



# Evaluation Report

NUMBER  
**MDA 02082**

## **DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit**



Immunology Quality Services

MDA Evaluation Report  
MDA 02082

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# **MDA Evaluation**

of the

## **DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit**

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## Summary

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The purpose of this evaluation was to assess the performance of the DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit in the detection and quantitation of TPO autoantibodies in serum / EDTA, heparin or citrated plasma. The DIASTAT™ Anti-thyroid Peroxidase (TPO) kit is IgG specific and utilises recombinant human TPO as the antigen. Assays were performed in strict accordance with the manufacturer's instructions and the distributor was given the opportunity to train the operators prior to the commencement of the evaluation. The analytical procedures were carried out at IMMQAS during April 2002

The evaluation included an assessment of packaging and labelling of the kit, clarity of operating instructions, safety and ease of use. The cost per test, based on the list price, is documented together with the technical requirements.

The status of all samples was confirmed using an established method, the Hycor Biomedical Autostat II Anti-Thyroid Peroxidase assay. The Hycor Biomedical Autostat II Anti-Thyroid Peroxidase assay is IgG specific and utilises purified human TPO as the antigen. IgG anti-TPO sensitivity in relation to Hycor Biomedical was 99% with a specificity of 86%. The overall agreement between the two methods was 91%. Within-assay imprecision ranged from 5.2% to 9.3%. Between-assay imprecision ranged from 2.3% to 10.4%. Linearity of dose response was good up to a concentration of 461 IU/ml. The DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit is calibrated against the WHO reference preparation MRC 66/387 and therefore results are reported in IU/ml. A mean value of 227.7 IU/ml was obtained for the WHO reference preparation, MRC 66/387 at a dilution of 1/4 against a target value of 1000 IU/ml. The product is CE marked with reference to the IVD Directive (Directive 98/79/EC).

Using the information provided by the manufacturer, sample values of less than 10 IU/ml were recorded as negative and values greater than or equal to 10 IU/ml were recorded as positive. There were 19 "false positive" results which comprised one sample from a male donor over the age of 50 years, three from female donors over the age of 50 years, one from a male donor under the age of 50 years, three from female donors under the age of 50 years, two lipaemic samples, four samples with haemolysis, one hyperproteinaemic sample and four hyperbilirubinaemic samples.

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## Introduction

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There are a number of autoantibodies associated with the autoimmune thyroid diseases, which are characterised as either primary or secondary antibodies. Primary antibodies are directly pathogenic and often directed against cell membrane receptors, whilst secondary antibodies do not appear to be involved in pathogenesis but can serve as a useful diagnostic marker for the presence of autoimmune thyroid disease. Thyroid peroxidase (TPO) antibodies are one of the major secondary antibodies associated with autoimmune thyroid disease [1].

TPO was previously known as thyroid microsomal antigen [2]. It is a 107 KD enzyme which is involved in thyroid hormone synthesis. TPO is located both on the cell surface and within the cytoplasm of thyroid acinar cells, bound to the vesicle which transports newly synthesised thyroglobulin, where it is involved in the iodination of thyroglobulin. High affinity antibodies (predominantly IgG) directed against TPO are found at elevated levels in the serum of patients with autoimmune thyroid disease such as Graves disease, Hashimoto's thyroiditis and myxoedema [3]. Diagnostic companies have recognised the importance of this antibody and have developed assays using either recombinant or purified human TPO as the antigen source.

## Serum panel

A panel of 228 sera was tested, in duplicate, using a total of eight kits. Four were drawn from lot number EVAL 03 kit, expiry September 02 and four from lot number EVAL 04 kit, expiry September 02.

