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Assessing post-analytical phase harmonization in European laboratories: a survey promoted by the EFLM Working Group on Harmonization

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Abstract

Objectives: Harmonization of the laboratory total testing process (TTP) is critical to improving patient outcome. In 2016, an EFLM survey on the harmonization of TTP underlined the serious shortcomings pertaining to the post-analytical phase. In 2023, the WG-H conducted a new survey aiming to update information in the 2016 harmonization report in order to ascertain whether countries that had declared they were keen to adopt SI units had continued with this program, the aim being to verify the state-of art in harmonization units in areas of laboratory medicine not included in the previous survey.

Methods: Questionnaires were distributed to the Presidents and National Representatives of EFLM Full Member Societies and EFLM affiliate Members. The survey questions were grouped into three categories: measurement units, reference intervals, and nomenclature/terminology, and results were evaluated using Survey Monkey software and Excel.

Results: A total of 123 questionnaires from 31 countries were analyzed. A trend (+19.3 %) was observed toward a wider use of SI units for general clinical biochemistry parameters. The results for tests not included in the 2016 survey (i.e., endocrinology diagnostics and coagulation panels), demonstrated that for reports on hormones, responses were satisfactory, 70–90 % of the responders adopting the recommended units, whereas for coagulation test panels, a serious lack of harmonization was found, "seconds", which are inaccurate and not recommended, being widely used units (91 %).

Conclusions: The findings made in the 2023 survey demonstrated a progressive, albeit slow, improvement in harmonization reports. However, further efforts at improvement are mandatory.

Keywords: harmonization; measurement units; reference intervals

Introduction

The conventional "brain-to-brain loop" model developed by George Lundberg and revised by Mario Plebani divides the laboratory total testing process (TTP) into three phases: pre-analytical, analytical, and post-analytical [1, 2]. Each phase is of fundamental importance in ensuring a reliable laboratory test result that supports and guides clinicians toward the appropriate management of patients throughout the healthcare process.

Laboratory TTP harmonization is crucial to improving patient outcome through the provision of accurate and actionable laboratory data [3, 4]. The Working Group on Harmonization (WG-H) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Science Committee is dedicated to the promotion of harmonization activities among EFLM member societies.

In 2016, the results of an EFLM survey on harmonization of TTP [5] evidenced great heterogeneity in all three phases, showing, in particular, that the post-analytical phase is open to the most criticism. It is well known that this phase includes reporting and interpretation of laboratory test results and, consequently, the harmonization of this phase aims to attenuate differences in laboratory reports in order to produce interchangeable, comparable data. The survey revealed two relevant aspects: (i) the failure to adopt standard international (SI) measurement units in several countries; (ii) for traditional reasons and resistance to change, a lack of criteria enabling the adoption of harmonized reference intervals, and harmonization initiatives. Such shortcomings, in the era of intensive mobility,

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raise the question of patient safety and call for prompt action, however, in this 2016 survey, some countries that were not using SI units, declared their intention to change (8/40, 20 %).

In 2023, the WG-H promoted a new survey focusing on the post-analytical phase of the laboratory TTP with a dual purpose: (i) to update information related to harmonization issues in order to verify whether, at least those countries that in the previous questionnaire had declared their interest in adopting the SI units, had continued with this program in the subsequent seven years; (ii) to verify the state-of-art in the harmonization of the measurement units in different and clinically relevant areas of laboratory medicine, not included in the previous survey.

In the present article, we analyze the responses collected during the 2023 survey as starting point for discussing advances and challenges in the harmonization process in Clinical Laboratory Medicine.

Materials and methods

The questionnaire, designed by the members of the EFLM WG-H, was distributed to the Presidents and National Representatives of the 41 EFLM Full Member Societies and 9 EFLM affiliate Members. Prospective participants were invited to take part in the survey by email; each participant could join only once. Since participants could skip some questions, not all completed the questionnaire. The SurveyMonkey platform (SurveyMonkey Inc.), used to administer the questionnaire, was accessible from July through November 2023.

General information provided included the name and surname of the responder, name of the EFLM National Society, and home country. Further survey questions (Table 1) were grouped into the following three categories:

(1) Measurement units (4 questions);
(2) Reference intervals (3 questions);
(3) Nomenclature/terminology (1 question).

