



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

**PARTICIPANTS**

The meeting attendance list is attached in appendix A.

Initials as used in the minutes can be found in appendix A as well.

**OPENING OF THE MEETING**

The chair (LT) welcomed the meeting attendees, presented the agenda and proposed to make a roll call. She conveyed excuses from Dr. F. Mackenzie.

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

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

- Van Houcke SK, Van Uytfanghe K, Shimizu E, Tani W, Umemoto M, Thienpont LM. IFCC international conventional reference procedure for the measurement of free thyroxine in serum. IFCC Working Group for Standardization of Thyroid Function Tests (WG-STFT). Clin Chem Lab Med 2011;49:1275-81.
- Van Houcke SK, Van Aelst S, Van Uytfanghe K, Thienpont LM. Harmonization of immunoassays to the all-procedure trimmed mean - proof of concept by use of data from the insulin standardization project. Clin Chem Lab Med 2013;51:e103-5. doi: 10.1515/cclm-2012-0661.
- Stöckl D, Van Uytfanghe K, Van Aelst S, Thienpont LM. A statistical basis for harmonization of thyroid stimulating hormone immunoassays using a robust factor analysis model. Clin Chem Lab Med 2014;52:965-72.
- Thienpont LM, Van Uytfanghe K, Van Houcke S, Das B, Faix JD, MacKenzie F, Quinn FA, Rottmann M, Van den Bruel A. A Progress report of the IFCC Committee for Standardization of Thyroid Function Tests. Eur Thyroid J 2014;3:109-116.
- Van Uytfanghe K, et al. A "Step-Up" approach for harmonization. Clin Chim Acta 2014;432:62-7.

**2. Status of preparation of final Phase IV method comparison:**

**For a general overview of the set-up of phase IV, see appendix B - slides of the meeting**

*Additional question by F. Mackenzie: should samples of NTI-patients be included.*

- LT reminds that in the past we discussed not to do so.
- JF arguments in favor of the previous decision. NTI-samples would only add a large amount of confusion. He refers to a recent example in a discussion at the FDA on the inclusion of "critically ill" patients in a study for capillary glucose. How to define "critically ill" caused controversy.
- GB adds that NTI is a very complex state of disease and that it will be very difficult to find a representative sample for this.
- LT also reminds on the difficulty of sample sourcing.
- JF reminds us of the fact that this is for sure something we should investigate in the future.

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

*A. Commitment of IVD partners with C-STFT regarding sample sourcing*

REDACTIONAL NOTE: adapted according to the discussion in the closed meeting with the manufactures.

- LT informs that in the meantime all manufacturers confirmed their intention to contribute.



- PS asked if we are aware of other manufacturers - should we not actively inform them on the activities of the C-STFT?
- LT agrees on this. Fujirebio has shown interest and is considering participation. She launches a call to share or forward coordinates of other possible candidates to join us.
- KVV will complete the preliminary list in appendix C.

*B. Ongoing joint efforts to sample sourcing*

- See slides in appendix B

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

*Study design*

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

*Inclusion criteria*

- See also slides.
- JF ask the rationale for excluding patients with psychiatric disorders.
- LT reminds that this was a strong demand upon sample collection in phase III, but does not recall why exactly.
- MP suggests that it is probably only for ethical reasons/credibility. E.g., some patients might not be aware of familial history of thyroid dysfunction, or "lie" about it.
- IY suggests to leave out psychiatric disorders as the term is too vague. E.g. people having a depression, or anxiety disorder (in the past) might be excluded while there is no reason for that. People with severe psychiatric disorders will be excluded anyway as they are on medication, and hence are covered by that exclusion criteria.
- FQ/JF question the exclusion of people taking supplements. E.g. in the US quite some people take multi-vitamin supplements, perhaps containing a small amount of iodine. Perhaps it should be changed to iodine containing medication (high doses).
- IY raises the question whether we should make sure that the samples in the cohort of 120 are from a iodine sufficient region. Iodine fortification is not globally implemented. Some regions on the other hand have a very high iodine status.
- LT adds that for example in the UK, and even in the US, separate RIs might be needed because of iodine insufficiency.
- AA asks if there are age criteria.



