IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)
Meeting at AACC 2014, Chicago, IL, USA, Monday July 28th (9:00 - 11:00 am)

PARTICIPANTS
The meeting attendance list is attached in appendix A. Initials as used in the minutes can be found in appendix A as well.

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 Dr. F. Mackenzie.

REDACTIONAL NOTE: wherever ‘standardization’ is written, we mean standardization (FT4 assays) / harmonization (TSH-assays).

1. Standardization/harmonization approaches scientifically supported by peer-reviewed publications

2. Status of preparation of final Phase IV method comparison:
   For a general overview of the set-up of phase IV, see appendix B - slides of the meeting
   Additional question by F. Mackenzie: should samples of NTI-patients be included.
   • LT reminds that in the past we discussed not to do so.
   • JF arguments in favor of the previous decision. NTI-samples would only add a large amount of confusion. He refers to a recent example in a discussion at the FDA on the inclusion of "critically ill" patients in a study for capillary glucose. How to define "critically ill" caused controversy.
   • GB adds that NTI is a very complex state of disease and that it will be very difficult to find a representative sample for this.
   • LT also reminds on the difficulty of sample sourcing.
   • JF reminds us of the fact that this is for sure something we should investigate in the future.

➔ In conclusion: NTI-samples will not be included in phase IV.

A. Commitment of IVD partners with C-STFT regarding sample sourcing
   REDACTIONAL NOTE: adapted according to the discussion in the closed meeting with the manufactures.
   • LT informs that in the meantime all manufacturers confirmed their intention to contribute.
PS asked if we are aware of other manufacturers - should we not actively inform them on the activities of the C-STFT?

LT agrees on this. Fujirebio has shown interest and is considering participation. She launches a call to share or forward coordinates of other possible candidates to join us.

KVU will complete the preliminary list in appendix C.

B. Ongoing joint efforts to sample sourcing

See slides in appendix B

C. Reference intervals (RI) (n = 120): in- and exclusion criteria, questions to be asked.

Study design

- The study design will include a cohort of 120 samples. It is up to each manufacturer to extend that cohort depending on its own needs and the requirements of the FDA.
- The aim of this study is to show that all manufacturers come to comparable RIs within preset limits. Only when this is true, manufacturers can move forward to extend the cohort in order to establish RIs with small confidence intervals, as is required by the FDA.
- The question was raised whether NHANES data can be used to establish RIs.
- HV explains the National Health and Nutrition Examination Survey (NHANES). It is a representative survey of the US population with a 2 year cycle (older than six years, mixed female/male, mixed ethnicity). Thyroid function is investigated with commercial clinical tests. This study can be used to validate normal ranges. It would also be possible to go back to old data.
- LT asks the FDA whether this is a fair proposal.
- It is, according to the FDA representatives.
- SH asks if each manufacturer has to test an additional 120 samples - in addition to the 120 C-STFT cohort- to verify the RI, or if each manufacturers can decide on n.
- The FDA representatives will take this question back.
- GB asks, concerning the NHANES study, whether we will use new analysis (of old samples) or whether we will just use old data.
- HV replies that we will use old data to study the impact of standardization. No new analysis is needed for that.
- LT questions whether this is not needed in the future. We will need to look into that to see whether it is useful to make the link between new and old data.

