

IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)
Meeting at Euromedlab 2013, Milano, Italy, Monday May 20th (13:30 - 15:30 pm)

PARTICIPANTS

The meeting attendance list is attached in annex 1.

OPENING OF THE MEETING

The chair (LT) welcomed the meeting attendees, presented the agenda and proposed to make a roll call. She conveyed excuses from F. Quinn for not being able to travel to Europe because of a health issue. Also G. Beastall let apologize him, because of conflicting activities at Euromedlab.

1. Important international developments related to standardization/harmonization of thyroid hormone testing

a. Partnership for Accurate Testing of Hormones (PATH) – Meeting held in February 2013

Attendees from C-STFT: J. Faix, F. Quinn

Rapporteur: J. Faix

Until now there is not too much outcome of the PATH initiative, apart from publications and brochures. The financial budget allocated to the PATH initiative is huge. A study to obtain realistic reference intervals (RI) for testosterone will be set up by the Centers for Disease Control and Prevention (CDC). Since February 2013, IVD manufacturers are on board of this partnership. It is the intention of the PATH to expand the target group from steroid hormones to all hormones. LT commented that in this regard, CDC is already in contact with her regarding the development of a FT4 conventional reference measurement procedure (cRMP).

b. UK consensus meeting on thyroid reference intervals (RIs) – March 2013

Attendees from C-STFT: F. MacKenzie, M. Rottmann, F. Quinn and G. Beastall

Rapporteurs: F. MacKenzie and M. Rottmann

This meeting on initiative of J Barth was related to the 'Pathology Harmony' group in the UK. This group aims at harmonization of RIs for TFT, and has done the same already on a fairly arbitrary basis for several common chemistry measurands. The driver to have comparable test results in the UK is the implementation of the 'electronical medical record', in which all results, regardless their origin, are compiled. In the meeting, F MacKenzie gave an outline of the problem of insufficient standardization/harmonization of thyroid function tests based on the UK NEQAS data, while G. Beastall took the opportunity to present the data from C-STFT.

In general, the audience in the meeting was happy to see that the analytical aspects of the standardization/harmonization issue are tackled by the IFCC C-STFT. They showed very much confidence about the quality of these activities.

The representative of the British Thyroid Association (BTA) in the meeting mentioned that clinicians do not like the idea of common RIs, but want to treat their patients as individuals. In addition, they seem to have adapted to the non-standardized situation, and can live with it.

One is also concerned about the practicality of the implementation of standardization. It was suggested to rather harmonize (instead of standardize) the FT4 assays to the all methods trimmed mean (AMTM), however, with knowledge of the relationship AMTM – cRMP. LT mentioned that she discussed this option, which is not new, already before with

the chair of the SD (Prof. I. Young) and found him very much reluctant. He stated that the IFCC would never agree to use this approach internationally, but will always adhere to traceability to the cRMP.

Instead of using an analytical basis for common RIs, a novel approach was tested. i.e. thousands of data points (only gender and age were known) were combined and a RI was proposed. Then the RI was broken down according to the used methods. For TSH no difference was found, for FT4 the differences were not as big as expected. LT argued that the fact that no big differences were seen between the data obtained by different methods most probably depends on which data were used, how they were pooled and interpreted.

Editorial note: according to a previous personal report by G. Beastall to LT, the representative of a thyroid patients' association had made a firm statement in the meeting in favor of standardization/harmonization to reassure patients and GPs.

Finally, the meeting did not result in a particular outcome.

1. Financing of scientific secretariat at Ghent University (UGent)

Until now, 4 manufacturers committed to financing, 2 declined and 2 others have their decision pending. Those who declined claimed that this was due to compliance issues. The question was raised how to behave towards those manufacturers who declined, e.g., can they simply continue to participate in the future activities of C-STFT, or should the conditions for participation be changed? After some discussion, it was suggested to ask a higher financial contribution for the phase IV sample collection.

2. "Go"-decision for standardization of FT4 testing and harmonization of TSH testing

Until now, only few manufacturers said "YES" to a "Go"-decision in a personal telephone conversation with LT. These were even highly surprised to hear that others were reluctant. However, it was the general feeling that "a 95% agreement should force the rest".

