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The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

eJIFCC

Harmonization initiatives in Europe

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ARTICLE INFO

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Key words:
harmonization, total testing process

ABSTRACT

Introduction: Modern medicine is more and more based on protocols and guidelines; clinical laboratory data play very often a relevant role in these documents and for this reason the need for their harmonization is increasing. To achieve harmonized results the harmonization process must not be limited to only the analytical part, but has to include the pre- and the post-analytical phases.

Results: To fulfill this need the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has started several initiatives. A Working Group on harmonization of the total testing process (WG-H) has been created with the aims of: 1) surveying and summarizing national European and pan European harmonization initiatives; 2) promoting and coordinating the dissemination of especially promising harmonization initiatives among the EFLM member societies; and 3) taking initiatives to harmonize nomenclature, units and reference intervals at a European level. The activity of the WG started this year with a questionnaire targeted at surveying the status of various harmonization activities, especially those in the pre- and post-analytical phase categories, among the European laboratory medicine societies.

Conclusions: Based on the results of the questionnaire, some activities promoting the dissemination of best practice in blood sampling, sample storage and transportation, in collaboration with WG on the pre-analytical phase, will be promoted, and initiatives to spread to all the European countries the use of SI units in reporting, will be undertaken. Moreover, EFLM has created a Task and Finish Group on standardization of the color coding for blood collection tube closures that is actively working to accomplish this difficult task through collaboration with manufacturers.

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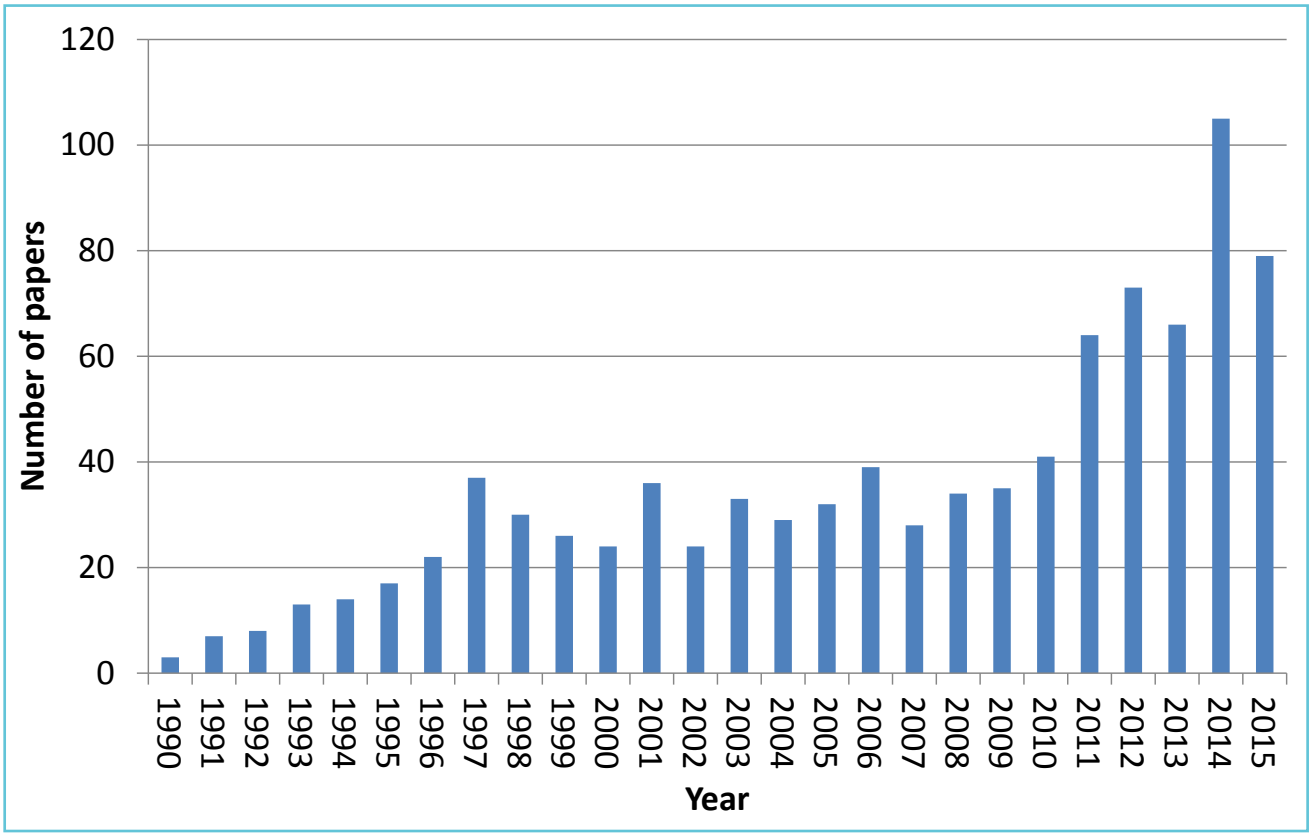
INTRODUCTION

