Malvern | Material relationships

LABEL-FREE ANALYSIS

MICROCALORIMETRY

MICROCAL **PEAQ-DSC**

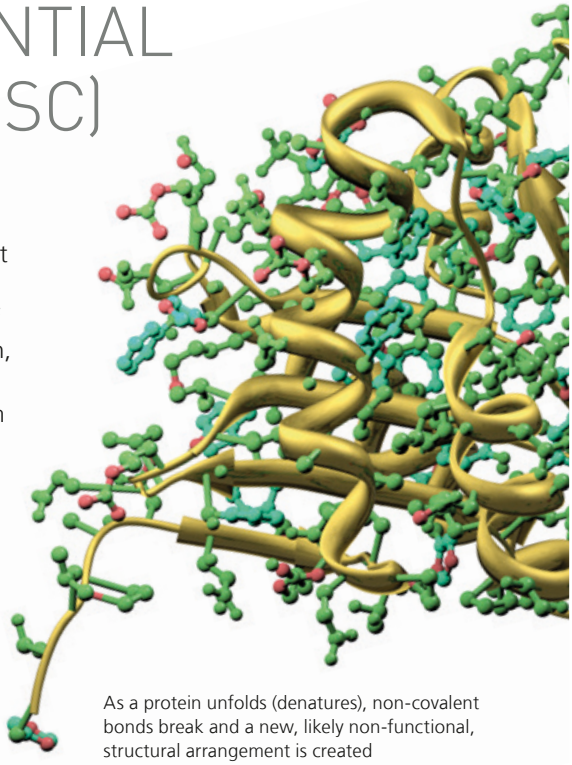
BIOMOLECULAR STABILITY ANALYSIS FOR THE REGULATED ENVIRONMENT

INTRODUCTION TO DIFFERENTIAL SCANNING CALORIMETRY (DSC)

WHAT IS DSC?

Differential Scanning Calorimetry (DSC) is a powerful analytical technique which characterizes the thermal stability of proteins and other biomolecules. In solution, these molecules often undergo thermally-induced conformational changes, such as the breaking of non-covalent bonds leading to the unfolding of a protein.

These types of structural rearrangement are detectable by DSC as they require the absorption of energy in the form of heat. Even in dilute solutions of protein, the new MicroCal PEAQ-DSC systems detect such heat changes and use them to accurately characterize the thermal stability of the molecule under analysis.



As a protein unfolds (denatures), non-covalent bonds break and a new, likely non-functional, structural arrangement is created

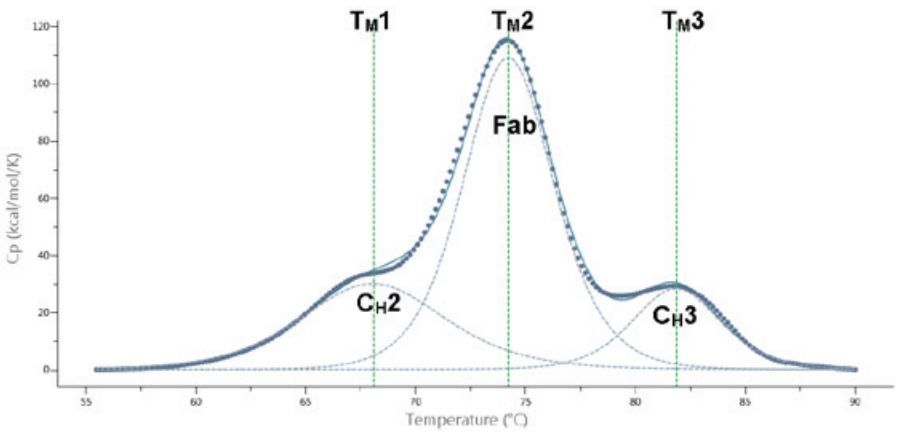
A typical DSC thermogram produced as a protein unfolds

Note the multiple peaks and shoulders detected for this multi-domain protein – vital stability data which is uniquely accessed via DSC.

The parameters that are derived using DSC allow for a quantitative assessment of the stability of the molecule. The peak of a DSC thermogram is the thermal transition midpoint (T_M).

T_M is considered a good indication of thermal stability – the higher the value, the more thermally stable the protein. Multi-domain proteins (like antibodies) typically have more than one peak on a DSC thermogram, so more than one T_M can be determined.

In addition to the T_M, there are other important parameters that can be used to characterize stability, such as the $T_{M\ onset}$ and $T_{1/2}$. More detailed analysis of the thermogram can also be performed to determine a number of thermodynamic properties including the enthalpy and heat capacity of the denaturation process, allowing for study of the underlying noncovalent interactions involved in the formation of the complex.



Representative DSC thermogram of a monoclonal antibody, with CH2, Fab, and CH3 domains identified. The dotted gray lines are the deconvoluted peaks of each domain transition, with the three T_Ms (transition midpoint temperatures) indicated

WHY USE DSC?

DSC analysis allows rapid identification of conditions that deliver optimum stability. The streamlined workflow and automated data analysis provided by MicroCal DSC systems accelerate screening of typical formulations and purification conditions, quickly delivering reliable results with minimum hands-on time, and driving productivity in research and development.

