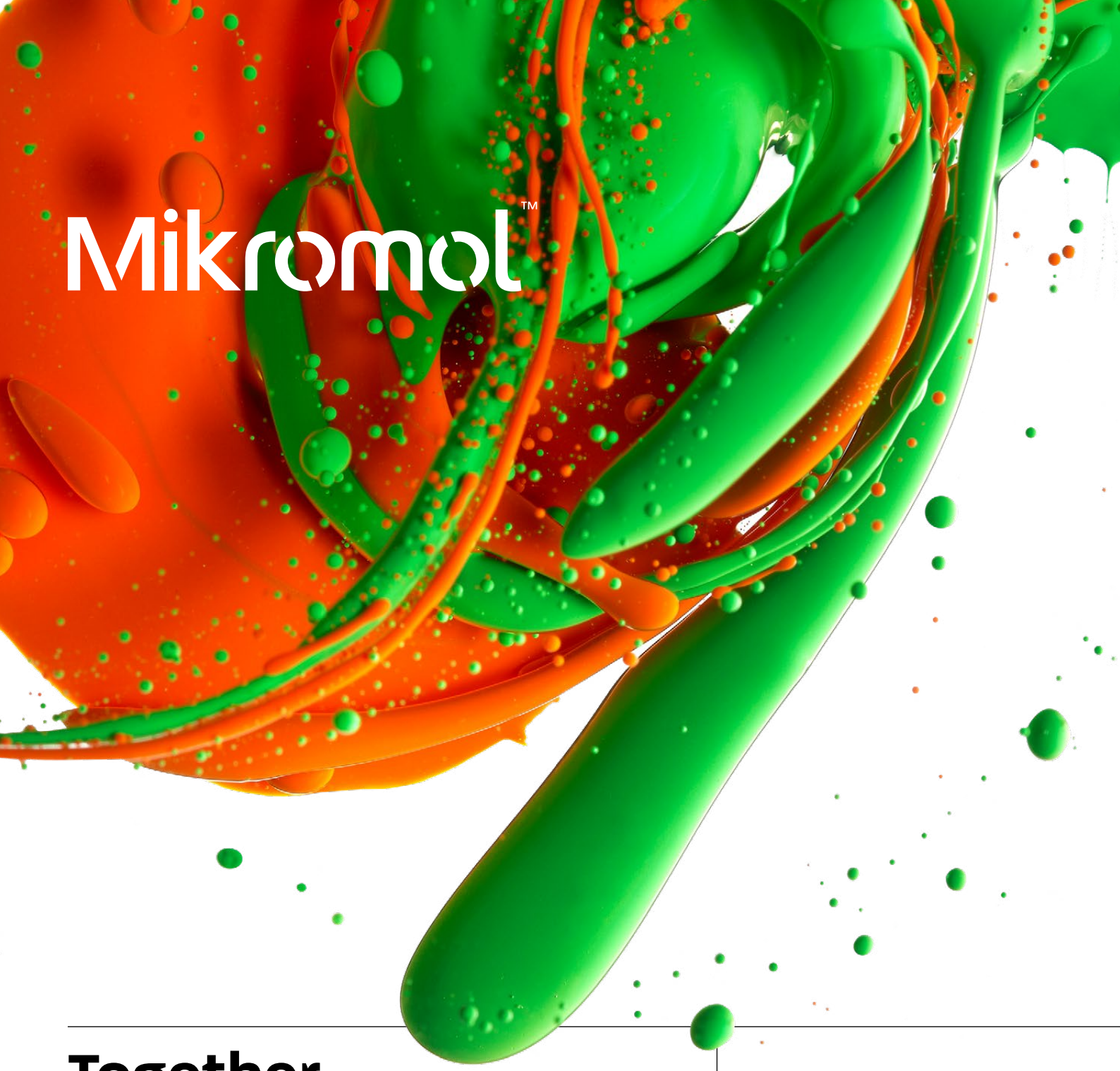


Together, beyond the standard.