The serum panel comprised the following samples:

- sera from normal blood donors under 50 years old (n= 50)
- sera from normal blood donors over 50 years old (n= 50)
- sera from hypothyroid patients with detectable anti-TPO antibodies as determined by the Hycor Biomedical Autostat II Anti-Thyroid Peroxidase ELISA (n= 50)
- sera from hyperthyroid patients with detectable anti-TPO antibodies as determined by the Hycor Biomedical Autostat II Anti-Thyroid Peroxidase ELISA (n= 25)
- sera from euthyroid patients with detectable anti-TPO antibodies as determined by the Hycor Biomedical Autostat II Anti-Thyroid Peroxidase ELISA (n= 13)
- sera to investigate the possible matrix effects of:
  - lipaemia (n= 10)
  - haemolysis (n= 10)
  - hyperproteinaemia (n= 10)
  - hyperbilirubinaemia (n= 10)

**Accuracy**

Accuracy was assessed with reference to the WHO reference preparation, MRC 66/387.

**Imprecision**

Sera with high, medium and low levels of anti-TPO antibodies were included in each assay run to determine between-assay imprecision.

The high, medium and low samples were tested twenty times in a single assay run to determine within-assay imprecision.

**Sensitivity and specificity**

Relative sensitivity and specificity of the assay were assessed in relation to the Hycor Biomedical assay. The overall agreement between the two methods is also documented.

**Matrix effects**

The effects of some potentially interfering substances were assessed by including appropriate samples as detailed in *Serum panel*.

**Linearity**

Two samples with known high concentrations of anti-TPO antibodies when previously assayed using the DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit were serially diluted to give a final dilution of 1/10. These dilutions were assayed in duplicate and the results shown on a graph (Figure 1).

**General**

The evaluation included an assessment of:

- packaging and labelling in accordance with IFCC guidelines and COSHH regulations
- contents of the kit insert and clarity of operating instructions
- ease of use of the kit
- cost per test and time taken
- compatibility with existing laboratory work.

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## Product details

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### ■ General information

<b>Product:</b>	DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit
<b>Product code:</b>	FTP0300
<b>Manufacturer:</b>	Axis Shield Diagnostics Limited The Technology Park Dundee DD2 1XA United Kingdom
<b>Distributor:</b>	As above  Tel: +44 (0) 1382 422 000
<b>Cost:</b>	The list price for a 96 well kit is given as £142.00 After due consideration for calibrators and controls, each kit provides sufficient reagents for 41 determinations in duplicate at a cost of £3.46 per sample. This cost does not take into account operator time and is exclusive of additional reagent costs, consumables and VAT.

### ■ Assay details

**Description:** The manufacturer's description of the kit and its intended use is given below:

*"The DIASTAT™ Anti-Thyroid Peroxidase (anti-TPO) test is a quantitative/qualitative enzyme-linked immunosorbent assay (ELISA) for the detection of the IgG class of autoantibodies specific for thyroid peroxidase in human serum or EDTA, heparin or citrated plasma. It is intended to aid in the diagnosis of autoimmune thyroid disorders and is not definitive in isolation. Autoantibody levels represent one parameter in a multicriterion diagnostic process."*

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**Principle:** The wells of the microtitre strips are coated with recombinant human TPO (rTPO). During the first incubation, specific autoantibodies in diluted serum or plasma bind to the antigen-coated surface. The wells are then washed to remove unbound components. In the second incubation, the conjugate, an enzyme-labelled monoclonal antibody to human IgG, binds any surface-bound autoantibodies. After further washing, specific autoantibodies are traced by incubation with the substrate. Addition of stop solution terminates the reaction, resulting in a coloured end-product. The amount of conjugate bound is measured in absorbance units. In the qualitative protocol, the amount of conjugate bound by the sample is compared with that bound by the reference control. In the quantitative protocol, the concentration of anti-TPO autoantibody can be estimated by interpolation from a dose-response curve based on standards. The standards are calibrated against NIBSC 66/387 thyroid microsomal antibody reference preparation.

