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CE IVD

EN

INSTRUCTIONS FOR USE

Reagents for professional use,
for *In Vitro* use only in clinical laboratory (IVD)

3diag - IgD - TIA

IgD Immunoglobulins
for Turbidimetry
REF TD-42651

INTENDED USE

Quantitative determination of IgD Immunoglobulins (IgD), in human serum, by turbidimetric method, in automatic Clinical Chemistry Analyzers.

The measurement of IgD can be used as an aid in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.

Assay results should always be used and interpreted in conjunction with clinical history and clinical manifestations, and other In Vitro and In Vivo diagnostic tests.

Do not make a diagnosis or decide on a treatment based solely on the assay results.

SUMMARY AND EXPLANATION[1]

Most of the IgD Immunoglobulins are bound to the membrane of circulating B lymphocytes and are the main antigen receptor on the membrane surface, where it is co-expressed with IgM.

Serum IgD represent only about 0.25% of the total immunoglobulins, are monomeric, and have a molecular weight of approximately 185 KDa, a half-life in serum of about 2.8 days and a daily renewal rate of 37 %.

Its concentration in serum is highly variable and does not follow a Gaussian distribution pattern. IgD can be also found in some other body fluids, such as the colostrum, milk and respiratory mucous.

Although in recent years there has been significant progress in clarifying the role of cellular IgD in the immune system, the role of secreted IgD is still uncertain.

Very high serum IgD concentrations are often found in patients with IgD monoclonal gammopathies.

The so-called Hyperimmunoglobulinemia D Syndrome (HIDS), or Hyper IgD Syndrome, a disease characterized by episodes of periodic fever and other affections, is another entity in which the IgD concentration is raised.

Elevation of serum IgD can also be seen in chronic infections (such as leprosy, tuberculosis, salmonellosis, infectious hepatitis, and malaria), in recurrent infections by staphylococci, in autoimmune diseases (such as rheumatoid arthritis or systemic lupus), in immunodeficiencies (such as AIDS) and allergic disorders, although the clinical relevance of this increase is not yet clear.

PRINCIPLE OF THE METHOD

The specific antibodies (Ab) of the reagent, bound to polystyrene particles, when combined with the antigens (Ag) of the patient sample, form insoluble compounds causing a change in the absorbance and dispersion of the light, proportional to the antigen concentration, which can be quantified by turbidimetric (TIA) or nephelometric (NIA) method, by comparison with calibrators of known concentration.

CONTENTS - COMPOSITION - PREPARATION

- Antiserum Reagent: **REAG | Ab | IgD**
  REF TD-42651-RA ▽100 test - 8.0 ml
  Anti-human IgD antibodies, bound to polystyrene particles.
- Reaction Buffer: **BUF | IgD**
  REF TD-42651-BF ▽100 test - 20 ml
  TRIS Buffer, with PEG.

As preservative, the reagents contain <0.1% (1 g/l) Sodium Azide (NaN_3).

The reagents are ready for use and require no preparation.

Before each use it is convenient that the reagents are homogenized, shaking them gently avoiding the formation of foam or bubbles.

If necessary, carefully transfer the reagents to the containers used by the analyzer, preventing leakage and foaming or bubbles.

Before use, it is always advisable to bring the reagents to their use temperature, waiting a while before using them.

WARNINGS - PRECAUTIONS

- Sodium Azide is toxic. Even if sodium azide is not harmful at the concentration present in the reagents, take the necessary precautions to avoid accidental ingestion or contact with the eyes.
- Sodium Azide can react with lead or copper to give explosive compounds. For disposal it is recommended to rinse with plenty of running water to avoid accumulation in drains.
- Materials of human origin have been tested and found negative for the presence of HBsAg, HCV, and anti-HIV 1 and 2 antibodies.
- Since the absence of infectious agents can not be proven with absolute certainty, components containing materials of human or animal origin must be handled with caution, as potentially infectious, following the recommended safety standards for biological risk.
- Dispose of contents, containers and any other waste material in accordance with applicable local, regional and national regulations.
- There are Safety Data Sheets (SDS) available in the *Documentation* section (select folders *## Other-Documents ##* and *SDS* - https://www.3diag.com/SDS) of the website (www.3diag.com) or upon request to the Customer Support Service (✉ support@3diag.com - ☎ +34 93 2448679).
- Do not use any material after its expiration date.
- Do not mix components belonging to different lot kits.
- Clinical diagnosis should not be based on the results of a single test, but should always integrate all relevant clinical and laboratory data.
- Any serious incident that has occurred in relation to the device shall be reported by the user to the manufacturer and to the competent authority of the Member State in which the user and/or the patient is established[2].