Primary Pharmaceutical Reference Standards and Reference Material Services

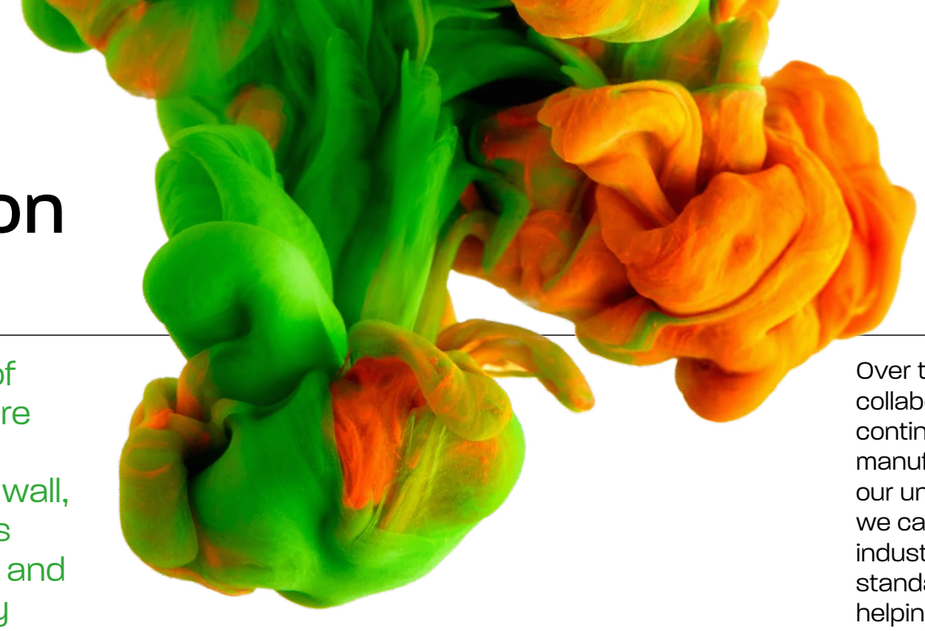
QUALITY | ISO 9001 | ISO/IEC 17025
ISO 17034 | GMP

LGC

An introduction to Mikromol.

Mikromol was born in a time of uncertainty, and out of a desire for progress and unification. Following the fall of the Berlin wall, two friends sitting in their labs realised that German science and industry lacked critical quality controls and were lagging behind on technological innovation; and set out to provide access to tools which would enable unified quality control systems in drug release.

Through speaking with members of the pharmaceutical production community, our founders identified an unmet demand for ketoprofen and ibuprofen degradation standards, crucial to ensure medications sitting on people's shelves remained safe. They rose to meet this need and resolved to build a world-leading catalogue of highly characterised quantitative primary API and impurity reference materials.
This initiative became Mikromol.



From the handful of scientists creating those first compounds, our team grew steadily, developing a reputation for quality, designing, and executing complex reference standard syntheses, and identification of unknown impurities appearing during production runs and stability testing. We brought in talented chemists from across the world, establishing today's first-class team of PhD and MSc scientists and laboratory technicians and ensuring the continued excellence of our dedicated analytical and synthesis departments.

Over the decades that followed, the collaborative spirit that defined our start has continued through our relationships with drug manufacturers and method developers to grow our understanding of your needs, so that today we can offer you one of the pharmaceutical industry's broadest portfolios of reference standards and reference material services – helping you create ever better, safer, medicines.

In choosing Mikromol today, you choose a top-quality reference standard manufactured in an ISO/IEC 17025 and 17034 accredited facility to help you achieve your highest testing accuracy.

You choose Certificates of Analysis (COAs) that give you market-leading levels of detail – part of our commitment to thorough and transparent documentation that enables you to audit by trace and mitigate risk to your organisation.

You choose expert support and advice from a global team about use and storage, transport, and technical applications, whether for pharmacopoeial methods or internally developed protocols.
You choose a heritage forged in the fire of progress and unification.

You choose Mikromol.

We were the first to create product families for these key drugs: adding impurity and excipient standards to the API compounds listed on the British and European Pharmacopoeias and building up a ground-breaking portfolio that now features 46 ibuprofen products.

The Mikromol difference, at a glance

We go beyond the standard to ensure the reliability of your analysis regardless of your method

- Robust internal quality control; including strict release criteria and continuous quality monitoring throughout lifecycle of standard, ISO accredited methodology, and homogeneity assessments
- Comprehensive COAs ensuring excellent transparency and availability of results - from 100% mass balance to volatile contents, original spectra, chromatograms, and method details
- Use of orthogonal methods to establish identity and assay, allowing quantitative use of the standard in any method being used in your laboratory
- Adherence to GMP and GDP principles, as shown by our EXCiPACT® certification
- Stringent packaging and labelling protocols, including low actinic pharmaceutical-grade, machine-controlled capping and Globally Harmonised System barcoding and labelling protocols, to ensure conformity of your standard

We go beyond the chemistry by offering a range of specialist services to give you confidence in the journey

- 20 offices around the world, providing consultations in local languages/time zones
- Expertise in shipping-controlled substances across borders, simplifying your local clearance and import procedures
- Global stocking and distribution through LGC hubs located in America, Europe and Asia equipped with state-of-the-art logistics, giving you confidence in the timely supply of quality materials
- Support for e-procurement and integrated purchasing

