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Assessment of Package Inserts for Diagnostic Kits

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To assure the quality of service in laboratory medicine, it is necessary to implement a quality system which comprises the entire testing process. The use of quality reagents is an important aspect of the process. Despite the fact that it is the responsibility of the laboratory to ensure the quality of the analytical system (including reagents) and since it is impossible to evaluate all commercial diagnostic kits, the laboratory often depends on statements issued by the manufacturer to select the most appropriate diagnostics for a particular laboratory.

In this study we report the results of the analysis of information provided in 887 package inserts enclosed in the more widely used commercial diagnostic kits, following the Standard for the labelling of clinical laboratory materials of the European Committee for Clinical Laboratory Standards (ECCLS). Only a third of these were in agreement with the guidelines of ECCLS Standard, reporting complete and correct information. We believe that it is necessary to implement a constructive cooperation between manufacturers of diagnostic materials and clinical laboratories to produce a more uniform approach to improvements in laboratory quality assurance.

Key words: External quality assurance; Package insert; Diagnostic kit.

Introduction

It has long been recognized that identifying and thoroughly describing the materials used in the laboratory is an important step in "good laboratory practice".

In 1971 the National Committee for Clinical Laboratory Standards (NCCLS) formed the Area Committee on Labelling to establish criteria for general labelling of laboratory reagents. The first standard, which identified the information required for labelling materials in the clinical laboratory and specified the minimum information to be given in a package insert for a kit, was approved in 1975 (1).

In 1985, the European Committee for Clinical Laboratory Standards (ECCLS) issued the document "Standard for the labelling of clinical laboratory materials" (2), which was based on, and was almost identical to, the guiding principles in the WHO Memorandum (3). It was also essentially similar to the recommendations published by the International Federation of Clinical Chemistry (IFCC, now International Federation of Clinical Chemistry and Laboratory Medicine) in 1978 (4). The current Standard on labelling EN 375, published in 1992 by the European Committee for Standardization (CEN), considers the same steps, but its requirements are sketchy compared to those of the ECCLS Standard (5). Therefore, in our evaluation we referred to the recommendations of ECCLS Standard.

This standard gives recommendations for labelling clinical laboratory materials, kits and kit components, reference materials, including calibrators and control materials, and where applicable, general laboratory materials.

For the package insert for a diagnostic kit in particular, the Standard specifies the following:

1. *Product name*
2. *Intended use(s)*
3. *Principle of test* with appropriate literature references
4. *Precautions*
5. *Suitability for use*: physical, biological, or chemical signs of instability or deterioration
6. *Reagents:* name, quantity, proportion or concentration of each reactive component and description of the other components such as additives which, if not known to the user, could affect the proper performance of the test; lists of materials supplied by the manufacturer and of those required but not supplied
7. *Equipment*
8. *Specimens:* special precautions for specimen collection including special preparation of the patient; additives; known interfering substances; and storage and handling instructions for maintenance of sample stability
9. *Procedure:* detailed description of each step required for the proper performance of the test (instructions for the preparation, stability and maintenance of the work solutions); calibration procedures; user's quality control procedure including recommended method of use of appropriate controls; experimental conditions with tolerance limits that must be met (e.g. pH, temperature, times for specific steps, wavelengths, and stability of final reaction mixture); calculation of results
10. *Discussion:* advantages, limitations (e.g. cross-immunoreactivity), expected range of results (with details of how data were derived, including the reference population studied); the value obtained after calibration of the kit against a specified recognized reference material; performance characteristics of the method (imprecision, specificity, test

range, linearity, sensitivity, comparison between methods)

11. *Supplier:* name and address of the manufacturer from whom further information on the product can be obtained
12. *Date:* when the package insert was issued or last revised.

Although the above standard has been available since 1985, only some manufacturers specify their methods according to it, and the identification of the method by package inserts can be difficult, because they sometimes lack the correct specification of the method's features.

Materials and Methods

The Center of Biomedical Research (CRB), which organizes the External Quality Assurance (EQA) programs for the Veneto Region of Italy, has evaluated the essential information provided in the package inserts for diagnostic kits that each laboratory, attending a specific scheme of the program, forwards to CRB for the classification of methods.

