

## Traceability of Nordic's D-dimer Calibrator

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There is no existing international standard for D-dimer. Nor does any international conventional reference measurement procedure exist. The situation is further complicated by the fact that two different units are often used for reporting results; D-dimer Units (DDU) and Fibrinogen Equivalent Units (FEU). This text shows how Nordic Biomarker has handled these problems; how we maintain lot-to-lot consistency and how our results, using both DDU and FEU, relate to results from other manufacturers of D-dimer kits.

### Reference System

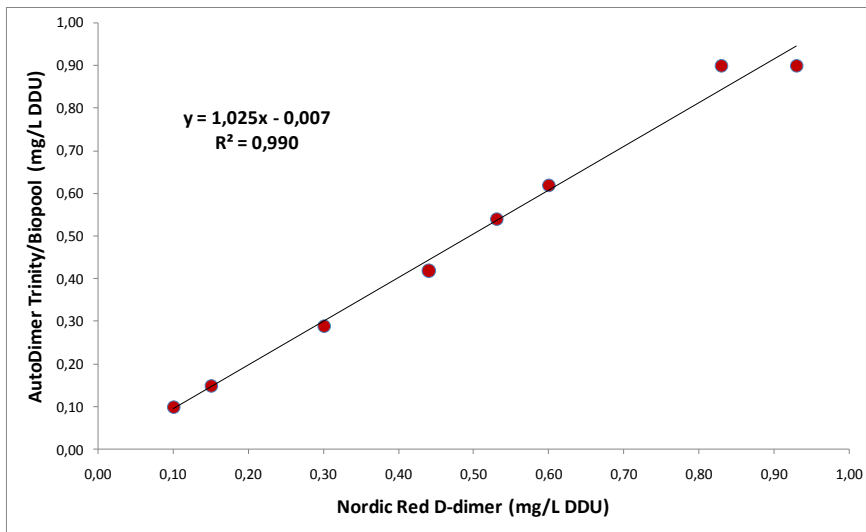
ISO 17511:2003 (In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control material) outlines the principles to follow to determine the traceability of calibration material. Section 5.6 deals with cases in which there is no international standard or method available. In fact, D-dimer is specifically mentioned in that section of the standard as an example of such a case. The standard shows that the manufacturer must maintain its own reference system, against which each new batch of produced calibrator is measured.

For stability, Nordic Biomarker keeps its in-house D-dimer Master stored under liquid nitrogen. Every new batch of D-dimer Calibrator, or D-dimer Control, is assayed and assigned against the D-dimer Master. Each time, a fresh kryo vial of the D-dimer Master is retrieved from the liquid nitrogen storage and thawed. The new batch and the D-dimer Master are thereafter assayed together, side-by-side.

### Comparisons with other manufacturers

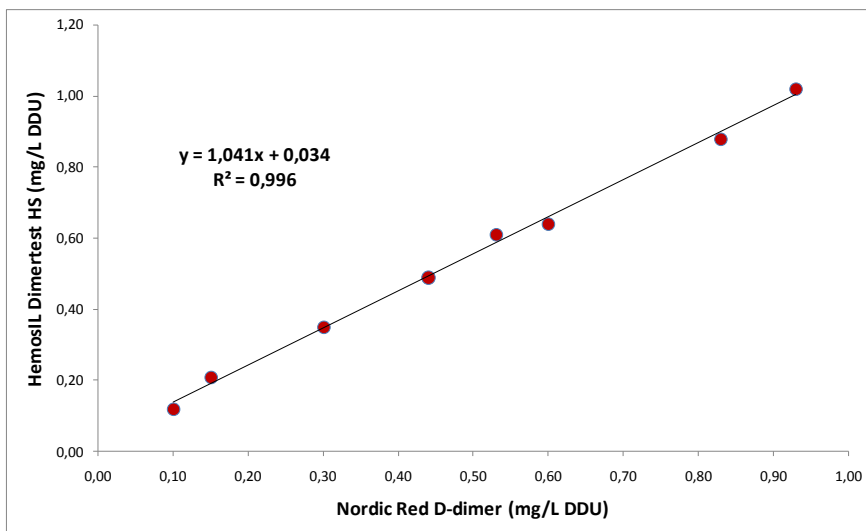
The amount of D-dimer in Nordic's D-dimer Master was determined in a one-time assignment against commercially available D-dimer kits. Following this, Nordic's D-dimer kits have been regularly monitored, four times each year, against several other commercially available D-dimer kits in the External Quality Assessment Programme of the ECAT Foundation (<http://www.ecat.nl/>). In the D-dimer Module of this Programme, two blind samples are sent out four times each year to the participating laboratories. To assess how the amount of D-dimer in Nordic's own calibrator, compares to assay results from several other manufacturers of D-dimer kits, the ECAT data from 2009 was used.

