IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)
Meeting at AACC 2012, Los Angeles, CA, Monday July 16th (2:30 - 5:00 pm)

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

See also: http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/.
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 skillful 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, $1.96*SD_{\%\text{-residuals}}$, 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:
(i) Rymer JC, et al. A new approach for clinical biological assay comparison and standardization: application of principal component analysis to a multicenter study of twenty-one carcinoembryonic antigen immunoassay kits. Clin Chem 1999;45:869-81;
(ii) Lawton WH, et al. Statistical comparison of multiple analytic procedures - application to clinical-chemistry. Technometrics 1979;21:397-409;
(iii) Carey RN, Wold S, Westgard JO. Principal component analysis: an alternative to "referee" methods in method comparison studies. Anal Chem 1975;47:1824-9.
-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

some assays that apparently had changed in Phase III compared to Phase II or III, LT mentioned that only the manufacturers of these assays know whether they changed something in the format or calibration of their assays. Manufacturers asked to send them an overview of their own codes used throughout the different phases.

The Chair pointed to the fact that she is currently awaiting for the in-house recalibrations by the manufacturers based on the FT4 & TSH targets she sent them (5 TSH and 6 FT4 recalibrated data sets yet received); master calibration curves might be needed.

The issue of disclosure of the identity of the manufacturers/assays was raised again. One of the corresponding members (from Japan) considered disclosure necessary to increase awareness of clinicians to the current problems. LT explained that the former WG-STFT had good reasons to not disclose the names of the manufacturers, and that the Committee would continue to respect this decision for Phase III. A representative of the Mayo Clinic mentioned that clinicians are sufficiently aware of the problems, and consequently repeat testing when they see a patient who was tested elsewhere.

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.
-With regard 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 C-STFT 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

Name	Affiliation	e-mail address
Linda Thienpont	Chair IFCC C-STFT	linda.thienpont@ugent.be
Sofie Van Houcke	University of Ghent, Belgium	sofie.vanhoucke@ugent.be
Hedwig Stepman	University of Ghent, Belgium	hedwig.stepman@ugent.be
Graham Beastall	IFCC-BTA	gbeastall@googlemail.com
Frank Quinn	Member of C-STFT (Abbott)	frank.quinn@abbott.com
Emmanuel Romeu	Beckman Coulter, Inc.	EROMEU@beckman.com
Michael Rottmann	Member of C-STFT (Roche)	michael.rottmann@roche.com
Philippe Gillery	Liaison to IFCC-SD	pgillery@chu-reims.fr
Paul Sibley	Corresponding member (Siemens Medical Diagnostics)	paul.sibley@siemens.com
Annette Adelmann	Beckman Coulter, Inc.	AMAdelmann@beckman.com
Jim Faix	Member of C-STFT (AACC; Stanford University)	jim.faix@stanford.edu
Barnali Das	Member of C-STFT (ACBI; Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute at Mumbai, India)	barnali.das@relianceada.com
Ravinder Singh	Mayo Clinic	Singh.Ravinder@mayo.edu
John Reid	Abbott	john.reid@abbott.com
Alberto Gutierrez	FDA	alberto.gutierrez@fda.hhs.gov
Judy Ogden	Tosoh Bioscience, Inc.	judy.ogden@tosoh.com
Susan Kolarik	Tosoh Bioscience, Inc.	susan.kolarik@tosoh.com
Shanti Narayanan	Tosoh Corporation	shanti.narayanan@tosoh.com
Sachiyuki Hasegawa	Tosoh Corporation	sachiyuki-hasegawa-de@tosoh.co.jp
Yasutami Mitoma	Tosoh Corporation	yasutami-mitoma-su@tosoh.co.jp
Yuki Furuta	Tosoh Corporation	yuki-furuta-ku@tosoh.co.jp
Hubert Vesper	CDC	hav2@CDC.GOV
Julianne Bothello	CDC	gur5@cdc.gov
Yasamin Ebrahimi Rahmani	CDC	vrd7@cdc.gov
Doug Clark	Siemens Medical Diagnostics	douglas.p.clark@siemens.com
Akira Hishinuma	Corresponding member (Dokkyo University)	a-hishi@dokkyomed.ac.jp
John Backus	Ortho Clinical Diagnostics	Jbackus@its.jnj.com

