Class II Special Controls Guideline: Tryptase Test System as an Aid in the Diagnosis of Systemic Mastocytosis

Guideline for Industry and Food and Drug Administration Staff

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostics and Radiological Health
Division of Immunology and Hematology Devices

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Preface

Public Comment

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Class II Special Controls Guideline: Tryptase Test System as an Aid in the Diagnosis of Systemic Mastocytosis

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I. Introduction

This document was developed as a special controls guideline to support the classification of a tryptase test system into class II (special controls). A tryptase test system is a device that aids in the diagnosis of systemic mastocytosis. 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.

A tryptase test system is not indicated for a stand-alone diagnosis of mastocytosis or in the evaluation of anaphylaxis.

This guideline identifies measures that FDA believes will mitigate the risks to health associated with these devices and provide a reasonable assurance of safety and effectiveness. Firms submitting a 510(k) for a tryptase test system must either to (1) comply with the particular mitigation measures set forth in the special controls guideline or (2) use alternative mitigation measures, but demonstrate to the Agency's satisfaction that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness.

II. Tryptase Test Systems Background

Human mast cells play a central role in inflammatory processes. During IgE mediated allergic reactions they are activated and release inflammatory mediators including tryptase. Baseline levels of tryptase in the circulation reflect the number of mast cells. The number of mast cells is increased in systemic mastocytosis. Persistently elevated levels of tryptase may serve as a clinical marker of systemic mastocytosis.

Systemic mastocytosis, often termed systemic mast cell disease (SMCD), is a heterogeneous clonal disorder of the mast cell and its precursor cells. The clinical symptoms and signs of systemic mastocytosis or SMCD are due to the accumulation of these clonally derived mast cells in different tissues, including bone marrow, skin, the gastrointestinal (GI) tract, the liver, and the spleen. The clinical presentation of mastocytosis can vary from a pruritic rash to unexplained collapse and sudden death. Patients with mastocytosis often have a long history of chronic and acute symptoms that were unrecognized as mastocytosis.

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 (WHO) Classification of Tumors.[1] 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.[2] The present valid criteria are described in a separate chapter in this 4th edition.[3]

The consensus proposal, citing 175 scientific publications spanning over several decades, was published in 2001.[4]

The basis of the consensus proposal (i.e., patients, parameters, and analyses) is described in Valent et al.[5] It 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. 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 in this retrospective analysis have been published previously.

The proposal was discussed and accepted by WHO at a final consensus meeting "Year 2000 Working Conference on Mastocytosis". The WHO criteria were published in 2001 in the 3rd

[1] 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.
[2] 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.
[3] 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.
[4] Valent P., Horny HP., Escribano L., et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leukemia Research 2001; 25: 603-625.
[5] Valent P., Horny HP., Escribano L., et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leukemia Research 2001; 25: 603-625.

edition of "WHO classification of tumors of hematopoietic and lymphoid tissues"[6] and were then transferred into the 4th edition,[1] published in 2008.

The WHO consensus diagnostic criteria for Systemic Mastocytosis (SM) are as follows:

> If at least 1 major and 1 minor, or at least 3 minor criteria, are met, the diagnosis of 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 ng/mL (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease).

Tryptase protein is present in different forms of which the α- and β-forms are significant for measurements of tryptase in plasma or serum. There are two predominant forms of α-tryptase (αI and αII) and three forms of β-tryptase (βI, βII and βIII). The α-tryptases show approximately 90% sequence homology to β-tryptases.[7]

Both α- and β-tryptases are processed from precursor or pre-pro-tryptases into pro-tryptases, which are enzymatically active. The processing of the α-tryptases stops at pro-tryptase whereas the β-tryptases can be further cleaved and processed to mature β-tryptase.

Both pro α-tryptase and pro β-tryptase are constantly produced and released from the mast cells and comprise the majority of circulating, baseline forms of tryptase, in the absence of a mast cell activation event. Mature β-tryptase is stored in mast cell granules and is only released upon mast cell activation.

III. Premarket Notifications - Background

FDA concludes that special controls, when combined with the general controls of the Federal Food, Drug & Cosmetic Act (the FD&C Act), are necessary to provide reasonable assurance of the safety and effectiveness of tryptase test system devices. A manufacturer who intends

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[6] 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).

