Melting Point Certified Reference Standards
Application Note #2

What is a Certified Reference Standard?

Certified Reference Standards (CRSs) are high-purity chemicals certified by national, local or international standards laboratories and pharmacopeias, which are produced and tested according to well established and easy-to-reproduce procedures.

Use CRSs for temperature scale calibration and determination of acceptability of melting point (MP) instruments including OptiMelt.

General Guidelines and Recommendations

- Use CRSs obtained from reputable standards and pharmacopeia Laboratories.

- Use CRSs with certificates of measurement including records of:

  (1) Lot/batch Identification number (for traceability)
  (2) Purity specification (analysis method, purity levels, etc.)
  (3) Detailed description of the instrumental setup used for the melting point determination (i.e. type of instrument, manual or automatic detection, hot bath or metal block oven, capillary tube dimensions, amount/height of sample packed, compaction method, etc.)
  (4) Preconditioning of the sample (i.e. drying, grinding, etc).
  (5) Detailed heating conditions, including initial temperature, ramping rate and any special comments required to properly reproduce the melting conditions used by the standards laboratory to certify the compound. Alternatively, a reference to a standardized MP determination method must be included.
  (6) Melting points and melting point ranges with well characterized uncertainty errors.

- Whenever possible, choose the CRSs with the smallest uncertainty errors. Remember that the accuracy of your OptiMelt is only as good as the accuracy of the standards used for its calibration. Note: As a general rule, avoid CRSs leading to uncertainty errors larger than 0.5 °C.

- Do not assume that a CRS compatible with one specific pharmacopeia procedure is compatible with the requirements of a different pharmacopeia protocol. For example, it is best to obtain CRSs directly from the US

Pharmacopeia Convention in order to determine the usability of the OptiMelt according to US Pharmacopeia protocols.

- Beware of standards laboratories offering CRSs compatible with multiple pharmacopeias. Ask for samples of Certificates of Measurement before ordering standards to assure the compatibility of their records with the Pharmacopeia protocol you plan to follow. Contact the laboratory director whenever in doubt. A reputable accreditation center will always be very helpful and forthcoming!

- Occasionally, accreditation centers will run out of stock of some CRSs. In that rare event, the standards lab should be able to recommend alternative sources for CRSs while they restock their supplies. It is always a good idea to have an emergency second source of standards identified in case a backup supplier is required.

- CRSs have expiration dates. Following strict GLP and GMP guidelines, QA labs must keep track of those dates, and never use expired CRSs for calibration or determination of acceptability of their melting point equipment.

- A slight drift in MP results is expected when the melt-point numbers obtained with a liquid bath oven are compared to those obtained with a metal block oven under the same ramping conditions. This difference is to be expected and generally ignored since it typically falls within the intrinsic uncertainty of the measurement.

- Use capillary tubes of the same kind (and from the same supplier) to perform calibrations and to carry out all subsequent measurements. Beware that some pharmacopeia protocols include specific capillary requirements.

- Failure to clean the tubing before making capillary melting tubes is one of the most common causes of low melting points and broad melting point ranges. Whenever possible buy pre-made tubes from reputable sources.

- Dry CRS samples carefully and store them in a vacuum dessicator between melting point determinations. Forty eight hours over P_2O_5 is a very common recommendation for drying standards. Follow all standard-specific recommendations.

- As the melting temperature increases, accuracy is degraded. Melting Point instrument manufacturers generally quote different MP accuracy values for different temperature ranges:

RT to 250 °C: +/- 0.3 °C to 0.5 °C (typical). Lots of good standards within this range (five very good ones).

250 to 400 °C: +/- 2 °C (typical). Standards have a typical error span of 2 °C and often decompose during the melt if small ramp rates are used. Visual determination of the melt is recommended within this range. Minimize the exposure time of the samples to high temperatures.

Accreditation Centers

The following table is a list of accreditation centers which stock melting point CRSs. Notice that the scope of the centers ranges from local to worldwide.

Warning!

Keep in mind that certification protocols are constantly being updated. Use this table as reference only and use the Internet to verify the records on this table if necessary.

Name	Address/Phone	E-Mail / Web
WHO Collaborating Center for Chemical Reference Substances (International)	Apoteket AB Produktion &Laboratorier Centrallaboratoriet, ACL Prismavägen 2, S-141 75 Kungens Kurva Sweden Telephone:(+ 46-8)466-1000 Fax: (+46-8) 740-6040	E-mail: who.apl@apoteket.se
U.S. Pharmacopeial Convention, Inc. (United States)	Reference Standards Order Department. 12601 Twinbrook Parkway Rockville, MD 20852 USA Telephone: US and Canada: (800) 227-8772 International : (+1-301) 881-0666 Fax: (+1-301) 816-8148	Web: http://www.usp.org
LGC PromoChem (US, UK, Europe	LGC Promochem Queens Rd	Web: http://www.lgcpromochem.c

and WHO standards)	TEDDINGTON Middlesex TW11 0LY United Kingdom Telephone: +44 (0)20 8943 7000 Fax : +44 (0)20 8943 2767	om E-mail uk@lgcpromochem.com
National Physical Laboratory (United Kingdom)	Teddington TW11 0LW UK	http://www.npl.co.uk.
European Directorate for the Quality of Medicines (Europe)	European Pharmacopeia Council of Europe B.P. 907, F-67029 Strasbourg Cedex 1 France. Telephone: (+33-(0)3) 88 41 20 35 Fax: (+33-(0)3) 88 41 27 71	E-mail: CRS@pheur.org Web: http://www.pheur.org
French Pharmacopeia Reference Substances (France)	Agence Française de Sécurité Sanitaire des Produits de Santé Direction des Laboratoires et des Contrôles Site de Montpellier-Vendargues 635 rue de la Garenne F-34740 Vendargues France Telephone: (+33-(0)4) 67 91 39 00 Fax: (+33-(0)4) 57 87 39 83	