From a manufacturers point of view, there are still several issues/questions raised as why not to commit to the "Go"-decision (*formulated by M. Rottmann and P. Sibley*)

- What will the position of regulatory bodies be with regard to standardization/harmonization? What efforts will be asked from IVD manufacturers in order to keep/renew approval/clearance of their assays? What pressure can be put on regulatory bodies?

Manufacturers need a formal written statement from the US Food and Drug Administration (FDA). This statement needs to be crystal clear with regard to the consequences, in particular also with regard to the validity of RIs. It should be a "push" message and should give a check for technical realization. In this regard, LT mentioned that she had sent a document to Dr. A. Gutierrez from FDA (see annex 2), who committed in a subsequent telephone call to provide a statement before the Annual AAC meeting in Houston 2013. She also mentioned that in a meeting on Sunday 19/05 with the IFCC Scientific Division (SD), she found Dr. G. Myers prepared to bring up this C-STFT document in his meeting planned in June with the FDA and IVD manufacturers.

- LT reiterated that for TSH the current WHO-traceability of the IVD assays would be preserved, and that harmonization would mean that a master equation for each individual assay is applied. Despite this, Finlay Mackenzie mentioned that he did not like the idea not to know what the next WHO reference standard would be. LT stressed that, whatever reference material would be used, be it recombinant TSH, it

will not serve harmonization. Indeed, it has been shown on many occasions before, that such standards dissolved in an artificial matrix (e.g., albumin) simply lack commutability.

- The manufacturers also pointed to other markets than the US one with a specific own regulation (e.g., China, Japan, Brazil). On the basis of their experience regulation adopted for those markets might cause a delay of 2 years before getting final acceptance of the regulatory bodies.
- Due to the big impact of standardization/harmonization (especially for FT4) and the big efforts needed, it should be done by IVD manufacturers as a group, all at the same time.
- A "Go"-decision will mean big investments, without obvious return.
- A lot of education and persuasion will be needed to convince the stakeholders of the benefits. Most clinicians do not want to change, because they are simply used to the situation.

Rebuttal by LT:

- CE-marking requires that manufacturers demonstrate traceability to reference measurement systems (RMSs), when available. For FT4, a RMS is available, thus legislation has to be complied with.
- It is to regret that the generally accepted concept of metrological traceability still has to be discussed again and again for every single measurand. This comment was also discussed in her meeting with the IFCC SD (19/05), where she addressed the question whether other IFCC working groups/committees experienced the same reluctance of IVD industry. The SD confirmed that it most probably will be the case, however, that other projects were not yet in the same phase as the C-STFT.
- Manufacturers should not forget that current practice guidelines recommend use of absolute decision limits (i.e., for TSH an upper limit of 2.5 mIU/L in pregnancy and 4.5 mIU/L for euthyroid), which does not work in a non-standardized/harmonized market. The IVD manufacturers' representatives argued that the use of practice guidelines is not mandatory.

Alternative proposal by F. MacKenzie:

- Instead of asking a formal "Go"-decision, follow the "HbA1c-approach", especially for TSH. This approach gradually narrowed the acceptance limits in the CAP proficiency testing (PT) surveys to push standardization forward. This is of course a long and winding process, but appeared to be successful in the end. LT argued that this approach puts the burden on laboratories, because to pass PT, they have to put pressure on manufacturers. This does not fit with her philosophy. She sees IVD manufacturers as key players in the standardization/harmonization process.

Timelines for the standardization/harmonization process:

- LT emphasized that it never will be the intention to seek for direct implementation, once the final method comparison (phase IV) is finished.
- It is proposed to perform the phase IV in 2014, and then prepare all stakeholders for implementation in 2018.
- It is proposed to combine the standardization/harmonization effort with the effort to establish common RIs, in cooperation with the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL). This committee does a very good job. It is to hope that working towards establishing RIs after standardization/harmonization will help in convincing manufacturers.

