BioVendor Group

ENG

Instructions for Use:

HUMAN CLUB CELL PROTEIN (CC16) ELISA

Catalogue number:

RD191022200

European Union:

IVD CE

Rest of the world:

For research use only!

BioVendor R&D

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CONTENT

HISTORY OF CHANGES

Previous version	Current version
ENG.008.A	ENG.009.A
PDS (Product Data Sheet)	IFU (Instructions for Use)
History of changes added.	
Symbol indicating a manufacturer added.	
Chapter 19. Additional information added.	

1. INTENDED USE

The RD191022200 Human Club Cell Protein (CC16) ELISA is a sandwich enzyme immunoassay for the quantitative measurement of human club cell protein.

Features

- **European Union: for *in vitro* diagnostic use**
- **Rest of the world: for research use only!**
- The total assay time is less than 4 hours
- The kit measures club cell protein in serum and plasma (EDTA, citrate, heparin)
- Assay format is 96 wells
- Quality Controls are human serum based
- Standard is recombinant protein (E.coli) based
- Components of the kit are provided ready to use, concentrated or lyophilized

2. STORAGE, EXPIRATION

Store the complete kit at 2-8°C. Under these conditions, the kit is stable until the expiration date (see label on the box).

For stability of opened reagents see Chapter 9.

3. INTRODUCTION

Human club cell protein (former Clara cell protein, CC16, CC10, uteroglobin, urinary protein 1 or club cell secretory protein) is a member of the secretoglobin family of proteins and is a secreted product of non-ciliated bronchiolar club cells. Its function remains to be fully elucidated but there is convincing data suggesting its role as an immune-modulating and anti-inflammatory agent. Club cell protein inhibits phospholipase A2 activity as well as interferon gamma signaling and Th1 vs. Th2 lymphocyte regulation.
Club cell protein concentrations have been determined in serum, plasma and bronchoalveolar lavage fluid in numerous studies since 1994. In serum, its increase is associated with age and asbestos, nitrogen chloride and ozone exposure. Higher levels of CC16 were demonstrated in patients with sarcoidosis, pulmonary fibrosis and high PEEP ventilation. Decreased serum CC16 levels are found after pulmonary resection in smokers and in subjects with chronic obstructive pulmonary disease, asthma or silica exposure.
Decreased CC16 concentrations were also found in the amniotic fluid of fetuses suffering from pulmonary hypoplasia caused by various mechanisms (diaphragmatic hernia, diabetic fetopathy, Turner and Down syndrome). In pleural effusions, the CC16 concentration appears to be associated with its diffusion from the lung as evidenced by high CC16 levels in cardiac pleural congestion.
Based on the above reports club cell protein might be perspective useful diagnostic marker of pulmonary diseases and injuries.

Clinical use and areas of investigation:
Pneumonia and bronchopneumonia
Chronic obstructive pulmonary disease, sarcoidosis, pulmonary fibrosis
Acute lung injury
Asthma and allergic rhinitis
Lung cancer
IgA-nephropathy

4. TEST PRINCIPLE

In the BioVendor Human Club Cell Protein (CC16) ELISA, standards, quality controls and samples are incubated in microplate wells pre-coated with polyclonal anti-human club cell antibody. After 60 minutes incubation and washing, biotin labelled polyclonal anti-human club cell protein antibody is added and incubated with captured club cell protein for 60 minutes. After another washing, streptavidin-horseradish peroxidase conjugate is added. After 60 minutes incubation and the last washing step, the remaining conjugate is allowed to react with the substrate solution (TMB). The reaction is stopped by addition of acidic solution and absorbance of the resulting yellow product is measured. The absorbance is proportional to the concentration of club cell protein. A standard curve is constructed by plotting absorbance values against concentrations of standards, and concentrations of unknown samples are determined using this standard curve.

5. PRECAUTIONS

- **For professional use only**
- Wear gloves and laboratory coats when handling immunodiagnostic materials
- Do not drink, eat or smoke in the areas where immunodiagnostic materials are being handled
- This kit contains components of human origin. These materials were found non-reactive for HBsAg, HCV antibody and for HIV 1/2 antigen and antibody. However, these materials should be handled as potentially infectious, as no test can guarantee the complete absence of infectious agents
- This kit contains components of animal origin. These materials should be handled as potentially infectious
- Avoid contact with the acidic Stop Solution and Substrate Solution, which contains hydrogen peroxide and tetramethylbenzidine (TMB). Wear gloves and eye and clothing protection when handling these reagents. Stop and/or Substrate Solutions may cause skin/eyes irritation. In case of contact with the Stop Solution and the Substrate Solution wash skin/eyes thoroughly with water and seek medical attention, when necessary
- The materials must not be pipetted by mouth

