pharmaceutical standards for quality control

The Life Science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Supelco®
Analytical Products

As a worldwide leading supplier to the global Life Science Industry, we are a key provider of standards for pharmaceutical quality testing. We maintain a comprehensive inventory to support your laboratory, and can provide a stress-free, time-saving and efficient route to procuring the standards you need.

- Primary standards from USP, EP and BP as described in Monograph methods
- Secondary Certified Reference Materials – a convenient alternative to preparing in-house working standards
- *Trace***CERT**® Elemental impurity standards for testing in accordance with testing limits per ICHQ3D Guidelines
- Certipur® pH Buffer Certified Reference Materials - ready to use and in convenient formats
- Extractables & Leachables – CRM Mixes and individual reference materials
- Custom services – customized certified reference materials & packaging services

SigmaAldrich.com/standards-pharma

Primary (Compendial) Standards

Primary Pharmaceutical Standards

A primary reference standard is a standard whose value is accepted without reference to other standards. In a pharmaceutical setting, primary standards are produced and supplied by scientific organizations such as the EDQM (European Pharmacopoeia) and USP (US Pharmacopeia).

We maintain inventory of a large number of these reference materials. Our web page provides up-to-date availability, and those not in stock will generally be delivered in 3-4 weeks.

Why Purchase Primary Standards from us?

- Ease of ordering through **SigmaAldrich.com**; save your favorites
- Order consolidation with all reference materials, saving you time
- Lead time reduction
- Consolidated shipping
- Reduced carbon footprint
- Technical support services

Almost 3000 EP and over 3500 USP products are available from:

SigmaAldrich.com/pharmaceuticalstandards

Use of Primary Pharmaceutical Standards

The use of Primary Reference Standards is prescribed by the issuing pharmacopeia. USP Reference Standards are intended only for use in analytical or laboratory applications as specified in USP compendia.

EP Materials are supplied exclusively as European Pharmacopoeia Chemical Reference Substances, Biological Reference Preparations or Reference Spectra (Ph. Eur. CRS, BRP or RS). These are only for use as reference standards in tests and assays carried out in accordance with the official methods of the European Pharmacopoeia (Ph. Eur.).

View our complete offering of pharmaceutical standards at:

SigmaAldrich.com/standards-pharma

Looking specifically for USP reference standards?

Check out our catalog of >3500 USP standards, with easy ordering and shorter lead times.

SigmaAldrich.com/USP

Pharma Secondary CRMs

Pharmaceutical Secondary Certified Reference Materials (CRMs) provide pharmaceutical laboratories and manufacturers with a convenient and cost-effective alternative to making in-house working standards.

Using these commercially available Secondary CRMs will reduce the need to spend time and resources preparing in-house working standards.

Important Features of Secondary CRMs:

- **Traceability** to United States Pharmacopeia (USP), European Pharmacopoeia (EP) and British Pharmacopoeia (BP) Primary Reference Standards if available.
- **Certified** purity value according to ISO 17034 utilizing mass balance and/or qNMR approaches
- **Comprehensive** certificate according to ISO Guide 31

Our Secondary Standards are Certified Reference Materials (CRMs) manufactured under the scope of ISO 17034 and tested in an ISO/IEC 17025 accredited testing lab. Comprehensive Certificates of Analysis demonstrate traceability to USP, EP and/or BP primary standards (where available). In addition, an independent certified purity value is provided. This allows these Secondary CRMs to be used as reference materials for quantitative uses in a variety of applications.

The US Food and Drug Administration (FDA) and the European Pharmacopoeia (EP) both recognize the use of secondary standards or working standards which are established with reference to the corresponding primary standard (references available on request).

Comprehensive Certificate

The certificate of analysis for Pharmaceutical Secondary CRMs typically contains:

- Certified purity value by mass balance or qNMR (according to ISO 17034)
- Traceability results versus Pharmacopeial primary Reference Standards (see the example certificate extract shown on the next page)
- Qualification data along with comprehensive details on the analytical methods used
- Detailed handling and storage instructions

You can view and download an example COA for any pharmaceutical secondary standard at **SigmaAldrich.com/pharmastandards**. Select your standard of interest, scroll down to the “Documentation” section, and click “View Sample COA.

Download the latest version of the certificate for your standard

The values on the certificate are always traceable to the current Pharmacopeial lots (where available). If a valid Pharmacopeial lot changes, our corresponding Pharmaceutical Secondary CRM will be re-certified with traceability to the new lot. Then, a new certificate will be made available on our website. For this reason, the valid certificate should always be downloaded from the website prior to use of the material. To do this, find your product at **SigmaAldrich.com** using the part number or via our standards explorer (located at **SigmaAldrich.com/reference-materials**; bottom of the page) and scroll down to the Documentation section. Here you can enter the lot number of your standard.

