Performance Evaluation of an Improved ARCHITECT LH Assay for the Quantitative Determination of Luteinizing Hormone in Human Serum and Plasma

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Abstract

Determination of the concentration of human luteinizing hormone plays an important role for the prediction of ovulation, evaluation of infertility, diagnosis of pituitary and gonadal disorders and in the differential diagnosis of puberty disorders. The ARCHITECT LH chemiluminescent-immunoassay for the quantitative determination of luteinizing hormone in human serum and plasma serves this clinical utility. The assay was re-designed to improve robustness in terms of better lot-to-lot consistency, allowing users to discontinue current practice of matching reagent, calibrators and controls. The re-designed ARCHITECT LH assay was evaluated on the ARCHITECT instrument-platform and compared to the predicate device: the previously marketed ARCHITECT LH assay.

Total imprecision of the assay was 2.4 - 8.9%CV across the claimed measuring interval (0.09 - 250.00 mIU/mL). Detection Limits were determined as Limit of Quantitation with 0.09 mIU/mL, Limit of Blank 0.01 mIU/mL and Limit of Detection 0.03 mIU/mL. Correlation slope to the predicate ARCHITECT LH assay was 1.04. Linearity was demonstrated in the claimed measuring interval. Mean recovery was determined to be 101.0 %. Process capability indices demonstrated excellent (>6 Sigma) lot-to-lot reproducibility. The re-designed ARCHITECT LH assay showed excellent performance and good correlation to the predicate device. The high lot-to-lot reproducibility demonstrates excellent process capability and allows more flexibility in managing inventory for end-users. Matching of reagents, calibrators and controls is no longer required. The ARCHITECT LH assay is a valuable tool in clinical laboratories for the accurate and precise quantitation of human luteinizing hormone.

Keywords: ARCHITECT instrument; chemiluminescence; endocrinology; fertility panel; immunoassay; luteinizing hormone.

Abbreviations

CLSI Clinical and Laboratory Standards Institute
Cp, Cpk Process capability indices
CV Coefficient of variation
EDTA: Ethylenediaminetetraacetic acid
$F(ab')_2$ Antibody fragment (antigen-binding)
FSH Follicle stimulating hormome
HAMA Human anti-mouse antibodies
hCG Human chorionic gonadotropin
HRT Hormone replacement therapy
IgG Immunoglobulin G
IU International units
LH Luteinizing hormone
LN List number
LoB Limit of Blank
LoD Limit of Detection
LoQ Limit of Quantitation
MCC Multi constituent control
RF Rheumatoid factor
RLU Relative light units
SCC Single constituent control
SD Standard deviation
TSH Thyroid stimulating hormome
WHO World Health Organization

1. Introduction

Determination of the concentration of human luteinizing hormone plays an important role for the prediction of ovulation, evaluation of infertility, diagnosis of pituitary and gonadal disorders [1, 2] and in the differential diagnosis of puberty disorders [3, 4]. Human luteinizing hormone (LH, lutropin) is a glycoprotein hormone with two dissimilar subunits (α and β). The α-subunit is essentially identical to the α-subunits of follicle stimulating hormone (FSH, follitropin), thyroid stimulating hormone (TSH, thyrotropin), and human chorionic gonadotropin (hCG) [5-8]. The β-subunit is considerably different from that of FSH and TSH [5, 8, 9]. However, the β-subunits of LH and hCG are very similar [5, 9, 10]. LH, together with FSH, is secreted by the gonadotroph cells in the pituitary [9, 11] in response to the secretion of the gonadotropin releasing hormone from the medial basal hypothalamus [12-14]. Ovarian steroids, principally estrogens, modulate the secretion of LH and FSH which in turn regulate the menstrual cycle in females. When the follicle and the ovum contained within it, reach maturity, a surge of LH causes the follicle to rupture releasing the ovum. The follicular remnant is transformed into a corpus luteum, which secretes progesterone and estradiol. During the follicular and luteal phases, LH concentrations are much lower than the levels observed at the time of the LH surge. During the follicular and luteal phases, the estrogens exert a negative feedback on the release of LH. Shortly before the mid-cycle surge in LH, ovarian steroids, specifically estradiol, exert a positive feedback on the release of LH [1, 15, 16].