Excused

Name	Affiliation	e-mail address
Pierre Carayon	Corresponding member (Société Française de Biologie Clinique)	pierre.carayon@univmed.fr
Anja Kessler	Corresponding member (chair IFCC C-TLM; DGKL)	akessler@uni-bonn.de
Finlay Mackenzie	Member of C-STFT (ACB;	Finlay.Mackenzie@uhb.nhs.uk

	UKNEQAS)	
The representatives of Diasorin Germany and Italy		DSchell@diasorin.de; Luigi.Nava@Diasorin.it; gmarkowitz@diasorin.de; Fulvio.Garetto@Diasorin.it; Nadia.Corocher@Diasorin.it
Roland Janzen	Siemens	roland.janzen@siemens.com
Gérard Baudino	BioMérieux	gerard.baudino@eu.biomerieux.com
David Montague	Ortho Clinical Diagnostics	DMontagu@ocdgb.JNJ.com
Brigitte Toussaint	IRMM, Belgium	Brigitte.TOUSSAINT@ec.europa.eu
Katleen Van Uytfanghe	University of Ghent, Belgium	Katleen.VanUytfanghe@UGent.be

Minutes made by:
Prof. Dr. Linda THIENPONT, Chair of the IFCC WG-STFT
Laboratory for Analytical Chemistry, Faculty of Pharmaceutical Sciences, UGent
Harelbekestraat 72, B-9000 GENT, Belgium
Tel. +32 9 264 81 04
e-mail: linda.thienpont@ugent.be

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 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

Patient category	Details	Target n
TSH A1 <<<conc.	Hyper-thyroid	10
A2: 0.01- 0.1 mIU/L		10
A3: 0.1-0.3 mIU/L		10
B: 0.3-3.0 mIU/L	Eu –	30
C1: 3.0-50 mIU/L	Hypo –	20
C2: >50 mIU/L		20
FT4 D: > 2.2 ng/dL	Hyper –	30
E: 0.8-2.2 ng/dL	Eu –	30
F: 0.2-0.8 ng/dL	Hypo –	30

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: Requirements & Sources

However, in view of the "torturous" way to get the samples ….

Clinical samples: Sources & requirements

Additional sources

SLR Research Corporation – Your Global Source for Biomaterials.

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

az sint-jan brugge - oostende av

UZ Universitair Ziekenhuis Gent

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

Clinical samples: Requirements & Sources

Final number of clinical samples: TSH n = 94; FT4 n = 74

Patient category	Details	Target n	Received
TSH A1 <<<conc.	Hyper-thyroid	10	4
A2: 0.01- 0.1 mIU/L		10	8
A3: 0.1-0.3 mIU/L		10	5
B: 0.3-3.0 mIU/L	Eu –	30	43
C1: 3.0-50 mIU/L	Hypo –	20	30
C2: >50 mIU/L		20	4
FT4 D: > 2.2 ng/dL	Hyper –	30	(RMP) 20 (APTM) 9
E: 0.8-2.2 ng/dL	Eu –	30	(RMP) 48 (APTM) 54
F: 0.2-0.8 ng/dL	Hypo –	30	(RMP) 6 (APTM) 11

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

- 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

Data treatment

Outlier identification and treatment

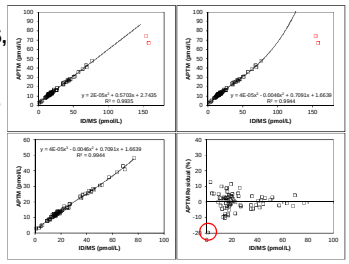
Sequ. #	Sample	C	D	E	G	H	J	L	M
1	P #001		X			X			
3	P #003				X		X		
7	P #007			X					
13	92236	X							
20	P #016		X			X			
31	P #023							X	X
71	P #052					X			

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

Data 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

Analytical goals for FT4 measurement (http://www.westgard.com/biodatabase1.htm)

CV (%)	Bias (%)	Total error (TE) (%)	TE ≤5 pmol/L
2.9	3.3	3.3% + 1.645*2.9% = 8.1% (+RM = 9.6%$)	0.48 pmol/L

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

Data interpretation

Assay quality (assay-specific outliers excluded)

Within-run CV (CVwr) (sorted ↑)

Range
1.6% (H) to 11.6% (F)

>4%: J (4.7%), M (5.0%), and F (11.6%)

Note: Max. CVa* = 2.9%

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

Assay	CVwr (%)
H	1.6
G	2.4
A	2.9
I	3.1
K	3.1
E	3.4
C	3.4
D	3.5
L	3.6
B	3.9
J	**4.7**
M	**5.0**
F	**11.6**

Data interpretation

Assay quality (cont.)