Our portfolio of pharmaceutical secondary standard CRMs is continually growing. See what’s new at:

SigmaAldrich.com/newsecondaries

and, for the full portfolio, visit

SigmaAldrich.com/standards-pharma

Comprehensive Certificate

Example COA: Ibuprofen, PHR1004

Traceability Assay:
Comparative assay demonstrates direct traceability to Pharmacopeial Standards

ASSAY vs. BP CRS (as is basis)

ASSAY VALUE	**vs. BP BATCH**
100.08 %	**4105** Labeled Content = 99.9 %

Method: HPLC (ref.: Ibuprofen, Current Compendial Monographs)

Column: Ascentis C18, 250 mm x 4.6mm, 5µm particle size
Mobile Phase A: (10 g/L Chloroacetic Acid in Water (pH 3.0)):(Acetonitrile)
Mobile Phase Ratio: 40:60
Flow Rate: 1.5 mL/min
Column Temperature: 30 °C
Injection Volume: 10 µL
Detector: DAD, Wavelength: 254 nm
Internal Standard: Valerophenone

ASSAY vs. USP REFERENCE STANDARD (1335508) (as is basis)

ASSAY VALUE	**vs. USP LOT**
100.24 %	**R13060** Labeled Content = 0.998 mg/mg

ASSAY vs. EP CRS (I0020000) (as is basis)

ASSAY VALUE	**vs. EP BATCH**
100.24 %	**6.0** Labeled Content = None Assigned Content = 99.7% *

*The assigned content of the EP CRS was determined by assay against the USP Reference Standard.

Method: HPLC (ref.: Ibuprofen, Current Compendial Monographs)

Column: Ascentis C18 4.6 x 250 mm, 5 µm particle size
Mobile Phase: 10 g/L Chloroacetic Acid in Water (pH 3.0), Acetonitrile (40:60)
Flow Rate: 1.5 mL/min
Column Temperature: 30 °C
Injection Volume: 10 µL
Detector: DAD, Wavelength: 254 nm
Internal Standard: Valerophenone

Secondary Standards for Pharmaceutical Quality Control

Save time, money, and effort with Supelco® Pharmaceutical Secondary CRMs as an alternative to in-house working standards.

Our up-to-date portfolio contains >2500 pharmaceutical secondary CRMs and continues to expand. Visit our website often to view new products.

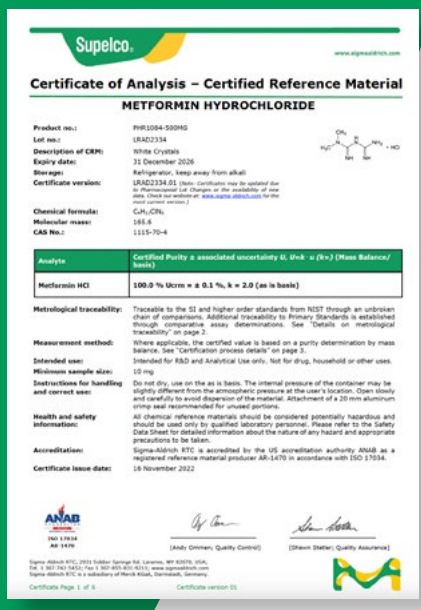
SigmaAldrich.com/pharmaimpurities

Monthly COA Updates

Did you know that Supelco® Pharmaceutical Secondary CRMs are continually updated, always providing traceability to the current Primary Reference Standard Batch?

You can be notified in advance of any COA changes that may occur due to re-qualification etc.
This service helps ensure that you always have the most current version of a product certificate.
Sign up for these email updates on our website:

SigmaAldrich.com/standards-pharma


Supelco

Certificate of Analysis – Certified Reference Material

METFORMIN HYDROCHLORIDE

Product no.: PHR1084-500MG
Lot no.: LRAD2334
Description of CRM: White Crystals
Expiry date: 31 December 2026
Storage: Refrigerator, keep away from alkali
Certificate version: LRAD2334.01

Chemical formula: $C_4H_{11}ClN_5$
Molecular mass: 165.6
CAS No.: 1115-70-4

Analyte	Certified Purity & associated uncertainty U, $U=k \cdot u$ (k=) (Mass Balance/ basis)
Metformin HCl	100.0 % Ucrm = ± 0.1 %, k = 2.0 (as is basis)

Metrological traceability: Traceable to the SI and higher order standards from NIST through an unbroken chain of comparisons. Additional traceability to Primary Standards is established through comparative assay determinations. See "Details on metrological traceability" on page 2.