Conclusion of this discussion and way forward:

- The official statement of the FDA will be awaited (hopefully it will be available before the upcoming AACC meeting in Houston).
- Then LT will send to all manufacturers 2 ballots, one for TSH – one for FT4, with the YES/NO question for going forward with standardization/harmonization. These ballots will be accompanied with a short/clear history on the project and objectives/outcome for the “Go”-decision (preferably to be done before the upcoming AACC meeting in Houston).
- After the “Go”-decision: the final method comparison (phase IV) will be organized. It is the intention to improve the panel in terms of diversification in ‘disease state’ and concentration range. LT recalls that this will only be possible, provided help from big hospital centers, worldwide. Regarding this, J. Faix committed to seek interest/engagement within the American Society of Clinical Endocrinologists (AACE) and will launch the call for support in his presentation in the Endocrine Society Meeting in June. Two corresponding members, A. Hishinuma and J Berg, committed to do the same within the Asian and Scandinavian market, respectively. LT promised that a sample procurement protocol will be distributed in due time. Note: “pregnancy” samples have until now and will be excluded. The rationale is that all immunoassays are to a certain (be it different) extent protein dependent, thus even when their results follow the same pattern as the cRMP during the different trimester of pregnancy, use of assay-specific RIs will remain mandatory (see also: Anckaert E, ... Thienpont LM. FT4 immunoassays may display a pattern during pregnancy similar to the equilibrium dialysis ID-LC/tandem MS candidate reference measurement procedure in spite of susceptibility towards binding protein alterations. *Clin Chim Acta* 2010;411:1348-53).
- A network of laboratories with proven competence for performing the FT4 cRMP will be established. Currently 2 laboratories are able to provide FT4 RMP services, i.e., UGent and the Reference Material Institute for Clinical Chemistry Standards (ReCCS, Japan). The CDC and Stanford University (J. Faix) committed to also develop the FT4 cRMP, hence will be included.

3. Preparation of stakeholders meeting: when (after “Go”-decision?), where?

Wait until “Go”-decision is made.

4. Status of manuscripts in preparation

General note before: there appears to be little awareness in the clinical community of the activities of the C-STFT, e.g., as heard on the latest American Thyroid Association (ATA) meeting. As long as publications do not reach the end users/decision makers, there will be no background for discussion/support. More publications in clinical journals, or in newsletters from clinical societies and others could be a good tool for further promotion of the C-STFT’s activities. All members are welcome to contribute. In this regard, Dr. Das has planned events in India to spread awareness about IFCC C-STFT work (on the occasion of World Thyroid Day on 25/05). Among others, to sensitize general population & clinicians, 500 free thyroid function tests will be offered (see also email from Dr. Das dd 17/05/2013).

- The 1st draft of the phase III manuscript is almost ready for distribution and review by the C-STFT members and participants in the study. As agreed upon in the past, the study will be presented with the manufacturers blinded. This jeopardizes the acceptance chance, because many journals signed the decision to not longer accept studies without identity disclosure of the results. Therefore, the phase III study will be

submitted to the journal European Thyroid Journal (ETJ), because in a personal meeting of LT with its editor, Prof. W. Wiersinga, she got the promise for acceptance, provided the manuscript would be accompanied by a well-sounding rationale for non-disclosure of the identity of results.

- LT also pointed to the fact that the journal ETJ is a journal addressing the clinical community" rather than laboratories. Therefore, the 1st draft of the manuscript will need cosmetic changes to make it more attractive for this readership. She counts on the members and manufacturers to help her in this regard.
- The manuscript on the statistical basis for the reference for TSH measurements is also in preparation.

Editorial note: other related publications:

Submitted:

-Determination of free thyroid hormones (authors: LM Thienpont, K Van Uytfanghe, K Poppe and B Velkeniers) (written for "Best Practice & Research Clinical Endocrinology & Metabolism")

-Principles and pitfalls of free hormone measurements (author: JD Faix) (written for "Best Practice & Research Clinical Endocrinology & Metabolism")

Published:

*Thyroid-Stimulating Hormone. Why Efforts to Harmonize Testing Are Critical to Patient Care. (JD. Faix, LM. Thienpont) in Clinical Laboratory News May 2013, No. 5

5. Working structure of C-STFT (management docs)

- The members of the Committee do not feel the need for a formal management structure and document control.
- It is agreed to use in presentation the slides provided by the chair.
- Within the C-STFT, there will only be the following positions: chair and scientific secretary, members and corresponding members. The IFCC itself acts as treasurer.
- It is the intention to develop a website for the C-STFT and start using a general email address.

