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Ref. No.: CML-HRM-1027A/04
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Certificate of Analysis

CERTIFIED REFERENCE MATERIAL
HRM – 1027A

Sibutramine Hydrochloride Monohydrate
(certified as sibutramine free base)

Batch Number
STY-0140-001

Description
A unit of the certified reference material (CRM) consists of 200 mg of sibutramine hydrochloride monohydrate ($C_{17}H_{26}ClN{\cdot}HCl{\cdot}H_2O$) in a screw-capped amber glass vial. Quantitative proton nuclear magnetic resonance (^{1}H qNMR) approach was adopted to determine the mass fraction (mg/g) of sibutramine free base ($C_{17}H_{26}ClN$) using an acesulfame potassium CRM (HRM-1012A) from the Health Sciences Authority (HSA), Singapore as internal standard.

The CRM was produced with reference to the requirements set out in ISO/IEC 17025:2017 [1], ISO 17034:2016 [2] and ISO Guide 35:2017 [3].

Certified Mass Fraction Value
A certified value is a value for which a laboratory has the highest confidence in its accuracy. The certified mass fraction value for anhydrous sibutramine free base given below is based on the results obtained by the qNMR approach:

Certified Mass Fraction Value: 833.7 ± 8.0 mg/g

The mass fraction value is expressed as the certified value ± the expanded uncertainty.

The uncertainty listed with the certified value is an expanded uncertainty about the mean, with coverage factor 2 (approximately 95 % confidence). The certified value has an associated measurement uncertainty attributed to uncertainty contribution from the characterisation of the material (u_{char}), uncertainty in the homogeneity of the material (u_{bb}) and uncertainty in the stability of the material (u_{stab}). The u_{char} was evaluated by combining uncertainties from method precision, purity of the internal standard, molecular weight of sibutramine free base, molecular weight of internal standard and weighing, in accordance with ISO/IEC Guide 98-3:2008 [4].

Homogeneity

Homogeneity testing on the sibutramine free base content was performed on two sub-samples taken from ten bottles (a total of 20 sub-samples) using qNMR technique. The sample size taken for homogeneity testing was approximately 14 mg. No significant differences in the between and within-bottle variances were found using one-way ANOVA at 95 % confidence level [3]. Thus, the sibutramine free base content was regarded to be sufficiently homogeneous. The u_{bb} was evaluated from the uncertainty due to between-bottle inhomogeneity.

Stability

Short-term stability of the sibutramine free base content was studied. The material was stored at 50 °C (maximum allowable transportation temperature) for up to 14 days. The results showed that the sibutramine free base content was stable over the study period.

Long-term stability of the sibutramine free base content was evaluated at storage temperature (2 to 8 °C) on three occasions up to about 4 months after preparation. The results showed that the sibutramine free base content was stable over the study period. The u_{stab} was evaluated from the standard error of the slope.

Validity of Certified Mass Fraction Value

The certified mass fraction value is valid within its measurement uncertainty until **24 Nov 2026**, provided that the CRM is subjected to the same handling and storage conditions as stated in this Certificate of Analysis (COA).

The CRM will be continuously monitored during the validity period to determine if any substantive change to the certified value has occurred. If necessary, its user will be advised or an updated COA may be issued when the property value of the CRM is found to have changed.

Analytical Methods

The determination of the purity of sibutramine free base was carried out using a 500 MHz NMR spectrometer (Bruker Avance Neo 500 MHz) at the Chemical Metrology Laboratory, HSA. Acesulfame potassium CRM (HRM-1012A) from HSA was used as the internal standard for the determination. The certified mass fraction was calculated from the mean of six results obtained from one determination each on the six sub-samples prepared from the CRM and the internal standard.

Other Characterisation Data

The CRM was also analysed by

(i) high performance liquid chromatography with diode array detection (HPLC-DAD) to determine the structurally-related organic compounds;
(ii) thermogravimetric analyser (TGA) to determine the total non-volatiles;
(iii) ion chromatography to determine the chloride anion content; and
(iv) Karl Fischer coulometer to determine the water content.

The Table below summarises the results (Informational values):

Component(s)	Technique	Mass Fraction (mg/g)	Standard Uncertainty (mg/g)
Structurally-related organic compounds	HPLC-DAD	1.90	0.027[2]
Total non-volatiles	TGA	< 5 (LOD*)	1.44
Chloride anion (Cl^-)	Ion Chromatography	104.6	0.57[2]
Water	Karl Fischer coulometry[1]	53.7	0.17[2]

*LOD: limit of detection

[1] Validated with water saturated 1-octanol (SRM 2890) from NIST, USA

[2] Standard deviation of replicate measurements

Metrological Traceability
The certified mass fraction is traceable to the International System of Units (SI) through the use of acesulfame potassium CRM (HRM-1012A) from HSA.

Intended Use
The CRM is intended for use as a primary calibrant for the determination of sibutramine free base.

Instructions for Use
Prior to use, the material should be equilibrated to room temperature and rotated gently before sampling. The minimum sample size for each use should be approximately 14 mg. After use, the bottle must be tightly re-capped and protected from moisture and light to ensure the validity of the certified value. If results differ from certified value in subsequent sampling, customers are advised to purchase a new CRM.

Transport and Storage
HRM-1027A is transported in ambient temperature. Upon receipt, the material should be stored at a temperature of 2 to 8 ^{o}C in its original bottle. Exposure to moisture and light should be avoided. Users should comply to their local regulations regarding the import, usage and disposal of sibutramine.

Safety Precautions for Users
Treat the material as hazardous substance. Use appropriate work practices when handling the material, in order to avoid skin or eye contact or ingestion.

Further Information
Please direct all enquiries regarding this CRM to the contact provided in this COA.

References

1. ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories.
2. ISO 17034:2016 General requirements for the competence of reference material producers.
3. ISO Guide 35:2017 Reference materials – Guidance for characterisation and assessment for homogeneity and stability.
4. ISO/IEC Guide 98-3:2008 Uncertainty of measurement – Part 3: Guide to the expression of uncertainty in measurement (GUM:1995).

Certificate Revision Record

Certificate Ref. No.	Date of issue	Reason for issuance
CML-HRM-1027A/01	24 Nov 2020	Issuance of first certificate
CML-HRM-1027A/02	21 Sep 2021	Extension of expiry date
CML-HRM-1027A/03	09 Sep 2022	Extension of expiry date
CML-HRM-1027A/04	07 Nov 2024	Extension of expiry date

Note
HSA does not assume any liability with respect to any loss caused by improper use and/or storage of the reference material by the customer.

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