The results of the survey were evaluated by one of the authors [LA] using the Survey Monkey software and Excel (Google sheets). Participants who failed to provide information on their National Society or Country were excluded from the analysis.

Results

General information

Among a total of 225 questionnaires collected from the survey, 102 were excluded from the final analysis because the National Society and/or home Country were not stated by

Table 1: The survey.

Category	Question	Answer
1. Measurement units	1.1 How is regulated use of measurement units for laboratory results reporting in your country?	– By governmental body – By official professional organization (e.g., professional chamber/ association) – By national society – There are no regulations related to use of measurement units on national level – Other (please, specify)
	– 1.2 Please, indicate the estimated extent of use SI measurement units in laboratories in your country (example of SI measurement units – glucose mmol/L):	– >80 % – 50–80 % – 25–50 % – 10–25 % – <10 %
	– 1.3 Does your national society scientific journal support study result reporting in SI units?	– Yes – No – Not applicable
	– 1.4 Please, indicate those measurement units used in laboratory practice in your country	**Cholesterol** – mg/dL – mmol/L – g/L **Total protein** – g/L – g/dL – **Calcium** – mmol/L – mg/dL – mEq/L **Iron** – µmol/L – µg/dL – µg/L **Hemoglobin** – g/L – g/dL – mmol/L **IgG** – g/L – mg/dL **C-reactive protein** – mg/L – mg/dL **Free T4** – pmol/L – ng/dL – ng/L – pg/mL **Prolactin** – mIU/L – ng/mL – µg/L **Progesterone** – nmol/L – ng/mL – µg/L **aPTT** – s -ratio -s and ratio **PT** – s -% -ratio -INR – combination (please, specify) **Blood leukocyte count** -10^9/L -/µL – other (please, specify)
2. Reference intervals	2.1 How are defined reference intervals for	– Harmonized by professional organization

Table 1: (continued)

Category	Question	Answer
	the routine analytes in your country?	– Harmonized by national society recommendation – Harmonized by international studies – Each laboratory uses its own RIs (from different sources) – Other (please, specify)
	2.2 Does your national society scientific journal support study result reporting in SI units?	– Yes – No
	2.3 For those laboratories using its own RIs, please, estimate percentage of source:	– RIs defined by their own validation study – RIs based on manufacturer's declaration – RIs based on various literature – Other (please, specify)
3. Nomenclature/ terminology	Please, specify the level of harmonization in nomenclature/terminology adopted in your country, for analytes in specific fields of laboratory diagnostics classifying from 1 (lowest degree of harmonization in terminology) to 5 (highest level of harmonization)	– Clinical biochemistry analytes – Hematology – Coagulation testing – Endocrinology – Tumor markers – Immunology – Allergy testing – Molecular testing

the responder, a total of 123 questionnaires from 31 countries being analyzed (Figure 1). Feedback from 10 countries (i.e., Austria, Germany, Iceland, Kosovo, Montenegro, Netherlands, North Macedonia, Poland, Slovenia, and Ukraine) was not provided. Participation varied from country to country: for 10 Societies, only one member participated in the survey, while for the remaining societies, several members (2–27) participated: the Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC, Italy) and Georgian Laboratory Medicine Association (Georgia), provided the largest number of completed questionnaires (Figure 2).

Measurement units

In this section (Table 1; 1.1), the state of the art in the measurement units' harmonization across different countries is investigated.

The first question explored was whether, in each country, a regulatory approach or a scientific body had been established in order to manage the harmonization of laboratory test results reporting: 52 % of the participants declared that no regulation existed for the adoption of the measurement units (neither traditional nor SI), while 28 % responded that the adoption of the measurement units was regulated by national societies or official professional organizations (Italy, Slovakia, Czech Republic, Bosnia-Herzegovina, Serbia, Hungary, Albania, Croatia, Norway, United Kingdom) and 13.8 %, by a governmental body (Russia, Turkey, Sweden, Belgium, Lithuania, Bulgaria, Israel, Denmark).