Increasing concentrations of LH precede ovulation and in cases in which the period of optimal fertility needs to be defined for the timing of intercourse or artificial insemination, the determination of daily concentrations of LH is important for the prediction of ovulation. More frequent sampling is required if the precise time of follicular rupture is needed for egg aspiration for in vitro fertilization [17].

At menopause, or following ovariectomy in women, concentrations of estrogens decline to low levels. The lowered concentrations of estrogens result in a loss of the negative feedback on gonadotropin release. The consequence is an increase in the concentrations of LH and FSH [1, 17, 18]. The primary role of LH in the male is to stimulate the production of testosterone by the Leydig cells. LH, through the production of testosterone together with FSH, regulates spermatogenesis in the Sertoli cells of the seminiferous tubules of the testes. Testosterone exerts a negative feedback on the release of LH [2]. In sexually mature adults gonadotropin deficiency is usually an early indication of the development of panhypopituitarism. Low concentrations of LH, FSH, and steroids are observed with this disorder. In contrast, gonadotropin secreting tumors of the hypothalamus and pituitary result in elevated concentrations of LH and FSH [17]. Gonadal failure, a cause of infertility, is indicated by elevated concentrations of LH and FSH accompanied by low concentrations of gonadal steroids [1, 2, 17]. In the female, elevated concentrations of LH can indicate primary amenorrhea [1], menopause [1, 17, 18], premature ovarian failure [17, 19], polycystic ovarian syndrome [19, 20], hypergonadotropic hypogonadism [1, 17], or ovulation. In the male, elevated concentrations of LH can result from primary testicular failure, seminiferous tubule dysgenesis (Klinefelter's syndrome), Sertoli cell failure, anorchia, or hypergonadotropic hypogonadism [21, 22].

A re-designed version of the ARCHITECT LH assay with List number (LN) 2P40 for the quantitative determination of human luteinizing hormone (LH) in human serum and plasma has now been made available worldwide. The improved assay allows the customer or end-user to discontinue the tedious and cumbersome current practice of matching reagent, calibrators and controls, which allows more flexibility in managing inventory in customer's laboratories. The assay is referenced to the WHO Luteinizing Hormone Human Pituitary 2nd International Standard 80/552 and uses a 6-point Standard Calibration curve, compared to the 2-point calibration curve adjustment performed on the predicate LH assay. The assay can be run with any commercially available single- (SCC) or multi-constituent (MCC) controls. Lot-to-lot reproducibility was enhanced by changes made by qualification of new raw materials for the Microparticle and Conjugate components. A state of-the-art mouse monoclonal anti-α-LH F(ab')$_2$ fragment was chosen to replace the former IgG based Conjugate. The stability of the calibrators was improved by replacing the plasma based diluent with an artificial matrix. In addition, the sample volume was reduced from 65µL to 25µL and an automated 1:4 dilution option was implemented for samples reading > 250 mIU/mL (up to 1000 mIU/mL).

Performance of this assay was evaluated in verification and validation studies and correlation to the predicate device was determined as summarized below.

2. Materials and Methods

The re-designed ARCHITECT LH assay (LN 2P40) was evaluated on the ARCHITECT instrument platforms and the assay performance characteristics were compared to the predicate ARCHITECT LH assay (LN 6C25).

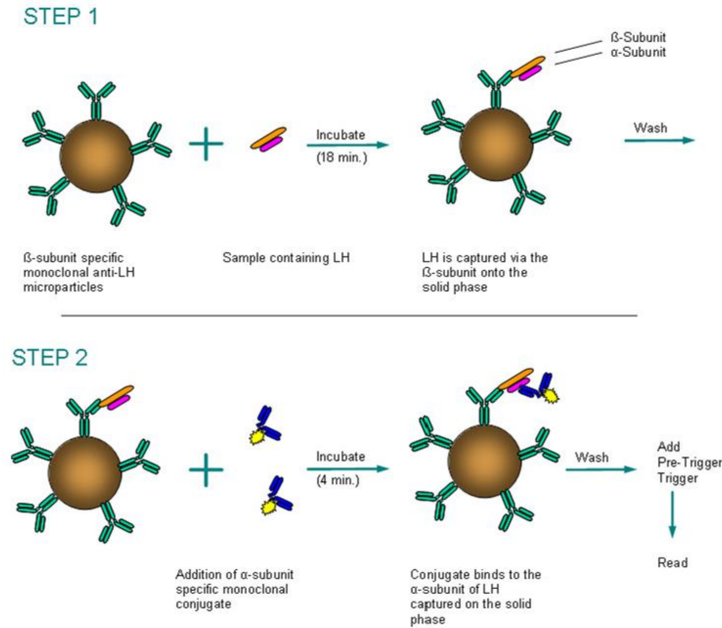

Figure 1. Assay format of the ARCHITECT LH assay (02P40)