- KVV explains there is a minimum, i.e. 18 years.
  - IY questions whether we also need an upper limit. Once over 65 years old there is an increased risk for potentially subclinical hypothyroidism and most people that age take medication.
  - GB questions the in- and exclusion criteria and the discussion in light of the purpose of the study. Is the study designed for standardization or to establish RIs.
  - LT explained that it is intended to set a first basis for new RIs, but more important to demonstrate that manufacturers are comparable when using the same subset of samples.
  - JF adds that it would also underpin the rationale against concerns of manufacturers on the change in RIs. It will be an added value to refer to a common first RI.
  - GB asks whether global RIs are achievable.
  - According to JF, there is no breakdown per country.
  - SN repeats that this is exactly why we included only 120 samples. Each manufacturer can add its own samples if he feels the need for it.
  - The FDA representatives point out to the fact that for FDA clearance a RI study on the 'US population' is needed. So, if we would go for a global cohort of 120 samples, each manufacturer needs to establish his own US population RI.
  - FQ questions the procedures needed for verification of the RIs. The CLSI 28 protocol might not be strong enough, 120 samples might not be sufficient.
  - MR points out to the strength of this study. It is a chance to demonstrate the benefits of standardization. Moreover, this will be a very unique study, never done before. If the study is successful, it demonstrates the benefits for the end-user.
  - LT stresses that it is our intention to source the samples in the US by working with Solomon Park Research Laboratories (SPRL).
  - FQ refers to the point of doing this study, i.e. to demonstrate equivalent RIs are achievable. However RIs which go into a manufacturers insert, go into a regulatory document. Each manufacturer's clinical research group has its own defined protocols for this.
  - LT repeats that it is not the intention of the C-STFT to develop the RIs, this is up to the manufacturers. We only want to show concordance.
  - MP asks who is going to do the non-US RIs.
  - LT repeats that this is for the manufacturers.
  - BD refers to the study she has done, see later, where she established RIs using 600 individuals. To do so, she needed to screen a 1000 volunteers, as 400 of them were high in anti TPO.
  - MR repeats that the outcome of phase IV is only a first shot, to see what the consequences are. Other cohorts should be discussed later on. If we put in too much, we might lose everything. E.g. we know that in pregnancy, there will be no benefit from standardization. Each manufacturer will have to investigate the consequences for his own assay.
  - GB summarizes that the study will give a nice indicative value.
  - JF stresses to the fact that this study should demonstrate that similar cut-off values and RIs are feasible. Otherwise, there is no point in standardizing.
  - IY notes that immunoassays are not identical in terms of performance. Hence we might expect some differences and it is unlikely to end up with identical RIs.
  - SN repeats that verifying this is the purpose of the study.
  - LT points to the fact that in phase III we already demonstrated that the limits are tightened. Of course there will always be slight differences.
- **In conclusion: the RI study design will remain the same, however excluding patients with psychiatric disorders will be left out. The RI will be established with a cohort of 120 US apparently healthy individuals.**



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

#### *Information on the volunteers*

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

### **3. International developments:**

#### *A. World thyroid day*

- BD summarizes her initiative. After screening of 1000 volunteers, she ended up with 600 samples useful to establish a RI for the Indian/Asian population. The FT4/TSH measurements were done using assays of 2 different manufacturers. She will repeat the initiative after standardization and start up a study to establish RIs in pregnancy and pediatric samples.

#### *B. Partnership for Accurate Testing of Hormones in preparation (PATH) (request from the Endocrine Society)*

- See slides, all the activities of the C-STFT will be added to those of the steroid hormones.

#### *C. Network of FT4 reference laboratories*

- See slides.
- The laboratory in Nijmegen is the one of Dr. A. Ross who helped the UGent develop and familiarize the ED-procedure.
- The UGent will value assign a panel of 20 high volume samples, which can be used by the other labs for validation purposes.
- It is not to be expected that the 3 candidates will be ready in 2015. Hence the UGent will be the only laboratory for value assignment. ReCCS will measure some of the samples "pars pro toto". When the others are ready, they can do the same.
- PS asks if we will publish on the reference laboratory network, once ready.
- LT confirms that this is of course the intention.

### **4. Visit to the FDA:**

#### *A. Summary of discussion based on the info given in appendix B*

- The question is raised by several manufacturers why imprecision/accuracy/linearity evaluation of the assays is needed, even though the assays themselves do not change. It is only the calibration set point which changes.
- FDA repeats that a verification is needed. Whether or not the CLSI protocols have to be followed in full or in a reduced form depends on how much the values change. So this will be different for each manufacturer.
- Several manufacturers question the use of a predicate assay, especially because the predicate assay will not be standardized, and hence results will not be comparable. In fact the ED-ID-LC/tandem MS will take over the function of the predicate for FT4, the all procedure trimmed mean (APTM) for TSH.
- The FDA agrees that for accuracy assessment, the comparison to the RMP/APTM will be accepted. No method comparison with a predicate will be needed.
- LT stresses again the request by FDA to submit the new 510(k) well in time.
- To monitor the stability of the standardization status over time, LT proposes to use 'The Percentiler'. Via this tool, developed by Dr. Stöckl (STT consulting) and LT, the moving median of FT4 and TSH results from outpatients can be monitored. To use this tool, participation of big "thyroid centers/laboratories" is needed. From a pilot study, our PhD-

students, working on the project, were able to demonstrate that, under stable analytical conditions, the moving median from a sufficient number of outpatients' results is very stable. In other words, The percentiler is an excellent tool to indicate assay (in)stability, shifts and drifts. For more information:

See <http://www.stt-consulting.com/news.php?rubriek=8>.

