IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)
Meeting at Euromedlab 2017, Athens, Greece, Tuesday June 13th (14 – 17:00 pm)

PARTICIPANTS

The meeting attendance list, as well as the list with excused people, is attached (Appendix A). The initials used in the minutes are contained in this list.

We recommend to read the minutes together with the accompanying slides (see Appendix B). Note that in the minutes certain statements/discussion points that were reiterated at different points in time during the meeting were grouped to make the reporting/reading more comprehensive.

OPENING OF THE MEETING

The chair (LT) welcomes the meeting attendees. She starts immediately with her slide presentation which is intended to evoke a lively discussion with the attendees about the following discussion items:

- C-STFT Phase IV studies: achieved milestones
- Logical next step after recalibration: implementation of the traceable assays
    - Risk for the patient?
    - Impact of recalibration?
    - Sustainability of the traceability basis?
- Develop a common strategy to estimate/prepare the impact of recalibration and waive the potential risks
- Report on a panel discussion with the IVD industry held on occasion of a AACB Harmonization Workshop in Sydney (May 18, 2017)
- Future of C-STFT.

(1) Question 1: Follow-up panels are sponsored by the IVD-manufacturers. Who has the proprietary rights? Can the panels be made available to new IVD companies on request? If yes, at which price (slide 13)?

- (MR) starts the discussion by saying that logically the IVD manufacturers, who participated in the C-STFT standardization/harmonization efforts, have interest in using the follow-up panels for assuring the sustainability. (SM) adds that strictly speaking for FT4 there is no need to strictly reserve the follow-up panel for the Phase IV participants, as there is always the possibility to let target new samples by one of the future network reference laboratories, however, that for TSH the situation is different. (LT) confirms this statement. Indeed, the participating manufacturers harmonized their TSH assays to the targets statistically set for the very 1st panel. Therefore, it is a prerequisite in the harmonization concept that it is assured that the future follow-up panels are traceable to the 1st harmonization panel. This is already a fact for the 1st follow-up panel in virtue of its targeting in parallel. For the future panels the same shall be accomplished by timely measuring each new panel in overlap with the previous one, thus before the latter is depleted (editorial note: this is explained in the TSH harmonization publication in Clin Chem, Ref 1).
- (LT) recalls that concerning the samples of the reference interval (RI) panel, the IVD manufacturers still need to receive the 2nd aliquot they were promised. Currently all repository samples are stored at NIBSC (UK), but it is of course possible to ship them to the manufacturers, who want to store them in their own facilities.
- Since there is no immediate reply from the IVD manufacturers – not on the question about the proprietary rights of the follow-up panels nor on whether they want to have the 2nd aliquot of the RI panel samples already at their disposal – (LT) concludes this discussion item by saying that there is no need to take the decision at this very moment. She will contact the participating IVD manufacturers later on to receive an answer.
- With regard to future FT4 measurements, (JR) wonders whether the costs will be in relationship to the service. (LT) explains that each member of the future reference

laboratory network will be free to define the costs for the reference measurement services on a contract basis with the requesting manufacturer. It is not her intention to interfere on that. Regarding the network laboratories/directors, they are: Ghent University (BE)/Ref4*U /*(KVU) and the lab director Prof. Christophe Stove, Reccs (Japan) (HU), CDC (USA) (HV) and Radboud UMC Nijmegen (NL) (TvH). (HV) and (TvH) mention that up to now they have not made calculations of what they will charge, since they did not yet complete the implementation of the equilibrium dialysis-isotope dilution-liquid chromatography-mass spectrometry (ED-ID-LC/tandem MS) conventional reference measurement procedure (RMP).

(2) Question 2: What is the impact and significance of recalibration on laboratory results and RIs? For FT4 and TSH (slide 15)?

- (JR) indicates that the upcoming publications in Clin Chem (Ref 1 and Ref 2) will be a good basis for discussion with the involved stakeholders. They are an important step forward to receive the stakeholders' feedback, but a lot of work still needs to be done concerning the risk/benefit analysis.
- (MR) joins the statement that the publications will be a good tool for communicating/discussion on standardization/harmonization with the end-users. From the discussions it should be possible to find out the clinical unmet need and impact. In addition, sending out questionnaires could help to get a clear answer. (JR) adds that the publications can serve as a catalyst for customers. (MR) The data in the publications can be used to demonstrate the possible outcome to the customers when they follow the recommendations. However, it has to be admitted that the discussion for FT4 will be more difficult than for TSH.
- (SM) states that to prevent that involved stakeholders are not willing to implement the standardized/harmonized assays, it might be necessary to communicate back why standardization/harmonization was needed. (SM) states that in this communication line stakeholders should also be informed on the consequences recalibration will have, i.e., change in measurement results and RI's. (LT) emphasizes that these messages are clearly contained in the upcoming Clin Chem publications, i.e., only when immunoassays give comparable results, a common RI can be used; the pre- and post-recalibration data are self-explaining for what concerns the consequences. She continues that in the aforementioned publications some cautionary notes on the use of a common RI also need attention, i.e., the RI's established in the Phase IV study are not the final ones, as they only served as proof-of-concept for FT4 standardization and TSH harmonization; although this proof-of-concept showed that it is possible to use a common RI, the latter does not mean that a "one size fits all-RI" is possible; a RI is always related to a specific population (reference population needs to be well defined). Therefore, she asks to interpret the Phase IV RI study with caution.
- The discussion about the RI's after standardization/harmonization is further addressed. (JR) indicates that it will be necessary to develop RI's with more than 120 samples, which is confirmed by (LT). She recalls that this was also demanded in former times by the US FDA in order to warrant that the uncertainty of the centiles is more reasonable than is the case with only 120 subjects. (FM) adds that different countries have different guidelines on establishing RI's and regrets that so many data is gathered on a daily basis, but is not used properly.
- Moreover, it was suggested that customers should verify their own RI with the one offered by the manufacturers.
- (JR) says that manufacturers have different RI's, e.g., for children, pregnant women, etc. In this regard (MR) notes that the need for having different RI's for some patient populations will not be circumvented by standardization/harmonization. (LT) joins this statement and explains by way of example that in a study she performed with colleagues from the Academic Hospital of the Free University of Brussels, it has been shown that, although FT4 immunoassays follow the same pattern as the RMP during the different semesters of

pregnancy, the relationship between the results in controls and pregnant females by the RMP and the individual assays was different for each of the latter. This proved that FT4 immunoassays all are susceptible to the alterations in binding proteins during pregnancy, but to a different extent. Thus even if manufacturers recalibrate their assays, for interpretation of results in pregnancy, they will have to establish their own RI's (Ref 3). For a summary of this study: see extra slides 59-68.

- Regarding the consequences of standardization/harmonization, a panel discussion with endocrinologists or clinicians is suggested. (LT) recalls that in the past she made already an attempt to realize this. She namely invited Prof. Paolo Beck Peccoz (Milano, It) (editorial note: Prof. Beck Peccoz was suggested by the IVD industry and C-STFT members) to one of the annual meetings of C-STFT. Unfortunately, in his talk he mainly focused on his own research, and surprisingly mentioned that he was happy with the thyroid function tests at that time. Upon further discussion with him it seemed that this statement was because he used to work with only one and the same laboratory in his hospital. Nevertheless, (LT) finds it a good suggestion that for the meeting next year the new chair (see further) would invite clinicians and/or endocrinologists to hear their opinion on the problems they encounter when working with different laboratories (and assays).
- (GB) reminds everybody that the opinion of the primary care sector on the impact should not be forgotten, as general practitioners (GPs) let perform an overwhelming number of thyroid function tests, in spite of the fact that they are not always "the" experts in interpreting subtle differences in values. He recommends that in addition, also the patients should be asked for their opinion on the impact.
- (AH) comes back to the discussion item "demonstrate the consequences of standardization/harmonization to clinicians". He proposes to use the data that are readily available from the Phase IV study/publications to this purpose, i.e., by calculating the relationship before and after standardization/harmonization. (MR) is also of the opinion that this relationship can demonstrate the consequences. (LT) proposes that manufacturers do these calculations by themselves. It is further suggested to make a link with existing literature to prevent/stop discussions on what is the true value. All this should help customers, who nowadays only see a heterogeneous picture.
- (AH) questions the possibility to report in parallel old and new values. (LT) says that this is indeed common practice in laboratory reports when changes are made. It is further suggested that this comparison may be useful in the outcome discussion. In the opinion of (JR) the requested comparisons are already clearly shown in the publications and the slides from this meeting. (MR) confirms that reporting old and new values in principle makes sense, but explains that manufacturers can only set one calibration.

(3) Question 3: Is there a need for a common strategy to adopt by IVD manufacturers to estimate/prepare the impact of recalibration (slide 28)?

With regard to the verification by manufacturers of their RI's before and after standardization/harmonization (note, particularly for TSH it might be possible that some IVD assays can continue to use the same RI), (LT) asks whether IVD manufacturers consider it desirable to use a common protocol , e.g., the CLSI EP-28 guideline, however, no real answer was given on this topic.

(4) Question 4: In how far is the impact a potential risk for patient safety? How can the C-STFT help to answer the "risk" question? How to minimize/waive the identified risks (slide 30)?

- (GB) comes back to the role of the patient with regard to impact and safety after recalibration of the assays. It should not be forgotten that "the patient" is actually the "final customer" of thyroid function tests. He recalls that in October 2015 he attended the international thyroid conference in Orlando (FL, USA) where he used the opportunity to speak for patients-members of the Thyroid Foundation International (= the overarching organization of individual national patient organizations). On this occasion, he found out

that more and more patients are working directly with laboratories and interpret their own results. When he told the audience that currently laboratory results differ among laboratories/assays, they showed horrified, because they use to base the interpretation of the reported values on what is available on internet or in literature. As a consequence, they deemed those differences in results “bad laboratory science”. Nevertheless, they did understand that as a consequence of standardization/harmonization the measurement results will change, and that this eventually will be beneficial, and lead to reduce risks of misinterpretation or wrong diagnosis. (TvH) confirms the involvement of patients. It is his experience that when patients still feel miserable in spite of therapy, they study their laboratory results and discuss them with their GP or endocrinologist. (GB) confirms that indeed the level of dissatisfaction of patients is high, since about 20% of them don’t feel right when on L-T4. It feels for them as if clinicians look too much at the laboratory results and don’t listen enough to the patient. Many then seek help from different GPs and sometimes make the switch to experimental medication. Therefore, it is important that patients know their numbers, and can be sure that e.g., 25 pmol/L is actually 25 pmol/L.

- It is stated that when communicating the changes, different groups have to be addressed:
    - (GB) Concerning the education of clinicians, it is generally believed that endocrinologists are competent enough to manage different results from different laboratories; in contrast, GPs mostly rely only on the information received from the laboratories, therefore, they might get confused when RI’s change.
    - (JR) also mentions that textbooks should not be forgotten when thinking about communicating changes to the clinical community.
    - (TvH) emphasizes that the experience of manufacturers regarding changes after standardization/harmonization is not to underestimate. He also thinks that patients are used to cope with the changes.
    - (SM) Also the external quality assessment (EQA)/proficiency testing (PT) providers should be contacted. (FM) joins this statement and remembers by way of example the case of standardization of folate assays. The changes confused the customers, so that a lot of laboratories interpreted results wrongly. Therefore, triangle communication is necessary. (JR) Since FT4 is a high volume test, it is to expect that the changes will be noticed/embraced sooner and faster. (MR) suggests that EQA/PT schemes should maybe report ‘old’ and ‘new’ values in the transition phase.
    - (AH) Other education should be done through the different guidelines (e.g., from the European and American Thyroid Associations (ETA ; ATA)). (GB) mentions that in the past he has been in touch with the ETA, who consider the non-standardized thyroid function testing a big issue. Therefore, they advised that the C-STFT work should be published before new guidelines are developed/published. At the time the first contact was made this was not yet possible, however, the ETA showed interested in involving the C-STFT in the writing of the guidelines. (GB) will pick up the contact again.
    - (BD) Also the accreditation bodies should be added to the list of stakeholders.
- (LT) Concerning contacts of C-STFT with important organizations, (LT) mentions that JF has been in touch with the new chair of the ATA Lab Services Committee, who is willing to collaborate with C-STFT; also contact with the president of the Japan TA (JTA) has been made by courtesy of (AH). (LT) asks (HV) whether it would be possible to incorporate FT4 and TSH into the “Partnership for the Accurate Testing of Hormones” (PATH) initiative, particularly because it has clinical societies/organizations on board (see http://www.hormoneassays.org/). (HV) confirms that communication through the latter could minimize the workload and improve the uniformity of the communication.
- It was also suggested that C-STFT (and the IVD partners) should reserve a time slot for a presentation in future AACB meetings on the topic “harmonization of laboratory testing”. (LT) mentioned that in the last meeting (May 2017) the AACB had already organized a panel discussion with the IVD industry on the implementation of standardized/harmonized

FT4 and TSH assays. Personally, she found the timing unfortunate, because C-STFT still had to discuss the implementation in the present meeting. Apparently this AACB initiative was based on a confusion. They were namely convinced that the implementation was fixed to take place in 2018. Admittedly, in former meetings, the C-STFT chair had always stated that the implementation could be aimed at in the year 2018, however, this was of course to understand as a tentative date.

(5) Question 5: Should the C-STFT help in minimizing/waiving the identified risks (slide 38)?

- (FM) suggests that it may be clearer to everyone that values have changed after standardization/harmonization when also the units are changed (as done for HbA1c testing). (LT) counters this suggestion by saying that changing the units for FT4 is not an option, because results have to be expressed in SI-units.
- (LT) mentions that up to now it has been the idea that C-STFT would coordinate the implementation of the standardized/harmonized assays, which should be done by all participating IVD manufacturers worldwide and at the same point in time. This would minimize the confusion of stakeholders. (CT) immediately replies that it will be difficult to coordinate rolling out all the standardized assays. This statement is joined by other IVD representatives. (LT) fears that a different timing among manufacturers might not be appreciated by the stakeholders. She namely recalls that the message in reply to the questionnaires sent around often was that stakeholders see it as a prerequisite that the implementation is done worldwide and at the same point in time.
- (MR) For a successful implementation, the awareness of the C-STFT work has to be increased, and as stated before, stakeholders should be convinced about the usefulness of the big changes after standardization/harmonization. (LT) mentions that again from the answers to the questionnaires it was clear that the involved stakeholders are convinced of the benefits of standardization/harmonization. She hopes that also for this group of IVD manufacturers it remains the final goal to actually have the implementation completed one day.
- (LT) proposes as a compromise that the implementation for FT4 and TSH should not necessarily be done at the same time. After some further discussion, the attendees agree that for TSH the implementation of the harmonized assays should be straightforward (only minor changes for most manufacturers, so less risks should be involved) and that lessons can be drawn from the TSH experience, which should allow a smoother implementation of the FT4 assays.
- (CH) emphasizes the need to also communicate with the regulatory bodies in order to obtain a proper coordination.
    - In Europe the new EU IVD Directive has entered into force. (SM) mentions that the implementation of the harmonized TSH assays should be quite easy. (MR) states that for FT4 the standardized assays will require a new registration.
    - The China and Japan FDA (CFDA, JFDA) might be more difficult (e.g., typo's can cause a delay of multiple months) (SM). (CH) The CFDA will require full analytical validation which is a cumbersome and long process. Also changes in RI's can take a long time to be accepted by the CFDA; in addition, the unmet clinical need has to be proven.
    - (LT) explains why she found it so important to have Chinese manufacturers on board of the C-STFT, i.e., to obtain the awareness of the CFDA, and facilitate getting into contact with them. She mentions that in the past on request of P. Sibley she had attended via Skype a meeting between C-STFT and Siemens. On this occasion she gave a presentation entitled "The Traceability Requirement for in vitro Diagnostic Medical Devices – The internationally accepted metrological approach" in which she gave the standardization of 25-OH-vitamin D and FT4 as examples. Unfortunately, no further contact was established. (DX) promises to bring (LT) in touch again with the right people from the CFDA. Editorial note: (DX) has already provided the contact details of Ms Yu from the National Institutes for Food and Drug

Control (NIFDC), which is a subordinate agency of the State Food and Drug Administration (SFDA). http://www.nicpbp.org.cn/en/CL0309/ (yuting@nifdc.org.cn). (LT) prepared a slide presentation on the C-STFT activities/milestones, incl. some pertinent questions, and sent it to Ms Yu. Until now, no reply was received.

- (AH) mentions that he plans to write a letter to the Japanese Health Ministry to create awareness about the international standardization/harmonization activities. This letter will be issued on behalf of the Japan Society of Clinical Chemistry (JSCC), the Japanese Society of Laboratory Medicine (JSLM), the JTA and the Japan Association of Clinical Reagents Industries (JACRI). Beforehand, the concerned organizations will have a meeting with representatives of all IVD companies who have approval for marketing thyroid function test kits in Japan. (AH) will keep the C-STFT informed.

(6) Question 6: What timeframe is needed for the actual implementation? Is coordination desirable/possible (slide 56)?

- As mentioned above, doing the implementation by all participating manufacturers worldwide and at the same point in time is deemed unrealistic. Several IVD representatives add that this does not mean that they are reluctant to do the implementation of the standardized/harmonized assays, but there are certain reasons that make setting timelines right away difficult. One reason is that IVD companies take the cost/benefits into account, which sometimes results in competing priorities. Another reason might be that the clinical unmet need still needs to be defined.
- As mentioned before, all agree that distinguishing between TSH and FT4 will be most effective, as the huge impact of FT4 standardization will require much more preparatory work. By splitting the implementation, TSH can serve as model, which should allow to define what needs to be done and figure out the timeframe. This is so-called “slow science”: it is better to take the time and get it right, than rush into it and get it wrong. By the way, (MR) asks what the root cause is for the big changes implied by FT4 standardization to the RMP: (LT) explains that up to now all FT4 assays were standardized to the Nichols predicate assay, whereas now the IFCC conventional RMP is the standard. The principle of the Nichols assay was published (Ref 4), from which it can be concluded that the ED step was not optimal to not disturb the equilibrium between free and protein bound T4. This is different for the current IFCC RMP which performs ED under optimal conditions (as described in CLSI C45-A). Therefore, the reason for the large bias between the immunoassays compared to the RMP is due to the link of the immunoassays with the predicate assay.
- (MR) It should also not be forgotten that the timeframe that will be needed for the implementation will be different among manufacturers, e.g., for some the TSH calibration changes following harmonization are ± 0%, while for others they exceed 10%, which leads to different FDA requirements.
- (JR) mentions that speaking for Abbott there is definitely interest in the implementation, but it will only be possible to give a timeline after funding has been allocated, which only happens once a year. Abbott will decide on what will be done in 2018 in the next two months. If on this occasion the implementation of standardization/harmonization is not prioritized, than it won’t happen in 2018. Therefore it would be desirable to also have the FT4 publication accepted within ± 4 weeks after the meeting, so that it can be put on the agenda. Editorial note, the FT4 publication was accepted for publication shortly after the C-STFT meeting (Ref 2); hopefully it will soon be available online (the C-STFT secretariat will keep the IVD industry informed); the TSH publication (Ref 1) is already available online and will be published in Clin Chem in the July issue.
- Other manufacturers confirm that their companies maintain similar strategies for allocating budgets.
- (MR) concludes that it is clear that there is heterogeneity in the desired timeframe for the implementation.

(7) Question 7: Sustainability of the new traceability basis: assessment. How can the C-STFT help to answer the "risk" question? How to minimize/waive the identified risks (slide 39)?