[7] Schwartz LB; Diagnostic Value of Tryptase in Anaphylaxis and Mastocytosis, Immunol Allergy Clin N Am 26 (2006), 451-463.

to market a device of this type must (1) conform to the general controls of the FD&C Act, including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific issues of safety and effectiveness identified in this guideline, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This guideline identifies the classification regulation for tryptase test system devices. In addition, other sections of this guideline list the risks to health and describe mitigation measures that, if followed by manufacturers and combined with the general controls, will address the risks associated with these devices and will generally lead to a timely premarket notification [510(k)] review. This document will supplement other FDA documents regarding the specific content requirements of a premarket notification submission for tryptase test system devices. For additional information regarding 510(k) submissions, refer to 21 CFR 807.87 and the Center for Devices and Radiological Health (CDRH) Device Advice: Comprehensive Regulatory Assistance.[8]

IV. Scope

The scope of this document is limited to devices identified and classified in 21 CFR 866.5760.

21 CFR 866.5760 Tryptase test system

a) *Identification:* A tryptase test system is a device that aids in the diagnosis of systemic mastocytosis. 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.

b) *Classification.* Class II (special controls). The special control is FDA's guideline entitled "Class II Special Controls Guideline: Tryptase Test System as an Aid in the Diagnosis of Systemic Mastocytosis." See § 866.1(e) for the availability of this guideline document.

V. Risks to Health

FDA has identified the risks of false negative and false positive test results and inappropriate use as risks to health associated with the use of this device that require special controls.

Failure of the assay to perform as indicated could lead to inappropriate assessment and improper management of patients with systemic mastocytosis. Specifically, a sufficiently falsely low tryptase level would produce a false negative test result and possibly a determination that the patient may not have systemic mastocytosis, which could lead to less than optimal patient management and a delay in diagnosis. A sufficiently falsely high tryptase level would produce a false positive test result and possibly a determination that the patient may have systemic mastocytosis which could also lead to inappropriate patient

[8] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm.

management and delay of the true diagnosis. Further, there are concerns about inappropriate use with this device. The tryptase test system described in this guideline document is not indicated for use as a stand-alone test for systemic mastocytosis. This tryptase test system described in this guideline also does not address the use of tryptase in the evaluation of anaphylaxis. Inappropriate use of the tryptase test system as a marker for anaphylaxis may lead to inappropriate patient management for allergic reactions.

FDA has identified the risks generally associated with the use of tryptase test system devices that require special controls. The measures to mitigate these identified issues are in this guideline, as shown in the table below, in combination with proposed subsection 21 CFR 866.5760. Under this guideline, manufacturers who intend to market a device of this type must conduct a risk analysis prior to submitting a premarket notification to identify any other risks specific to their device. The premarket notification must describe the risk analysis method used. If you elect to use an alternative approach to mitigate a particular risk identified in this guideline, or if you or others identify additional potential risks from use of a device of this type, you must provide sufficient detail regarding the approaches used to mitigate these risks and a justification for your approach.

Table 1 – Identified Risks to Health and Mitigation Measures

Identified risk	Mitigation Measures
False negative result	Device description containing the information specified in the special control guideline (Section VI) Analytical performance validation (Section VII) Software (Section VIII) Clinical performance evaluation (Section IX) Labeling (Section X)
False positive result	Device description containing the information specified in the special control guideline (Section VI) Analytical performance validation (Section VII) Software (Section VIII) Clinical performance evaluation (Section IX) Labeling (Section X)
Inappropriate use	Labeling (Section X)

VI. Device Description

In your 510(k) submission, you must include a device description that meets the requirements of 21 CFR 807.87(a) and (f) and you must identify the legally marketed predicate device as required by 21 CFR 807.92(a)(3). Furthermore, you must also identify the applicable regulation and the product code(s) for your device; you must include a table that outlines the similarities and differences between the predicate device (or another legally marketed device for the same intended use) and your device. You may reference appropriate peer-reviewed

articles that support the use of your device for its intended diagnostic use and the specific test principles incorporated into the device design. You must describe each of these device elements in detail.