**End point measurement:** Photometric measurement at 550 nm

**Isotype specificity:** IgG

**Antigen source:** Recombinant human TPO

**Specimen type:** Human serum/EDTA, heparin or citrated plasma

**Required sample size:** 10 µl of sample to be diluted 1:100 with sample diluent

**Additional reagents required:** Distilled or deionised water

**Major equipment required:**

- 96-well microplate reader with 550 nm filter
- Automatic plate washer (optional)
- Data reduction software (optional)

**Other equipment required:**

- Appropriate tubes for sample dilution
- Precision pipettes to deliver volumes of 10 µl, 100 µl and 1000 µl
- Repeating dispenser or multichannel pipette to deliver volumes of 100 µl
- 60 minute timer

## ■ Packaging and labelling

The packaging and labelling of the kits were assessed in accordance with a modified form of the IFCC guidelines (detailed in the *Appendix*) and with COSHH regulations. The degree of conformity to these criteria is shown in table 1.

### Packaging

Packaging consists of a cardboard box. Reagent containers are secured in wells that are cut into an inner cardboard insert. Microstrips are stored in a plastic frame in a resealable foil sachet.

### Labelling

All components are clearly labelled in English, German, Italian, French and Spanish with details of the contents, lot number, storage requirements and expiry date. The conjugate is colour-coded blue. The outer package bears a label stating the name of the kit with a list of its contents, storage requirements, lot number and expiry date. The product is CE marked with reference to the IVD Directive (Directive 98/79/EC).

## ■ Quality controls and calibrators

A series of five prediluted calibrators at concentrations of 0 - 500 IU/ml are provided in the kit. A positive control with an acceptable range of 24 - 47 IU/ml and a negative control with an acceptable concentration of < 10 IU/ml is also provided. Results are interpreted as follows:

< 10	IU/ml	negative
≥ 10	IU/ml	positive

**Table 1. Conformity to IFCC guidelines on packaging and labelling**

1. Description of test and method	Y
2. Principles of test	Y
3. Reagents supplied	Y
4. Quality control sera supplied with kit	Y
5. Additional reagents required	Y
6. Equipment required	Y
7. Hazard warnings	Y
8. Examples of results	Y
9. Reference ranges	Y
10. Working range	Y
11. Within-assay imprecision	Y
12. Between-assay imprecision	Y
13. Specificity	Y
14. Sensitivity	Y
15. Accuracy	N
16. Effects of anticoagulants	Y
17. High dose hook effect	N/A
18. Matrix effects	Y
19. Collection and storage of samples	Y
20. Kit storage and shelf life	Y
21. COSHH information	Y
22. Pack dimensions (height x depth x width)	95 x 130 x 166 mm

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## Assay procedure

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### ■ Assay protocol

The assay protocol described in the kit insert was strictly followed, without modification. A summary of the procedure is given below together with the approximate times taken to complete each step when a full plate was tested.

• Dilute wash buffer and prepare standard curve	10 mins
• Dilute patient samples 1:100 in sample diluent	15 mins
• Pipette 100 µl calibrators, controls and diluted patient samples to appropriate wells	5 mins
• Incubate at room temperature	60 mins
• Wash five times in wash buffer	7 mins
• Add 100 µl conjugate to all wells	2 mins
• Incubate at room temperature	30 mins
• Wash five times in wash buffer	7 mins
• Add 100 µl substrate solution to all wells	2 mins
• Incubate at room temperature	30 mins
• Add 100 µl stop solution to all wells	2 mins
• Read absorbance at 550 nm within 24 hours	5 mins
Total number of steps	12
Number of wash steps	2
Total assay time	175 mins
Estimated operator hands-on time	55 mins
Sample volume	10 µl

## ■ Ease of use

The clarity of the operating instructions and the ease of use of the kit were assessed by two independent operators. The criteria used were scored on a scale of 1 to 5. The findings are recorded in table 2.