6. TECHNICAL HINTS

- Reagents with different lot numbers should not be mixed
- Use thoroughly clean glassware
- Use deionized (distilled) water, stored in clean containers
- Avoid any contamination among samples and reagents. For this purpose, disposable tips should be used for each sample and reagent
- Substrate Solution should remain colourless until added to the plate. Keep Substrate Solution protected from light
- Stop Solution should remain colourless until added to the plate. The colour developed in the wells will turn from blue to yellow immediately after the addition of the Stop Solution. Wells that are green in colour indicate that the Stop Solution has not mixed thoroughly with the Substrate Solution
- Dispose of consumable materials and unused contents in accordance with applicable national regulatory requirements

7. REAGENT SUPPLIED

Kit Components	State	Quantity
Antibody Coated Microtiter Strips	ready to use	96 wells
Biotin Labelled Antibody	ready to use	13 ml
Streptavidin-HRP Conjugate	ready to use	13 ml
Master Standard	lyophilized	2 vials
Quality Control HIGH	lyophilized	2 vials
Quality Control LOW	lyophilized	2 vials
Dilution Buffer	ready to use	20 ml
Wash Solution Conc. (10x)	concentrated	100 ml
Substrate Solution	ready to use	13 ml
Stop Solution	ready to use	13 ml

8. MATERIAL REQUIRED BUT NOT SUPPLIED

- Deionized (distilled) water
- Test tubes for diluting samples
- Glassware (graduated cylinder and bottle) for Wash Solution (Dilution Buffer)
- Precision pipettes to deliver 5-1000 µl with disposable tips
- Multichannel pipette to deliver 100 µl with disposable tips
- Absorbent material (e.g. paper towels) for blotting the microtitrate plate after washing
- Vortex mixer
- Orbital microplate shaker capable of approximately 300 rpm
- Microplate washer (optional). [Manual washing is possible but not preferable.]
- Microplate reader with 450 ± 10 nm filter, preferably with reference wavelength 630 nm (alternatively another one from the interval 550-650 nm)
- Software package facilitating data generation and analysis (optional)

9. PREPARATION OF REAGENTS

All reagents need to be brought to room temperature prior to use.

Always prepare only the appropriate quantity of reagents for your test.

Do not use components after the expiration date marked on their label.

Assay reagents supplied ready to use:

Antibody Coated Microtiter Strips

Stability and storage:
Return the unused strips to the provided aluminium zip-sealed bag with desicant and seal carefully. Remaining Microtiter Strips are stable 3 months when stored at 2-8°C and protected from the moisture.

Biotin Labelled Antibody

Streptavidin-HRP Conjugate

Dilution Buffer

Substrate Solution

Stop Solution

Stability and storage:
Opened reagents are stable 3 months when stored at 2-8°C.

Assay reagents supplied concentrated or lyophilized:

Human club cell protein Master Standard

Refer to the Certificate of Analysis for current volume of Dilution Buffer needed for reconstitution of standard!!!
Reconstitute the lyophilized Master Standard with Dilution Buffer just prior to the assay. Let it dissolve at least 15 minutes with occasional gentle shaking (not to foam). The resulting concentration of the human club cell protein in the stock solution is **50 ng/ml**.

Prepare set of standards using Dilution Buffer as follows:

Volume of Standard	Dilution Buffer	Concentration
Stock	-	50 ng/ml
150 µl of stock	150 µl	25 ng/ml
150 µl of 25 ng/ml	150 µl	12.5 ng/ml
150 µl of 12.5 ng/ml	150 µl	6.25 ng/ml
150 µl of 6.25 ng/ml	150 µl	3.13 ng/ml
150 µl of 3.13 ng/ml	150 µl	1.57 ng/ml

Dilute prepared standards (50 – 1.57 ng/ml) 25x with Dilution Buffer just prior to the assay, e.g. 10 µl of Standard + 240 µl of Dilution Buffer for duplicates. Mix well (not to foam). Vortex is recommended.

Stability and storage:
Do not store the diluted Standard solutions.

Quality Controls HIGH, LOW

Refer to the Certificate of Analysis for current volume of Dilution Buffer needed for reconstitution and for current Quality Control concentration!!!
Reconstitute each Quality Control (HIGH and LOW) with Dilution Buffer just prior to the assay. Let it dissolve at least 15 minutes with occasional gentle shaking (not to foam).
Dilute reconstituted Quality Controls 25x with Dilution Bufffer, e.g. 5 µl of Quality Control + 120 µl of Dilution Buffer when assaying samples in singlets, or preferably 10 µl of Quality Control + 240 µl of Dilution Buffer for duplicates. **Mix well** (not to foam). Vortex is recommended.

Stability and storage:
Do not store the diluted Quality Controls.

Note:
Concentration of analyte in Quality Controls need not be anyhow associated with normal and/or pathological concentrations in serum or another body fluid. Quality Controls serve just for control that the kit works in accordance with IFU and CoA and that ELISA test was carried out properly.

Wash Solution Conc. (10x)

Dilute Wash Solution Concentrate (10x) ten-fold in distilled water to prepare a 1x working solution. Example: 100 ml of Wash Solution Concentrate (10x) + 900 ml of distilled water for use of all 96-wells.

