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Global Biomarkers Standardization Consortium

Reference Methods Teleconference Minutes

Tuesday January 31, 2012

Co-Chairs: Henrik Zetterberg & Kaj Blennow

Facilitator: Maria Carrillo, Alzheimer's Association

Attendance: June Kaplow, Chritopher Spedaliere Saladax, Holly Soares, Marcel Veerbek, Hugo Vanderstichele, Bub Umek, Les Shaw, Adam Simon, Johannes Streffer, Andy Lockhart, Bill Mylott PPD, Rien Blankenstein, Omnia Ismaiel, Moucun Yuan, Omar Laterza

FINAL ACTION ITEMS from previous meeting:

Ab42 MS-MRM: PPD, Waters and ASM abstracts; Kaj, Henrik and Les (LC or UC separation method).

Ab42 Immunoassays: Rien and Charlotte, and Hugo will take a look at this and gather information.

Rand sent a poster MS based assay for amyloid beta and CSF. Les mentions that he is working with Rand on this and has been able to replicate what Rand has described and the relationship they are building is very collaborative and are working towards the possibility of exchanging samples and trying to replicate results.

June asked if the fragment measured is 1-42. Immunoassays are measuring multiple species and this creates a bit of a challenge. Rand went with the 1-42 and Les narrowed to 1-38 1-42 realizing that the other peptides may be of interest. Hugo comments on the selectivity, Hugo confirms that they only use 1-42 because it gives a better selection for AD patients. Highest dx accuracy need to have 1-42. Bob Umek mentioned that Kaj showed that x-40, x-42 was giving the same resolution as 1-40 or 1-42. Rien mentions that this group is all about the goal of getting a view of a ref method and measure the same anywhere and asks what is the nature of the preparation on the poster by Jenkins. Les mentions that the preparation is synthetic.

MS are close to being developed for 1-42 and various companies seem to be working on getting the full validation. MS method to look at the following: 1-34, 37, 38, 42, 43, 39 and believe the robustness will be improved. PPD goal is to validate two assays for Abeta. If only want 42 it is very easy according to PPD representatives. If aim is ref method for 1-42, then this group might want to decide that this is the best way to go or select another analyte to include at some sacrifice to the accuracy. So PPD, Waters and Les all have

something being developed. Holly asks the group what the strategy should be, should we pick one and validate it? PPD 1-40 and 1-43 first, then 1-14 through 1-17 second. Then PPD has not yet considered -1-42 alone. PPD says that sponsors all have different wish lists for abetas, some want 37 and 39 others 43.

Rien suggested some of the joint committee of traceability of lab methods, ICC committee. He sent a file to the group which is attached to these minutes. Holly agrees with this but resolving the validation for the assays so some steps are missing. Holly mentions how some of the materials are monitored is missing a bit. But Holly agrees that once the method is validated we should be able to get this moving. Adam asks if we should summarize the analytical performance that others have put into place and review them to see which is most suitable as a candidate reference method?

Les will work with Omar and come up with a discussion for the next call that will evaluate the current methods to bring to the group on the next call. Validation exercise also needs to be done and then IFCC would need to recognize this reference method. Holly mentions that there are questions like Is 1-42 the right one to measure and a few other correlation with MS and immunoassay to understand what we are nominating. CSF QC method is not using MS right now, Les mentions that methods have not been felt to be ready for this.

Need a validation exercise, and need to agree on the peptide to be used and artificial CSF or what will be used. Omar asks what would it take for Les or PPD to put together a validation plan? Omar mentions that if we can start taking some steps forward for a validation this would be good step. Bill asks if validation includes only 42? Les shares that he focuses on the 42 but realistically and with what the field needs they have settled for 38, 40 and 42. Ref method for 42 is important, and provides for ADNI samples the addition of 40. The smaller fragments are not being specifically targeted in ADNI. Holly asks if we need to focus on the smaller fragments? Adam mentions that we need to know what an immunoassay is going to be measuring.

First we will focus on 1-42 and once there is an assay identified that is validatable, we can pick a few assays to see if they are compatible. Omar says correlations should be with validated assays.

ACTION ITEMS:

Les and Omar will report and Holly and Adam will draft a validation plan and both will be discussed on the next call.

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RAND BLANKENSTEIN:

GBSC – Thoughts on Reference Methods and Materials for CSF Biomarker

Reference Methods

Definition of the analyte or measured

- Chemical Nature
- Chemical form: existing in multimers of identical or different subunits, complexes with other components, derivatives e.g. glycosylated forms, interconversion of the different forms, …
- Measuring Unit SI? / Conversion factor(s)
- Matrix in which measurement is to occur

Establishment of Primary Reference Material (PRM)

- Source
- Concentration
- Purity
- Nature of impurities
- Stability Long-Term
- Availability Long-Term
- Values assigned to reference material should be traceable to established reference methods

Establishment of a reference method

- Secondary Reference Material (SRM) or calibrator traceable to PRM?
- Properties of SRM: Matrix; stability
- Calibrator commutable to different assays?
- Description of Conditions for measurement
- Method and Material commutable to other laboratories

Harmonization of Results

For most analytes Reference methods and materials are not available. Laboratory results can be harmonized until the time a reference method is available. Harmonization has successfully been reported for e.g. the assessment of growth hormone levels in serum. (Ross HA et al. Clin Chem Lab Med. 2008;46:1334-5. Reporting growth hormone assay results in terms of one consensus recombinant standard preparation offers less than optimal reduction of between-method variation. And HA Ross et al, Clin Chem. 2011;57:1463. The consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays lacks a recommendation to attempt efficacious harmonization.)

The success of harmonization is critically dependent on the quality and commutability of the material that is used for the conversion of the assay results to the harmonized values.

Useful links:

- Joint Committee on Traceability in Laboratory Medicine (JCTLM)

http://www.bipm.org/en/committees/jc/jctlm/jctlm-wg1/wg1_quality-manual.html

- Procedures for evaluation of reference methods and materials:

http://www.bipm.org/utils/en/pdf/WG1-P-01.pdf

Relevant ISO Standards for higher order RMs and RMPs

ISO 17511 In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials

ISO 18153 Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials

ISO 15193 Presentation of reference measurement procedures

ISO 15194 Description of reference materials

ISO 15195 Reference Measurement Laboratories

Amsterdam; January 31st, 2012 Rien Blankenstein

NEXT CALL DATES:

Wednesday, February 08, 2012 – 7:30 am PST / 9:30 am CST / 10:30 am EST / 4:30 pm Sweden

Monday, March 5, 2012 – 7:30 am PST / 9:30 am CST / 10:30 am EST / 4:30 pm Sweden CSF OVERVIEW

Monday, March 15, 2012 – 7:30 am PST / 9:30 am CST / 10:30 am EST / 4:30 pm Sweden

Friday, April 5, 2012 – 7:30 am PST / 9:30 am CST / 10:30 am EST / 4:30 pm Sweden

Thursday, April 19, 2012 – 8:30 am PST / 10:30 am CST / 11:30 am EST / 5:30 pm Sweden

Wednesday, May 2, 2012 – 7:30 am PST / 9:30 am CST / 10:30 am EST / 4:30 pm Sweden

Wednesday, May 16, 2012 – 7:30 am PST / 9:30 am CST / 10:30 am EST / 4:30 pm Sweden

Wednesday, May 29, 2012 – 7:30 am PST / 9:30 am CST / 10:30 am EST / 4:30 pm Sweden