ImmunoCAP™ Specific IgG4

Fluoroenzymeimmunoassay

Directions for Use 52-5716-EN/01

INTENDED USE

ImmunoCAP Specific IgG4 is an immunoassay for the quantitative measurement of allergen-specific IgG4 antibodies in human serum or plasma. It is intended for in vitro diagnostic use to assess IgG4 associated immune responses, as an aid to evaluate development of allergic tolerance in conjunction with other clinical findings. ImmunoCAP Specific IgG4 is to be used in clinical laboratories with the instruments Phadia 200, Phadia 250, Phadia 1000, Phadia 2500 or Phadia 5000.

SUMMARY AND EXPLANATION OF THE TEST

Measurements of specific IgG4 antibodies are commonly used for monitoring allergen immunotherapy (AIT) (1-8). Increased levels of allergen-specific IgG4 are generally seen after AIT (1, 9, 10). Several studies have indicated a role of allergen-specific IgG4 antibodies in the development of tolerance (1, 7, 11-13).

PRINCIPLE OF THE PROCEDURE

The allergen of interest, covalently coupled to ImmunoCAP, reacts with the specific IgG4 antibodies in the patient sample. After washing away non-specific IgG4, enzyme labeled antibodies against IgG4 are added to form a complex. Following incubation, unbound enzyme-anti-IgG4 is washed away and the bound complex is then incubated with a developing agent. After stopping the reaction, the fluorescence of the eluate is measured. The higher the response value, the more specific IgG4 is present in the sample. To evaluate the test results, the responses for the patient samples are transformed to concentrations with the use of a calibration curve.

REAGENTS AND MATERIAL

Reagents are packaged as described below, each purchased separately. The two-digit suffix (-xx) on the article number may vary between countries. All kits are not available in all countries.

The expiration date and storage temperature are stated on the labels. Do not use reagents beyond their expiration dates or if damaged or incorrectly stored.

Note: It is not recommended to pool any reagents.

Keep the ImmunoCAP carrier closed to avoid evaporation of buffer.

Reagents for Phadia 200

- **ImmunoCAP Specific IgG4 Conjugate 50** (Art No 10-9549-01: for 2 x 50 determinations)
- **ImmunoCAP Specific IgG Sample Diluent** (Art No 10-9542-01: 6 vials à 20.5 ml)
- **ImmunoCAP Specific IgG4 Calibrator Strip** (Art No 10-9550-01: for 1 calibration curve)
- **ImmunoCAP IgA/IgG Calibrator ImmunoCAP** (AGcal) (Art No 14-4424-01: carriers of 16 ImmunoCAP)
- **ImmunoCAP Specific IgG4 Curve Control Strip** (CC-1 and CC-2) (Art No 10-9551-01: for 1 x 3 sets of curve controls)
- **ImmunoCAP Allergen** (See Product catalogue: carriers of 16 or 10 ImmunoCAP)
- **Development Solution** (Art No 10-9441-01: for 6 x 200 determinations; Art No 10-9440-01: for 6 x 315 determinations)
- **Stop Solution** (Art No 10-9442-01: for 6 x 185 determinations; Art No 10-9479-01: for 6 x 100 determinations)
- **Washing Solution** (Art No 10-9422-01: 6 x 1 l)
  - Washing Solution Additive, 6 x 17.2 ml
  - Washing Solution Concentrate, 6 x 80 ml
- **Washing Solution** (Art No 10-9202-01: 2 x 5 l)
  - Washing Solution Additive, 2 x 86 ml
  - Washing Solution Concentrate, 2 x 400 ml
- **ImmunoCAP Specific IgG/IgG4 Control L** (Art No 10-9473-01: for 6 x 4 determinations)
- **ImmunoCAP Specific IgG/IgG4 i1 Control H** (Art No 10-9475-01: for 6 x 4 determinations)

