PARTICIPANTS
The meeting attendance list is attached in annex. 
Note: the list only contains the names of the colleagues we could remember after returning back home, since, unfortunately, we forgot to circulate our attendance list. Please be so kind to circulate the minutes to the colleagues we forgot and/or were accompanying you.

OPENING OF THE MEETING
The chair (LT) welcomed the meeting attendees, presented the agenda and proposed to make a roll call.

OBJECTIVES OF THE MEETING
LT chair explained that the main objectives of the meeting were:
- Presentation/discussion of the Phase III method comparison study for FT4 and TSH (data treatment and interpretation).
- Path forward.

However, because of the recent (spring 2012) transformation of the WG-STFT into a Committee (C-STFT), she also briefly commented on the new structure by:
- Introducing the members, corresponding –, liaison person to the Scientific Division of IFCC.
- Recalling the terms of reference
LT further proposed, as part of a marketing strategy for the C-STFT, the construction of a website (with logo) linked to the IFCC website. Note the logo is open for discussion, since one of the C-members claimed it to be very similar to the one previously used by Abbott in a project about thyroid function tests.

Note: these minutes will be accompanied by the slides presented in the meeting.

PHASE III METHOD COMPARISON
LT first expressed her gratitude to all colleagues involved in the “great” Phase III study. She particularly appreciated the timely performance of the measurements and reporting of the results by all manufacturers, in spite of the tight deadline she had set after shipment of the samples. She also explicitly thanked the staff of her reference laboratory at UGent, on the one hand for their skilful measurement of FT4 with the conventional reference measurement procedure (cRMP) based on equilibrium isotope dilution-liquid chromatography/tandem mass spectrometry (ED ID-LC/tandem MS), on the other hand for data treatment, and writing of the report.

LT mentioned that in the Phase III method comparison 8 manufacturers had participated with 13 FT4 (14 TSH) assays. For FT4, immunoassay results were compared with ED ID-LC-tandem MS, whereas for TSH with the all-procedure trimmed mean (APTM).

Sources and requirements for clinical samples
LT reviewed the sources [ProMedDx (contact person: Dr. Jim Boushell), SRL Research (Dr. J. Bickford), 2 Belgian endocrinologists from the Hospital AZ Sint-Jan Brugge (Dr. A. Van de Bruel), and the UGent Academic Hospital (Dr. Y. Taes)] that were used to provide clinical samples. She also recalled the number and patient “categories” to cover the FT4 and TSH measurement ranges, as well as the in/exclusion criteria set for patient enrollment. With regard to the special request to have all information on treatment of the thyroid-diseased donors, she mentioned this has not been a problem (all information is available at UGent and can be provided on request). With regard to sourcing of the specimens, LT pointed to the fact that this has been a particularly challenging experience. Instead of the 90 (100) samples for FT4 (TSH) aimed at, it only had been possible to obtain 74 (94) samples in a timespan starting in fall 2010 and ending in February 2012. Hence, for the future it will be important to work on the establishment of a better sample procurement infrastructure, based on a solid relationship not only with commercial suppliers, but also with a significant number of committed clinicians in hospitals. Also, if the group will decide for a Phase IV (see below), it will be essential to start sufficiently early with procurement of clinical samples of the required quality.

LT discussed with the manufacturers the fact that the Phase III samples from research donors had not been tested for infectious diseases (in contrast to the donations from healthy donors of Phase I & II from Solomon Park). She explained that she had been told by PromedDx that testing of research donors is not required by FDA. Therefore, unless explicitly requested as part of the “in- and exclusion requirements”, viral testing is not done. LT questioned whether the manufacturers see this a prerequisite for future method comparisons. The answer was negative, as they don’t test themselves the samples they collect for own purposes. Dr. A. Gutierrez clarified the FDA requirement for the US: “shared” clinical samples utilized for research purposes don’t have to be tested for infectious diseases; on the contrary, if used for commercial purposes and sold, testing is required.

Data treatment and interpretation of the Phase III method comparison for FT4
LT gave an overview of the concentration range covered by the FT4 panel. She recalled the measurement protocol used by manufacturers and explained how the data were treated and interpreted against analytical quality specifications from the biological variation concept (for details: see slides series attached “C-STFT-AACC 2012-part 1”). She further discussed why certain samples were omitted from the evaluation. Unfortunately, this applied to 2 of the fortified samples for FT4, received through courtesy of Roche: they showed (most probably) not commutable (see slide 14 representing the APTM- versus ED ID-LC/tandem MS results); in addition they had a concentration too far outside the range of the other samples. The C-STFT member on behalf of Roche called the characteristics of these samples a disappointment and most unfortunate, because they could have been a solution to cover the difficult-to-obtain high FT4 samples.

LT further discussed typical performance characteristics inferred from the method comparison, such as within-run CV, 1.96*SD-%-residuals, between-run differences, shifts/drifts, assay comparability, between-assay CV, bias versus the cRMP.

Finally, she pointed to the dramatic changes that would occur on the market upon standardization of the FT4 immunoassays against the cRMP. In the same time, she re-emphasized that standardization of FT4 measurements in pregnancy would not be possible and referred to a publication of her group in collaboration with the University Hospital of Brussels (Anckaert et al. Clin Chim Acta 2010;411:1348-53).
She then opened the discussion on the FT4 Phase III study. Below a summary of comments/questions.