Inclusion criteria

- See also slides.
- JF ask the rationale for excluding patients with psychiatric disorders.
- LT reminds that this was a strong demand upon sample collection in phase III, but does not recall why exactly.
- MP suggests that it is probably only for ethical reasons/credibility. E.g., some patients might not be aware of familial history of thyroid dysfunction, or "lie" about it.
- IY suggests to leave out psychiatric disorders as the term is to vague. E.g. people having a depression, or anxiety disorder (in the past) might be excluded while there is no reason for that. People with severe psychiatric disorders will be excluded anyway as they are on medication, and hence are covered by that exclusion criteria.
- FQ/JF question the exclusion of people taking supplements. E.g. in the US quite some people take multi-vitamin supplements, perhaps containing a small amount of iodine. Perhaps it should be changed to iodine containing medication (high doses).
- IY raises the question whether we should make sure that the samples in the cohort of 120 are from a iodine sufficient region. Iodine fortification is not globally implemented. Some regions on the other hand have a very high iodine status.
- LT adds that for example in the UK, and even in the US, separate RIs might be needed because of iodine insufficiency.
- AA asks if there are age criteria.
• KVU explains there is a minimum, i.e. 18 years.
• IY questions whether we also need an upper limit. Once over 65 years old there is an increased risk for potentially subclinical hypothyroidism and most people that age take medication.
• GB questions the in- and exclusion criteria and the discussion in light of the purpose of the study. Is the study designed for standardization or to establish RIs.
• LT explained that it is intended to set a first basis for new RIs, but more important to demonstrate that manufacturers are comparable when using the same subset of samples.
• JF adds that it would also underpin the rationale against concerns of manufactures on the change in RIs. It will be an added value to refer to a common first RI.
• GB asks whether global RIs are achievable.
• According to JF, there is no breakdown per country.
• SN repeats that this is exactly why we included only 120 samples. Each manufacturer can add its own samples if he feels the need for it.
• The FDA representatives point out to the fact that for FDA clearance a RI study on the ‘US population’ is needed. So, if we would go for a global cohort of 120 samples, each manufacturer needs to establish his own US population RI.
• FQ questions the procedures needed for verification of the RIs. The CLSI 28 protocol might not be strong enough, 120 samples might not be sufficient.
• MR points out to the strength of this study. It is a chance to demonstrate the benefits of standardization. Moreover, this will be a very unique study, never done before. If the study is successful, it demonstrates the benefits for the end-user.
• LT stresses that it is our intention to source the samples in the US by working with Solomon Park Research Laboratories (SPRL)).
• FQ refers to the point of doing this study, i.e. to demonstrate equivalent RIs are achievable. However RIs which go into a manufacturers insert, go into a regulatory document. Each manufacturer’s clinical research group has its own defined protocols for this.
• LT repeats that it is not the intention of the C-STFT to develop the RIs, this is up to the manufacturers. We only want to show concordance.
• MP asks who is going to do the non-US RIs.
• LT repeats that this is for the manufacturers.
• BD refers to the study she has done, see later, where she established RIs using 600 individuals. To do so, she needed to screen a 1000 volunteers, as 400 of them were high in anti TPO.
• MR repeats that the outcome of phase IV is only a first shot, to see what the consequences are. Other cohorts should be discussed later on. If we put in too much, we might lose everything. E.g. we know that in pregnancy, there will be no benefit from standardization. Each manufacturer will have to investigate the consequences for his own assay.
• GB summarizes that the study will give a nice indicative value.
• JF stresses to the fact that this study should demonstrate that similar cut-off values and RIs are feasible. Otherwise, there is no point in standardizing.
• IY notes that immunoassays are not identical in terms of performance. Hence we might expect some differences and it is unlikely to end up with identical RIs.
• SN repeats that verifying this is the purpose of the study.
• LT points to the fact that in phase III we already demonstrated that the limits are tightened. Of course there will always be slight differences.

→ In conclusion: the RI study design will remain the same, however excluding patients with psychiatric disorders will be left out. The RI will be established with a cohort of 120 US apparently healthy individuals.

Anti TPO testing
• See also slides.
• JF and Tosoh offer both to screen for the anti TPO and TSH on the leftovers from SPRL.
• LT/KVU will make arrangements with both SPRL and JF/TOSOH.

Information on the volunteers
• See slides.
• This proposal is acceptable for the FDA.
• SM suggests to ask women (in a certain age group) if they are pre- or post-menopausal.
• GB points out that we should not forget the intended use of the test, i.e. in post-menopausal women, therefore an upper age limit is maybe not a good idea.
• SM notes that with the use of special statistical software, it is possible to investigate whether for certain subcategories there is the likelihood of a different RI.