Reagents for Phadia 250

- **ImmunoCAP Specific IgG4 Conjugate 50** (Art No 10-9549-01: for 2 x 50 determinations)
- **ImmunoCAP Specific IgA/IgG Sample Diluent** (Art No 10-9361-01: 6 vials à 50 ml)
- **ImmunoCAP Specific IgG4 Calibrator Strip** (Art No 10-9550-01: for 1 calibration curve)
- **ImmunoCAP IgA/IgG Calibrator ImmunoCAP** (AGcal) (Art No 14-4424-01: carriers of 16 ImmunoCAP)
- **ImmunoCAP Specific IgG4 Curve Control Strip** (CC-1 and CC-2) (Art No 10-9551-01: for 1 x 3 sets of curve controls)
- **ImmunoCAP Allergen** (See Product catalogue: carriers of 16 or 10 ImmunoCAP)
- **Development Solution** (Art No 10-9441-01: for 6 x 200 determinations; Art No 10-9440-01: for 6 x 315 determinations)
- **Stop Solution** (Art No 10-9442-01: for 6 x 185 determinations)
- **Washing Solution** (Art No 10-9422-01: 6 x 1 l)
  - Washing Solution Additive, 6 x 17.2 ml
  - Washing Solution Concentrate, 6 x 80 ml
- **Washing Solution** (Art No 10-9202-01: 2 x 5 l)
  - Washing Solution Additive, 2 x 86 ml
  - Washing Solution Concentrate, 2 x 400 ml
- **ImmunoCAP Specific IgG/IgG4 Control L** (Art No 10-9473-01: for 6 x 4 determinations)
- **ImmunoCAP Specific IgG/IgG4 i1 Control H** (Art No 10-9475-01: for 6 x 4 determinations)

Reagents for Phadia 1000

- **ImmunoCAP Specific IgG4 Conjugate 50** (Art No 10-9549-01: for 2 x 50 determinations)
- **ImmunoCAP Specific IgA/IgG Sample Diluent** (Art No 10-9361-01: 6 vials à 50 ml)
- **ImmunoCAP Specific IgG4 Calibrator Strip** (Art No 10-9550-01: for 1 calibration curve)
- **ImmunoCAP IgA/IgG Calibrator ImmunoCAP** (AGcal) (Art No 14-4424-01: carriers of 16 ImmunoCAP)
- **ImmunoCAP Specific IgG4 Curve Control Strip** (CC-1 and CC-2) (Art No 10-9551-01: for 1 x 3 sets of curve controls)
- **ImmunoCAP Allergen** (See Product catalogue: carriers of 16 or 10 ImmunoCAP)
- **Development Solution** (Art No 10-9439-01: for 6 x 1200 determinations; Art No 10-9314-01: for 6 x 2000 determinations)
- **Stop Solution** (Art No 34-2271-51: for 1200 determinations)
- **Washing Solution** (Art No 10-9202-01: 2 x 5 l)
  - Washing Solution Additive, 2 x 86 ml
  - Washing Solution Concentrate, 2 x 400 ml
- **ImmunoCAP Specific IgG/IgG4 Control L** (Art No 10-9473-01: for 6 x 4 determinations)
- **ImmunoCAP Specific IgG/IgG4 i1 Control H** (Art No 10-9475-01: for 6 x 4 determinations)

Reagents for Phadia 2500 and Phadia 5000

- **ImmunoCAP Specific IgG4 Conjugate 50** (Art No 10-9549-01: for 2 x 50 determinations)
- **ImmunoCAP Specific IgA/IgG Sample Diluent** (Art No 10-9361-01: 6 vials à 50 ml)
- **ImmunoCAP Specific IgG4 Calibrator Strip** (Art No 10-9550-01: for 1 calibration curve)
- **ImmunoCAP IgA/IgG Calibrator ImmunoCAP** (AGcal) (Art No 14-4424-01: carriers of 16 ImmunoCAP)
- **ImmunoCAP Specific IgG4 Curve Control Strip** (CC-1 and CC-2) (Art No 10-9551-01: for 1 x 3 sets of curve controls)
- **ImmunoCAP Allergen** (See Product catalogue: carriers of 16 or 10 ImmunoCAP)
- **Development Solution** (Art No 10-9314-01: for 6 x 2000 determinations)
- **Stop Solution** (Art No 34-2337-11: for 4600 determinations)
- **Washing Solution Concentrate** (Art No 34-2337-21: 1 x 2800 ml)
- **Washing Solution Additive** (Art No 10-9518-01: 4 x 850 ml)
- **ImmunoCAP Specific IgG/IgG4 Control L** (Art No 10-9473-01: for 6 x 4 determinations)
- **ImmunoCAP Specific IgG/IgG4 i1 Control H** (Art No 10-9475-01: for 6 x 4 determinations)