Measurement method: Where applicable, the certified value is based on a purity determination by mass balance. See "Certification process details" on page 2.

Intended use: Intended for R&D and Analytical Use only. Not for drug, household or other uses.

Minimum sample size: 10 mg

Instructions for handling and correct use: Do not dry, use on the as is basis. The internal pressure of the container may be slightly different from the atmospheric pressure at the user's location. Open slowly and carefully to avoid dispersion of the material. Attachment of a 20 mm aluminum crimp seal recommended for unused portions.

Health and safety information: All chemical reference materials should be considered potentially hazardous and should be used only by qualified laboratory personnel. Please refer to the Safety Data Sheet for detailed information about the nature of any hazard and appropriate precautions to be taken.

Accreditation: Sigma-Aldrich RTC is accredited by the US accreditation authority ANAB as a registered reference material producer AR-1470 in accordance with ISO 17034.

Certificate issue date: 16 November 2022

ANAB ISO 17034 AR 1470

(Andy Ommen, Quality Control) (Shawn Stetler, Quality Assurance)

Certificate Page 1 of 6 Certificate version 01

Testing for impurities?

Our growing portfolio of Pharmaceutical Secondary CRMs includes both APIs and associated impurities.

SigmaAldrich.com/pharmaimpurities

NOW AVAILABLE!

Human Insulin Secondary CRM

Worldwide, diabetes is one of the most common health conditions requiring treatment. The discovery of a therapy using insulin extracted from bovine pancreas was awarded the Nobel Prize in medicine in 1923. Today, insulin and several analogs are produced recombinantly, and save lives globally every day.

The new human insulin Pharmaceutical Secondary CRM, PHR8925, is traceable to the current USP reference standard and can be used as a working standard to determine identity or potency.

Elemental Impurity Mixes for Pharma QC

Metallic contamination in drug products, referred to as elemental impurities, may arise from several sources. The main source of contamination are equipment and utensils used in processing, holding, transferring and packaging, A second source can be residual metals used as process catalysts.

Elemental impurities provide no therapeutic value to the patient and can present a toxicity risk. Thus, their levels in drug products should be actively controlled. The guidelines to measure and control the presence of metal impurities within acceptable limits have been developed by the International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human use (ICH). These guidelines, known as ICH Q3D, categorize the elements to be monitored into three classes based on their toxicity and likelihood of occurrence in the drug products.

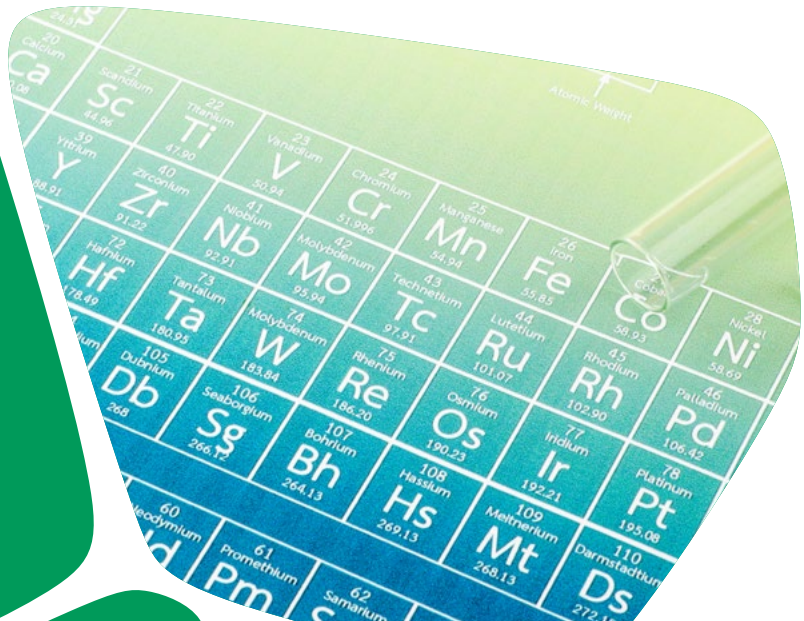
Since January 1st, 2018, USP and EP adopted the ICH Q3D guidelines for elemental impurities and implemented the limits in their general chapters: USP <232>, <233> and EP 11, general chapter 5.20 and 2.4.20.

To accommodate testing per the ICH Q3D guidelines, we offer *Trace***Cert**® certified reference material (CRM) mixes with compositions to cover classes I, IIA, IIB and III elemental impurities according to the oral, parenteral, inhalational and dermal permitted daily exposure limits (PDEs).

