Roche

Diagnostics

Performance Evaluation of the CoaguChek XS Plus System

Study LB 157-2005

Evaluation Report

Rev. 1

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1. Summary

This study was performed at one external study site (Zwolle, NL) according to the protocol LB 157-2005 (Evaluation of the CoaguChek XS Plus System -- Equivalency to the CoaguChek XS System, September 26, 2005, rev 1). The goal of this study was to confirm the CoaguChek XS Plus System performance in comparison to the CoaguChek XS System. The CoaguChek XS System was previously extensively evaluated (reports LB 110-2004, LB 132-2004, LB 155-2005 and LB 156-2005).

9 CoaguChek XS Plus meters, 9 CoaguChek XS meters, and 3 CoaguChek XS PT test strip lots were included. All testing was performed using venous whole blood samples. Samples from 81 patients on oral anticoagulation therapy (OAT) and 21 normal donors were tested.

Acceptance criteria:
The acceptance criteria for the assessment of equivalency to the CoaguChek XS system were fixed to (study protocol LB 157-2005):

INR range 0.8 to 2.0 INR (venous blood): Bias <0.10 INR
INR range 2.0 to 4.5 INR (venous blood): Bias <0.15 INR

From the Technical Design Goal document for the New Coagulation PT-System (document no. NCP 085, rev. 3):
- imprecision of determinations using venous blood: <3.5%
- imprecision of determinations using liquid controls: <6%
- imprecision meter-to meter ≤1.5%

In the package insert of the test strips the range of slopes in regression analysis compared to Innovin is given as 0.93 to 1.04.

Additional evaluation criteria were set for information only according to the draft ISO standard 17593 [1], which requires a
- mean bias of ≤0.3 INR (in the INR range 2.0 – 4.5) and
- a total of >90% of all data bias within +/- 0.5 INR (for INRs <2) or within +/- 30% (for INRs >2)

compared with a laboratory reference thromboplastin.
Furthermore an MRD below 10% in method comparison to a laboratory reference method is set for information only.

Results:
For the three test strip lots the maximum mean bias between the CoaguChek XS Plus and the CoaguChek XS System was 0.03 INR for samples in the range below an INR of 2.0, and 0.07 INR for samples in the therapeutic range of OAT (INR 2.0 – 4.5).

All regression lines between systems for the low and therapeutic INR range were equal to the line of identity (y = x). The coefficients of correlation were > 0.97. The measuring range from 0.8 to 8.0 INR was covered by the samples.

Each of the three CoaguChek XS PT lots met the acceptance criteria set in the standard ISO/DIS 17593 versus Innovin and Recombiplastin.

The slopes of the regression lines in method comparisons versus Innovin were found in the range given in the package insert of the CoaguChek XS Test strips.

Agreement rating showed "excellent" agreement with Innovin (MRD <6.6%), and "very good" agreement with Recombiplastin (MRD < 9%).

There is no difference in INR results from battery powered CoaguChek XS Plus meters compared with meters on power supplies (mean bias 0.01 INR).

In whole blood testing the mean coefficient of variation (CV) of the CoaguChek XS Plus PT determinations was calculated to be in the range 1.3% to 1.6%. CVs were found equivalent for both systems.

In quality control testing the mean CV of the CoaguChek XS Plus PT determinations was calculated to be in the range 0.0% to 3.2% for level 1 (mean INR: 1.19 – 1.22), 1.9% to 2.2% for level 2 (mean INR: 2.47 – 2.57), and 2.6% to 2.8% for level 3 (mean INR: 1.86 – 1.94). CVs were found equivalent for both systems.

All INR values matched the assigned control ranges.

The between instrument imprecision (CV) in whole blood testing was found with a mean meter-to-meter CV of 0.7% in samples from normal donors, and 0.6% for patients in the therapeutic range of OAT for the CoaguChek XS Plus instruments. CVs were found equivalent for both systems.

The between instrument imprecision (CV) in quality control testing was found with a mean meter-to-meter CV of 0.8% for the CoaguChek XS Plus instruments. CVs were found equivalent for both systems.

Conclusion:
The new CoaguChek XS Plus System demonstrated equivalency to the CoaguChek XS System in performance characteristics.

In control testing all values were found in the assigned control ranges. Performance met the criteria of the Technical Design Goal document for the New Coagulation PT-System. The liquid quality controls are a suitable sample material for the CoaguChek XS Plus System.

All acceptance criteria were met.

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3. Introduction

3.1 The CoaguChek XS Plus System

The CoaguChek XS Plus system is designed for use in the professional setting, while the CoaguChek XS system is designed for use in patient self testing. The CoaguChek XS system has been launched in October 2005. In comparison with this system the CoaguChek XS Plus instrument offers additional features such as a bar-code reader to automatically identify the test strip lot in use, a touch-screen as user interface, an extended capacity of the data memory, and several additional firmware functionalities, e.g. operator and sample identification and QC lock-outs which can be activated by the administrator.

The CoaguChek XS system was previously extensively evaluated (reports LB 110-2004, LB 132-2004, LB 155-2005 and LB 156-2005).

The CoaguChek XS Plus System and the CoaguChek XS system use the identical detection technology and the same test strip for PT testing. The systems quantitatively determine the prothrombin time (PT) in INR, %Quick or Seconds using capillary blood from a fingertip or untreated venous whole blood. The test strip contains a human recombinant thromboplastin with an ISI of 1.01 (document NCP 378 „EBC03 Master Lot Calibration“) and a peptide substrate. The enzyme thrombin (factor IIa) cleaves the peptide substrate, generating an electrochemical signal. This signal is converted into INR by means of an algorithm, and the result is displayed. The required lot specific information is stored on a Code Chip which comes with each vial of test strips. The Code Chip must be inserted into the respective instrument.

The CoaguChek XS PT test strip contains an integrated QC. A separate chemical pathway in the reaction pad detects any deterioration of the strip chemistry due to exposure to humidity, heat or light outside specified conditions.

Besides the integrated QC liquid controls are available for control testing according to regulatory requirements for the CoaguChek XS Plus system. With each CoaguChek XS Plus control a Code Chip is provided containing the relevant information for assessment of results, i.e. the assigned control ranges. The liquid controls are intended to be used in the field with the CoaguChek XS Plus system only.

3.2 Goals of the study

The goals of the CoaguChek XS Plus Performance Evaluation study were:

- Comparison of the CoaguChek XS Plus System performance versus the CoaguChek XS system.
- Comparison of the CoaguChek XS Plus System performance versus the laboratory thromboplastin Innovin.
- Check the system performance concerning imprecision with venous whole blood and liquid controls versus the requirements of the Technical Design Goal document.

3.3 Study protocol

The study protocol for the CoaguChek XS Plus Performance Evaluation study (LB 157-2005) was set up on September 26, 2005 (rev 1) by W. Plesch.

3.4 Acceptance criteria

The acceptance criteria for the assessment of equivalency to the CoaguChek XS system were fixed to (study protocol LB 157-2005):

- INR range 0.8 to 2.0 INR (venous blood)
  Bias <0.10 INR

- INR range 2.0 to 4.5 INR (venous blood)
  Bias <0.15 INR

The acceptance criteria for the assessment of imprecision come from the Technical Design Goal document for the New Coagulation PT-System (document no. NCP 085, rev. 3):

- imprecision of determinations using venous blood: <3.5%
- imprecision of determinations using liquid controls: <6%
- imprecision meter-to meter ≤1.5% (INR) for normal donors
- imprecision meter-to meter ≤1.5% (INR) for patients in INR range 2.0 – 4.5
- imprecision meter-to meter ≤1.5% (INR) in liquid control testing

3.5 Evaluation criteria for information only

Additional evaluation criteria were set for information only according to the draft ISO standard 17593 [1], which requires a

- mean bias of ≤0.3 INR (in the INR range 2.0 – 4.5) and
- a total of >90% of all data bias within +/- 0.5 INR (for INRs <2) or
  within +/- 30% (for INRs >2)

compared with a laboratory reference thromboplastin.
Furthermore an MRD below 10% in method comparison to a laboratory reference method is set for information only.
For comparing INR results received from meters on batteries versus meters on power supply the bias should be <0.15 INR.

These additional evaluations provide relevant information about the performance of the CoaguChek XS Plus system compared to laboratory methods which are very useful for marketing and explaining the performance characteristics to customers. They are not relevant for the assessment of the CoaguChek Plus in terms of acceptance criteria. Nonetheless in case of violations the reason for not meeting these criteria must be investigated and sufficiently explained.