The second question was designed to ascertain the rate of SI use in each country. Most countries (55 %) indicated "more than 80 %" (Figure 3). Answers from Georgia and Italy were heterogeneous: 51 % of the responders from Georgia reported 50–80 %, and 28 %, more than 80 %; 53 % of responders from Italy reported that SI units were used by 25–50 % of the laboratories, and 21 % by more than 80 %.

In order to clarify the role of the national scientific societies and the national scientific journal in promoting and to supporting the use of the recommended SI units, the following non-specific question was introduced: *Does your national society scientific journal support study result reporting in SI units*?. Almost all participants belonging to the Societies with an official journal gave an affirmative response, except Finland, Greece, Latvia, and Romania.

The last question in this section, concerned the use of SI units in laboratory practice for each country. However, several participants (76 %) skipped this question, no answer being provided by the members of four national societies (Order of Biochemists, Biologists and Chemists in the Romanian Health System, Romanian Society; Société Luxembourgeoise de Biologie Clinique, Luxembourg Society; Hellenic Society for Clinical Chemistry-Clinical Biochemistry, Greece Society; Swiss Society of Clinical Chemistry, Switzerland Society). Figure 4, which summarizes the results, shows that SI units are used mainly for the biochemical parameters widely adopted in clinical practice, such as cholesterol, total protein, calcium, iron, electrolytes, C-reactive protein (CRP) and, to a lesser extent, IgG measurements.

Furthermore, on considering several clinically relevant and widely measured hormonal parameters (e.g., free T4 (fT4), prolactin and progesterone), it was found that a significant percentage of the laboratories use SI measurement (pmol/L, mIU/L, and nmol/L, respectively) at a range from 90 % (fT4) to 70 % (progesterone). Interestingly, in a low percentage of laboratories, in fT4 reporting the SI units are provided in addition to the traditional units; this might

Figure 1: EFLM affiliated countries that participated in the survey (countries shown in color participated, those in white did not).

be a useful approach for raising awareness and making clinicians confident in using these recommended measurement units. Worthy of note was the finding (Figure 4) that, currently, four different measurement units are used in Europe for reporting fT4 results (pmol/L, ng/dL, ng/L, pg/mL), three for prolactin (mIU/L, ng/mL, µg/L) and three for progesterone (nmol/L, ng/mL, µg/L).

Of particular interest were the results concerning the measurement units for coagulation and hematological tests. Indeed, for blood count leukocytes, great harmonization has been achieved, 90 % of the responders using the recommended unit (10^9/L), and for hemoglobin, about 60 - % adopting g/L and 10 % a combination between traditional (mg/dL) and SI (g/L) units.

A different, critical situation was observed for coagulation tests (i.e., PT and aPTT). Specifically, for PT results, more than 60 % of the participants declared that they used a combination of the proposed units; among these, the combination including all measurements units (seconds, %, ratio, and INR) and "s and INR" units were the most common, while 16 % adopt INR only. Regarding aPTT, 48 % of the laboratories used "seconds", while 43 % used a combination of seconds and ratio, the "seconds" unit being adopted overall by 91 % of the laboratories.

Reference intervals

The rate of harmonization in reference intervals (RIs) is summarized in Table 2. For three national societies (Greek Society of Clinical Chemistry and Clinical Biochemistry, Luxembourg Society of Clinical Biology, and Swiss Society of Clinical Chemistry), this information was unavailable because the members skipped the answer.

Regarding the source of RIs for routine tests reporting (Table 1(1.2)), different approaches were described, although the more frequent (83.5 % of cases) answer was "*its own RIs*".However, 21.9 % of the countries (Belgium, Cyprus, Georgia, Israel, Latvia, Lithuania, Romania, Russia, and Spain) declared that they followed those proposed by the