- Apparently immunoassays compare better with each other than with the cRMP.
- In view of the tremendous change in values for FT4 (values will increase by 40-50%), when standardized against the cRMP, it was questioned whether, in view of the 17511 ISO standard, a cRMP is really needed for FT4.
- It will be a difficult task to convince clinicians. Education will be needed to prevent misdiagnosis of patients in clinical practice, in particular because the upper limit of the reference interval (RI) will be affected. Also monitoring of patients, already tested in the pre-standardization phase, will be difficult. This is a reason to only standardize when all manufacturers do it for all countries where they are on the market. Besides method recalibration, implementation of standardization will be important to avoid the HbA1c confusion. This will imply, among others, adequate curve fitting, QC-materials and procedures, in-house stability, education of doctors, etc. In reply, LT confirmed that she absolutely shares this point of view and emphasized that standardization (or harmonization for TSH) is not for tomorrow, even if the group/manufacturers are technically ready to go for it. She also understands the tremendous financial burden that standardization could bring along. Therefore, implementation should be carefully prepared by involving all stakeholders.

With regard to the impact on patient care, she also mentioned a positive consequence, i.e. the possibility to develop guidelines with recommendations for common clinical decision limits.

- Do manufacturers currently distinguish between RIs for, e.g., the USA and Europe? Apparently not, but there are publications on ethnic differences.
- The importance of standardization with a panel covering an extended concentration range (as was the case in Phase III) was re-emphasized. A broad concentration range also means that samples from euthyroid subjects are combined with samples from real thyroid-diseased patients (hypo-, and hyperthyroid). This allows evaluation whether the performance of the immunoassays is similar for all type of samples, which is a conditio sine qua non for standardization.

- Will the FT4 cRMP be sustainable over the years? LT replies that as known, the cRMP has been transferred to the ReCCS laboratory in Japan (Dr. M. Umemoto). She continuously looks for other laboratories to implement it. She got already a declaration of interest from Prof. Jim Faix (member of the C-STFT, Stanford University, CA) and Dr. Hubert Vesper (Protein Biomarkers Laboratory in the Division of Laboratory Sciences, CDC, Atlanta). LT’s laboratory is prepared to offer any assistance for implementation of the cRMP.

Other matter of concern were:
- What about change in absolute values of a RI and regulation?
- What about assay-specific reference intervals in pregnancy?

**Data treatment and interpretation of Phase III method comparison for TSH**

LT explained the data treatment and interpretation of the Phase III method comparison for TSH. The approach is mostly similar to the one used for FT4, apart from the fact that the APTM was used for comparison. LT informed the manufacturers that the APTM used for the Phase III report is not the final one. Her lab currently works together with a statistician of UGent to estimate the APTM by a robust principal component analysis (PCA) method (outcome expected in fall 2012).

Finally, LT showed that harmonization for TSH would have no dramatic effects on the overall market.
Comments/questions:
-is the PCA approach suited for harmonization of TSH assays? LT affirmed this and referred to 3 publications and will send them on request:
-The worse comparability for TSH in the pathophysiological ranges might be due to a difference in assays or to a difference in physiological TSH forms (i.e., changes in glycosylation). LT replied that the data do not support this supposition, as all assays are within ±10% from the APTM, apart from a few. She recalled that the peculiar observation for TSH in Phase II (i.e., high between-assay variation for certain assays in the elevated TSH range; in that Phase this was also suspected to be due to differences in recognition of different glycosylation forms) could not be reproduced; finally, from additional experiments, the observation had to be attributed to (unknown) matrix effects of the Phase II samples. Also the stability in performance for TSH over the 5 years (Phase I started in 2007!) (see below) was seen as another argument to state that physiological differences had not been influencing the performance of the TSH assays.
-Assuming that all assays are standardized to the WHO, should this traceability be given up when harmonizing? LT confirmed traceability of all assays to the WHO standard and stressed that the harmonization approach would preserve it (after all, the APTM is estimated from measurement results by immunoassays traceable to the WHO standard, thus the IU of the WHO is transferred to the APTM). She explained that for harmonization, manufacturers in the end will only have to use a master equation, that relates their values to the APTM of the panel. (cf. HbA1c). The FDA representative added that the need for a new clearance or not should then be discussed.
-Maintaining harmonization will be difficult and shifts in time might occur. What to do with new assays? LT replied that she sees the first panel as a sort of predicate panel for harmonization of all assays that participated in the method comparison from which the APTM was calculated. Most probably a 2nd predicate panel should be developed, but this should only be measured by 3 selected assays, so that it can be used for sustainability and made available to new manufacturers. Each follow-up panel has then to be measured in overlap with the predicate panel to ensure continuity. In this way, a stable APTM should be maintained. Some attendees doubt about this statement when using different panels. They fear that measuring of the panel by a new cohort of assays might change the APTM.
-Changes in the euthyroid range will be small when harmonization is done. This will make it difficult to convince stakeholders that harmonization would be beneficial.
-What about preservation of the log-lin relationship between TSH and FT4? Reply by LT: has not been assessed.