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

#### *Risk analysis*

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

#### *Outreach program*

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





near future (2015) will only be very general communication to raise attention for what is coming.

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

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

## **CLOSURE OF MEETING**

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



**As a result of the above discussions, the following “actions items” were defined for the project partners:**

From now on		Responsibility	Timelines
2014-01	Template for risk management	KVU	ASAP
2014-02	Share updated general slides	UGent	ASAP
2014-03	Develop timelines for communication	UGent, Manufacturers	February 2015
2014-04	Identify laboratories running a high volume of thyroid function tests	Manufacturers	End 2014
2014-05	Complete the template for risk management	Manufacturers, others	February 2015

**Minutes made by:**

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

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## Appendix A

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### Excused

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## **Appendix B**

Slides from the annual meeting in conjunction with the AACC 2014 Conference



## IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

Annual meeting in conjunction with  
the AACC 2014 Conference



Chair  
Linda Thienpont  
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Scientific Secretary  
Katrien Van Uytendaele  
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## Agenda

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



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2

## Standardization/harmonization approaches Supported by publications in peer reviewed journals

- Van Houcke SK, Van Uytendaele K, Shimizu E, Tani W, Umemoto M, Thienpont LM. IFCC international conventional reference procedure for the measurement of free thyroxine in serum. IFCC Working Group for Standardization of Thyroid Function Tests (WG-STFT). *Clin Chem Lab Med* 2011;49:1275-81.
- Van Houcke SK, Van Aelst S, Van Uytendaele K, Thienpont LM. Harmonization of immunoassays to the all-procedure trimmed mean - proof of concept by use of data from the insulin standardization project. *Clin Chem Lab Med* 2013;51:e103-5. doi: 10.1515/cclm-2012-0661.
- Stöckl D, Van Uytendaele K, Van Aelst S, Thienpont LM. A statistical basis for harmonization of thyroid stimulating hormone immunoassays using a robust factor analysis model. *Clin Chem Lab Med* 2014;52:965-72.
- Thienpont LM, Van Uytendaele K, Van Houcke S, Das B, Faix JD, MacKenzie F, Quinn FA, Rottmann M, Van den Bruel A. A Progress report of the IFCC Committee for Standardization of Thyroid Function Tests. *Eur Thyroid J* 2014;3:109-116.
- Van Uytendaele K, et al. A "Step-Up" approach for harmonization. *Clin Chim Acta* 2014;432:62-7.



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3

## Status final Phase IV method comparison Experimental set-up

- Method comparison with 8 manufacturers
- Samples

Panel	Hypo	Eu	Hyper
FT4 harmonization panel	30	120	30
TSH harmonization panel	30	120	40
TSH follow-up panel	30	40	30
FT4 follow-up panel	30	40	40

- Target values
  - FT4: ED ID-LC/tandem MS RMP-values
  - TSH: APTM (from robust Alternating regression)



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4

## Status final Phase IV method comparison Experimental set-up (cont.)



Include additional set of NTI-samples?  
(proposed by F. MacKenzie)



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5

## Status final Phase IV method comparison Commitment of IVD partners regarding sample sourcing

- 6 manufacturers agreed to fund
- 1 decision still pending
- 1 manufacturer declined



How to handle this? Will be discussed in the  
closed meeting after this open meeting



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6



## Status final Phase IV method comparison

### Ongoing joint efforts to sample sourcing

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



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7

## Status final Phase IV method comparison

### Ongoing joint efforts to sample sourcing

#### Overview collections

Analyte	Concentration range	Needed	Collected	Short
TSH	~ 0.01 mIU/L	20	23	*
	0.01 - 0.1 mIU/L	20	11	9
	0.1 - 0.3 mIU/L	20	10	10
	0.3 - 3.0 mIU/L	150	11	139
	3.0 - 50 mIU/L	40	27	13
FT4	> 50 mIU/L	40	4	36
	> 2.2 ng/dL	60	28	32
	0.78 - 2.2 ng/dL	150	5	145
	0.23 - 0.78 ng/dL	60	2	58

\*FT4 > 2.2 ng/dL possible



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8

## Status final Phase IV method comparison

### Reference intervals for FT4 and TSH

#### Study design

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



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



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9

## Status final Phase IV method comparison

### Reference intervals (cont.)

#### Inclusion criteria

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



Anything else?