STORAGE - SHELF LIFE

- Store refrigerated at +2...+8ºC. Do not freeze, as the functionality of the reagents may be altered.
- Properly stored and unopened, the reagents are stable until the expiration date indicated on the label.
- Once opened, provided that they are handled with adequate precautions to avoid contamination, the shelf life of the reagents is at least 4 weeks, provided that after each use they are stored immediately in the original containers, tightly capped and refrigerated at +2...+8ºC.

The indicated shelf life must be taken as a guideline given that, obviously, it depends on the particular environmental and use conditions, which may differ from those of the stability studies carried out.

MATERIALS NEEDED, NOT SUPPLIED

- Automatic Clinical Chemistry Analyzer, capable of running photometric assays at 600…700 nm, and accessories: reagent containers, cuvettes, etc..
- 3diag - IgD - CAL SET — REF TD-42642
- 3diag - IgD - CONTROL — REF TD-42643

SAMPLES

Fresh Serum.

Samples with presence of fibrin, hemolyzed, lipemic or turbid, and frozen samples after thawing, should be centrifuged prior to testing. Samples, which cannot be clarified by centrifugation, should not be used in turbidimetric or nephelometric assays as turbidity and particles can interfere with the determination.

In bibliography[3] a stability of 28 days in refrigerated serum (preferred sample) is reported.

Specific guidelines[4] establish that it is the responsibility of each laboratory to consult all available references or to carry out its own studies to determine its specific stability criteria.

For transport, specimens must be packaged and labeled in accordance with applicable regulations and recommendations governing the transport of clinical specimens and potentially infectious substances.

PROCEDURE

To program and calibrate assays, follow the instructions for use of the analyzer used, with the recommended general parameters that are detailed below.

Further information about applications to specific analyzers can be found in the *Documentation* section (select folders *IgD* and ~~ *Applications* ~~ - https://www.3diag.com/A08) of the website (www.3diag.com), or upon request to the Customer Support Service (✉ support@3diag.com - ☎ +34 93 2448679).

Assay Parameters

- ①Dispense and mix:
  - Sample/Control: 6 µl (diluted 1:10)
  - Calibrator: 6 µl (diluted 1:5)
  - BUF | IgD 200 µl
- ②Incubate a fixed time of about 5 minutes
- ③Dispense and mix:
  - REAG | Ab | IgD 80 µl
- ④Read absorbance A1 (Blank) at 600…700 nm
- ⑤Incubate a fixed time of about 5 minutes
- ⑥Read absorbance A2 (End Point) at 600…700 nm
- ⑦Interpolate the absorbance increment (A2-A1) of the samples and controls in the curve obtained with the calibrators

Warnings - Results

Samples with concentrations higher than the upper limit of the assay range should be analyzed again, manually diluted with Physiological Solution in successive steps of 1:5 (recommended), or by programming a larger sample dilution in the analyzer, to recover a value close to the midpoint of the measurement range.

The stability of the dilutions is limited to their immediate use.

Calibration Parameters

- Use the 3diag - IgD - CAL SET.
- If the analyzer allows it, it is recommended to program two replicates of each calibration point.
- The calibrations are Non-linear. For the calculation it is recommended to use a Spline, a Logit or a Polygonal adjustment.

Warnings - Calibration

The calibration curves have a limited validity, which depends on the particular conditions of use.

The assay should be recalibrated:

- when a new lot of reagents, buffer, or diluent is used,
- when established internal quality control procedures do not deliver the expected results, or
- after performing maintenance operations on the analyzer.

PERFORMANCES OF THE METHOD

Detailed information on the characteristics and performances of assays is given in the Technical Reports, available in the *Documentation* section (select folders *IgD* and *Technical Reports* - https://www.3diag.com/T08) of the website (www.3diag.com) or upon request to the Customer Support Service (✉ support@3diag.com - ☎ +34 93 244 86 79).

The reported data are typical results and should not be considered as assay specifications, as the results obtained on another analyzer or at another time may be different.

Warnings - Antigen Excess

The IgD Immunoglobulins (IgD) of the sample, especially if they are monoclonal, can react in a way that is not proportional to the calibration (lack of linearity), just as it happens in the immunochemical quantification of other monoclonal immunoglobulins.

Although the measurement assay does not enter into antigen excess up to very high concentrations of IgD, as a precaution it is recommended to analyze the samples of patients who, due to their history, clinical data or other laboratory results, are suspected of having extreme values of IgD, or a non-proportional reaction, at two dilutions, the usual working one and prediluded manually (for example 1:10). A recovered result of the prediluted sample significantly higher than the working dilution result is indicative of an eventual excess of antigen or non-linearity, and should be taken as a more reliable result. In order to obtain a result as accurate as possible, it is recommended to dilute the sample by the necessary factor in order to recover a value close to the midpoint of the measurement range.