After the discussion of the 2 reports, the Chair showed an overview of the method comparisons for FT4 & TSH in Phase I, II and III. The performance compared with the cRMP (FT4) and the APTM was for certain assays particularly stable over the years. For most assays, the observed differences were within the lot-to-lot variation (i.e. 10%). LT interpreted this as a proof of the stability of the cRMP and the APTM. With regard to the performance of
she sees the fact that the group is contrary (her timelines do not foresee to complete the project before “03 2018”). However, mean that standardization decision “2013 timelines/tas consider special attention to the timeline “02 201

LT will ask him the accepted, maybe an analytical or clinical journal should be cho committed to write a sort of rebuttal against the initiative of the aforementioned editor would endanger preamble will be needed to explain why in this highly sensitive project transparency of results because it may help to make stakeholders interested. To get it accepted, maybe a sort of every agreed that the results of Phase III should be offered to a journal for publication, because it may help to make stakeholders interested. To get it accepted, maybe a sort of preamble will be needed to explain why in this highly sensitive project transparency of results would endanger it rather than be productive. The Abbott representative (Dr. F. Quinn) committed to write a sort of rebuttal against the initiative of the aforementioned editor s. If not accepted, maybe an analytical or clinical journal should be chosen for submission. Maybe the editor of the IFCC journal (Clinical Chemistry and Laboratory Medicine) should be asked.

LT pointed to the fact that most probably it would be impossible to get the results of Phase III published. She referred to the initiative by certain editors to not accept anonymous research studies anymore (see; Rifai N, Plebani M, Wu A, Brugnara C, Delvin E, Lamb EJ, Ness PM, Wick MR, Berg JP. Full disclosure in industry-sponsored laboratory medicine research studies: statement by the Consortium of Laboratory Medicine Journal Editors. Clin Chem 2011;57:359-60). Therefore, she asked whether the report at least should be put on the planned website of the C-STFT. The president of the IFCC clarified that the requirement for absolute “transparency” of results is based on the fundamental assumption that diagnostics should be treated as pharmaceuticals. Therefore, the industry representatives concluded that there was a need to communicate to the outside (editors in first instance) why this group had decided to keep the results of the 3 phases anonymous (in short: the main objective of this project is not to compare manufacturers but to improve patient care; to do so, the group looks into the feasibility of finding a basis for standardization/harmonization).

Everyone agreed that the results of Phase III should be offered to a journal for publication, because it may help to make stakeholders interested. To get it accepted, maybe a sort of preamble will be needed to explain why in this highly sensitive project transparency of results would endanger it rather than be productive. The Abbott representative (Dr. F. Quinn) committed to write a sort of rebuttal against the initiative of the aforementioned editor s. If not accepted, maybe an analytical or clinical journal should be chosen for submission. Maybe the editor of the IFCC journal (Clinical Chemistry and Laboratory Medicine) should be asked.

LT will ask him.

PATH FORWARD?

LT presented the planning-in-time she had in mind for management of the project. She drew special attention to the timeline “02 2013” for the “GO-decision: Technical Part”. She considers the “Go-decision” by the manufacturers crucial to commit for the next timelines/tasks, i.e., “03 2013 – Define design Phase IV; start sample procurement”, “04 2013 – Plan Stakeholder Meeting”, and so on. She clarified that in her mind, after the “Go-decision”, the Phase IV method comparison should be the basis for the technical process of standardization (FT4)/harmonization (TSH). She clarified in the same time that this does not mean that she wants to implement standardization already at that point in time, quite on the contrary (her timelines do not foresee to complete the project before “03 2018”). However, she sees the fact that the group is ready from the technical point of view and, therefrom,
knowing the consequences of standardization as the best starting point to involve stakeholders. For the case manufacturers would consider it very early to take the “Go-decision” already beginning 2013, she recalled that it will take another year for sample collection/preparation, etc.

This timeline proposal was intensively discussed. Addressed topics were:
-How can the selection of new samples be justified? Answer (LT): it will be essential to collect an adequate number of samples, with FT4/TSH concentrations representative for euthyroid individuals as well as patients affected by hypo- and hyperthyroidism, all together reasonably covering the measurement range of the assays, and concentrations at equal distance along that range.
-Regarding to the number of samples: there is a cloud of uncertainty. Answer (LT): this is true, and normally, one should ask a statistician. Indeed, on the basis of the uncertainty of measurements by the assays and the acceptable uncertainty for reliable recalibration, one can do power calculation to derive the required number of samples. However, this is what one can theoretically do, but according to her experience, the answer statisticians give, mostly misses any relationship to practicality. This was affirmed by others, who advised to rather calculate the minimum number. Another attendee came back to the importance of taking the variability between assays and sample-related effects into account, which would probably result in a different number for each assay. He continued that, therefore, the approach followed by the group should be well explained. Another colleague suggested that the objective of explaining the approach to clinicians definitely should be to convince them that the used approach is the adequate one, to make sure that the highly sensitive standardization/harmonization of thyroid function tests doesn’t follow the HbA1c example. Another colleague commented that TSH harmonization would not be that difficult (as shown in the report, the current standardization status is not that bad and the limit of quantification of current assays is OK), but that FT4 standardization would require much more work. From this point of view, a member of the C-STFT suggested it might be better to start with TSH, also from the point of view of the importance of the test. The previous colleague agreed.
-What about PT/EQA schemes and accuracy/bias? Contact should be made with typical schemes like UKNEQAS, CAP, and others. Two members of the C-STFT committed to do so.
-Intensification of contact with important stakeholders: a member of the C-STFT (J. Faix) wants to propose something about the C-STFT activities in the meeting of the ATA next September. He will meet the thyroid testing expert Dr. C. Spencer and will try to let her something say about this (topic of her presentation: Pitfalls in the analysis of FT4/TSH). Another member referred to the efforts already done by LT to get in touch with important associations/societies (i.e. the “Endocrine Society”…). The President of the IFCC (also representative for the BTA) commented that according to his experience, clinicians in the UK were first horrified when they saw the results of our studies, but that they now are absolutely in favor of the project. He re-iterated that the clinical user (mainly endocrinologists, but it should not be forgotten that hypothyroidism is also treated by non-) should become an important partner in the information campaign. Maybe one should explicitly point to the risk attributed to wrong values.
-LT wanted to come back to the real item of discussion at this point and asked whether the participants were confident about the results of Phase III or agreed that another panel (Phase IV) for standardization/harmonization will be needed? She added that the manufacturers didn’t have to decide immediately, but that it was her intention to mandate them with internal discussions on the “Go-decision”. A member of the C-STFT (representing
the IVD industry) answered that the decision will take some time in view of the open items, such as how many samples are needed, which patient categories should be included to do the standardization/harmonization properly, what will be the quality of the data, what will be the consequences for each manufacturer, what will be the feedback from clinicians, laboratories, etc.