CLOSURE OF MEETING

The chair thanked the attendees for their contribution to the meeting.

As a result of the above discussions, the following “actions items” (2013-Ax) were defined for the project partners:

| From now on | | Responsibility | Timelines |
|---------------------|---|--|------------------|
| 2013-A1 | Obtain a written statement of the FDA | UGent | Before AACC-2013 |
| 2013-A2 | Send out the 2 ballots for the “Go”-decision for TSH and FT4 | UGent | Before AACC-2013 |
| 2013-A3 | Complete the ballots and return | IVD manufacturers | |
| 2013-A4 | Finish 1 st draft of the phase III manuscript and send out for review by the C-STFT members and study participants | UGent, C-STFT members, participants from IVD manufacturers | |
| 2013-A5 | Develop a network of FT4 reference laboratories | UGent | |
| After “Go”-decision | | | |
| 2013-A6 | Prepare phase IV sample procurement | UGent | |
| 2013-A6 | Prepare stakeholders meeting | UGent. | |

Minutes made by:

Dr. Kathleen Van Uytfanghe, on behalf of Prof. Dr. Linda Thienpont, chair of the IFCC WG-STFT

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Annex 1

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Excused

| Name | Affiliation | e-mail address |
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Annex 2

Document to Dr. A. Gutierrez (FDA) from LT

Dear Dr. Guttierrez,

I hope this e-mail finds you well.

You will remember that on the last occasion we met (Los Angeles, CA, AACC 2012), we discussed whether harmonization of existing IVD assays for Thyroid-stimulating hormone (also known as TSH or thyrotropin) according to the approach used by the IFCC Committee for Standardization of Thyroid Function tests (C-STFT) would require a new FDA clearance. You heard in every meeting of the C-STFT you attended, that it is of big concern for the IVD industry that harmonization (implying assay recalibration) would entail major regulatory activities, such as a new assay registration.

You proposed that I would provide you with data to demonstrate the impact of harmonization of TSH assays. These data should allow you to internally discuss with your colleagues at FDA. Since we now completed our Phase III study, I am ready to do so.

Foreword

-In general the harmonization approach used by the C-STFT is based on a method comparison study with a panel of clinical samples, reasonably covering the measurement range of the concerned assays. Therefore, we call the approach the “Predicate Panel” approach (alluding to the “Predicate Assay” approach of FDA). This predicate panel would thus serve as basis for establishing traceability of assays’ calibration.

For TSH, value assignment will be done by a statistically valid method (robust principal component analysis or an alternating regression approach) leading to the “all-procedure trimmed mean (APTM)”. Note that current TSH assays all are traceable to the same World Health Organization (WHO) TSH International Reference Preparation.

-The TSH predicate panel approach requires assurance of continuity of the calibration/traceability basis. The very first predicate panel will fix the calibration basis. In consequence, before depletion of that panel, the follow-up panel will be value assigned in overlap with the first one, so that the new APTM perfectly matches with the calibration fixed point of the first panel, similar to the WHO process tracing the international unit.

-According to the predicate panel approach, the current traceability basis of assays to the WHO standard for TSH will be maintained.

Outcome of the feasibility study Phase III

The figures below demonstrate on the one hand the current standardization status and between-assay CV of 14 commercial (FDA cleared) TSH assays, on the other hand what the harmonization approach by the C-STFT can achieve.

The left plot in Fig. 1 shows the current %-difference of all individual assays (compared to the above explained APTM). Note that the most discrepant assays are indicated by “blue circles” and “red triangles”. One assay showing a particular difference profile in the low concentration end (<1.1 mIU/L) is marked by “yellow squares”. All other assays are presented by the symbol “X”.

The right plot in Fig. 1 shows the %-difference of the same assays after harmonization against the APTM. It shows that harmonization is capable to eliminate the calibration differences between the assays, so that the remaining scatter in the %-difference plot is now only due to within-assay random error components.

