510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION

DECISION SUMMARY

A. 510(k) Number:

k103039

B. Purpose for Submission:

New analyte

C. Measurand:

Tryptase

D. Type of Test:

Fluorescence immunoassay

E. Applicant:

Phadia US Inc

F. Proprietary and Established Names:

ImmunoCAP Tryptase

G. Regulatory Information:

1. Regulation section:

   21 CFR §866.5760 – Tryptase test system

2. Classification:

   Class II

3. Product code:

   OYL, tryptase assay system

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use(s):

   ImmunoCAP Tryptase is an in vitro semi-quantitative assay for measurement of tryptase in human serum or plasma (EDTA, lithium heparin or sodium heparin). It is intended for in vitro diagnostic use as an aid in the clinical diagnosis of patients with a suspicion of systemic mastocytosis in conjunction with other clinical and laboratory findings.

   ImmunoCAP Tryptase is to be used with the instruments Phadia 100, Phadia 250, or Phadia 1000.

2. Indication(s) for use:

   Same as intended use.

3. Special conditions for use statement(s):

   Prescription use only.

4. Special instrument requirements:

   For use with the Phadia 100, Phadia 250, or Phadia 1000 instrument.

I. Device Description:

ImmunoCAP Tryptase is a fluorescence immunoassay for the measurement of human tryptase based on ImmunoCAP solid phase. ImmunoCAP Tryptase measures the total tryptase levels including all forma of α-tryptase and β-tryptase. ImmunoCAP Tryptase concentrations are quantitatively reported in microgram/L (µg/L).

ImmunoCAP Tryptase consists of assay specific reagents to be used as part of Phadia Laboratory Systems along with already cleared instruments (including instrument and data management software) and system reagents (system reagents were cleared in k051218).

ImmunoCAP Tryptase kits (for the Phadia 100, Phadia 250, and Phadia 1000) contain the following reagents:

- ImmunoCAP Tryptase Conjugate (b) (4) (b) (4)
- ImmunoCAP Tryptase Anti-Tryptase (b) (4) bound to ImmunoCAP carrier
- Development solution (b) (4)
- Stop solution (b) (4)
- Washing solution
- IgE/ECP/Tryptase sample diluent (available separately, not included in the ImmunoCAP Tryptase kit)
- ImmunoCAP Tryptase Control (prepared from selected pooled human serum and

lyophilized)

In addition, the Phadia 100 kit includes the following reagents:

- Tryptase calibrators (1, 5, 12.5, 50, and 200 µg/L human tryptase in buffer)
- Tryptase Curve Control 1 (single dose vials of human tryptase in buffer)

In addition, the Phadia 250 and Phadia 1000 kits include the following reagents:

- ImmunoCAP Tryptase Calibrator Strip (1, 5, 12.5, 50, and 200 µg/L human tryptase in buffer)
- Tryptase Curve Control Strip (human tryptase in buffer)

J. Substantial Equivalence Information:

1. Predicate device name(s):

   None

2. Predicate 510(k) number(s):

   None

3. Comparison with predicate:

   Not applicable.

K. Standard/Guidance Document Referenced (if applicable):

Not applicable

L. Test Principle:

Anti-tryptase, covalently coupled to ImmunoCAP, reacts with the tryptase in the patient sample. After washing, enzyme-labeled antibodies against tryptase are added to form a complex. After incubation, unbound enzyme-anti-tryptase 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 tryptase 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision studies were conducted in alignment with CLSI EP5-A2. Precision studies were conducted on the Phadia 100, Phadia 250, and Phadia 1000 instruments. Total

imprecision was calculated as the square root of the sum of the squares of each imprecision component (between instruments, between runs, within run).

The acceptance criteria for precision were:

Phadia 100:

CVtotal% (b) (4)

CVtotal%

CVtotal%

Phadia 250 and Phadia 1000:

CVtotal% (b) (4)

CVtotal%

CVtotal%

Phadia 100: Ten serum samples with different levels of tryptase were assayed on three different instruments. Each sample was tested in multiple runs (9 runs for samples #1-5, 6 runs for samples #6-10). Four replicates were tested per run. All acceptance criteria were met. The results are shown in the following table:

Sample	N	Mean µg/L	Between Instruments %CV	Between Runs %CV	Within Run %CV	Total %CV
1	108	(b) (4)				
2	108					
3	108					
4	108					
5	108					
6	72					
7	72					
8	72					
9	72					
10	72					

Phadia 250: The precision results are presented in the following table. 16 different serum samples with different levels of tryptase were assayed on three different instruments. Each sample was tested in 6 runs, and four replicates were tested per run. Acceptance criteria for CVtotal% were met for all samples, with the exception of two samples in the very low range (Sample 1 and 2), which were both marginally out of specification. The result was considered acceptable since tryptase values in these samples are well below any relevant clinical decision points.