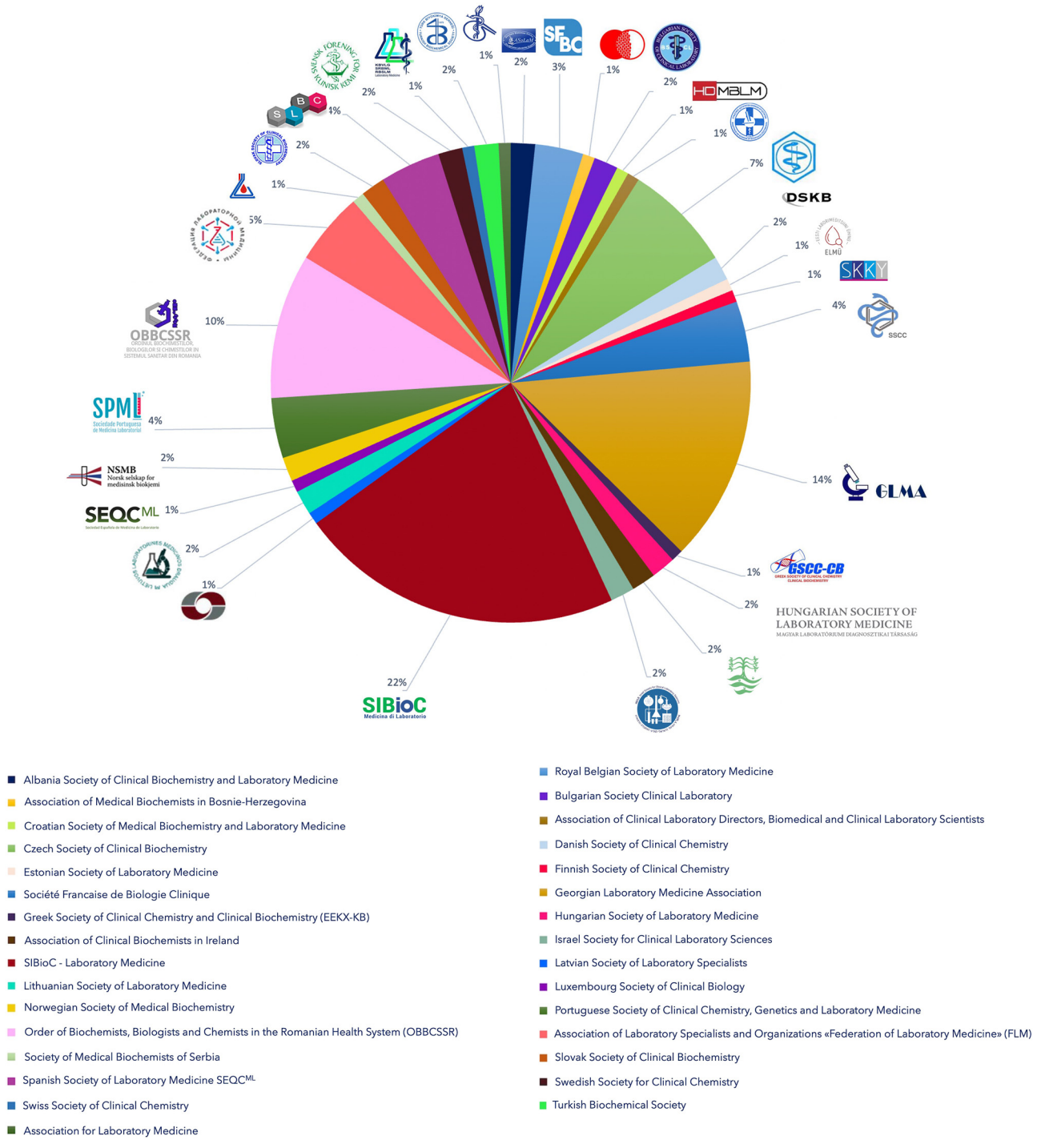

Figure 2: Percentage of participants in the survey for each Society.

manufacturers, while 7.3 % (Albania, Serbia, and United Kingdom) used those recommended by their national society, and Bosnia-Herzegovina and Bulgaria, those established in international studies. Multiple responses were provided by 31.7 % of the members (i.e., Croatia, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Ireland, Italy, Norway, Slovakia, Sweden, and Turkey).

As reported in Table 2, the sources of RIs in most countries declaring the use of "*own RI's*", are actually those specified by the manufacturers.