With these *Trace*CERT® mixes you can expect:

- Produced under ISO 17034 accreditation and analyzed in ISO/IEC 17025 accredited analytical laboratories
- Values traceable to at least two independent references (NIST® or BAM)
- Expiry date
- Storage Information
- Proper uncertainty calculation
- Special fluoropolymeric bottles and gas-tight aluminum foil bags for extended stability
- Comprehensive documentation according to ISO Guide 31
- Unsurpassed level of accuracy and lot-specific value
- Convenient 100 mL package size
- Concentrations set according to the Permitted Daily Exposure (PDE) as described in the ICH Q3D guidelines

For more information and to browse products, visit:
SigmaAldrich.com/ICHQ3D



pH Buffer CRM's

Buffer solutions are essential to maintain proper calibration of pH instruments. Organizations such as the United States Pharmacopeia (USP) and the European Pharmacopoeia (EP) describe preparation of buffer solutions from solid starting material, but this process can be time consuming and error prone.

Ready To Use Certipur® pH Buffer Solutions

The accuracy of your pH measurements is directly affected by the buffer reference materials used in calibration. It is important to consider both quality of the raw materials used, as well as the accuracy of the preparation. With ready-to-use ISO 17034 & ISO/IEC 17025 compliant Certipur® certified reference buffer solutions from Supelco® analytical products, you benefit from maximum accuracy, reliability, and convenience, ensuring consistent results and avoiding costly repeat analyses.

Available in PE bottles, convenient single-use sachets, and award-winning Titripac® formats, there is a pH buffer solution format to suit your unique needs.

- Compliant: Produced according to EP and USP guidelines
- Secure: Produced & tested in our ISO 17034 and ISO/IEC 17025 accredited facilities
- Ready for Audits: Detailed CoA provided for every product
- Convenient: Simply open & use for quick, accurate pH calibration
- Always Fresh: Available single-use sachets
- Long Lasting: Up to 5-year shelf life, depending on format
- Innovative & Eco-Friendly Titripac® Format: Award winning with ensured long-term stability, even after opening. Also offered with stability datasheet.
- 5-Point calibration certification for high-accuracy pH determinations
- Certified pH values at both 20°C and 25°C to meet your calibration needs

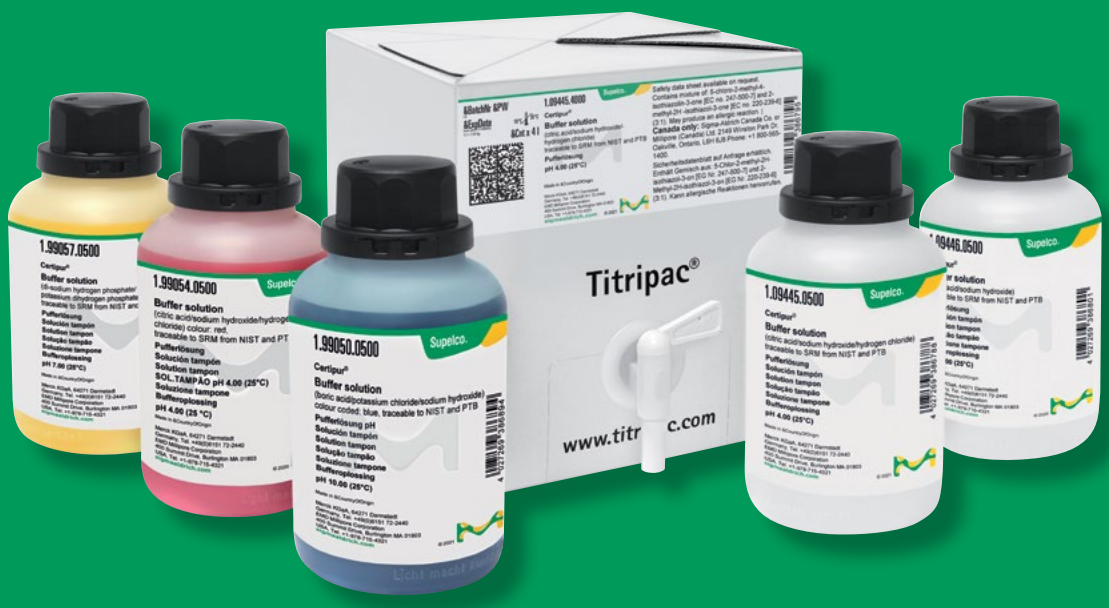
Visit **SigmaAldrich.com/phbuffers** to learn more.