-LT asked what should be done in the meantime and within which time span. She proposed to start contacting stakeholders. It was agreed to do so early enough, since the opinion of stakeholders can facilitate the decisions to take.

-How will manufacturers ensure in-house stability after standardization/harmonization? Will this be done with samples obtained according to the normal process, or by pooling and by whom? LT replied that to ensure stability in time, manufacturers have their processes in place. During the standardization/harmonization measurement process with native samples, they use to include their own pools for value assignment and subsequent use. LT continued that this process would already be important in Phase IV too, because she has in mind that, for the sake of preserving as much left-over volume as possible of the precious clinical samples, she will ask manufacturers to only participate with their master assays. The latter will then be used for in-house recalibration of their other assays. The manufacturers agreed.

-LT asked the opinion of the attendees about the proposed timelines. The answer was that they were agreeable as guideline or template but with wide “confidence intervals”. Each of the manufacturers will discuss them in their own companies. An American colleague pointed to the fact that for the US, involvement of CDC and NIST would be important (the president of the IFCC pointed to the European equivalent of NIST, i.e., the IRMM). Another question was whether in each region an “institution” should be mandated to ensures sustainability, e.g., in India. LT answered that the efforts towards sustainability should be centralized. The representative from CDC replied that from his point of view involvement of CDC as another reference lab was realistic, however, he stressed that for CDC to be involved a public health need should be defined. Therefore, he considers it as utmost important to bring clinicians around the table to know what their opinion is, and reach a consensus, as CDC did for steroid hormones. He declared prepared to look for the possibility to collaborate with the CSTFT in approaching clinicians and other stakeholders. LT would be happy with the proposed collaboration. HV further stressed that reference laboratories need to work together to obtain consistent measurements.
As a result of the above discussions, the following “actions items” were defined for the project partners:

1. Estimate the APTM for TSH by PCA (UGent).
2. Perform in-house recalibrations for Phase III on the basis of the FT4 & TSH targets and send results to UGent; provide master calibration curves when requested (IVD manufacturers).
3. Contact the FDA with regard to the question whether harmonization for TSH (and standardization for FT4) will require a new FDA clearance (LT).
4. Think of publishing or not the Phase III method comparison study: if yes, write a rebuttal to the decision of the aforementioned editors to not accept anonymous reports of studies with IVD manufacturers (F. Quinn) or select a journal that may accept the manuscript without disclosure of the results (all).
5. Consider the opportunity of organizing a workshop/symposium at the 2013 AACC meeting (all).
6. Look at the perspectives of standardization/harmonization: discuss in-house the reasons for doing it, but also the problems (IVD manufacturers).
7. Decide whether a final panel (Phase IV) for the technical process of standardization is desirable. If so, define the design of Phase IV (i.e. number of samples…) (LT with IVD manufacturers).
8. Discuss appropriateness of the proposed timelines (IVD manufacturers).
9. Consider collaboration between CDC and C-STFT to invite involved stakeholders around the table (LT).
10. Discuss acceptability of proposed logo with Abbott and IFCC (F. Quinn to send to LT the logo of Abbott he referred to; LT to discuss with IFCC).

CLOSURE OF MEETING
The chair thanked the attendees for their contribution to the meeting.
**Annex**

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The representatives of Diasorin Germany and Italy

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<td>Gérard Baudino</td>
<td>BioMérieux</td>
</tr>
<tr>
<td>David Montague</td>
<td>Ortho Clinical Diagnostics</td>
</tr>
<tr>
<td>Brigitte Toussaint</td>
<td>IRMM, Belgium</td>
</tr>
<tr>
<td>Kathleen Van Uytfanghe</td>
<td>University of Ghent, Belgium</td>
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</tbody>
</table>

Minutes made by:
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Laboratory for Analytical Chemistry, Faculty of Pharmaceutical Sciences, UGent
Harelbekestraat 72, B-9000 GENT, Belgium
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**IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)**

Annual meeting in conjunction with the AACC 2012 Conference

Linda Thienpont
Linda.thienpont@ugent.be

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**Introduction**

- **Agenda**
  - Welcome and roll call
  - Report: Phase III method comparison (FT4 & TSH)
  - Discussion of reports
  - Path forward?