We use our excellence in analytical scienceand manufacturing to provide the standards you need

- Over 5,700 high quality primary pharmaceutical reference standards (as defined by ICH guidelines) are stocked, representing >1700 best-selling and niche API families
- Large and ever-increasing portfolio of ISO 17034 accredited API and excipient reference standards
- Leading range of degradant, by-product and intermediate impurities, the majority of which measured under the scope of our ISO 17025 accreditation
- Technically relevant pack sizes depending on nature of analyte and application, ranging from 25 to 500 mg
- Dedicated reference materials management services as well as custom standard manufacturing

Over

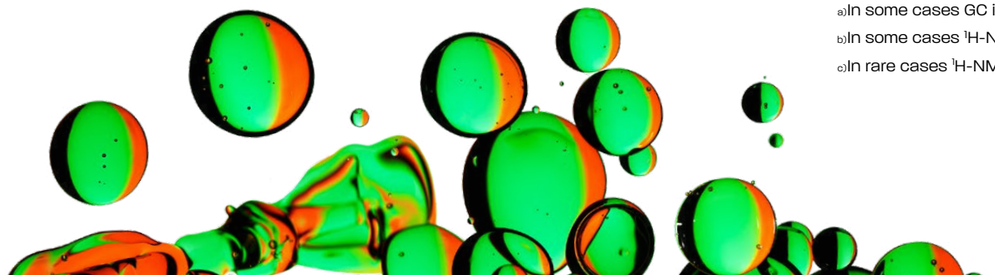
5,700

pharmaceutical reference standards

Typical CoA Content for Mikromol Products

	Mikromol Impurities	Mikromol APIs + Excipients	Pharmacopoeial Standards	How Mikromol makes a positive, measurable difference to you
General Information				
Product Code, Lot no, CAS no, molecular weight, formula and structure, appearance, melting point, long-term storage, hygroscopy	✓	✓	(✓)	- Clearly defines the identity of the substance - Information useful for substance handling - Provides batch traceability
ISO 17034 accreditation	✗	(✓)	(✓)	- Confirmation from the accrediting authority (DAkkS), that we are competent to produce reliable reference materials - Increases acceptance or our reference materials by auditors and authorities
Assay				
Assay value	✓	✓	(✓)	- Assay 'as is' determined by an accredited method, in most cases 100% mass balance or qNMR is used; no further corrections are necessary
Second, independent assay	(✓)	✓	✗	- A second assay value determined by an independent technique verifies the assigned assay - Strict acceptance criteria for deviation between both assay values ensures reliability of assigned content and enables usage of the material in any method that is used in your laboratory
Measurement uncertainty	(✓)	✓	✗	- Transparency on accuracy of the assigned assay value - Enables you to make an informed decision if the standard is fit for purpose for your specific application
The combination of 2 assays and measurement uncertainty allows the universal use				
Purity by HPLC[a)]				**HPLC is the most commonly used method for purity determination in organic chemistry**
- HPLC Chromatogram	✓	✓	✗	- Reviewing the chromatogram gives an impression of the method and the quality of the material
- HPLC Method details	✓	✓	✗	- Necessary information if you want to reproduce the method in your own lab
- HPLC Peak-Table	✓	✓	✗	- Information about number and relative amount of impurities - Confirmation, that impurity contents and purity of the material sum up to 100%
Volatile Contents				
Either combined volatile contents by LOD or separately water by KFT + residual solvents by GC Headspace[b)]	✓	✓	✗	- Necessary Information to calculate the assay by 100%-Method
Statements				
DAkkS accreditation	✗	(✓)	✗	- Provides transparency on our accreditation; accreditation number is given on the CofA and on our accreditation certificate, which can be downloaded on the web, detailing the scope of our accreditation
All measurements performed under the scope of our ISO 17025 accreditation	(✓)	✓	(✓)	- Regular participation in proficiency tests guarantees reliability of analytical results - Traceability to SI units ensures international acceptance of the standards
Confirmation of primary standard status	(✓)	✓	✗	- Assures you that the reference material conforms to the characteristics of a primary standard as described in the ICH Guidelines
Separate homogeneity test on sales units + homogeneity statement	✗	(✓)	✗	- Ensurance that the material is homogeneous, ensuring repeatability of measurements
Stability statement	✗	(✓)	✗	- Ensurance that the material is stable under the recommended storage conditions
Exclusion of inorganic residues by sulphated ash or CHN analysis	(✓)	✓	✗	- Assures you that the material does not contain inorganic residues
Intended use	(✓)	✓	✓	- Clear Information for which use the reference material is suitable
Identity				**Combination of the results at least of three different methods listed below ensures correctness of the substance identity**
^{1}H-NMR[c)] (Spectrum, conditions and structure confirmation statement)	✓	✓	✗	- Provides transparency as it allows independent interpretation by yourselves or auditors even if no literature data is available - Powerful method to establish identity of organic small molecules - provides confidence - Impurities and residual solvents can be detected - Confirms plausibility of the HPLC result
^{13}C-NMR (Spectrum, conditions and structure confirmation statement)	✗	(✓)	✗	
MS (Spectrum, conditions and structure confirmation statement)	✓	✓	✗	- Confirms correct molecular weight of the substance - May show characteristic fragmentation patterns depending on molecular structure
IR (Spectrum, peak table, conditions and structure confirmation statement)	✓	✓	✗	- Presence or absence of characteristic bands for certain structural elements of a molecule can support confirmation of the identity - Structure can be confirmed by comparison with literature data

