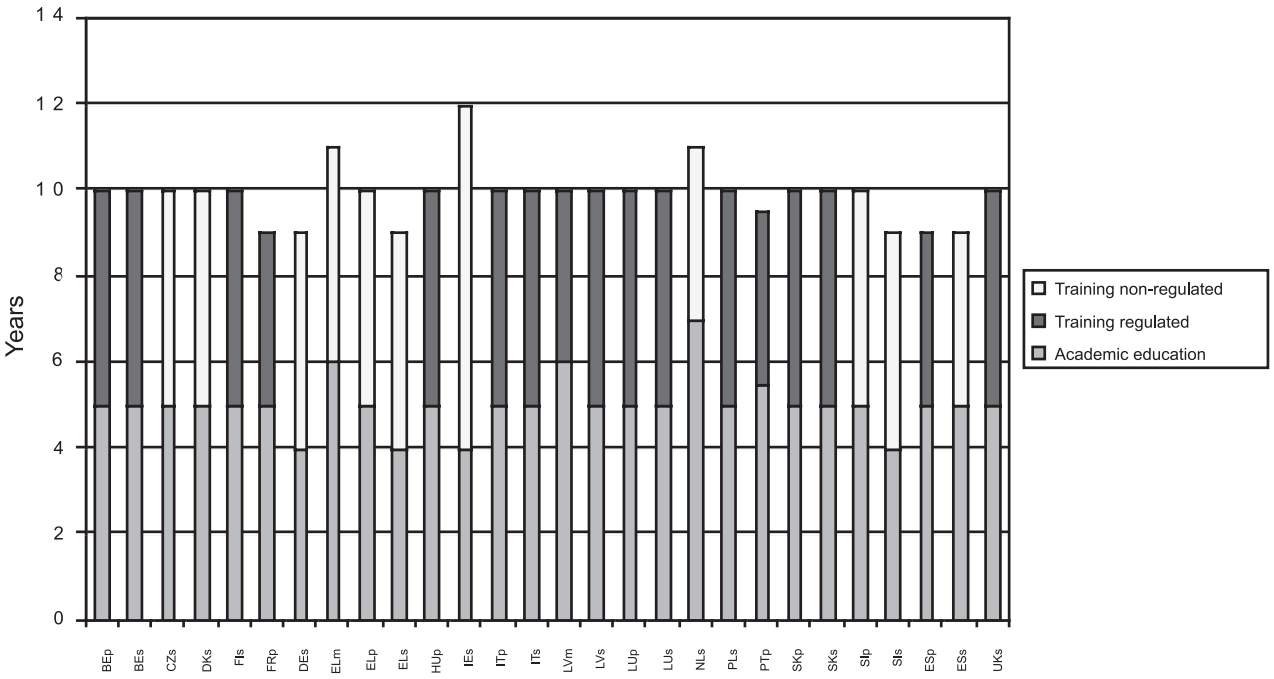

Figure 2. Duration of training for specialists in clinical chemistry and laboratory medicine in EU countries.