Details of reagents

ImmunoCAP Specific IgG4 Conjugate 50	
ß-Galactosidase-anti-IgG4 Approximately 1.5 µg/ml (mouse monoclonal antibodies) Sodium azide 0.06%	Ready for use. Store at 2 – 8 °C until expiration date. **Do not freeze!**

ImmunoCAP Specific IgA/IgG Sample Diluent	
(buffer solution with chicken serum) Preservative* <0.003%	Ready for use. Store at 2 – 8 °C until expiration date.

ImmunoCAP Specific IgG Sample Diluent	
(buffer solution with chicken serum) Preservative* <0.003%	Ready for use. Store at 2 – 8 °C until expiration date.

ImmunoCAP IgA/IgG Calibrator ImmunoCAP	
(mouse monoclonal antibodies) Preservative* <0.0015%	Ready for use. Store at 2 – 8 °C until expiration date.

ImmunoCAP Specific IgG4 Calibrator Strip	
(human IgG4 in buffer) Conc. 0; 3; 15; 35; 120 and 300 µg/l Preservative* <0.003%	Ready for use. Store at 2 – 8 °C until expiration date.

ImmunoCAP Specific IgG4 Curve Control Strip	
(human IgG4 in buffer) Preservative* <0.003%	Ready for use. Store at 2 – 8 °C until expiration date.

ImmunoCAP Allergen	
Preservative* <0.0015%	Ready for use. Store at 2 – 8 °C until expiration date.

Development Solution	
4-Methylumbelliferyl-ß-D-galactoside 0.01% Preservative* <0.0010%	Ready for use. Store at 2 – 8 °C until expiration date. **Do not freeze!**

Stop Solution	
Sodium carbonate 4%	Ready for use. Store at 2 – 32 °C until expiration date.

Washing Solution
For information, see separate Directions for Use for Washing Solution.

ImmunoCAP Specific IgG/IgG4 Control L	
Antibody level L (low) Sodium azide 0.05% Preservative* <0.003%	Ready for use. Store at 2 – 8 °C until expiration date.
The control sample is prepared from selected pooled human samples.	

ImmunoCAP Specific IgG/IgG4 i1 Control H	
Antibody level H (high) Sodium azide 0.05% Preservative* <0.003%	Ready for use. Store at 2 – 8 °C until expiration date.
The control samples are prepared from selected pooled human samples containing IgG4 antibodies to i1, *Apis mellifera*.	

***Preservative:** Reaction mass of CMIT/MIT (3:1), (CAS No: 55965-84-9).

Precautions

Warning

- For in vitro diagnostic use. Not for internal or external use in humans or animals.
- Some reagents are manufactured from human blood components. The source materials have been tested by immunoassay for hepatitis B surface antigen, for antibodies to HIV1, HIV2 and hepatitis C virus and found to be negative. Nevertheless, all recommended precautions for the handling of blood derivatives should be observed.

Please refer to Human Health Service (HHS) Publication No. (CDC) 93-8395 or other local/national guidelines on laboratory safety procedures.