We provide the spectra so you can check the result yourself



a) In some cases GC is used instead of HPLC due to substance properties

b) In some cases ^{1}H-NMR is used instead of GC Headspace to determine residual solvents

c) In rare cases ^{1}H-NMR may be replaced by a ^{13}C-NMR due to substance properties

Key

✓ = Always supplied

(✓) = Partially supplied

✗ = Not supplied

Quality principles and market-leading Certificates of Analysis you can rely on

Every day at Mikromol, our work is underpinned by a Quality assurance approach that strives for continuous improvement in synthesis and analysis.

That's why each Mikromol product you receive comes with a comprehensive COA, which provides a complete description of the material it relates to, as well as a summary of the analyses and details of the methods used during the characterisation process.

Our COAs are designed to provide you with transparency about the quality and characterisation of your standards – by featuring comprehensive quality assurance information and data beyond even the requirements of the preeminent international standard ISO Guide 31*. This approach – together with the measurement uncertainty values documented for many of our products - ensures that you and your auditors can be confident that the Mikromol reference standard you choose is fit for your analytical measurement purposes.

LGC | Mikromol™

Certificate of Analysis **ISO 17034**

Reference Material

Product name
Glibenclamide

Product code MM0008.00-0250	**Lot number** G1015075
CAS number 10238-21-8	**Appearance** white solid
Molecular weight 494.00	**Melting point** 172 °C
Molecular formula $C_{23}H_{28}ClN_3O_5S$	**Long-term storage** 2 to 8 °C, dark

Assay[1] "as is" **99.7 %**	Uncertainty[2] U **0.4 %**

Intended Use: Use for identification and quantification. The assay is verified by a second testing method. Due to the homogeneity studies, the minimum amount of sample to be used is 10 mg.

Date of shipment: **09 Apr 2020**

Producer confirms that this reference material (RM) meets the specification detailed on this Certificate of Analysis for **two years** from the date of shipment, provided the substance is stored under the recommended conditions unopened in the original container.

Release by:	**Date of Release:**		Product Release
Dr. Sabine Schröder	Luckenwalde, 27 Nov 2019		

[1] Calibration and verification were carried out using standards traceable to SI-units. The value is expressed on an "as is" basis.

[2] The uncertainty "U" is the expanded uncertainty of the testing method for the assigned value estimated in accordance with the Guide to the Expression of Uncertainty in Measurement (GUM). It corresponds to a level of confidence of about 95%. Coverage factor k =2.

Organisation certified to ISO 9001 | DQS 102448 and GMP (EXCiPACT™)
RM Production accredited to ISO 17034 | DAkkS D-RM-14176-01-00 |
Test methods used for characterisation are accredited to ISO/IEC 17025 |
DAkkS D-PL-14176-01-00

Producer:
LGC GmbH
Louis-Pasteur-Str. 30
D-14943 Luckenwalde
Germany
www.lgcstandards.com