3. International developments:
A. World thyroid day
• BD summarizes her initiative. After screening of 1000 volunteers, she ended up with 600 samples useful to establish a RI for the Indian/Asian population. The FT4/TSH measurements were done using assays of 2 different manufacturers. She will repeat the initiative after standardization and start up a study to establish RIs in pregnancy and pediatric samples.
B. Partnership for Accurate Testing of Hormones in preparation (PATH) (request from the Endocrine Society)
• See slides, all the activities of the C-STFT will be added to those of the steroid hormones.
C. Network of FT4 reference laboratories
• See slides.
• The laboratory in Nijmegen is the one of Dr. A. Ross who helped the UGent develop and familiarize the ED-procedure.
• The UGent will value assign a panel of 20 high volume samples, which can be used by the other labs for validation purposes.
• It is not to be expected that the 3 candidates will be ready in 2015. Hence the UGent will be the only laboratory for value assignment. ReCCS will measure some of the samples “pars pro toto”. When the others are ready, they can do the same.
• PS asks if we will publish on the reference laboratory network, once ready.
• LT confirms that this is of course the intention.

4. Visit to the FDA:
A. Summary of discussion based on the info given in appendix B
• The question is raised by several manufacturers why imprecision/accuracy/linearity evaluation of the assays is needed, even though the assays themselves do not change. It is only the calibration set point which changes.
• FDA repeats that a verification is needed. Whether or not the CLSI protocols have to be followed in full or in a reduced form depends on how much the values change. So this will be different for each manufacturer.
• Several manufacturers question the use of a predicate assay, especially because the predicate assay will not be standardized, and hence results will not be comparable. In fact the ED-ID-LC/tandem MS will take over the function of the predicate for FT4, the all procedure trimmed mean (APTM) for TSH.
• The FDA agrees that for accuracy assessment, the comparison to the RMP/APTM will be accepted. No method comparison with a predicate will be needed.
• LT stresses again the request by FDA to submit the new 510(k) well in time.
• To monitor the stability of the standardization status over time, LT proposes to use ‘The Percentilier’. Via this tool, developed by Dr. Stöckl (STT consulting) and LT, the moving median of FT4 and TSH results from outpatients can be monitored. To use this tool, participation of big “thyroid centers/laboratories” is needed. From a pilot study, our PhD-
students, working on the project, were able to demonstrate that, under stable analytical conditions, he moving median from a sufficient number of outpatients' results is very stable. In other words, The percentiler is an excellent tool to indicate assay (in)stability, shifts and drifts. For more information:

The help of each manufacturer in identifying laboratories running high volumes of their thyroid function assays (FT4 and TSH) is necessary. In this way, the C-STFT will be able to ensure that for each manufacturer the stability of its assay is adequately monitored, as required by the FDA.

Risk analysis

- It is decided that a name changes is not needed.
- JF explains his plans to investigate the effect of standardization on clinical outcome by using historical data. Using equations for the relationship of the immunoassays to the reference (ED-ID-LC/tandem MS or APTM) derived in phase III, one could study the effect on clinical decisions after standardization. It should show a positive effect on diagnosis.
- IY mentions that this is also of interest to the IFCC Laboratory Errors and Patient Safety Working Group (WG-LEPS).
- JF mentioned that he can contact them.
- LT mentions that she asked GB for support in all future efforts, because of his contacts with e.g. patient organizations, which he will do.
- MR provided a template for the risk analysis. It can be used to create the first draft, which can be presented to the FDA. The risk analysis should follow different approaches, i.e. from the perspective of industry, the patient and the laboratory staff. From this analysis we will also be able to derive our needs in terms of education. Input should come from as many sources as possible. In this way we will be able to provide the whole picture.
- KVU will create a dropbox and share its coordinates so that all members and industry partners can give their input in the risk assessment document. In the closed meeting, it was agreed that we should mention all names of whom participated to complete the document, but that it is written on behalf of the C-STFT. Hence it will include a clear statement that it is not written on behalf of any of the companies involved in the project. Please use track changes. It will be the intention to create on the first page some kind of document control tool, so that the UGent can keep track of the status of the document.