We analyzed 887 package inserts enclosed in the more widely used commercial kits for determining 32 constituents of clinical chemistry, seven of which were specific proteins and nine of which were enzymes: sodium, potassium, chloride, copper, calcium, phosphate, iron, magnesium, glucose, urea, creatinine, uric acid, cholesterol, triglycerides, total bilirubin, total proteins, albumin, α_1-glycoprotein, haptoglobin, transferrin, IgA, IgG, IgM, alanine and aspartate aminotransferases, γ-glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, creatine kinase, total amylase, pancreatic amylase and cholinesterase; (Table 1).

Results

Only 285 package inserts contained all the information required by the ECCLS Standard; another 544 allowed a correct classification of the method for which the kit was employed, but lacked important information, for example the performance characteristics (accuracy, precision, specificity, test range, linearity, sensitivity, expected range of results and limitations of the procedure).

Thirty-three package inserts, particularly for enzymes determination, did not describe in detail the chemical composition of the reagents (e.g. the buffer of choice was not specified or the substrate for amylase was reported as "blocked" p-nitrophenylmaltoheptaoside without specifying the blocking agent), the initial concentration of the reagents or, even worse, the final concentration of the components of the reaction mixture.

Tab. 1 Evaluation of package inserts following ECCLS Standard.

Constituents	Number of different manufacturers	Number of different package inserts	Package inserts with complete and correct information	
			(n)	(%)
Sodium and potassium	17	22	12	55
Chloride	18	23	11	48
Copper	9	10	0	0
Calcium	25	37	16	43
Phosphate	28	36	14	39
Iron	23	33	9	27
Magnesium	24	31	10	32
Glucose	26	40	16	40
Urea	28	40	17	43
Creatinine	23	38	13	34
Uric acid	27	38	13	34
Cholesterol	29	40	14	35
Triglycerides	29	39	15	38
Total bilirubin	27	40	14	35
Total protein	26	40	13	32
Albumin	21	31	13	42
α_1-Acid glycoprotein	9	11	4	36
Haptoglobin	7	8	2	25
Transferrin	10	11	3	27
IgG–IgA–IgM	11	12	4	33
Aspartate aminotransferase	28	42	7	17
Alanine aminotransferase	27	41	7	17
γ-Glutamyltransferase	25	38	7	18
Alkaline phosphatase	25	47	17	36
Lactate dehydrogenase	26	41	13	32
Creatine kinase	21	30	8	27
Total amylase	25	35	6	17
Pancreatic amylase	2	2	–	–
Cholinesterase	21	31	7	23

Twenty-five package inserts gave indications that were misleading to the users, since they declared that the reagents formulation was in agreement with the recommendations of a scientific society while the final concentrations were quite different from those recommended, if not even in accordance with those of a different society. For example, a package insert of a kit for the determination of lactate dehydrogenase declared that the method followed the IFCC recommendations, based on the conversion of lactate to pyruvate with reduction of NAD^+ (6). Instead, the substrate used in the kit was pyruvate and consequently the reaction was based on the conversion of pyruvate to lactate.

Discussion

To ensure quality of service in laboratory medicine, a quality system that comprises the entire testing process is required. The use of quality reagents is an important aspect of the process. Although it is the responsibility of the laboratory to ensure the quality of the analytical system (including reagents), it is not yet possible to evaluate all commercial diagnostic kits, and the laboratory often depends on statements issued by the manufacturer to select the most appropriate reagents for a particular laboratory.

This study raises the question of the completeness and/or the accuracy of information given in the package inserts of kits issued by the manufacturer. In fact, on the basis of the present evaluation, only a third of the package inserts (issued by 13 out of 45 different manufacturers) reported complete and correct information.

From a practical view point, not only the inaccuracy but also the simple incompleteness of information in the package inserts has important repercussions: it can induce users to make distorted technical choices; it also precludes the correct evaluation of results for homogeneous methods in EQA programs; it can induce inaccurate writing out of the procedures required to perform analytical tests by certification/accreditation programs, in the implementation of a quality system.

In conclusion, to follow the process of certification/accreditation in the qualification of clinical laboratory suppliers (7, 8), the users should carefully examine the documentation in order to evaluate the competence of the manufacturers and the quality of their products, as manufacturers should conform to recommendations established by a recognized body in order to be fully qualified suppliers.

It is necessary, therefore, to implement a constructive cooperation between manufacturers of diagnostic materials and clinical laboratories in order to produce a more uniform approach to improvements in laboratory quality assurance.

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