In addition, you must include the following descriptive information to adequately characterize your tryptase test system.

a. **Intended Use/Indications for Use**:
Your submission must include an intended use/indications for use statement in accordance with 21 CFR 807.87(e) and 21 CFR 807.92 (a)(5). In complying with this requirement you must summarize how you, the manufacturer, intend the product to be used, and the clinical purpose of the test. The intended use for tryptase test systems must include the name of the test, that it is semi-quantitative or quantitative, the specimen type, the test method, and that it is an aid in the diagnosis of systemic mastocytosis. This test is not a stand-alone test and test result must be interpreted in conjunction with other laboratory and clinical findings.

b. Test Components and Methodology
You must describe in detail the reagents, assay format/methodology, instruments and software used in your device.

Test Reagents: You must provide a description of all reagents and components (including calibrators, controls, and instruments) provided or recommended for use. Include a description of the source of each reagent (e.g., mouse, cell line), its purification method, and the verification process for use in the test. You must provide certificates of analysis if the reagent is obtained from an outside vendor. A summary of this information in table format for the individual assays must be provided.

Test Methodology: You must provide a description of the test methodology employed by your device. This must include the test platform(s) and method of measurement.

Test Results: You must state the description of the nature of the test result output (e.g., a continuous numerical value to which a cut-off is applied with the specified unit of measure (e.g. ng/mL, etc.)) and interpretation of the test result.

VII. Analytical Performance Validation

In your 510(k) submission, you must detail the study design you used to evaluate each of the performance characteristics outlined below. All analytical performance studies must be conducted using the final version of your tryptase test system device. For each of the analytical performance studies described below, you must state your predetermined acceptance criteria.

a. Precision / Reproducibility

You must provide an evaluation of the precision of your test system. The Clinical and Laboratory Standards Institute (CLSI) document EP5-A2 "Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline" includes guidelines that may be helpful for developing design and computations of the data in the precision studies.

The samples in the precision study must span the reportable range of the assay; you must include several samples with values close to the cut-off of the tryptase test system.

You must provide an evaluation of the repeatability (within-run precision), between-run, between-instrument, and between-lot components of imprecision. Include a detailed description of the number of days, number of operators, assays, instruments, and lots evaluated in the study. For lot-to-lot reproducibility, you must use at least three lots with unique combinations of batches of your critical reagents (e.g. antibodies, antibody conjugates.)

For qualitative tests, you may refer to CLSI document EP12-A, "User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline" for design of your reproducibility studies.

b. Linearity

For quantitative or semi-quantitative tests, you must provide a demonstration of linearity for the tryptase test system across the reportable range of the assay by comparing the observed results to expected results. You may refer to CLSI document EP6-A "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline" for more information about conducting linearity studies. Acceptance criteria for linearity must be pre-determined before performing these studies.

c. Performance at Low Levels

For quantitative or semi-quantitative tests, you must demonstrate the limit of blank, limit of detection and limit of quantitation for your assay. You may refer to CLSI document EP17-A "Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline" for more information about conducting limit of detection and limit of quantitation studies.

d. Interference

If your specimen type is serum or plasma (specify type(s) of anti-coagulants used for the plasma samples), you must indicate in tabular format the concentrations of interferents evaluated and whether your assay is subject to interference by hemoglobin, bilirubin F/bilirubin C, triglycerides/chyle, heterophilic antibodies (HAMA), rheumatoid factor and other relevant interferents. You must demonstrate the percentage difference in assay results by comparing a sample with interferent to the same sample without interferent for its impact on the result along with the 95% confidence interval. Reporting the percentage difference for each analyte from this analysis is helpful as well. Generally one analyte concentration near the clinical decision point must be evaluated for all interferents, as

well as at least one low-level (but above the limit of quantitation) and one medium-high level analyte.

e. Hook Effect

When applicable (for example, with sandwich immunoassay methods), you must demonstrate that excess analyte does not cause a hook (prozone) effect.

f. Matrix comparison

If your test recommends more than one sample type, you must evaluate the possibility of matrix effects on the test. We encourage you to refer to CLSI document EP-14A2, "Evaluation of Matrix Effects; Approved Guideline – Second Edition."

g. Stability

You must describe your study design for determining the real-time stability of the reagents, calibrators and controls, and, if applicable, shelf-life, open vial and on-board stability. Your stability studies must include information about the times, temperatures, and storage of your test system and reagents. For each study, you must provide your acceptance criteria and a description of how you selected the acceptance criteria values (i.e., concluded that the limit of the acceptance criteria did not impact the results). We encourage you to refer to CLSI document EP25-A "Evaluation of Stability of In Vitro Diagnostic Method Products; Approved Guideline" for more information about conducting stability studies.