More evaluations for information only are requested in the study protocol LB 157-2005 with respect to comparisons of the CoaguChek XS / XS Plus system to the current CoaguChek S system. The results of these comparisons will be presented in a separate report later.

3.6 Study site

This study was performed at one external site:

- Isala klinieken
  Groot Wezenland 20
  8011 JW Zwolle, The Netherlands
  Investigator:
  Dr. Bert Dikkeschei
  phone + 31-38-424 2688, fax + 31-38-424 2676
  e-mail: L.D.Dikkeschei@isala.nl

3.7 Study time frame

Data were collected in the period from October 10 to 12, 2005.

3.8 Informed consent

All patients gave informed consent to participate in the study.

4. Material and Methods

4.1 CoaguChek XS Plus and XS study supplies

- 9 CoaguChek XS Plus monitors (Zero Series) with Software Version 3.23, Hand Held Basic Version 3.15, Firmware 17.00

CoaguChek XS Plus monitor serial numbers
Set A: 507, 653, 635 Set B: 638, 642, 656 Set C: 651, 634, 645
(spare monitors: 606, 607, 655)

- 9 CoaguChek XS monitors with Software Version 3.23

CoaguChek XS monitor serial numbers
Set A: 13697, 13704, 13701 Set B: 13705, 13694, 13699 Set C: 13702, 13695, 13706
(spare monitors: 13700, 13696, 13698)

- Three lots of CoaguChek XS PT Test strips
  - lot # 201480 (Code 028, 1st pilot, exp. 30.06.2006)
  - lot # 201481 (Code 029, 2nd pilot, exp. 30.06.2006)
  - lot # 201482 (Code 030, 3rd pilot, exp. 30.06.2006)

- Three levels of CoaguChek XS PT Control
  - Level 1 lot # GPILOT03 (exp. 30.06.2006)
  - Level 2 lot # GPILOT03A (exp. 30.06.2006)
  - Level 3 lot # GPILOT03B (exp. 30.06.2006)

4.2 CoaguChek S study supplies

- 3 CoaguChek S monitors

CoaguChek S monitor serial numbers
Meter A: UF0007428 Meter B: UF0018998 Meter C: UF0026460
(spare monitor: UF0007053)

- Three lots of CoaguChek S PT Test
  - Lot 1, lot # 982 (exp. 07-2006)
  - Lot 2, lot # 107A (exp. 01-2006)
  - Lot 3, lot # 121A (exp. 01-2006)

- One level of CoaguChek S PT Control
  - Level 2 lot # 800039 (exp. 04-2006)

4.3 Laboratory thromboplastins

Testing from fresh plasma

- Innovin (Dade-Behring, lot 536913; Sysmex CA1500; ISI 1.02; MNPT 10.3 s)

Testing from frozen plasma

The laboratory of Dr. van den Besselaar, Leiden, NL, performed the reference testing on frozen plasmas

- Innovin (Dade-Behring, lot 526909; Sysmex CA1500; ISI 1.11; MNPT 10.09 s)
- Recombiplastin (HSIL, lot N0740293; MLA 1800; ISI 0.95; MNPT 10.89 s)

4.4 Haematocrit

- XE 2100 (Goffin Meyvis) from citrate blood, results corrected for citrate dilution (factor 10/9)

4.5 Fibrinogen

- Fibrinogen Clauss-Method (Dade Behring, Trombine, lot# 537561)

4.6 Venous testing procedure

From a venepuncture approximately 10 mL of blood was drawn into a syringe. Blood was transferred into a 4.5 mL Vacutainer tube (Becton-Dickinson lot 5006351; 105 mMol Citrate) for reference testing. The remaining blood in the syringe was used for dosing the test strips. Each CoaguChek XS PT test strip lot was tested in triplicate on three meters of the CoaguChek XS Plus and XS system. The meter to test strip lot assignment was changed each day of testing. Thus each strip lot was tested on nine different meters throughout the study.

The CoaguChek S PT test strip lots were tested in single determinations on one meter each.

Haematocrit determination was performed from citrate blood.

The citrated blood in the Vacutainer tubes was processed to plasma according to the routine procedures of the laboratory. The routine lab method was performed to determine the INR from fresh plasma samples. Additionally fibrinogen was determined.

The remainder of each plasma was frozen in two cryo vials, and stored at -78°C. A set of frozen samples was shipped to the Leiden lab for reference testing.

4.7 Data collection and recording

Test results of the CoaguChek XS Plus, XS and S systems were recorded in INR, %Quick and seconds on the data sheets. Any error message shown on the CoaguChek XS Plus / XS meter display had to be entered in the appropriate column of the data sheet.
Subject information regarding gender, age, indication for anticoagulation and anticoagulation drug used were collected.

4.8 Data exclusion

A total of 102 subjects were included in the study. The data set of one patient (#48) was excluded from the evaluation because the blood sample for the lab had clotted. Therefore no lab results were available.
All haematocrit and fibrinogen data were within the ranges specified in the package insert. No data had to be excluded.

4.9 Subjects characteristics

A total of 101 subjects were included in the data evaluation. The mean age was 58.3 years, about 1/3 of subjects were female, and about half of the patients were on anticoagulation treatment because of atrial fibrillation. The demographics for patients and normal donors are given in Table 1.

Table 1 Study subjects and their demographics

				Gender		Indication for anticoagulation (fraction of patients)				
Site	normal donors	patients	mean age (range)	female	male	MHV	AF	TE/Thr	MI	other
Total	21	80	58.4 (20 – 88)	36% (36)	64% (65)	11% (9)	43% (34)	16% (13)	0% (0)	30% (24)

4.10 Statistical Analysis

Imprecision of the CoaguChek XS test strips was calculated from the triplicate determinations for whole blood and is expressed as coefficient of variation (CV).

Regression analysis was performed after the method of Passing-Bablok [2], the coefficient of correlation (r) was calculated, and Bland-Altman [3] plots (BA) were generated. The mean absolute bias of the data is given in INR (= bias).

Additional assessment of agreement of methods was performed according to the rating scale of J. Hill (Table 2) based on the calculation of the mean absolute relative deviation (MRD).

All statistical analysis was performed using the EASY-Software package, provided by Roche Diagnostics.

Table 2 Agreement rating scale [4]

MRD	Agreement rating
< 6.6%	excellent
6.7% – 9.2%	very good
9.3% - 11.8%	good
11.9% - 14.5%	acceptable
14.6% - 20.3%	marginal
20.4% - 27.0%	very poor

$$\text{MRD (\%)} = 100 \text{ x } \frac{\sum \frac{|test - reference|}{reference}}{n}$$

5. Method comparison of the CoaguChek XS Plus System versus the CoaguChek XS System

Acceptance criteria:
from study protocol LB 157-2005 (INR; venous data; single determinations):

INR range 0.8 to 2.0 INR: Bias <0.10 INR
INR range 2.0 to 4.5 INR: Bias <0.15 INR

Data in file: *LB 157 XS vs XS plus.xls*

For the three test strip lots the mean bias between the CoaguChek XS Plus and the CoaguChek XS System was found in the range -0.01 to 0.03 INR for samples with an INR below 2.0 (Table 3), and in the range 0.01 to 0.07 INR for samples in the therapeutic range of OAT (INR 2.0 – 4.5; Table 4). All bias are well below the given limits.

All regression lines in Tables 3 and 4 are equal to the line of identity. The coefficients of correlation were >0.97.

In method comparisons using the entire data sets up to an INR of 8 two out of the three lots give regression lines equal to the line of identity (Fig. 1 and 2). For the 3rd pilot lot a slight deviation from the line of identity is observed, which is not significant (Fig. 3; slope 1.03, CI: 1.000 – 1.043; intercept -0.03, CI: -0.080 – 0.000). All coefficients of correlation were >0.99.

With these data the equivalence of INR results on the CoaguChek XS Plus with those on the CoaguChek XS system is proven across the measuring range (0.8 to 8.0 INR).