Figure 1. Correlation between Nordic Red D-dimer and Biopool Auto Dimer, using the eight D-dimer samples from ECAT during 2009.



The assay results from Nordic Red D-dimer are well in line with the assays results from Biopool AutoDimer (Figure 1), showing that the calibrator levels, as measured in DDU, are similar in both kits. Biopool AutoDimer was subsequently sold, rebranded, and is now marketed by Tcoag under the name TriniLIA Auto Dimer.

Figure 2. Correlation between Nordic Red D-dimer and HemosIL Dimertest HS, using the eight D-dimer samples from ECAT during 2009.



Nordic's calibrator is also well in line with HemosIL Dimertest HS from Instrumentation Laboratory (Figure 2). In contrast, when compared to ILs other kit, HemosIL Dimertest, the slope is not unity and the correlation poor (data not shown). However, as the two different D-dimer kits from IL do not correlate well against each other (Figure 3), Nordic Red D-dimer could not possibly correlate well with both!

Figure 3. Correlation between the two different D-dimer kits from Instrumentation Laboratory, using the eight D-dimer samples from ECAT during 2009.

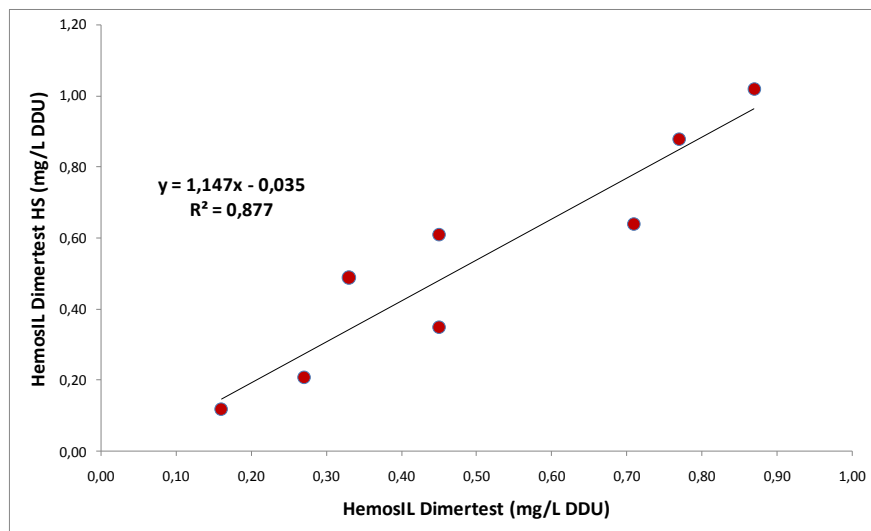
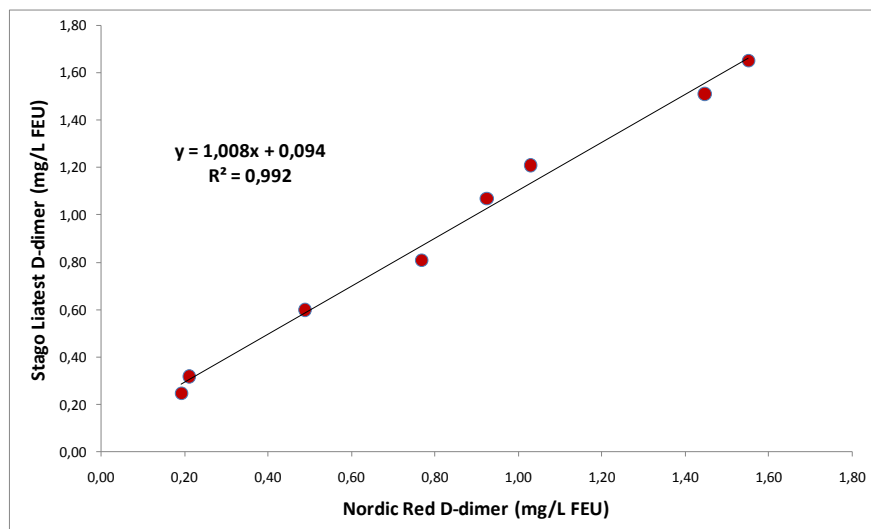