Outreach program

- With respect to the outreach program FQ wonders whether it is possible to publish equations for each manufacturer’s assay, so that laboratories can transform their own values to the new values.
- LT and JF confirm that this will be done as it is one of the firm requirements of the FDA. It will be done in multiple ways. As we agreed to break the codes of the assays, this can be done after phase IV.
- Several committee members stress on the fact that timing will be critical. We should be very careful in communicating when the standardized assays will be available. Perhaps we should provide some tight rules for communication and detailed timelines need to be developed. This will also be part of the risk analysis. The outreach program will need to involve all stakeholders, especially primary care workers and general practitioners. It should be a joint effort and we should speak with one voice.
- JF will submit an abstract for the American Academy of Family Physicians (AAFP) to write an insert for the physician office. It will be a very general text describing towards what we are moving. As for all other planned communication, the draft will be shared with the committee members and manufactures representatives for approval. He will also be attending the ATA meeting in October and do a webinar in September for the American Society for Clinical Laboratory Science (ASCLS). All communication so far and in the
near future (2015) will only be very general communication to raise attention for what is coming.

- GB will seek contact with the British and Asian Thyroid Association. We should try to get them actively cooperating at their level, as they are key stakeholders.
- BD stresses that we should arrange communication on all levels, on behalf of the IFCC. Manufacturers should be responsible for communication with their customers.
- LT ask that all slides and communications by members and industry partners will be shared amongst all members. The UGent will update and recirculate the common slides provided earlier. We will also share them in the dropbox. In appendix D, you find the slides LT presented at the IFCC WorldLab in Istanbul.
- GB suggests to make a roadmap/timelines for communication. We probably do not need long lead times, however the risk analysis will also be very critical in this.
- LT ask how we best establish the timelines.
- JF suggests to work backwards from 2018.
- MR suggests that at this point we can only make rough estimates about timing as it will also depend on the start and finish of phase IV. In our first communication, we should spread what we have done, show the existing and new world. Ask for active feedback and evaluate, based on that, whether a change is supported by the end users (general practitioners, ...) and patients.
- JF mentioned that general practitioners, lab supervisors, ... in general hate to change RIs.
- GB adds that from his discussions with thyroid physicians, it is clear that also patients do not like changes. Hence good planning will be needed. However, there are some good examples from the past from Australia and Asia. Also, now is the time to start, as 2018 is not that far away anymore.
- MP stresses the need for a solution on how to deal with patients who are monitored for their thyroid status in the period of introducing the standardized assays. How should we deal with historical data?
- According to JF monitoring of patients is usually not done for a long time. Hence the overlap for clinical concern will be short. Moreover, since most monitoring is done based on TSH results, and since the changes for these assays are minor, the transition, for patient being monitored should be manageable.
- MR points to the fact that marketing 2 different sets of standardized assays is not possible. Also, the timeslots needed/foreseen will not be exactly the same amongst the different manufacturers. This should be an important issue in future discussions. We will probably even deal with country specific timelines. Although these will be different for each manufacturer, at least we should agree that they are all set within the same timeframe.
- JF repeats the need to contact also other regulatory agencies, such as in China. Here the AACC could be of help. UGent will also ask for extra support from Donna Young (Vice President, Regulatory Affairs, Roche Diagnostics, Indianapolis, IN).
- GB has close contact with the Chinese Laboratory Association and could try to seek contact with the Chinese regulatory agency through them.
- BD wonders whether we also have to inform accreditation bodies.
- PS adds that at some point in time EQA organizers should also be involved
- GB refers to the European Organisation of External Quality Assurance Providers in Laboratory Medicine (EQALM), an organization which covers national EQA schemes.
- From the closed meeting: should we seek some support from pharmaceutical companies involved in thyroid medication?

→ Other suggestions for the risk analysis or dissemination of our work are welcome. we need to do this in a joint effort.

CLOSURE OF MEETING
The chair thanked the attendees for their constructive contribution to the meeting.
As a result of the above discussions, the following “actions items” were defined for the project partners:

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<th>From now on</th>
<th>Responsibility</th>
<th>Timelines</th>
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<tbody>
<tr>
<td>2014-01</td>
<td>Template for risk management</td>
<td>KVU</td>
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<tr>
<td>2014-02</td>
<td>Share updated general slides</td>
<td>UGent</td>
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<tr>
<td>2014-03</td>
<td>Develop timelines for communication</td>
<td>UGent, Manufacturers</td>
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<tr>
<td>2014-04</td>
<td>Identify laboratories running a high volume of thyroid function tests</td>
<td>Manufacturers</td>
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<tr>
<td>2014-05</td>
<td>Complete the template for risk management</td>
<td>Manufacturers, others</td>
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</tbody>
</table>