Sample	Mean µg/L	Between Instruments %CV	Between Runs %CV	Within Run %CV	Total %CV
1	2	(b) (4)			
2	2				
3	4				
4	8				
5	18				
6	34				
7	59				
8	99				
9	110				
10	114				
11	178				
12	21				
13	20				
14	19				
15	182				
16	173				

Phadia 1000: The precision results for Phadia 1000 are presented in the following table. 15 different serum samples with different levels of tryptase were assayed on two different instruments. Each sample was tested in 9 runs, and four replicates were tested per run. All specifications for CVtotal% were met for all samples. Since only two

instruments were used to evaluate the first 10 samples, CV between instruments is not applicable for those samples.

Sample	N	Mean µg/L	Between Instruments %CV	Between Runs %CV	Within Run %CV	Total %CV
1	72	(b) (4)				
2	69*					
3	72					
4	72					
5	72					
6	72					
7	72					
8	72					
9	72					
10	72					
11	72					
12	72					
13	72					
14	72					
15	72					

*three observations less due to laboratory error

Lot-to-lot reproducibility: Seven different samples with tryptase concentrations ranging 8-192 µg/L were tested using 3 different lots of ImmunCAP Tryptase Conjugate and 3 different lots of ImmunoCAP Tryptase Anti-Tryptase in different combinations of conjugate and anti-tryptase. All assays were performed on the Phadia 250 instrument. Each sample was tested with each of five different reagent combinations in 3 assay runs, with 3 replicates per run. The data are summarized in Table 4:

Sample	Mean µg/L	Between Lots %CV	Between Runs %CV	Within Run %CV	Total %CV
1	(b) (4)				
2					
3					
4					
5					
6					
7					

b. *Linearity/assay reportable range:*

Linearity experiments were performed according to CLSI EP6-A. Six different serum samples with tryptase levels ranging 30 µg/L to 194 µg/L were manually diluted in two-fold dilutions in near tryptase free serum (tryptase level of 0.46 µg/L). The samples were tested with ImmunoCAP Tryptase in 2 replicates in 1 assay run.

The assays were performed according to ImmunoCAP Tryptase Directions for Use using the Phadia 250 instrument. Recoveries were in the range (b) (4) except for some of the intermediate dilutions for the 134 µg/L sample.

Sample	Dilution	Observed Mean (µg/L)	Expected Mean (µg/L)	Recovery (%)
194 µg/L	1:1	(b) (4)		
	1:2			
	1:4			
	1:8			
	1:16			
	1:32			
	1:64			
	1:128			

Sample	Dilution	Observed Mean (µg/L)	Expected Mean (µg/L)	Recovery (%)
169 µg/L	1:1	(b) (4)		
	1:2			
	1:4			
	1:8			
	1:16			
	1:32			
	1:64			
	1:128			
134 µg/L	1:1			
	1:2			
	1:4			
	1:8			
	1:16			
	1:32			
	1:64			
101 µg/L	1:1			
	1:2			
	1:4			
	1:8			
	1:16			
	1:32			
73 µg/L	1:1			
	1:2			

Sample	Dilution	Observed Mean (µg/L)	Expected Mean (µg/L)	Recovery (%)
	1:4	(b) (4)		
	1:8			
	1:16			
	1:32			
30 µg/L	1:1			
	1:2			
	1:4			
	1:8			

c. *Recovery*

A recovery study was performed on the Phadia 100 instrument using purified tryptase (with known concentration) spiked into serum samples containing different basal levels of tryptase. Recovery values are shown in the chart below. Recovery values met the pre-determined specification of (b) (4)

Sample	Level	Tryptase (µg/L), Serum + Tryptase (A)	Tryptase (µg/L) Serum only (B)	Tryptase (µg/L) Buffer + Tryptase (C)	Recovery (%) A/(B+C)
1	1	(b) (4)			
	2				
	3				
2	1				
	2				
	3				
3	1				
	2				
	3				

d. Traceability. Stability. Expected values (controls. calibrators. or methods):

Traceability: There is no internationally traceable standard for tryptase. The original reference standard was produced in-house and its concentration determined by the supplier. Each subsequent lot is standardized against reference standards. New reference standard is produced approximately every three years.