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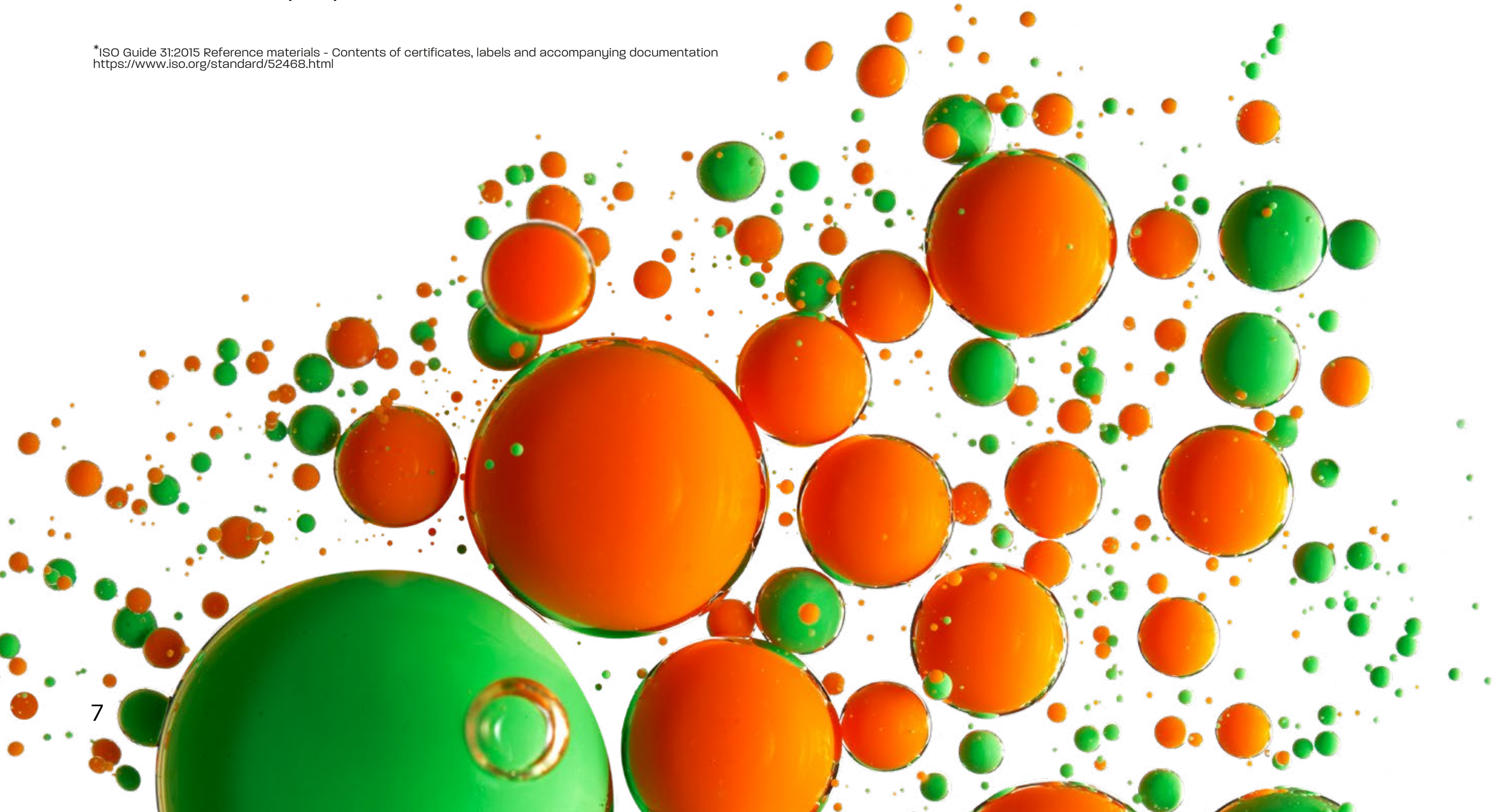
*ISO Guide 31:2015 Reference materials - Contents of certificates, labels and accompanying documentation
https://www.iso.org/standard/52468.html



Active Pharmaceutical Ingredient (API) primary reference standards

Mikromol reference standards for Active Pharmaceutical Ingredients (APIs) are primary quantitative standards – the majority accredited to ISO 17034 and designed to ensure the highest analytical accuracy and reliability. Their intended use is for potency assessments, drug substance and drug product release testing, therefore they have a tight target measurement uncertainty – M(u) - of 0.5 per cent.

Many of our API reference standards fulfil International Council for Harmonisation (ICH), Food and Drug Administration (FDA) and other regulatory requirements for pharmaceutical quality control. They also come with detailed COAs, including identity checks by several qualitative techniques. Assay information is usually provided by an ISO/IEC 17025 accredited technique, such as 100% mass balance, and is confirmed by a second independent method (e.g. Quantitative Nuclear Magnetic Resonance Spectroscopy (qNMR).

Active Pharmaceutical Ingredients

ISO 17034

accredited

Impurity reference standards

Impurities are always present in a therapeutic substance and can significantly alter a drug's effects on the patient, potentially putting their health at risk. Legislators and official bodies, therefore, set limit and threshold values as well as guidelines requiring the detection, identification, quantification, and qualification of impurities. The Mikromol portfolio of over 4,000 impurity reference standards is of the highest quality and designed to aid your detection of degradation products in APIs and excipients, as well as process impurities, with a renewed focus on genotoxic impurities. The standards may be used for the quantification of impurities, as well as for identity and limit tests, according to ICH guides Q2, Q3A, and Q3B.