Assay Format: The re-designed ARCHITECT LH assay is a two-step chemiluminescent immunoassay (see **Figure 1**). In the first step, sample and anti-β LH coated paramagnetic microparticles are combined. LH present in the sample binds to the anti-β LH coated microparticles. After washing, anti-α LH acridinium-labeled conjugate is added. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of LH in the sample and the RLUs detected by the ARCHITECT i System optics. The ARCHITECT LH calibrators A-F have concentrations spanning the entire measuring range of the assay (A: 0.0, B: 1.0, C: 3.5, D: 15.0, E: 50.0 and F: 250.0 mIU/mL). The ARCHITECT i System calculates the calibrator A through F mean chemi-luminescent signal from two replicates, generates a calibration curve and stores the result.

The medical decision points for LH are typically the upper and lower limits of the central 95% population distribution for males, post menopausal females, follicular and luteal phases for women of child bearing age and the lower 2.5% percentile limit for the mid cycle peak phase. Since many of these decision points are proximal to each other, general target values of 1, 10, and 70 mIU/mL were chosen as medical decision points for performance testing.

The imprecision of the ARCHITECT LH assay was determined using both serum (n=4) and plasma based panels (n=4), which spanned the entire measuring range (0-250 mIU/mL). The protocol employed for this testing was based on guidance from CLSI protocol EP5-A2 [23]. Three replicates of all panels were assayed at 2 separate times per day over a 20 day period using two reagent lots and on two instruments. The study was conducted on all three platforms of the ARCHITECT instrument family (i2000SR, i2000 and i1000SR) to assess equivalent performance, resulting in a total of six instruments used for this study. To further assess serum to plasma equivalency, matched serum and plasma specimens were prepared for this test setup.

The sensitivity was determined as Limit of Quantitation (LoQ), Limit of Blank (LoB) and Limit of Detection (LoD) based on guidance from CLSI EP17-A [24]. The LoQ is defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable error, which was specified at 22% for the re-designed LH assay. The LoD is defined as the lowest amount of analyte that can be reliably identified as being qualitatively present in the sample. The study was performed with four blank (zero-level) samples and eight samples with LH concentrations ranging from 0.05 - 0.11 mIU/mL. These samples were tested over a period of three days using two reagent lots and two instruments. This testing was repeated on each platform of the ARCHITECT instrument family (i2000SR, i2000 and i1000SR) to assess performance equivalency.

The Limit of Blank (LoB) and Limit of Detection (LoD) of the ARCHITECT LH assay was determined using proportions of false positives (α) and false negatives (β) less than 5%. This analysis was performed using four blank (n=240 replicates) and eight low level LH samples (n=478 replicates).

To establish the measuring interval (reportable range) of the assay an additional study was conducted to confirm the linear range of the assay. This study was performed on all 3 family members of the ARCHITECT instrument platform based on guidance from CLSI protocol EP6-A [25].

The measuring interval is defined as the range of values expressed in mIU/mL which meet the limits of acceptable performance for both imprecision and bias for an undiluted sample. Precision by the CLSI EP5-A2 [23] protocol was performed at the assay limits, CLSI EP17-A [24] employed to determine LoQ (low point) and CLSI-EP6-A [25] to determine the upper end of linearity (high point).

The expected values were established for normal males (n=199), normally cycling females (n=64) and post-menopausal females (n=124, not on hormone replacement therapy (HRT)). For this study, the follicular phase was defined as the period of time from 10 to 4 days prior to the mid-cycle peak. The luteal phase was defined as the period of time from 4 to 10 days following the mid-cycle peak. Cycle days were synchronized to the mid-cycle peak, the day on which the LH concentration was most elevated. Specimens used were serum samples sourced from commercial supplier (ProMedDx, Norton (MA), USA; and Bioreclamation, Hicksville (NY), USA) and tested in single replicates. ARCHITECT i2000SR and i2000 instruments were utilized for testing.