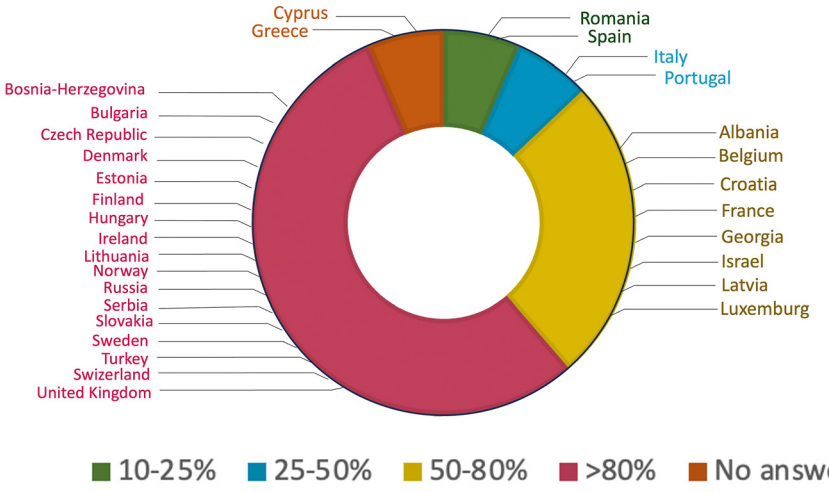

Figure 3: SI measurement units' adoption for laboratory results reporting across countries.

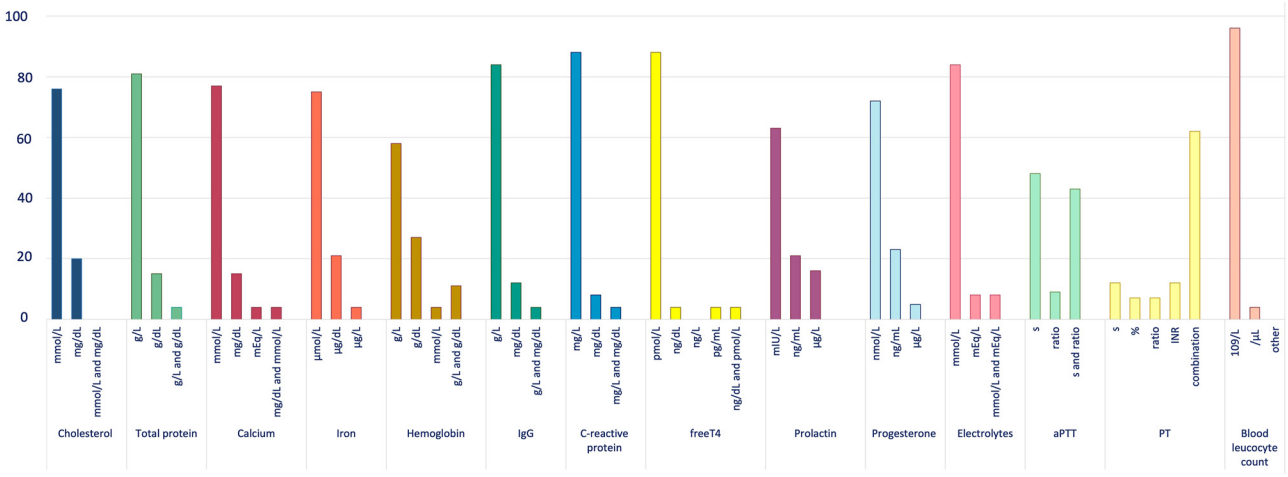

Figure 4: Share of measurement units adopted in laboratory practice for different tests.

Regarding the question "*Does your national society scientific journal support study result reporting in SI units?*", of the countries that declared the availability of a scientific journal from their own national society, 30 % either failed to answer or stated 'non-applicable'.

Nomenclature/terminology

The answers concerning the level of harmonization in nomenclature/terminology across countries demonstrate that clinical biochemistry and hematology parameters are the most harmonized across countries (78 % reported scores of 4–5 in a scale between 1-low level and 5-high level) as well as tumor markers (79 %, scores 4–5), while the lowest scores (2–3 in 51 % and 47 % of responders, respectively) were for molecular diagnostics and allergy testing (Figure 5).

Discussion

Harmonization of laboratory reports is a continuous challenge for laboratory professionals. The harmonization of measurement units, reference intervals, and nomenclature/terminology, the three key factors characterizing laboratory reports [6], must be achieved by sharing and adopting the recommendations as well as by following the suggestions by guidelines of the National and International Societies [7, 8].