Each Mikromol impurity standard comes complete with information on two assay methods unless not technically feasible – in which case we measure additional parameters internally to ensure quality and reliability to give you greater analytical certainty and confidence that your results are accurate.

Over

4,000

impurity reference standards

Excipient and Concomitant component standards

Designed to deliver the highest accuracy and reliability, Mikromol excipient standards are primary quantitative standards that are suitable for calibration, assay development or as working standards. Most of the 170+ excipient products in our range are ISO 17034 accredited, and all are supplied with detailed COAs featuring identity, purity, and assay data. Although there is not yet an official guideline for excipient testing, our excipient standards are manufactured according to the same stringent requirements as our API standards, as excipients are a significant component of the drug product being released for human consumption.

We also provide the impurity and concomitant substance standards required to assess an excipient's quality and performance. The analysis of concomitant substances is the main challenge in achieving excipient quality control, as they are often a natural part of the excipient and can also influence its performance significantly. Mikromol offers high-quality concomitant component standards to enable you to set meaningful excipient specifications.

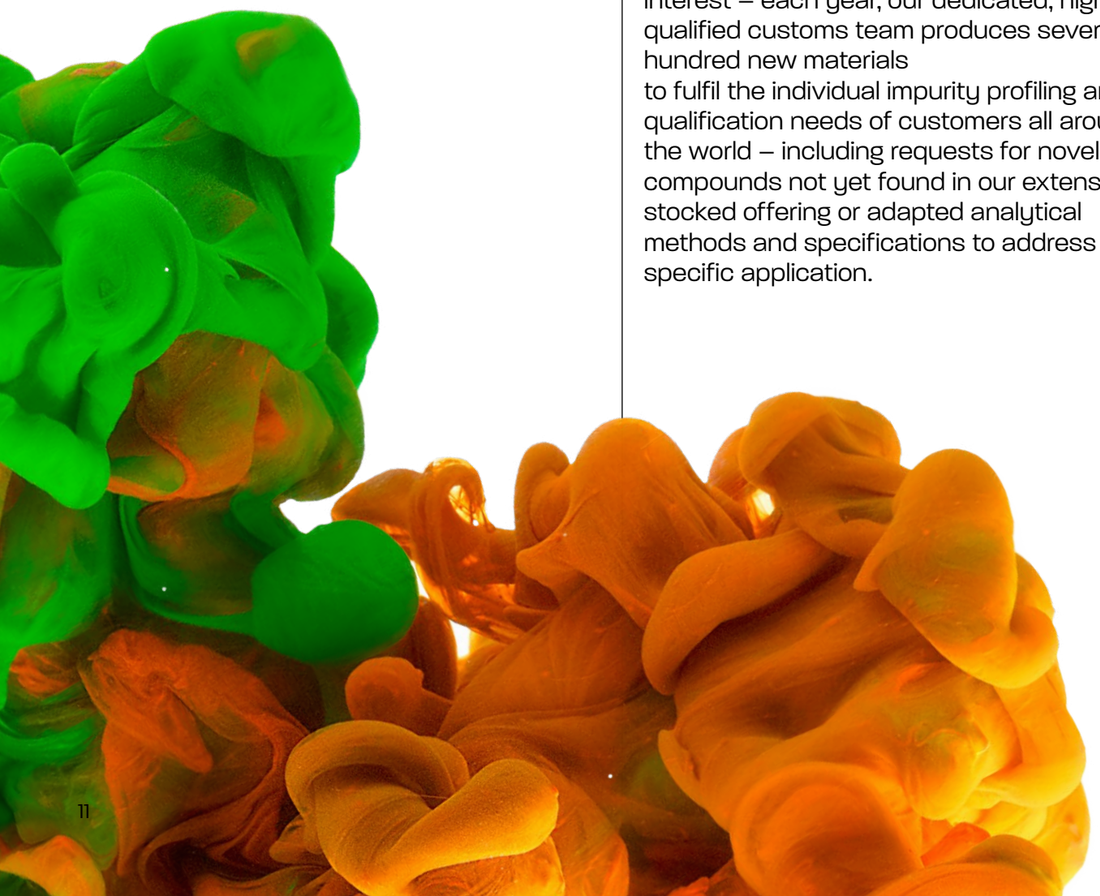
More than

170

excipient products in our range

Custom reference standards

Creating pharmaceutical reference standards to customer specification has always been at the heart of the Mikromol business. We understand that you are constantly discovering new actives and impurities of interest – each year, our dedicated, highly-qualified customs team produces several hundred new materials to fulfil the individual impurity profiling and API qualification needs of customers all around the world – including requests for novel compounds not yet found in our extensive stocked offering or adapted analytical methods and specifications to address your specific application.