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10

## Status final Phase IV method comparison

### Reference intervals (cont.)

#### Anti-TPO testing

- SPRL provides ~200 leftovers from its pool of apparently healthy donors for screening\*
- Testing for anti-TPO by manufacturer(s)
- Selection of the final donors
- No confirmatory measurement on the final sample (restricted sample volume)



Is n = 200 enough?  
\*Screening for TSH?  
Who volunteers for screening/testing?



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11

## Status final Phase IV method comparison

### Reference intervals (cont.)

#### Information that should be available

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



What else?



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12

### Reference interval

World Thyroid Day (May 2014)

Thyroid camp for 600 Indian individuals

Study done by B. Das

- TSH, FT4 and anti TPO measured on the same samples

### International developments

Partnership for Accurate Testing of Hormones (PATH)

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



### International developments

Network of FT4 reference laboratories

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



Network most probably not ready by 2015

### Visit to the FDA

“Conditional” agreement with the technical concepts proposed by the C-STFT

Conditions for manufacturers: new 510(k) clearance

- Common FDA guidance document on the requirements for the pre-submission process will not be provided
- Group submission is not possible
  - In all contacts with the FDA, manufacturers should refer to participation in the C-STFT activities
  - FDA will do coordinated assignment of reviewers (who have background on the project)

### Visit to the FDA

Conditions for manufacturers: new 510(k) clearance (cont.)

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

### Visit to the FDA

Conditions to be met by the C-STFT in the pre-submission process

“Formally” described outreach program

- For communication/education of changes in test results to the practicing medical community ( $\Delta$  of reference range values, patient values)
- FDA should be continuously involved/informed on every planned step towards communication
  - As such, FDA can point to issues before the action is undertaken



### Visit to the FDA

Conditions to be met by the C-STFT in the pre-submission process (cont.)

#### Risk-benefit analysis

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



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19

### Visit to the FDA

Conditions to be met by the C-STFT in the pre-submission process (cont.)

#### "Formally" defined procedure for

- Distribution of standardization material to the manufacturers
- Maintenance of adequate supply of panels
- Establishment of the APTM in the follow-up harmonization panels so that the new APTM perfectly matches with the first calibration set-point
- Handling of requests to join from new manufacturers
- Monitoring of the stability of the standardization panel (and how to identify if something is wrong)
- Monitoring of the stability of performance

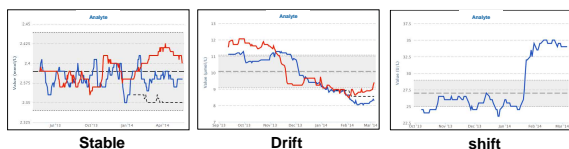


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20

### Stability of performance

To assess under field conditions – the "Percentiler#"



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

#Van Houcke SK, Stepman HC, Thienpont LM, Fiers T, Stove V, Couck P, Anckaert E, Goris F. Long-term stability of laboratory tests and practical implications for quality management. *Clin Chem Lab Med* 2013;51:1227-31.

EMPOWER IVD GLOBE



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21

### First plans for risk assessment

To include/discuss

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

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



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22

### First plans for risk assessment

Initiatives proposed

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



Others?



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23

### First plans for risk assessment

Initiatives proposed (cont.)

- First template (M. Rottmann)

Risk Analysis: Comparison of Current and Modified Device – XXX FT4 Assay

Current FT4 Feature	Modified FT4 Feature	Potential Hazard Identified	Modes of Control, Steps to Minimize Hazard	Actions to be taken
The following table summarizes all changes to the xxx FT4 package insert caused by a new reference standardization. These changes were proven not to affect the safety and effectiveness of the device (see the risk assessment) and were addressed via internal documentation. The intended use of the device is not changed.				
1. Reference standardization existing assay to be filled	Reference standardization equilibrium dialysis followed by ID-LC tandem MS	Change in absolute values > 25%	Show validity of reference range	New measurement > 120 samples evaluated in subjects 95% central percentiles
2.		Patients were not informed of the change	Hand out information material patient readable	Authorship: general practitioner Form: hand out, one pager
3. Reference standardization existing assay to be filled	Reference standardization equilibrium dialysis followed by ID-LC tandem MS	Clinicians were not informed of the change	Send bulletin letters to the Lab customer and clinicians	> 1 information material



Proposals from other IVD manufacturers?