Table 3 CoaguChek XS Plus versus CoaguChek XS (INR range 0.8 to 2.0)

Strip lot	n	mean bias [INR]	assessment	min bias [INR]	max bias [INR]	mean rel. bias	B/P regression	r
1st pilot; #480	96	**0.02**	+	-0.1	0.2	1.5%	y = x	0.984
2nd pilot; #481	97	**0.03**	+	-0.1	0.2	2.6%	y = x	0.988
3rd pilot; #482	97	**-0.01**	+	-0.2	0.2	-1.0%	y = x	0.979

Table 4 CoaguChek XS Plus versus CoaguChek XS (INR range 2.0 to 4.5)

Strip lot	n	mean bias [INR]	assessment	min bias [INR]	max bias [INR]	mean rel. bias	B/P regression	r
1st pilot; #480	186	**0.07**	+	-0.3	0.5	2.0%	y = x	0.977
2nd pilot; #481	175	**0.01**	+	-0.4	0.4	0.5%	y = x	0.971
3rd pilot; #482	177	**0.02**	+	-0.4	0.5	0.4%	y = x	0.971

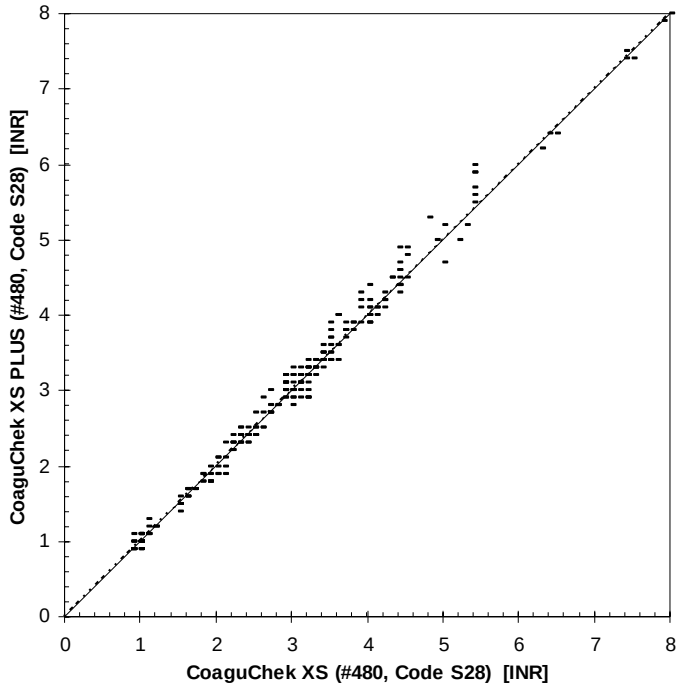

Fig. 1 Method comparison CoaguChek XS Plus versus CoaguChek XS (lot 201480, Code 028, venous blood)
Bablok-Passing: y = x; n = 302; r = 0.995

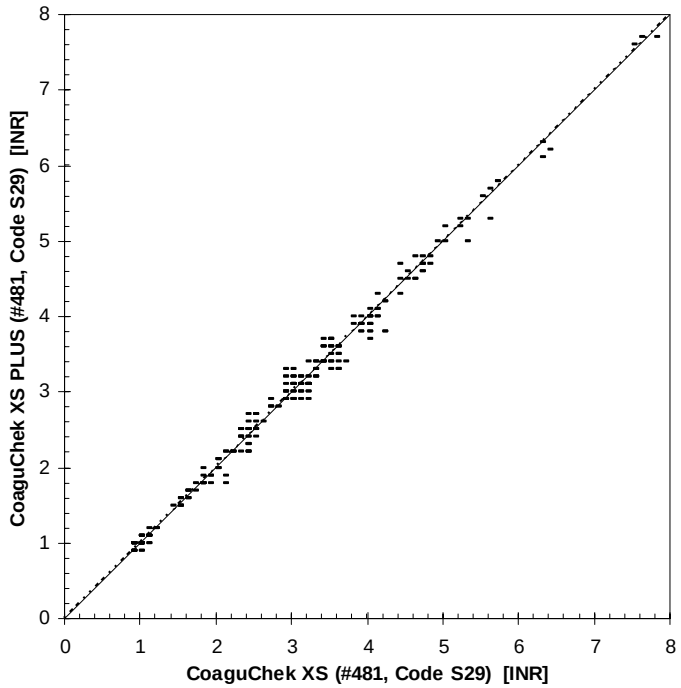

Fig. 2 Method comparison CoaguChek XS Plus versus CoaguChek XS (lot 201481, Code 029, venous blood)
Bablok-Passing: y = x; n = 300; r = 0.996

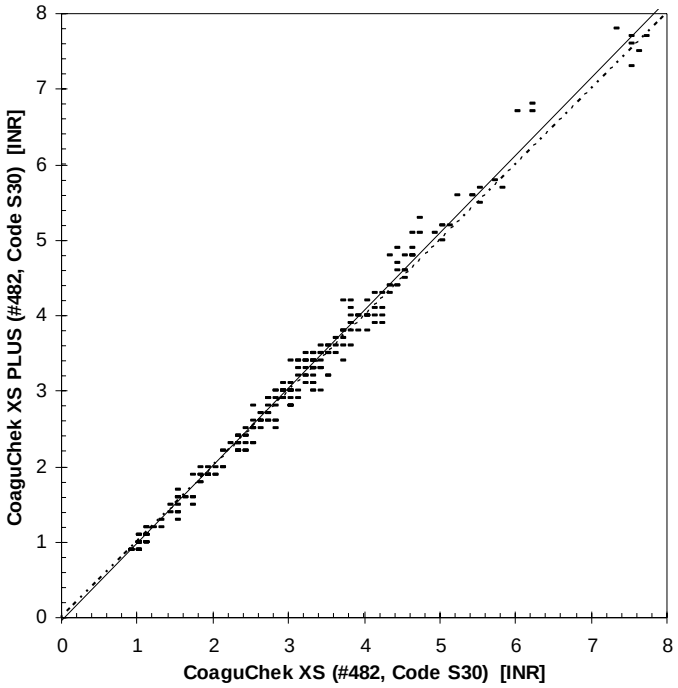

Fig. 3 Method comparison CoaguChek XS Plus versus CoaguChek XS (lot 201482, Code 030, venous blood)
Bablok-Passing: $y = 1.03x - 0.03$; $n = 302$; $r = 0.995$

Conclusion: For the three test strip lots the maximum mean bias between the CoaguChek XS Plus and the CoaguChek XS System was 0.03 INR for samples in the range below an INR of 2.0, and 0.07 INR for samples in the therapeutic range of OAT (INR 2.0 – 4.5).
All regression lines between systems for the low and therapeutic INR range were equal to the line of identity ($y = x$).
Passing-Bablok regression using the entire data sets shows agreement between the systems. The measuring range from 0.8 to 8.0 INR was covered by the samples.

The results meet the acceptance criteria. These findings confirm the equivalence of INR results determined on the CoaguChek XS Plus system with the INR results determined on the CoaguChek XS system.

6. Results of method comparisons according to ISO/DIS 17593 criteria

Acceptance criteria:

- *mean bias versus Innovin (INR range 2.0 – 4.5): ≤0.3 INR*
- *differences to Innovin within +/- 0.5 INR (INR <2) or +/- 30% (INR range 2.0 – 4.5) for >90% of data*

Data in files: *LB 157 MV CC XS plus vs Inn Lei ISO.xls / LB 157 MV CC XS plus vs Rec Lei ISO.xls*

The data set was used to perform method comparisons according to the ISO/DIS standard. The data distribution across the INR range did not meet the ISO requirements.

All three CoaguChek XS PT lots were compared versus Innovin and Recombiplastin as the most important human recombinant laboratory thromboplastins. The laboratory thromboplastins were tested in Dr. van den Besselaar' s lab in Leiden from frozen plasma samples.

For each test strip lot 100% of all INR differences were found within the limits +/- 0.5 INR or +/- 30% compared to Innovin, and more than 98% of all INR differences were found within the limits compared to Recombiplastin (Tables 5 and 6).

Table 5 CoaguChek XS Plus versus Innovin (ISO assessment)

Strip lot	n	within ISO limits (n)	within ISO limits (%)	mean bias
1st pilot; #480	288	288	**100%**	**0.08 INR**
2nd pilot; #481	288	288	**100%**	**0.07 INR**
3rd pilot; #482	288	288	**100%**	**0.08 INR**

Strip lot	n	within +/- 20% or +/- 0.5 INR (n)	within +/- 20% or +/- 0.5 INR (%)
1st pilot; #480	288	282	97.9%
2nd pilot; #481	288	288	100%
3rd pilot; #482	288	285	99.0%

Strip lot	n	within +/- 10% or +/- 0.3 INR (n)	within +/- 10% or +/- 0.3 INR (%)
1st pilot; #480	288	255	88.5%
2nd pilot; #481	288	253	87.8%
3rd pilot; #482	288	246	85.4%

In comparisons to Innovin more than 97% of the data meet the 20% limit of agreement, more than 85% of the data meet the 10% limit.