- (LT) recalls that for the US FDA it was a requirement that the sustainability of the new traceability basis is demonstrated. She refers to the Percentiler application as tool to monitor the sustainability of the new traceability basis (Ref 5). She mentions that 20-25 laboratories per peer group are enough to judge the stability/sustainability. She calls upon the manufacturers for support in recruitment of laboratories, particularly those whose platform/assay is not yet represented as a peer group or whose peer group needs to be substantiated. As alternative, she points to the possibility of using EQA/PT schemes for monitoring the sustainability, but then under the condition that commutable samples are used.
- (JR) points to the importance that EQA/PT schemes make sure that after standardization/harmonization the right picture is provided. This is important as all customers are involved in these schemes. (LT) states that it is her conviction that EQA/PT schemes that use traditional samples (to understand as adulterated/processed samples, e.g., by pooling, spiking, lyophilizing etc.) should restrict to peer group evaluations; however, if they want to compare the results among peer groups, they have to use "native" samples; the same is true if they want to assess the trueness/accuracy. (FM) counters that he does not like the use of the term "traditional" EQA/PT samples, and says that according to him spiked samples are not un-useful. (MR) Up to now, these are all assumptions; we actually don't know whether the existing EQA/PT schemes use materials that are commutable; therefore, let us take the opportunity to find this out now (statement joined by (CD)). (SM) suggests to use one native sample, while the other samples are spiked. (FM) is willing to share one of the UK NEQAS samples and proposes to have it measured by the RMP at Ghent University (UGent). (KVU) mentions that measuring only one sample with the RMP might not be conclusive. She would prefer to do a real feasibility/commutability study and test several samples from different EQA schemes. She proposes to include the study in the efforts of the future network reference laboratories, and will make a proposal on this. Nevertheless, she wants to recall that in one of the former method comparisons, 3 spiked materials (prepared by Roche) had already been included. The intention was to cover concentrations that were not achieved with the sourced clinical samples. Since these samples were measured in parallel with native samples, it was possible to assess their commutability. The outcome was definitively that they were not (editorial note: 3 different concentrations were spiked, however, these concentrations were not recovered). (KVU) proposes to make a summary of this study. She mentions in addition that meanwhile the UGent reference laboratory had more bad experience with measuring commercially available lyophilized samples. The RMP uses to find up to five fold differences in concentration in comparison to the claimed concentrations.
- (MR) reiterates that with EQA/PT schemes which only send <u>one</u> sample bearing a RMP target, the pitfall could be that after standardization/harmonization companies do not comply anymore with the specifications set in the schemes. (HV) mentions that there are actually alternative ways to check the sustainability, which each have their pro's and con's. With regard to the option EQA/PT, he reiterates the statement by (LT): as we actually know that in traditional schemes the used materials are non-commutable, this pitfall can only be circumvented by using accuracy-based EQA/PT schemes, which is to understand as schemes that use "native" and "unadulterated" materials targeted with the RMP. These schemes also give a more accurate estimate of changes compared to traditional schemes. He continues that accuracy based EQA/PT schemes proved already to work quite well – be it for other analytes – and that there are definitely programs worth trying to work around the disadvantages. (TvH), who is involved in the Dutch EQA scheme, mentions that they use blood from donors as sample material, which is then targeted with a RMP. The commutability for FT4 should be tested.

(8) The future of the C-STFT (slide 58).

- (LT) mentions that both the chair and members of the C-STFT are end of term by December, 31st 2017. In a meeting she had before with the IFCC SD chair (PG), she heard that IFCC decided to continue the C-STFT and will launch a call for nominations by the end of the year. The final decision on the new chair and members lies in the hands of the IFCC.
- Last not least, before adjourning the meeting, LT thanks as chair of C-STFT everybody for the excellent collaboration over the years. She expresses the hope that the work of the C-STFT will continue in the right direction.

Summary of actions-to-take and pending questions to answer:

1. **(KVU and LT): Find out the opinion of the different IVD manufacturers regarding the proprietary rights of the FT4/TSH follow-up panel and whether they want to keep the extra aliquot of the RI panel at NIBSC or receive it for further storage at their own premises.**

2. **(LT): Do the follow-up of the new contact laid with the CFDA.**

3. **(AH): Inform C-STFT on the reaction of the Japanese Ministry of Health on the letter sent on behalf of the JSCC, the JSLM, the JTA and the JACRI.**

4. **(GB): Contact the ETA again regarding the collaboration of the C-STFT with writing the new guidelines.**

5. **(KVU): Make a summary of the commutability assessment of the spiked samples in one of the previous method comparison studies.**

6. **(KVU): Make a proposal for doing a real feasibility/commutability study of several samples from different EQA schemes and how to include this study in the efforts by the future network of reference laboratories.**

7. **(KVU and LT): Keep the IVD manufacturers informed about the publication of the FT4 manuscript in Clin Chem.**

8. **(IFCC): Launch a call for nomination of a new chair and members for C-STFT.**

Minutes made by:
Katleen Van Uytfanghe, PhD with help of Linde De Grande, PhD
Minutes approved by Prof. Dr. Linda Thienpont, chair of the IFCC C-STFT

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References

1. De Grande LAC, Van Uytfanghe K, Reynders D, Das B, Faix JD, MacKenzie F, Decallonne B, Hishinuma A, Lapauw B, Taelman P, Van Crombrugge P, Van den Bruel A, Velkeniers B, Williams P, Thienpont LM on behalf for the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT). Standardization of free thyroxine measurements paves the way for the adoption of a more uniform reference interval. Clin Chem 2017 (Accepted for publication).
2. Thienpont LM, Van Uytfanghe K, De Grande LAC, Reynders D, Das B, Faix JD, MacKenzie F, Decallonne B, Hishinuma A, Lapauw B, Taelman P, Van Crombrugge P, Van den Bruel A, Velkeniers B, Williams P on behalf for the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT). Harmonization of serum thyroid-stimulating hormone measurements paves the way for the adoption of a common reference interval. Clin Chem 2017 May 18. pii: clinchem.2016.269456. doi: 10.1373/clinchem.2016.269456. [Epub ahead of print].
3. Anckaert E, Poppe K, Van Uytfanghe K, Schiettecatte J, Foulon W and 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.
4. Nelson JC, Tomei RT. Direct determination of free thyroxin in undiluted serum by equilibrium dialysis/radioimmunoassay. Clin Chem 1988;34:1737-44.
5. De Grande LAC, Goossens K, Van Uytfanghe K, Das B, MacKenzie F, Patru MM, Thienpont LM; IFCC Committee for Standardization of Thyroid Function Tests (C-STFT). Monitoring the stability of the standardization status of FT4 and TSH assays by use of daily outpatient medians and flagging frequencies. Clin Chim Acta 2017;467:8-14.

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Appendix A

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Excused

Name	Affiliation	e-mail address
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Appendix B

Slides from the annual meeting in conjunction with the Euromedlab 2017 Conference.

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

2017 Annual meeting

Athens
Tuesday, 12th of June 2017

Chair
Linda Thienpont
Linda.thienpont@ugent.be

Scientific Secretary
Katleen Van Uytfanghe
Katleen.vanuytfanghe@ugent.be

C - STFT ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Agenda

Discussion items

- C-STFT Phase IV studies: achieved milestones
- Logical next step after Phase IV: implementation
- Questions to discuss/answer before implementation:
  - What is the impact and significance of recalibration on reference intervals (RIs)? FT4? TSH?
  - Is there a need for a common strategy to adopt by IVD manufacturers to assess the impact?
  - In how far is the impact a potential risk for patient safety?
  - How can the C-STFT help to answer the “risk” question?
  - How to minimize/waive the identified risks?
- Sustainability of the new traceability basis: assessment
- Timelines for implementation? Coordination desirable/ possible?
- Report on a panel discussion with the IVD industry (AACB Harmonization Workshop, Sydney; May 18, 2017)
- Future of C-STFT

C-STFT Phase IV studies

Achieved milestones

Phase IV studies

Recall

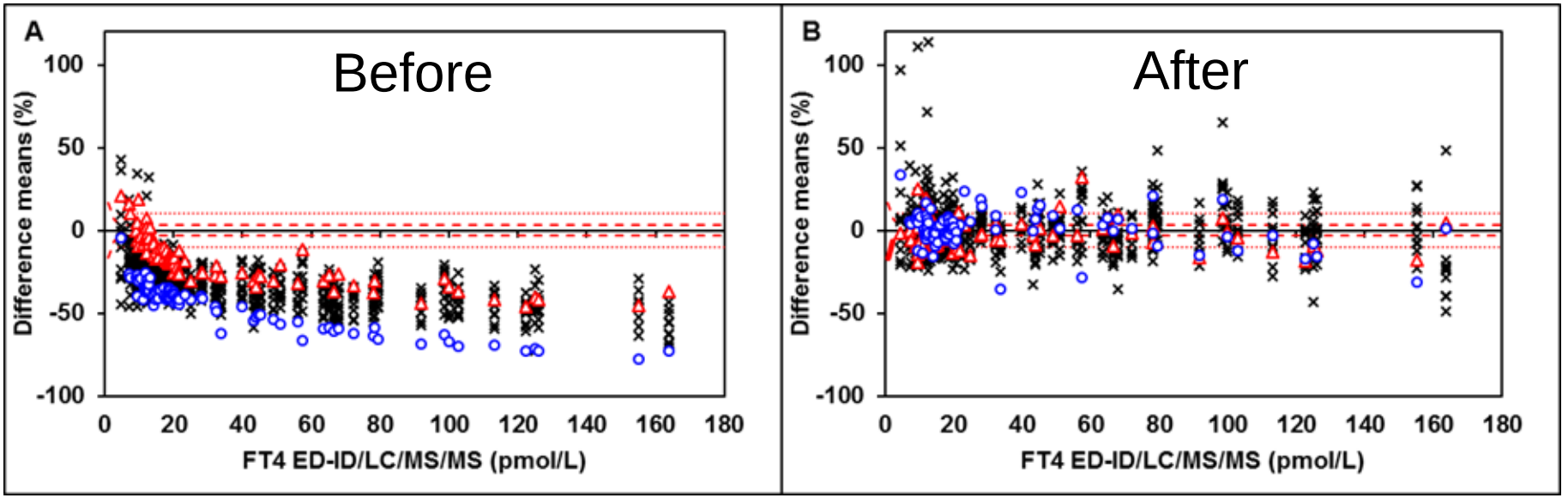
Objectives

- Perform the final method comparison studies for FT4 and TSH with clinically relevant panels; let IVD manufacturers (MFs) include their assay master calibrators
- Target the panel samples (by the ED-MS RMP & robust factor analysis model/APTM)
- Let IVD MFs recalibrate their assays by assigning new values to their master calibrators
- Estimate the impact of recalibration
- Provide a proof-of-concept by performing reference interval (RI) studies with the traceable assays

Collaborating IVD manufacturers

Achieved milestones for FT4

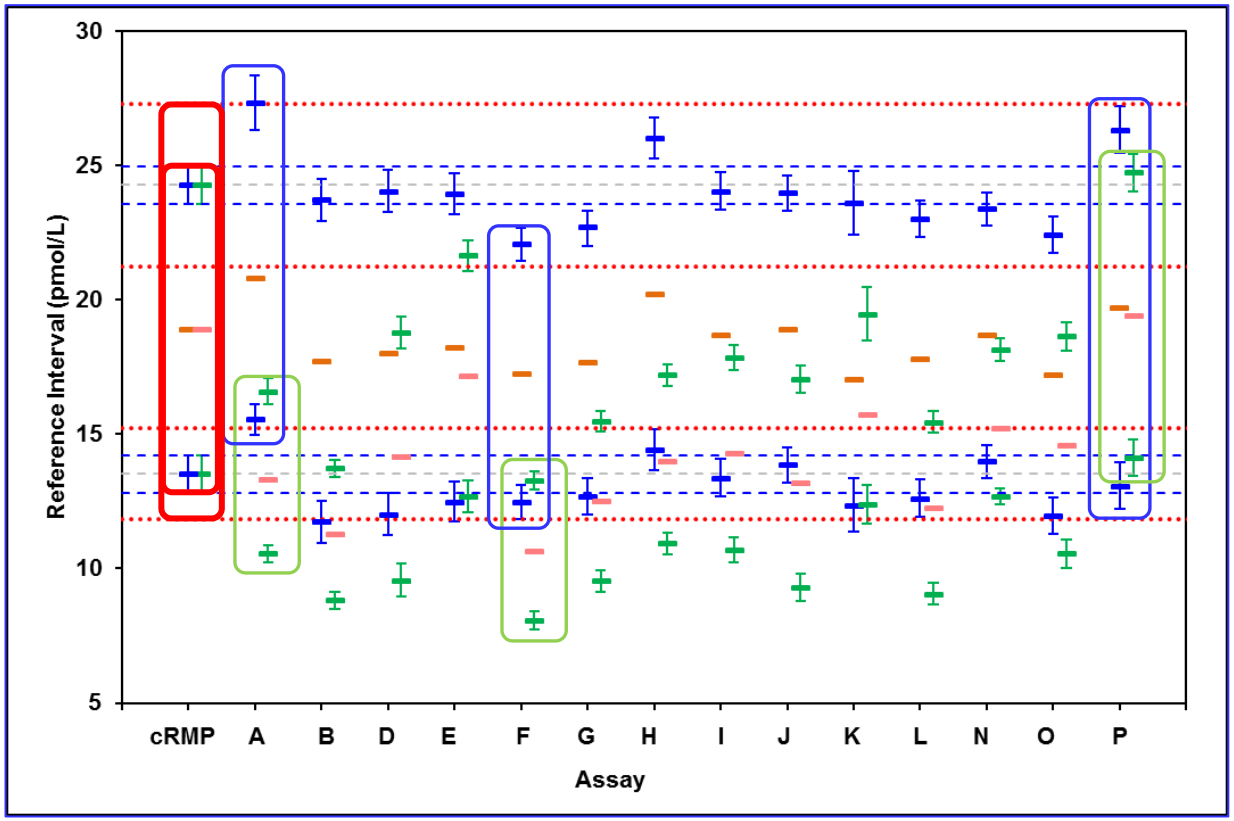
Recalibration of FT4 assays to the RMP
See difference plots (%) pre- and post recalibration



➔Recalibration eliminates the biases of the immunoassays to the ED-ID/LC/MS/MS RMP

Achieved milestones for FT4

Reference interval study



RI by the RMP

(parametric)

Mean: 18.9 pmol/L

Width: 10.7 pmol/L

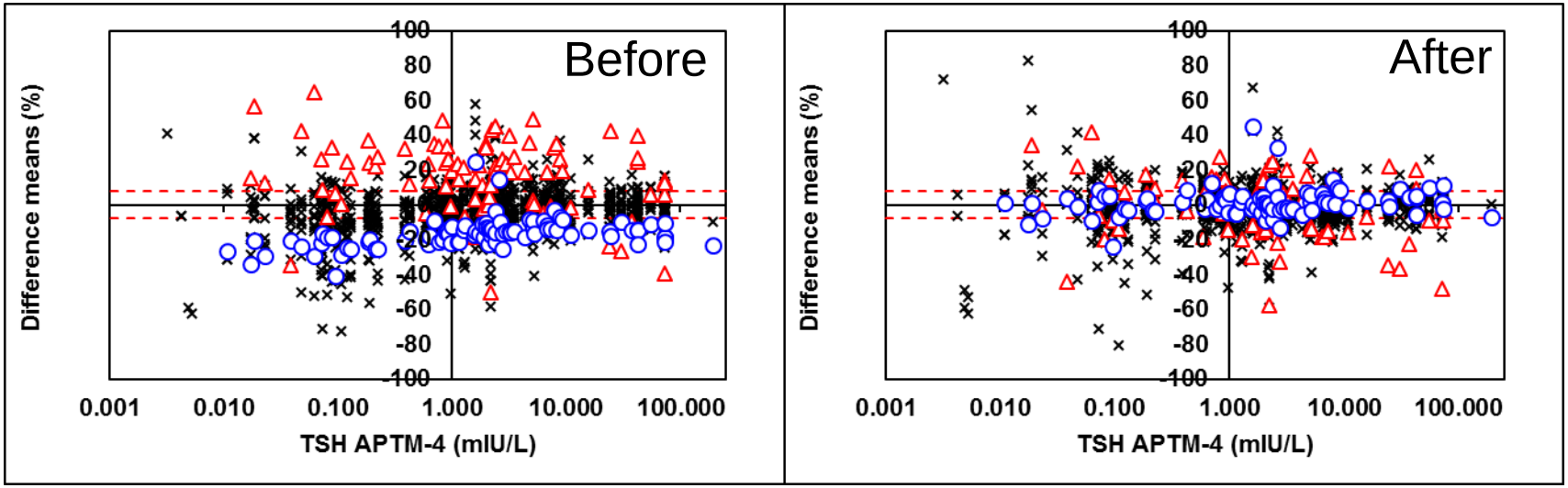
2.5 Percentile (90% CI): 13.5 pmol/L (12.8 – 14.2 pmol/L)

97.5 Percentile (90% CI): 24.3 pmol/L (23.6 – 25.8 pmol/L)

➔Proof-of-concept: after recalibration, RI by the RMP is suited for common use (±margin of 12.5%)

Achieved milestones for TSH

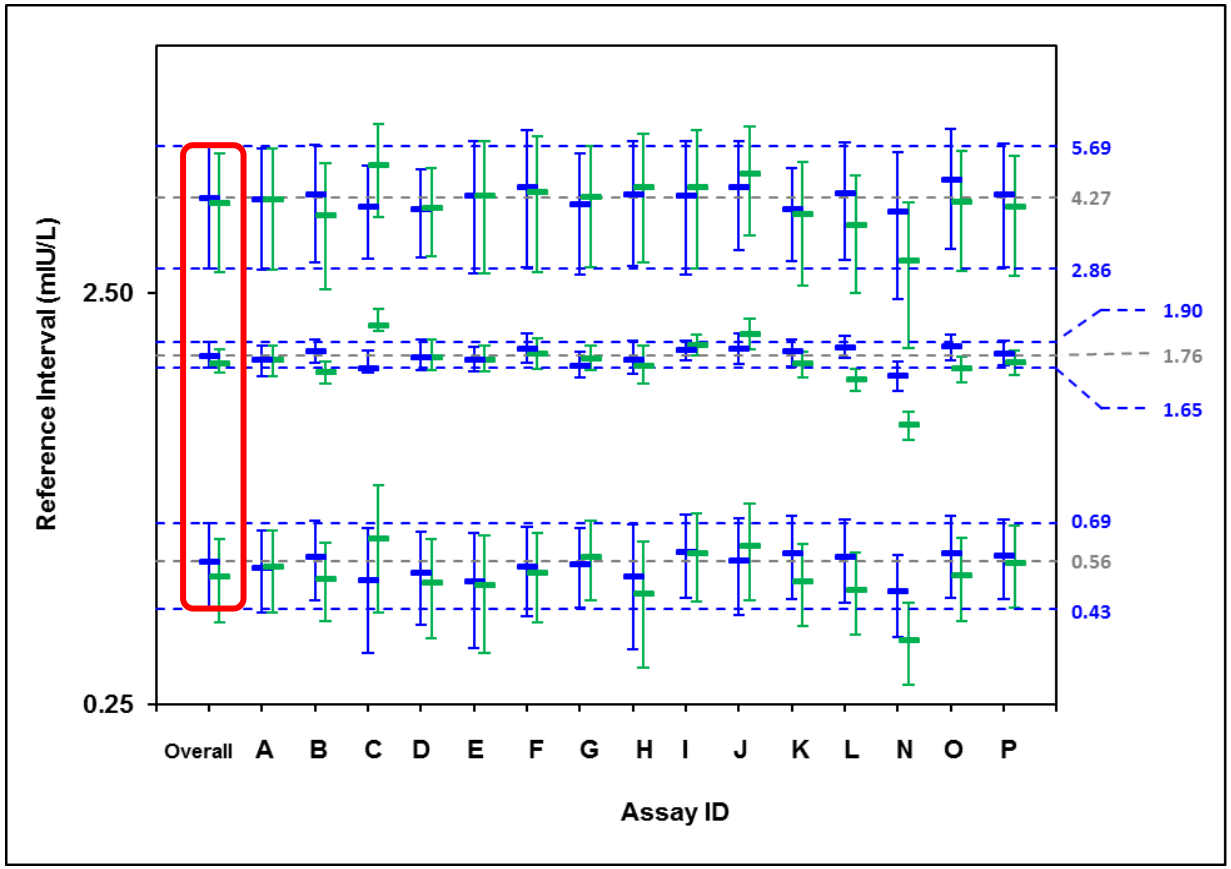
Recalibration of TSH assays to the APTM
See difference plots (%) pre- and post recalibration