The use of complementary assays, for example the determination of the Free Light Chains in serum and urine, the determination of other immunoglobulins, or electrophoretic assays, can be a useful alarm signal in case of obtaining discordant results.

QUALITY CONTROL

To monitor performances, it is recommended to use the controls of the 3diag - IgD - CONTROL.

The insertion of internal controls is recommended:

- in each analytical series,
- when using a new reagent kit from the same lot, and
- after performing a calibration.

Each laboratory should establish its own quality scheme and corrective actions if controls do not meet the assigned tolerances, based on the applicable government regulations, the homologation requirements, and the general published recommendations, such as the guideline C24[5] of the *Clinical and laboratory Standards Institute* (*CLSI*), or others.

The reagents have been subjected to quality control checks and should react as described in these instructions. Therefore, as a general recommendation, in the event that controls do not give the expected results, the following should be done:

- repeat controls,
- if the deviation persists, repeat with new controls,
- if the deviation persists, calibrate again, and
- if the deviation persists, contact the Customer Support Service (✉ support@3diag.com - ☎ +34 93 2448679), or fill the *Technical Support Form* in the *Technical Support* section of the website (www.3diag.com).

As a precaution, until the causes of the deviation have been identified and corrected:

- all reagents should be considered unreliable, and
- sample results should not be validated.

Warnings

In some analyzers, in order to process the controls, it may be necessary to deactivate the clot detection system.

TRACEABILITY

Values in U/ml are referred to the *British Research Standard for IgD* (code: *67/037*) (*National Institute for Biological Standards and Controls* (a *World Health Organization* (*WHO*) *Laboratory for Biological Standards*), *NIBSC*)[6][7].

For the values in mg/dl, since certified reference materials are not available in these units, the conversion factor related in the literature[1] has been taken: 100 U/ml ≈ 14.1 mg/dl

REFERENCE INTERVALS

It is always advisable for each laboratory to establish its own reference values.

The bibliography reports variable reference values between publications, depending on the method and the standardization used, and the population analyzed:

- up to 15 mg/dl[8],
- 0.02 - 12.1 mg/dl[9],
- 1.4 - 8.5 mg/dl[10],
- 1.0 - 11.2 mg/dl[11],
- 0.5 - 24 mg/dl[12],
- up to 10 mg/dl[13],
- 0.77 - 13.21 mg/dl[14][15], and
- 0.13 - 15.27 mg/dl[16].

Based on the above data, a concentration higher than about 100 U/ml, equivalent to about 14 mg/dl, can be taken as a significant value. Analyzing serum samples of 20 presumably healthy adults from the Barcelona area, all results except one were lower than this concentration (range: <0.1 - 16.7 mg/dl).

LIMITATIONS OF THE PROCEDURE

- Samples containing circulating immune complexes (CICs) / heterophilic antibodies can lead to erroneously increased or decreased results in immunoassays. Unexpected or inconsistent results should be confirmed using alternative methods.
- The product must be used as described in these instructions by suitably trained personnel. Any modification made to the assay and its necessary validation is the sole responsibility of the user.
- Samples from internal quality controls other than the recommended one, or from external quality controls, may give different results than those obtained by other methods, due to matrix effects. To evaluate the results it may be necessary to establish specific target values for the method.
- It is well known that immunochemical assays are not suitable for the measurement of paraproteins, due to the possibility of a non-linear response and therefore lack of accuracy and inconsistent results. Furthermore, an immunochemical measurement cannot distinguish between monoclonal and polyclonal proteins. IgD concentration can never be considered as a measure of the monoclonal component.

SYMBOLS

In addition to the harmonized symbols provided on the ISO 15223-1:2021[17] norm, in the labels and instructions of use has been used the complementary symbology proposed[18] by the *EDMA* (*European Diagnostic Manufacturers Association*), whose meaning is detailed below.

REAG	Reagent
Ab	Antibody / Antiserum
BUF	Buffer
IgD	IgD Immunoglobulins

BIBLIOGRAPHY

(1) A.O. Vladutiu: "*MINIREVIEW - Immunoglobulin D: Properties, Measurement, and Clinical Relevance*" - Clin Diagn Lab Immunol 2000 March; 7(2): 131-140.

(2) "*Regulation (UE) 2017/746 of the European Parliament and of the Council* on In Vitro Diagnostic Medical Devices ", 5 April 2017.

(3) *Mayo Medical Laboratories* website (www.mayomedicallaboratories.com), date of consultation: 24th November 2019.

(4) Clinical and Laboratory Standards Institute (CLSI), Doc. GP44-A4, May 2010: "*Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Test; Approved Guideline - Fourth Edition*".