Stability and storage:
The diluted Wash Solution is stable 1 month when stored at 2-8°C. Opened Wash Solution Concentrate (10x) is stable 3 months when stored at 2-8°C.

10. PREPARATION OF SAMPLES

The kit measures club cell protein in serum and plasma (EDTA, citrate, heparin).

Samples should be assayed immediately after collection or should be stored at -20°C. Mix thoroughly thawed samples just prior to the assay and avoid repeated freeze/thaw cycles, which may cause erroneous results. Avoid using hemolyzed or lipemic samples.

Dilute serum or plasma samples 25x with Dilution Buffer just prior to the assay, e.g. 5 µl of sample + 120 µl of Dilution Buffer for singlets, or preferably 10 µl of sample + 240 µl of Dilution Buffer for duplicates. **Mix well** (not to foam). Vortex is recommended.

Stability and storage:
Samples should be stored at -20°, or preferably at -70°C for long-term storage. Avoid repeated freeze/ thaw cycles.
Do not store the diluted samples.

See Chapter 13 for stability of serum and plasma samples when stored at 2-8°C, effect of freezing/thawing and effect of sample matrix (serum/plasma) on the concentration of club cell protein.

Ask for information at info@biovendor.com if assaying bronchoalveolar lavage fluid or urine.

Note: It is recommended to use a precision pipette and a careful technique to perform the dilution in order to get precise results!

11. ASSAY PROCEDURE

1. Pipet **100 µl** of diluted Standards, Quality Controls, Dilution Buffer (=Blank) and samples, preferably in duplicates, into the appropriate wells. See *Figure 1* for example of work sheet.
2. Incubate the plate at room temperature (ca. 25°C) for **1 hour**, shaking at ca. 300 rpm on an orbital microplate shaker.
3. Wash the wells 3-times with Wash Solution (0.35 ml per well). After final wash, invert and tap the plate strongly against paper towel.
4. Add **100 µl** of Biotin Labelled Antibody into each well.
5. Incubate the plate at room temperature (ca. 25°C) for **1 hour**, shaking at ca. 300 rpm on an orbital microplate shaker.
6. Wash the wells 3-times with Wash Solution (0.35 ml per well). After final wash, invert and tap the plate strongly against paper towel.
7. Add **100 µl** of Streptavidin-HRP Conjugate into each well.
8. Incubate the plate at room temperature (ca. 25°C) for **1 hour**, shaking at ca. 300 rpm on an orbital microplate shaker.
9. Wash the wells 3-times with Wash Solution (0.35 ml per well). After final wash, invert and tap the plate strongly against paper towel.
10. Add **100 µl** of Substrate Solution into each well. Avoid exposing the microtiter plate to direct sunlight. Covering the plate with e.g. aluminium foil is recommended.
11. Incubate the plate for **10 minutes** at room temperature. The incubation time may be extended [up to 20 minutes] if the reaction temperature is below than 20°C. Do not shake the plate during the incubation.
12. Stop the colour development by adding **100 µl** of Stop Solution.
13. Determine the absorbance of each well using a microplate reader set to 450 nm, preferably with the reference wavelength set to 630 nm (acceptable range: 550 – 650 nm). Subtract readings at 630 nm (550 - 650 nm) from the readings at 450 nm. **The absorbance should be read within 5 minutes following step 12.**

Note 1: If some samples and standard/s have absorbances above the upper limit of your microplate reader, perform a second reading at 405 nm. A new standard curve, constructed using the values measured at 405 nm, is used to determine club cell protein concentration of off-scale standards and samples. The readings at 405 nm should not replace the readings for samples that were “in range” at 450 nm.

Note 2: Manual washing: Aspirate wells and pipet 0.35 ml Wash Solution into each well. Aspirate wells and repeat twice. After final wash, invert and tap the plate strongly against paper towel. Make certain that Wash Solution has been removed entirely.

	strip 1+2	strip 3+4	strip 5+6	strip 7+8	strip 9+10	strip 11+12
A	**Standard 50**	**QC LOW**	Sample 8	Sample 16	Sample 24	Sample 32
B	**Standard 25**	Sample 1	Sample 9	Sample 17	Sample 25	Sample 33
C	**Standard 12.5**	Sample 2	Sample 10	Sample 18	Sample 26	Sample 34
D	**Standard 6.25**	Sample 3	Sample 11	Sample 19	Sample 27	Sample 35
E	**Standard 3.13**	Sample 4	Sample 12	Sample 20	Sample 28	Sample 36
F	**Standard 1.57**	Sample 5	Sample 13	Sample 21	Sample 29	Sample 37
G	**Blank**	Sample 6	Sample 14	Sample 22	Sample 30	Sample 38
H	**QC HIGH**	Sample 7	Sample 15	Sample 23	Sample 31	Sample 39

Figure 1: Example of a work sheet.

12. CALCULATIONS

Most microplate readers perform automatic calculations of analyte concentration. The standard curve is constructed by plotting the mean absorbance (Y) of Standards against the known concentration (X) of Standards in logarithmic scale, using the four-parameter algorithm. Results are reported as concentration of club cell protein ng/ml in samples.