**Table 2. Ease of use**

Labelling	5
Reagent colour coding	5
Clarity of written instructions	4
Ease of reagent preparation	4
Ease of sample preparation	4
Ease of test procedure	4
Ease of use of required equipment	5
Result interpretation	5
Overall test time	4
Compatibility with other laboratory work	5
COSHH information	5
<b>TOTAL</b>	<b>50/55</b>
<b>Key:</b> 1 - Very poor or very difficult 2 - Poor or difficult 3 - Adequate 4 - Good or easy 5 - Excellent or very easy	

## ■ General comments

- All assay components must be allowed to warm to room temperature before use.
- Samples for linearity and any beyond the assay range were diluted in the sample diluent provided in the kit.
- Reagents were added using a Biohit Proline electronic repeating dispenser.
- Optical densities were measured using the DYNEX plate reader in conjunction with Revelation data reduction software.
- Plates were washed using a programmable automatic washer (DYNEX MRW 4 bottle plate washer).

## ■ Sensitivity and specificity

Table 3a summarises the results obtained by Hycor Biomedical and DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit with sera from patients with raised TPO antibodies and normal blood donors. Relative sensitivity and specificity were calculated from the data and are recorded in table 3b.

**Table 3a. DIASTAT™ Anti-Thyroid Peroxidase (TPO)**

		DIASTAT™ Anti-Thyroid Peroxidase (TPO)		Total
		Positive	Negative	
Hycor Biomedical TPO	Positive	87	1	88
	Negative	19	121	140
Total		106	122	228

**Table 3b. Relative sensitivity and specificity**

Sensitivity (%)	99
Specificity (%)	86
Overall agreement (%)	91

## ■ Imprecision

### Within-assay imprecision

Three samples containing high, medium and low levels of TPO antibodies were assayed 20 times each in a single assay run. The results are summarised in table 4.

**Table 4. Within-assay imprecision (n=20)**

	*Sample 1	Sample 2	Sample 3
Mean (IU/ml)	608.8	265.1	69.1
SD	119.3	24.5	3.6
CV%	19.6	9.3	5.2

\* Some samples gave results > 500 IU/ml and extrapolated data have been used for calculations in these instances. Results are for information only.

## Between-assay imprecision

**Table 5. Between-assay imprecision**

	<b>*Sample 1</b>	<b>Sample 2</b>	<b>Sample 3</b>
<b>Mean (IU/ml)</b>	530.5	258.6	70.6
<b>SD</b>	108.5	23.7	2.2
<b>CV%</b>	20.5	9.2	3.1

**Table 6. Between-assay imprecision (EVAL 03 kit)**

	<b>*Sample 1</b>	<b>Sample 2</b>	<b>Sample 3</b>
<b>Mean (IU/ml)</b>	518.8	248.4	71.3
<b>SD</b>	94.1	16.0	2.7
<b>CV%</b>	18.1	6.4	3.8

**Table 7. Between-assay imprecision (EVAL 04 kit)**

	<b>*Sample 1</b>	<b>Sample 2</b>	<b>Sample 3</b>
<b>Mean (IU/ml)</b>	542.2	268.8	69.9
<b>SD</b>	135.1	27.9	1.6
<b>CV%</b>	24.9	10.4	2.3

\* Some samples gave results > 500 IU/ml and extrapolated data have been used for calculations. Results are for information only.

## ■ Accuracy

Accuracy was assessed in relation to the WHO reference preparation MRC 66/387, assigned value 1000 IU/ml. This sample was diluted 1/4 to give a final value of 250 IU/ml and included in all assay runs. Results are recorded in table 8.