All mean bias were below +/- 0.1 INR versus Innovin, and below +/- 0.2 INR versus Recombiplastin (Fig. 4 to 9).

Conclusion: All three CoaguChek XS PT lots meet the acceptance criteria according to the ISO/DIS standard 17593 for agreement of methods with the reference thromboplastins Innovin and Recombiplastin.

Table 6 CoaguChek XS Plus versus Recombiplastin (ISO assessment)

Strip lot	n	within ISO limits (n)	within ISO limits (%)	mean bias
1st pilot; #480	291	287	**98.6%**	**0.15 INR**
2nd pilot; #481	291	288	**99.0%**	**0.14 INR**
3rd pilot; #482	291	288	**99.0%**	**0.16 INR**

Strip lot	n	within +/- 20% or +/- 0.5 INR (n)	within +/- 20% or +/- 0.5 INR (%)
1st pilot; #480	291	278	95.5%
2nd pilot; #481	291	288	99.0%
3rd pilot; #482	291	281	96.6%

Strip lot	n	within +/- 10% or +/- 0.3 INR (n)	within +/- 10% or +/- 0.3 INR (%)
1st pilot; #480	291	243	83.5%
2nd pilot; #481	291	237	81.4%
3rd pilot; #482	291	210	72.2%

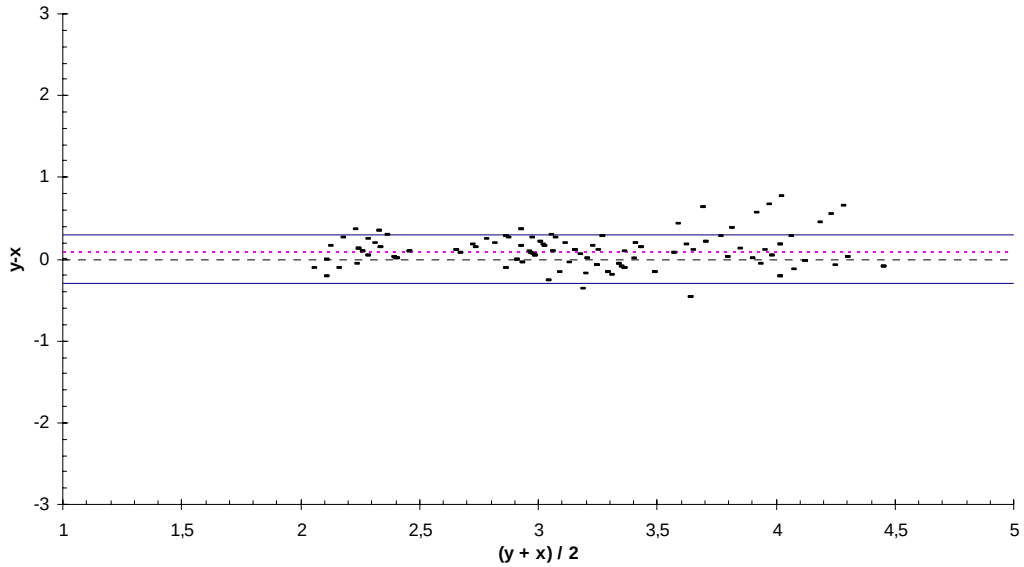

Fig. 4 Method comparison CoaguChek XS Plus Lot 480 (y) versus Innovin (x) (Bland Altman plot, sheet BA.MV.64)

mean bias = 0.08 INR; *n = 174; r = 0.946* ***venous blood***
patient data in INR range 2.0 to 4.5

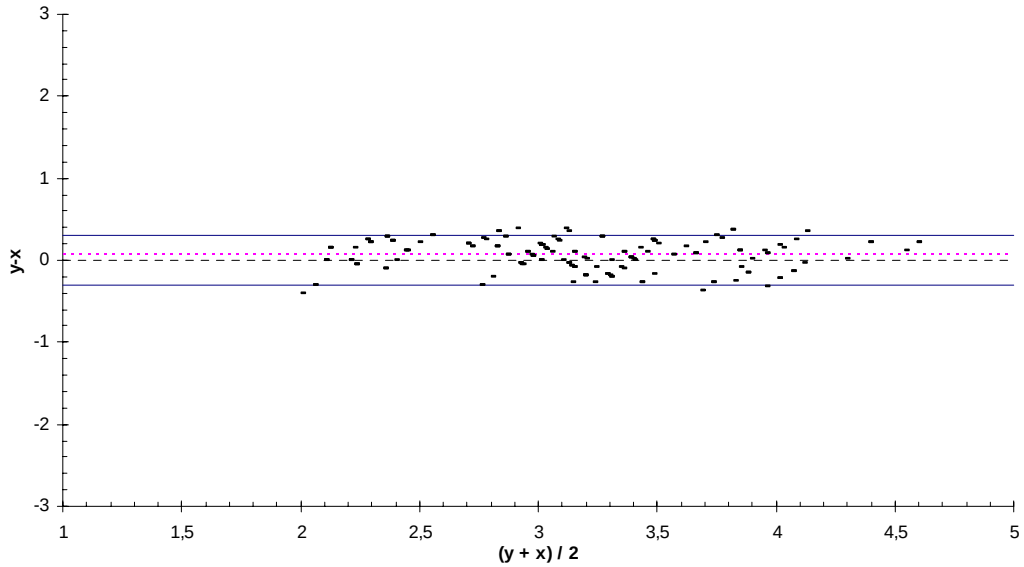

Fig. 5 Method comparison CoaguChek XS Plus Lot 481 (y) versus Innovin (x) (Bland Altman plot, sheet BA.MV.65)

mean bias = 0.07 INR; *n = 174; r = 0.955* ***venous blood***
patient data in INR range 2.0 to 4.5

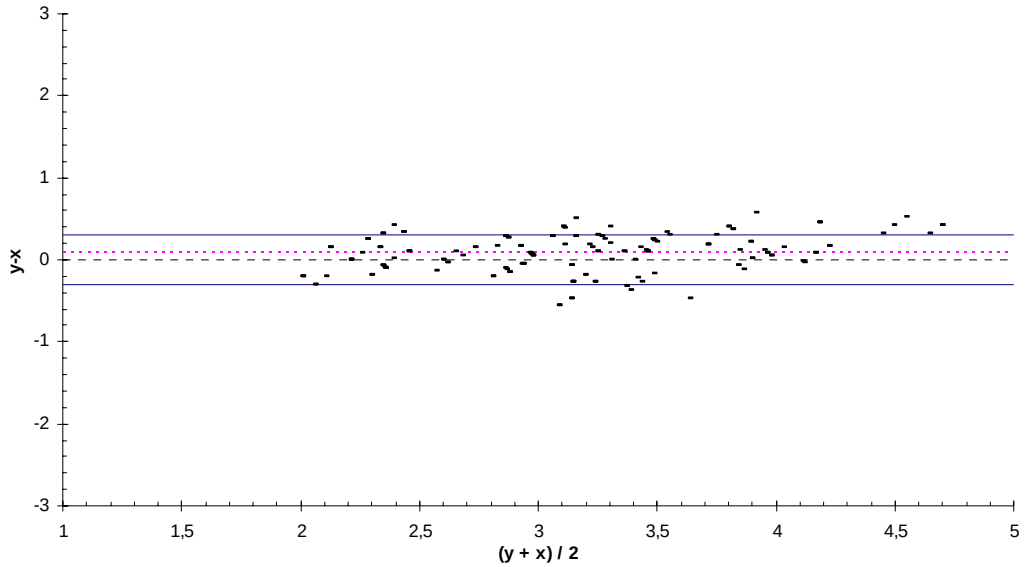

Fig. 6 Method comparison CoaguChek XS Plus Lot 482 (y) versus Innovin (x) (Bland Altman plot, sheet BA.MV.66)

mean bias = 0.08 INR; *n = 174; r = 0.943* ***venous blood***
patient data in INR range 2.0 to 4.5