Minutes made by:
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# Appendix A

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Appendix B
Slides from the annual meeting in conjunction with the AACC 2014 Conference
IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

Annual meeting in conjunction with the AACC 2014 Conference

Chair
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Scientific Secretary
Katleen Van Uytfanghe
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Agenda
- Standardization/harmonization approaches
- Status of final Phase IV method comparison
- International developments
- Visit to the FDA
- First plans for risk assessment
- Financing of scientific secretariat at Ghent University
- Other items?

Standardization/harmonization approaches
Supported by publications in peer reviewed journals

Status final Phase IV method comparison
Experimental set-up
- Method comparison with 8 manufacturers
- Samples
  - FT4: ED ID-LC/tandem MS RMP-values
  - TSH: APTM (from robust Alternating regression)

Status final Phase IV method comparison
Experimental set-up (cont.)
Include additional set of NTI-samples? (proposed by F. MacKenzie)

Status final Phase IV method comparison
Commitment of IVD partners regarding sample sourcing
- 6 manufacturers agreed to fund
- 1 decision still pending
- 1 manufacturer declined

How to handle this? Will be discussed in the closed meeting after this open meeting
**Status final Phase IV method comparison**

**Ongoing joint efforts to sample sourcing**

- Commercial sources
  - in.vent Diagnostica GmbH (Germany)
  - Part of the clinical samples
  - Solomon Park Research Laboratories (USA)
  - Euthyroid samples, preparation of the sample sets for the participants
- Clinicians, 7 centers
  - University Hospitals of Ghent, Louvain & Brussels
  - General hospitals Maria Middelares (Ghent) and Sint-Jan (Bruges) (all from Belgium)
  - Dokkyo Medical University (Japan)
  - University of Sydney (Australia)

**Overview collections**

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<th>Short</th>
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<td>~ 0.01 mIU/L</td>
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<td>23</td>
<td></td>
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<td></td>
<td>0.01 - 0.1 mIU/L</td>
<td>20</td>
<td>11</td>
<td>9</td>
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<td></td>
<td>0.1 - 0.3 mIU/L</td>
<td>20</td>
<td>10</td>
<td>10</td>
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<td>0.3 - 3.0 mIU/L</td>
<td>150</td>
<td>11</td>
<td>139</td>
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<tr>
<td></td>
<td>&gt; 3.0 - 50 mIU/L</td>
<td>40</td>
<td>27</td>
<td>13</td>
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<tr>
<td>FT4</td>
<td>&gt; 2.2 ng/dL</td>
<td>60</td>
<td>28</td>
<td>32</td>
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<tr>
<td></td>
<td>0.78 - 2.2 ng/dL</td>
<td>150</td>
<td>5</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>0.23 - 0.78 ng/dL</td>
<td>60</td>
<td>2</td>
<td>58</td>
</tr>
</tbody>
</table>

**Reference intervals for FT4 and TSH**

**Study design**

- 120 samples measured with 8 immunoassays
  - FT4 also with ED ID-LC/tandem MS
- Each manufacturer is expected to extend the cohort (recommendation of FDA: to n = 600?)
- Compilation of results?
- Cooperate with Committee on Reference Intervals and Decision Limits (C-RIDL; chair Dr. Ichihara)?

**Use NHANES data (after standardization or harmonization of the used assays?)**

**Reference intervals (cont.)**

**Inclusion criteria**

- No family history of thyroid dysfunction, euthyroid subjects
- No medications except contraceptives
- Females: not pregnant
- Negative for anti-TPO
- No visible or palpable goiter
- No psychiatric disorder
- Not taking supplements containing iodine

**Use NHANES data (after standardization or harmonization of the used assays?)**

**Information that should be available**

- Source of the samples
- Gender
- If female, +/- contraceptives
- Ethnicity
- Age
- BMI
- (non)-smoker