Alternatively, the *logit log* function can be used to linearize the standard curve, i.e. *logit* of the mean absorbance (Y) is plotted against *log* of the known concentration (X) of Standards.

Samples, Quality Controls and Standards are all diluted 25x prior to analysis, so there is no need to take this dilution factor into account.

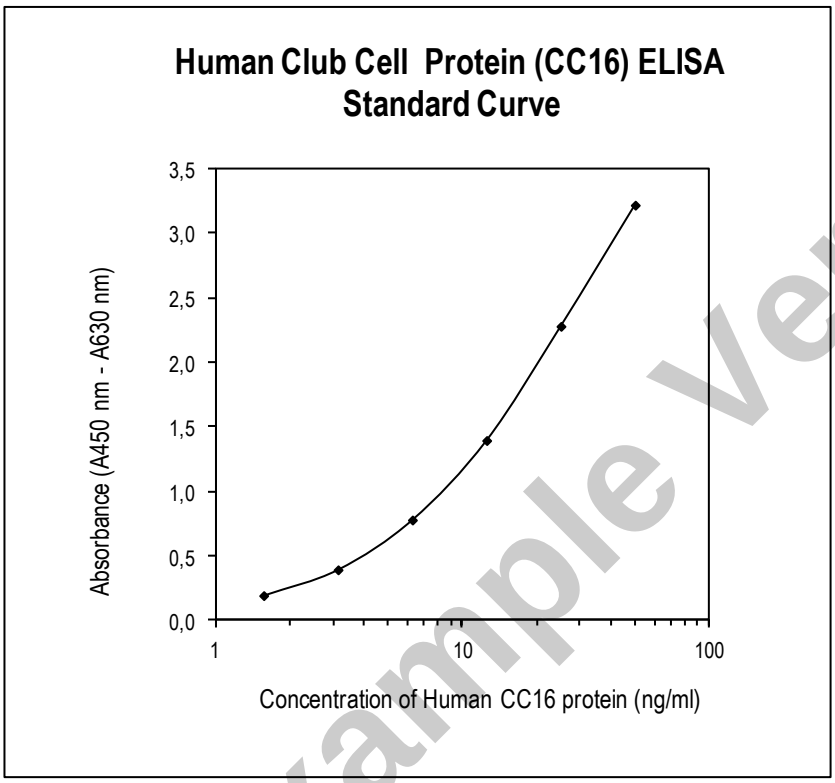

Figure 2: Typical Standard Curve for Human Club Cell Protein (CC16) ELISA.

13. PERFORMANCE CHARACTERISTICS

Typical analytical data of BioVendor Human Club Cell Protein (CC16) ELISA are presented in this chapter

Sensitivity

Limit of Detection (LOD), defined as concentration of analyte giving absorbance higher than mean absorbance of blank* plus three standard deviations of the absorbance of blank: $A_{blank} + 3xSD_{blank}$, is calculated from the real club cell protein values in wells and is 46 pg/ml.
*Dilution Buffer is pipetted into blank wells.

Limit of assay

Samples with absorbances exceeding the absorbance of the highest standard should be measured again with higher dilution. The final concentration of samples calculated from the standard curve must be multiplied by the respective dilution factor.

Specificity

The antibodies used in this ELISA are specific for human club cell protein with no detectable crossreactivities to the cytokines that may be present in human serum.
Determination of club cell protein does not interfere with hemoglobin (1.0 mg/ml), bilirubin (170 µmol/l) and triglycerides (5.0 mmol/l).

Sera of several mammalian species were measured in the assay. See results below.
For details please contact us at info@biovendor.com.

Mammalian serum sample	Observed crossreactivity
Bovine	no
Cat	no
Dog	no
Goat	no
Hamster	no
Horse	no
Monkey	yes
Mouse	yes
Pig	no
Rabbit	no
Rat	no
Sheep	no

Precision

Intra-assay (Within-Run) (n=8)

Sample	Mean (ng/ml)	SD (ng/ml)	CV (%)
1	14.28	0.55	3.82
2	5.31	0.16	2.96

Inter-assay (Run-to-Run) (n=4)

Sample	Mean (ng/ml)	SD (ng/ml)	CV (%)
1	5,37	0.22	4.09
2	7.75	0.49	6.36
3	16.59	0.63	3.78

Spiking Recovery

Serum samples were spiked with different amounts of human club cell protein, diluted with Dilution Buffer 25x and assayed.

Sample	Observed (ng/ml)	Expected (ng/ml)	Recovery O/E (%)
1	4.57	-	-
	7.36	7.7	95.6
	10.69	10.8	98.8
	17.37	17.1	101.8
2	6.36	-	-
	8.69	9.5	91.6
	12.28	12.6	97.4
	17.17	18.9	91.0

Linearity

Serum samples (diluted 25x with Dilution Buffer) were serially diluted with Dilution Buffer and assayed.