Stability: Real-time stability was evaluated for ImmunoCAP Tryptase Anti-Tryptase and for the ImmunoCAP Tryptase Conjugate. Three independent preparations of Anti-Tryptase were stored at 2-8^{o}C and were tested at various time points using the Phadia 100 instrument. Anti-tryptase was shown to be stable for up to 25 months when stored at this temperature.

Three independent preparations of ImmunoCAP Tryptase Conjugate were stored at 2-8^{o}C and were tested at various time points using the Phadia 100 instrument. Conjugate was shown to be stable for up to 25 months when stored at this temperature.

On board stability of open ImmunoCAP Tryptase Conjugate bottles on the Phadia 250 instrument was determined by storing the conjugate under transport-simulated conditions. Conjugate was stored at 32^{o}C for one week, followed by movement to 2-8^{o}C for two 18-24 hour periods, then stored at 2-8^{o}C. Prior to each test occasion (0, 13, and 25 months), the conjugate bottles were uncapped for 7 days at 2-8^{o}C to simulate on-board conditions. The results demonstrated that ImmunoCAP Tryptase Conjugate was stable under these conditions.

The short term stability of samples was investigated. Samples from 15 self-reported healthy volunteers containing various levels of tryptase were used for this study. The assays were performed using the Phadia 250 instrument. The results of the study demonstrated that samples could be stored at room temperature for up to 48 hours, could be frozen and thawed for up to 5 cycles, and could be stored at 2-8^{o}C for up to 7 days.

ImmunoCAP Tryptase Calibrators and Calibrator Strip:

The raw material for ImmunoCAP Tryptase Calibrators and Curve Control is tryptase protein purified from human lung. For the Phadia 100, calibrators at five levels (1; 5; 12.5; 50 and 200 μg/L) are provided in individual vials. For the Phadia 250 and Phadia 1000, the ImmunoCAP Tryptase Calibrator Strip contains calibrators at five levels (1; 5; 12.5; 50 and 200 μg/L).

The stability of the ImmunoCAP Tryptase Calibrators (as used on the Phadia 100) was investigated. Three lots of calibrators were tested. The assays were performed using the Phadia 100 instrument. Each lot was stored under transport-simulated conditions—at 30^{o}C for one week followed by 25 months at 2-8^{o}C. The calibrators were found to be stable for up to 25 months when stored under these conditions.

An on-board stability study was performed with the ImmunoCAP Tryptase Calibrator

Strip. This study is applicable to the Phadia 250 and Phadia 1000 instruments. One lot of ImmunoCAP Tryptase Calibrator Strip was transport-simulated by storage at 32°C for one week, followed by movement to 2-8°C for two 18-24 hour periods, then stored at 2-8°C. To demonstrate on-board stability, the calibrator strip was stored at 32°C for 28 days. The studies demonstrated that calibrators in the strip were stable under these conditions.

ImmunoCAP Tryptase Curve Control and Curve Control Strip:

The ImmunoCAP Tryptase Curve Control is packaged in either a vial format (Phadia 100) or the strip format (Phadia 250 and Phadia 1000) which consists of the same material as two of the five calibrators. The Curve Controls are automatically performed with each new run as a check on the overall curve performance. The stability data for calibrators also applies to this material.

ImmunoCAP Tryptase Control:

The stand-alone ImmunoCAP Tryptase Control is prepared using tryptase purified from human lung. Three lots of (b) (4) were tested utilizing the Phadia 100 instrument. The results showed that (b) (4) ImmunoCAP Tryptase Control is stable for 26 months when stored at 2-8°C, and (b) (4) control is stable for 4 weeks when stored at 2-8°C.

e. *Detection limit:*

Limit of detection (LoD) studies were performed as follows. 24 replicates of the ImmunoCAP IgE/ECP/Trptase Sample Diluent and 24 replicates of the lowest ImmunoCAP Tryptase Calibrator (1 µg/L) were tested using the Phadia 100, Phadia 250, and Phadia 1000 instruments in one assay run each. The acceptance criteria were that the LoD should be (b) (4) Calculations of Limit of Blank (LoB) and LoD were performed according to CLSI EP17-A. The table below summarizes the results of the Limit of Detection studies. Calculations were performed on Fluorescence Response Units (RU) since no tryptase concentrations are calculated below the lowest calibrator.