**Is n = 200 enough?**

*Screening for TSH? Who volunteers for screening/testing?*
Reference interval
World Thyroid Day (May 2014)
Thyroid camp for 600 Indian individuals
Study done by B. Das
• TSH, FT4 and anti TPO measured on the same samples

International developments
Partnership for Accurate Testing of Hormones (PATH)
• Invitation from the Endocrine Society (Dr. J. Laakso) to C-STFT to contribute to the PATH website regarding standardization of free and total thyroid hormones, as well as harmonization of TSH
• J. Faix and L. Thienpont prepared a text (under consideration of the Endocrine Society)
• http://www.hormoneassays.org/thyroid/

International developments
Network of FT4 reference laboratories
• Ready to provide FT4 RMP services:
  - UGent - JCTLM listed (L. Thienpont)
  - Reference Material Institute for Clinical Chemistry Standards (ReCCS, M. Umemoto)
• Committed to develop the FT4 conventional RMP:
  - CDC (H. Vesper)
  - Stanford University (J. Faix)
  - Radboud University Medical Center (A.E. van Herwaarden)

Network most probably not ready by 2015

Visit to the FDA
“Conditional” agreement with the technical concepts proposed by the C-STFT
Conditions for manufacturers: new 510(k) clearance
• Common FDA guidance document on the requirements for the pre-submission process will not be provided
• Group submission is not possible
  ➔ In all contacts with the FDA, manufacturers should refer to participation in the C-STFT activities
  ➔ FDA will do coordinated assignment of reviewers (who have background on the project)

Visit to the FDA
Conditions for manufacturers: new 510(k) clearance (cont.)
• New studies on imprecision, accuracy, linearity
• “Special 510(k)” procedures may not be appropriate for all assays
  ➔ will depend on the impact of recalibration (shift)
• FDA recommends that manufacturers have their 510(k) submission ready well ahead in time (before implementation intended for 2018)
• The need for a comparison to predicate assay in the 510(k) submission will internally be discussed

Visit to the FDA
“Formally” described outreach program
• For communication/education of changes in test results to the practicing medical community (Δ Δ Δ of reference range values, patient values)
• FDA should be continuously involved/informed on every planned step towards communication
  ➔ As such, FDA can point to issues before the action is undertaken
Visit to the FDA
Conditions to be met by the C-STFT in the pre-submission process (cont.)

Risk-benefit analysis
- Can best be done as a group
- Not enough to rely only on a flagging system from a LIS to point out to the changes
- Upfront communication is advisable; in addition to each manufacturer’s internal communication process
- New reference intervals after recalibration (discussed before)

First plans for risk assessment
Initiatives proposed
- Modeling experiment to demonstrate missed diagnosis or misdiagnosis when using non-standardized testing (data from the Stanford University School of Medicine) (J. Faix)
- NHANES study data for a similar modeling to demonstrate differences in disease prevalence because of a lack of standardization (H. Vesper)
- Contact the Laboratory Errors and Patient Safety Working Group (WG-LEPS) (IFCC)
- Seek closer contact with international patient organizations (G. Beastall)

Stability of performance
To assess under field conditions – the “Percentile#”

Moving median calculated from daily medians of outpatient results must be stable within preset limits

First plans for risk assessment
To include/discuss
- How much change will matter?
- Is a name change of the assay preferable/needed?
- What can go wrong if someone does not capture the change?
- Risk if a non-standardized assay is used? (at some point in time, the clinical community will assume that all assays are equivalent/provide comparable results)
- Final number of samples needed to define the reference interval?

Note: Risk assessment can recognize the joint effort by C-STFT and its positive effect on the risk (dixit FDA)

Proposals from other IVD manufacturers?
Plans for dissemination

Initiatives proposed (cont.)

- Abstract for the American Association of Clinical Endocrinologists (AACE) 2015 meeting in Nashville (J. Faix)
- Contact with primary care providers through the American Academy of Family Practice (AAFP) (J. Faix)
- Contact with the Endocrine Society - one page contribution in their “patient education” magazine (J. Faix)
- Link all future communication to PATH (H. Vesper)
- Contact thyroid associations (J. Faix, G. Beastall)

Other items

- Contact with primary care providers through the American Academy of Family Practice (AAFP) (J. Faix)
- Brief National Societies member of IFCC (G. Beastall) (ask for a contact person)
- Brief national regulatory agencies through contact person (China, Japan, ...)