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24



### Plans for dissemination

#### Initiatives proposed (cont.)

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



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25

### Plans for dissemination

#### Initiatives proposed (cont.)

- Brief National Societies member of IFCC ([G. Beastall](#)) (ask for a contact person)
- Brief national regulatory agencies through contact person (China, Japan, ...)



Others?



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### Other items



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27





## Appendix C

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

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

- Fujirebio
- Mindray

Others:

- Philips
- Samsung
- From CAP Today (<http://www.captodayonline.com/productguides/instruments/automated-immunoassay-analyzers-june-2013.html>)
  - [www.monobind.com](http://www.monobind.com)
  - [www.immunospec.com](http://www.immunospec.com)
  - [www.rapidtest.com](http://www.rapidtest.com)
  - [www.alpco.com](http://www.alpco.com)
  - [www.drq-diagnostics.de](http://www.drq-diagnostics.de)
  - <http://diamedix.com/>
  - <http://www.randox.com/>

Other possible sources of information:

- QC-providers (Biorad, ...)
- FDA-list of 510(k) cleared assays.



## **Appendix D**

“Progress in Standardization of Thyroid Function Tests”

IFCC WorldLab 2014 – Istanbul - Symposium: Standardization of common endocrine tests

## Progress in Standardization of Thyroid Function Tests



IFCC WorldLab Istanbul 2014  
22-26 June 2014  
Istanbul, Turkey  
Istanbul Congress Center

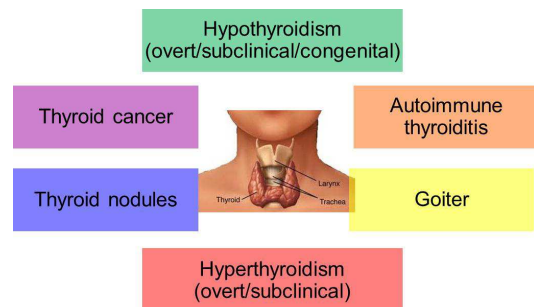
### Symposium: Standardization of common endocrine tests

Linda Thienpont  
Linda.thienpont@ugent.be



Faculty of Pharmaceutical Sciences  
Department of Pharmaceutical Analysis  
Laboratory for Analytical Chemistry

## Spectrum of thyroid disease



**"The silent epidemic"**

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2

## Thyroid disease: "the silent epidemic"

### Given the severity of the disease

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

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3

## Economic impact of thyroid testing

### High burden on the healthcare system

Yearly  $180 \times 10^6$  TSH- &  $60 \times 10^6$  FT4 tests performed worldwide

### Testing volume might even increase

- The informed patient often goes for a 2<sup>nd</sup> & 3<sup>rd</sup> opinion; results in repeat measurements
- Recent research and meta-analysis link subclinical thyroid dysfunction to coronary heart disease & cardiovascular &/or all-cause mortality#
- Pregnancy outcome may drive the decision to screen or treat subclinical thyroid disease

→ **Underpins the indisputable value of efforts towards the "ideal" thyroid function test**

# Singh et al. *Int J Cardiol* 2008;125:41-8.

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4

## The "ideal" thyroid function test/assay

### Clinically & analytically valid

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

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5

## Benefits of using standardized assays

### Fit to address modern clinical & public health needs

- Definition of common reference intervals/clinical decision limits
- Development of evidence-based clinical practice guidelines (application of consistent standards of medical care)
- Translation of research into patient care & disease prevention activities (by aggregation of laboratory data across studies)
- Introduction of electronic patient records
- In publications on clinical studies, no need to mention the laboratory assay used
- **Whether these needs can be met, indeed depends on the availability of laboratory results that are comparable over time, location & across assays**

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6

## IFCC Working Group/Committee for Standardization of Thyroid Function Tests (C-STFT) Chair: Prof. Dr. L. Thienpont



### Terms of reference

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

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

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7

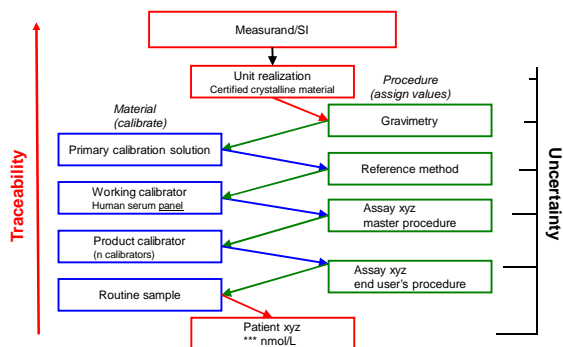


## Development of a reference measurement system for FT4

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8

## Reference measurement system\*



\*ISO 17511:2003

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9

## Definition of the measurand FT4

### Component#

Thyroxine that is not bound to proteins  
Name: "Thyroxine(free)"; abbreviation: FT4