---

**C-STFT**

Phase III method comparison

- **FT4**
  - 13 assays from 8 manufacturers compared with ED ID-MS
  - **Report**

---

**Clinical samples: Sources & requirements**

**Source**

Contact: Dr. Jim Boushell (Norton, MA 02766, USA)

---

**Clinical samples: Requirements & Sources**

**Concentration ranges – Categories**

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Details</th>
<th>Target n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSH</strong> A1 &lt; conc.</td>
<td>Hyper-thyroid</td>
<td>10</td>
</tr>
<tr>
<td>A2: 0.01-0.1 mIU/L</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>A3: 0.1-0.3 mIU/L</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>B: 0.3-3.0 mIU/L</td>
<td>Eu –</td>
<td>30</td>
</tr>
<tr>
<td>C1: 3.0-10 mIU/L</td>
<td>Hypo –</td>
<td>20</td>
</tr>
<tr>
<td>C2: &gt;10 mIU/L</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><strong>FT4</strong> D: &gt; 2.2 ng/dL</td>
<td>Hyper –</td>
<td>30</td>
</tr>
<tr>
<td>E: 0.6-2.2 ng/dL</td>
<td>Eu –</td>
<td>30</td>
</tr>
<tr>
<td>F: 0.2-0.6 ng/dL</td>
<td>Hypo –</td>
<td>30</td>
</tr>
</tbody>
</table>

**TSH: n = 100 – FT4: n = 90**

---

**Clinical samples: Sources & requirements**

**Requirements – Exclusion criteria**

- Individuals not meeting the established inclusion criteria
- Previously enrolled into this clinical study
- Undergoing ANY treatment for thyroid dysfunction. **OMITTED, but:** If treated, capture information on the type of treatment and when it has been started
- Diagnosed with a severe non-thyroidal illness (NTI) (abnormal levels of T3, T4, FT3 and/or FT4, although thyroid gland not dysfunctional; NTI is mostly associated with chronic renal failure, liver cirrhosis, advanced (active) malignancy, sepsis, trauma, prolonged fasting/starvation, heart failure, MI
- Diagnosed with a psychiatric disorder
Clinical samples: Sources & requirements

Requirements – Testing for infectious disease?
- Donations from healthy donors Phase I & II (<Solomon Park) tested for viral markers, as required by FDA
- Phase III samples from research donors not tested: not required by FDA, therefore, typically not done unless part of the “In- and Exclusion requirements”
- If required, aliquot sent to a reference laboratory for certification
- What should we do for the future?

Note: in most cases, the patients in our research studies are in fact viral negative, because we can see this in their medical charts...however we don’t officially test them unless requested (dixit PromedDx)

Clinical samples: Sources & requirements

Additional sources

Contact: J. Bickford (Carlsbad, CA 92018 USA)

Contact: A. Van den Bruel, MD and Y. Taes; MD

Clinical samples: Requirements & Sources

However, in view of the “torturous” way to get the samples....

Clinical samples: Requirements & Sources

Clinical samples: Requirements & Sources

Clinical samples: Requirements & Sources

Data treatment

Outlier identification and treatment
- Assay-specific outliers
- Visual identification in difference plots of the duplicate averages and %-residuals vs ED ID-MS
- Limit for outlier detection – 3SD
- Identified outliers substituted with values that fitted best in the %-residual plot, whereby both replicates were given the same value
- Substituted values excluded for CVwr and between-run differences

Clinical samples

Characteristics
- FT4: concentration range (ED ID-MS): 3 – 77 pmol/L
- 1 sample (P#049) < LoQ* of ED ID-MS
- n = 3 fortified samples (<Roche)

Measurement protocol
- In duplicate within one run
- 1st Replicate in ascending order, 2nd replicate in descending –
- Inclusion of master calibrators
- Free IQC protocol

*LoQ = 1.3 pmol/L (Clin Chem 2006;52:1817)
**Data treatment**

Outlier identification and treatment

<table>
<thead>
<tr>
<th>Sequ. #</th>
<th>Sample</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>G</th>
<th>H</th>
<th>J</th>
<th>L</th>
<th>M</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>P #001</td>
<td>X</td>
<td></td>
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<td>31</td>
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<tr>
<td>71</td>
<td>P #052</td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>

Result: 11 outliers (out of a total of 923 data)

**Data interpretation**

**Assay quality**

Analytical goals for FT4 measurement

(http://www.westgard.com/biodatabase1.htm)

<table>
<thead>
<tr>
<th>CV (%)</th>
<th>Bias (%)</th>
<th>Total error (TE) (%)</th>
<th>TE ≤ 5 pmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9</td>
<td>3.3</td>
<td>3.3% + 1.645*2.9% = 8.1% (+RM = 9.6%)</td>
<td></td>
</tr>
</tbody>
</table>

$Taking the imprecision of the ED ID-MS method into consideration

**Outlier identification and treatment**

**“All-procedure trimmed mean” (APTM) versus ED ID-MS**

Without 2 fortified samples (P#054; P#055, non-commutable, too far outside the range), best fit with 3rd degree polynomial function

%-Residuals within ±10%, except -20% for the sample (P#049) <LoQ

- Three samples excluded from further data treatment

**Data interpretation**

Assay quality (sorted by %)

<table>
<thead>
<tr>
<th>Range</th>
<th>Assay</th>
<th>CVwr (%)</th>
<th>H</th>
<th>G</th>
<th>A</th>
<th>I</th>
<th>K</th>
<th>L</th>
<th>J</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.96% (H) to 11.6% (F)</td>
<td></td>
<td></td>
<td>1.6</td>
<td>2.4</td>
<td>2.9</td>
<td>3.1</td>
<td>3.1</td>
<td>3.4</td>
<td>3.5</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>4%: J (4.7%), M (5.0%), and F (11.6%)</td>
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<tr>
<td>Note: Max. CVa* = 2.9%</td>
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</tbody>
</table>

*http://www.westgard.com/biodatabase1.htm

**Data interpretation**

Assay quality (cont.)

