biomnis
SPECIALISED MEDICAL PATHOLOGY
Focus
issue 38

Accreditation in medical biology
reagent vigilance and external quality control evaluation

The choice of an assay system and the reagents that go with it must partly rely on organisational criteria and performance, which are notably founded on the information obtained relative to reagent vigilance and external quality control evaluations.

Since the 1998 European directive, in vitro diagnostic medical devices (IVDMD) no longer require national registration; currently they are labelled with the CE mark (order of 1st March 2001, implementing decree published in 2003 and 2004).

1. In vitro diagnostic medical device (IVDMD): definition

"Product, reagent, material, instruments and systems, their components and accessories, as well as their sample recipients, specifically destined for in vitro use, either singly or in combination, for the examination of samples from the human body, in order to provide information concerning a physiological or pathological state, whether confirmed or potential, or a congenital anomaly, to verify therapeutic measures, or to determine the safety of a sample of elements from the human body or its compatibility with potential receivers."

The procedure of CE marking

The placing on the market of annex II IVDMDs (see box) is done through batch control testing and the delivery of a conformity certificate by the notified organisms.

However, the CE marking procedure for devices not listed in annex II (the majority) requires "only" self-certification by the industrialist. The apposition of CE marking is the guarantee of its conformity to the essential requirements of conception, manufacturing and packaging that are linked to the safety and performance aspects of the products. However, the placing on the market of these devices is seemingly done without performing any checks, through simple notification to the competent authorities by the manufacturer or its authorised representative.

As it is, pathologists must read the reagent user notice very carefully; the information indicated is necessary for the correct and safe use of the device (be cautious of bibliographical references; bring all details of its use (false positives, false negatives etc.) to the attention of ANSAM (French National Safety Agency for Drug and Health Products).

DEVICES IN ANNEX II: REAGENTS AND REAGENT PRODUCTS, INCLUDING MATERIAL FOR CALIBRATION AND CONTROL PURPOSES

Auto tests

List A

- Determination of blood group antigens: ABO system: ABO1(A), ABO2(B), ABO3(AB) RH system: RH1(D), RH2(C), RH3(E), RH4(c), RH5(e), KEL system: KEL1(K)
- Detection, confirmation and quantification of HIV (1 and 2) / HTLV I and II/ hepatitis B/ hepatitis C/ hepatitis D. Additional requirements: combined antibodies tests/ HIV antigen and nucleic acid amplification techniques.

List B

- Duffy and Kidd blood group screening:
- Indirect antiglobulin test (IAT/RAI) (anti-erythrocyte screening)
- Detection and quantification of rubella and toxoplasma infections
- Diagnosis of the following hereditary disease: phenylketonuria
- Cytomegalovirus, Chlamydia infection screening
- Determination of the following HLA tissue groups: DR, A and B
- PSA tumour marker assay
- Reagents and software, designed to evaluate the risk of trisomy 21
- Auto diagnostic testing for measuring blood glucose levels

2. Reagent vigilance

The purpose of reagent vigilance is to monitor incidents and the probability of incidents occurring through the use of an IVDMD. The management team of the medical pathology laboratory (MPL) must designate someone responsible for the reagent vigilance and declare this on the ANSAM website. (http://ansm.sante.fr/var/ansm_site/storage/original/ application/716cf94ff93de26529b36a3231d65bbb.rtf)

NOTE: for laboratories based outside of France, please contact your local competent authorities for IVDMDs other than ANSM. In Ireland, this is the IMB (http://www.imb.ie/), in the UK it is the MHRA (http://www.mhra.gov.uk/#page=DynamicListMedicines)

Declaration of an incident or the possibility of an incident occurring: reporting obligations

The manufacturer or its authorised representative, the importer, the distributor, the health professionals using the device (pathologists, technicians, doctors and nurses) must report any failure or alteration of an IVDMD that could cause adverse effects on the health of a person to the ANSM immediately. The manufacturer or its authorised representative must inform

ANSM of all IVDMD follow-ups and report, upon request, any useful information concerning the implementation of patient health protection measures.

The declarant: the person responsible for declaring incidents or the probability of an incident occurring that have been reported to them to ANSM This includes:

- local reagent vigilance correspondents of health establishments and blood transfusion establishments;
- health professionals using the devices who do not work in a health establishment or a blood transfusion establishment (no local reagent vigilance correspondent);
- manufacturers, authorised representatives, importers and distributors. In this case, the declaration is made by the person in charge of reagent vigilance, who is designated by the manufacturer or its authorised representative.