**Table 8. Accuracy**

Mean (IU/ml)	227.7
SD	11.8
GSD	1.1
CV%	5.2

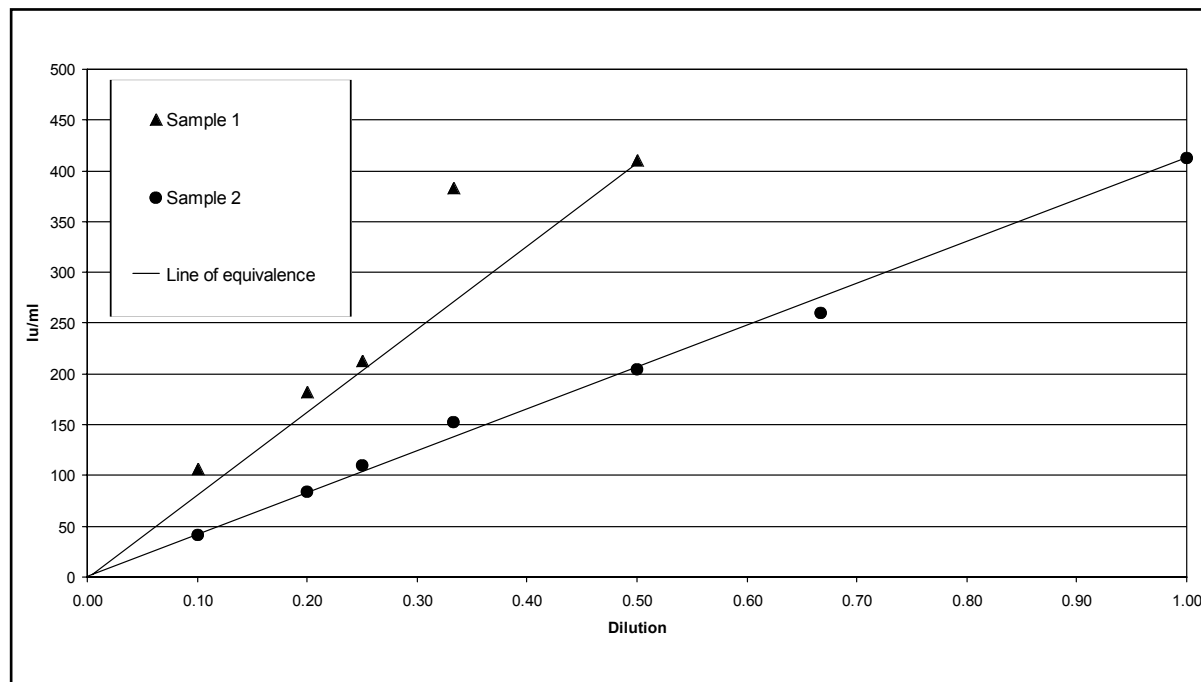
## ■ Linearity

Two samples containing high levels of anti-TPO antibodies when previously assayed using the DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit were serially diluted in sample diluent to a final dilution of 1/10. These dilutions were assayed in duplicate. Results are shown in table 9 and figure 1.

**Table 9. Linearity**

Dilution	Sample 1 IU/ml	Sample 2 IU/ml
Neat	-	412.3
2/3	-	260.6
1/2	409.8	204.8
1/3	383.1	152.6
1/4	212.5	109.7
1/5	181.5	83.4
1/10	106.6	41.2