➔**Recalibration eliminates the calibration differences between the immunoassays**

Achieved milestones for TSH

Reference interval study



"Overall" RI after recalibration
(non-parametric)
Median: 1.76 mIU/L
Width: 3.72 mIU/L

2.5 Percentile (90% CI): 0.56 mIU/L
(0.43 – 0.69 mIU/L)

97.5 Percentile: 4.27 mIU/L
(2.86 – 5.69 mIU/L)

➔ **Proof-of-concept: after recalibration, adoption of a more uniform RI is possible**

Achieved milestones for FT4 and TSH

Manuscripts on the Phase IV studies

- **Harmonization of serum thyroid-stimulating hormone measurements paves the way for the adoption of a more uniform reference interval[1]**
- **Harmonization: its time has come[1] *(accompanying editorial by WG Miller)***
- **Standardization of free thyroxine measurements paves the way for the adoption of a more uniform reference interval[2]**

Authors: L.A.C. De Grande, K. Van Uytfanghe, D. Reynders, B. Das, J.D. Faix, F. MacKenzie, B. Decallonne, A. Hishinuma, B. Lapauw, P. Taelman, P. Van Crombrugge, A. Van den Bruel, B. Velkeniers, P. Williams, L.M. Thienpont, for the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

[1]Accepted and "early published" in Clin Chem
[2]Revision submitted to Clin Chem

Achieved milestones for FT4 and TSH

Follow-up panels (stored at NIBSC, Pottersbar, UK)

- **FT4 1st follow-up panel (n = 95); concentration range (by RMP): 4 – 202 pmol/L**
- **TSH 1st follow-up panel (n = 95); concentration range: ~0.002 – to 169 mIU/L**
- **Homogeneity of the panels proven**
- **Stability study ongoing**

NOTE: panels and target setting sponsored by the participating IVD manufacturers

Achieved milestones for FT4 and TSH

Follow-up panels

1. **Who has the proprietary rights?**
2. **Can the panels be made available to new IVD companies on request?**
3. **If yes, at which price?**

NOTE: It can be anticipated that FT4 RMP services by several competent laboratories will be offered from 2018 on, since the network under construction is almost reality

Logical next step after Phase IV

Implementation

but, before this should be done, several questions to discuss/answer

Before implementation

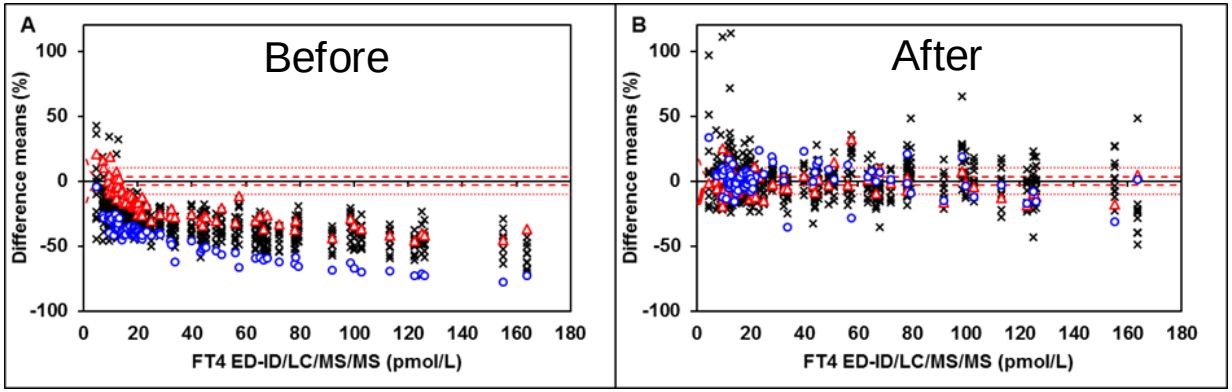
What is the impact and significance of recalibration on laboratory results and RIs? FT4? TSH?

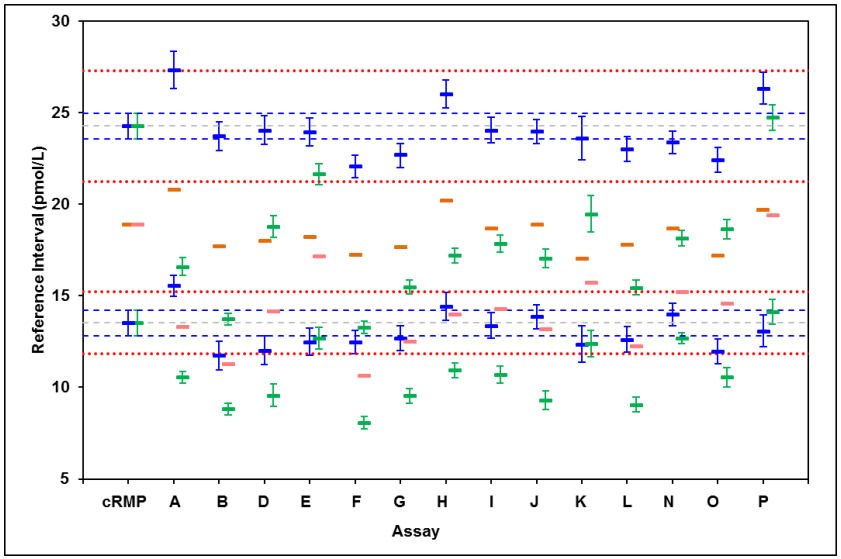
Importance

- **Patient safety: clinicians/patients should not be confused; if changes are not captured, the impact potentially can cause misdiagnosis, errors in therapy and follow-up, non-compliance with the prescribed doses, etc.**
- **Regulatory requirements will depend on the impact**

Impact of recalibration – FT4

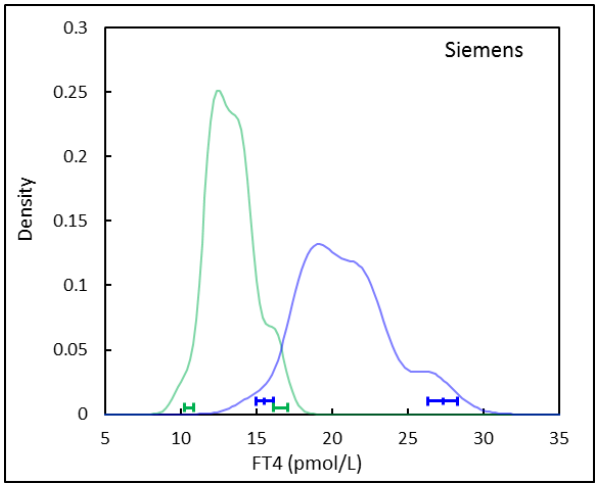
On laboratory results and RI

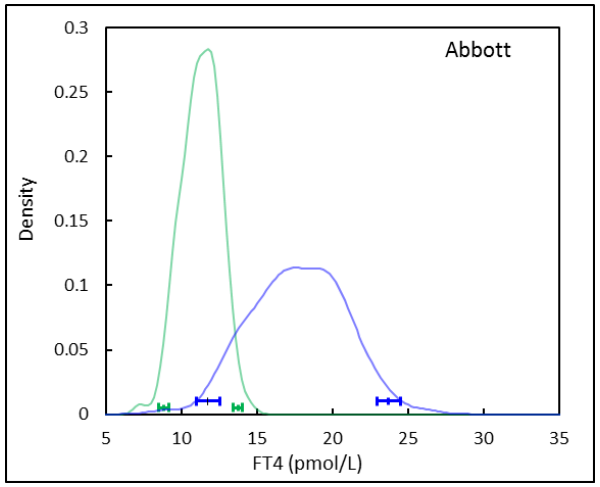


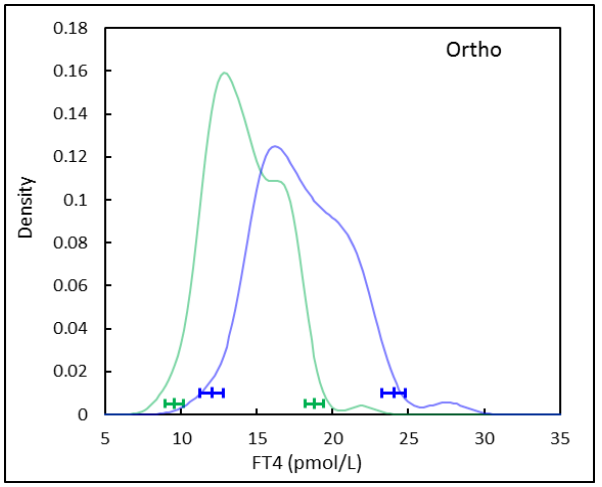


➔Impact is for almost all assays huge

Individual impact of recalibration – FT4





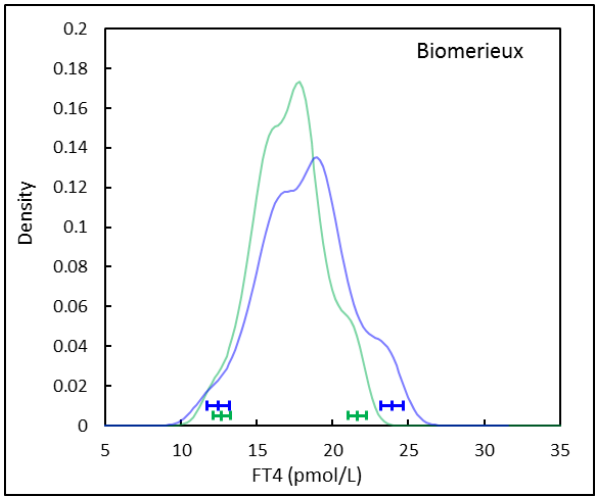


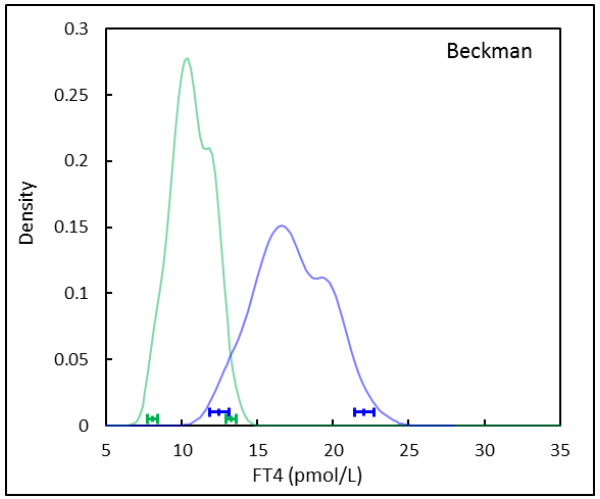
% Δ between pre- and post-recalibration	
2.5 centile	47.3
97.5 centile	64.7
Overlap between pre- and post-recalibration CIs around centiles?	
	No

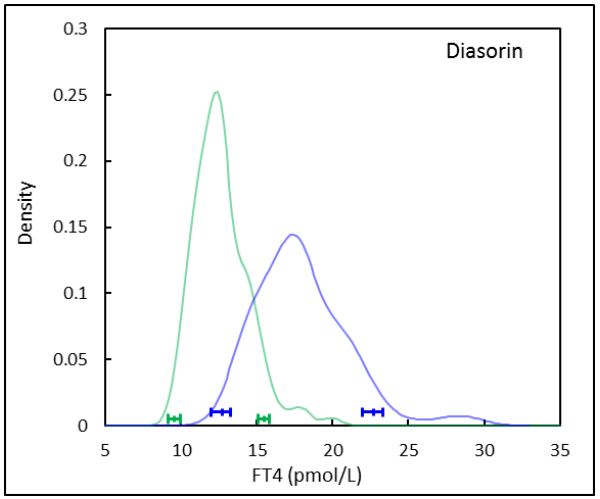
% Δ between pre- and post-recalibration	
2.5 centile	33.2
97.5 centile	72.6
Overlap between pre- and post-recalibration CIs around centiles?	
	No

% Δ between pre- and post-recalibration	
2.5 centile	25.6
97.5 centile	28.0
Overlap between pre- and post-recalibration CIs around centiles?	
	No

Individual impact of recalibration – FT4





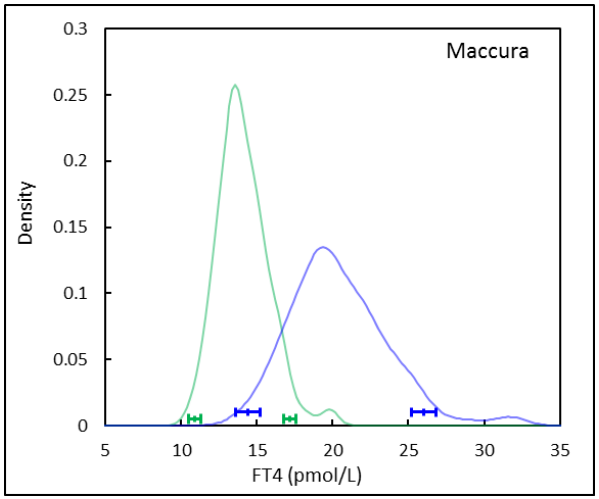


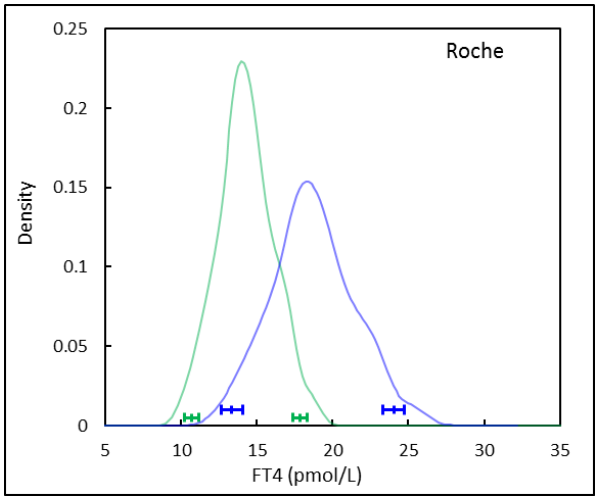
% Δ between pre- and post-recalibration	
2.5 centile	-1.6
97.5 centile	10.6
Overlap between pre- and post-recalibration CIs around centiles?	
	2.5 centile

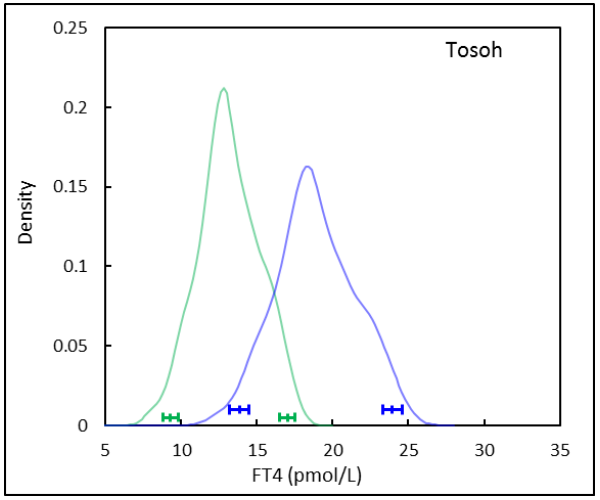
% Δ between pre- and post-recalibration	
2.5 centile	54.5
97.5 centile	66.4
Overlap between pre- and post-recalibration CIs around centiles?	
	No

% Δ between pre- and post-recalibration	
2.5 centile	33.2
97.5 centile	46.7
Overlap between pre- and post-recalibration CIs around centiles?	
	No

Individual impact of recalibration – FT4





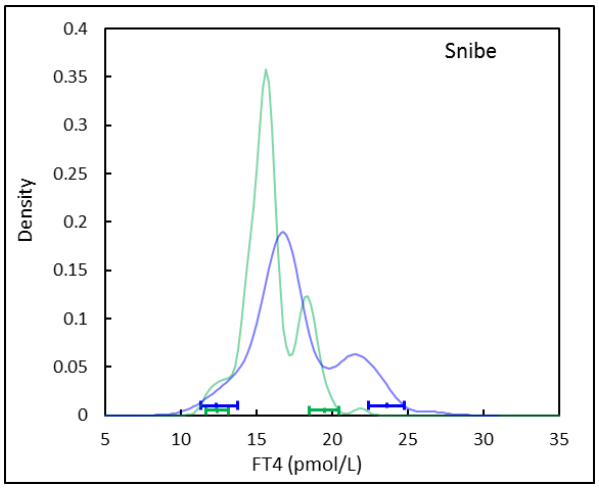


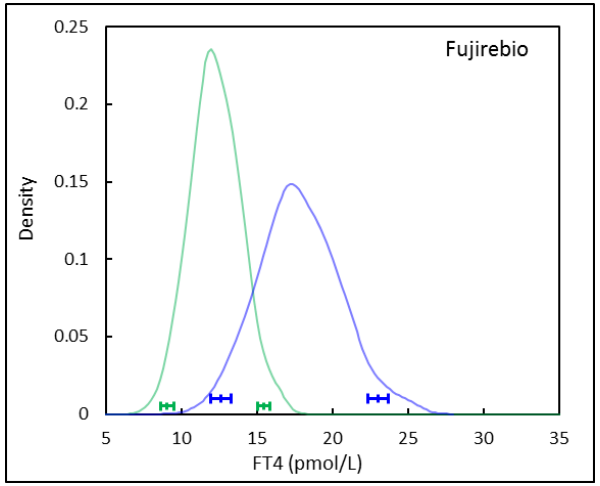
% Δ between pre- and post-recalibration	
2.5 centile	31.8
97.5 centile	51.2
Overlap between pre- and post-recalibration CIs around centiles?	
	No

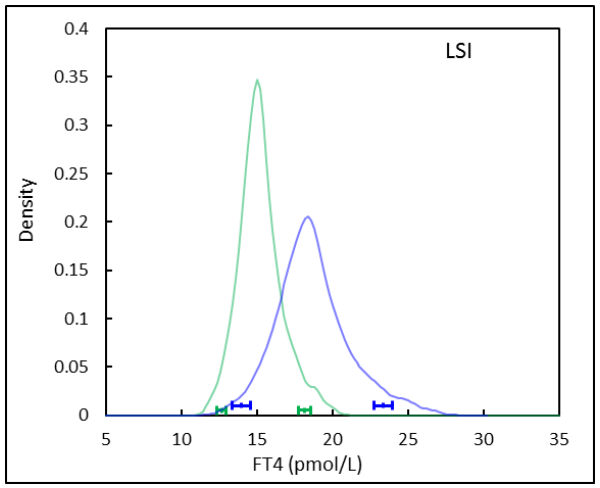
% Δ between pre- and post-recalibration	
2.5 centile	24.8
97.5 centile	34.7
Overlap between pre- and post-recalibration CIs around centiles?	
	No

% Δ between pre- and post-recalibration	
2.5 centile	48.8
97.5 centile	40.6
Overlap between pre- and post-recalibration CIs around centiles?	
	No