Instrument	Mean Calibrator 1 (RU)	Mean Sample diluent (RU)	LoB (RU)	LoD (RU)
Phadia 100	(b) (4)			
Phadia 250				
Phadia 1000				

The results showed that the LoB and LoD for each of the three instruments were (b) (4)

f. Hook effect:

Five samples from different matrices (two serum samples and one sample each of EDTA plasma, lithium heparin plasma, and sodium heparin plasma) with tryptase concentrations approximately 10 times the highest ImmunoCAP Tryptase calibrator point (b) (4) were used to assess any potential hook effects. No hook effect was detected for any of these samples.

g. Analytical specificity:

In one study, interference testing performed with two serum samples, 13.2 µg/L and 1.8 µg/L tryptase with Bilirubin F (b) (4) Bilirubin C (b) (4), Hemoglobin (b) (4) Chyle (b) (4) and Rheumatoid Factor (b) (4) All samples exhibited recoveries of (b) (4)

In a second study, interference testing performed with three serum samples, (b) (4) of tryptase with Bilirubin F (b) (4)), Bilirubin C ((b) (4) Hemoglobin ((b) (4) Chyle ((b) (4)) and Rheumatoid Factor ((b) (4)). All samples exhibited recoveries of (b) (4).

Interference testing was also performed with heparin (concentrations ranging (b) (4)) spiked into blank samples, as well as in samples containing tryptase levels ranging (b) (4) All samples exhibited recoveries of (b) (4). No effect of heparin was observed on blank samples.

Interference testing was also performed with human anti-mouse antibodies (HAMA) with concentrations up to (b) (4) spiked into serum samples containing tryptase levels ranging from (b) (4) Two different studies were performed, each using a different master lot of ImmunoCAP Tryptase assay reagents and using the Phadia 250 system. The results from the studies met the acceptance criteria (b) (4) observed/expected for spiked sample/unspiked sample), with the exception of one borderline result (b) (4) for a sample containing (b) (4)

h. Assay cut-off:

The cut-off limit of 20 µg/L tryptase is internationally accepted as a minor criterion for systemic mastocytosis, and is defined by the World Health Organization Classification of Tumors. The WHO classification criteria are based on a consensus process as described in the introduction of the present 4th edition of "WHO classification of tumors of hematopoietic and lymphoid tissues from 2008[1]. The present valid criteria are described in a separate chapter in this volume[2].

[1] Harris NL, Campo E, Jaffe S et.al. Introduction. In: 4th edition of WHO classification of tumours of haematopoietic and lymphoid tissues.: (eds) Swerdlow SH, Campo E, Harris NL et al., Lyon: IARC; 2008:14-15

[2] Horny HP, Metcalfe DD, Bennet JM et al. Mastocytosis. In: 4th edition of WHO classification of tumours of haematopoietic and lymphoid tissues.: (eds) Swerdlow SH, Campo E, Harris NL et al., Lyon: IARC; 2008: 54-63.

The consensus proposal, citing 175 scientific publications spanning over several decades, was published in 2001.

The basis of the consensus proposal, i.e. patients, parameters, and analyses are described in Valent et al.[3]: The consensus proposal is a retrospective analysis of a large number of patients with established mastocytosis in different centers of Europe and North America. In addition, a larger number of control cases without mastocytosis (myeloid neoplasms) were examined. In all cases, clinical findings, laboratory findings, histologic and immunohistologic data were collected for all patients. The clinical course was compared to, and correlated with, laboratory and histologic parameters. Data from almost all patients have been published previously. In addition, the entire literature was reviewed whenever possible to compare and discuss their findings.

The proposal was discussed and accepted by WHO at a final consensus meeting "Year 2000 Working Conference on Mastocytosis" and the WHO criteria were published 2001 in the 3rd edition of "WHO classification of tumors of hematopoietic and lymphoid tissues"[4] and were then transferred into the 4th edition[1], published in 2008.

The WHO consensus Diagnostic Criteria for Systemic Mastocytosis (SM) are listed as follows:

If at least 1 major and 1 minor, or at least 3 minor criteria, are met, the diagnosis of Systemic Mastocytosis (SM) can be established.

Major Criteria: Multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous organ(s) (>15 mast cells in aggregate).