### Kind-of quantity; units#

Amount-of-substance concentration; pmol/L

### System#

Plasma or serum under physiological conditions  
(pH 7.4, temperature 37°C)

### IUPAC/IFCC format:

**"Plasma/Serum - Thyroxine(free); amount-of-substance concentration" (pmol/L)**

#Thienpont et al. Measurement of free thyroxine in laboratory medicine – Proposal of measurand definition. IFCC WG-STFT. *Clin Chem Lab Med* 2007;45:563–4.

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10

## FT4 reference measurement procedure

### International conventional reference measurement procedure (RMP) based on

- Equilibrium dialysis (ED)
- Quantification of thyroxine in the dialysate with a "trueness-based" reference measurement procedure

→ ED ID-LC/tandem MS

### NOTE

The measurand is *operationally defined* as  
**"Thyroxine in the dialysate from ED of serum prepared under defined conditions"**

#Thienpont et al. Proposal of a candidate international conventional reference measurement procedure for free thyroxine in serum. IFCC Working Group for Standardization of Thyroid Function Tests (WG-STFT). *Clin Chem Lab Med* 2007;45:934-6.

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11

## FT4 reference measurement procedure

### Development & validation

Van Uytendange K, Stöckl D, Ross HA, Thienpont LM. Use of frozen sera for FT4 standardization: investigation by equilibrium dialysis combined with isotope dilution-mass spectrometry and immunoassay. *Clin Chem* 2006;52:1817-21.

Van Houcke SK, Van Uytendange K, Shimizu E, Tani W, Umamoto M, Thienpont LM. IFCC Working Group for Standardization of Thyroid Function Tests (WG-STFT). IFCC international conventional reference procedure for the measurement of free thyroxine in serum. *Clin Chem Lab Med* 2011;49:1275-81.

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12



## Development of a reference measurement system for TSH

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13

## Definition of the measurand TSH

The problem: TSH analysis is “mixture” –

### Component#

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

### Kind-of quantity; units#

Arbitrary amount-of-substance concentration (mIU/L)

### System#

Serum

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

#Thienpont et al. *Clin Chim Acta* 2010;411:2058-61.



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14

## TSH reference material & -procedure

### The problem

- IU defined by a WHO standard
- WHO IRP 80/558 (also 81/565) mixture components differ from those in serum (purified cadaver pituitary)
- Dissolved as calibrator in a reduced matrix (e.g. albumin) does not exhibit the same dose/response relationship in assays as in a natural environment  
→ **WHO IRP is a non-commutable reference material (& not suited for standardization)**
- Reference measurement procedure for TSH technically not feasible in the short- to midterm  
→ **Harmonization instead of standardization#**

#Miller et al. Roadmap for Harmonization of clinical laboratory measurement procedures. *Clin Chem* 2011;57:1108-17.



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15

## TSH harmonization approach

### Proposal by C-STFT#

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

### NOTE

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

#Van Houcke et al. Harmonization of immunoassays to the all procedure trimmed mean - proof of concept by use of data from the insulin standardization project. *Clin Chem Lab Med* 2013;51:e103-5. doi: 10.1515/cclm-2012-0661.

#Stöckl et al. A statistical basis for harmonization of thyroid stimulating hormone assays using a robust factor analysis model. *Clin Chem Lab Med* 2014;52:965-72.



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16



## Milestones achieved with the developed FT4 & TSH reference measurement systems

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17

## Method comparisons

### Three studies performed

Phase I – III (2008 - 2012)

### Objectives – Assess/Investigate the

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



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18

## Collaborating IVD manufacturers

IVD Manufacturer	Assay
Abbott Diagnostics (Abbott Park, IL, USA)	Architect i2000SR
Beckman Coulter, Inc. (Brea, CA, USA)	Access 2
bioMérieux s.a. (Marcy-l'Etoile, France)	VIDAS FT4; VIDAS TSH & TSH3
DiaSorin S.p.A. (Saluggia, Italy)	Liaison
Ortho-Clinical Diagnostics (Buckinghamshire, UK)	VITROS Immunodiagnostic Systems (ECiQ and 3600)
Roche Diagnostics GmbH (Mannheim, Germany)	Elecsys
Siemens Healthcare Diagnostics Inc. (Deerfield, IL, USA)	ADVIA Centaur; ADVIA Centaur TSH3-UL; Dimension R&L; Dimension EXL with LOCI module; Dimension EXL with LOCI module (3 <sup>rd</sup> generation); Dimension Vista 1500; IMMULITE 2000; IMMULITE 2000 (3 <sup>rd</sup> Generation TSH)
Tosoh Corporation (Tokyo, Japan)	AIA-2000 (ST AIA-PACK)