Individual impact of recalibration – FT4





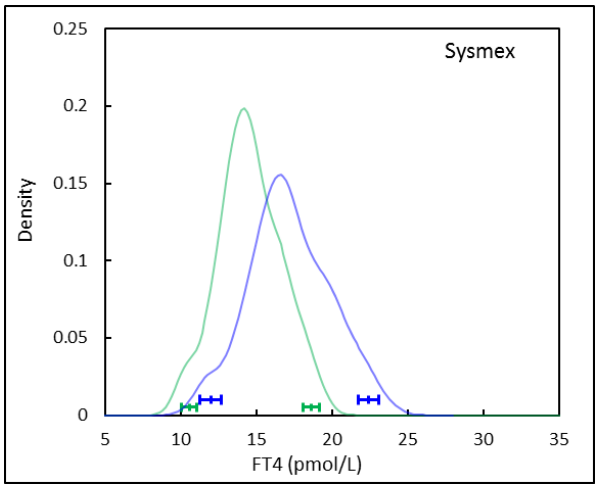


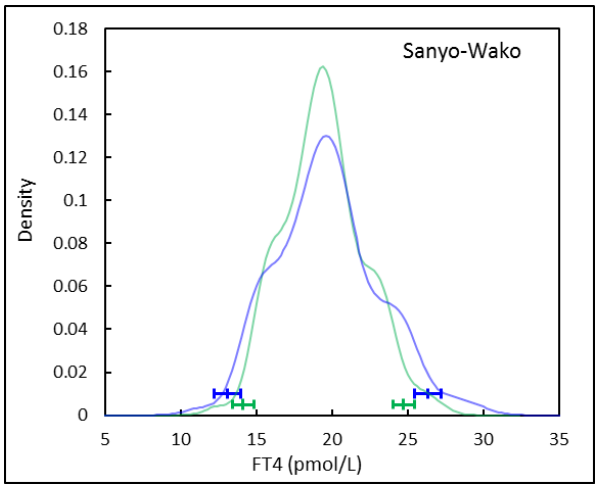
% Δ between pre- and post-recalibration	
2.5 centile	-0.3
97.5 centile	21.3
Overlap between pre- and post-recalibration CIs around centiles?	
	2.5 centile

% Δ between pre- and post-recalibration	
2.5 centile	39.2
97.5 centile	48.9
Overlap between pre- and post-recalibration CIs around centiles?	
	No

% Δ between pre- and post-recalibration	
2.5 centile	10.5
97.5 centile	28.8
Overlap between pre- and post-recalibration CIs around centiles?	
	No

Individual impact of recalibration – FT4



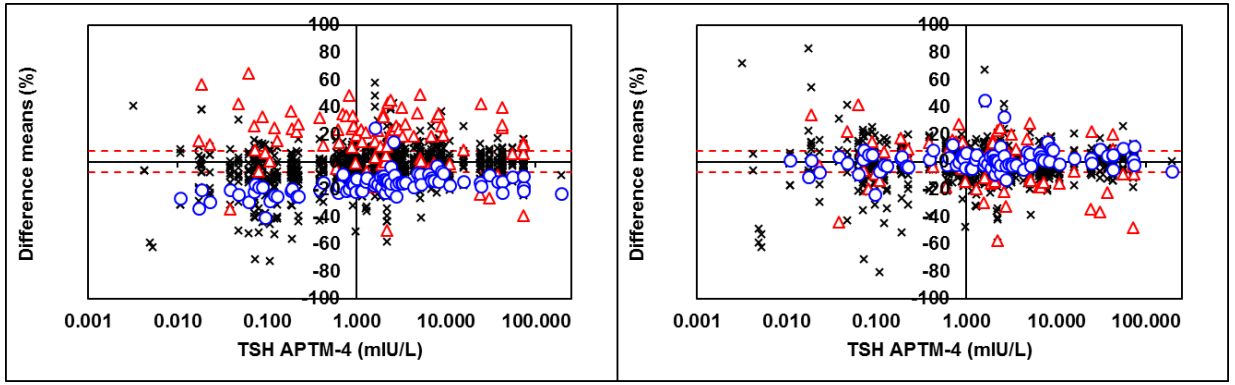


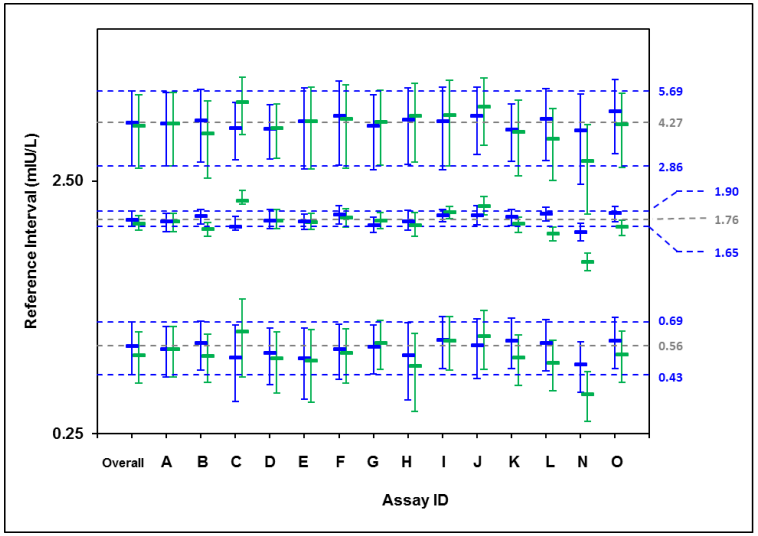
% Δ between pre- and post-recalibration	
2.5 centile	13.5
97.5 centile	20.3
Overlap between pre- and post-recalibration CIs around centiles?	
	No

% Δ between pre- and post-recalibration	
2.5 centile	-7.5
97.5 centile	6.5
Overlap between pre- and post-recalibration CIs around centiles?	
	2.5 centile

Impact of recalibration – TSH

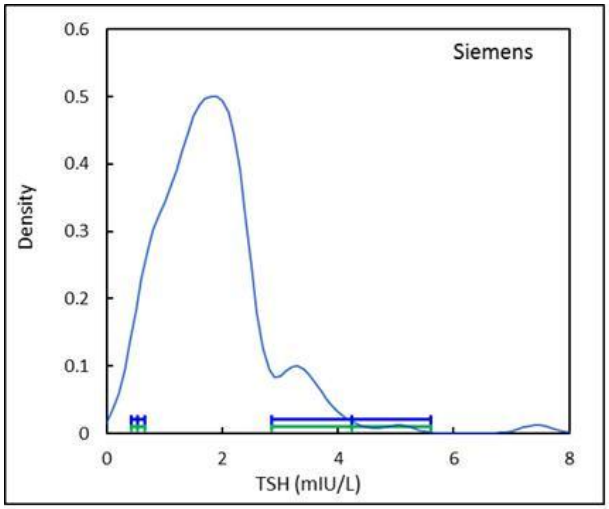
On laboratory results and RI

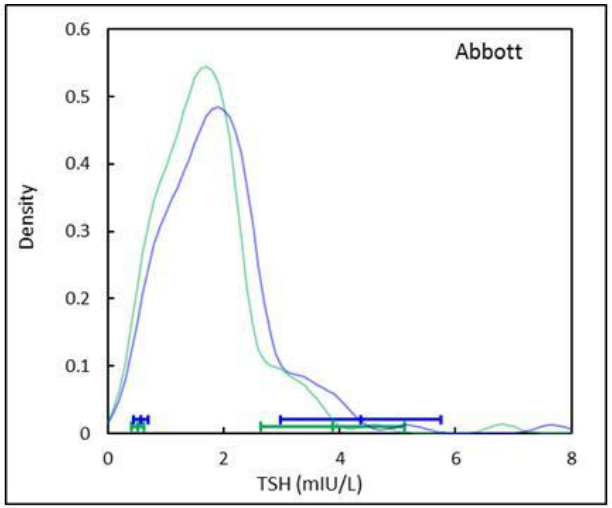


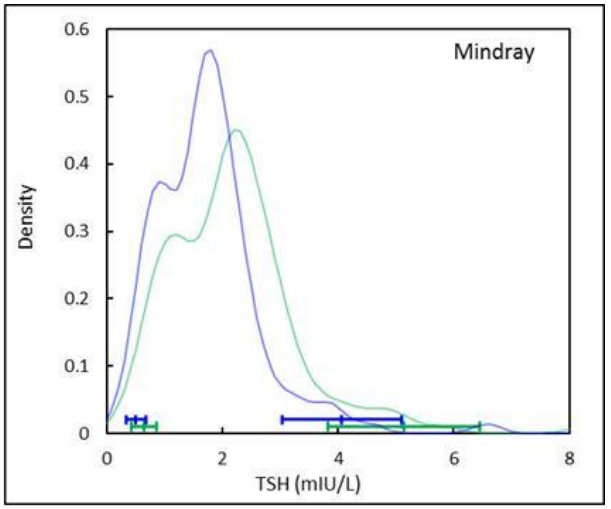


➔Impact is for most assays moderate

Individual impact of recalibration – TSH





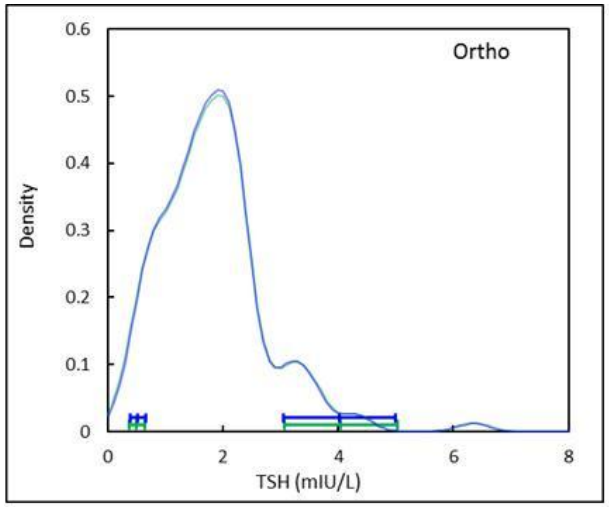


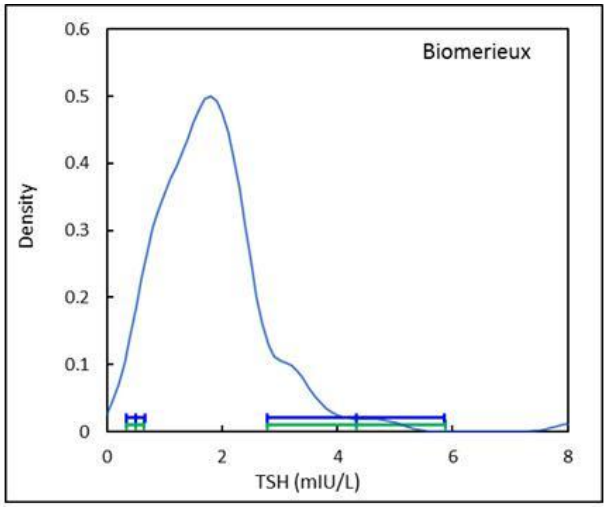
% Δ between pre- and post-recalibration	
2.5 centile	0.0
97.5 centile	0.0
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

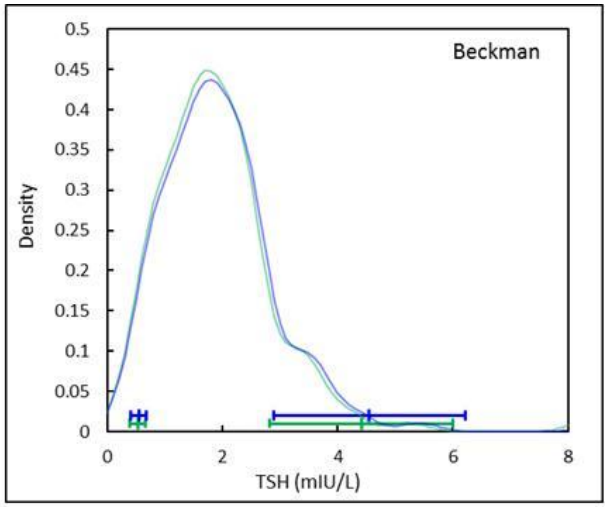
% Δ between pre- and post-recalibration	
2.5 centile	12.7
97.5 centile	12.5
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

% Δ between pre- and post-recalibration	
2.5 centile	-20.7
97.5 centile	-20.8
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

Individual impact of recalibration – TSH





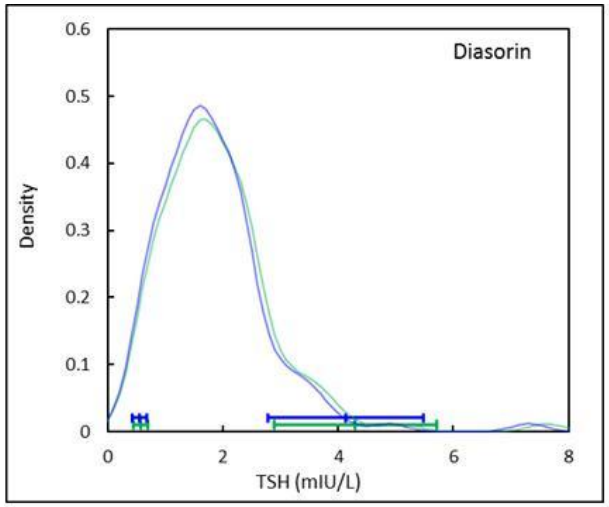


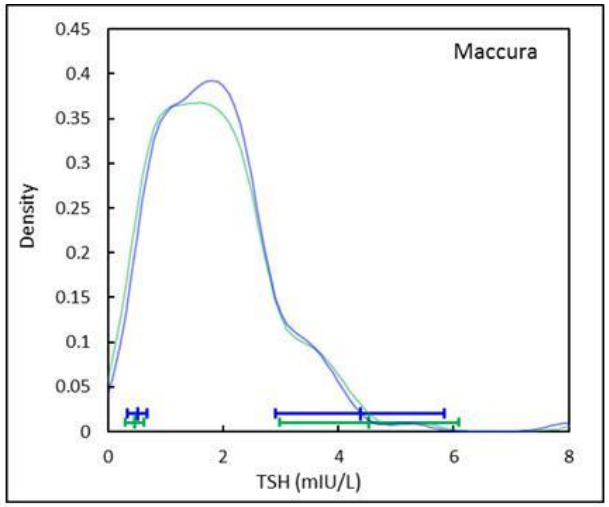
% Δ between pre- and post-recalibration	
2.5 centile	5.3
97.5 centile	-0.6
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

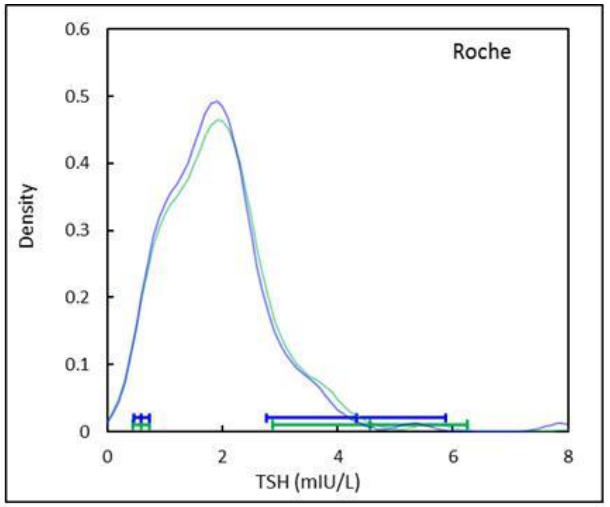
% Δ between pre- and post-recalibration	
2.5 centile	1.8
97.5 centile	-0.1
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

% Δ between pre- and post-recalibration	
2.5 centile	3.5
97.5 centile	3.2
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

Individual impact of recalibration – TSH





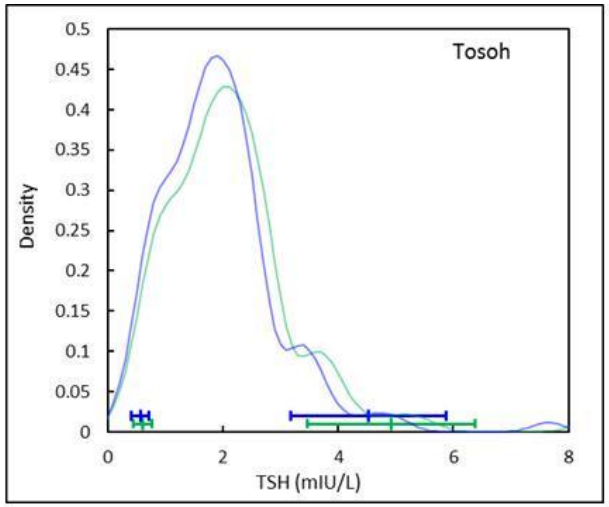


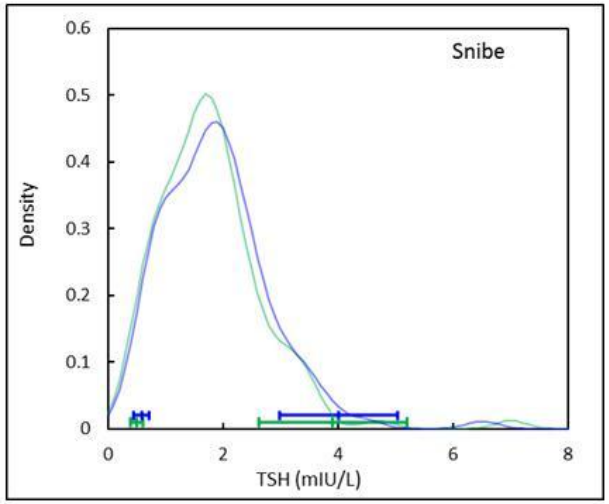
% Δ between pre- and post-recalibration	
2.5 centile	-3.9
97.5 centile	-4.0
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

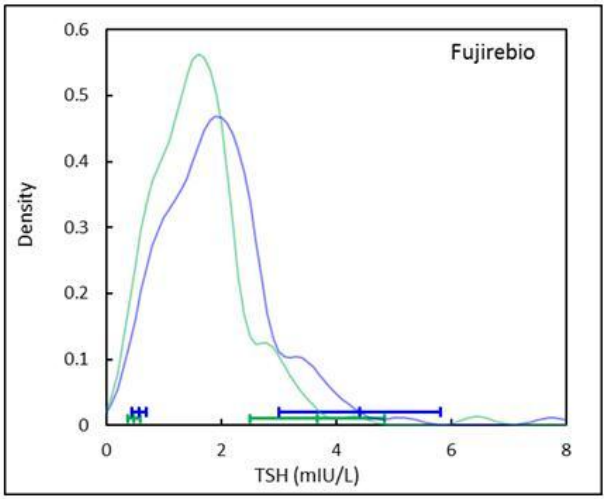
% Δ between pre- and post-recalibration	
2.5 centile	10.0
97.5 centile	-3.4
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

% Δ between pre- and post-recalibration	
2.5 centile	0.4
97.5 centile	-5.1
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

Individual impact of recalibration – TSH





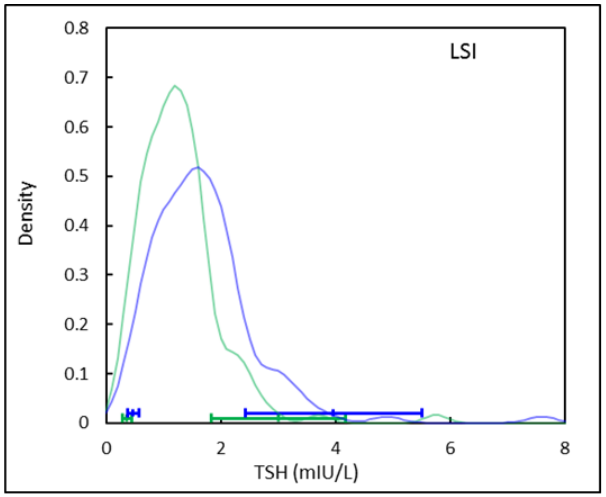


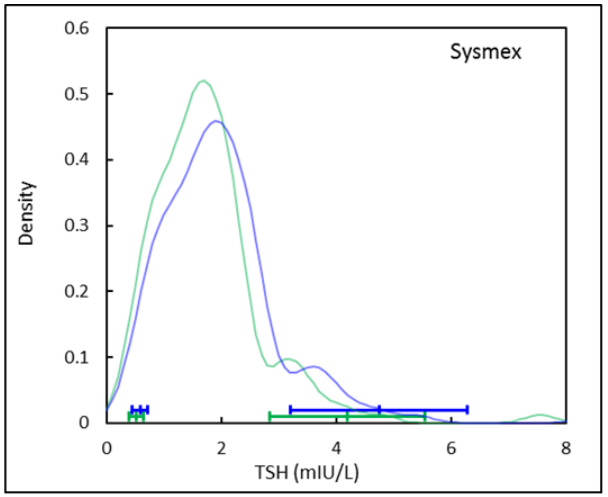
% Δ between pre- and post-recalibration	
2.5 centile	-7.7
97.5 centile	-8.0
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

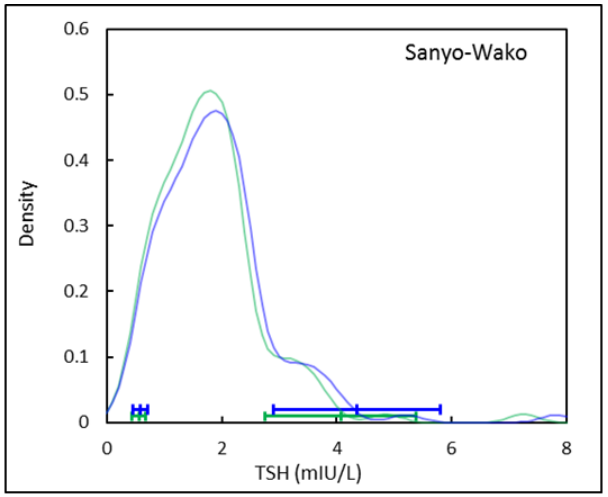
% Δ between pre- and post-recalibration	
2.5 centile	16.6
97.5 centile	2.6
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

% Δ between pre- and post-recalibration	
2.5 centile	20.0
97.5 centile	20.1
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

Individual impact of recalibration – TSH







% Δ between pre- and post-recalibration	
2.5 centile	31.0
97.5 centile	31.9
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

% Δ between pre- and post-recalibration	
2.5 centile	13.2
97.5 centile	13.2
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

% Δ between pre- and post-recalibration	
2.5 centile	4.2
97.5 centile	6.9
Overlap between pre- and post-recalibration CIs around centiles?	
	Yes

Before implementation

Impact of recalibration: is there a need for a common strategy to adopt by IVD manufacturers?