1.96 SD of the %-residuals (replicate 1) (1.96 $SD_{\%-res}$)#

Range
8.2% (K) to 20.8% (F)

For C through F, 1.96 $SD_{\%-res}$ >> 9.6% = Max. TE

14.5% for H (despite best CVwr) >major sample-related effects

Assay	1.96 $SD_{\%-res}$ (Rep 1)	Outliers
K	8.2	
G	8.6	1
E	9.6	1
L	9.6	1
J	10.4	1
I	11.2	
B	11.6	
A	11.8	
C	**13.3**	1
H	**14.5**	3
D	**14.7**	2
M	**15.7**	1
F	**20.8**	

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

Data interpretation

Assay quality (cont.)

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

Range
0.3% (E) to 3.3% (B)

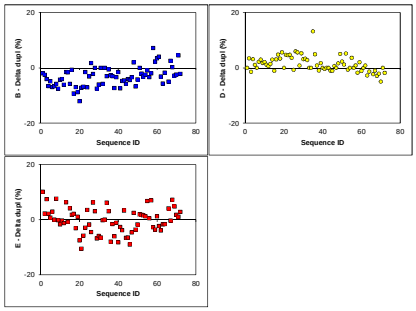
>2% for I, G & B

Assay	Abs. difference (%)	CI (%)	Signifi-cance
E	0.3	1.1	no
J	0.4	1.5	no
F	0.5	3.9	no
M	0.6	1.5	no
C	1.0	1.2	no
H	1.0	0.4	yes
A	1.1	0.9	yes
L	1.1	1.2	no
K	1.2	0.9	yes
D	1.4	0.7	yes
I	**2.8**	0.8	yes
G	**3.0**	0.5	yes
B	**3.3**	0.8	yes

Data interpretation

Assay quality (cont.)

Shifts and drifts: B, D & E ~5 – 10%



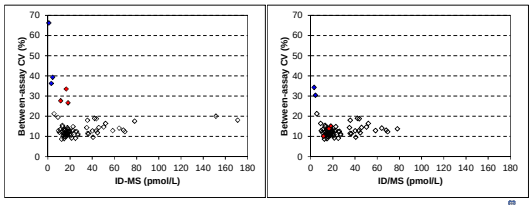
Data interpretation

Assay comparability (assay-specific outliers excluded)

CVba vs sample concentration before (left) & after (right) outlier adaptation and exclusion of 3 samples (P#049,54,55)

Left: 10 – 20%, except <5 pmol/L (blue symbols) and for 3 samples in the conc. range of 10 – 30 pmol/L (red symbols)

Right: ~10%; significantly >20% for samples <5 pmol/L



Data interpretation

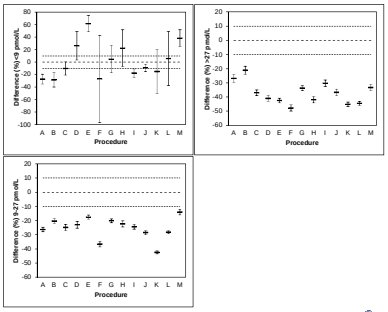
Assay comparability

Assay bias (%, average) vs ED ID-MS

9–27 pmol/L:
-25% (-14% to -42%)

<9 pmol/L:
2% (-28% to 62%)

>27 pmol/L:
-37% (-21% to -48%)



Data interpretation

Assay comparability

Assay bias (%, average) vs ED ID-MS

B & A
fairly constant over the complete range

M, E, G, H, D, & L
tend to positive biases in the low range

Assay bias (%, average) vs ED ID-MS (sorted by bias in the range 9 – 27 pmol/L)			
Assay	<9 pmol/L	9-27 pmol/L	>27 pmol/L
M	38.4	**-14.0**	-33.3
E	**61.6**	-17.5	-42.5
G	4.6	-20.2	-33.8
B	**-28.3**	-20.4	**-21.2**
H	22.5	-22.4	-42.0
D	26.0	-23.0	-40.9
I	-17.8	-24.3	-30.3
C	-10.2	-24.8	-37.1
A	-27.3	-26.3	-26.9
L	5.7	-28.2	-44.5
J	-9.3	-28.5	-36.8
F	-27.1	-36.7	**-47.7**
K	-15.2	**-42.4**	-45.1