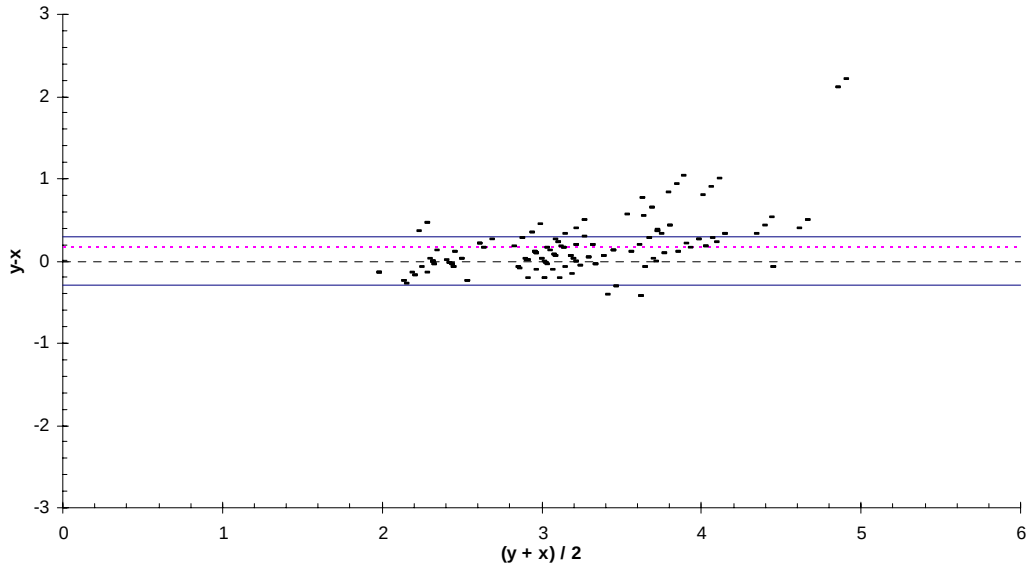

Fig. 7 Method comparison CoaguChek XS Plus Lot 480 (y) vs. Recombiplastin (x) (Bland Altman plot, sheet BA.70)

mean bias = 0.15 INR; *n = 189; r = 0.890* ***venous blood***
patient data in INR range 2.0 to 4.5

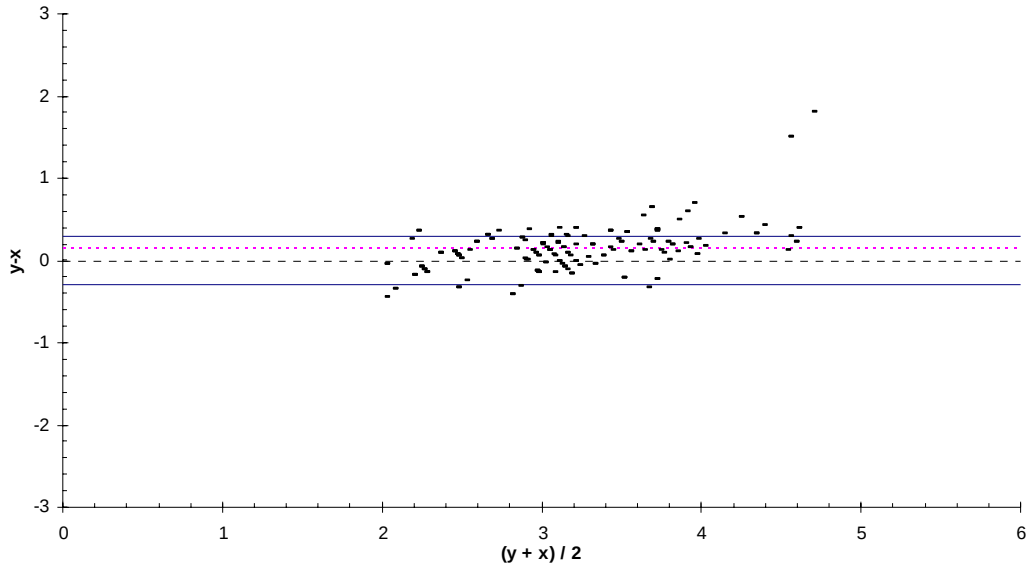

Fig. 8 Method comparison CoaguChek XS Plus Lot 481 (y) vs. Recombiplastin (x) (Bland Altman plot, sheet BA.71)

mean bias = 0.14 INR; *n = 189; r = 0.927* ***venous blood***
patient data in INR range 2.0 to 4.5

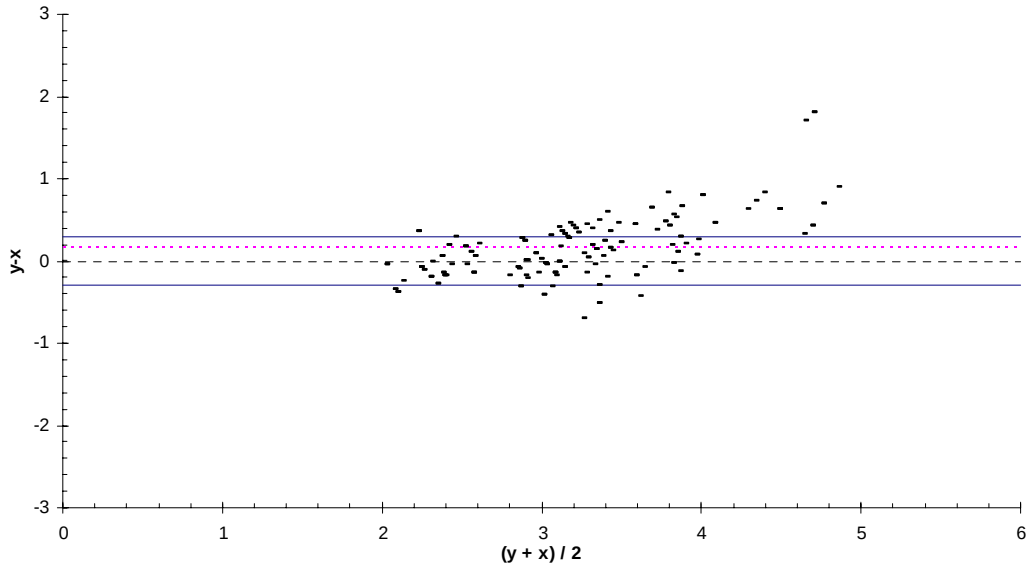

Fig. 9 Method comparison CoaguChek XS Plus Lot 482 (y) vs. Recombiplastin (x) (Bland Altman plot, sheet BA.72)

mean bias = 0.16 INR; *n = 189; r = 0.908* ***venous blood***
patient data in INR range 2.0 to 4.5

7. Results of regression analysis in method comparisons versus Innovin

Criteria:

The package insert of the CoaguChek XS PT Test states that the majority of slopes versus Innovin were found in the range 0.93 to 1.04 in a clinical study.

Data in file: *LB 157 MV CC XS plus vs Lab gefroren.xls*

The INR results for the three different test strip lots were compared to the INR results of Innovin from frozen samples tested in the Leiden laboratory. The slopes of the regression lines according to Passing-Bablok were calculated to be 1.01, 1.01, and 1.05 (CI: 1.037 – 1.071), for the 1st, 2nd, and 3rd pilot lot of test strips, respectively (Fig. 10 -12). The slopes of the 1st and 2nd pilot lot are not significantly different from 1, the slope of the 3rd pilot lot is not significantly different from 1.04.

Conclusion: All three CoaguChek XS PT lots run on the CoaguChek XS Plus meters meet the performance claim given in the package insert of the CoaguChek XS PT Test.