A study was performed to determine accuracy of the assay by verifying the percentage (%) recovery of LH. This was achieved by preparing LH stock solutions using human pituitary luteinizing hormone (lyophilized, >95% purity, SCRIPPS (CA), USA) diluted in normal human male serum. Known concentrations of LH were then added using the prepared stock solutions to 15 specimens with varying endogenous LH levels (10 - 70 mIU/mL). The concentration of LH was obtained using the ARCHITECT LH assay and the resulting percent recovery calculated as follows:

$$\%\,Recovery = \frac{Value\ obtained - Endogenous\ level \times 100}{LH\ added}$$

The study was conducted on all three family members of the ARCHITECT instrument platform to assess equivalent performance.

The correlation with the predicate ARCHITECT LH assay was evaluated per CLSI EP9-A2-IR [26] protocol. In these evaluations 107 unique specimens across the range of 0 - 250 mIU/mL were used. Specimen concentrations ranged from 1.00 - 207.80 mIU/mL with the ARCHITECT LH (2P40) assay and from 1.11 - 236.20 mIU/mL with the ARCHITECT LH (6C25) assay. The specimens included in the study were sourced from external commercial vendors (ProMedDx, Norton (MA), USA; and Bioreclamation, Hicksville (NY), USA) and derived from different sample categories (normal males, normally menstruating females, and postmenopausal females without HRT). Since samples > 100 mIU/mL are rarely expected in normal populations, 7 normal male samples were spiked with LH stock solutions to cover the upper range of the assay. All samples were tested in replicates of two on both the investigational and comparator assays. Regression analysis was performed on the mean of the two replicates using the Passing-Bablok [27] and least squares regression methods.

Lot-to-lot reproducibility for the redesigned ARCHITECT LH assay was assessed by testing BIO-RAD Liquicheck Immunoassay Plus Control, composed of three different LH levels with 3, 15, and 45 mIU/mL across three reagent and calibrator lots resulting in nine different combinations per level. For each level the standard deviation (SD) and %CV was calculated from the means of each Reagent-Calibrator lot combination. In addition, process capability indices (Cp, Cpk) were calculated based on the calculated standard deviation and the BIO-RAD package insert specifications (ranges of means).

Potential Interference of the ARCHITECT LH assay with hemoglobin (≥500 mg/dL), bilirubin (≥20 mg/dL), trigylcerides (≥3000 mg/dL), and protein (≥12 g/dL) is designed to be within +/-8% in the range 10-70 mIU/mL and was evaluated by a study based on guidance from the CLSI protocol EP7-A2 [28].

The assay is designed to have a recovery of 100 +/-8% when analyzing rheumatoid factor (RF) or human anti-mouse antibodies (HAMA) positive samples spiked with known amounts of LH across the range of 10-70 mIU/mL. Spiked test and reference specimen samples were evaluated in replicates of four and the normal human control samples in replicates of 14 with one reagent lot on one ARCHITECT i2000SR instrument. Specimens containing HAMA and RF were sourced from a commercial supplier (ProMedDx, Norton (MA), USA). Normal human serum specimens obtained from German blood donor service (DRK Transfusion Center Plauen) were pooled and used as the normal control sample.

Human pituitary luteinizing hormone diluted in normal human male serum was used for spiking. A total of six serum pools were prepared using 292 specimens in the LH concentration range 1.5 - 6.0 mIU/mL.

The specificity of the ARCHITECT LH assay was determined for the potential cross-reacting hormones FSH, TSH, and hCG at 150 mIU/mL, 100 µIU/mL and 200,000 mIU/mL, respectively. Aliquots of ARCHITECT LH Calibrator A, analyte free (0 mIU/mL), in addition to a pool of normal male serum (≤10 mIU/mL) and spiked normal male serum samples (50 - 70 mIU/mL) were supplemented with potential cross-reactants at different concentrations and tested for LH. The following formulation was employed to calculate the cross-reactivity:

$$\%\,Cross\text{-}Reactivity = \frac{mean\ LH\ conc. - mean\ LH\ reference\ conc. \times 100}{conc.\ of\ cross\ reactant}$$

With regards to tube type equivalency the assay is designed to have a bias of < 8% when testing samples at the two medical decision points 10 and 70 mIU/mL. Following tube types have been evaluated: Serum separator tubes, potassium-EDTA and sodium-heparin.