Data interpretation

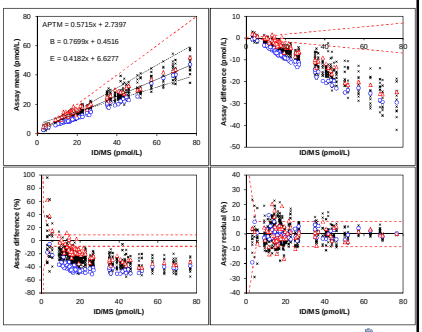
Assay comparability

Summary figures

M & K most deviating (34%) (9 - 27 pmol/L); -little difference >50 pmol/L

B & E most extreme combinations of slope & intercept (conc.-dependent biases)

%-Residual plot: Expected distribution of data after optimal recalibration



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 $SD_{\%\text{-res}}$ 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 (2.8%, 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

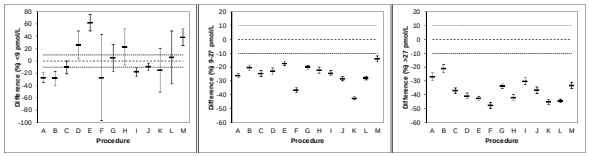
Assays compared to ED ID-MS

- Biases dependent on the concentration range: > 27 pmol/L: -37%; 9 – 27 pmol/L: -25%; <9pmol/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!#



#Anckaert E, Poppe K, Van Uytfanghe K, Schiettecatte J, Foulon W, 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

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

Sequ #	Sample	A	B	C	D	E	F	G	H	I	J	K	M	N
7	P #007	X												X
15	100942						X	X						
25	P #021			X										
27	P #023			X	X									
28	P #024		X	X										
33	99155				X									
37	P #029	X												
38	P #030					X								
44	P #036	X												
55	P #043		X	X	X	X				X		X		
84	P #068		X		X		X	X	X	X	X		X	X
88	92244		X											

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

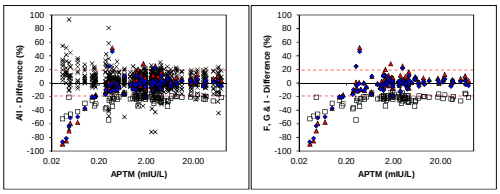
First investigate all assays for any particular feature/influence on the "raw" APTM, and if necessary exclude from the APTM

- **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.)

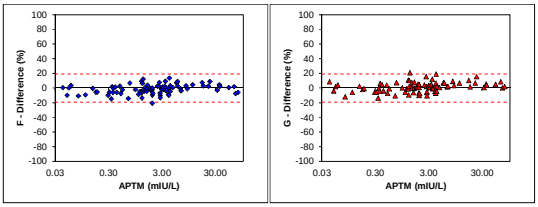
- **F, G, and I showed a strongly negative deviation from the other assays in the low concentration range (see Fig.)**
- **I, additionally, deviated most from the other assays**
- **Exclusion of I from the APTM (note: the company participated with other assay(s) in the study)**
- **Alternatively, I could have been calibrated to the APTM and then included with the other assay(s) from the same company**



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.)**

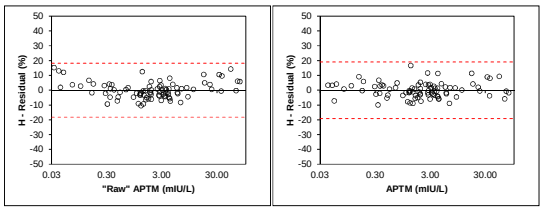


%-difference of assays F & G after correction in the range <1.1 mIU/L APTM

APTM target values

Procedure for APTM calculation (ctd)

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 a unmodified power equation

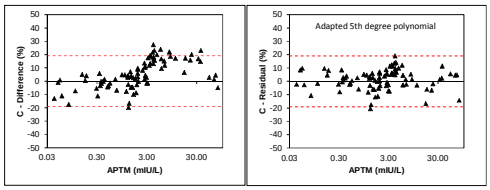


Residuals of H vs the "raw" (left) and the final APTM (right)

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 and %-residual plot for assay C with unmodified data

APTM target values

Procedure for APTM calculation (ctd.)