Minor Criteria:

a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (> 25%)

b) C-kit mutation at codon 816 in extracutaneous organ(s). (Activating mutations at codon 816; in most cases, c-kit D816V)

c) Mast cells in bone marrow express CD2 and/or CD25

d) Serum total tryptase > 20 µg/L (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease).

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[3] Valent P., Horny HP., Escribano L., et al. Diagnostic criteria and classification of mastocytosis: a concensus proposal. Leukemia Research 2001; 25: 603-625.

[4] Valent P, Horny H, Li C, et al: Mastocytosis. In: 3rd edition of World health organization classification of tumors. Pathology and genetics of tumors of hematopoietic and lymphoid tissue. (eds) Jaffe E, Harris N, Stein H, Vardiman J, Lyon, LARC Press, 2001: 293-302. (Not available, replaced by 4th edition)

2. Comparison studies:

a. *Method comparison with predicate device:*

Not applicable.

b. *Matrix comparison:*

Two matrix comparison studies were performed on the Phadia 250 instrument. All samples were tested with two replicates in one assay run.

The first matrix comparison study (serum and EDTA plasma) was performed using samples from 21 healthy patients with tryptase levels ranging from (b) (4) Ratios for EDTA plasma/serum ranged (b) (4), consistent with acceptance criteria of (b) (4) for all samples.

The second matrix comparison study (serum, lithium heparin plasma and sodium heparin plasma) was performed using samples from 20 healthy patients with tryptase levels ranging from (b) (4). Ratios for lithium heparin plasma/serum and sodium heparin plasma/serum ranged (b) (4), consistent with acceptance criteria of (b) (4) for all samples.

For both studies, the plasma/serum ratio was within the range (b) (4) for samples close to the assay cutoff of 20 µg/L. Deming regression was performed for each comparison. Slopes and intercepts from this regression analysis are shown in the table below.

Deming Regression Analysis		Estimate	Lower 95%	Upper 95%
Serum vs EDTA plasma	Intercept	(b) (4)		
	Slope			
Serum vs lithium heparin plasma	Intercept			
	Slope			
Serum vs sodium heparin plasma	Intercept			
	Slope			

c. Instrument comparison:

To determine the conformity between the Phadia 100, Phadia 250, and Phadia 1000 instruments, the following study was conducted. The ImmunoCAP Tryptase Calibrators, 50 individual samples, 3 pooled internal control samples and two lots of ImmunoCAP Tryptase Control were assayed in 6 replicates with four different

Phadia 100 instruments (3 runs each), 3 different Phadia 250 instruments (2 runs each) and 3 different Phadia 1000 instruments (2 runs each). For each sample, the natural log of the ratio of the mean tryptase results between the two instruments was calculated (for example, to compare the Phadia 100 and Phadia 250 results, the calculation was ln(mean result$_{250}$/mean result$_{100}$). Acceptance criteria were (b) (4) for this calculation. Samples that tested above the reportable range (b) (4) were not included in the calculations. The results are summarized as follows:

Conformity calculation	Average result
ln(250/100)	(b) (4)
ln(1000/100)	
ln(250/1000)	

A Deming regression analysis of the instrument conformity data was also performed, with the following results:

Phadia Instrument Comparison	Intercept (95% CI)(µg/L tryptase)	Slope (95% CI)
Phadia 100 vs. Phadia 250	(b) (4)	
Phadia 1000 vs. Phadia 250		

3. Clinical studies:

   a. *Clinical Sensitivity and Specificity:*

Adult patients

Samples from 138 adult patients (63 male and 75 female, age range 24-81) with a suspicion of mastocytosis (all comers) were collected at routine patient visits over a 3-year period. The reasons for referral included skin lesions (61 patients), anaphylaxis (54 patients), mast cell activation (15 patients), and other clinical findings (8 patients). ImmunoCAP Tryptase assays were performed on these samples, using the Phadia 250 instrument. Sample collection was coordinated by the Spanish Network on Mastocytosis and performed at one site in Spain. Patients were classified according to the WHO recommendations for mastocytosis, without consideration of the fourth minor criterion of tryptase levels persistently exceeding 20 µg/L.