In the last few years there has been a continuous growth in the awareness of the importance of harmonization in all medical fields. A PubMed search for the words "harmonization" or "harmonisation" in the title field resulted in 972 items, with a sharp increase in the numbers of publications in the last 5 years (fig. 1).

The importance of harmonization in Laboratory Medicine and the reasons for improving it are clearly stated in several papers (1-6). The message that comes from these papers is that the standardization of the analytical phase is crucial, but the harmonization process has to include the total testing process, from the pre-pre-analytical to the post-post-analytical phase (2-6).

Starting from these considerations, the Executive Board of EFLM (European Federation of Clinical Chemistry and Laboratory Medicine) decided to create an ad hoc working group within the Science Committee.

Figure 1 Papers in PubMed with the word "harmonization" or "harmonisation" in the title (last 25 years)



The Working Group on the "Harmonisation of total testing process" (WG-H) has the following terms of reference:

- Survey and summarize national European and pan European harmonization initiatives.
- Promote and coordinate the dissemination of at least two especially promising harmonization initiatives among the EFLM Member Societies.
- Undertake initiatives to harmonize nomenclature, units and reference intervals at a European level.

The plan of action for the first two years is the following:

1. WG-H will act as a collector of the harmonization initiatives arising from other WGs or Task and Finish Groups of EFLM and from National Member Societies active in the field and will disseminate them to all the EFLM Member Societies to monitor their application and effects.
2. WG-H will survey and promote the use of harmonized nomenclature for measurands and promote the use of amount of substance units in the European countries.
3. WG-H will promote the implementation of common reference intervals for the measurands where this approach is feasible.

The European situation regarding harmonization is particularly critical essentially for two reasons: there are many different countries (the members of EFLM equal 40), each one with unique traditions, culture and legislation as well as many different languages. The first initiative taken by the WG-H was a survey aimed at identifying those harmonization initiatives already in place in the different European countries and to obtain a picture of the units of measurement presently in use.

EFLM SURVEY ON HARMONIZATION OF TOTAL TESTING PROCESS

The survey aimed to collect information on the harmonization activities already carried out, or currently on-going, by the different national societies of Europe. It was mainly based on the ideas presented in the references 4 and 5 and covered the 3 main phases of the clinical laboratory process: pre-analytical (8 questions), analytical (5 questions) and post-analytical (8 questions). It was distributed to the Presidents and National Representatives of the 40 EFLM Member Societies in 2 phases. In the first phase held at the end of March 2015 the complete survey consisting of 21 questions was sent out. After an evaluation of the replies received from 22 National Societies, it was decided to send a second reduced version (with only 9 of the original 21 questions) and to focus on the most relevant aspects of the pre- and post-analytical phases. This second questionnaire was sent in July 2015 only to the representatives of the 18 National Societies that did not reply in the first phase. This second phase was successful and we received 14 replies, with only 4 countries not responding, hence allowing us to draw an almost complete picture of the European situation regarding the harmonization activities in the pre- and post-analytical phases.

I will present hereafter only the results relative to the 9 questions that received a reply from 36 out of 40 countries.