- Reagents containing ≥0.00015% reaction mass of CMIT/MIT (3:1) (CAS No: 55965-84-9) may produce an allergic reaction (EUH 208). For more information see Safety Data Sheet.
- Reagents containing ≥0.0015% reaction mass of CMIT/MIT (3:1) (CAS No: 55965-84-9) may cause an allergic skin reaction (H317). Wear protective gloves/protective clothing/eye protection (P280). Gloves: Nitrile rubber EN374. For more information see Safety Data Sheet.
- Reagents containing ≥0.0025% reaction mass of CMIT/MIT (3:1) (CAS No: 55965-84-9) are classified as harmful to aquatic life with long lasting effects (H412). Avoid release to the environment (P273). Dispose of contents/container in accordance with local/national regulations (P501). For more information see Safety Data Sheet.

Disposal

Follow local disposal regulations based on your location along with recommendations and content in the Safety Data Sheet to determine the safe disposal of the products.

INSTRUMENTS

Phadia 200 processes all steps of the assay and prints results automatically after the assay is completed[a]. Phadia 250, Phadia 1000, Phadia 2500 and Phadia 5000 are continuous random access systems that perform all steps of the assay[a].

On board stability

Information on reagent storage for the intended locations on the Phadia instruments is shown below.

	Phadia 200	Phadia 250	Phadia 1000	Phadia 2500, Phadia 5000
Calibrator/ Curve Control	28 days.			N/A
Conjugate	4 days. Recap bottles every night.		7 days.	
Development Solution	5 days. Recap bottles every night.		14 days.	5 days.
Stop Solution	14 days. Recap bottles every night.		14 days.	31 days.
Washing Solution *(prepared solution)*	7 days. Discard every seventh day and perform weekly maintenance according to respective instrument user manual.			
Washing Solution Concentrate	N/A			30 days.
Washing Solution Additive	N/A			30 days.
Sample Diluent	7 days. Recap bottles every night.		N/A	
ImmunoCAP Carrier	No provision for on board storage.	Until expiration date.		

SPECIMEN COLLECTION AND PREPARATION

Specimen collection

Collect blood samples and prepare serum or plasma (EDTA or heparin) according to standard procedures. Store at 2 °C to 8 °C for up to one week, or else at –20 °C. Storage at room temperature is not recommended. However, for shipping purposes, specimens may be kept at room temperature (not exceeding 32 °C) for up to one week[b]. Avoid repeated freezing and thawing (14). For further reading on interfering substances and IgG4 stability in specimens, see references (15, 16).

Note: It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory. In general, laboratories should perform validation studies before implementing a change in specimen acceptance criteria (14).

Preparation of samples

Before assaying, dilute the samples 1:100 with ImmunoCAP Specific IgA/IgG Sample Diluent or ImmunoCAP Specific IgG Sample Diluent. The diluted sample is stable 1 week at 2 °C to 8 °C.

Dilute manually‡ or automatically in the instrument for use in Phadia 200 and Phadia 250.
Dilute manually‡ for use in Phadia 1000, Phadia 2500 and Phadia 5000.

‡For example 10 µl sample + 990 µl sample diluent.

If the concentration of specific IgG4 in the sample is greater than the upper limit of the measuring range (30 mg_A/l), the sample can be further diluted to fall within the calibrator range, in which case the chosen dilution factor must be manually adjusted in the software.

Handling of control specimen

ImmunoCAP Specific IgG/IgG4 Controls are ready for use and must not be further diluted. The dilution factor has to be set to 100 in Phadia Prime/Phadia Information Data Manager software. In all other aspects it should be treated in the same way as patient samples and run in accordance with this Directions for Use.

It is recommended to remove and recap the control vials from the instrument as soon as the pipetting of the samples is finished and the sample incubation is started. It is also recommended to gently stir the vial before use.

PROCEDURES

Procedural steps[a]

For procedural steps, see **Notes** a.

Parameters of the procedure

Patient samples are run in single determinations.

Volumes per determination:

Sample, diluted	40 µl
Conjugate	50 µl
Development Solution	50 µl
Stop Solution	600 µl

Incubations are performed at 37 °C by Phadia instruments.

Phadia 200: Total time for one assay is up to 4 hours.

Phadia 250, Phadia 1000, Phadia 2500 and Phadia 5000: The process time is 1 hour and 45 minutes from entering the first sample until the result is available.