Reference Materials Management

To support you in bringing even safer medicines to the market, we go far beyond supplying you with the right reference standards. From impurity profiling and working standards outsourcing services, all the way to managing inventory and logistics of your reference standards, we're fully equipped to provide you with a wide range of collaborative reference material management services.

Mikromol's strength in impurity profiling is built on an expert in-house team uniquely familiar with a broad range of APIs, degradation profiles and complex matrices. Whether you are dealing with an unknown impurity due to a change of formulation, method, dosage form or even profiling a new API, we can quickly identify your unknown peak(s) and propose likely mechanism(s) of formation to keep your project on track. Due to our company-wide scientific resources and state of the art analytical instrumentation, we can offer additional follow up services, including analytical method recommendations, method validation and provision of reference standards for the unknown species.

The flexibility offered by our global production sites means we can guarantee large volumes of API impurity working standards you need – combining ISO 17034 vial-to-vial homogeneity and validated peace of mind with the efficiency of outsourcing to a reliable, high-value technical partner. The fact that our API standards are of the highest quality – traceable, and immediately fit for purpose as working standards – reduces your risk, the need for analytical qualification, and time-consuming paperwork.

We can guarantee large volumes of API impurity working standards you need.

Mikromol™ worldwide

We understand that you may not always be able to store large quantities of stock on-site due to the capacity and resources that need to be allocated to handling this critical material, so let us handle it for you. Thanks to our +4,000m² warehouse, we can receive, store, maintain, and deliver pharmaceutical standards. Our warehouse meets strict storage and stability specifications – including validity and purity trend analysis and maintaining chemicals at temperatures from -80°C to 21°C in different zones. When you call on your standard to support your project our globally experienced Supply Chain and Export departments effortlessly take charge of the distribution, management, and importation of our products in more than 130 countries.

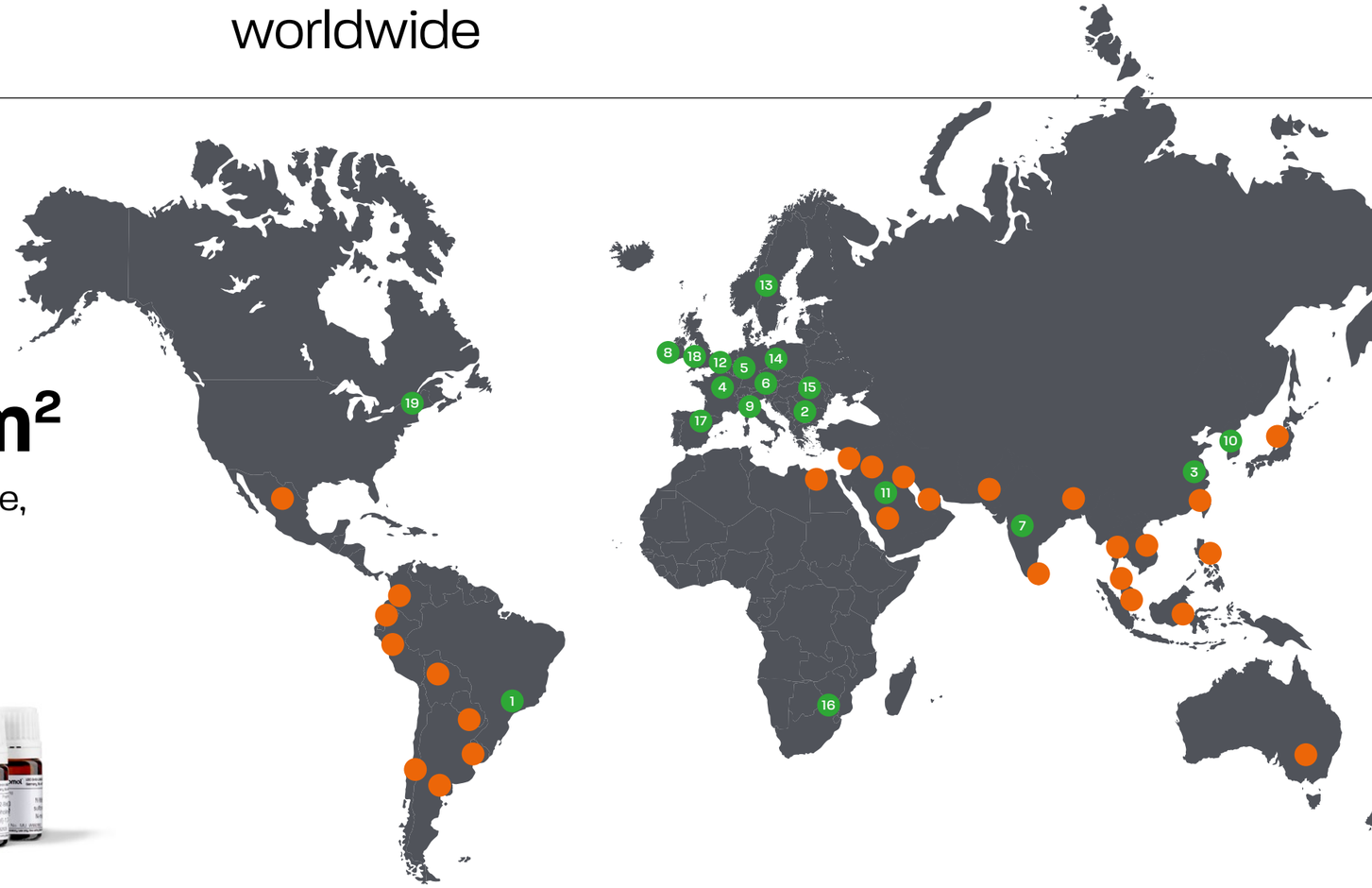
Although moving scientific products across borders is becoming ever more complex, we continually stay up to date with new developments. You can rely on our global compliance specialists to assess every substance for air, land and sea transportation hazards and controls by CAS number or structure – in addition to ensuring adherence to national and international regulations. These include management of controlled substances, dangerous goods, military export lists and drug/chemical weapon precursors.