Some thoughts

Possible common strategy to ESTIMATE the impact

- **Verify the significance of the changes in RI centiles/ means/medians estimated in the C-STFT study**
- **Answer the questions:**
  - **does the RI study after recalibration warrant that the previous one can be continued, or**
  - **can the old and new RI be bridged by a conversion factor, or**
  - **are the changes that significan that they require establishment of a new RI?**
- **Is it desirable to reach a consensus on the verification protocol to use? e.g., CLSI. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline — 3rd Ed doc EP28-A3c…**

Before implementation

1. **In how far is the impact a potential risk for patient safety?**
2. **How can the C-STFT help to answer the “risk” question?**
3. **How to minimize/waive the identified risks?**

Some thoughts

Support by the C-STFT to ANSWER the “risk” question

- Liaise with the involved stakeholders
- Establish a communication platform
- Identify together with stakeholders what is needed before implementation
- …

Some thoughts

Liaise with key stakeholders

First define who is involved as stakeholders

- IVD manufacturers
- Laboratories (& their societies/associations)
- Clinicians/nurses (& their societies/associations)
- Patients (Thyroid Federation International)
- International/national regulators (in the broader sense: USA, Asia/China/Japan, Europe, PT/EQA, etc.)

Establish a communication platform

- Via intra/internet
- Via the websites of societies/associations
- Send questionnaires
- Organize meetings, give presentations at symposia
- Publish

Some thoughts

Identify together with stakeholders what is needed before implementation

- **Benefit/risk analysis**
- **If risks are identified, define the actions that can be undertaken to minimize/waive them**
- **Find out about the regulatory requirements**
- **Contact/re-contact the regulatory authorities as a group?**
- **Educate the stakeholders**
- **…**

First contacts established by C-STFT

With key associations/societies

- **American Thyroid association (ATA) (courtesy: J. Faix)**

  Contact: Alicia Algeciras-Schimnich, chair of the ATA's Lab Services Committee
- **Japan Thyroid Association TA (courtesy A. Hishinuma)**

  Contact: Prof. Dr. Akamizu, President

Other contacts to establish?

- **Endocrine Societies (US, Europe)**
- **Partnership for the Accurate Testing of Hormones (PATH) (courtesy H. Vesper?)**
- **…**

First benefit/risk analysis

LM Thienpont, JD Faix, and G Beastall

"Standardization of Free Thyroxine and Harmonization of Thyrotropin Measurements: A Request for Input from Endocrinologists and Other Physicians/Patients."

1. Thyroid 2015;25:1379-80.
2. Clin Endocrinol (Oxf) 2015 Jul 23. [Epub ahead of print]. Endocr J 2015;62:855-6.
3. Exp Clin Endocrinol Diabetes 2016;124:61-2.
4. Endocrine 2015;50:826-7.
5. Eur Thyroid J 2015;4:217-2.
6. Endocr Pract 2016;22:374.
7. AACC Endocrinology Division Newsletter 2016; vol 2: issue 1.
8. ThyroWorld Volume 18 Summer 2015; 13-4.

Benefit/risk analysis – Input

Benefits

Unquestionable

Potential risks for patient safety related to the

- **Impact of recalibration thus the changes that will be involved**
- **Willingness of all involved stakeholders to accept these changes and accommodate for in practice**
- **Coordination of the implementation by all IVD manufacturers at the same point in time and worldwide**
- **Sustainability of the traceability basis**

To minimize/waive the identified risks, all involved stakeholders should contribute

Minimize/waive the identified risks

Involve all levels of stakeholders

IVD manufacturers

Should duly communicate to laboratories on recalibration/changes in RIs/decision limits, if any

Laboratories

Should properly inform clinicians/nurses/patients about changes after recalibration (via several channels)

Clinicians

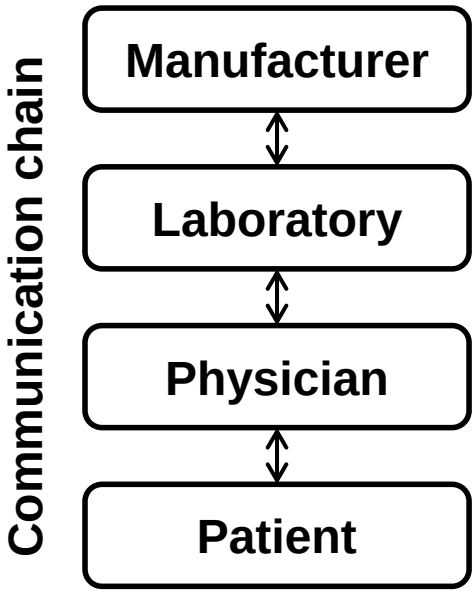
Should accommodate for the changes in their diagnostic and patient monitoring strategies; should inform their patients

Patients

Should rely on the information received from their doctor and not be confused by the changes

Minimize/waive the identified risks

Questionnaires



- Communication chain amongst all stakeholders exist
- Using reviewed literature, newsletters, circulars, oral communications, …
- In meetings and workshops, through the intranet, the LIS, …

First (cautious) conclusions

- Communication chains are well established
- Stakeholders seem familiar with handling changes
- Unlikely that changes will not be captured

Before implementation

Sustainability of the new traceability basis: assessment

Sustainability of the traceability basis

EQA/PT schemes

Issues

- Non-commutability of sample material traditionally used in EQA/PT
- Native samples needed but prohibitive by dificult sourcing process/logistics for shipment
- Peer groups with sufficient “n” often not possible in individual schemes
- Specifications used for the assessment of bias (sustainability) are not uniform across the schemes
- Surveys conducted at low frequency, thus outcome mostly only retrospective
- …

Sustainability of the traceability basis

New project "The Percentiler"

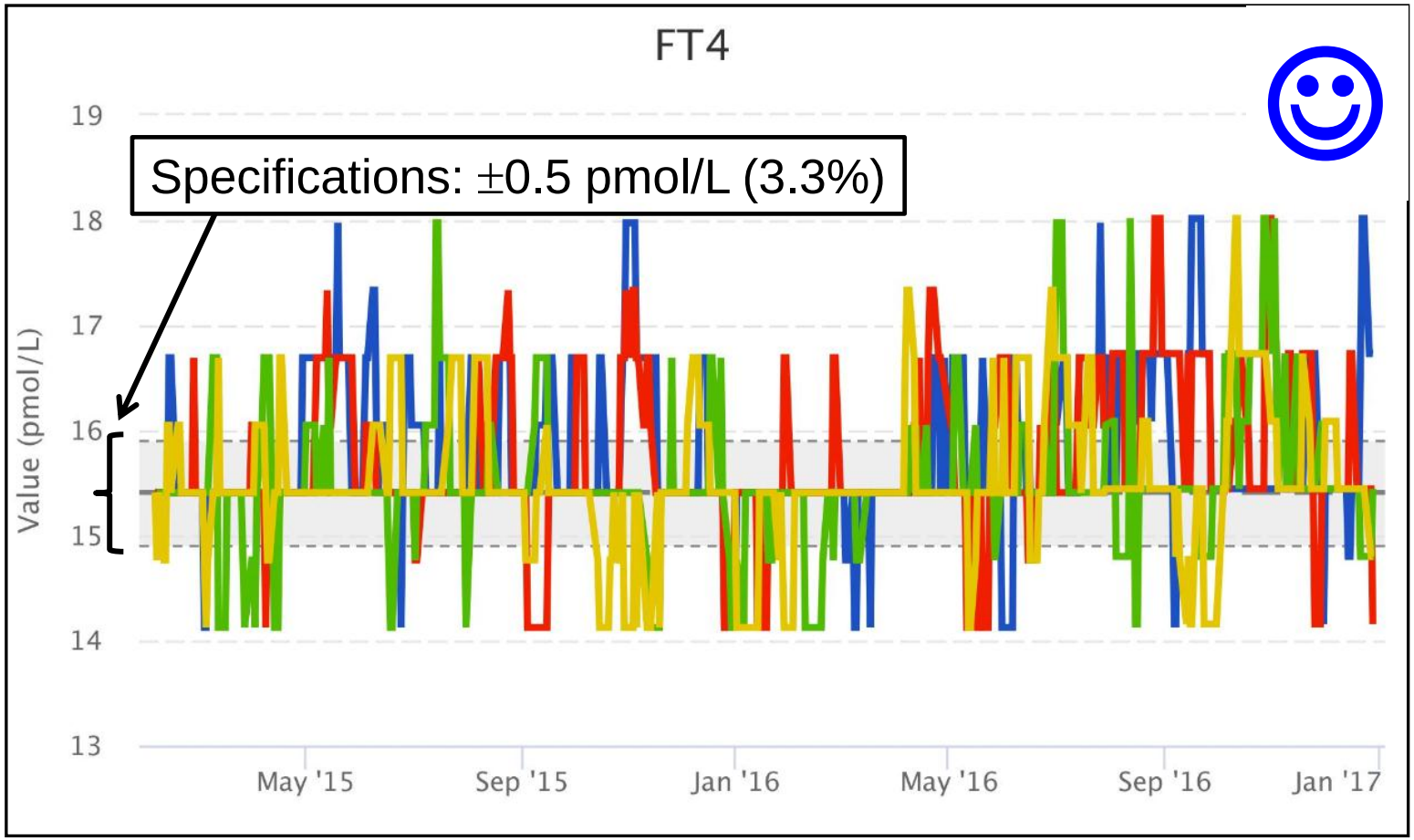
- Basis: individual laboratories send instrument-specific daily medians from outpatients
- Asset:
  - uses data from commutable samples
  - laboratories are grouped by peer
- Methods:
  - for each individual laboratory and peer group, the course of the moving median is plotted to assess under quasi real time conditions the stability of performance against realistic quality goals
  - peer group overviews (box and whisker plots) are made to assess/demonstrate the sustainability of the new traceability basis

EMPOWER IVD GLOBE

Sustainability of the traceability basis

EMPOWER IVD GLOBE

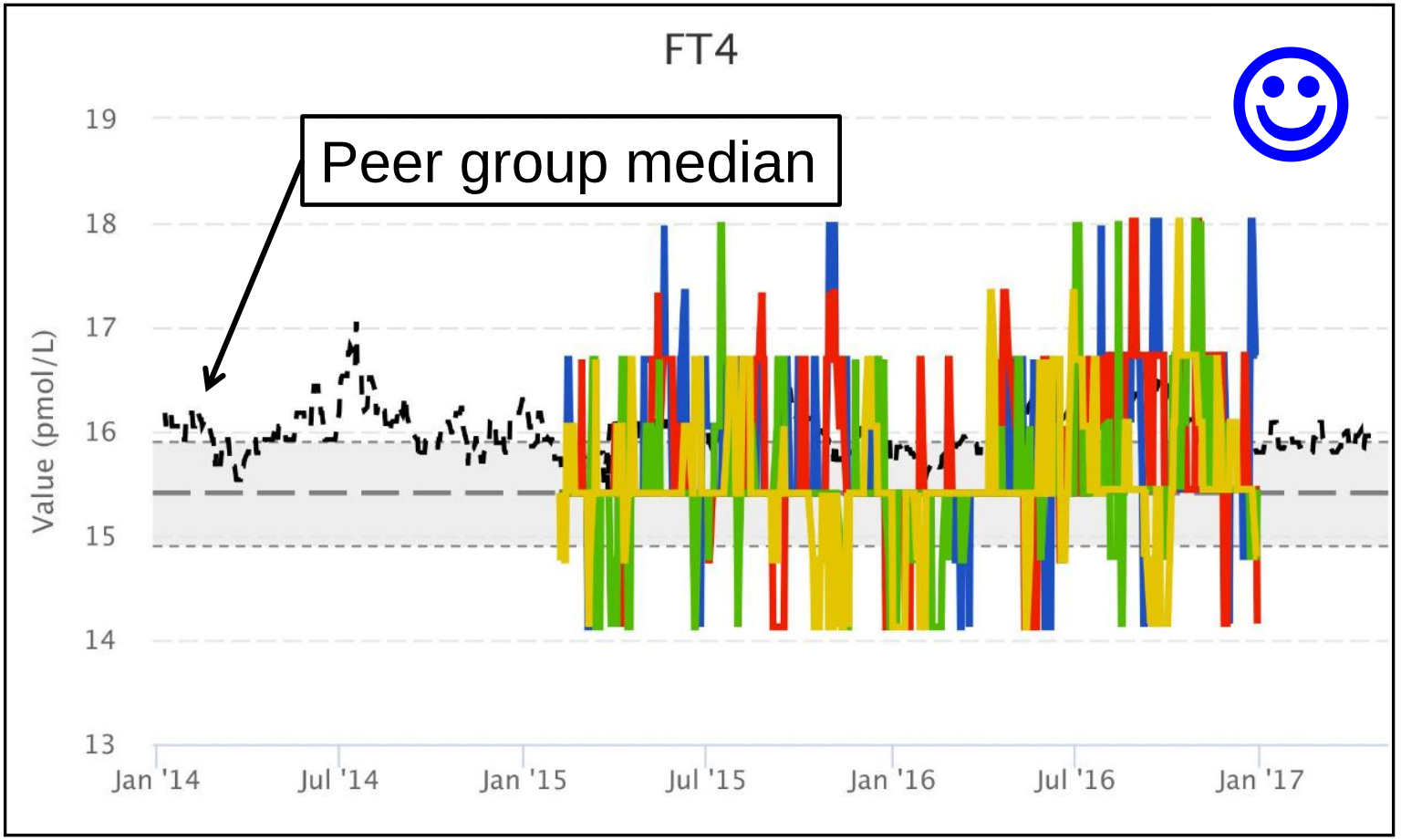
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

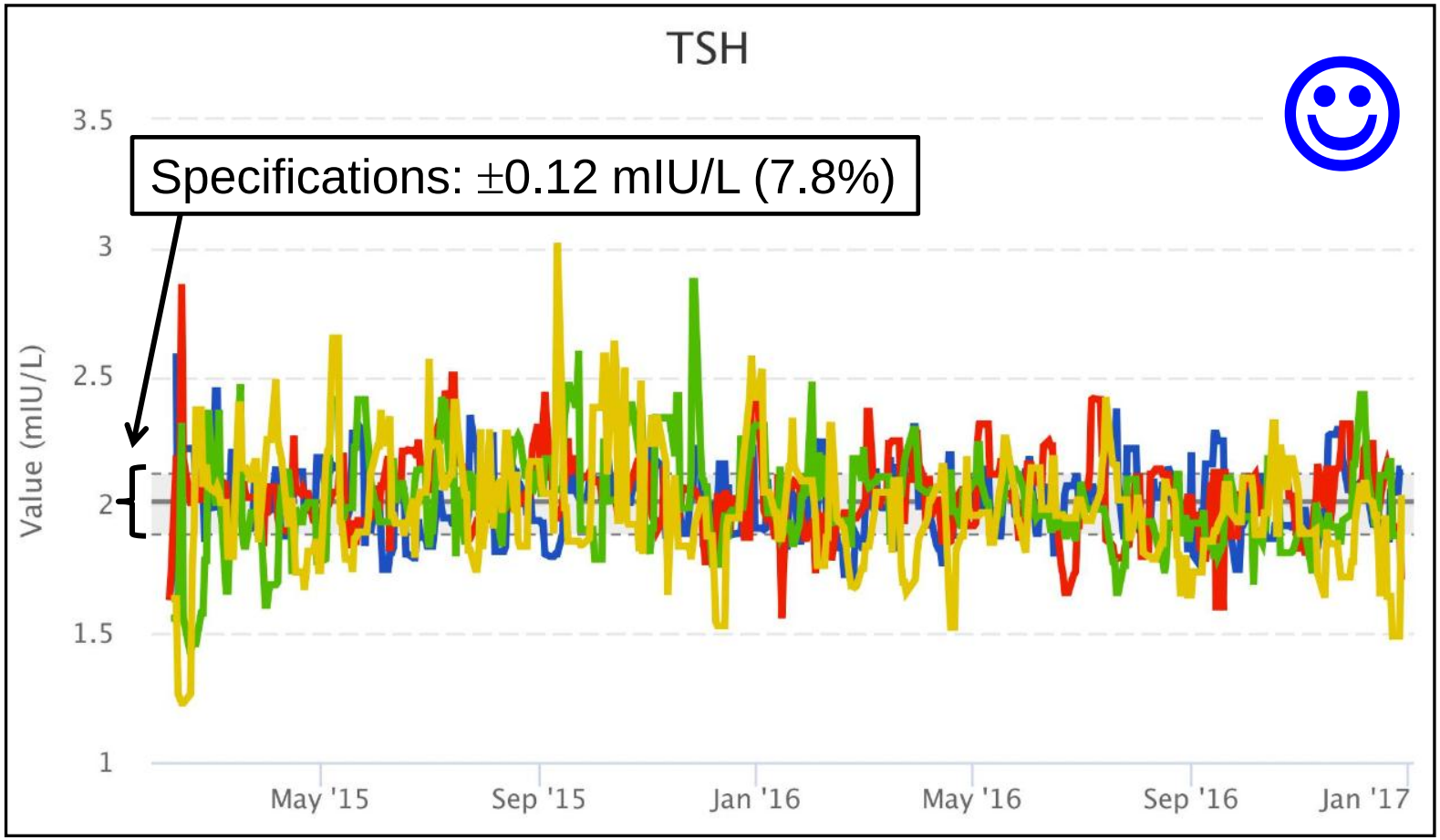
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