Result (cont.)

- **Finally, assays from the same company were averaged and their average was used for the calculation of the final APTM (in total, 8 data sets). Rationale: Give each manufacturer the same weight and fairly balance sample-related effects**
- **The finally calculated APTM covered the concentration range from 0.042 to 80 mIU/L**

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)

CV (%)	Bias (%)	Total error (TE) (%)
9.7	7.8	7.8% + 1.645*9.7% = 23.8%

Data interpretation

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

CVwr (sorted ↑ for range 1-10 mIU/L)

Full range
0.9% (E) to 8.9% (K)

>5% I (5.1%), H (6.5%) and K (8.9%)

CVwr similar across range

Assay	Full range	0-1 mIU/L	1-10 mIU/L	>10 mIU/L
E	**0.9**	0.8	1.1	0.9
F	1.3	2.0	1.4	0.4
M	2.1	2.0	2.2	2.0
J	2.2	1.9	1.6	3.2
C	2.8	2.9	3.1	2.3
A	3.1	4.0	3.1	2.1
G	3.6	2.8	3.9	4.0
D	3.7	2.5	3.7	4.8
L	3.7	3.5	4.4	3.1
B	4.3	6.7	4.1	2.0
N	4.9	6.3	5.5	2.9
I	5.1	5.0	3.7	6.7
H	6.5	5.9	4.2	9.4
K	**8.9**	7.6	8.4	10.8

Max. CVa = 9.7%; www.westgard.com/biodatabase1.htm

Data interpretation

Assay quality (replicate 1)

1.96 $SD_{\%\text{-res}}$

Range
8.7% (J) to 21% (K)

All assays had 1.96 $SD_{\%\text{-res}}$ < max. TE 23.8%

Assay	1.96 $SD_{\%\text{-res}}$ (Rep 1)	Outliers
J	**8.7**	1
D	9.9	4
I	10.0	2
A	10.6	3
H	11.9	1
F	12.1	2
G	12.8	2
M	13.5	1
E	14.1	2
C	14.9	4
N	15.0	2
B	15.6	4
L	15.9	
K	**21.0**	1

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

Data interpretation

Assay quality

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

Range
0.1% (M) to 5.2% (K)

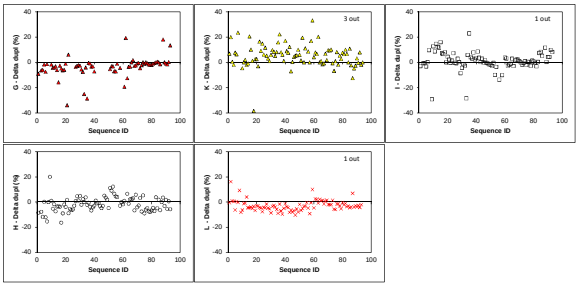
>2%:
G (2.9%), L (3.3%), & K (5.2%)

Assay	Abs. difference (%)	CI (%)	Signifi-cance
M	**0.1**	0.7	no
A	0.3	0.9	no
E	0.3	0.3	yes
J	0.4	0.5	no
B	0.4	1.2	no
F	0.5	0.8	no
D	0.5	1.0	no
C	1.1	0.9	yes
N	1.3	1.4	no
I	1.8	1.4	yes
H	1.9	1.2	yes
G	**2.9**	1.4	yes
L	**3.3**	0.6	yes
K	**5.2**	1.7	yes

Data interpretation

Assay quality

Shifts and drifts: G, H, I, K & L ~5 – 10%



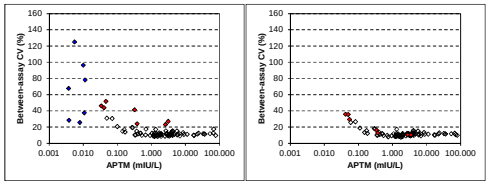
Data interpretation

Assay comparability

CVba vs sample concentration before (left) & after (right) outlier adaptation and reduction of range

Left: 10 – 20%, except <0.012 mIU/L (blue symbols; excl. from APTM) and several samples with assay-specific outliers (red symbols)