You must demonstrate the stability of the specimens across the extremes of these parameters (e.g., temperature, time to freezing, freeze-thaw, and shipping) for use in your test. The results of your study must demonstrate that samples can be stored, frozen/thawed, and transported under the appropriate conditions.

h. Calibrators and Controls

You must describe the following for your control and calibration materials:

- The nature of the calibrators that you include with your system
- The nature and function of the various controls that you include with, or recommend for, your system.
- The methods for value assignment and validation of control and calibrator material.
- Stability of calibrators and controls.
- Include certificates of analysis if any reagents incorporated into your test system are supplied by a vendor.

i. Traceability

For a quantitative tryptase assay, you generally must demonstrate traceability of your tryptase assay calibrators to an international standard for tryptase if one exists. Other approaches to demonstrate traceability may be considered, such as the preparation of tryptase assay calibrators by traceable gravimetric methods or using absolute analytical

methods such as amino acid analysis. Such alternative approaches may be discussed with FDA.

For a semi-quantitative tryptase assay you must document how your tryptase assay calibrators are prepared and traced to an international standard for tryptase, if one exists, or to your own internal standards.

VIII. Software

If the instrument and current version of the software used with your test have not yet been reviewed and cleared by FDA, you must submit software information detailed in accordance with the level of concern associated with your software (See the guidance entitled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm for information on how FDA believes the level of concern should be determined.). You must determine the level of concern prior to determining how to mitigate the hazards associated with your device's software. *In vitro* diagnostic devices of this type are typically considered a moderate level of concern because software flaws could indirectly affect the patient and potentially result in injury when the healthcare provider and patient do not get accurate information.

You must include the following points, as appropriate, in preparing software documentation for FDA review:

- Full description of the software design. You must also consider privacy and security issues in your design. Information about some of these issues may be found at http://www.hhs.gov/ocr/privacy/hipaa/understanding/index.html,[9] a Web site regarding the Health Insurance Portability and Accountability Act.
- Hazard analysis based on critical thinking about the device design and the impact of any failure of subsystem components, such as signal detection and analysis, data storage, system communications, and cyber security in relationship to incorrect patient reports, instrument failures, and operator safety.
- Documentation of complete verification and validation (V&V) activities for the version of software that will be submitted to demonstrate substantial equivalence. You must also submit information regarding validation of the compatibility of test software with any instrumentation software.
- If the information you include in the 510(k) is based on a version other than the release version, identify all differences in the 510(k) version and detail how these differences (including any unresolved anomalies) impact the safety and effectiveness of the device.

[9] This website was accessed on July 31, 2014. However, since this is not an FDA website, we cannot ensure the continued availability or accuracy of its contents after the publication of this guideline.

Below are additional references to consider in developing and maintaining your device under good software life cycle practices consistent with FDA regulations.

- The guidance entitled "General Principles of Software Validation" found at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM085371.pdf.

- The guidance entitled "Off-the-Shelf Software Use in Medical Devices" found at http://www.fda.gov/ MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073778.htm.21 CFR 820.30 Subpart C – Design Controls of the Quality System Regulation;

- ISO 14971-1; Medical devices - Risk management - Part 1: Application of risk analysis; and

- AAMI SW68:2001; Medical device software - Software life cycle processes.

If the instrument and current version of the software have previously been cleared by FDA, you must document any significant changes that have been made to the software associated with implementation of your tryptase test system. You may list the different version numbers of the software used with their corresponding date of clearance.

IX. Clinical Performance Evaluation

The data from your clinical studies must support the indications for use and claims for your device. The clinical validation study must use patient samples that are obtained from the intended use population. You must describe the protocol of each clinical study, including the inclusion and exclusion criteria, study design, statistical analysis method, and statistical justification of the sample size.

Your clinical studies must be analyzed in two ways: without inclusion of tryptase as a minor criterion and with inclusion of tryptase as a minor criterion. This will allow you to assess the impact of the tryptase measurement as a contributor to the overall diagnosis of SM Unless your indication specifically states that the device is not intended for use in pediatric populations, any differences in sensitivity or specificity between adult and pediatric populations must be documented and supported by providing evidence of tryptase distributions in non-mastocytosis patient groups (acute myelogenous leukemia, chronic myelogenous leukemia, other) in the adult vs. pediatric data sets.

a. Cut-Off/ Clinical Decision Point

As of the time of writing this document, the cut-off limit of 20 µg/L tryptase has been 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 [Ref. 1]. The present valid criteria are described in a separate chapter in Ref. 2.