(5) Clinical and Laboratory Standards Institute (CLSI), September 2016: "C24 - *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions - 4th Edition*".

(6) D.S. Rowe, S.G. Anderson and L. Tackett: "*A research standard for human serum immunoglobulin D*" - Bull World Health Organ. 1970; 43(4): 607-609.

(7) National institute for Biological Standards and Control: "*Non WHO Reference Material - Immunoglobulin D (IgD) Serum, Human - NIBSC code 67/037 - Instructions for Use (Version 5.0, Dated 04/04/2008)*".

(8) *"AEFA/AEBM Nomenclator de Laboratorio Clínico"* (*ISBN*: 84-486-0117-3).

(9) V. Fayol, D.J. Hartmann, I. Sabbagh, and G. Ville: "*Dosage radioimmunologique de l'IgD sérique*" - C. R. Soc. Biol. 1986; 180: 337-346.

(10) S. Sirisinha, C. Charupatana, and T. Ramasoota: "*Serum immunoglobulins in leprosy patients with different spectra of clinical manifestations*" - Proc. Soc. Exp. Biol. Med. 1972; 140: 1062-1068.

(11) R.H. Buckley, and H.R. Trayer: "*Serum IgD concentrations in sarcoidosis and tuberculosis*" - Clin. Exp. Immunol. 1972; 10: 257-265.

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(13) J.P. Barreto, G. Martins et al.: "*Immunoglobulin D measurement by two different immunoassays*" - 13ª Reunião Cientí fica da SPML. 2021; P44

(14) The Binding Site Group Ltd.: "*Human IgD Kit for use on SPAplus® (Insert Code: SIN169, Version 01st September 2014)*".

(15) The Binding Site Group Ltd.: "*Optilite® IgD Kit (Insert Code: INS013, Version 15th October 2014)*".

(16) The Binding Site Group Ltd.: "*Human IgD Liquid Reagent Kits for use on the Siemens BN™II (Insert Code: SIN088, Version 27th November 2012)*".

(17) International Organization for Standardization: "*ISO 15223-1:2021 Medical devices - Symbols to be used with information to be supplied by the manufacturer*".

(18) EDMA Labelling Task Force: "*EDMA Symbols for IVD Reagents and Components - Revision, October 2009*".

TEXT REVISION DATE

14th September 2021.

Modifications highlighted in blue .

Due to the continuous process of monitoring and improvement of the performance and safety of the products, the Instructions for Use are periodically updated. Therefore, users must ensure that they are working with the appropriate revision.

To facilitate this task, an electronic version of the Instructions for Use specific to each batch of the product is available in the *Documentation* section of the *TRIMERO Diagnostics* website (www.3diag.com), which the user can access by selecting the family and product type, or using the *Search by batch* option. Additionally, a QR code and a link to the appropriate folder are provided on the external labels and documentation accompanying the product.

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CE IVD

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INSTRUCTIONS FOR USE

Reagents for professional use,
for *In Vitro* use only in clinical laboratory (IVD)

3diag - IgD - CAL SET

IgD Immunoglobulins
Calibrators (6 lev.)
REF **TD-42642**
(Product included in REF TD-42640, and TD-42655)

INTENDED USE

Elaboration of the calibration curve for the quantitative determination of IgD Immunoglobulins (IgD), in human serum, by immunochemical methods, with *TRIMERO Diagnostics*' reagents.

PRINCIPLE OF THE METHOD

The specific antibodies (Ab) of the reagent, bound to polystyrene particles, when combined with the antigens (Ag) of the patient sample, form insoluble compounds causing a change in the absorbance and dispersion of the light, proportional to the antigen concentration, which can be quantified by turbidimetric (TIA) or nephelometric (NIA) method, by comparison with calibrators of known concentration.

CONTENTS - COMPOSITION - PREPARATION

• Calibrator Level 1:	CAL 1 IgD	
REF TD-42642-1	CONT	1 ml
• Calibrator Level 2:	CAL 2 IgD	
REF TD-42642-2	CONT	1 ml
• Calibrator Level 3:	CAL 3 IgD	
REF TD-42642-3	CONT	1 ml
• Calibrator Level 4:	CAL 4 IgD	
REF TD-42642-4	CONT	1 ml
• Calibrator Level 5:	CAL 5 IgD	
REF TD-42642-5	CONT	1 ml
• Calibrator Level 6:	CAL 6 IgD	
REF TD-42642-6	CONT	1 ml

The calibrators are human serum solutions, delipidated, filtered by 0.2 µm.
As preservatives, the calibrators contain <0.1% (1 g/l) Sodium Azide (NaN_3), <0.02% (0.2 g/l) Methylisothiazolone and <0.02% (0.2 g/l) Bromonitrodioxane.
The calibrators are ready for use and require no preparation.
Before each use it is convenient that the calibrators are homogenized, shaking them gently avoiding the formation of foam or bubbles.
The values of the calibrators are lot dependent and are indicated in the table of values of their Instructions for Use.
If necessary, carefully transfer the calibrators to the sample cups used by the analyzer, preventing foaming or bubbles.
Before use, it is always advisable to bring the calibrators to their use temperature, waiting a while before using them.