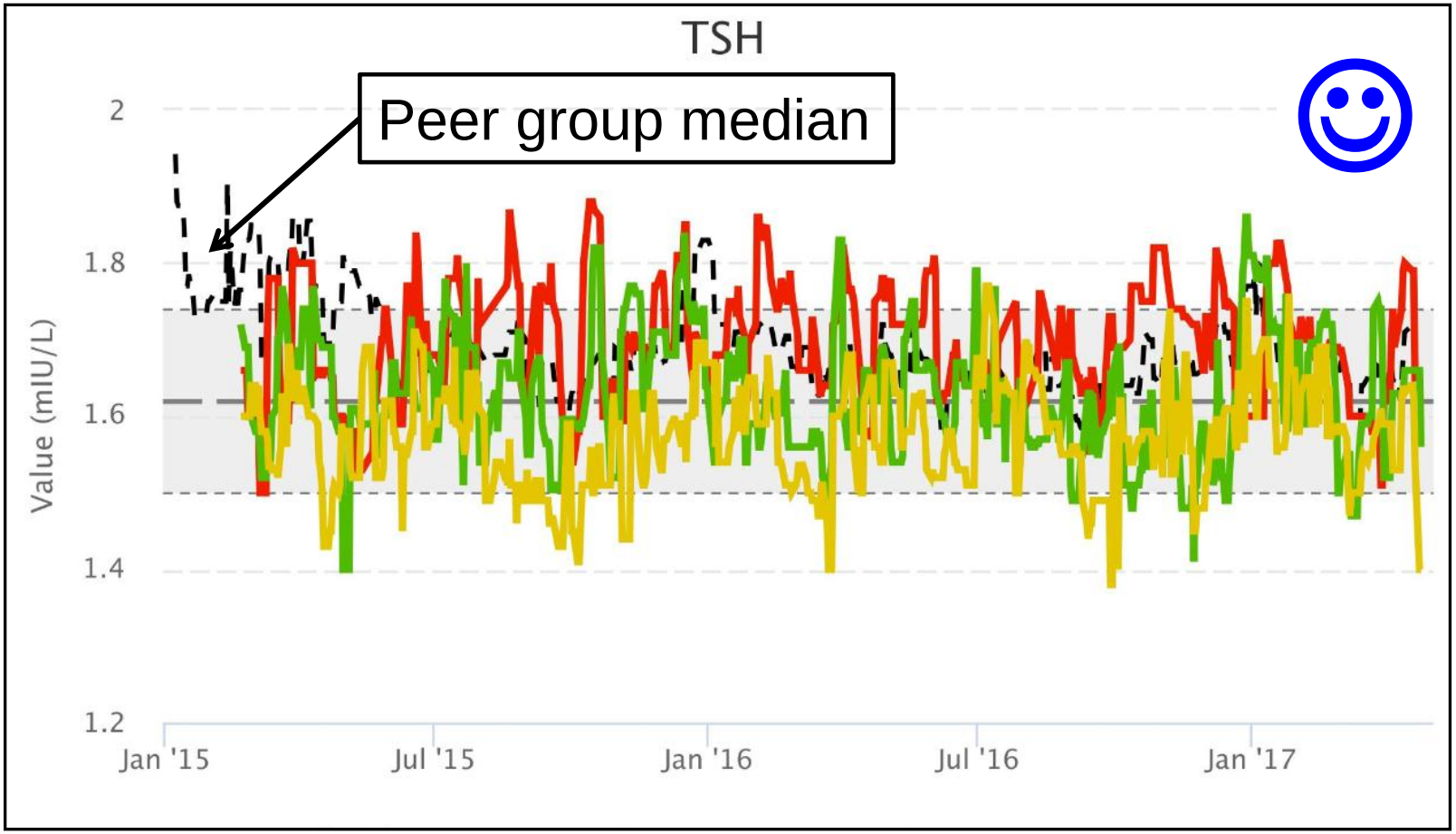
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

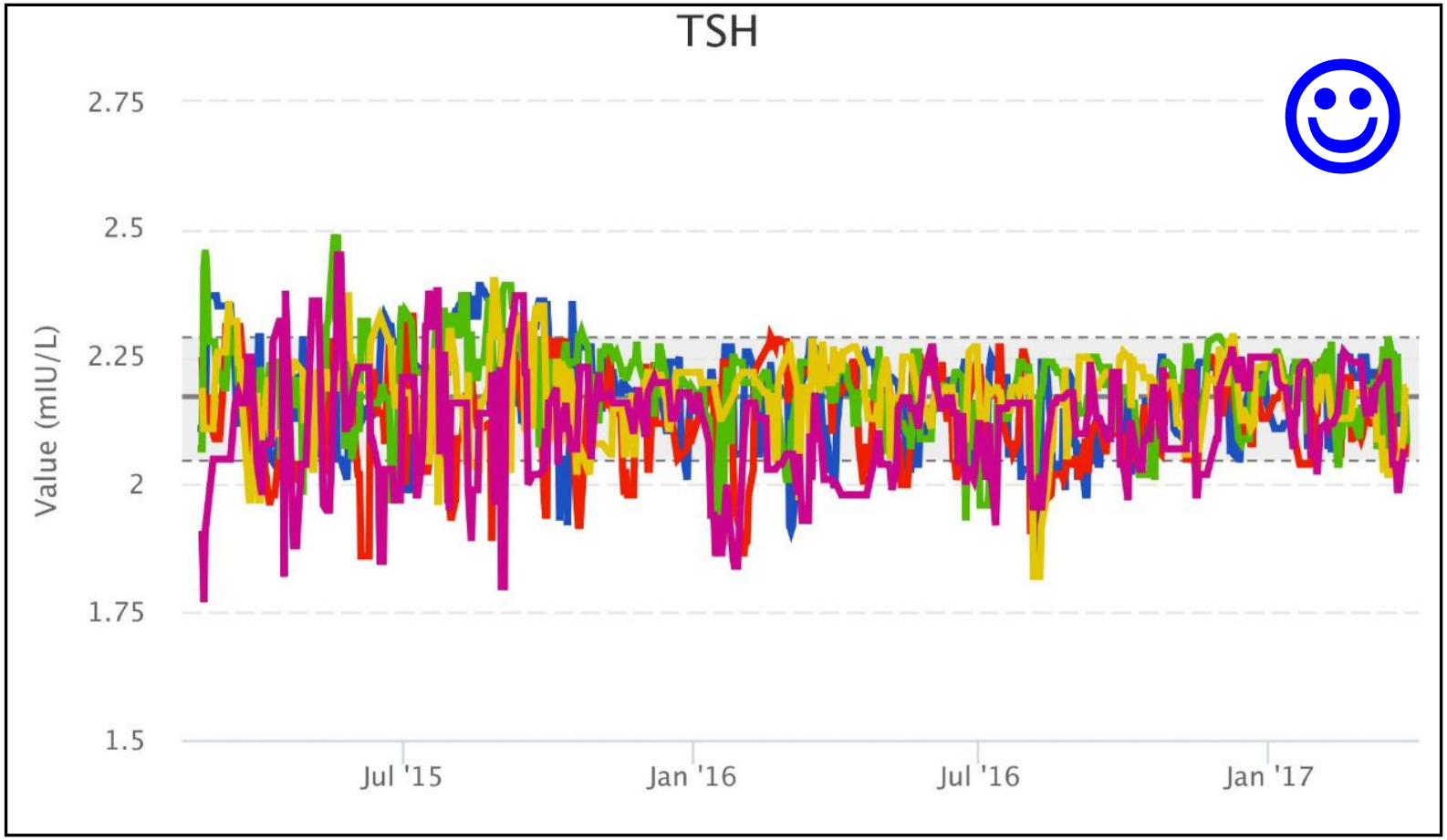
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

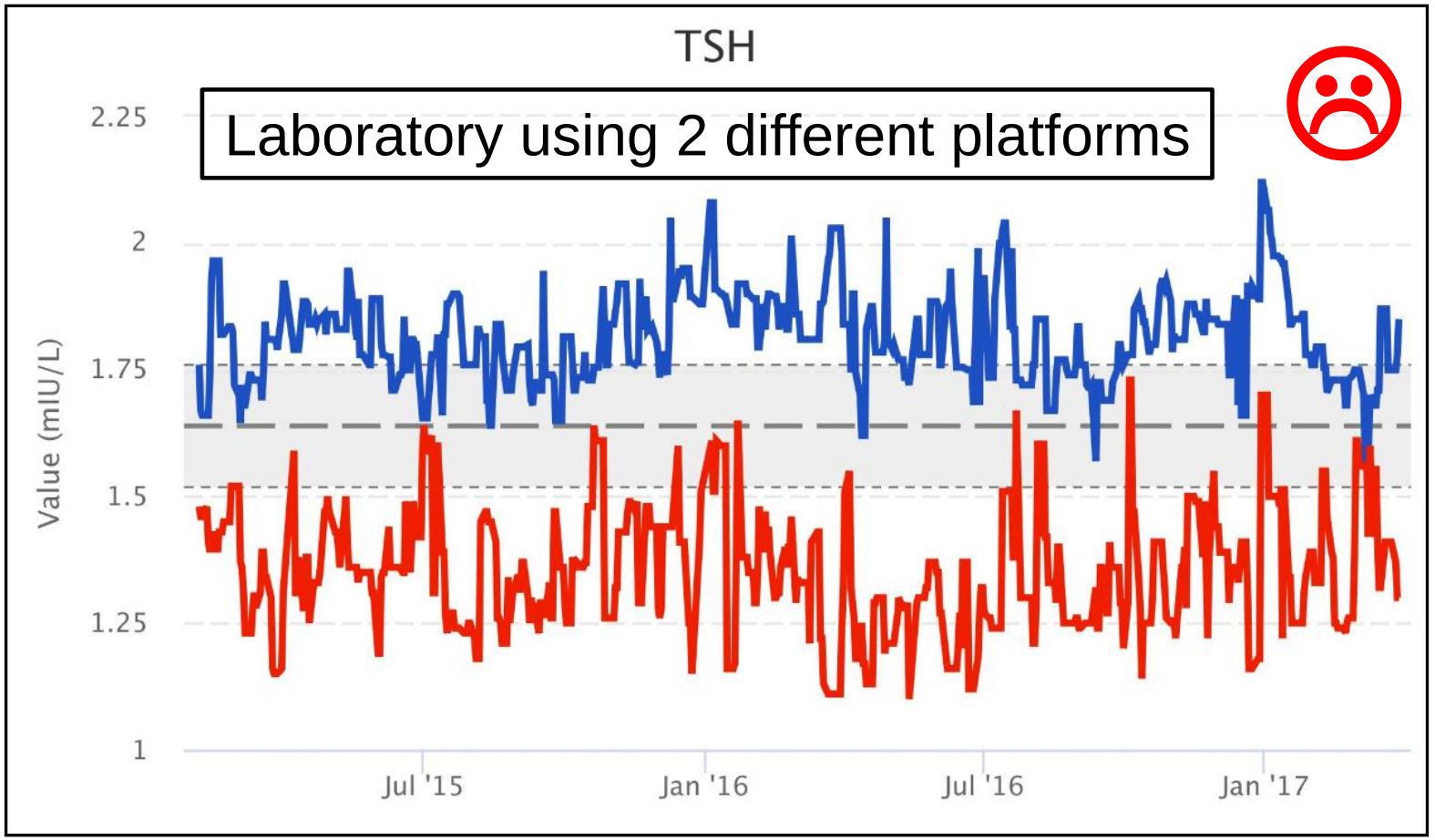
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

The percentiler application



Sustainability of the traceability basis

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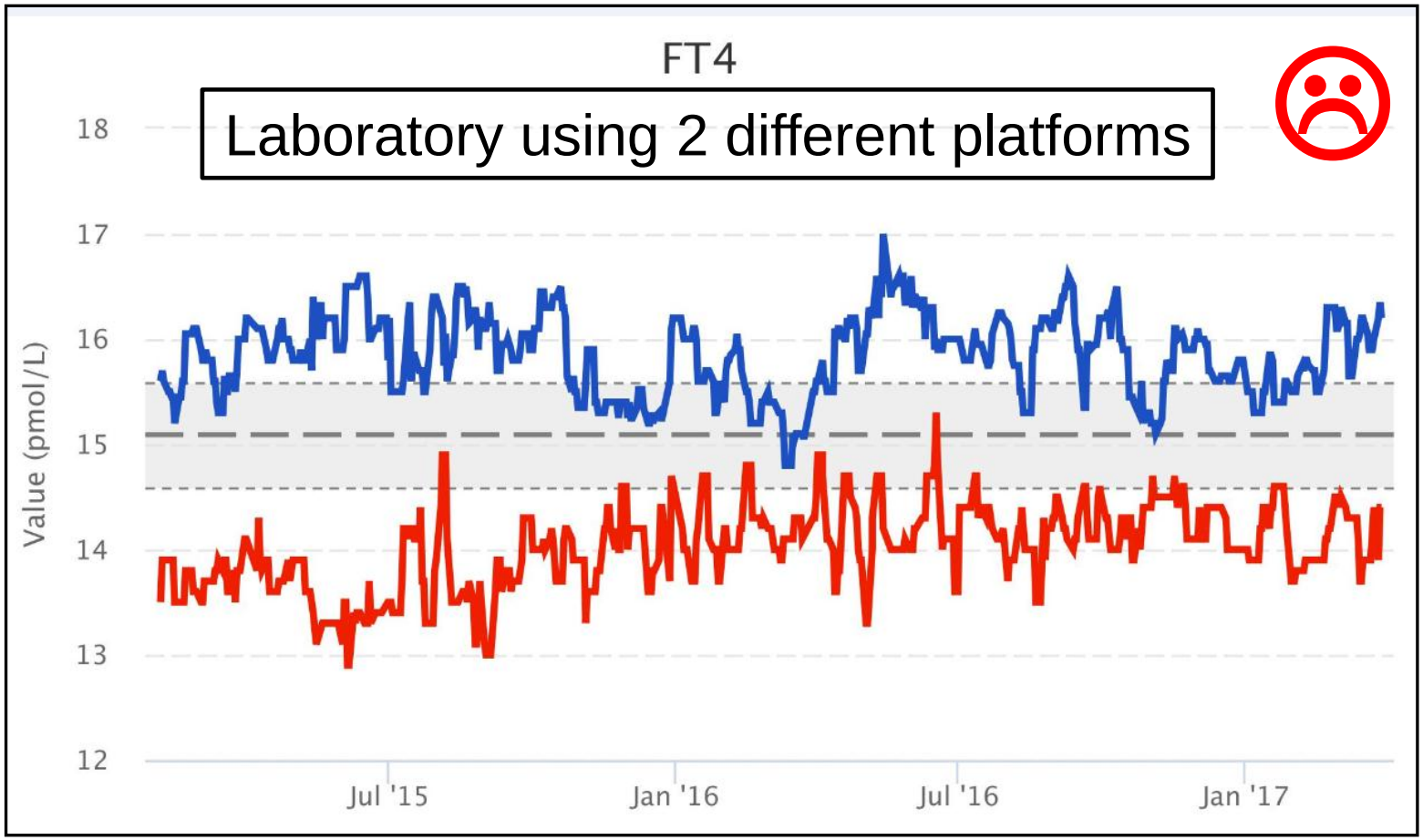
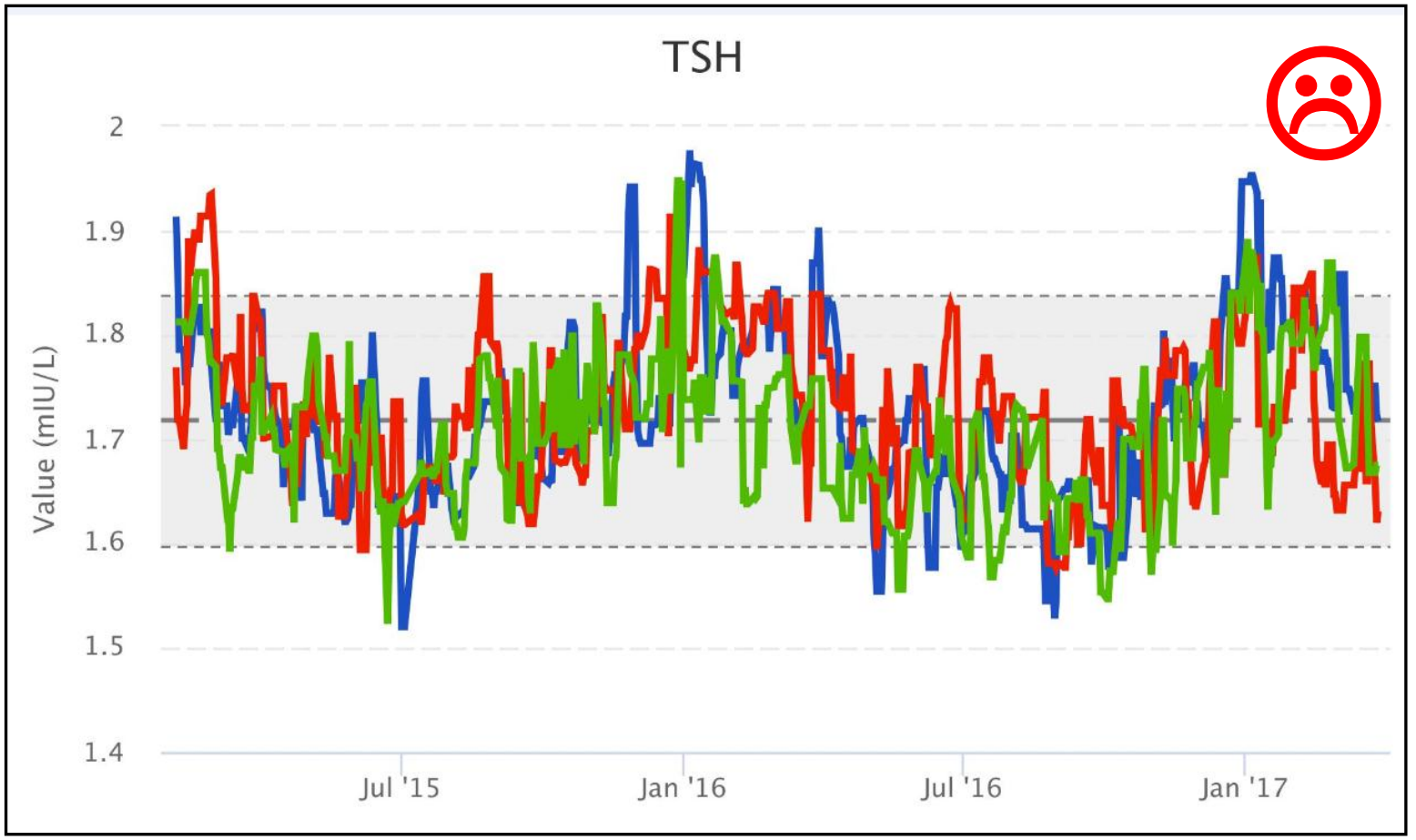
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