Sample	Dilution	Observed (ng/ml)	Expected (ng/ml)	Recovery O/E (%)
1	-	10.47	-	-
	2x	5.33	5.2	101.8
	4x	2.87	2.6	109.6
	8x	1.37	1.3	104.8
2	-	13.94	-	-
	2x	6.82	7.0	97.8
	4x	3.76	3.5	107.8
	8x	1.74	1.7	99.9

Effect of sample matrix

EDTA, citrate and heparin plasmas were compared to respective serum samples from the same 10 individuals. Results are shown below:

Volunteer No.	Serum (ng/ml)	Plasma (ng/ml)		
		EDTA	Citrate	Heparin
1	4.74	3.28	4.51	4.71
2	8.61	8.57	6.72	8.63
3	1.94	1.88	1.54	2.02
4	9.06	8.28	6.88	8.56
5	8.24	9.96	7.58	8.67
6	4.77	4.80	4.83	4.53
7	5.87	5.56	4.86	5.93
8	3.95	3.81	3.08	3.76
9	4.08	3.75	3.19	4.06
10	6.49	6.07	5.18	5.91
Mean (ng/ml)	**5.77**	**5.60**	**4.84**	**5.68**
Mean Plasma/Serum (%)	**-**	**96.9**	**83.8**	**98.3**
Coefficient of determination R^2		**0.91**	**0.93**	**0.98**

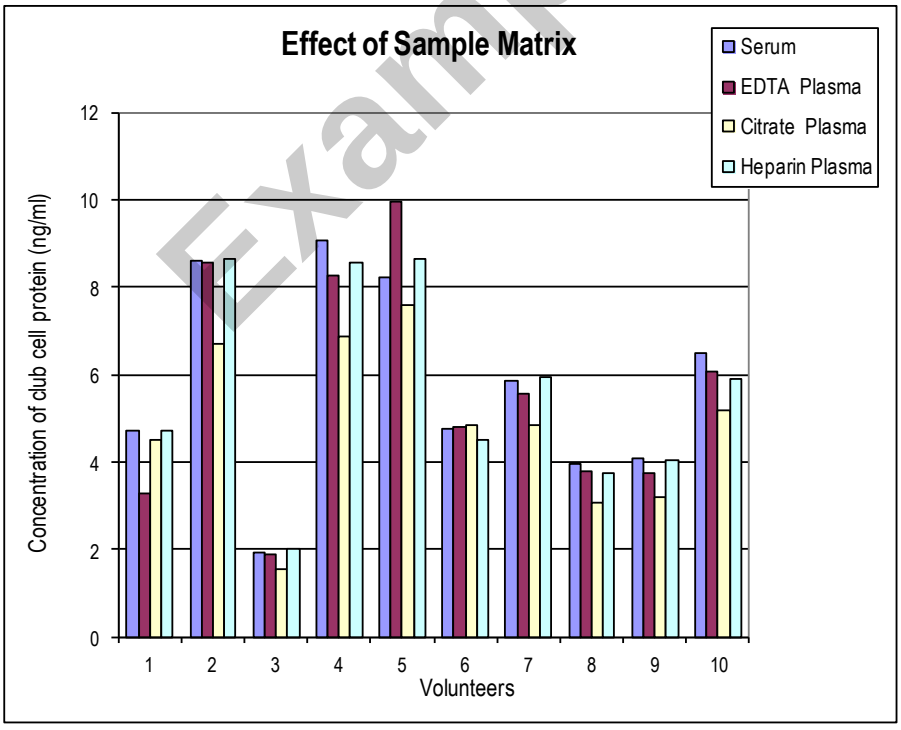

Figure 3: Human club cell protein levels measured using Human Club Cell Protein (CC16) ELISA from 10 individuals using serum, EDTA, citrate and heparin plasma, respectively.

Stability of samples stored at 2-8°C

Samples should be stored at –20°C. However, no decline in concentration of club cell protein was observed in serum and plasma samples after 7 days when stored at 2-8°C. To avoid microbial contamination, samples were treated with ε-aminocaproic acid and sodium azide, resulting in the final concentration of 0.03% and 0.1%, respectively.

Effect of Freezing/Thawing

No decline was observed in concentration of human club cell protein in serum and plasma samples after repeated (3x) freeze/thaw cycles. However it is recommended to avoid unnecessary repeated freezing/thawing of the samples.

14. DEFINITION OF THE STANDARD

The recombinant protein produced in E. coli is used as the Master Standard in this assay. The club cell protein is a 9.2 kDa protein consisting of 80 amino acids.