Between-run differences (sorted by abs. diff.)

<table>
<thead>
<tr>
<th>Range</th>
<th>Assay</th>
<th>Abs. difference (%)</th>
<th>CI (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3% (E) to 3.3% (B)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;2% for I, G &amp; B</td>
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</table>

Note: Max. TE = 2.9%

$Taking the imprecision of the ED ID-MS method into consideration

Note: Max. CVa* = 2.9%

*Reflects combined effect of assay imprecision and sample-related effects; is an indication of TE after correction of calibration bias
Summary

Phase III method comparison

General
- Conc. range covered: 3 to 77 pmol/L (ED ID-MS)
- ED ID-MS values for samples P #049, P #054, and P #055 given for information, only (<LoQ; non-commutability; concentration too far apart from the range of the other samples)
- The best fit of the APTM vs ED ID-MS data gave %-residuals in the range of ±10%
Summary

Phase III method comparison
Assay quality
- CVwr ~ max. CVwr (2.9%) from biological variation; >4% for 3 assays (4.7%, 5.0%, 11.6%), only
- 1.96 SDw, ext within the expanded biol. TE limit (9.6%), except for 5 assays (13.3% – 20.8%). For the last assay with a CVwr of 1.6%, mainly due to the presence of sample-related effects
- Between-run differences >2% for 3 assays (2.6%, 3.0%, 3.8%)
- Shifts or drifts in the order of 5 – 10% for 3 assays
- Between-assay CV in the order of 10 ~ 20%, except for the samples <5 pmol/L (after outlier adaptation and exclusion of low and fortified samples)

Summary

Phase III method comparison
Assays compared to ED ID-MS
- Biases dependent on the concentration range:
  > 27 pmol/L: -37%; 9 – 27 pmol/L: -25%; <9 pmol/L: 2%
- Bias for some assays constant over the complete conc. range; others even tend to positive biases in the low range
- Most extreme deviation (34%) between assays M & K in the conc. range 9 – 27 pmol/L, but difference small >50 pmol/L
- Assays B & E had the most extreme combinations of slope and intercept (B = 0.77x + 0.45; E = 0.42x + 6.63); demonstrates additionally the importance of concentration-dependent biases

Standardization – Effect on market

Dramatic changes on the market!
CAVE: No standardization for pregnancy!

C-STFT

Phase III method comparison
- TSH -
14 assays from 8 manufacturers compared with the APTM

Report

Data treatment

Outlier identification and treatment
- Assay-specific outliers
- Visual identification in difference plots of the duplicate averages and %-residuals vs the "raw" APTM
- Limit for outlier detection – 3SD
- Identified outliers substituted with values that fitted best in the %-residual plot, whereby both replicates were given the same value
- Substituted values excluded for CVwr and between-run differences
- APTM calculated with the adapted assay-specific outliers; process done iteratively (adaptation of outliers changes the APTM)

Data treatment

Outlier identification and treatment

<table>
<thead>
<tr>
<th>Sequ #</th>
<th>Sample</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
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<td>7</td>
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</tbody>
</table>

Without P #068, 20 outliers (out of a total of 1218 data)
APTM target values

APTM calculated for the reduced concentration range (0.04 – 80 mIU/L), only

Rationale: 7 samples had TSH concentrations below the functional sensitivity (<0.012 mIU/L); no results reported by 3 to 6 assays; APTM values given for information, only

Procedure for APTM calculation
First investigate all assays for any particular feature/influence on the “raw” APTM, and if necessary exclude from the APTM

Result: Exclusion of B, because of lower dynamic range (no results reported for the 2 lowest and the 2 highest samples of the “reduced range”); note: the company participated also with other assay(s)

APTM target values

Procedure for APTM calculation (ctd.)
- Then, F and G were calibrated to the APTM in the concentration range <1.1 mIU/L by adding a constant factor (F: 0.038 mIU/L; G: 0.042 mIU/L). This greatly improved the comparability of the assays to the APTM (see Fig.)
- Result: Exclusion of I from the APTM (note: the company participated with other assay(s) in the study)
- Alternatively, I could have been calibrated to the APTM and then included with the other assay(s) from the same company
- Calibration of F & G to the APTM had beneficial effect on the fit of, e.g., H (similar for several other assays). Without calibration, a typical “u”-shaped form of the residuals is seen when data are fit with an unmodified power equation

APTM target values

Procedure for APTM calculation (ctd.)