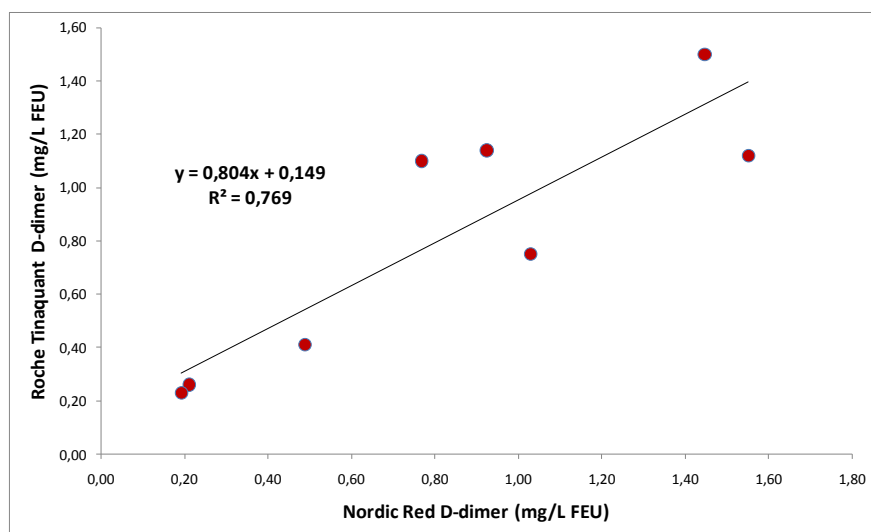
Figure 4. Correlation between Nordic Red D-dimer and Stago Liatest D-dimer, using the eight D-dimer samples from ECAT during 2009.



With Figure 4 we are now switching from DDU to FEU, which deserves an explanation. Each lot of calibrator manufactured by Nordic Biomarker is assigned a value in both units, DDU and FEU. It is a common approximation that the molecular weight of Fibrinogen is double that of D-dimer. However, as explained in detail by Edlund & Nilsson<sup>1</sup>, the relation is closer to 1.74. That is the conversion factor we use at Nordic Biomarker. So, by simply multiplying any assay results from our kits given in DDU, by the factor 1.74, will get the result in FEU. Figure 4 shows that the D-dimer reference system at Nordic Biomarker is well in line with Liatest D-dimer kit from Stago; the slope is unity.

<sup>1</sup> Edlund & Nilsson, Clin. Biochem. 39 (2006) 137 – 142

Figure 5. Correlation between Nordic Red D-dimer and Roche Tinaquant D-dimer, using the eight D-dimer samples from ECAT during 2009.



The calibrator setting is somewhat lower in the Tinaquant kit from Roche, as compared to Stago or Nordic Biomarker (Figure 5). The correlation is also relatively poor with both Stago and Nordic Biomarker. But, it is well known that Tinaquant D-dimer is much better at detecting early/large Fibrin Degradation Products, than smaller FDPs and D-dimer itself<sup>1,2</sup>, which might explain this discrepancy.

Figure 6. Correlation between Nordic Red D-dimer and Siemens Innovance D-dimer, using the eight D-dimer samples from ECAT during 2009.

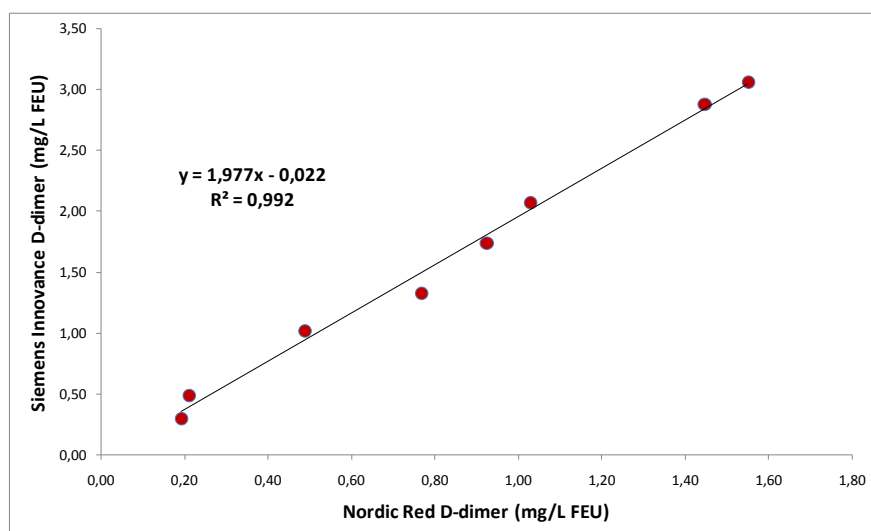


Figure 6 shows that Siemens, for some reason, has chosen a numerical value for their FEU units that is much higher, at least double, than any other manufacturer on the market. This should not be misinterpreted as a high linear range for the Innovance D-dimer kit.

<sup>2</sup> Dempfle et al., Thrombosis and Haemostasis 85 (2001) 671 – 678.

## **Conclusion**

Nordic Biomarker's D-dimer Reference System is well in line with Tcoag and IL, using DDU.

Nordic's kits is also well in line with Stago, using FEU.

For stability, Nordic Biomarker's D-dimer Master is stored in liquid nitrogen. Lot-to-lot consistency is ensured by running each new lot of manufactured calibrators, or controls, side by side with the D-dimer Master.