**Figure 1. Linearity**



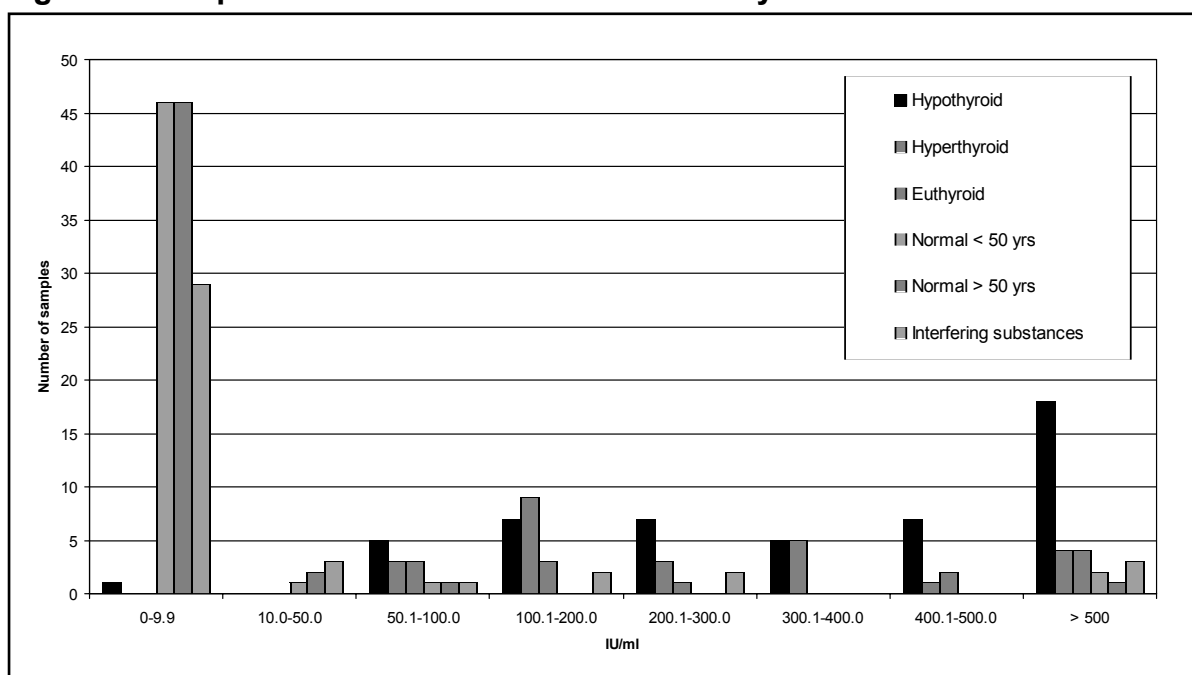
## ■ Matrix effects

“False positive” results were obtained from nineteen samples: one sample from a male donor over the age of 50 years, three from female donors over the age of 50 years, one from a male donor under the age of 50 years, three from female donors under the age of 50 years, two lipaemic samples, four samples with haemolysis, one with hyperproteinaemia and four with hyperbilirubinaemia.

**Table 10. Sample distribution of anti-TPO antibody levels**

TPO IU/ml	Hypo thyroid	Hyper thyroid	Euthyroid	Normal < 50 yrs	Normal > 50 yrs	Interfering substances
0-9.9	1	0	0	46	46	29
10.0-50.0	0	0	0	1	2	3
50.1-100.0	5	3	3	1	1	1
100.1-200.0	7	9	3	0	0	2
200.1-300.0	7	3	1	0	0	2
300.1-400.0	5	5	0	0	0	0
400.1-500.0	7	1	2	0	0	0
> 500	18	4	4	2	1	3
<b>Total</b>	<b>50</b>	<b>25</b>	<b>13</b>	<b>50</b>	<b>50</b>	<b>40</b>

**Figure 2. Sample distribution of anti-TPO antibody levels**



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## Conclusion

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The DIASTAT™ Anti-Thyroid Peroxidase (TPO) Kit is presented in a standard 96-well microplate format familiar to most immunology laboratories, providing an assay which is easy to use. The kit packaging provided adequate protection for transit and storage. The written instructions are clear and easy to follow.

Sensitivity of the assay in relation to the Hycor Biomedical Autostat II Anti-Thyroid Peroxidase assay was found to be 99% with a specificity of 86%. The overall agreement between the two methods was 91%. “False positive” results were seen in 19 samples: one sample from a male donor over the age of 50 years, three from female donors over the age of 50 years, one from a male donor under the age of 50 years, three from female donors under the age of 50 years, two lipaemic samples, four with haemolysis, one with hyperproteinaemia and four with hyperbilirubinaemia. A matrix effect was observed in the groups of sera containing bilirubin and haemoglobin. The manufacturer recommends that lipaemic, haemolysed or turbid samples should not be used. However, there is no mention of hyperbilirubinaemic samples in the kit insert.