For C, a suitable fit vs the APTM could be found only after multiplying the results in the conc. range 2.5 – 40 mIU/L with the factor 0.87

%Difference of assays F & G after correction in the range <1.1 mIU/L APTM

Residuals of H vs the “raw” (left) and the final APTM (right)

%Difference and %residual plot for assay C with unmodified data

Note: Currently, the APTM is calculated also by use of Principal Component Analysis (PCA). Final calculations may be ready in autumn, only
Data interpretation

Assay quality
Analytical goals for TSH measurement
(http://www.westgard.com/biodatabase1.htm)

<table>
<thead>
<tr>
<th>CV (%)</th>
<th>Bias (%)</th>
<th>Total error (TE) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.7</td>
<td>7.8</td>
<td>7.8% + 1.645*9.7% = 23.8%</td>
</tr>
</tbody>
</table>

Data interpretation

Assay quality (replicate 1)
1.96 SD_{true}

<table>
<thead>
<tr>
<th>Range</th>
<th>Assay</th>
<th>1.96 SD_{true} (rep 1)</th>
<th>Outliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.7% (J) to 21% (K)</td>
<td>J</td>
<td>8.7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>9.9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>10.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>10.6</td>
<td>3</td>
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<tr>
<td></td>
<td>H</td>
<td>11.9</td>
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<td></td>
<td>F</td>
<td>12.1</td>
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<td>G</td>
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<td></td>
<td>B</td>
<td>15.6</td>
<td>4</td>
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<tr>
<td></td>
<td>L</td>
<td>15.9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>K</td>
<td>21.0</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: reflects combined effect of assay imprecision and sample-related effects; indication of TE after correction of calibration bias

Data interpretation

Assay quality (replicate 1)
1.96 SD_{true}

<table>
<thead>
<tr>
<th>Range</th>
<th>Assay</th>
<th>1.96 SD_{true} (rep 1)</th>
<th>Outliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.7% (J) to 21% (K)</td>
<td>J</td>
<td>8.7</td>
<td>1</td>
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<tr>
<td></td>
<td>D</td>
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<tr>
<td></td>
<td>K</td>
<td>21.0</td>
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</tr>
</tbody>
</table>

Data interpretation

Assay quality (assay-specific outliers excluded, reduced range and adapted outliers)

<table>
<thead>
<tr>
<th>Assay</th>
<th>Full range</th>
<th>0.1 mIU/L</th>
<th>1-10 mIU/L</th>
<th>&gt;10 mIU/L</th>
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<tbody>
<tr>
<td>E</td>
<td>0.9</td>
<td>0.8</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>F</td>
<td>1.3</td>
<td>2.0</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>J</td>
<td>2.2</td>
<td>1.9</td>
<td>1.6</td>
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<tr>
<td>A</td>
<td>3.1</td>
<td>4.0</td>
<td>3.1</td>
<td>2.1</td>
</tr>
<tr>
<td>G</td>
<td>3.6</td>
<td>2.8</td>
<td>3.9</td>
<td>4.6</td>
</tr>
<tr>
<td>D</td>
<td>3.7</td>
<td>2.5</td>
<td>3.7</td>
<td>4.8</td>
</tr>
<tr>
<td>L</td>
<td>3.7</td>
<td>3.5</td>
<td>4.4</td>
<td>3.1</td>
</tr>
<tr>
<td>K</td>
<td>4.3</td>
<td>6.7</td>
<td>4.1</td>
<td>2.0</td>
</tr>
<tr>
<td>N</td>
<td>4.9</td>
<td>6.3</td>
<td>5.5</td>
<td>2.9</td>
</tr>
<tr>
<td>H</td>
<td>6.5</td>
<td>5.9</td>
<td>4.2</td>
<td>9.4</td>
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<tr>
<td>M</td>
<td>8.9</td>
<td>7.6</td>
<td>8.4</td>
<td>10.8</td>
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</table>

Max. CVs = 9.7%: www.westgard.com/biodatabase1.htm
Data interpretation

Assay comparability: Assay bias (% average) vs APTM

- Maximum difference (whole conc. range): ~33%; assay I lowest; assay K highest; direction of bias for some assays conc. dependent
- Assays outside ±10% of the APTM: 4 (low), 2 (mid), and 4 (high); >good comparability in the normal range
- Harmonization would benefit comparability in the pathophysiological ranges

Data interpretation

Assay comparability

- Summary Figures
  - I & K most deviating: 45% in range 0.03 – 0.5 mIU/L, 33% in range 0.5 – 5.0 mIU/L, >5.0 mIU/L
  - y = 0.79x + 0.03
  - % Residual plot expected distribution of data after optimal recalibration

Data interpretation

Assay comparability

- Functions for best fit and correction factors

Data interpretation

Assay comparability

- Assay bias (% average) vs APTM (sorted by bias in the range 0.5 – 5 mIU/L)

Data interpretation

Assay comparability

- Assay quality
  - CVwr similar across the concentration range: from 0.9% (E) to 8.9% (K); >5% for 3 assays (5.1%, 6.5%, 8.9%) (<max. CVwr of 9.7% from biological variation)
  - 1.96 SDm range from 8.7% to 21%; for all assays smaller than the biological TE limit of 23.8%
Summary
Phase III method comparison
Assays compared to the APTM
- Max. deviation between the assays ~33% over the whole concentration range
- Deviation most extreme between I (most neg. biased -21 to -33%) and K (most pos. biased 8 to 12%)
- Deviations between I & K: 45% in the conc. range 0.03 – 0.5 mIU/L; 32% in range 0.5 – 5.0 mIU/L; 33% >5.0 mIU/L
- Good comparability of the assays in the normal concentration range
- Harmonization of the assays would improve comparability in particular in pathophysiological ranges