The reporter: a health professional who uses an IVDMD and who notices an incident or the possibility of an incident involving the device occurring. He/she reports this, using a previously defined support, to the local reagent vigilance correspondent within their establishment.

In practice, the declaration is made using a reagent vigilance declaration report form (on the ANSM website).
For health establishments and blood transfusion establishments, except in the case of an emergency, the form will be completed by the local reagent vigilance correspondent who works in cooperation with the reporter. In the case of an emergency, it is the reporter who declares the incident directly to ANSM, he/she then informs the correspondent at a later date.

Declaration of an incident or the possibility of an incident occurring: points to be verified by the declarant before completing the form.

- the IVDMD was used according to the manufacturer's instructions given in the leaflet or user manual;
- the incident is not linked to possible interference or to known restrictions in the method;
- maintenance of the IVDMD has been performed;
- all the rules defined by the GBEA have been respected.

ANSM's duties

The declaration of any incident or the possibility of an incident occurring leads to the registration, evaluation and exploitation of this information, the performance of studies on the quality or safety of use of the IVDMD and the implementation and the following of corrective actions decided upon.

The pathologists must declare all incidents (it is the number of declarations that count). These declarations do not necessarily lead to the removal of the batch of reagents, but, for example to the updating of leaflets (which allows the system to run).

If necessary, upon ANSM's agreement on the contents of the document, the incident is diffused in the form of a letter by the manufacturer to the directors of health establishments, laboratory managers and reagent vigilance correspondents, as well as the ANSM's website (http://www.ansm.sante.fr)

3. External quality control evaluation (EQC)

Further to the order of 13 January 2010 relative to medical pathology, an evaluation of unknown sample results for all pathology investigations is obligatory. This obligation is removed when no **European** organism offers an adapted EQC service.
Once the MPL has been informed, the EQC organisms must report anomalies noticed during control testing that could lead to a major risk to patients' health to the regional health agency. EQC organisms must be accredited in accordance with the standard EN 17043. Their list (not exhaustive) is found on the Cofrac document (LAB INF 19): "List of inter laboratory comparison organisms".

National Quality Control (NQC): what you need to know...

Since the decree of 7 December 1978, MPLs must participate in NQC, which is, at present, organised by ANSM.
After the closing of a NQC operation, ANSM fully analyses the results provided by the laboratories and, if necessary, proceeds with discussions with the manufacturers (reagent vigilance). An individual report is sent to the MPL after each control test operation, an individual report of participation in NQC operations and a quality indicator is supplied thanks to the overall result of the results analysed. Furthermore, the NCQ annals are published on the ANSM website, they are a rich source of information, and a highly recommended read!

Quality indicator or QI_{NQC}

- **for quantitative analysis:** the result R of the MPL is compared to all of the results obtained by the MPL using the same IVDMD. R is evaluated in relation to a target value M (mean or trimmed mean). The difference is expressed as a normalised standard deviation (SD) or in acceptable limits (AL) and grades are given accordingly: A, B (good results), C, D (to be repeated).
- **for qualitative tests:** the answer is nominal (e.g.: identification of a bacteria, specificity and anti-nuclear antibodies) or binary (e.g.: "positive/negative", "absence/presence"). The result is interpreted as **A:** a good result **B:** an acceptable result, **C:** error, or **D:** major error.

This evaluation provides a calculation for the year giving an "overall evaluation of laboratory quality score " (A = 4, B = 3, C = 1, D = 0), expressed as a percentage of the maximum value that the laboratory is likely to obtain.

Quality indicator or QI_{NQC}

$$= \frac{[\,(\text{Nb A} \times 4) + (\text{Nb B} \times 3) + (\text{Nb C} \times 1) + (\text{Nb D} \times 0)\,]}{[\text{Nb of total results} \times 4] \times 100}$$

In the case of a punctual non-satisfactory result from a NQC, you must react: do a cause analysis, perform a study on the possible consequences on examination validity and mend errors (non-conformity and tracked corrective actions). Without a reaction, a COFRAC auditor can refuse or suspend the accreditation for the group of tests or the test(s) in question.

Carole Emile, following a communication from Bach-Nga Pham, CNRGS (The French national reference centre for blood groups), INTS, Paris.