Calibration[a]

The calibrators, provided in ImmunoCAP Specific IgG4 Calibrator Strip, are run in duplicates to obtain a full calibration curve. The calibration curve will be stored for use in subsequent assay runs.

The two curve controls CC1 and CC2, each in single determinations, are used to approve the validity of the previously stored calibration curve. The software for Phadia instruments have built-in acceptance limits for the calibration curve and the curve controls.

Calibrator range: 0-300 µg/l.

Measuring range: 0.3 - 30 mg_A/l, after correction with the dilution factor (1:100). The software automatically displays the results for undiluted samples according to the default (1:100) or manually entered dilution factor.

Reference material: The calibrators are traceable (via an unbroken chain of calibrations) to the International Reference Preparation (IRP) 67/86 for Human Serum Immunoglobulins A, G, and M from World Health Organisation (WHO). The concentration of subclass IgG4 in IRP 67/86 has been established through calibration to WHO IRP 67/97 for which IgG subclass concentrations are reported (17).

Accuracy[b]: Measured values of ImmunoCAP Specific IgG4 are, with 95% probability, within ± 7% of the WHO IgG4 reference value.

Trueness[b]: The bias of ImmunoCAP Specific IgG4 Calibrators is, with 95% probability, within ± 3% compared to the WHO IgG4 reference value.

QUALITY CONTROL

Record keeping for each assay

It is good laboratory practice to record the lot numbers of the components used, the dates when they were first opened and the remaining volumes.

Control specimen

Good laboratory practice requires that quality control specimen should be included in every run. Any material used should be assayed repeatedly to establish mean values and acceptable ranges.

Controls available from Phadia AB for day to day quality control:

- ImmunoCAP Specific IgG/IgG4 Control L (Art No 10-9473-01)
- ImmunoCAP Specific IgG/IgG4 i1 Control H (Art No 10-9475-01)

Both controls are to be used with ImmunoCAP Allergen i1 (Art No 14-4143-01).

Intended use for ImmunoCAP Specific IgG4 Controls

ImmunoCAP Specific IgG/IgG4 Controls are used for monitoring ImmunoCAP Specific IgG4 measurements performance in Phadia instruments.

Expected values for ImmunoCAP Specific IgG4 Controls

As with all immunoassays the results are affected by the testing procedures and equipment used by different laboratories. It is therefore recommended that each laboratory establishes its own target value for each actual lot of control together with criteria of acceptance (recommended range: target value ± 30%).

Until each laboratory has obtained enough results for establishing its own target value and range, a range will be found on the vial label. The laboratory's target value is expected to fall within this range.

The range for each specific lot of ImmunoCAP Specific IgG/IgG4 i1 Control H is the mean concentration ± 2 standard deviations (SD), where the mean value has been determined from 6 consecutive assays, each in 6 replicates using ImmunoCAP Specific IgG4. The standard deviation is based on the expected long-term variation for the ImmunoCAP Specific IgG4 assay. ImmunoCAP Specific IgG/IgG4 Control L will give results below 0.3 mg_A/l for ImmunoCAP Specific IgG4 (i1).

RESULTS

For Phadia instruments using Phadia Prime or Phadia Information Data Manager software, all calculations are automatically performed[a].

For ImmunoCAP Specific IgG4, results are expressed as concentration in mg_A/l, where A represents allergen-specific IgG4 antibodies.

LIMITATIONS OF THE PROCEDURE

A definitive clinical diagnosis should only be made by the physician after all clinical and laboratory findings have been evaluated. It should not be based on the results of any single diagnostic method.

Note: The following ImmunoCAP Allergens should not be used in the ImmunoCAP Specific IgG4 assay due to their content of native IgG or unspecific background binding which will cause misleading assay results: f2, f82, h1, h2, o70 and t14.

Note: For the following ImmunoCAP Allergens, high non-specific binding makes it particularly important that each laboratory establishes its own background levels: f27, f236, f300 and f442.