Others?
Appendix C
Possible candidates to join the C-STFT group of manufacturers (preliminary)

Candidates who confirmed their interest after a first contact with LT:
- Fujirebio
- Mindray

Others:
- Philips
- Samsung

  - www.monobind.com
  - www.immunospec.com
  - www.rapidtest.com
  - www.alpco.com
  - www.drg-diagnostics.de
  - http://diamedix.com/
  - http://www.randox.com/

Other possible sources of information:
- QC-providers (Biorad, …)
- FDA-list of 510(k) cleared assays.
Appendix D

“Progress in Standardization of Thyroid Function Tests”
IFCC WorldLab 2014 – Istanbul - Symposium: Standardization of common endocrine tests
Progress in Standardization of Thyroid Function Tests

Spectrum of thyroid disease

Thyroid disease: “the silent epidemic”
Given the severity of the disease
- Timely diagnosis & treatment are compelling
- Diagnosis and management of disease require integrated clinical-laboratory approaches
- Identification of subclinical dysfunction (hyper- and hypo) relies on laboratory data
- Cascade laboratory testing panel
  - TSH as hallmark test
  - FT4/FT3 (TT4/TT3) testing
  - Antibodies (Abs) (Thyroid Stimulating Immunoglobulin, Anti-Thyroid Peroxidase-, Thyrotropin Receptor- and Thyroglobulin Abs)

Economic impact of thyroid testing
High burden on the healthcare system
Yearly $180*10^6$ TSH- & $60*10^6$ FT4 tests performed worldwide

Benefits of using standardized assays
Fit to address modern clinical & public health needs
- Definition of common reference intervals/clinical decision limits
- Development of evidence-based clinical practice guidelines (application of consistent standards of medical care)
- Translation of research into patient care & disease prevention activities (by aggregation of laboratory data across studies)
- Introduction of electronic patient records
- In publications on clinical studies, no need to mention the laboratory assay used

The “ideal” thyroid function test/assay
Clinically & analytically valid
- Clinical validity, depends on:
  - Ability to accurately reflect the activity of the thyroid gland & hormone concentrations
- Analytical validity, reflected by:
  - Fitness-to-purpose – Intrinsic quality
  - Results comparable with those from other assays
  - To achieve by standardization/traceability of assays to a higher order reference
  - Responsibility of laboratory community in close collaboration with IVD industry

Underpins the indisputable value of efforts towards the “ideal” thyroid function test
IFCC Working Group/Committee for Standardization of Thyroid Function Tests (C-STFT)
Chair: Prof. Dr. L. Thienpont

Terms of reference
• Develop reference measurement systems for free thyroid hormones and TSH
• Establish a network of competent reference laboratories
• Liaise with key stakeholders to implement traceable methods in routine clinical practice

http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/

Development of a reference measurement system for FT4

Reference measurement system*

FT4 reference measurement procedure

International conventional reference measurement procedure (RMP) based on
- Equilibrium dialysis (ED)
- Quantification of thyroxine in the dialysate with a “trueness-based” reference measurement procedure

ED ID-LC/tandem MS

NOTE
The measurand is operationally defined as
“Thyroxine in the dialysate from ED of serum prepared under defined conditions”


Definition of the measurand FT4

Component#
Thyroxine that is not bound to proteins
Name: “Thyroxine(free)”; abbreviation: FT4
Kind-of quantity; units#
Amount-of-substance concentration; pmol/L
System#
Plasma or serum under physiological conditions
(pH 7.4, temperature 37°C)
IUPAC/IFCC format:
“Plasma/Serum – Thyroxine(free); amount-of-substance concentration” (pmol/L)


FT4 reference measurement procedure

Development & validation

**Definition of the measurand TSH**

The problem: TSH analysis is “mixture” –

- **Component**
  - Human TSH – intact, total, glycosylation encountered in diagnostic applications which should be specified

- **Kind-of quantity: units**
  - Arbitrary amount-of-substance concentration (mIU/L)