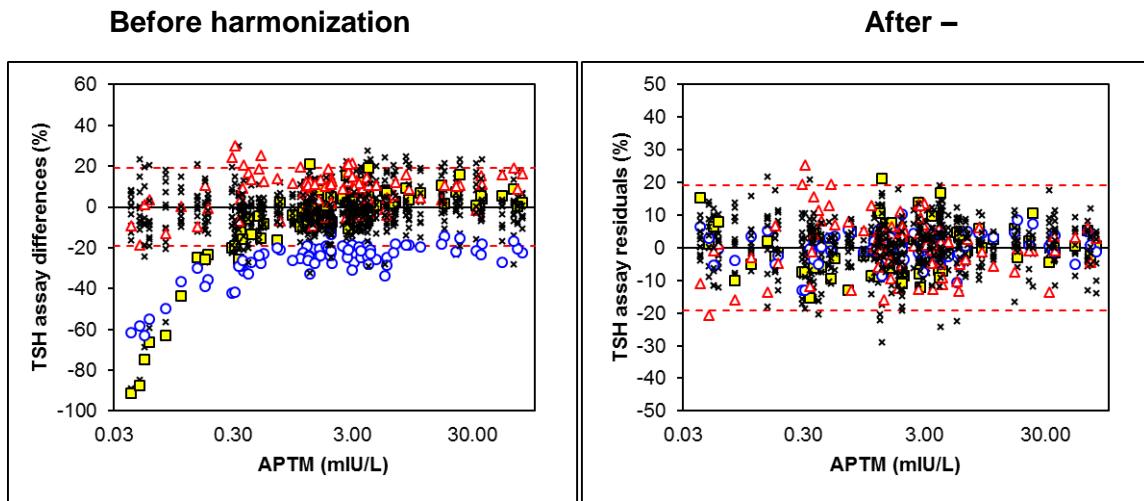


Figure 1: %-Difference plot from the APTM before and after harmonization of TSH assays

The next figure shows how the between-assay CV before harmonization (black squares) is reduced (red triangles) by harmonization. In the concentration range >0.5 mIU/L, the between-assay CV is reduced from ~9% to ~6.0%. In the lower end (where the CV was up to 45%), the effect of harmonization is even more spectacular.

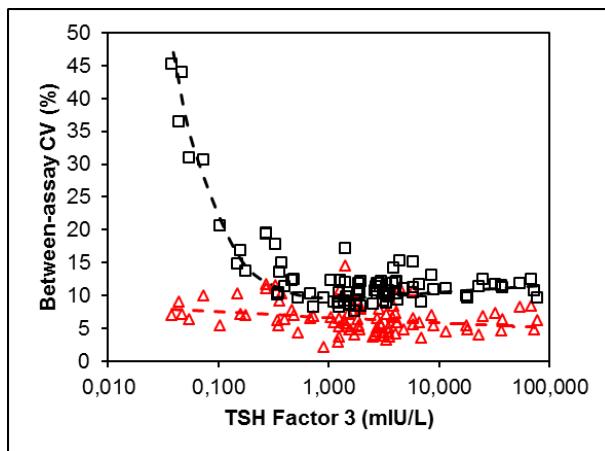


Figure 2: Between-assay CV before and after harmonization

In summary the outcome of harmonization is as follows:

1. Assay case 1 (red triangles; most positively deviating assay): to eliminate the bias, recalibration by ~12% is needed.
2. Assay case 2 (blue circles; most negatively deviating assay): to eliminate the bias (of up to 60%) in the concentration end <1.1 mIU/L, recalibration needs to consider a constant factor of ~0.02 mIU/L, whereas in the concentration range above 1.1 mIU/L, recalibration by ~30% is needed. This constant factor most probably might affect the limit of quantitation of that assay.

3. Assay case 3 (yellow squares): to eliminate the bias, only recalibration in the concentration end <1.1 mIU/L by adding a constant factor of ~0.04 mIU/L is needed. Again, the constant factor might most probably have an effect on the limit of quantitation of that assay. Above this range, calibration is all right.

4. For all other assays, no recalibration is needed since the bias they show, is typically within the lot-to-lot changes of assays (~10%).

My concrete questions for you:

For the cases 1 to 3, provided recalibration, could you explain what the FDA would require from the manufacturers in terms of FDA clearance?

In case you need further explanation, don't hesitate to contact me.

Thanks in advance for your consideration.
Linda Thienpont

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