15. PRELIMINARY POPULATION AND CLINICAL DATA

The following results were obtained when serum samples from 55 unselected donors (34 men + 21 women) 22 - 61 years old were assayed with the Biovendor Human Club Cell Protein (CC16) ELISA in our laboratory:

Age and Sex dependent distribution of human club cell protein

Sex	Age	n	Mean	SD	Min	Max	Median
	years				ng/ml		
Men	20-39	18	6.4	1.9	3.7	9.4	6.2
	40-69	16	7.1	2.8	4.2	14.9	6.4
Women	20-39	12	7.3	2.3	3.6	11.1	7.4
	40-69	9	9.5	4.1	4.5	17.1	8.5

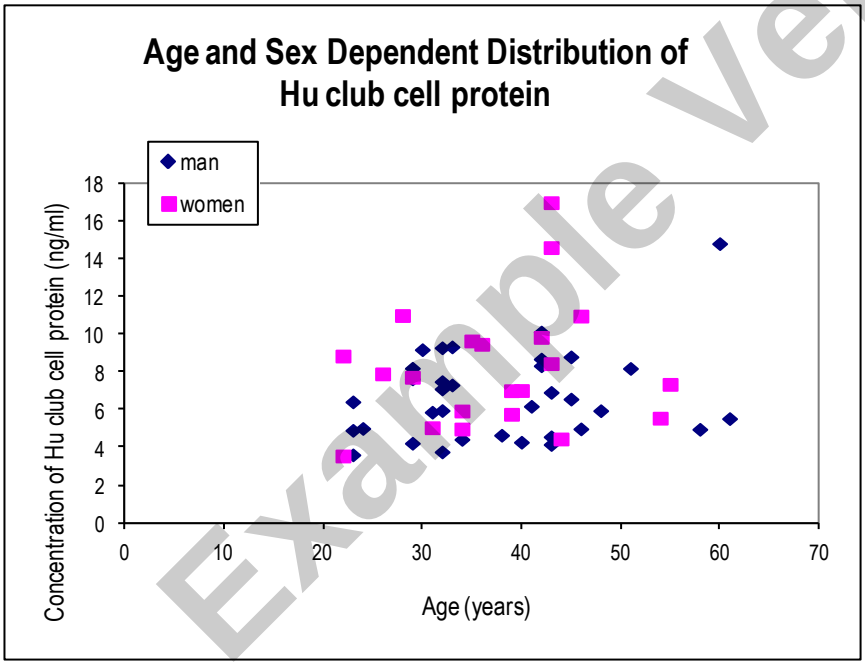

Figure 4: Human club cell protein concentration plotted against donor age and sex.

Typical distribution of club cell protein in various body fluids

Sample	Mean (ng/ml)	Range (ng/ml)
Serum	12.6	3.7 – 23.2
Urine	18.7	0.2 – 88.6
Seminal fluid	1 030.0	145 – 8 600
BAL	1 360.0	154 – 4 300
Synovial fluid	9.1	2.8 – 16.4
Pleural fluid	11.4	0.7 – 32.8
Cerebrospinal fluid	0.5	0 – 5.7
Gastric juice	185.0	0 – 1 220
Bile	0.7	0 – 2.3

Concentrations of club cell protein are expressed as ng/ml. See for details:

Shijubo N., Kawabata I., Sato N., Itoh Y.: Clinical Aspects of Clara Cell 10-kDa Protein/ Uteroglobin (Secretoglobin 1A1), Current Pharmaceutical Design, 9, 1139-1149, (2003)

Reference range

It is recommended that each laboratory include its own panel of control sample in the assay. Each laboratory should establish its own normal and pathological reference ranges for club cell protein levels with the assay.

16. METHOD COMPARISON

The BioVendor's Human Club Cell Protein (CC16) ELISA was compared to the previous version of the ELISA. The following correlation graph was obtained.