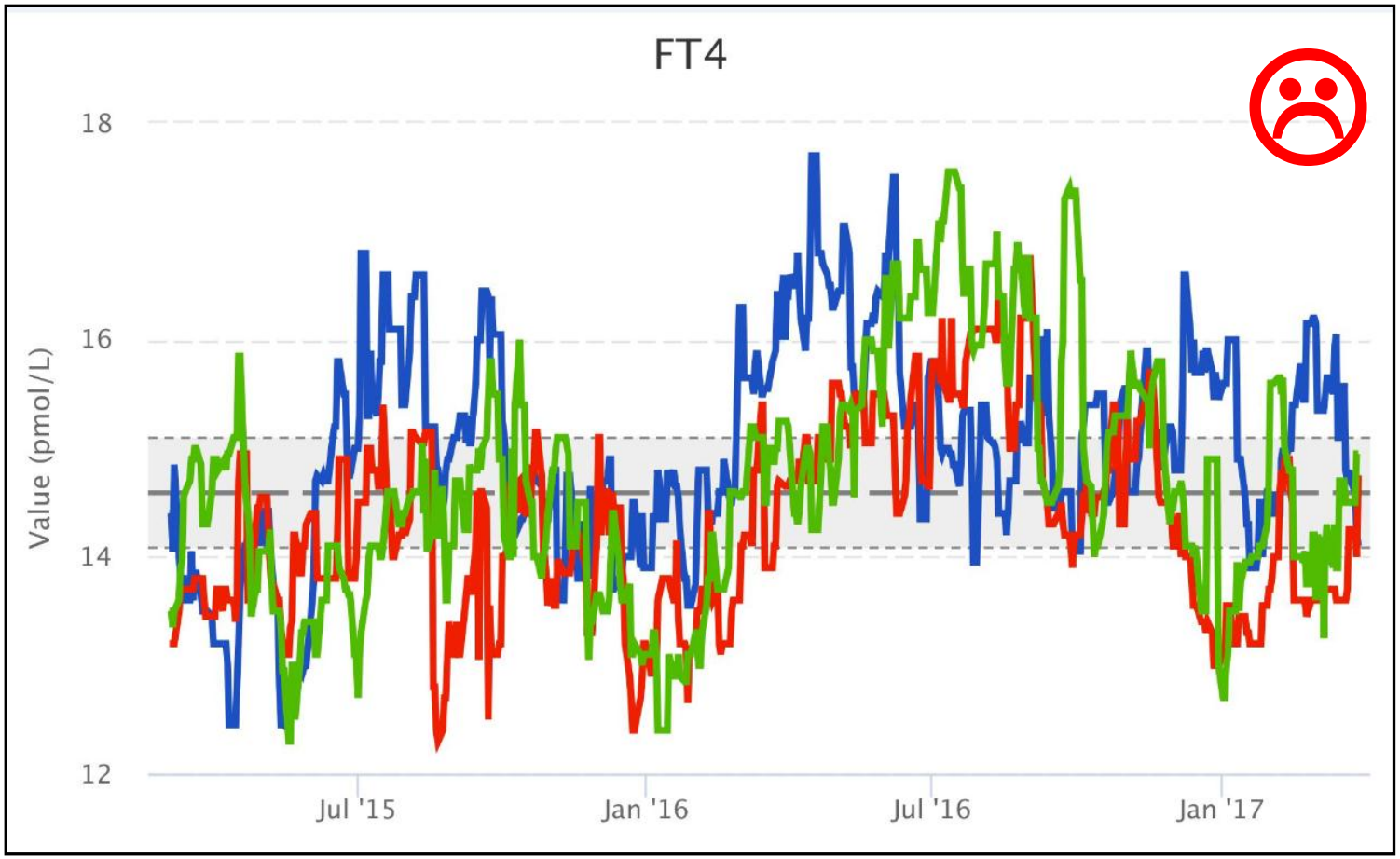
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

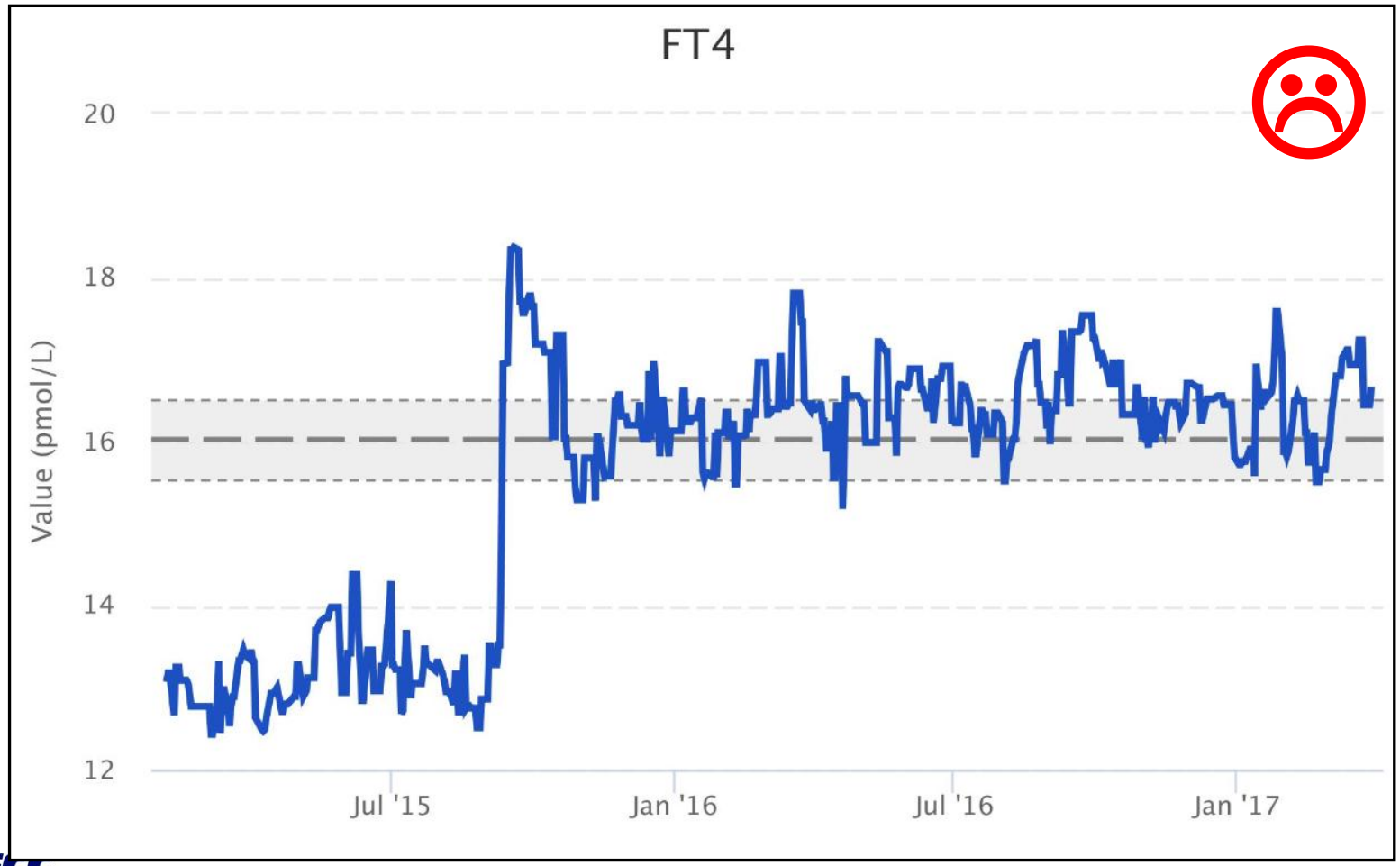
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

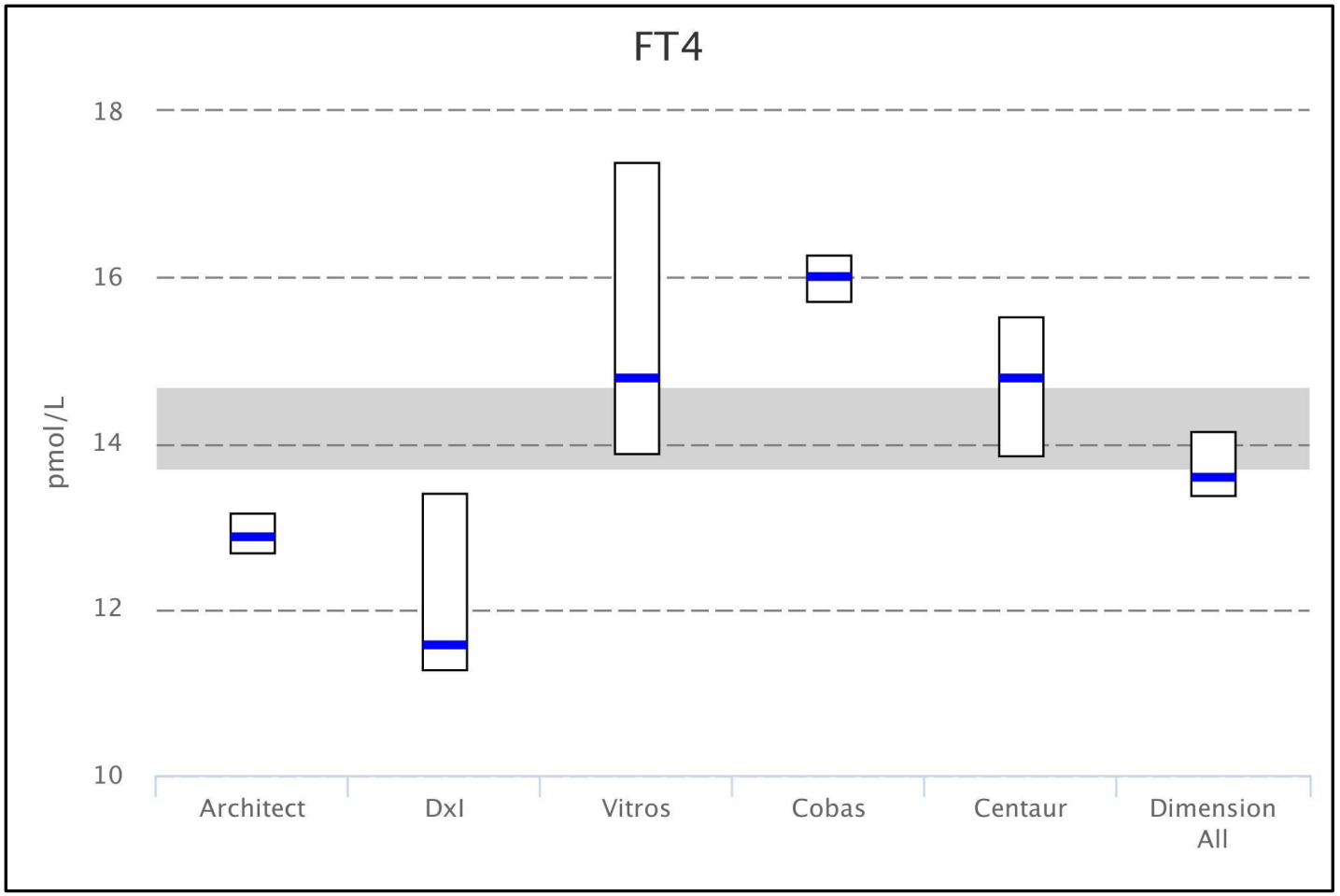
The percentiler application



Sustainability of the traceability basis

EMPOWER IVD GLOBE

The percentiler application



Sustainability of the traceability basis

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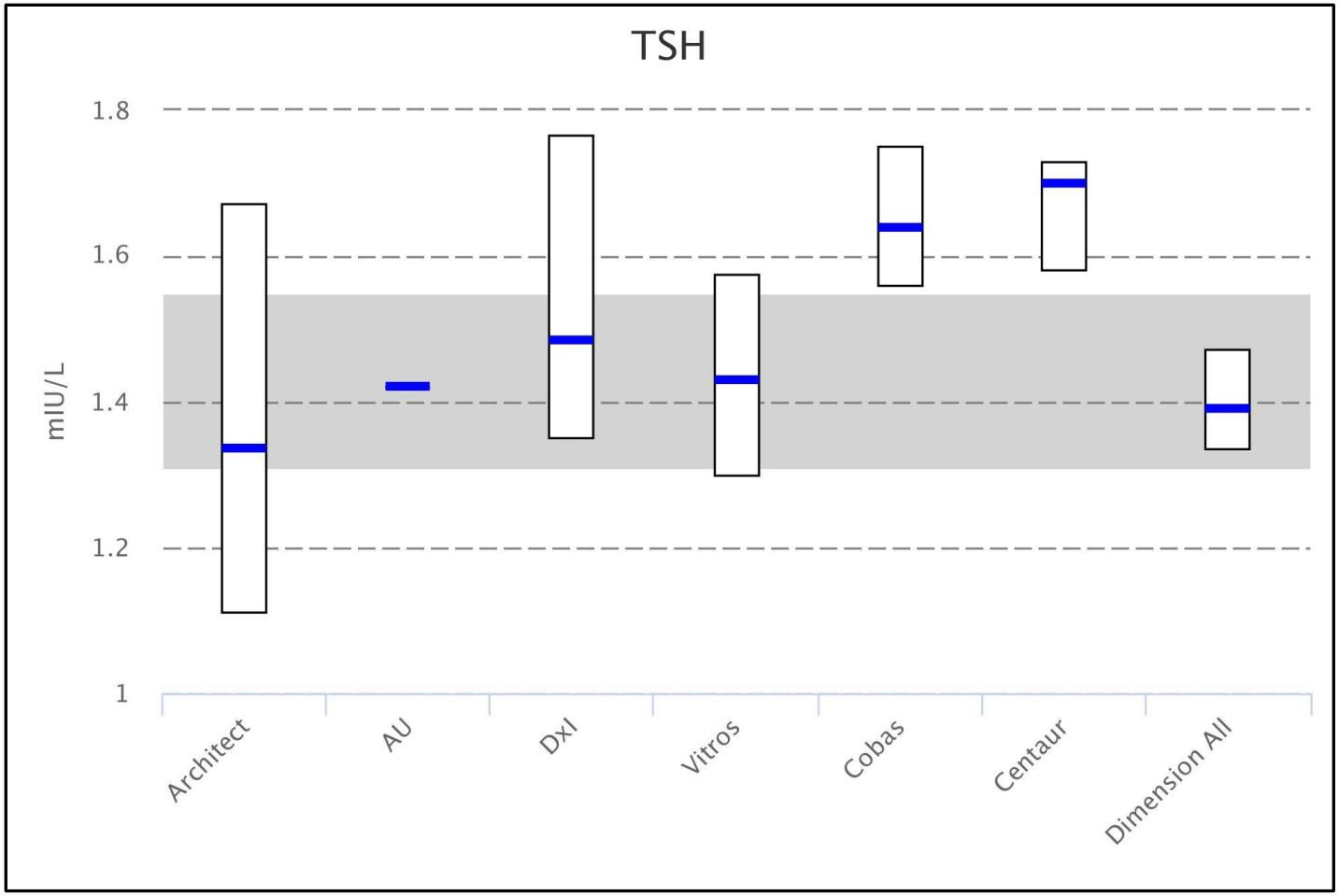
The percentiler application



Sustainability of the traceability basis

Current project status for FT4 and TSH (Percentiler)

Peer Group	Instruments
Abbott Architect	23
Beckman DxI	11
Roche Cobas ElecSys	78
Ortho Vitros	11
Siemens Advia Centaur	25
Siemens Dimension	7

EMPOWER IVD GLOBE

Sustainability of the traceability basis

EMPOWER IVD GLOBE

The percentiler application

Call to manufacturers

Support the project with recruiting customers for participation so that all platforms/assays are on board and/or peer groups are substantiated

Before implementation

1. **Timelines for implementation?**
2. **Coordination desirable/possible?**

Panel discussion with the IVD industry held on occasion of a AACB Harmonization workshop

(Sydney, AUS, May 2017)

(in conjunction with the Royal College of Pathology & Endocrine Society in Australia)

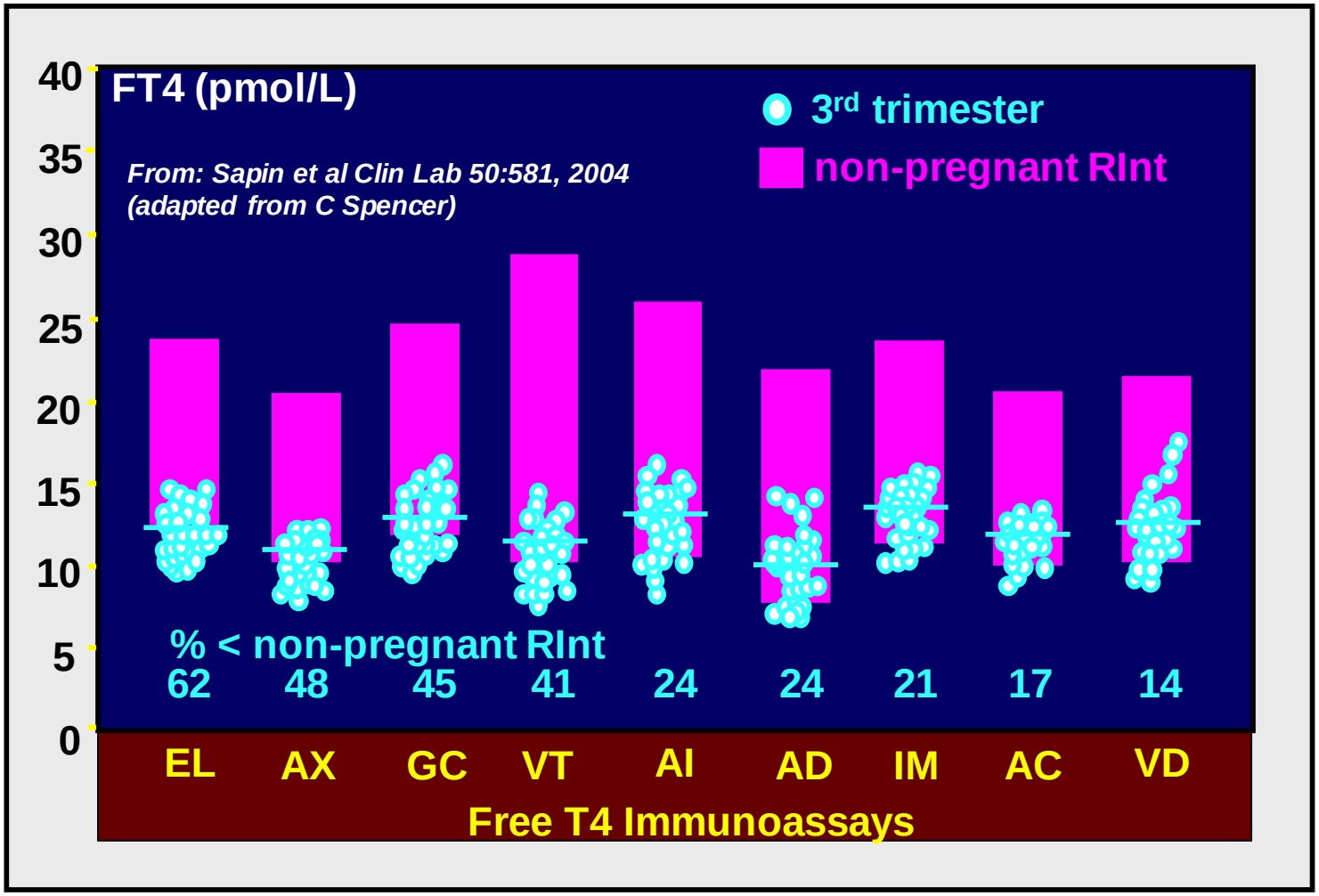
Report

Future of the C-STFT

Chair and members: end of term 31st of December 2017

Free T4 in pregnancy
–
Immunoassays compared with equilibrium dialysis ID-MS

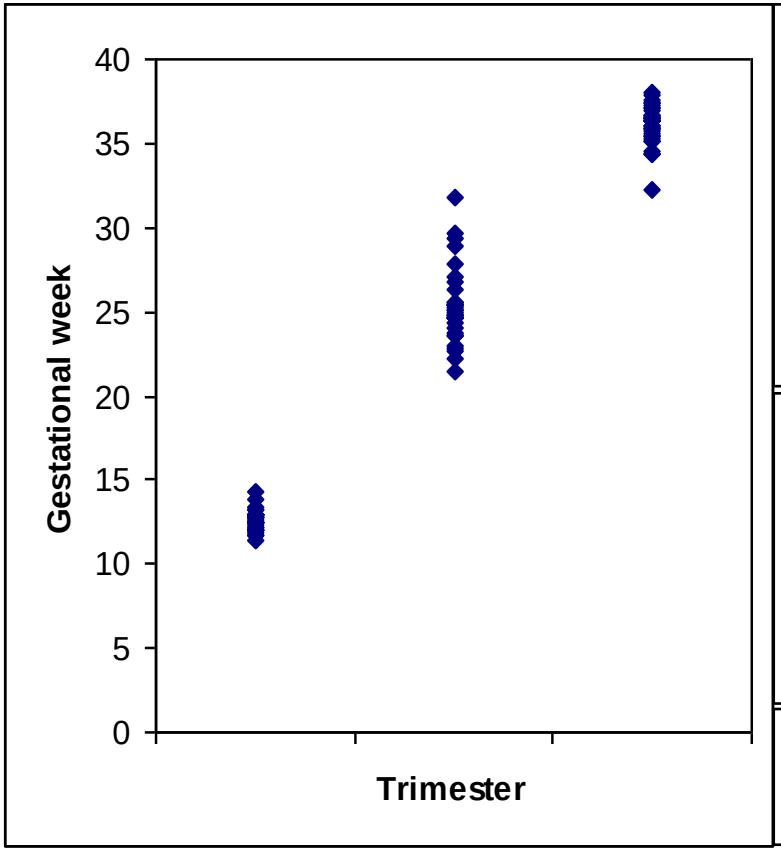
Problems with FT4 immunoassays



IAs are not standardized & have different sensitivities to BPs

Study pregnancy versus controls

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.