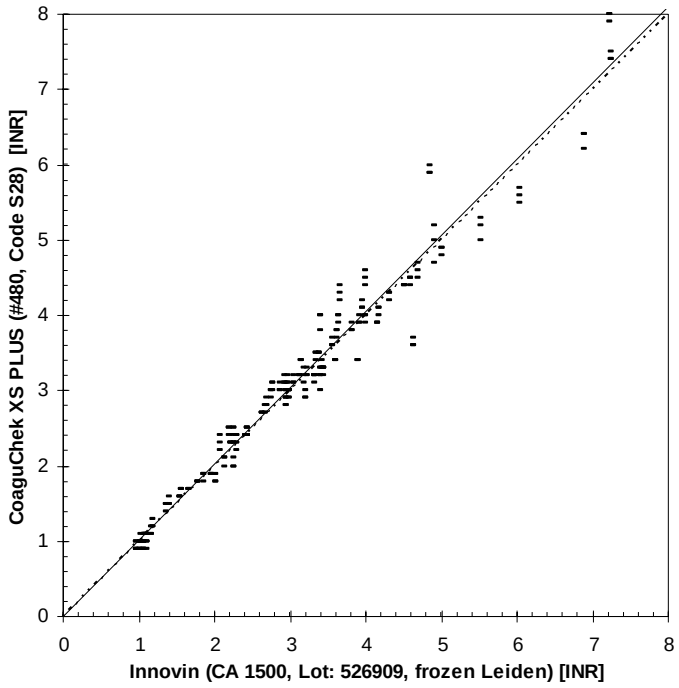

Fig. 10 Method comparison CoaguChek XS Plus versus Innovin (venous blood, Lot 201480, Code 028; sheet: MvKurv.56) Bablok-Passing: y = 1.01x + 0.01; n = 300; r = 0.985

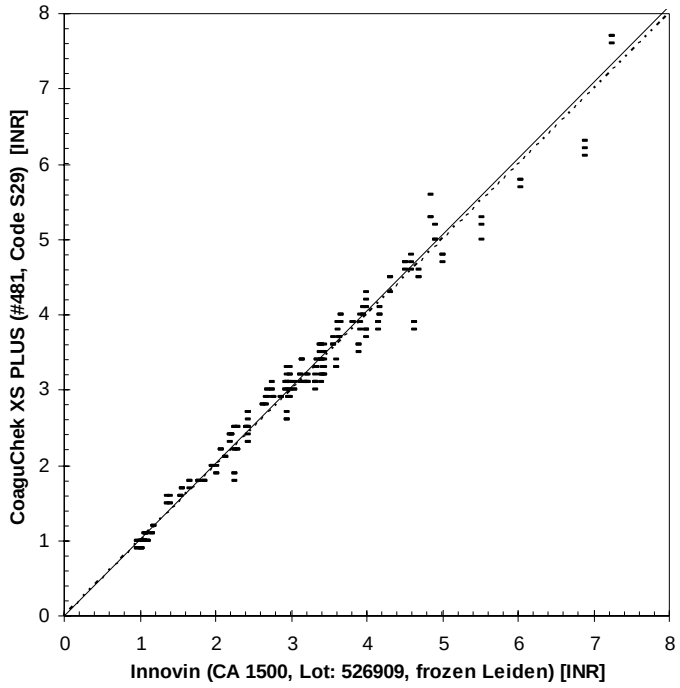

Fig. 11 Method comparison CoaguChek XS Plus versus Innovin (venous blood, Lot 201481, Code 029; sheet: MvKurv.57) Bablok-Passing: y = 1.01x + 0.01; n = 297; r = 0.989

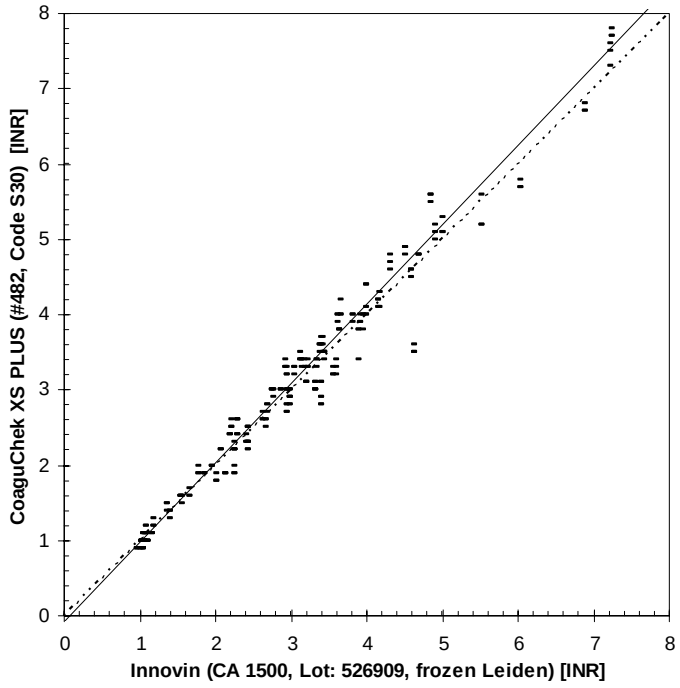

Fig. 12 Method comparison CoaguChek XS Plus versus Innovin (venous blood, Lot 201482, Code 030 sheet: MvKurv.58) Bablok-Passing: y = 1.05x - 0.08; n = 300; r = 0.987

8. Results of agreement ratings (MRD) in method comparisons versus laboratory thromboplastins

Acceptance criteria:
from Technical Design Goal Document (no. 53):
MRD <10% versus lab method (for information only)

Data in file: *LB 157 MRDs.xls*

From the triplicate INR data of the 80 patients on OAT the MRDs were calculated for all three CoaguChek XS PT test strip lots versus Innovin (from frozen samples, lot 526909) and Recombiplastin (Table 7). Only complete data sets with all CoaguChek XS PT test results were used for analysis. All MRDs versus Innovin are below 6.6% and correspond to agreement ratings in the „excellent " range. All MRDs versus Recombiplastin are below 9% and correspond to agreement ratings in the „very good" range.

Conclusion: All three CoaguChek XS PT lots show an „excellent" agreement with the INR results of Innovin, and a „very good" agreement with the INR results of Recombiplastin from frozen samples including INR values up to 8.0 INR.

Table 7 MRDs and agreement ratings for the CoaguChek XS Plus system versus laboratory thromboplastins

	Innovin			Recombiplastin		
CoaguChek XS Plus	**n**	**MRD**	**rating**	**n**	**MRD**	**rating**
1st pilot; #480	235	**5.8 %**	**excellent**	231	**6.9 %**	**very good**
2nd pilot; #481	235	**5.9 %**	**excellent**	231	**6.8 %**	**very good**
3rd pilot; #482	235	**6.5 %**	**excellent**	231	**8.3 %**	**very good**

9. Method comparison of INR results of battery powered CoaguChek XS Plus meters versus INR results of meters on power supplies

Criteria (for information only):

- *mean bias < 0.15 INR*

Data in file: *LB 157 MV Batt vs Power Sup.xls*

In each set of three CoaguChek XS Plus meters assigned to a specific lot of test strips, one meter was run on batteries while the other two meters were run on power supplies. The combined data from all three lots were evaluated.

The mean bias between meters on battery and meters on power supplies was 0.01 INR. The regression line after Passing-Bablok is equal to the line of identity. The coefficient of correlation was 0.998 (Fig. 13).

Conclusion: There is no difference in INR results from battery powered CoaguChek XS Plus meters compared with meters on power supplies.

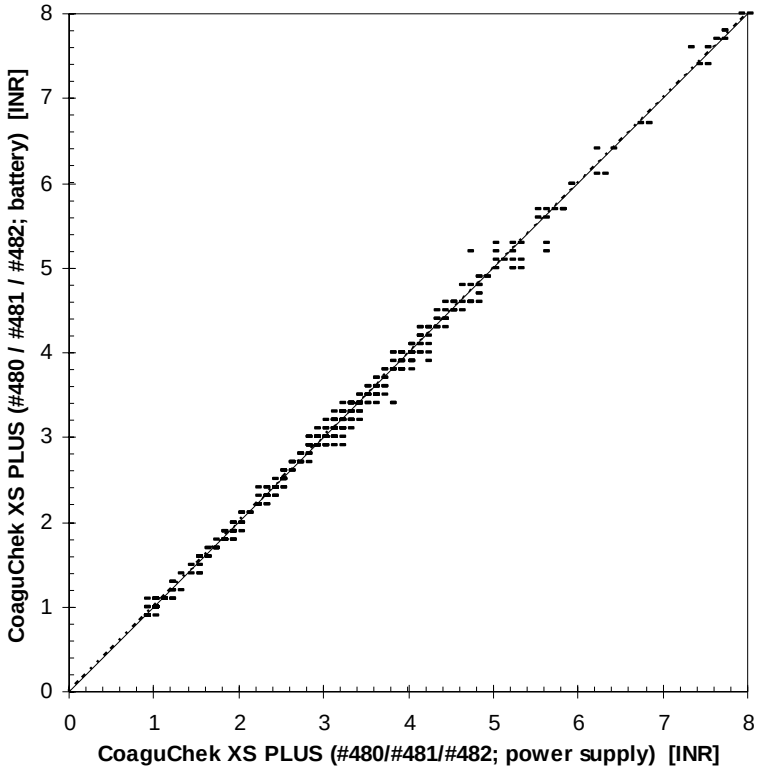

Fig. 13 Method comparison CoaguChek XS Plus on battery vs. CoaguChek XS Plus on power supply Bablok-Passing: y = x; n = 604; r = 0.998

10. Results of method comparisons lot to lot (lot-to-lot agreement)

No criteria set in the study protocol

Data in file: *LB 157 Tentativ CoaguChek XS Plus.xls*

The CoaguChek XS PT test strip pilot lots 2 and 3 were compared to the 1st pilot lot using the single determinations in triplicate for each lot and each sample. An excellent agreement was found with low scatter (Fig. 14 and 15). The regression lines are equal to the line of identity. The coefficients of correlation are >0.99. The mean relative bias is 0.09% and -0.11%, respectively.