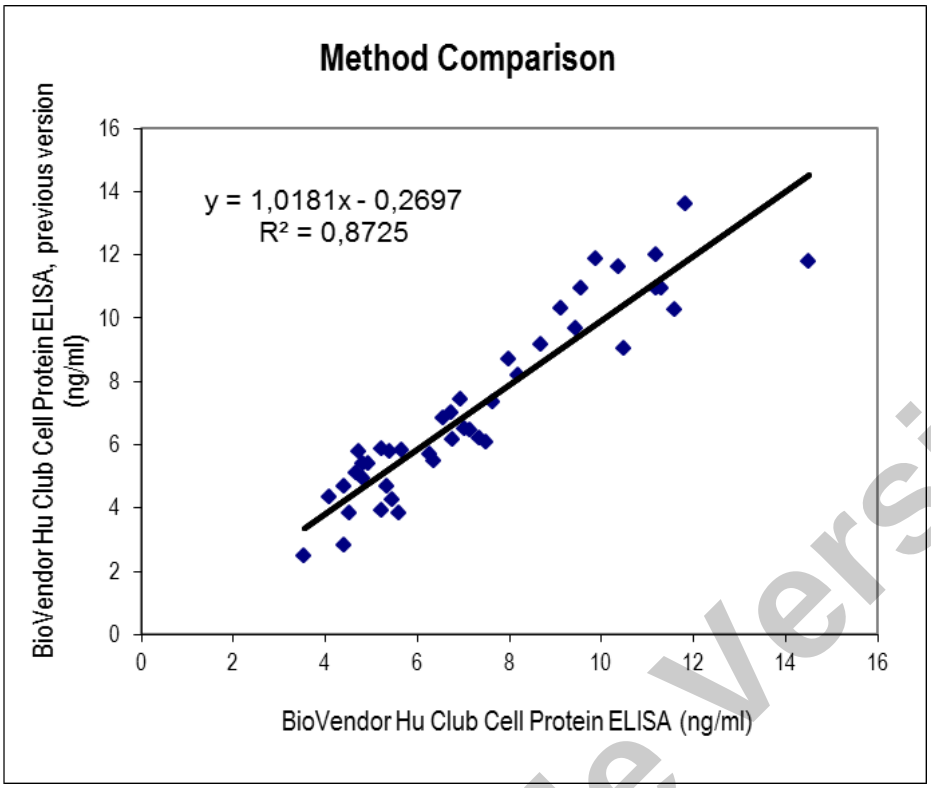

Figure 5: Method comparison

17. TROUBLESHOOTING AND FAQS

Weak signal in all wells
Possible explanations:
- Omission of a reagent or a step
- Improper preparation or storage of a reagent
- Assay performed before reagents were allowed to come to room temperature
- Improper wavelength when reading absorbance

High signal and background in all wells
Possible explanations:
- Improper or inadequate washing
- Overdeveloping; incubation time with Substrate Solution should be decreased before addition of Stop Solution
- Incubation temperature over 30°C

High coefficient of variation (CV)
Possible explanation:
- Improper or inadequate washing
- Improper mixing Standards, Quality Controls or samples

18. REFERENCES

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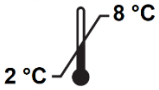
For more references on this product see our web pages at www.biovendor.com.