Find more information about these products in our newly launched brochure:

Buffer Calibration Standards for pH Measurements

For detailed information on our sustainable packaging format known as "Titripac®":

Analytix Reporter Journal Issue 13/2022



Extractables & Leachables Testing

Extractables and leachables (E&L) are chemical compounds with the potential to migrate into pharmaceutical or clinical products from packaging materials, tubing, or medical devices, resulting in patient exposure. Manufacturers of pharmaceutical products and medical devices are obligated to perform extensive E&L studies to identify compounds that might leach into the product and, if necessary, assess the toxicity of these chemicals.

Since it is never entirely predictable which migrants may occur, it is crucial that no analytes are overlooked. Depending on the nature of the packaging material, the product, and the applied conditions, new unexpected or unknown compounds can be found. Therefore, there is no finite list of analytes to be tested for. However, there are certain monomers or additives that are often detected in extractables and leachables studies.

To help streamline your analysis and facilitate in identification and quantification of these compounds, we developed two calibration mixes. Both are Certified Reference Materials (CRMs) produced under ISO 17034 and tested under ISO/IEC 17025 accreditations. One mix is designed for LC (21 components) and another one for GC analysis (14 components). The components were chosen to reflect a broad spectrum of typical E&L compound classes, taking into account the toxicity and frequency with which they are identified during testing.

Compositions of *Trace*CERT® HPLC and GC Extractables & Leachables CRM Mixes	LC Mix 50 µg/mL in acetonitrile (Cat. No. 95636)	GC Mix 50 µg/mL in TBME (Cat. No. 01829)
Irganox 1010 (Ir1010)	X	
Irganox 1076 (Ir1076)	X	X
Dometrizol	X	
ε-Caprolactam (CAP)	X	X
Dibenzylamine (DBA)	X	
Benzoic acid (BA)	X	
2-Mercaptobenzothiazole (2-MBT)	X	X
Bisphenol A (BPA)	X	X
2-Ethylhexanoic Acid (EHA)	X	
Bis(4-chlorophenyl)sulfone (CPS)	X	
2,6-Di-tert-butyl-4-hydroxymethylphenol (DBOHP)	X	
Butylhydroxytoluene (BHT)	X	X
1,3-Di-tert-butylbenzene (DBB)	X	X
Oleamide (Ole)	X	X
Bis (2-ethylhexyl) phthalate (DEHP)	X	X
Stearic acid (SA)	X	X
Erucamide (Eruca)	X	X
Irganox 3114 (Ir3114)	X	
Irgafos 168-oxide	X	X
2,4-di-tert-Butylphenol	X	X
Palmitic acid	X	X
2,6-di-tert-Butylphenol		X

In addition to the mixes, we can provide individual component reference materials for E&L testing. These products are provided with a NIST SRM traceable certified purity value determined by quantitative NMR (qNMR) in accordance with ISO 17025. The values are given with an uncertainty value which takes the stability and homogeneity of the material into account.

To see the full line of reference materials for E&L testing, please visit **SigmaAldrich.com/extractablesandleachables**

Performing Karl Fischer Titration?

Aquastar® ready-to-use Karl Fischer certified reference materials

Ensure the reliability of your water determination results with Aquastar® Karl Fischer Certified Reference Materials (CRMs). These CRMs are produced and tested in accordance with both ISO 17034 and ISO/IEC 17025, including documented uncertainty and traceability. Our portfolio offers liquid and solid water standards for both volumetric and coulometric applications, as well as standards for special applications, e.g. Aquastar® Water Standard Oven or Aquastar® Water Standard Oil to be used for oil analysis.

See Full Karl Fischer Standards Portfolio

See tips on handling & usage of our water standards!

See Karl Fischer Titration Videos

Did you know we also offer a full portfolio of Karl Fischer reagents?

See Karl Fischer Reagents

Could Not Find What you Were Looking For?

We can make high-quality reference materials customized to your specifications!

Let us partner with your organization to provide packaging and manufacturing services customized to your specifications. Our scopes of accreditation include a broad range of technologies and competencies, ensuring that your custom project can be accommodated with the highest quality.

- **Packaging services** customized to your specifications
- **Synthesis** from milligram to kilo scale
- **Custom reference materials** based on your specific needs and following your required specifications

Inquire about custom reference materials.

Supelco®

Analytical Products

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt, Germany

SigmaAldrich.com

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France: 0825 045 645
Germany: 069 86798021
Italy: 848 845 645
Spain: 901 516 645 Option
Switzerland: 0848 645 645
United Kingdom: 0870 900 4645

For other countries across Europe, please call: +44 (0) 115 943 0840
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Millipore® Sigma-Aldrich® Supelco® Milli-Q® SAFC® BioReliance®

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