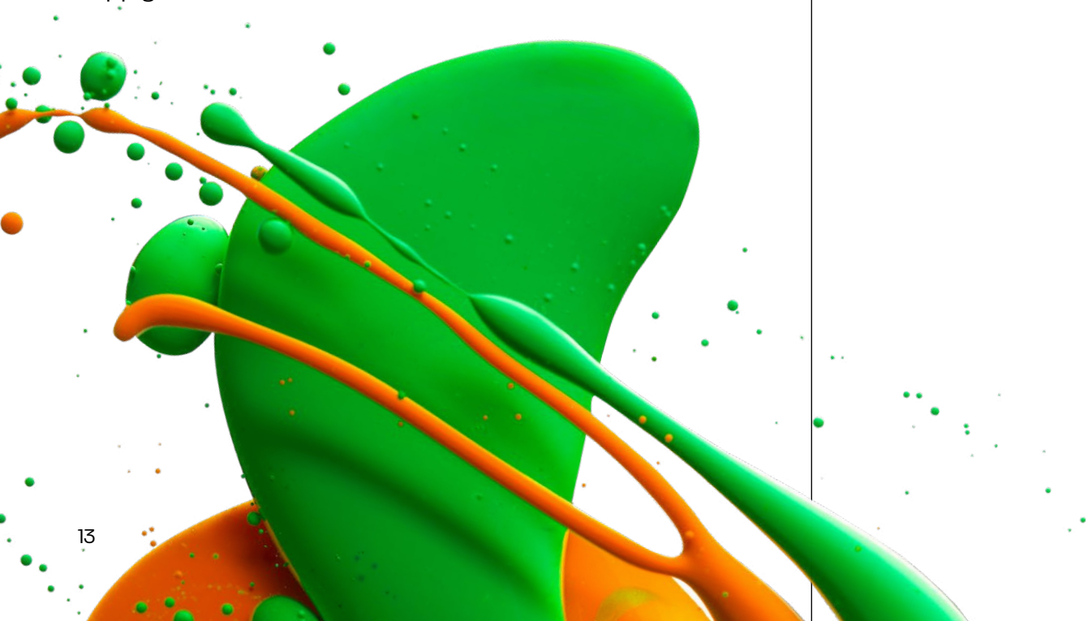
We regularly stress-test our distribution processes, making sure they work even in the most challenging countries because we know it is imperative for you to have a robust supply chain.

A warehouse that is over

4,000m²

where we receive, store, maintain, and deliver pharmaceutical standards





Mikromol™

Acetylation of 2,6-Dimethylaniline during the synthesis of Lidocaine.
(Impurity N-(2,6-Dimethylphenyl) acetamide, MM0102.08).