Questions on harmonization activities in the pre-analytical phase

1. *Is it common practice in your country to use "profiles" (e.g. liver function, electrolytes, etc.) for test requesting?*
2. *If YES, did/does your society produce some document on harmonization of test requesting profiles?*

The questions aimed at identifying how widespread the practice of requesting tests by profiles instead of test by test was and if the societies gave any indication of their intention to standardize the content of each profile (e.g. Electrolytes as only sodium, potassium and chloride or to include also bicarbonate and anion gap). Twenty countries replied that the use of profiles is common practice, but only 7 of them had undertaken test profile harmonization initiatives and only 3 sent us their practice documents indicating the suggested profile contents (Russia, Kazakhstan, The Netherlands); unfortunately all were in the national language and were not understandable (a translation is in progress).

3. *Did/does your society, alone or in collaboration with clinical societies, elaborate guidelines for diagnostic approaches to specific diseases? (e.g. myocardial infarction, coeliac disease, etc.)*

Eighteen societies gave a positive reply and we received several documents. The topics addressed were the following: Autoimmune diseases, Coeliac disease, Chronic Kidney Disease (CKD), Diabetes and Gestational Diabetes, Dyslipidemia and Lipoprotein reporting, Myocardial infarction (MI), Proteinuria, Thyroid diseases and Thyroid disease in pregnancy, Tumor markers.

Several topics (diabetes, MI, CKD, tumor markers) were covered by guidelines in various countries; the material received was heterogeneous and, as expected, in many different languages. The WG-H has not yet been able to examine all of them in detail, but probably there is a need to promote European or international guidelines from which each country can derive its own document. In this way all 40 countries will be able to propose a harmonized approach to the diagnosis of at least the most common diseases.

4. *Did/does your society publish indications for optimal timing for test repetition or minimal retesting intervals?*

Most of the replies (30) were negative with 6 positive. However, only the UK has officially published a document (7). The minimum retesting interval is an important element for governing the appropriateness of test requesting and initiatives to expand similar documents at the European level are planned.

5. *Did/Does your society produce a document on quality of the diagnostic samples or have some activity currently on this topic?*

This is a very sensitive topic, especially in this period when centralization and laboratory consolidation is occurring throughout Europe. Twenty-two societies replied 'No', 14 'Yes' and two of them (Spanish and German Societies) sent us very detailed documents. The EFLM working group on the pre-analytical phase (WG-PRE) is working on this matter and specific documents are in preparation.

Another important harmonization activity in the pre-analytical phase is the harmonization of blood sampling processes. Several European scientific societies have produced documents on this topic namely: Italy (8, 9), Croatia (10), Slovenia, Norway, Russia, and The Netherlands. Moreover the EFLM WG-PRE has already prepared a specific document (11) after conducting a survey of national guidelines, education and training in phlebotomy (12).

An important initiative for the safety of the operator during blood drawing is the European Directive 2010/32/EU implementing the Framework Agreement on prevention from sharps injuries in the hospital and healthcare sector concluded by HOSPEEM (European Hospital and Healthcare Employers' Association) and EPSU (European Federation of Public Service Unions) (13). This directive has been converted in national law by each member state, but its application is not yet

complete and the use of safety-engineered devices for blood sampling has to be fully implemented.

A comprehensive overview of harmonization activities in the pre-analytical phase was published by the EFLM WG-PRE (14).

A further harmonization initiative of EFLM is the creation of a Task and Finish Group on Standardization of the colour coding for blood collection tube closures. This group is trying to define a road map to arrive at a uniform coloring of the tube caps produced by the different manufacturers with the aim of reducing the possible errors when changing manufacturer or when receiving tubes from different laboratories (15). All stakeholders, including all manufacturers working in the field, have been invited to join a dialogue to establish a universally acceptable colour coding standard for blood collection tube closures.