The present paper reports the results of an EFLM survey aiming to evaluate the harmonization of these three factors in Clinical Laboratories across Europe. While several considerations can be made based on the data obtained, it is important to bear in mind that some countries in Europe expressed little interest in this specific topic, 25 % of the countries failing to participate. This poor participation represents a limitation of the study, the aim of which was to

Table 2: Estimated percentage of source of reference intervals across countries (for those laboratories declaring using its own RIs).

Countries	RIs defined by their own validation study	RIs based on manufacturer's declarations	RIs based on various literature	Other comment
Slovakia	10%	80%	10%	
Denmark	20%	20%	20%	Nordic Reference Interval Project
Norway	20%	40%	40%	
Estonia		95%	5%	
Lithuania	1%	90%	9%	
Czech Republic		90%	10%	
Portugal		80%	20%	
Finland	10%	80%	10%	
United Kingdom	25%	50%	25%	
Belgium	10%	60%	30%	
Ireland	10%	70%	20%	CALIPER for paediatrics
Croatia	5%	80%	15-20%	
Latvia			90%	
Cyprus		> 50%		
Hungary	0%	90%	10%	
Italy	10%	60%	30%	
Turkey	30%	30%	30%	
Russia	0%	70%	30%	
Spain	10%	80%	10%	
France	20%	50%	30%	

gain a complete picture of the state-of art of the specific topic, but also indicates the slight importance that laboratory medicine professionals attach to this problem [9, 10]. A further limitation may depend on the survey design, the initial idea being to send the survey to the National Representatives (NR) only but unfortunately some countries sent answers from NRs while others them from other society members, on the basis of individual decisions.

Considering the reported results, there appears to be a trend towards a wider adoption of SI units for the general clinical biochemistry parameters. With respect to the data reported in the 2016 survey [5], in four out of 31 national societies responders (13 %), the estimated rate of SI units adoption shifted from 10 % to 25–50 % and, in most cases (55 %) >80 %, although for some widely used parameters (electrolytes and calcium), the obsolete mEQ/L units are still used (in a small percentage, 7.7 %).In addition, in reporting specific proteins results, a significant compliance with the recommendations [11] seems to have been achieved: currently in about 80 % of the laboratories in Europe, CRP and IgG values are expressed in mg/L and g/L, respectively.