Within-assay imprecision ranged from 5.2 to 9.3%. Between-assay imprecision ranged from 2.3% to 10.4%. Linearity of dose response was good up to a concentration of 461 IU/ml. Accuracy was assessed in relation to the WHO standard preparation MRC 66/387. A mean value of 227.7IU/ml was recorded against the assigned value of 250 IU/ml when the standard preparation was at a dilution of 1/4.

A total assay time of approximately 3 hours gives rise to a rapid and absolute result. Since the assay is presented in a standard 96-well format, it is likely to be compatible with existing work in most immunology laboratories. Special instrumentation is not required.

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## References

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1. Milford Ward A, Wild G, Riches P G and Sheldon J (1999). *SAS Protein Reference Units Handbook of Autoimmunity* 1st Ed. PRU Publications, Sheffield. **34-36**
2. Czarnocka B, Ruf J, Ferrand M, Carayon P and Lissitzky S (1985). Purification of the human thyroid peroxidase and its identification as the microsomal antigen involved in autoimmune thyroid diseases. *FEBS Letters*. **190**: 147-152
3. Whitham K, Patel D and Milford Ward A (2000). Epitope Expression in Nine Commercial Kits for the Determination of Anti-Thyroid Peroxidase (TPO) Antibodies. *J Clin Lab Immunol*. **51**: 21-38

### ■ IFCC guidelines on packaging and labelling

IFCC guidelines, modified for autoimmune serology kits, suggest that the following details be included in the kit insert:

1. Description of test and method.
2. Principle of the assay.
3. Reagents supplied (contents and concentrations)
4. Extra reagents required but not supplied.
5. Equipment required.
6. Hazard warnings.
7. Example of results.
8. Reference ranges
  - i) sample size
  - ii) description of population.
9. Working range.
10. Within-assay imprecision.
11. Between-assay imprecision.
12. Sensitivity.
13. Specificity.
14. Accuracy.
15. Effects of anticoagulants.
16. High dose hook or prozone effects.
17. Matrix effects.

## ■ Manufacturer's comments



**AXIS-SHIELD**

**Axis-Shield Diagnostics Ltd**

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Mrs Rachel Sanderson  
MDA Evaluation Unit  
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Sheffield  
S5 7AU

08 August 2002

Dear Rachel

**Re: MDA Report on the evaluation of DIASTAT Anti-TPO antibodies ELISA kit**

Thank you for the opportunity to comment on the above report. Our comments are as follows:

- Sensitivity 99%

Our own clinical data on the following patient groups:

Hashimoto's	49/51	(96.1%)
Graves'	38/52	(73%)

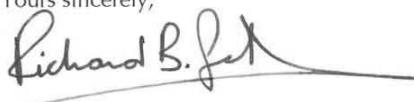
We recognise that the figure you generated is relative to pre-selected samples tested on an alternative ELISA method.

- Specificity 86%


We would expect about 8-10% of a healthy population to have raised anti-TPO antibody levels and this is well cited in the literature. However, the specificity is a little lower than expected, but still acceptable. Our own data: 172 samples from asymptomatic apparently healthy donors, with an age range of 21-51 years were tested on both DIASTAT anti-TPO and another test device. 16 sample (7%) were positive by the other test device and excluded from the calculation. 153/156 samples (98%) gave a value of less than 10 IU/ml.

In summary, we are very pleased with the performance of the DIASTAT Anti-TPO assays in terms of accuracy, linearity, precision, clinical specificity and clinical sensitivity, as depicted in your report.


Yours sincerely,




Richard B Seaton  
**MARKETING MANAGER**  
Autoimmune Diseases



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