WARNINGS - PRECAUTIONS

- Sodium Azide is toxic. Even if at the concentrations present neither Sodium Azide nor the other preservatives are harmful, take the necessary precautions to avoid accidental ingestion or contact with the eyes.
- Sodium Azide can react with lead or copper to give explosive compounds. For disposal it is recommended to rinse with plenty of running water to avoid accumulation in drains.
- Materials of human origin have been tested and found negative for the presence of HBsAg, HCV, and anti-HIV 1 and 2 antibodies.
- Since the absence of infectious agents can not be proven with absolute certainty, components containing materials of human or animal origin must be handled with caution, as potentially infectious, following the recommended safety standards for biological risk.
- Dispose of contents, containers and any other waste material in accordance with applicable local, regional and national regulations.
- There are Safety Data Sheets (SDS) available in the *Documentation* section (select folders *## Other-Documents ##* and *SDS* - https://www.3diag.com/SDS) of the website (www.3diag.com) or upon request to the Customer Support Service (support@3diag.com - ☎ +34 93 2448679).
- Do not use any material after its expiration date.
- Do not mix components belonging to different lot kits.
- Clinical diagnosis should not be based on the results of a single test, but should always integrate all relevant clinical and laboratory data.
- Any serious incident that has occurred in relation to the device shall be reported by the user to the manufacturer and to the competent authority of the Member State in which the user and/or the patient is established[(1)].

STORAGE - SHELF LIFE

- Store refrigerated at +2...+8ºC. Do not freeze, as the functionality of the calibrators may be altered.
- Properly stored and unopened, the calibrators are stable until the expiration date indicated on the label.
- Once opened, provided that they are handled with adequate precautions to avoid contamination, the shelf life of the calibrators is at least 4 weeks, provided that after each use they are stored immediately in the original containers, tightly capped and refrigerated at +2...+8ºC.
  The indicated shelf life must be taken as a guideline given that, obviously, it depends on the particular environmental and use conditions, which may differ from those of the stability studies carried out.
- In unsuitable storage conditions, for example with sudden or frequent changes in temperature or in case of freezing, a non-specific precipitate or turbidity may form in the calibrators, which is not due to microbial contamination. Although the performance of the product should not be affected, if the quality controls do not give the expected results, it is recommended to discard the affected unit.

MATERIALS NEEDED, NOT SUPPLIED

The calibrators are intended to be used in conjunction with the Reagents and Controls:

• 3diag - IgD - 800	REF TD-42641
• 3diag - IgD - TIA	REF TD-42651
• 3diag - IgD - CONTROL	REF TD-42643

PROCEDURE

To program and calibrate assays, follow the Instructions for Use of the analyzer used, with the recommended general parameters that are detailed in the Instructions for Use of the Reagents.
Further information on the intended use, materials, samples, procedure, performance and reference intervals of the assays is provided in the Instructions for Use of the Reagents.

Calibration Parameters

- Use the **3diag - IgD - CAL SET**.
- If the analyzer allows it, it is recommended to program two replicates of each calibration point.
- The calibrations are Non-linear. For the calculation it is recommended to use a Spline, a Logit or a Polygonal adjustment.

Warnings - Calibration

In some analyzers, in order to process the calibrators it may be necessary to deactivate the clot detection system.

The calibration curves have a limited validity, which depends on the particular conditions of use.

The assay should be recalibrated:

- when a new lot of reagents, buffer, or diluent is used,
- when established internal quality control procedures do not deliver the expected results, or
- after performing maintenance operations on the analyzer.

QUALITY CONTROL

To monitor performances, it is recommended to use the controls of the **3diag - IgD - CONTROL**.

The insertion of internal controls is recommended:

- in each analytical series,
- when using a new reagent kit from the same lot, and
- after performing a calibration.

Each laboratory should establish its own quality scheme and corrective actions if controls do not meet the assigned tolerances, based on the applicable government regulations, the homologation requirements, and the general published recommendations, such as the guideline C24[(2)] of the *Clinical and laboratory Standards Institute* (*CLSI*), or others.