Table 1 Current use of SI units in Europe

	Nation	Use of SI units	Intention to promote SI		Nation	Use of SI units	Intention to promote SI
1	Albania	<10%	NO	21	Latvia	-	-
2	Austria	-	-	22	Lithuania	>80%	Yes
3	Belgium	50 – 80%	Yes	23	Luxembourg	-	-
4	Bosnia Herzegovina	100%	Yes	24	Macedonia	>80%	Yes
5	Bulgaria	100%	NO	25	Montenegro	>80%	Yes
6	Croatia	>80%	Yes	26	Norway	>80%	Yes
7	Cyprus	<10%	NO	27	Poland	50 - 80%	Yes
8	Czech Republic	>80%	NO	28	Portugal	10 – 25%	NO
9	Denmark	>80%	Yes	29	Romania	10 – 25%	Yes
10	Estonia	50 – 80%	Yes	30	Russia	100%	Yes
11	Finland	>80%	Yes	31	Serbia	100%	Yes
12	France	100%	Yes	32	Slovak Republic	>80%	Yes
13	Germany	25 – 50%	Yes	33	Slovenia	100%	Yes
14	Greece	<10%	Yes	34	Spain	<10%	Yes
15	Hungary	>80%	NO	35	Sweden	>80%	Yes
16	Iceland	>80%	Yes	36	Switzerland	>80%	Yes
17	Ireland	<10%	Yes	37	The Netherlands	>80%	Yes
18	Israel	<10%	Yes	38	Turkey	<10%	Yes
19	Italy	<10%	Yes	39	Ukraine	100%	Yes
20	Kosovo	-	-	40	UK	>80%	Yes

Questions on harmonization in the post-analytical phase

1. *Did/does your society make documents or guidelines on use or definition of autovalidation rules?*

Six societies replied 'Yes', but only Switzerland supplied a document that is now in evaluation for possible promotion at the European level.

2. *Do you have any data on the diffusion of the use of SI unit (amount of substance units, e.g. mmol/L) in your country?*
3. *Did/does your society promote officially the use of SI units?*
4. *Would your society be in favour of initiatives devoted to the introduction of SI units (mmol/L)?*

The replies to these questions are summarized in Table 1 (above).

After the distribution of the survey we posed a further question on the use of katal for the expression of enzyme catalytic activity. Five countries replied that µkat/L is the unit used by all of the clinical laboratories in Slovenia, Slovakia, Sweden, Czech Republic and Ukraine, 22 use U/L and we received no replies from the 13 other countries.

Another critical issue of the post-analytical phase that requires harmonization is the communication of critical values. EFLM has established a Task and Finish Group with the aim of surveying the critical result management procedures and policies laboratories currently have and how critical values are established and used in European laboratories.

CONCLUSIONS

There are several harmonization initiatives in place in different European countries, but these initiatives are not coordinated. The problem of the different languages precludes the possibility of sharing easily the documents within Europe. EFLM WG-PRE has produced several documents on which harmonization of several aspects of the pre-analytical phase can be based. Implementing these on a European scale and verifying the effectiveness of their application will be the real challenge for the future. The harmonization and standardization of the analytical phase is already covered at the international level by IFCC and by the American Association for Clinical Chemistry's International Consortium on Harmonization of Clinical Laboratory Results (AACC ICHCLR) (1). EFLM is now working on the definition of quality performance specifications (16) that represent the basis for the harmonization of analytical quality.

The most problematic situation regards the post-analytical phase. The unit of measurement problem is really important. While most of the northern European countries (excluding Ireland) declare an almost total adoption of the amount of substance (mole) unit for expressing the laboratory results, the southern countries (Spain, Italy, Albania, Greece, Turkey, Cyprus) are still using traditional units and in some countries like Italy, clinical laboratories use up to 5 different units for the same test (e.g. Free T3: pg/mL, ng/L, pmol/L, pg/dL and ng/dL). Moreover, many of the countries that adopted the SI units do not use katal for reporting enzymatic activity. It may be easier to ask countries that adopted katal to change back to international units rather than moving all the others to katal. Changing old habits is difficult, and requires coordination and collaboration; however, some countries like Albania, Cyprus and Portugal have declared that they are not in favor of any change. WG-H will promote initiatives in the southern European countries to gradually move toward a larger use of the SI units, starting with electrolytes. Finally the problem of reference intervals remains untouched. Initiatives, similar to the Australasian one (17), are very difficult at the European level.

There is an initiative in the UK (18) and the previous studies of the Nordic Countries (19) but I do not foresee pan European initiatives in the short period except for a few specific analytes.

Most of the work has yet to be done – we are just at the beginning. Communication and collaboration with the National Societies will be the key to achieving some progress in this field which is crucial not only for our profession but for medicine as a whole.

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