Note: ImmunoCAP Allergen Mixes, ImmunoCAP Antigens, ImmunoCAP Phadiatop and ImmunoCAP Phadiatop Infant are not included in the ImmunoCAP Specific IgG4 assay and should not be used.

EXPECTED VALUES

Good laboratory practice recommends that each laboratory establishes its own expected range of values (18).

Under circumstances of natural exposure, the majority of individuals have low or undetectable levels of IgG4 to airborne allergens while significant levels to allergens from foods such as milk and egg may frequently occur (19-21). Allergen immunotherapy (AIT) typically induces high levels of IgG4 to the treatment allergen (22).

Biomarkers for investigating the immunological response to AIT (22, 23), or natural allergen exposure (19, 24-26), include increased specific IgG4 levels, as well as reduced specific IgE/specific IgG4 ratios.

PERFORMANCE CHARACTERISTICS

Instrument comparison[b]

In an instrument comparison study with 74 patient samples and 6 ImmunoCAP Allergens, the following average differences between each Phadia instrument system and the overall mean were estimated:

Phadia instrument	Average difference to mean (%)
Phadia 200	-2
Phadia 250	-0.1
Phadia 1000	-3
Phadia 2500/5000	6

Precision[b]

The following pooled coefficients of variation have been obtained in a study with Phadia 1000 when testing representative allergens from 4 allergen groups, in total 4-8 samples/level. Each sample has been assayed in 4 replicates on 7 different occasions using the same lot of reagents and stored calibration curves. The values are representative for all Phadia instruments.

Sample level (mg_A/l)	Coefficients of variation (%)	
	Within assay	Between assay
0.3 – 1.5	5	6
1.5 – 15	4	4
15 – 30	5	5

Limit of Quantitation[b]

The Limit of Quantitation (27) is 3 μg_A/l, corresponding to 0.3 mg_A/l in undiluted sample.

Analytical specificity[b]

No interference of rheumatoid factor (<500 IU/ml), hemoglobin (<10 g/l), triglycerides (chyle <16,300 FTU) or bilirubin (bilirubin coupled <42 mg/dl, bilirubin free <40 mg/dl) has been observed in studies, when tested at recommended test concentrations (28).

No cross-reactivity with other human immunoglobulins has been observed at physiological concentrations of IgG1, IgG2, IgG3, IgA, IgD, IgM and IgE.

Linearity[b]

Dilution linearity has been demonstrated in studies peformed on representative allergens from 7 allergen groups and 3 samples/allergen. The relationship between observed and expected concentration was evaluated with linear regression analysis (per sample on $\log_{10}$ concentration). The estimated slopes were within 0.88 – 1.15 and the intercepts were within -0.27 – 0.26.

WARRANTY

The performance data presented here was obtained using the procedure indicated. Any change or modification in the procedure not recommended by Phadia AB may affect the results, in which event Phadia AB disclaims all warranties expressed, implied or statutory, including the implied warranty of merchantability and fitness for use. Phadia AB and its authorized distributors, in such event, shall not be liable for damages indirect or consequential.

IMPORTANT NOTICE

For healthcare professionals in the European Union and in countries with identical regulatory regime (Regulation 2017/746/EU on In vitro Diagnostic Medical Devices); if, during the use of this device or as a result of its use, a serious incident has occurred, please report it to the manufacturer and/or its authorized representative and to your national authority.

SYMBOLS

	Use-by date	IVD	*In vitro* diagnostic medical device
LOT	Batch code		Temperature limit
	Date of manufacture		Consult instructions for use
REF	Catalogue number		Biological risks
	Caution	**Rx only**	For prescription use only – only applicable under US legislation
	Manufacturer	Warning	Warning
Σ	Contains sufficient for <n> tests		

Full symbol glossary is available at: https://symbols_glossary.phadia.com.

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Notes

[a]For more information, see Phadia 200, Phadia 250, Phadia 1000 and/or Phadia 2500/Phadia 5000 user manual.

[b]Studies performed at Phadia AB, Uppsala, Sweden.

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