3. Results and Discussion

Table 1 shows results obtained on the i2000SR instrument, including within-run (replicate to replicate) and total (within laboratory) SD and %CV results. The assay demonstrated an excellent precision across the entire measurement range. In addition no performance difference was observed between serum and plasma samples (n=60, regression slope 1.00; r=1.00; not shown). Results across the measuring interval ranged from 2.3 to 8.9% on the ARCHITECT i2000SR instrument, 2.3% to 4.8% on the ARCHITECT i2000, and 2.4 to 4.3% on the ARCHITECT i1000SR.

The re-designed ARCHITECT LH assay demonstrated linearity within the range of 0.09 - 250.00 mIU/mL on all three ARCHITECT instrument platforms. The absolute deviation from linearity of < 1 mIU/mL was observed for samples within LoQ and 10 mIU/mL, ≤11% for samples within 10 and 70 mIU/mL, and ≤15% for samples above 70 mIU/mL. Values up to 1000 mIU/mL have been determined using the manual or automated dilution procedure. Also these samples showed linearity with less than 15% absolute deviation from linearity.

For the verification studies described, the measuring interval (reportable range) was 0.09 mIU/mL (LoQ) - 250.00 mIU/mL. When using the manual or automated dilution procedure (1:4 dilution), the assay can determine values up to 1000.00 mIU/mL.

Expected values, as shown in **Table 3**, were established from normal males, normally menstruating females (three cycle phases) and postmenopausal females (without HRT). The reference ranges were comparable to the predicate device and are in line with those described in literature [29].

Results from the ARCHITECT i2000SR instrument demonstrated a LoQ of 0.09 mIU/mL, LoB of 0.01 mIU/mL and LoD of 0.03 mIU/mL. **Table 2** shows results obtained with all three ARCHITECT instrument types.

The determined reference range is comparable to that of the predicate device and to reference ranges described in the literature [29]. However, it is recommended that each laboratory establish its own reference range that is appropriate for the laboratory's patient population (i.e. a normal range that reflects the type of specimen and demographic variables such as age and sex, as applicable) and/or correlation data to predicate assays. Variables such as sampling size and sample population may impact individual results.

Mean recovery was calculated to be 101.0% across all ARCHITECT instrument platforms. Mean recovery was 101.2% on the ARCHITECT i2000SR platform, 98.8% on the ARCHITECT i2000 and 103.0% on the ARCHITECT i1000SR.

Method Comparison (Correlation) with the predicate device was determined and evaluated according to the Passing-Bablok and the least squares regression method. The re-designed ARCHITECT LH assay had a Passing-Bablok method correlation slope of 1.04 (y=1.04x – 0.27) and a Pearson correlation coefficient of r=0.99 to the predicate device. Refer to **Figure 2A** for the corresponding Passing-Bablok [27] and **Figure 2B** for Bland-Altman [30] correlation plots.

Table 1: Precision study on the i2000SR instrument platform (SP=serum panel; PP=plasma panel).

Sample Type	Instrument	Reagent Lot	Mean (mIU/mL)	Within-Run SD	Within-Run %CV	Total SD	Total %CV
SP 1	A	1	3.52	0.099	2.8	0.101	2.9
		2	3.39	0.068	2.0	0.087	2.6
	B	1	3.79	0.122	3.2	0.130	3.4
		2	3.40	0.124	3.6	0.131	3.9
SP 2	A	1	16.01	0.297	1.9	0.389	2.4
		2	15.84	0.307	1.9	0.464	2.9
	B	1	17.18	0.487	2.8	0.533	3.1
		2	15.56	0.454	2.9	0.502	3.2
SP 3	A	1	47.69	1.086	2.3	1.291	2.7
		2	47.82	1.012	2.1	1.442	3.0
	B	1	51.03	1.522	3.0	1.989	3.9
		2	46.55	1.200	2.6	1.633	3.5
SP 4	A	1	222.58	4.913	2.2	7.937	3.6
		2	228.31	5.188	2.3	8.962	3.9
	B	1	239.29	7.147	3.0	7.927	3.3
		2	220.87	4.888	2.2	6.160	2.8
PP 1	A	1	1.00	0.029	2.9	0.035	3.5
		2	0.95	0.023	2.4	0.028	2.9
	B	1	1.08	0.037	3.5	0.044	4.1
		2	0.94	0.028	3.0	0.031	3.3
PP 2	A	1	5.21	0.109	2.1	0.230	4.4
		2	5.01	0.121	2.4	0.149	3.0
	B	1	5.58	0.171	3.1	0.180	3.2
		2	5.00	0.134	2.7	0.187	3.7
PP 3	A	1	46.23	0.787	1.7	1.073	2.3
		2	46.08	1.271	2.8	1.738	3.8
	B	1	49.17	1.581	3.2	1.827	3.7
		2	45.76	1.032	2.3	1.227	2.7
PP 4	A	1	93.33	2.949	3.2	8.152	8.7
		2	93.21	2.942	3.2	8.316	8.9
	B	1	96.54	3.524	3.6	5.342	5.5
		2	91.25	2.295	2.5	4.871	5.3