Conclusion: The three CoaguChek XS PT lots show excellent agreement with each other over the entire measuring range up to INR 8.

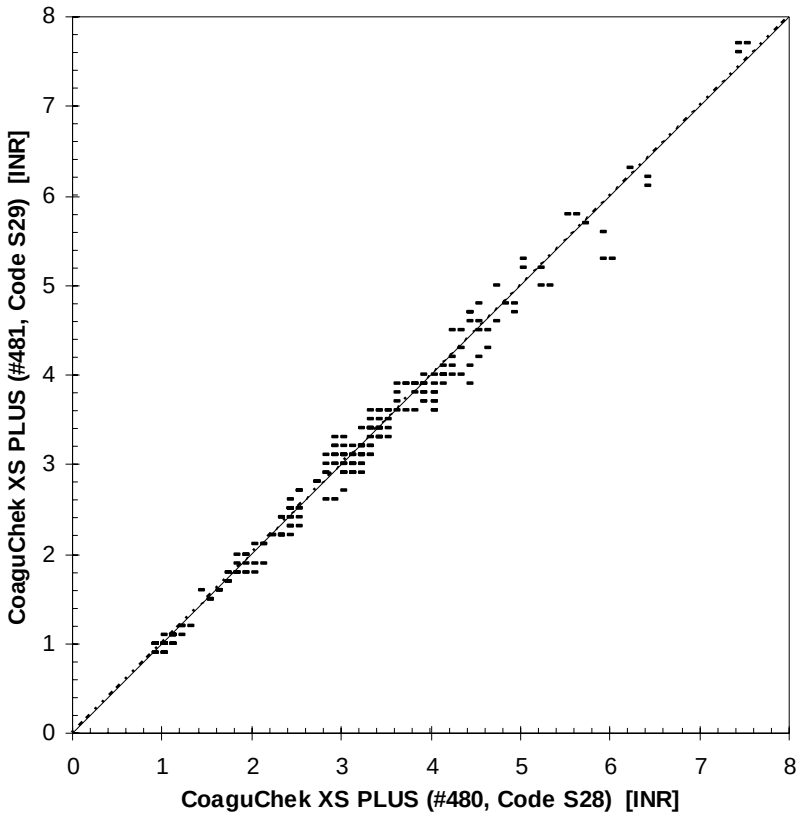

Fig. 14 Method comparison CoaguChek XS Plus lot 481 versus lot 480 (2nd vs. 1st pilot lot; venous blood; sheet MvKurv.28vs29) Bablok-Passing: y = x ; n = 300; r = 0.994

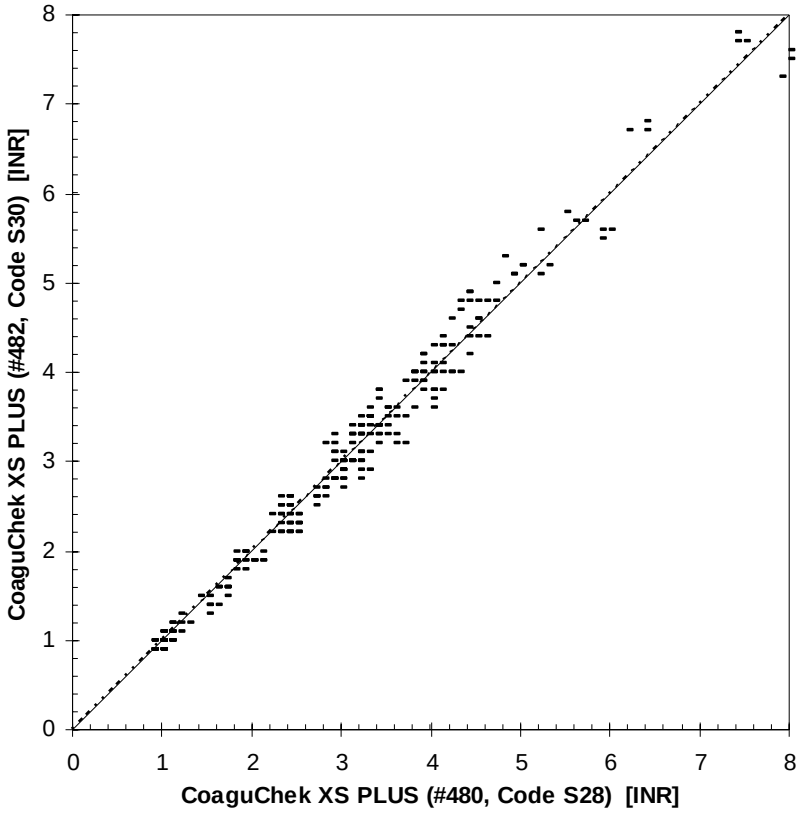

Fig. 15 Method comparison CoaguChek XS Plus lot 482 versus lot 480 (3^{rd} vs. 1^{st} pilot lot; venous blood; sheet MvKurv.28vs30) Bablok-Passing: y = x ; n = 303; r = 0.992

11. Imprecision of CoaguChek XS Plus INR determinations in venous whole blood

Acceptance criteria (venous whole blood measurements):

- *CV <3.5%*

from Technical Design Goal document NCP 085, rev. and given in the package insert for venous blood:

Data in files: *LB 157 Whole Blood Precision alle.xls / LB 157 Whole Blood Precision Normals.xls / LB 157 Whole Blood Precision Pat.xls*

From the triplicate determinations of each sample with each lot of test strips on both systems CVs were calculated for venous blood testing (Tables 8 and 9). These CVs still include a contribution from the meter to meter bias as the triplicates were run on three different meters.

Three different CVs were calculated for the CoaguChek XS Plus and the CoaguChek XS system:

- for normal donors only
- for patients in the therapeutic range (INR 2.0 – 4.5)
- for all subjects

The relevant CVs from venous blood in the therapeutic range of patients are determined to be 1.6% to 1.8%. All CVs with venous blood are found below 2% in this study, clearly matching the 3.5% CV which is given as performance claim in the package insert of the test strips. The CoaguChek XS Plus and the CoaguChek XS system showed equivalent precision with whole blood.

The median CVs of 0% in normal donor testing can be explained by the fact that the CoaguChek XS / XS Plus system only displays the INR result to one decimal. Therefore a typical series of triplicate results is 1.0 / 1.0 / 1.0, giving a virtual CV of 0%. This happened for many normal donors. On the other hand a series of 1.0 / 1.1 / 1.0 gives a CV of 5.6%. Therefore in the normal range CVs should not be assessed too much in detail.