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19

## Approach for the method comparisons

### Step-up approach#

**Phase I:** Method comparison with high-volume sera from volunteers; mathematical recalibration<sup>1</sup>

**Phase II:** Proof-of-concept but with inclusion of master calibrators & recalibration by IVD manufacturers<sup>2</sup>

**Phase III:** Method comparison with a clinically relevant panel (again with inclusion of master calibrators & recalibration by IVD manufacturers)<sup>3</sup>

#Van Uytfanghe et al. *Clin Chim Acta* 2014;432:62-67.

<sup>1</sup>Thienpont et al. *Clin Chem* 2010;56:912-20.

<sup>2</sup>Thienpont et al. *Clin Chem Lab Med* 2010;48:1577-83.

<sup>3</sup>Thienpont et al. *Eur Thyroid J*. DOI: 10.1159/000358270.

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20

## Standardization status – FT4

### Phase III Biases to ED ID-MS

9–27 pmol/L:

-25% (mean)

Range: -14% to -42%

>27 pmol/L:

-37% (mean)

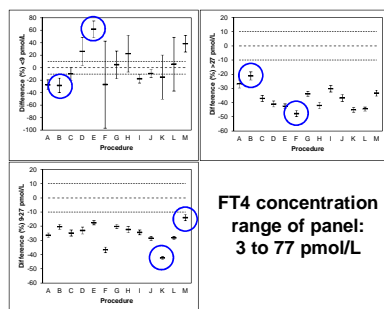
Range: -21% to -48%

<9 pmol/L:

2% (mean)

Range: -28% to 62%

→ All assays strongly negatively biased



FT4 concentration  
range of panel:  
3 to 77 pmol/L

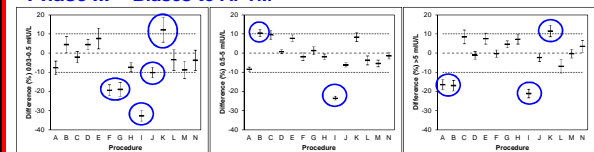
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21

## Standardization status – TSH

### Phase III – Biases to APTM



TSH conc. range covered by the panel: 0.04 – 80 mIU/L

→ Normal range (0.5 – 5 mIU/L): comparability quite good; only 2 assays differ by >10% from APTM

→ Low (<0.5 mIU/L) & high (>5) range: max 5 out of 14 assays outside the ±10% limit

→ Assay I & K deviate most extremely from each other over the whole range (~33%)

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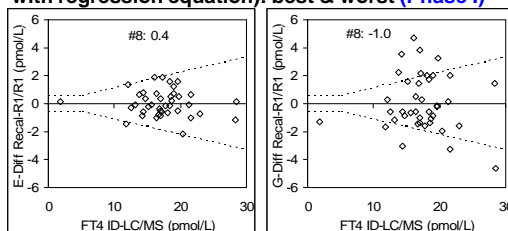


22

## Intrinsic quality of performance – FT4

No standardization without sufficient quality

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



Other performance attributes: imprecision, correlation, stability (within-run, between-), IQC performance

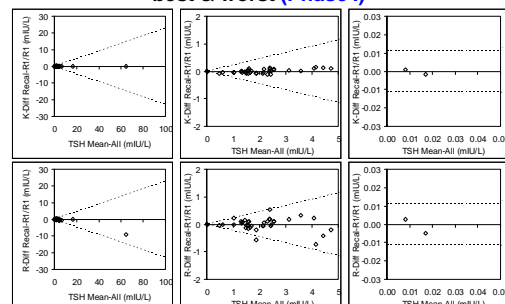
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23

## Quality of performance – TSH

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



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24



### Quality of performance – TSH

Correlation of assay results with the APTM (Phase I)

Code	$r^2$	Code	$r^2$
K	0.998	M	0.991
H	0.997	I	0.990
J	0.997	L	0.990
F	0.993	O	0.988
P	0.993	E	0.987
A	0.992	C	0.961
B	0.992	G	0.955
N	0.992	R	0.948

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

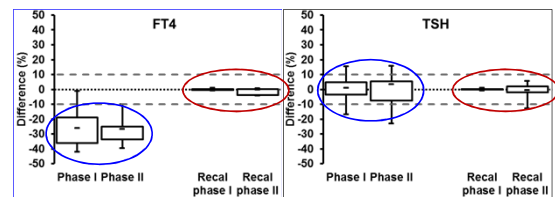
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25