Table 2: Sensitivity (LoB, LoD, and LoQ).

	Instrument	N	[mIU/mL]
LoB	i2000SR	240	0.01
	i2000	240	0.01
	i1000SR	240	0.00
LoD	i2000SR	N/A	0.03
	i2000	N/A	0.01
	i1000SR	N/A	0.01
LoQ	i2000SR	N/A	0.09
	i2000	N/A	0.09
	i1000SR	N/A	0.07

Table 3: Expected Values obtained from normal males, normally menstruating females and postmenopausal females without hormone replacement therapy (HRT).

Category	N	LH values [mIU/mL] Central 95% of Data		
		Median / Mean *	Lower Limit	Upper Limit
Normal Males	199	2.96	0.57	12.07
Normally Menstruating Females – Follicular Phase	303	3.98	1.80	11.78
Normally Menstruating Females – Mid-Cycle Peak	64	26.00 *	7.59	89.08
Normally Menstruating Females – Luteal Phase	294	2.79 *	0.56	14.00
Postmenopausal Females without HRT	124	25.73 *	5.16	61.99

* mean was calculated when population was normally distributed.

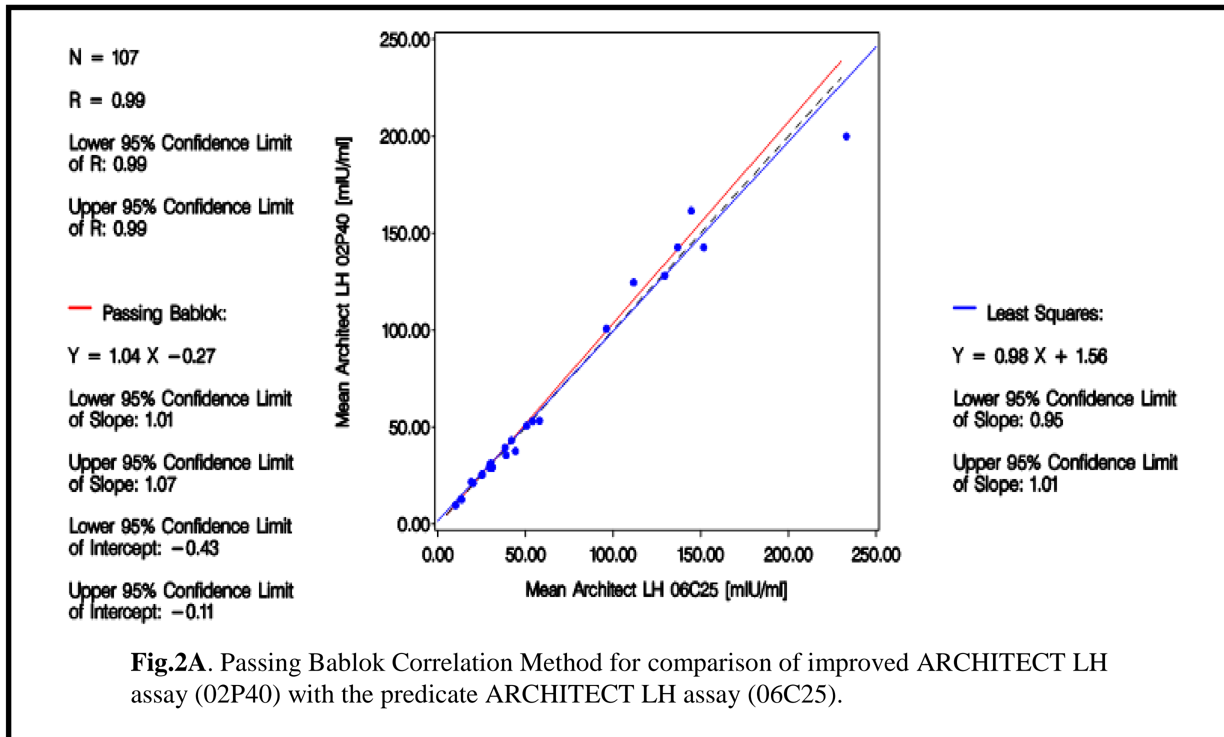

Fig.2A. Passing Bablok Correlation Method for comparison of improved ARCHITECT LH assay (02P40) with the predicate ARCHITECT LH assay (06C25).

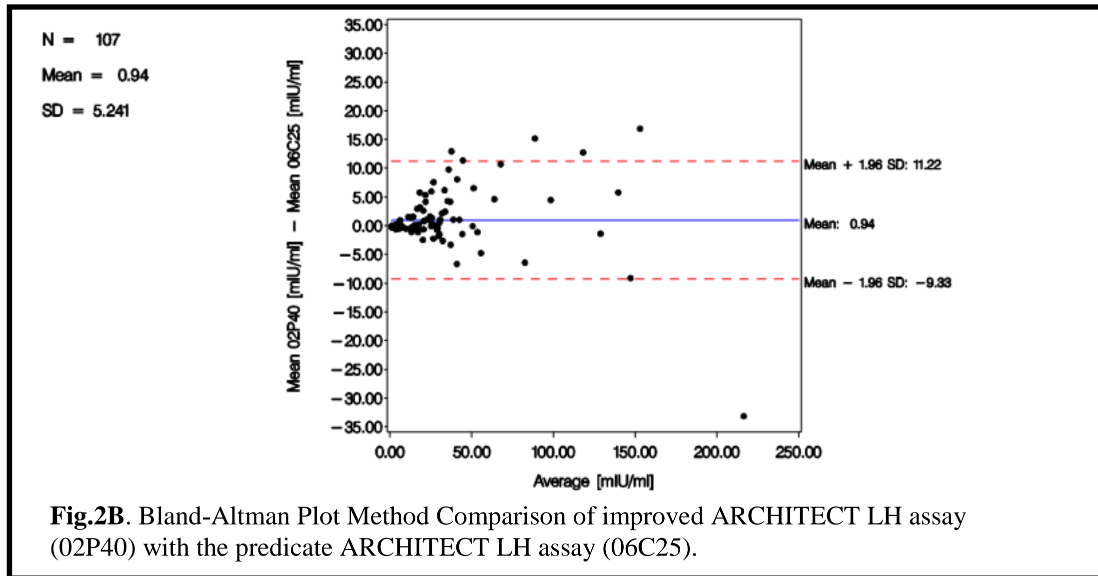

Fig.2B. Bland-Altman Plot Method Comparison of improved ARCHITECT LH assay (02P40) with the predicate ARCHITECT LH assay (06C25).