Study subjects

107 healthy pregnant women (ic)
- 35 1st trimester
- 35 2nd trimester
- 37 3rd trimester

26 controls (age-matched)

Mean gestational age

1st trimester: 12.6 weeks
(after occurrence of hCG peak)
2nd: 25.3 weeks
3rd: 36.1 weeks

Immunoassays tested

Cobas – Architect - Immunlite

Results – Pregnant vs controls

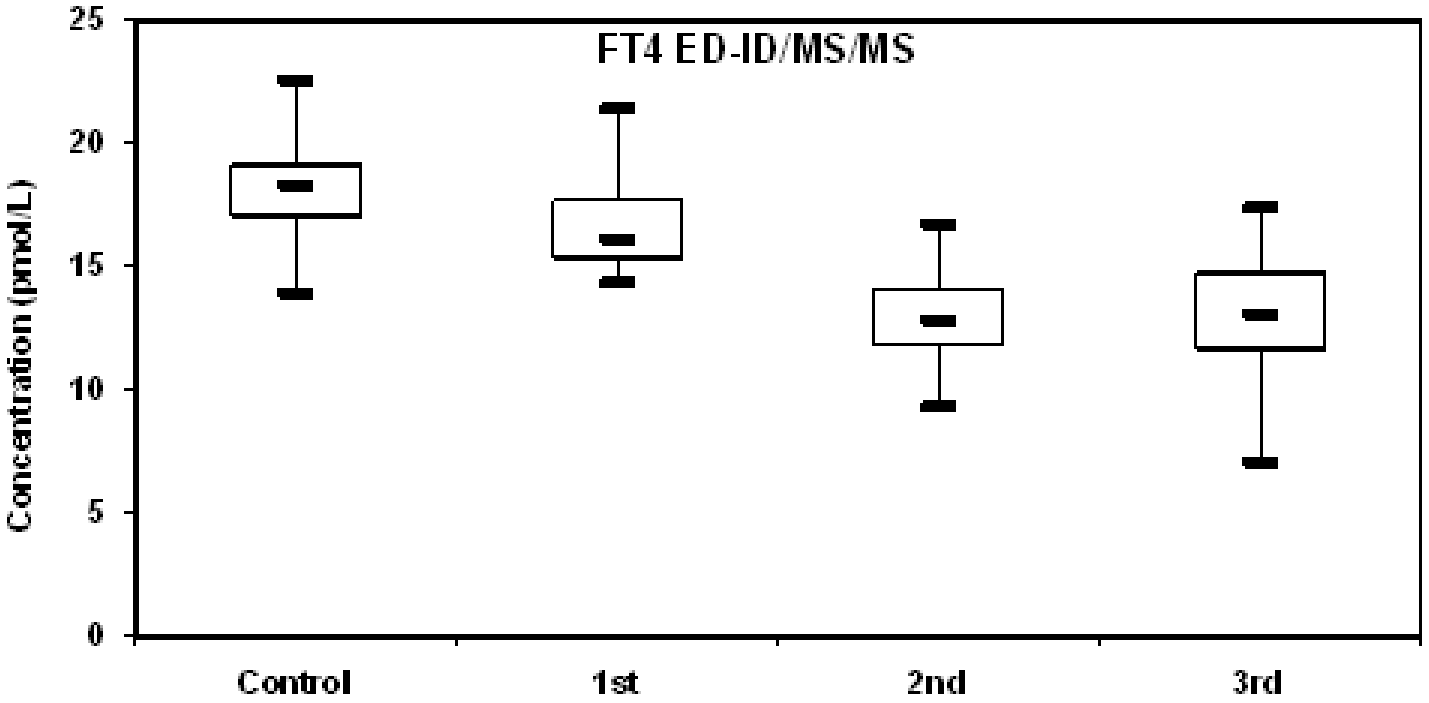
Table 1. Parameters from Deming regression analysis of the method comparison data (x = cRMP; y = each of the 3 immunoassays) for all subjects combined (n = 133), for the non-pregnant controls (n = 26) and the pregnant subjects (n = 107).

	Slope	CI(slope)[a]	Intercept (pmol/L)	CI(intercept)[a] (pmol/L)	SDyx (pmol/L)	*r*
Cobas						
All	0.7788	0.04	2.2	0.6	0.67	0.9598
Controls	0.9704	0.11	-1.3	2.0	0.75	0.9460
Pregnant	0.7378	0.05	2.7	0.7	0.62	0.9498
ARCHITECT						
All	0.5164	0.06	4.8	0.8	0.77	0.8874
Controls	0.8418	0.27	-1.8	4.8	1.08	0.8539
Pregnant	0.5412	0.05	4.6	0.7	0.56	0.9266
Immulite						
All	0.6038	0.04	2.2	0.5	0.60	0.9483
Controls	0.7465	0.12	-0.3	2.1	0.57	0.9477
Pregnant	0.5601	0.05	2.8	0.6	0.57	0.9289

[a] 95% confidence interval

Results – Trimester specific values

ED-ID/MS



Relative difference to controls (all Δ's significant)

1st : -9%

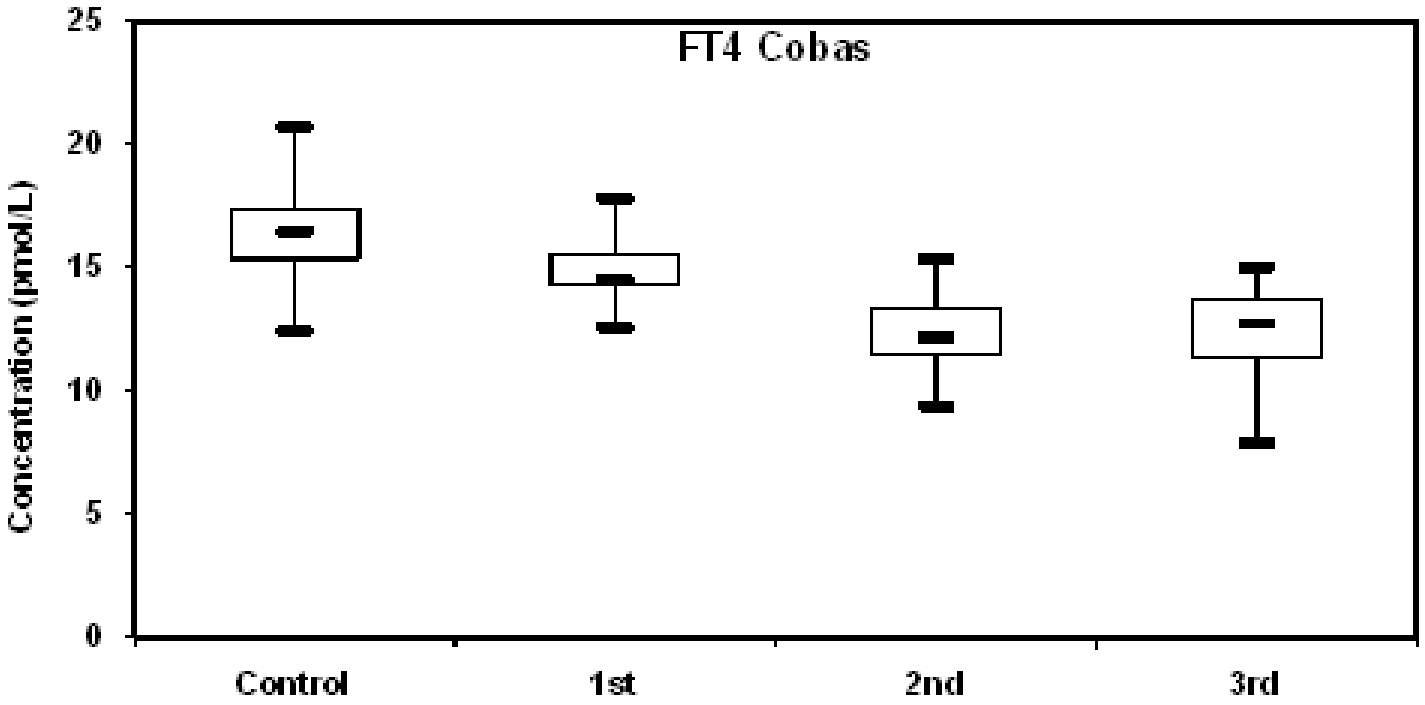
2nd : -29%

3rd : -29%

n.s., $p = 0.99$

Results – Trimester specific values

Cobas



Relative difference to controls (all Δ's significant)

1st : -9%

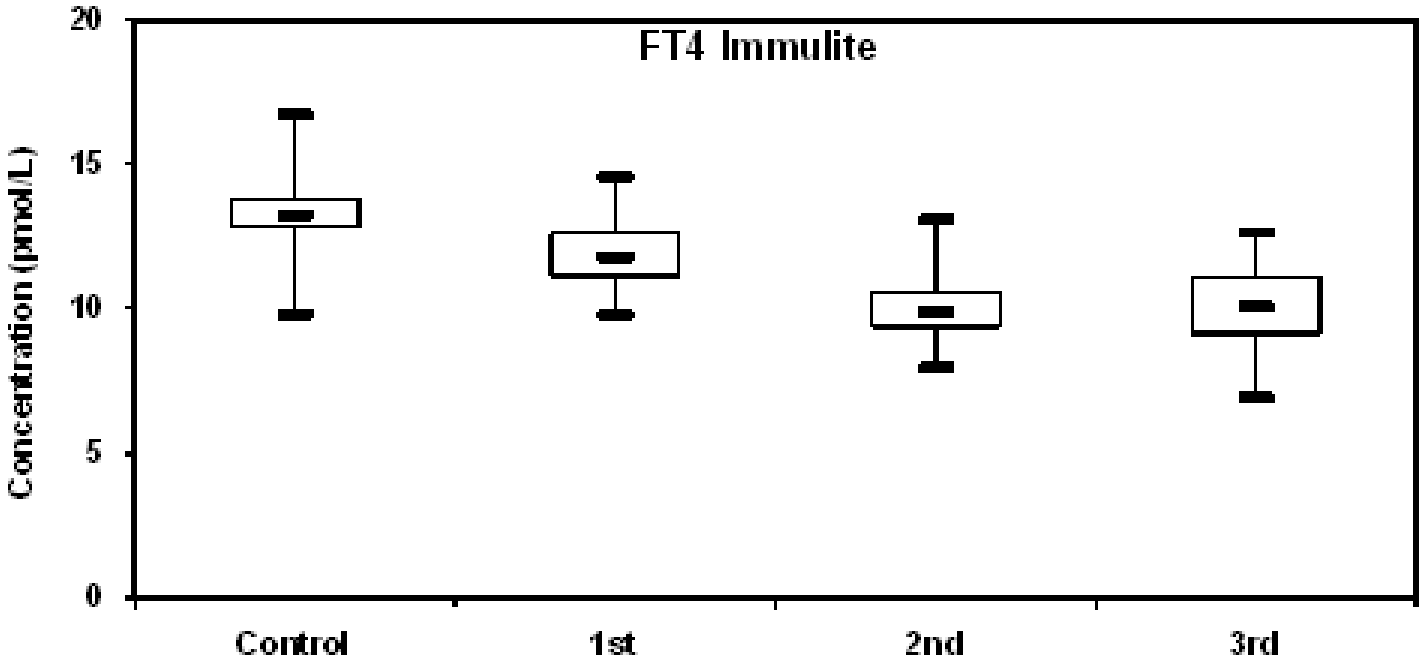
2nd : -25%

3rd : -24%

n.s., *p* = 0.85

Results – Trimester specific values

Immulite



Relative difference to controls (all Δ's significant)

1st : -10%

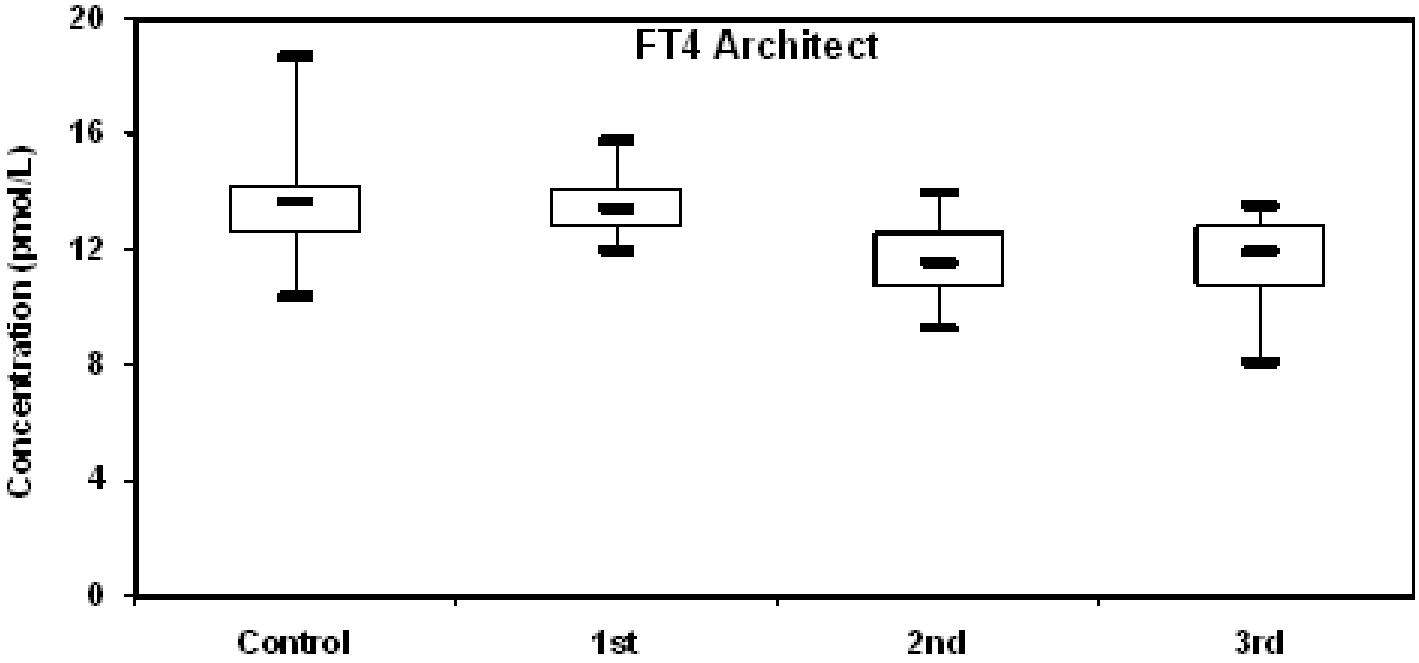
2nd : -25%

3rd : -24%

n.s., $p = 0.80$

Results – Trimester specific values

ARCHITECT



Relative difference to control

1st : -1.3% (not significant)

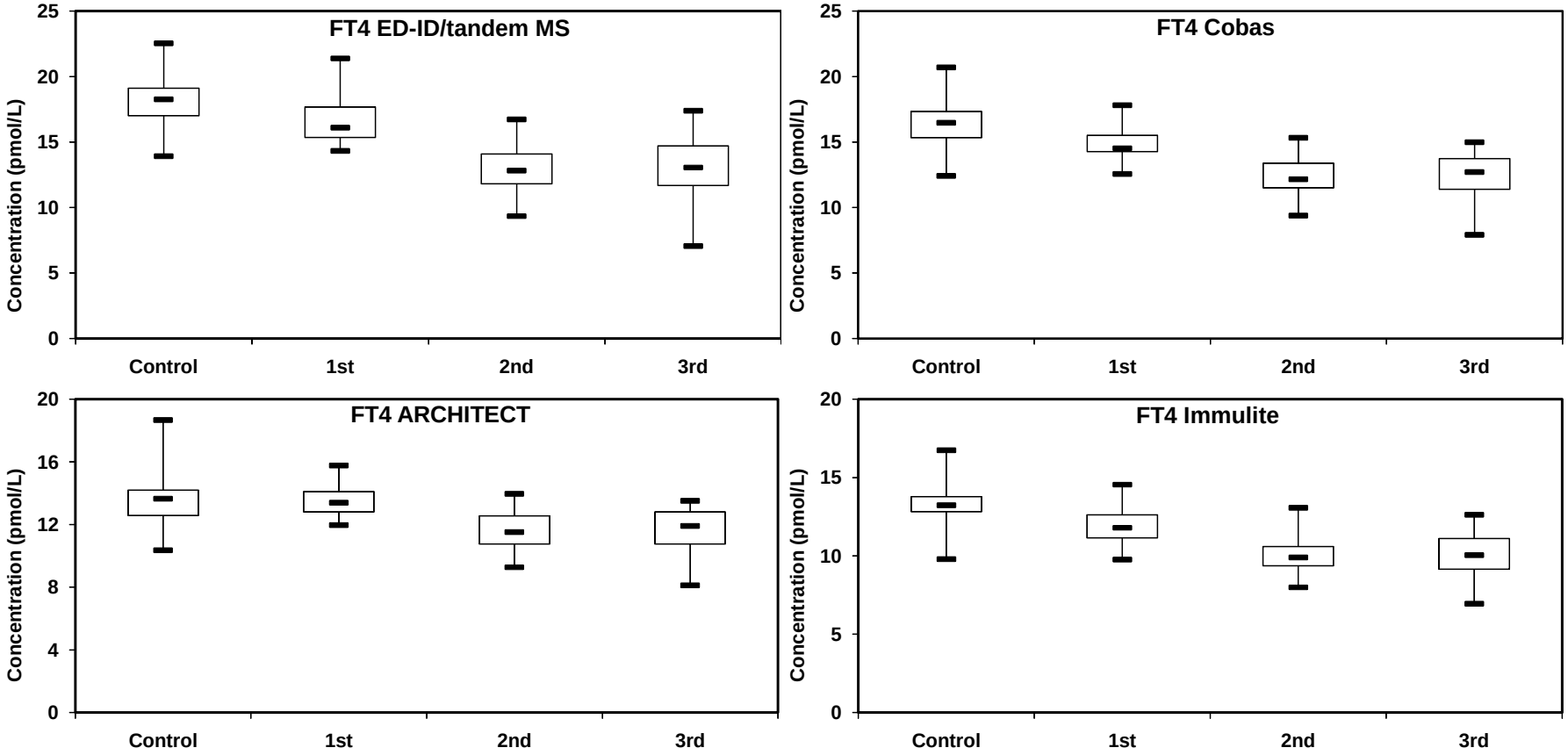
2nd : -15% (s.)

3rd : -14% (s.)

n.s., $p = 0.80$

Results – Trimester specific values

All



Conclusion

FT4 immunoassays are sensitive to binding protein alterations, but to a grossly different extent

Some FT4 immunoassays are capable of showing the "true" changes of "FT4" during pregnancy (as observed with ED-ID/MS)

FT4 results in pregnancy have to be interpreted test-specific; the same test should be used for follow-up during pregnancy