### Proof-of-concept – FT4 & TSH

Relationship RMP\*/APT – Routine assays#



→ Relationship stable within the typical batch to batch variation of current assays

→ Recalibration# removes assay-specific biases

\*Reference measurement procedure

#Phase I: mathematical

#Phase II: master calibrator-based

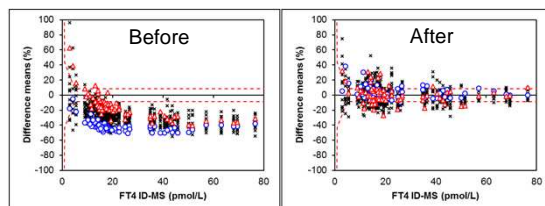
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26

### Effect of standardization/recalibration

FT4 – Phase III



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

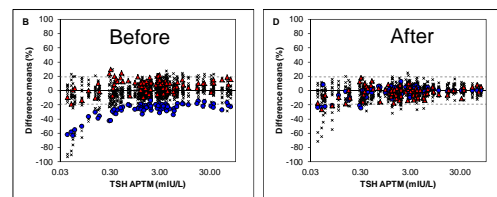
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27

### Effect of harmonization/recalibration

TSH – Phase III



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

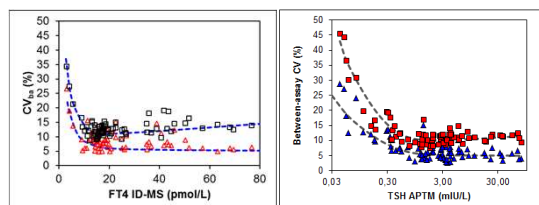
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28

### Effect of recalibration

FT4 & TSH – Phase III



→ Between-assay CV decreases from 9.7% (FT4) & 9.1% (TSH) to 3.4% (FT4) & 5.9% (TSH) (after –) (mid concentration range, before recalibration)

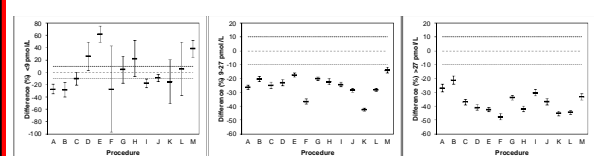
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29

### Impact of standardization/recalibration

FT4 – Phase III



→ Most pronounced effect in the eu- & hyperthyroid range  
→ FT4 concentrations will increase in general by 30 – 50%  
→ Reference intervals will change

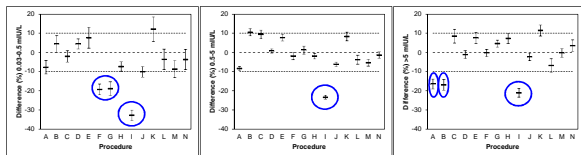
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30

## Impact of harmonization

### TSH – Phase III



→ No dramatic impact for most assays, except for

Assay I: overall effect high but status after harmonization quite impressive

Assays F & G: effect of recalibration (by a constant factor) mainly in the low range

A: recalibration effect mainly in the high range

B: Limited dynamic range, reformulation?

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31



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



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32

## Way Forward?



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33

## Way Forward

### Phase IV (timeline 2014-'15)

To technically prepare standardization/harmonization without direct implementation though; clinically relevant panel currently collected#

Establish an infrastructure to sustain standardization and harmonization

Set-up a network of FT4/FT3 reference laboratories  
Currently: UGent (L. Thienpont) & ReCCS (M. Umemoto);  
potential other candidates: Stanford University (J. Faix);  
CDC (H. Vesper); Radboud UMC (AE van Herwaarden)

Liaise with regulatory authorities (FDA; EC)

#Van Houcke SK, Thienpont LM. "Good samples make good assays" - The tortuous way to sourcing clinical samples for the thyroid standardization project. *Clin Chem Lab Med* 2013;51:967-72.

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34

## Way Forward

### Liaise with key stakeholders

Clinicians & patients, laboratories, manufacturers

### Educate stakeholders about the impact

In collaboration with IFCC Education & Management Committees

### Do risk-benefit analysis with stakeholders

### Establish reference intervals with standardized assays

In cooperation with IFCC Committee on Reference Intervals & Decision Limits (C-RIDL)

### Coordinate implementation of standardization & harmonization

All manufacturers/assays at the same time

**Timeline: 2018?**

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35

**Linda Thienpont**

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36