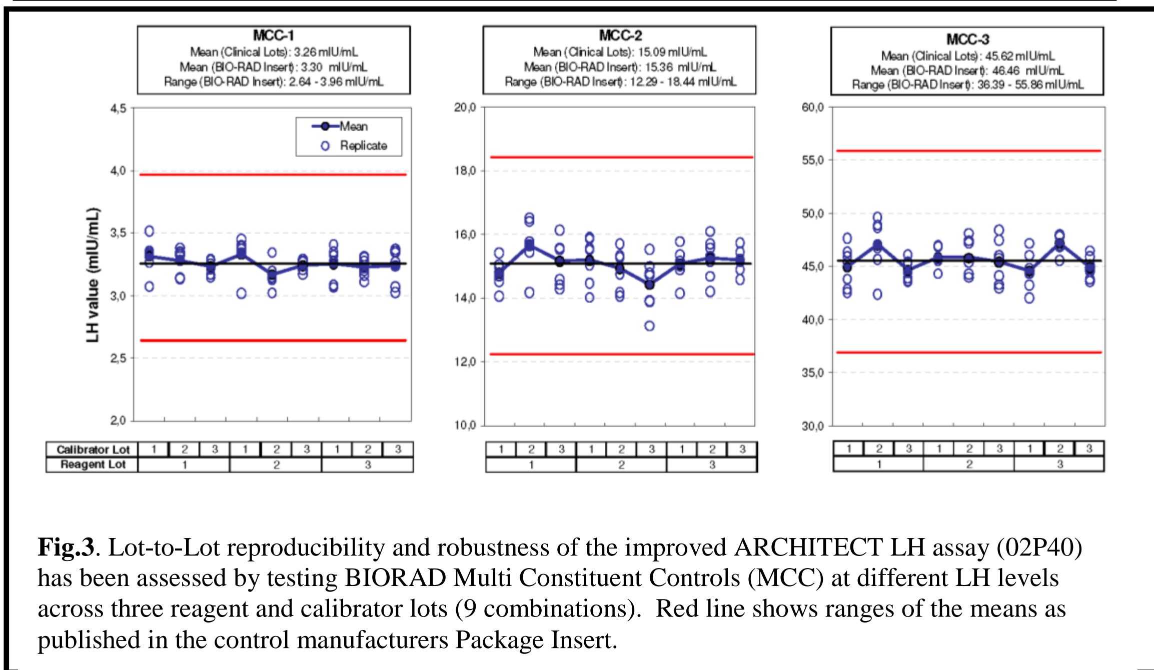

Fig.3. Lot-to-Lot reproducibility and robustness of the improved ARCHITECT LH assay (02P40) has been assessed by testing BIORAD Multi Constituent Controls (MCC) at different LH levels across three reagent and calibrator lots (9 combinations). Red line shows ranges of the means as published in the control manufacturers Package Insert.

Lot-to-lot reproducibility for the re-designed ARCHITECT LH assay has been assessed by testing BIO-RAD multi-constituent control (MCC) at three different LH levels i.e. 3 mIU/mL (MCC-1), 15 mIU/mL (MCC-2), and 45 mIU/mL (MCC-3)). Refer to **Figure 3** for results of lot-to-lot comparison. Individual results obtained for all combinations were within the ranges of the means as described in Package Insert of the control manufacturer. Total %CVs of Reagent-Calibrator lot combinations were 1.5% (MCC-1), 2.3% (MCC-2) and 2.1% (MCC-3). Cp / Cpk index values were 4.50 / 4.21 (MCC-1), 2.99 / 2.72 (MCC-2) and 3.24 / 2.96 (MCC-3), respectively. Thus, this indicates an excellent process capability (> 6 Sigma) across all reagent combinations and assay runs.

Endogenous compound interference of the ARCHITECT LH assay was tested to be maximum 8% in measured concentration with high protein concentrations (≥12 g/dL) and less than 2% for bilirubin (≥20 mg/dL), triglycerides (≥3000 mg/dL) and hemoglobin (≥500 mg/dL). RF and HAMA interference revealed an overall mean % recovery rate of 94% and 99%, respectively.

Cross-reactivity of the assay with FSH, TSH and hCG at high LH levels (50 – 70 mIU/mL) was 0.15%, 0.69% and < 0.01% respectively.

The following specimen collection tubes have been verified for use with the redesigned ARCHITECT LH assay: Human serum (including serum separator tubes), human plasma collected in potassium-EDTA and sodium-heparin. Predicted bias was 2.04% at 10 mIU/mL and 1.16% at 70 mIU/mL. Other specimen collection tubes have not been tested with this assay. The re-designed ARCHITECT LH assay allows also the use of sodium-heparin tubes, which can not be used in the predicate device.

4. Conclusions

The re-designed ARCHITECT LH assay showed excellent performance and a very good correlation with the predicate device. The high lot-to-lot reproducibility demonstrates an outstanding assay run performance (> six sigma quality process) and allows the end-users more flexibility in the management of reagent inventory thus allowing the elimination of the tedious and cumbersome matching of reagents and calibrators.

An accurate and precise measurement of luteinizing hormone concentrations is important in the diagnosis, treatment and monitoring of many different conditions. The re-designed ARCHITECT LH assay is a valuable tool available to clinical laboratories for determination of luteinizing hormone in human serum and plasma. The re-design of the assay improved performance as well as process- and run-capability compared to the predicate device.

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