The reagents have been subjected to quality control checks and should react as described in these instructions. Therefore, as a general recommendation, in the event that controls do not give the expected results, the following should be done:

- repeat controls,
- if the deviation persists, repeat with new controls,
- if the deviation persists, calibrate again, and
- if the deviation persists, contact the Customer Support Service (✉ support@3diag.com - ☎ +34 93 2448679), or fill the *Technical Support Form* in the *Technical Support* section of the website (www.3diag.com).

As a precaution, until the causes of the deviation have been identified and corrected:

- all reagents should be considered unreliable, and
- sample results should not be validated.

Warnings

In some analyzers, in order to process the controls, it may be necessary to deactivate the clot detection system.

TRACEABILITY

Values in U/ml are referred to the *British Research Standard for IgD* (code: *67/037*) (*National Institute for Biological Standards and Controls* (a *World Health Organization* (*WHO*) *Laboratory for Biological Standards*), *NIBSC*)[(3)(4)].

For the values in mg/dl, since certified reference materials are not available in these units, the conversion factor related in the literature[(5)] has been taken: 100 U/ml ≈ 14.1 mg/dl

LIMITATIONS OF THE PROCEDURE

- Samples containing circulating immune complexes (CICs) / heterophilic antibodies can lead to erroneously increased or decreased results in immunoassays. Unexpected or inconsistent results should be confirmed using alternative methods.
- The product must be used as described in these instructions by suitably trained personnel. Any modification made to the assay and its necessary validation is the sole responsibility of the user.
- Samples from internal quality controls other than the recommended one, or from external quality controls, may give different results than those obtained by other methods, due to matrix effects. To evaluate the results it may be necessary to establish specific target values for the method.
- It is well known that immunochemical assays are not suitable for the measurement of paraproteins, due to the possibility of a non-linear response and therefore lack of accuracy and inconsistent results. Furthermore, an immunochemical measurement cannot distinguish between monoclonal and polyclonal proteins. IgD concentration can never be considered as a measure of the monoclonal component.

SYMBOLS

In addition to the harmonized symbols provided on the ISO 15223-1:2021[(6)] norm, in the labels and instructions of use has been used the complementary symbology proposed[(7)] by the *EDMA* (*European Diagnostic Manufacturers Association*), whose meaning is detailed below.

CAL	Calibrator
n	Level n (n=1..6)
IgD	IgD Immunoglobulins
CONT	Contents

BIBLIOGRAPHY

(1) "*Regulation (UE) 2017/746 of the European Parliament and of the Council* on In Vitro Diagnostic Medical Devices ", 5 April 2017.

(2) Clinical and Laboratory Standards Institute (CLSI), September 2016: "C24 - *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions - 4th Edition*".

(3) D.S. Rowe, S.G. Anderson and L. Tackett: "*A research standard for human serum immunoglobulin D*" - Bull World Health Organ. 1970; 43(4): 607-609.

(4) National institute for Biological Standards and Control: "*Non WHO Reference Material - Immunoglobulin D (IgD) Serum, Human - NIBSC code 67/037 - Instructions for Use (Version 5.0, Dated 04/04/2008)*".

(5) A.O. Vladutiu: "*MINIREVIEW - Immunoglobulin D: Properties, Measurement, and Clinical Relevance*" - Clin Diagn Lab Immunol 2000 March; 7(2): 131-140.

(6) International Organization for Standardization: "*ISO 15223-1:2021 Medical devices - Symbols to be used with information to be supplied by the manufacturer*".

(7) EDMA Labelling Task Force: "*EDMA Symbols for IVD Reagents and Components - Revision, October 2009*".

TEXT REVISION DATE

15th September 2021.

Modifications highlighted in blue.

Due to the continuous process of monitoring and improvement of the performance and safety of the products, the Instructions for Use are periodically updated. Therefore, users must ensure that they are working with the appropriate revision.

To facilitate this task, an electronic version of the Instructions for Use specific to each batch of the product is available in the *Documentation* section of the *TRIMERO Diagnostics* website (www.3diag.com), which the user can access by selecting the family and product type, or using the batch number finder. Additionally, a QR code and a link to the appropriate folder are provided on the external labels and documentation accompanying the product.

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CE IVD

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INSTRUCTIONS FOR USE

Reagents for professional use,
for *In Vitro* use only in clinical laboratory (IVD)

3diag - IgD - CONTROL

IgD Immunoglobulins
Controls (2 lev.)
REF **TD-42643**
(Product included in REF TD-42640, and TD-42655)

INTENDED USE

Internal controls, with assigned values, for the quantitative determination of IgD Immunoglobulins (IgD), in human serum, by immunochemical methods, with *TRIMERO Diagnostics*' reagents.