Right: 10% >0.5 mIU/L; 0.5 to 0.04 mIU/L, increase to ~40%



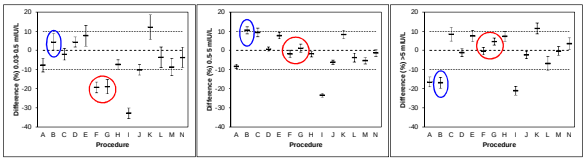
Data interpretation

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

Assay bias (%, average) vs APTM

I: most neg. biased
-21 to -33%
K: most pos. biased
8 to 12%
B: pos. bias <5 mIU/L
>5 mIU/L: neg. bias

F & G: strong neg. bias in the range <0.5 mIU/L

Assay bias (%, average) vs APTM (sorted by bias in the range 0.5 – 5 mIU/L)			
Assay	0.03-0.5	0.5-5	>5
I	-32.8	-23.4	-21.1
A	-7.7	-8.4	-16.5
J	-10.2	-6.2	-2.3
M	-8.7	-5.4	-0.3
L	-3.6	-3.8	-6.8
F	-19.3	-1.9	-0.3
H	-7.4	-1.9	7.4
N	-3.7	-1.4	3.5
D	4.4	0.7	-1.2
G	-19.0	1.2	4.6
E	7.6	7.7	7.6
K	12.1	8.3	11.5
C	-2.1	9.4	8.4
B	4.4	10.5	-16.9

Data interpretation

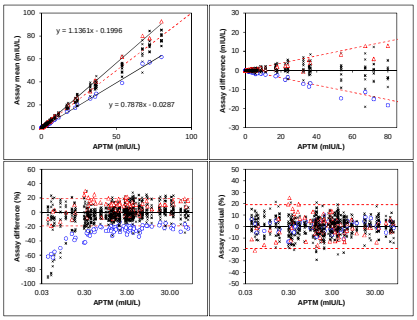
Assay comparability

Summary Figures

I & K most deviating:
45% in range 0.03 – 0.5 mIU/L;
32% in range 0.5 – 5.0 mIU/L;
33% >5.0 mIU/L

I: y = 0.79x – 0.03
K: y = 1.14x – 0.2

%-Residual plot expected distribution of data after optimal recalibration



Data interpretation

Assay comparability

Functions for best fit and correction factors

Assay	Fit	Factor	Note
A	Power		
B	Modified 5th degree		Not in APTM
C	Modified 5th degree	x 0.87 (2.5 – 40)	
D	Power		
E	Power		
F	Modified 3rd degree	+ 0.038 (<1.1)	
G	Modified 3rd degree	+ 0.042 (<1.1)	
H	Power		
I	Modified 2nd degree	[+ 0.017 (<0.6)]	Not in APTM
J	Power		
K	Power		
L	Power		
M	Power		
N	Power		

Summary

Phase III method comparison

General observations

- **Concentration range covered: 0.042 to 80 mIU/L**
- **7 samples <0.012 mIU/L; results not reported by 3 to 6 assays; therefore, values given for information, only**

Summary

Phase III method comparison

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 $SD_{\%\text{-res}}$ ranged from 8.7% to 21%; for all assays smaller than the biological TE limit of 23.8%**
- **Between-run differences (%) ranged from 0.1% to 5.2%; >2% for 3 assays (2.9%, 3.3%, 5.2%)**
- **Shifts or drifts in the order of 5 – 20% for 5 assays**
- **Between-assay CV in the order of 10% >0.5 mIU/L (after outlier adaptation and reduction of range); increased gradually from ~10% to ~40% in the concentration range from 0.5 to 0.04 mIU/L**

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

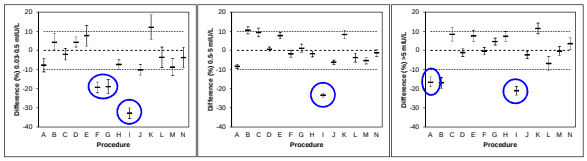
B: Limited dynamic range, reformulation?

A: high range adaptation

F & G: low range adaptation (+ 0.038/0.042 mIU/L?)