Your submission must explain how your clinical cut-off relates to the internationally accepted criterion of 20 µg/L tryptase. Future modifications to the WHO criterion as stated above must be documented within your submission along with an explanation, as appropriate, as to why the original cut-off limit of 20 µg/L tryptase is modified. Any decision to use a cut-off other than the standard internationally accepted criterion must be justified.

X. Labeling

Tryptase test system devices, like other devices, are subject to statutory requirements for labeling (including sections 201(n) and 502(a) of the FD&C Act; 21 USC § 321(n) and 352(a).) These *in vitro* diagnostic (IVD) devices must provide adequate directions for use and adequate warnings and precautions (Section 502(f) of the FD&C Act; 21 USC § 352(f)). Labeling requirements for IVD devices are set forth in 21 CFR Parts 801 and 809.

Your 21 CFR 809.10(b) compliant labeling for your tryptase test system must also include the information described below. This labeling information helps to mitigate the risks identified previously in this guideline to ensure safe and effective use of these devices. All requirements in 21 CFR 809.10 must be addressed in device labeling even if not mentioned below.

A. Intended use

The intended use must specify what the test measures, the clinical indications for which the test is to be used and the specific population, as applicable, for which the test is intended. The intended use must specify whether the test is quantitative, and the sample type must be specified. You must include a statement that the test is not a stand-alone test and that the test result must be interpreted in conjunction with other laboratory and clinical findings.

B. Summary and Explanation of the Test

You must provide background to the role that tryptase plays as a minor criterion in the diagnosis of systemic mastocytosis.

C. Test Principle

You must describe the test components (specific reagents, calibrators, and instruments) or test methodology used in this type of device.

D. Limitations of the Procedure

At a minimum, you must include the following two limitations in your labeling:

- Not for standalone diagnosis of systemic mastocytosis
- Not for diagnosis of anaphylaxis, or for evaluation of a potential anaphylactic reaction

You must include any other appropriate limitations to your procedure, which include conditions that affect the sample, conditions specified in any other applicable manufacturer package insert for components of your test, and potential laboratory hazards.

E. Reagents and materials

You must provide a list of the specific reagents required for your test system including the calibrators and controls. You must provide the user a summary of any expectations for the performance of the assay that are relevant to your test performance, including, but not limited to, measuring ranges, measurement units, and quality control measures. Include any specific storage requirements for the reagents.

You must state the sample matrix used with your test, instructions for sample handling, and stability information (including storage and temperature).

F. Calibration

You must explain how your assay is calibrated. You must provide the calibrator range and the reference material, if appropriate. You must provide information on the traceability of your calibrators (see "Traceability" section in (VII)(i)) and how your calibrators are prepared.

G. Quality Control

You must provide an explanation for how quality control specimens should be utilized. If controls are provided, you must provide information on how your controls are prepared and how value assignment is performed. In addition, you must provide a summary of stability data for your controls.

H. Procedure

This section must include clear and concise instructions for the procedure, from specimen handling through to result reporting. Specific and sufficient instructions, including any troubleshooting recommendations for software installations, must be provided.

I. Clinical Performance Studies

You must include in the package insert a summary of the demographic characteristics and pathology for all evaluable subjects in your study. You must include a summary of your study designs and the results from the studies. This section must include a description of performance, including the 95% CI, at the location in the labeling where you discuss the sensitivity and specificity, for the results of tryptase; defining the gold standard first with the inclusion of tryptase and then with the exclusion of tryptase.

J. Analytical Performance Results

You must provide summaries of the key analytical performance results for your test system. This data must include, when appropriate, precision (repeatability/reproducibility), linearity, measuring range of numerical test results, traceability/ value assignment, stability, , limit of detection, interference, hook effect, cross-reactivity, matrix comparison, cut-off, and expected values.

XI. References

[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.

[3] Valent P., Horny HP., Escribano L., et al. Diagnostic criteria and classification of mastocytosis: a consensus 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)