PRINCIPLE OF THE METHOD

The specific antibodies (Ab) of the reagent, bound to polystyrene particles, when combined with the antigens (Ag) of the patient sample, form insoluble compounds causing a change in the absorbance and dispersion of the light, proportional to the antigen concentration, which can be quantified by turbidimetric (TIA) or nephelometric (NIA) method, by comparison with calibrators of known concentration.

CONTENTS - COMPOSITION - PREPARATION

- High Control: CONTROL | H | IgD
  REF TD-42643-H — CONT 1 ml
- Low Control: CONTROL | L | IgD
  REF TD-42643-L — CONT 1 ml

The controls are human serum solutions, delipidated, filtered by 0.2 µm.
As preservatives, the controls contain <0.1% (1 g/l) Sodium Azide (NaN_3), <0.02% (0.2 g/l) Methylisothiazolone and <0.02% (0.2 g/l) Bromonitrodioxane.
The controls are ready for use and require no preparation.
Before each use it is convenient that the controls are homogenized, shaking them gently avoiding the formation of foam or bubbles.
The values of the controls are lot dependent and are indicated in the table of values of their Instructions for Use.
If necessary, carefully transfer the controls to the sample cups used by the analyzer, preventing foaming or bubbles.
Before use, it is always advisable to bring the controls to their use temperature, waiting a while before using them.

WARNINGS - PRECAUTIONS

- Sodium Azide is toxic. Even if at the concentrations present neither Sodium Azide nor the other preservatives are harmful, take the necessary precautions to avoid accidental ingestion or contact with the eyes.
- Sodium Azide can react with lead or copper to give explosive compounds. For disposal it is recommended to rinse with plenty of running water to avoid accumulation in drains.
- Materials of human origin have been tested and found negative for the presence of HBsAg, HCV, and anti-HIV 1 and 2 antibodies.
- Since the absence of infectious agents can not be proven with absolute certainty, components containing materials of human or animal origin must be handled with caution, as potentially infectious, following the recommended safety standards for biological risk.
- Dispose of contents, containers and any other waste material in accordance with applicable local, regional and national regulations.
- There are Safety Data Sheets (SDS) available in the *Documentation* section (select folders *## Other-Documents ##* and *SDS* - https://www.3diag.com/SDS) of the website (www.3diag.com) or upon request to the Customer Support Service (✉ support@3diag.com - ☎ +34 93 2448679).
- Do not use any material after its expiration date.
- Do not mix components belonging to different lot kits.
- Clinical diagnosis should not be based on the results of a single test, but should always integrate all relevant clinical and laboratory data.
- Any serious incident that has occurred in relation to the device shall be reported by the user to the manufacturer and to the competent authority of the Member State in which the user and/or the patient is established[1].

STORAGE - SHELF LIFE

- Store refrigerated at +2...+8ºC. Do not freeze, as the functionality of the controls may be altered.
- Properly stored and unopened, the controls are stable until the expiration date indicated on the label.
- Once opened, provided that they are handled with adequate precautions to avoid contamination, the shelf life of the controls is at least 4 weeks, provided that after each use they are stored immediately in the original containers, tightly capped and refrigerated at +2...+8ºC.
  The indicated shelf life must be taken as a guideline given that, obviously, it depends on the particular environmental and use conditions, which may differ from those of the stability studies carried out.
- In unsuitable storage conditions, for example with sudden or frequent changes in temperature or in case of freezing, a non-specific precipitate or turbidity may form in the controls, which is not due to microbial contamination. Although the performance of the product should not be affected, if the quality controls do not give the expected results, it is recommended to discard the affected unit.

MATERIALS NEEDED, NOT SUPPLIED

The controls are intended to be used in conjunction with the Reagents and Calibrators:

- 3diag - IgD - 800 — REF TD-42641
- 3diag - IgD - TIA — REF TD-42651
- 3diag - IgD - CAL SET — REF TD-42642

PROCEDURE - Calibration

To program and calibrate assays, follow the Instructions for Use of the analyzer used, with the recommended general parameters that are detailed in the Instructions for Use of the Reagents.
Further information on the intended use, materials, samples, procedure, performance and reference intervals of the assays is provided in the Instructions for Use of the Reagents.

Calibration Parameters

- Use the 3diag - IgD - CAL SET.
- If the analyzer allows it, it is recommended to program two replicates of each calibration point.
- The calibrations are Non-linear. For the calculation it is recommended to use a Spline, a Logit or a Polygonal adjustment.

Warnings - Calibration

In some analyzers, in order to process the calibrators it may be necessary to deactivate the clot detection system.

The calibration curves have a limited validity, which depends on the particular conditions of use.

The assay should be recalibrated:

- when a new lot of reagents, buffer, or diluent is used,
- when established internal quality control procedures do not deliver the expected results, or
- after performing maintenance operations on the analyzer.