		Systemic Mastocytosis (without tryptase consideration)		
		+	-	Total
ImmunoCAP Tryptase Assay (20 µg/L cutoff)	+	72	27	99
	-	17	22	39
	Total	89	49	138

Sensitivity (72/89) = 80.9% (95% CI: 71.5% to 87.7%)

Specificity (22/49) = 44.9% (95% CI: 31.8% to 58.7%)

Elevated tryptase level is one of several minor criteria for a diagnosis of mastocytosis. Tryptase levels are known to be increased in a number of disorders apart from mastocytosis, e.g. in AML patients and in patients with CML and other myeloid neoplasms not classified as systemic mastocytosis. This results in a low (~45%) specificity of the tryptase assay in adults if used as the sole criterion for mastocytosis. However, since tryptase is used in conjunction with other clinical and diagnostic criteria, tryptase is a useful diagnostic tool despite of its low specificity in adults.

The data from the adult clinical study was reanalyzed to include the tryptase result in the calculations. Inclusion of tryptase would have changed the diagnosis for three patients:

		Systemic Mastocytosis (with tryptase consideration)		
		+	-	Total
ImmunoCAP Tryptase Assay (20 µg/L cutoff)	+	75	24	99
	-	17	22	39
	Total	92	46	138

Sensitivity (75/92) = 81.5% (95% CI: 72.4% to 88.1%)

Specificity (22/46) = 47.8% (95% CI: 34.1% to 61.9%)

Pediatric patients:

Samples from 156 pediatric patients (ages <1-19) with a suspicion of mastocytosis were collected at routine patient visits over an eight year period (2003-2011). The type of symptoms leading to referral included maculopapular (76 patients), nodular

(34 patients), diffuse (19 patients), mastocytoma (18 patients), and plaque (9 patients). ImmunoCAP Tryptase assays were performed on these samples, using the Phadia 250 instrument. Sample collection was coordinated by the Spanish Network on Mastocytosis and performed at one site in Spain. Patients were classified according to the WHO recommendations for mastocytosis, without consideration of the fourth minor criterion of tryptase levels persistently exceeding 20 µg/L.

		Systemic Mastocytosis (without tryptase consideration)		
		+	-	Total
ImmunoCAP Tryptase Assay (20 µg/L cutoff)	+	19	4	23
	-	4	129	133
	Total	23	133	156

Sensitivity (19/23) = 82.6% (95% CI: 62.9% to 93.0%)

Specificity (129/133) = 97.0% (95% CI: 92.5% to 98.8%)

The data from the pediatric clinical study was reanalyzed to include the tryptase result in the calculations. Inclusion of tryptase would have changed the diagnosis for four patients:

		Systemic Mastocytosis (with tryptase consideration)		
		+	-	Total
ImmunoCAP Tryptase Assay (20 µg/L cutoff)	+	23	0	23
	-	4	129	133
	Total	23	133	156

Sensitivity (23/27) = 85.2% (95% CI: 67.5% to 94.1%)

Specificity (129/129) = 100.0% (95% CI: 97.1% to 100.0%)

Children seen by physicians for the suspicion of mastocytosis do not typically have other diseases that may elevate tryptase levels (e.g. AML, CML) to the same extent as adults. Therefore the clinical specificity for tryptase is higher in children than in adults.

The diagnosis of systemic mastocytosis has been established using worldwide criteria that included input from U.S. clinicians and scientists. The population demographics

are similar between Spain and the U.S. Systemic mastocyosis occurs in all ethnic groups, but is seen more often in Caucasians[2].

b. Other clinical supportive data (when a. is not applicable):

Not applicable.

4. Clinical cut-off**:**

See Assay Cut-off.

5. Expected values/Reference range:

Serum samples from 124 healthy individuals between 3-67 years of age were analyzed in duplicate using the ImmunoCAP Tryptase assay on the Phadia 250 instrument. The results showed that tryptase concentrations in this population had a mean concentration of tryptase of 4.4 µg/L and an upper 95th percentile at 12.0 µg/L.

The results for adults only (89 individuals, ages 22-67) had a mean concentration of tryptase of 5.0 µg/L and an upper 95th percentile at 13.5 µg/L. Thus, there were no major differences observed in expected values between healthy adults and healthy children, consistent with data reported in the literature[5].

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The petition for Evaluation of Automatic Class III Designation for this device is accepted. The device is classified as Class II under regulation 21 CFR 866.5760 with special controls. The special control guidance document "*Class II Special Controls Guidance Document: Tryptase Test System as an Aid in the Diagnosis of Systemic Mastocytosis*" will be available shortly.

[5] Komarow, HD et al. (2009) J. Allergy Clin. Immunol 124 (4), 845-848