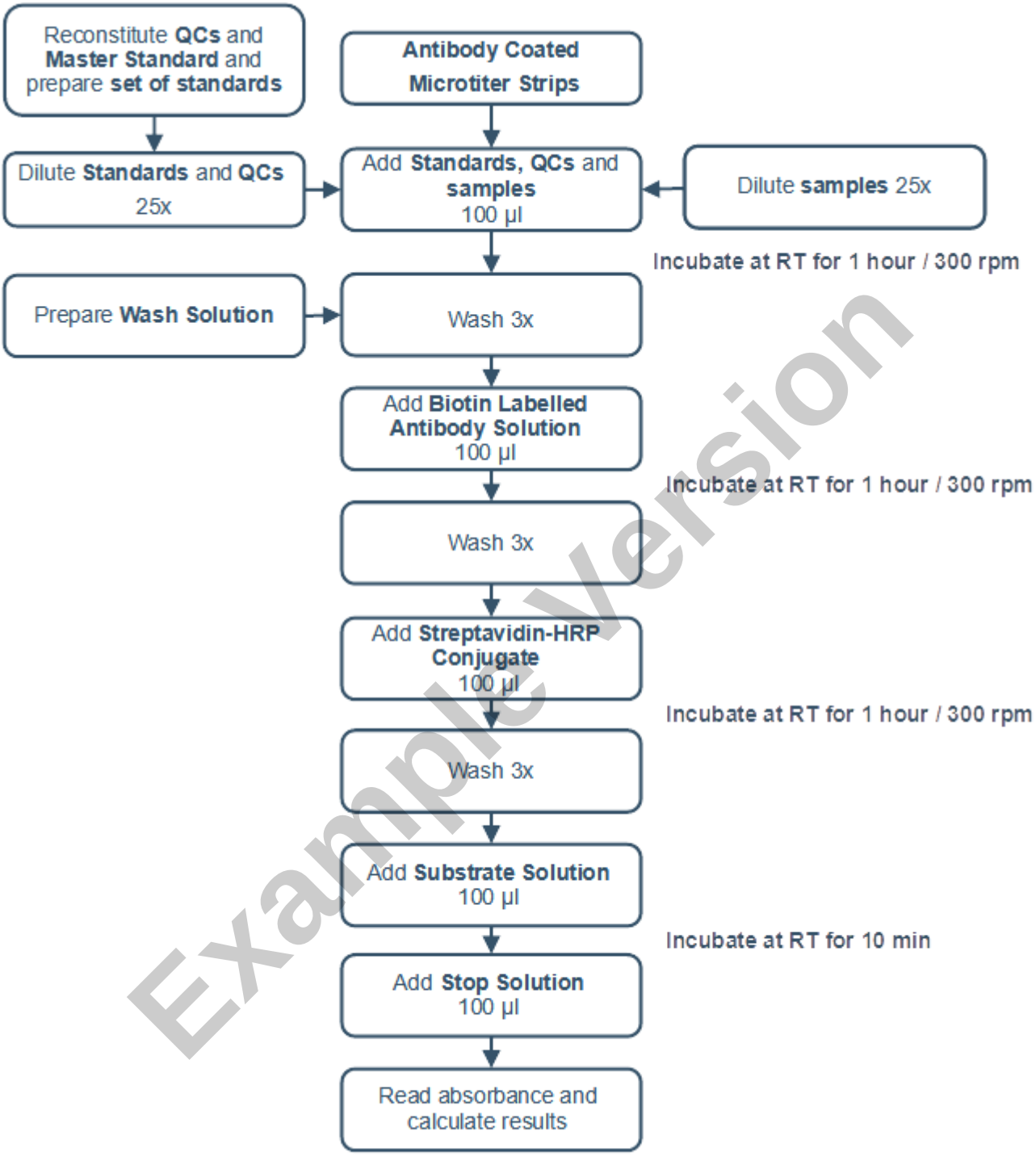
19. ADDITIONAL INFORMATION

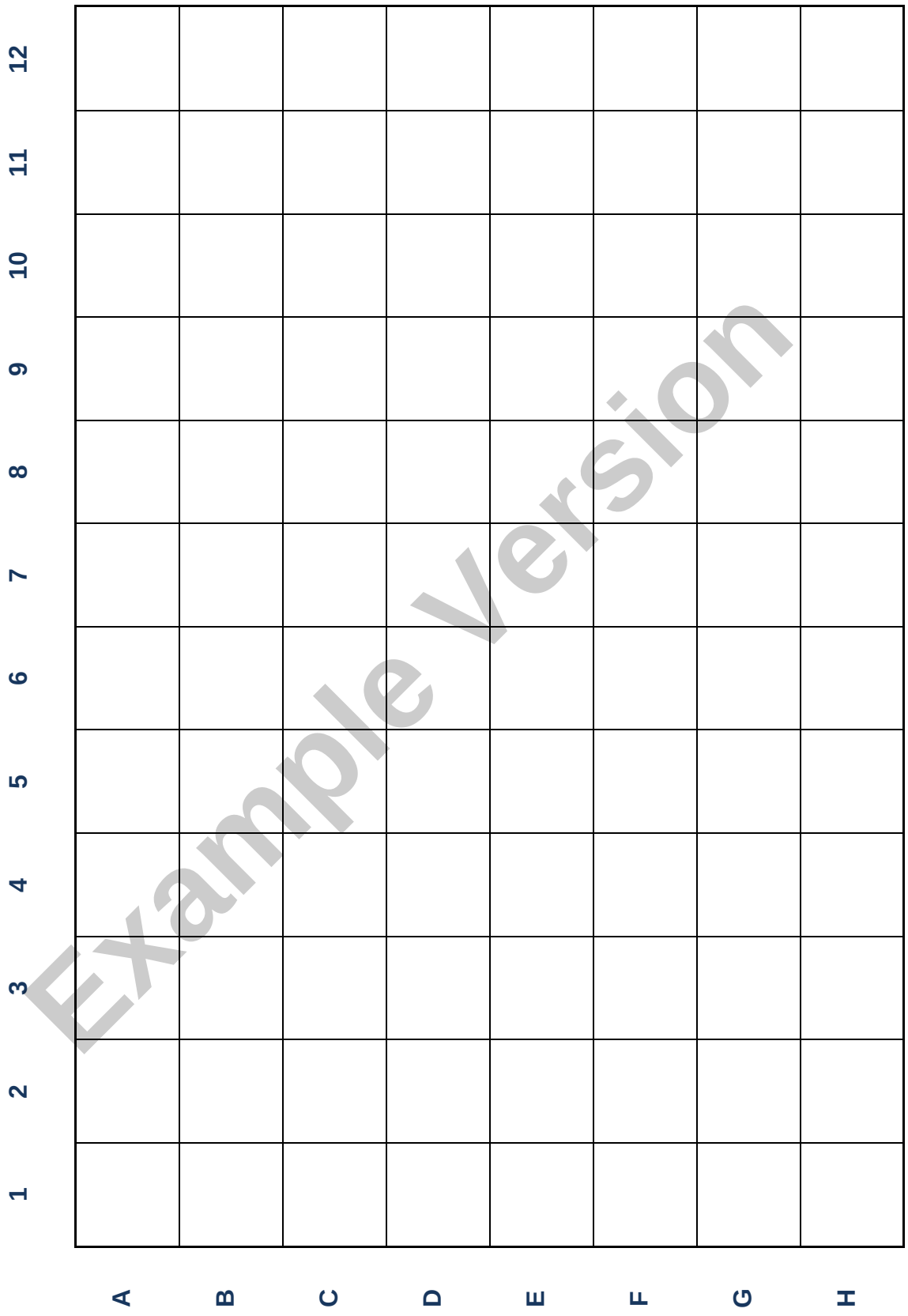
Any serious incident occurring in connection with the device must be reported to the manufacturer and to the competent authority of the Member State in which the user or patient is located.

20. EXPLANATION OF SYMBOLS

	Catalogue number
	Batch code
	Caution
	Use by date
	Temperature limit
	Manufacturer
	Read electronic instructions for use - eIFU
	The content is sufficient for 96 tests
	Biological risks
	In vitro diagnostic medical device
	CE marking of conformity

21. ASSAY PROCEDURE - SUMMARY





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