QUALITY CONTROL

To monitor performances, it is recommended to use the controls of the **3diag - IgD - CONTROL**.

The insertion of internal controls is recommended:

- in each analytical series,
- when using a new reagent kit from the same lot, and
- after performing a calibration.

Each laboratory should establish its own quality scheme and corrective actions if controls do not meet the assigned tolerances, based on the applicable government regulations, the homologation requirements, and the general published recommendations, such as the guideline C24[(2)] of the *Clinical and laboratory Standards Institute* (*CLSI*), or others.

The reagents have been subjected to quality control checks and should react as described in these instructions. Therefore, as a general recommendation, in the event that controls do not give the expected results, the following should be done:

- repeat controls,
- if the deviation persists, repeat with new controls,
- if the deviation persists, calibrate again, and
- if the deviation persists, contact the Customer Support Service (✉ support@3diag.com - ☎ +34 93 2448679), or fill the *Technical Support Form* in the *Technical Support* section of the website (www.3diag.com).

As a precaution, until the causes of the deviation have been identified and corrected:

- all reagents should be considered unreliable, and
- sample results should not be validated.

Warnings

In some analyzers, in order to process the controls, it may be necessary to deactivate the clot detection system.

TRACEABILITY

Values in U/ml are referred to the *British Research Standard for IgD* (code: *67/037*) (*National Institute for Biological Standards and Controls* (a *World Health Organization* (*WHO*) *Laboratory for Biological Standards*), *NIBSC*)[(3)(4)].

For the values in mg/dl, since certified reference materials are not available in these units, the conversion factor related in the literature[(5)] has been taken: 100 U/ml ≈ 14.1 mg/dl

LIMITATIONS OF THE PROCEDURE

- Samples containing circulating immune complexes (CICs) / heterophilic antibodies can lead to erroneously increased or decreased results in immunoassays. Unexpected or inconsistent results should be confirmed using alternative methods.
- The product must be used as described in these instructions by suitably trained personnel. Any modification made to the assay and its necessary validation is the sole responsibility of the user.
- Samples from internal quality controls other than the recommended one, or from external quality controls, may give different results than those obtained by other methods, due to matrix effects. To evaluate the results it may be necessary to establish specific target values for the method.
- It is well known that immunochemical assays are not suitable for the measurement of paraproteins, due to the possibility of a non-linear response and therefore lack of accuracy and inconsistent results. Furthermore, an immunochemical measurement cannot distinguish between monoclonal and polyclonal proteins. IgD concentration can never be considered as a measure of the monoclonal component.

SYMBOLS

In addition to the harmonized symbols provided on the ISO 15223-1:2021[(6)] norm, in the labels and instructions of use has been used the complementary symbology proposed[(7)] by the *EDMA* (*European Diagnostic Manufacturers Association*), whose meaning is detailed below.

CONTROL	Control
H	High
L	Low
IgD	IgD Immunoglobulins
CONT	Contents

BIBLIOGRAPHY

(1) "*Regulation (UE) 2017/746 of the European Parliament and of the Council* on In Vitro Diagnostic Medical Devices ", 5 April 2017.

(2) Clinical and Laboratory Standards Institute (CLSI), September 2016: "C24 - *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions - 4th Edition*".

(3) D.S. Rowe, S.G. Anderson and L. Tackett: "*A research standard for human serum immunoglobulin D*" - Bull World Health Organ. 1970; 43(4): 607-609.

(4) National institute for Biological Standards and Control: "*Non WHO Reference Material - Immunoglobulin D (IgD) Serum, Human - NIBSC code 67/037 - Instructions for Use (Version 5.0, Dated 04/04/2008)*".

(5) A.O. Vladutiu: "*MINIREVIEW - Immunoglobulin D: Properties, Measurement, and Clinical Relevance*" - Clin Diagn Lab Immunol 2000 March; 7(2): 131-140.

(6) International Organization for Standardization: "*ISO 15223-1:2021 Medical devices - Symbols to be used with information to be supplied by the manufacturer*".

(7) EDMA Labelling Task Force: "*EDMA Symbols for IVD Reagents and Components - Revision, October 2009*".

TEXT REVISION DATE

15th September 2021.

Modifications highlighted in blue.

Due to the continuous process of monitoring and improvement of the performance and safety of the products, the Instructions for Use are periodically updated. Therefore, users must ensure that they are working with the appropriate revision.

To facilitate this task, an electronic version of the Instructions for Use specific to each batch of the product is available in the *Documentation* section of the *TRIMERO Diagnostics* website (www.3diag.com), which the user can access by selecting the family and product type, or using the batch number finder. Additionally, a QR code and a link to the appropriate folder are provided on the external labels and documentation accompanying the product.