- **System**
  - Serum

**NOTE:** Definition requires that TSH assays deliver a measure for “total TSH” & measure the specified TSH-glycoforms in an equimolar way


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**TSH harmonization approach**

**Proposal by C-STFT**

Statistical “all-procedure trimmed mean” (APTM) from a method comparison with a clinically relevant panel and participation by (as many as possible) assays to serve as “surrogate RMP”

**NOTE**

- Statistical basis: robust factor analysis model
- Requires excellent correlation of results to the APTM


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**Method comparisons**

**Three studies performed**

- Phase I – III (2008 - 2012)

**Objectives – Assess/Investigate the**

- Standardization status of current FT4 & TSH assays
- Assays’ intrinsic quality of performance
- Feasibility of standardization of FT4 assays by method comparison with the conventional reference measurement procedure on a clinical panel
- Feasibility of harmonization of TSH assays by method comparison and the APTM
- Impact of standardization/recalibration

---

**Milestones achieved with the developed FT4 & TSH reference measurement systems**
Collaborating IVD manufacturers

Approach for the method comparisons

Step-up approach#

Phase I: Method comparison with high-volume sera from volunteers; mathematical recalibration

Phase II: Proof-of-concept but with inclusion of master calibrators & recalibration by IVD manufacturers

Phase III: Method comparison with a clinically relevant panel (again with inclusion of master calibrators & recalibration by IVD manufacturers)


3 Thienpont et al. Eur Thyroid J. DOI: 10.1159/000358270.

Intrinsic quality of performance – FT4

No standardization without sufficient quality

Total error (TE): estimated in difference plot vs biological limits for TE (9.6%) (recalculated data with regression equation): best & worst (Phase I)

Quality of performance – TSH

Total error: estimated vs biological limits (22.8%): best & worst (Phase I)

20140828_minutes C STFT meeting_Chicago.doc
Draft 1
Quality of performance – TSH
Correlation of assay results with the APTM (Phase I)

<table>
<thead>
<tr>
<th>Code</th>
<th>$r^2$</th>
<th>Code</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>0.998</td>
<td>M</td>
<td>0.991</td>
</tr>
<tr>
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<td>0.997</td>
<td>I</td>
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<tr>
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<td>N</td>
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</tr>
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</table>

- High in general; best $r^2 = 0.998$; worst still ~0.95

Proof-of-concept – FT4 & TSH
Relationship RMP*/APTM – Routine assays#

- Relationship stable within the typical batch to batch variation of current assays
- Recalibration# removes assay-specific biases

- *Reference measurement procedure
- #Phase I: mathematical
- #Phase II: master calibrator-based

Effect of standardization/recalibration
FT4 – Phase III

- Bias to ED ID-LC/tandem MS removed
- Residual dispersion nearly entirely due to within-assay effects

Effect of harmonization/recalibration
TSH – Phase III

- Recalibration nicely centers the distribution of the assay differences around zero
- Remaining dispersion from within-assay effects
- Indirect proof of glycosilation blind assays

Impact of standardization/recalibration
FT4 – Phase III

- Most pronounced effect in the eu- & hyperthyroid range
- FT4 concentrations will increase in general by 30 – 50%
- Reference intervals will change
No dramatic impact for most assays, except for
Assay I: overall effect high but status after
harmonization quite impressive
Assays F & G: effect of recalibration (by a constant
factor) mainly in the low range
A: recalibration effect mainly in the high range
B: Limited dynamic range, reformulation?

C-STFT Chair grateful for
IVD industry sponsorship of the
Phase I to III study panels

Way Forward
Phase IV (timeline 2014-'15)
To technically prepare standardization/harmonization
without direct implementation though; clinically relevant
panel currently collected#
Establish an infrastructure to sustain standardization
and harmonization
Set-up a network of FT4//FT3 reference laboratories
Currently: UGent (L. Thienpont) & ReCCS (M. Umemoto);
potential other candidates: Stanford University (J. Faix);
CDC (H. Vesper); Radboud UMC (AE van Herwaarden)
Liaise with regulatory authorities (FDA; EC)
#Van Houcke SK, Thienpont LM. “Good samples make good assays” - The
torturous way to sourcing clinical samples for the thyroid standardization

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