Harmonization – Effect on market
Manufacturers affected by harmonization
I: overall, then harmonization status in the normal range quite impressive
B: Limited dynamic range, reformulation?
A: high range adaptation
F & G: low range adaptation (+ 0.038/0.042 mIU/L?)
Maybe most drastic because it may affect the sensitivity claim
No dramatic effects on the overall market

Comparison Phase I – III
Standardization status FT4 compared to ED ID-MS

Comparison Phase I – III
Standardization status TSH compared to ED ID-MS

Comparison Phase I – III
Currently awaiting …
In-house recalibration based on FT4 & TSH targets
- Received 5 TSH and 6 FT4 recalibrated data sets
- We may need your master calibration curves (number of points and fit, e.g., 4 parameter logistic (4PL)

With thanks to…
Path forward
Design for standardization & harmonization
“Step-up” design

Phase I: Familiarization
- High-volume single donations from apparently healthy volunteers
- Provided a general picture of assay quality and comparability

Phase II: Proof-of-concept
- Confirm the concept and allow decision to step-up to phase III

Phase III: Step-Up – clinical samples
- Provide detailed insight in assay quality and comparability by use of “normal” and “clinical” samples
- Allow decision to standardization/harmonization
- Set preliminary target values for standardization/harmonization

Phase IV: Go for standardization/harmonization
- Provide a panel for standardization/harmonization that covers the measurement range, without inclusion of “problematic” samples
- Establish a protocol for sustainability (transfer of values to follow-up panels); treatment of assays that are newly launched on the market
- Requires a 2nd panel (“Predicate panel”)

Note: In view of the restricted sample volume, we recommend that each manufacturer participates with his “master” assay; this can subsequently be used internally for standardization/harmonization of the other assays in the company

Path forward?
“Go” decision?
February 2013?

“Go” decision: technical part of sample collection, for measurement in February 2014

Path forward?
Timelines overview
2012
10 Phase III Final Report
10 Project Charter & Management concept
2013
01 Milestone Feasibility
02 “GO”-decision: Technical Part
03 Define design Phase IV; start sample procurement
04 Plan Stakeholder Meeting
2014
02 Phase IV Measurements
03 1st Stakeholder Meeting

Path forward?
Timelines overview
2015
02 2nd Stakeholder Meeting
03 Milestone Sustainability
04 “GO”-decision: Implementation
2016
02 Stakeholder Feedback Report
2017
01 Implement FT4 Standardization
02 Implement TSH Harmonization
11 Final Stakeholder Feedback Report
2018
03 Final Project Report
03 Project finished
IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

Annual meeting in conjunction with the AACC 2012 Conference

Linda Thienpont
Linda.thienpont@ugent.be

Introduction

Agenda
- Welcome and introduction
- Report of WG-STFT meeting on 6 & 8 March
- Discussion of important issues
- Path forward?
- Transformation of the WG-STFT into a Committee
- Path forward?
- Closure of meeting

Transformation of WG into Committee

Standardization of Thyroid Function Tests (C-STFT)

Membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Country</th>
<th>Term</th>
<th>Time in Office</th>
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<tr>
<td>L. Thienpont</td>
<td>Chair</td>
<td>BE</td>
<td>1st</td>
<td>2012-01 - 2014-12</td>
</tr>
<tr>
<td>B. Das</td>
<td>Member</td>
<td>IN</td>
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<td>2012-01 - 2014-12</td>
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<tr>
<td>J.D. Fox</td>
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<td>US</td>
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<td>2012-01 - 2014-12</td>
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<td>F. Macfarlane</td>
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<td>1st</td>
<td>2012-01 - 2014-12</td>
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<tr>
<td>F. Quinn</td>
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<td>2012-01 - 2014-12</td>
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<tr>
<td>M. Rothmann</td>
<td>Member</td>
<td>DE</td>
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<td>2012-01 - 2014-12</td>
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<td>Rh. Gilhory</td>
<td>Liaison</td>
<td>FR</td>
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Budget from IFCC
- CHF 12,000

C-STFT

Activities status
- Members selected (April 2012)
- Electronic kick off (May 2012)
- Planning project management structure (June 2012)
  - Project charter and management concept
  - Responsibilities
  - Milestones, achievements
  - Resources needed
  - Stakeholders and tasks
  - ...
**Path forward?**

**Timelines overview: 2012 – 2018**

- **2012**
  - 10 Phase III Final Report
  - 10 Project Charter & Management concept

- **2013**
  - 01 Milestone Feasibility
  - 02 “GO”-decision: Technical Part
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- **2016**
  - 02 Stakeholder Feedback Report

- **2017**
  - 01 Implement FT4 Standardization
  - 02 Implement TSH Harmonization
  - 11 Final Stakeholder Feedback Report

- **2018**
  - 03 Final Project Report
  - 03 Project finished

---

**Path forward?**

**Some highlights**

**Define design Phase IV**
- Samples
- Experiments
- Statistical protocol for recalibration
- Quality specifications

**Define stakeholders**
- Reference Laboratories
- Manufacturers
- EQA/PT providers
- Routine laboratories
- Journal editors
- Regulatory authorities
- Clinical Societies
- Patient organizations

**How to involve them?**

---

**Path forward?**

**Marketing**
- Website
- Presentations at symposia
- Publications
- Webinars
- AACC podcast
- ...
Path forward?

See you at
Euromedlab 2013
in Milano

Monday 20th June