Table 8 Coefficients of variation for venous blood testing with the CoaguChek XS Plus system

	lot 201480 1st pilot lot			**lot 201481** 2nd pilot lot			**lot 201482** 3rd pilot lot		
	normals	**therapeutic range**	**all data**	**normals**	**therapeutic range**	**all data**	**normals**	**therapeutic range**	**all data**
Excel sheet	CC XS plus 480	CC XS plus 480	CC XS plus 480	CC XS plus 481	CC XS plus 481	CC XS plus 481	CC XS plus 482	CC XS plus 482	CC XS plus 482
n	21	60	101	21	60	100	21	59	101
Median CV	(0%)	**1.6%**	**1.5%**	(0%)	**1.6%**	**1.4%**	(0%)	**1.7%**	**1.6%**
Mean CV	1.9%	1.4%	1.6%	0.6%	1.4%	1.3%	1.0%	1.6%	1.6%

Table 9 Coefficients of variation for venous blood testing with the CoaguChek XS system

	lot 201480 1st pilot lot			**lot 201481** 2nd pilot lot			**lot 201482** 3rd pilot lot		
	normals	**therapeutic range**	**all data**	**normals**	**therapeutic range**	**all data**	**normals**	**therapeutic range**	**all data**
Excel sheet	CC XS 480	CC XS 480	CC XS 480	CC XS 481	CC XS 481	CC XS 481	CC XS 482	CC XS plus 482	CC XS 482
n	21	64	100	21	60	101	21	60	100
Median CV	(0%)	**1.6%**	**1.4%**	(0%)	**1.8%**	**1.7%**	(0%)	**1.8%**	**1.6%**
Mean CV	1.4%	1.5%	1.5%	2.0%	1.8%	1.8%	1.6%	1.6%	1.6%

Conclusion: All three CoaguChek XS PT lots show very good precision in venous blood testing on CoaguChek XS Plus and CoaguChek XS meters fulfilling the acceptance criteria. The CoaguChek XS Plus demonstrated equivalent precision to the CoaguChek XS system in whole blood testing.

12. Performance of the CoaguChek XS Plus system in liquid control testing

Acceptance criteria:
from Technical Design Goal document NCP 085, rev. 3:
- *CV <6% (one lot, different meters)*

from study protocol LB 157-2005:
- *>95% of determinations within control range (≤ 2 fail results per level)*

Data in file: *Control precision.xls*

Liquid control testing was performed with three levels of control in the beginning and at the end of each day of testing on all 18 meters (9 CoaguChek XS Plus and 9 CoaguChek XS meters). This testing resulted in 6 determinations per lot of test strips and level of control on each day for both systems. Over the three days of testing 18 determinations were run on each system with each lot of test strips at each level of control. In total 162 determinations each were performed on the CoaguChek XS Plus and the CoaguChek XS system in control testing.

The results for the three pilot lots of test strips are given in Tables 10 to 12.

The mean CV of the CoaguChek XS Plus PT determinations was calculated to be in the range 0.0% to 3.2% for control level 1,
1.9% to 2.2% for control level 2,
2.6% to 2.8% for control level 3.
CVs were found equivalent for both systems.

The CVs of 0% can be explained by the fact that the CoaguChek XS / XS Plus system only displays the INR result to one decimal. Therefore a series of identical results gives a virtual CV of 0%. This happened in four cases where all 18 determinations had the same INR value, e.g. for CoaguChek XS and CoaguChek XS Plus with the 3rd pilot lot of test strips in level 1: all results were displayed as 1.2 INR.

Combining the 54 INR results of all three lots per level of control an estimated "System CV" may be calculated including 9 meters, 3 lots of test strips and three days of testing:
The "System CV" of the CoaguChek XS Plus system was calculated to be
2.3% for control level 1,
2.8% for control level 2,
3.4% for control level 3.

The "System CV" of the CoaguChek XS system was calculated to be
1.1% for control level 1,
2.3% for control level 2,
2.1% for control level 3.

Table 10 Coefficients of variation for control testing with the CoaguChek XS Plus and the CoaguChek XS system (1st pilot lot of test strips)

	CoaguChek XS Plus, all meters			CoaguChek XS, all meters		
	1st Pilot Lot # 201480 Code = S_028			1st Pilot Lot # 201480 Code = S_028		
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
mean INR	1.19	2.47	1.86	1.19	2.48	1.87
n	18	18	18	18	18	18
SD	0.02	0.05	0.05	0.02	0.04	0.05
CV	**2.0%**	**1.9%**	**2.8%**	**2.0%**	**1.7%**	**2.5%**

Table 11 Coefficients of variation for control testing with the CoaguChek XS Plus and the CoaguChek XS system (2nd pilot lot of test strips)

	CoaguChek XS Plus, all meters			CoaguChek XS, all meters		
	2nd Pilot Lot # 201481 Code = S_029			2nd Pilot Lot # 201481 Code = S_029		
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
mean INR	1.22	2.57	1.94	1.20	2.53	1.90
n	18	18	18	18	18	18
SD	0.04	0.06	0.05	0.00	0.06	0.00
CV	**3.2%**	**2.2%**	**2.6%**	**(0%)**	**2.3%**	**(0%)**

Table 12 Coefficients of variation for control testing with the CoaguChek XS Plus and the CoaguChek XS system (3rd pilot lot of test strips)

	CoaguChek XS Plus, all meters			CoaguChek XS, all meters		
	3rd Pilot Lot # 201482 Code = S_030			3rd Pilot Lot # 201482 Code = S_030		
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
mean INR	1.20	2.47	1.87	1.20	2.47	1.87
n	18	18	18	18	18	18
SD	0.00	0.05	0.05	0.00	0.06	0.05
CV	**(0%)**	**2.0%**	**2.6%**	**(0%)**	**2.3%**	**2.5%**

All 324 INR determinations on the two systems were found within the assigned control ranges. That means that 100% of the INR values received from the CoaguChek XS Plus system in liquid control testing matched the respective control range.

The minimun and maximum INR values on the CoaguChek XS Plus system are shown for all three strip lots combined in Table 13.

Conclusion: The CoaguChek XS Plus system demonstrated very good performance in liquid control testing. The majority of CVs were found even below 3%, including the "System CV". All INR values matched the assigned control ranges.
The acceptance criteria are met.

The liquid controls are a suitable sample material for use with the CoaguChek XS Plus system.

Table 13 Min/max range of INR values in control testing with the CoaguChek XS Plus system

	Level 1	Level 2	Level3
Control range [INR]	**1.0-1.4**	**2.1-3.0**	**1.3-2.3**
n	54	54	54
min [INR]	**1.1**	**2.4**	**1.8**
max [INR]	**1.3**	**2.7**	**2.0**

13. Instrument precision of the CoaguChek XS Plus meters (meter-to-meter CV)

Acceptance criteria:
according to the Technical Design Goal Document
- *CV <1.5% for venous blood from normal donors*
- *CV <1.5% for venous blood from patients in the therapeutic range*
- *CV <1.5% for controls*

Data in files*: Instrument precision Patdaten.xls /Instrument precision Control.xls)*

From the triplicate determinations within each lot of test strips for each sample the meter-to-meter variability was calculated in each set of three meters. The results are summarized in Table 14.

In venous blood testing with samples from normal donors the mean meter-to-meter CV was found to be
0.7% for the CoaguChek XS Plus meters, and
0.9% for the CoaguChek XS meters.

In venous blood testing with samples from patients in the therapeutic range the mean meter-to-meter CV was found to be
0.6% for the CoaguChek XS Plus meters, and
0.6% for the CoaguChek XS meters.

In control testing the mean meter-to-meter CV was found to be
0.8% for the CoaguChek XS Plus meters, and
0.5% for the CoaguChek XS meters.

All meter-to-meter CVs were found below 1.5%, the mean CVs are around 0.7%.

Conclusion: The CoaguChek XS Plus system demonstrates a very low instrument imprecision with meter-to-meter CVs below 1%:
The acceptance criteria are fulfilled.

Table 14 Meter-to-meter CVs of the CoaguChek XS Plus and the CoaguChek XS system

	CoaguChek XS Plus			**CoaguChek XS**		
Control	meter Set A	meter Set B	meter Set C	meter Set A	meter Set B	meter Set C
Level 1	0.8%	1.4%	0%	0.8%	0%	0%
Level 2	0.8%	0.4%	0.7%	0.8%	1.0%	0.8%
Level 3	1.4%	1.0%	0.9%	0.5%	0%	0.5%

14. Final conclusions

All acceptance criteria of the performance evaluation study were met.

The CoaguChek XS Plus system gives equivalent results to the CoaguChek XS system.

The CoaguChek XS Plus system demonstrated a high level of accuracy and trueness, and very good imprecision in INR testing.

The performance with liquid quality controls was very good, with very low imprecision and all results matching the respective control ranges. The liquid quality controls proved to be a suitable sample material for the CoaguChek XS Plus system.

15. References

1) ISO/DIS 17593 (November 15, 2004)
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2) Passing H, Bablok W: A new biometrical procedure for testing the equality of measurements from different analytical methods, Part I.
J Clin Chem Clin Biochem 1983;21:709

3) Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-310

4) Hill J: Determination of INR accuracy: Methods of analysis.
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