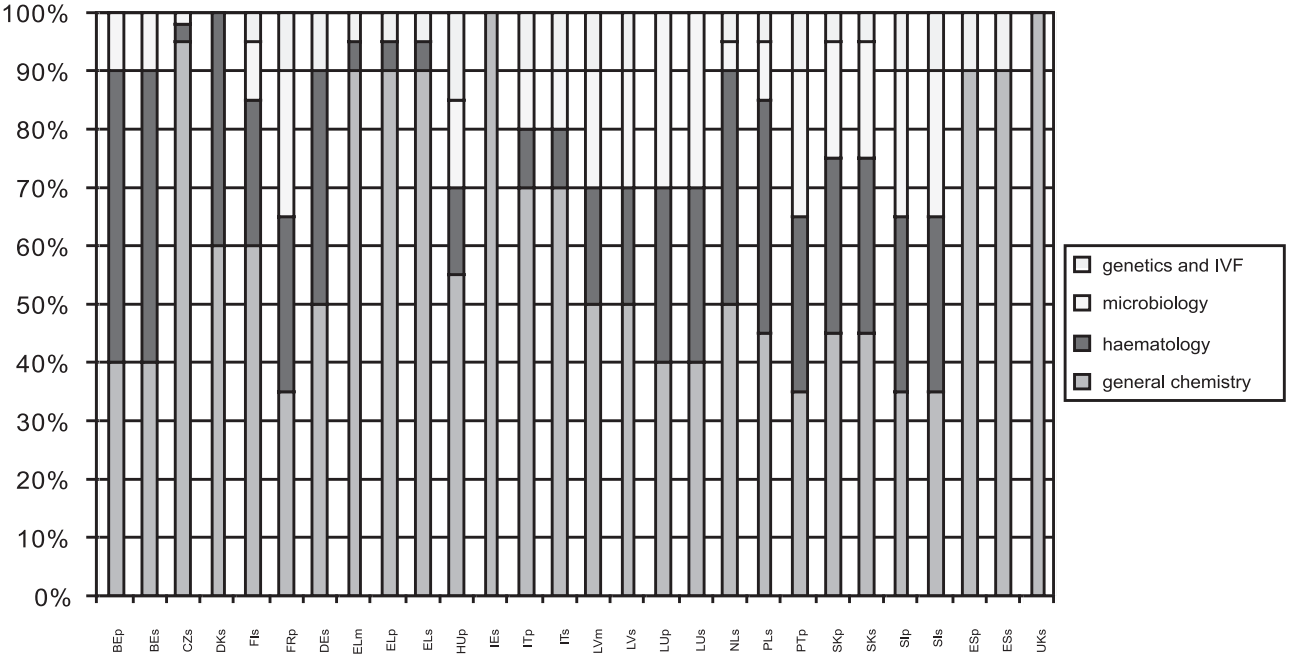

Figure 3. Content of training for specialists in clinical chemistry and laboratory medicine in EU countries.

submitted an inventory of the education and training in the European Union, describing the differences between the countries, and an establishing document defining tools to balance the differences. Although an inventory was made including the medically educated professionals, the pertinent inventory for the Common Platform included only pharmacy and science educated professionals. Figure 2 shows the inventory of the duration and figure 3 of the content of the training in the EU countries.

The requirements for the duration of training, as defined in the establishing document of the Common Platform, and the tools to balance differences, comprise a total duration of 10 years (academic education plus training), total academic development of 5 years, including a minimum of 4 years completed with a master's in medicine, pharmacy or science, and flexibility in the remaining academic year, i.e. further academic education, or a PhD, or scientific research resulting in peer reviewed paper. Next a total training period of five years is required, including a structured training of a minimum of 4 years, registration in the appropriate national register if it exists, and flexibility in the remaining training year, i.e. extra academic education, or work experience, or extra training years, or courses, or traineeships.

The requirements and tools to balance differences for the content of the training include general chemistry 35%, general chemistry plus haematology 65%, and flexibility in the remaining 35%, preferably including microbiology and genetics/IVF, work experience, or accredited courses, or relevant exams of national training program, or traineeships.
To have the Common Platform adopted after presenting the platform to the European Commission, the Member States should be consulted, discussing the platform within the Group of Experts. Next a set of draft measures should be submitted to the « Article 54 Committee », and adoption of a European Commission decision should be obtained, which then should be followed-up.
Proposed directive on Services
Health care is presently excluded from the proposed directive on Services in the internal market. European Health Ministers have recently participated in a first round table discussion on Health Services. A broad public consultation was launched that focuses on how to ensure legal certainty for cross-border healthcare under EU law, and to support co-operation between the health systems of the Member States. The Commission will detail proposals in 2007. The objective is to seek views on how a clear legal framework can be ensured within which patients and health care professionals have the chance to move freely in Europe, while at the same time fostering sustainable health care systems. Very recently proposals were launched to re-include health care in the proposed Services directive.

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Ned Tijdschr Klin Chem Labgeneesk 2007; 32: 188-191

Mitochondrial medicine

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Do human disorders as diverse as diabetes, migraine, premature menopause, parkonsonism, blindness, deafness, cancer, cardiomyopathy and encephalopathy have a common denominator? The answer is yes, the above described disease states are just examples of the broad spectrum of clinical signs and symptoms associated with defects in the mitochondrial oxidative phosphorylation (OXPHOS) system. The reason for this large difference in pathology is not clear. Why do certain mutations in the mitochondrial OXHPOS complex II on the one hand lead to Leigh syndrome whereas on the other hand mutations in the same enzyme lead to hereditary paraganglioma? In this review we will not and cannot provide good answers to these questions, however we will highlight two of the aspects of mitochondria which can contribute to the clinical outcome of a defect in this organelle. Firstly, the great complexity of the OXPHOS system requires many genes for its assembly. Secondly, defects in this system will not only lead to decreased ATP production but also execute different cellular metabolic consequences.

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Many proteins involved in OXPHOS biosynthesis
In textbooks, mitochondria are often depicted as oval shaped organelles, which are the “power plants” of the cell. In these organelles the main production of ATP, the free currency of energy in a cell, is produced by the OXPHOS system (1). This system comprises five complexes (complex I-V) (Fig. 1) embedded in the mitochondrial inner membrane which are build from numerous peptides, called subunits. These subunits are encoded by both the mitochondrial and nuclear genome. For instance complex I, the largest complex of the OXPHOS system contains 45 subunits of which 7 are encoded by the mitochondrial