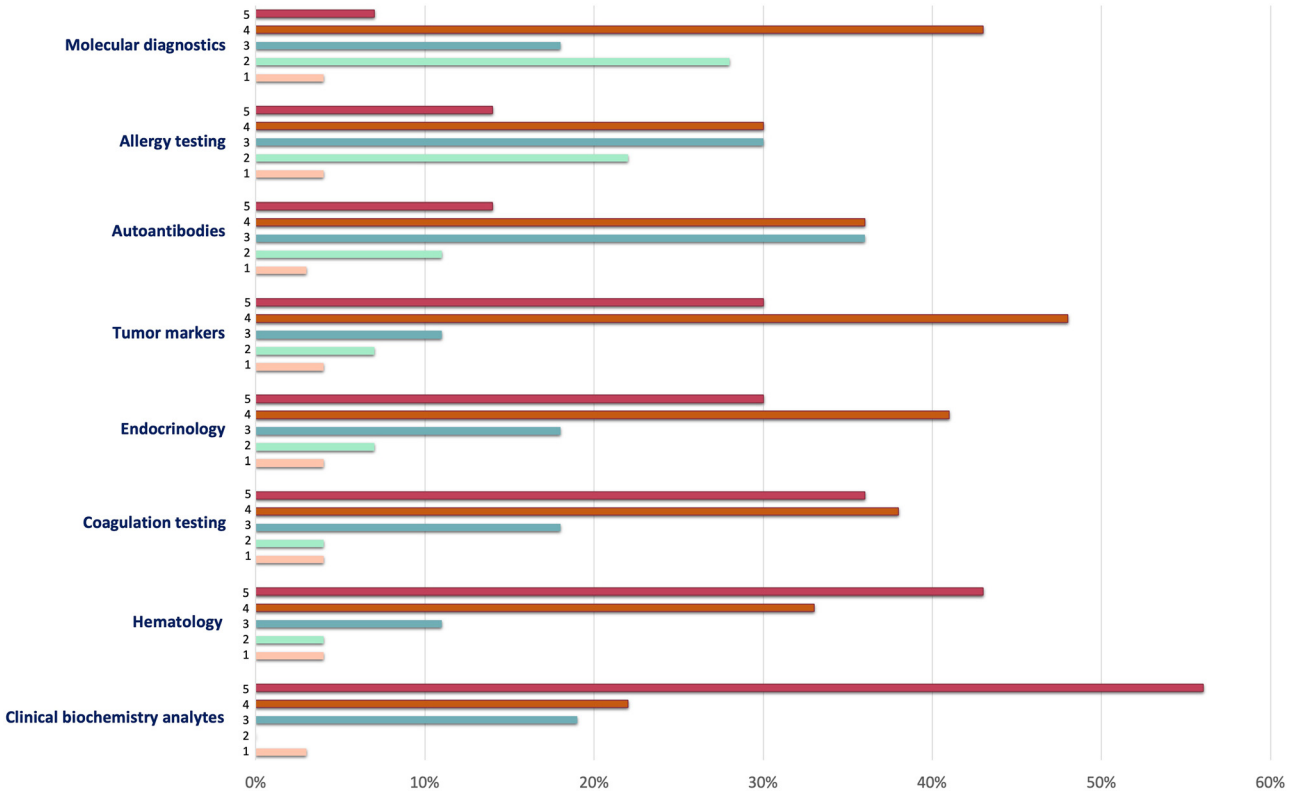

Figure 5: Level of harmonization in nomenclature/terminology in specific fields of laboratory diagnostics across countries (X-axis: 60 % represents maximum level of harmonization). The classification ranges from 1 (lowest degree of harmonization in terminology) to 5 (highest level of harmonization).

The real focus might be on tests not considered in 2016 survey, such as those included in endocrinology diagnostics and in coagulation panels. While for hormone reporting, a satisfactory approach appears to have been reached, a significant number of responders using the recommended units (range 70–90 % depending on the test), the coagulation test panels seem to suffer from a serious lack of harmonization, exacerbated by the evidence that "seconds", a well-known inaccurate, not recommended units is widely used (91 % of cases) [12]. However, as underlined in several recent papers [13–16], overall this criticism is to be expected.

Finally, the answers to the last questions on the reference intervals and nomenclature/terminology, demonstrate that the majority of the laboratories use the reference intervals proposed by the manufacturers, and this maybe a pragmatic key to harmonization. It should be highlighted that survey does not go into merits of the harmonization in the use of decisional levels as recommended for the report of several analytes [17]. Concerning nomenclature/terminology, allergy diagnostics and molecular biology lack harmonization [18]. This result, which may be attributable to the relatively low diffusion in clinical laboratories of the tests included in these diagnostic settings and carried out as second level tests in specific and in-depth clinical contexts, make the need for harmonization less pressing.

In conclusion, although overall a progressive, albeit slow, improvement has been achieved in harmonization of reports provided by clinical laboratories in Europe, the real message arising from the present survey is that there is an urgent need for a change in attitude from all stakeholders involved in this process [19, 20]. In order to accelerate harmonization activities, national societies should be supported by European scientific bodies providing guidelines and specifying the time-frame for the update. The first step might consist in strongly encouraging EQA scheme providers to use only SI units in reporting results: as is well known, EQA performance is a fundamental prerequisite for ISO 15189 accreditation, and, according to the proposed strategy, laboratories should adopt the SI units to evaluate their analytical performance through the EQA scheme [21]. A further step might be to oblige manufacturers to exclusively include in their Instructions For Use (IFU), the SI units in their product description, in declaring the specific analytical performance and in reporting the proposed reference intervals [22]. Currently, in the IFU of the main manufacturers of reagents and systems, SI units are reported in

brackets, or named as "alternative" to the traditional units, the latter being identified as principal or "standard" units. Concerning this approach, the working groups and the official bodies managing the *in vitro* diagnostic medical device regulation requirements [23, 24] can play a strategic role in the promotion and in the simplification of the harmonization process following the three key issues considered in the survey: measurements units, reference intervals, and nomenclature.

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