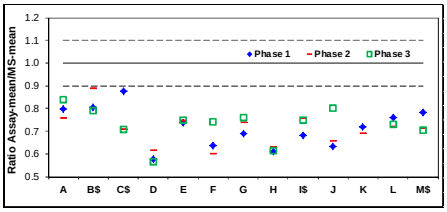
Maybe most drastic because it may affect the sensitivity claim

No dramatic effects on the overall market



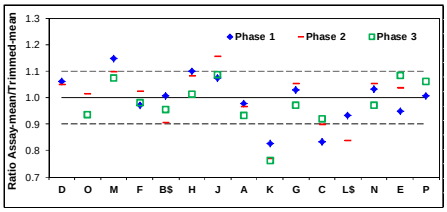
Comparison Phase I – III

Standardization status FT4 compared to ED ID-MS



Comparison Phase I – III

Standardization status TSH compared to ED ID-MS



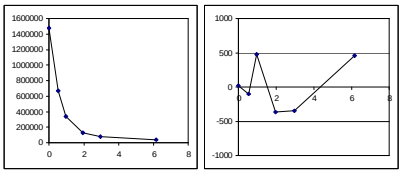
Comparison Phase I – III

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)

Curve **Residuals**



With thanks to…

Phase III – Open for discussion

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

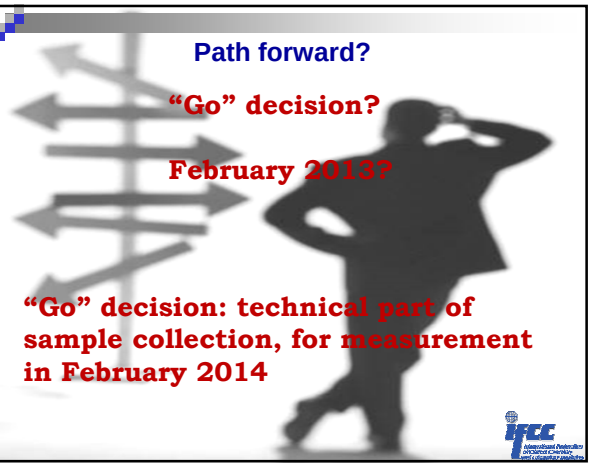
Path forward

Design 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 roll call
- ❑ Report: Phase III method comparison (FT4 & TSH)
- ❑ Discussion of reports
- ❑ 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

Name	Position	Country	Term	Time in Office
L. Thienpont	Chair	BE	1st	2012 01 - 2014 12
B. Das	Member	IN	1st	2012 04 - 2014 12
J.D. Faix	Member	US	1st	2012 04 - 2014 12
F. MacKenzie	Member	UK	1st	2012 04 - 2014 12
F. Quinn	Member/Abbott	US	1st	2012 04 - 2014-12
M. Rottmann	Member/Roche	DE	1st	2012 04 - 2014 12
Ph. Gillery	Liaison to SD	FR		

Transformation of WG into Committee

List of Corresponding Members, nominated by National Societies

Name	Full Member Society
Paul Williams	Australasian Association of Clinical Biochemists (AACB)
Pierre Carayon	Société Française de Biologie Clinique (SFBC)
Jens Berg	Norwegian Society of Medical Biochemistry(NSCB)
Akira Hishinuma	Japan Society of Clinical Chemistry (JSCC)
Anja Kessler	Deutsche Gesellschaft für Klinische Chemie & Laboratoriumsmedizin (DGKL)

List of Corresponding Members, nominated by Corporate Members

Name	Corporate Member
Paul Sibley	SIEMENS

Transformation of WG into Committee

Terms of Reference

- To develop reference measurement systems for free thyroid hormones and TSH
- To establish a network of laboratories competent to offer reference measurement services for thyroid hormones
- To provide an infrastructure for procurement of serum panels
- To define reference intervals with standardized assays and consult with clinicians about the need for ethnic, age- or sub-population-specific reference intervals in co-operation with C-RIDL.
- To liaise with key stakeholders to implement the use of methods traceable to agreed reference methods in routine clinical practice
- Through collaboration with IFCC EMD, to provide educational materials for manufacturers, clinicians and patients which will support the implementation of traceable methods as described under 3 above

Current Projects

- Method comparison study for FT4 and TSH measurement in clinical samples; FT4 measurements to be assessed against the conventional reference measurement procedure, TSH against the all-procedure trimmed mean.

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?

Path forward?

Timelines overview: 2012 – 2018

2012

10 Phase III Final Report

10 Project Charter & Management concept

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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

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Path forward?

Timelines overview

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01 Implement FT4 Standardization

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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?

Some highlights

Marketing

- Website
- Presentations at symposia
- Publications
- Webinars
- AACC podcast
- …

Path forward?

Website

Path forward?

See you at
Euromedlab 2013
in Milano

Monday 20th June