MicroCal DSC instruments are found in many laboratory settings including those in the biopharmaceutical & pharmaceutical industries, contract research and manufacturing organizations, government institutions and academia.

A choice of two systems meets the diverse requirements of different laboratories.

How can DSC help me?

The information delivered by DSC is 'gold standard', label-free stability data which can be used for a variety of purposes:

In biopharmaceutical development & manufacture:

- Predict & maximize a product's developability & shelf-life
- Optimize purification strategies
- Reliably assess biosimilarity and batch:batch comparability (e.g. validation of process changes)

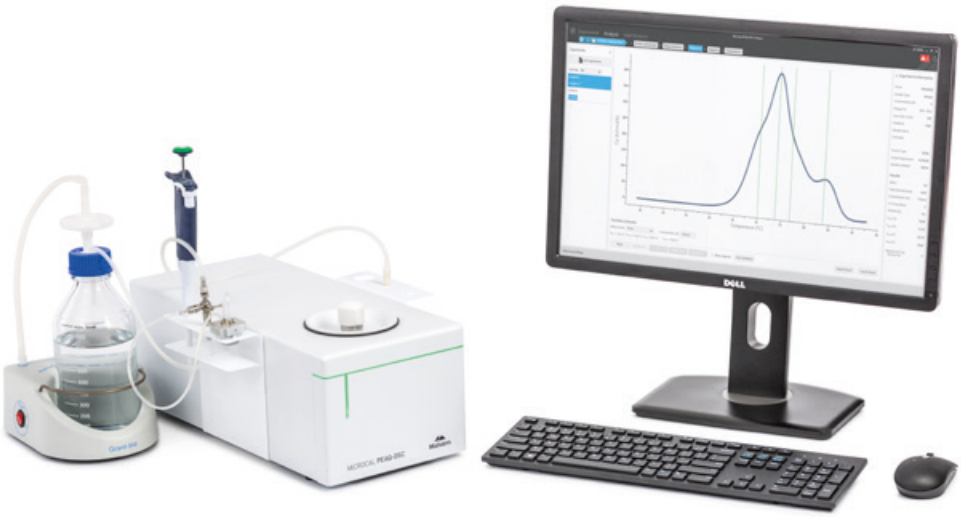
In small molecule drug development & manufacture:

- Rapidly rank ligand affinities to protein target
- Characterize a drug's protein target

In academia:

- Sensitive and reproducible analysis of protein folding and unfolding
- Characterize lipid and detergent micelles
- Measure thermodynamics of nucleic acid transitions
- Research drug delivery mechanisms

MICROCAL PEAQ-DSC



MicroCal PEAQ-DSC

The MicroCal PEAQ-DSC system provides highly sensitive, easy-to-use microcalorimetry that helps reduce the time and cost associated with stability testing and comparability analysis. This is a manual instrument with a cleaning device, which can be upgraded to the automated version upon request. This complete system requires no additional accessories, reagents or consumables.

The integrated software and automated data analysis support the generation of non-subjective, highly reproducible thermal stability data and help deliver compliance with regulatory requirements, increasing productivity in biopharmaceutical research.

KEY FEATURES:

- Screens up to 6 samples/8h with unattended operation after sample loading
- Manual system with cleaning device. Upgrade path to MicroCal PEAQ-DSC Automated is available
- Measurement of very tight binding constants, up to $10^{20}M^{-1}$
- 21 CFR Part 11- and Annex 11-ready (PEAQ-Compliance software option)
- PEAQ-Performance – validates your instrument to optimize its performance
- PEAQ-Smart (including PEAQ-Finder) – SOP-based operation and data analysis
- PEAQ-Compare – for quantitative comparability (batch-to-batch and biosimilarity) studies
- Network ready - email updates sent during the analysis to keep you informed

MICROCAL PEAQ-DSC AUTOMATED

MicroCal PEAQ-DSC Automated

The MicroCal PEAQ-DSC Automated system delivers high throughput and sensitivity, with low sample consumption, in an integrated platform for increased productivity. All cell filling and cleaning functions are fully automated, for walk-away operation.

Automated data analysis supports the generation of high integrity thermal stability data and delivers compliance with regulatory requirements, whilst allowing easy integration into existing data handling and transfer systems.

KEY FEATURES:

- Screens up to 50 samples per day with unattended operation
- Automated cell filling and cleaning
- Standard 96-well plate sample format
- Thermostatically-controlled storage of up to 6 plates
- Measurement of very tight binding constants, up to $10^{20}M^{-1}$
- 21 CFR Part 11- and Annex 11-ready (PEAQ-Compliance software option)
- PEAQ-Performance – validates your instrument to optimize its performance
- PEAQ-Smart (including PEAQ-Finder) – SOP-based operation and data analysis
- PEAQ-Compare – for quantitative comparability (batch-to-batch and biosimilarity) studies
- Network ready - email updates sent during the analysis to keep you informed

PEAQ-COMPLIANCE

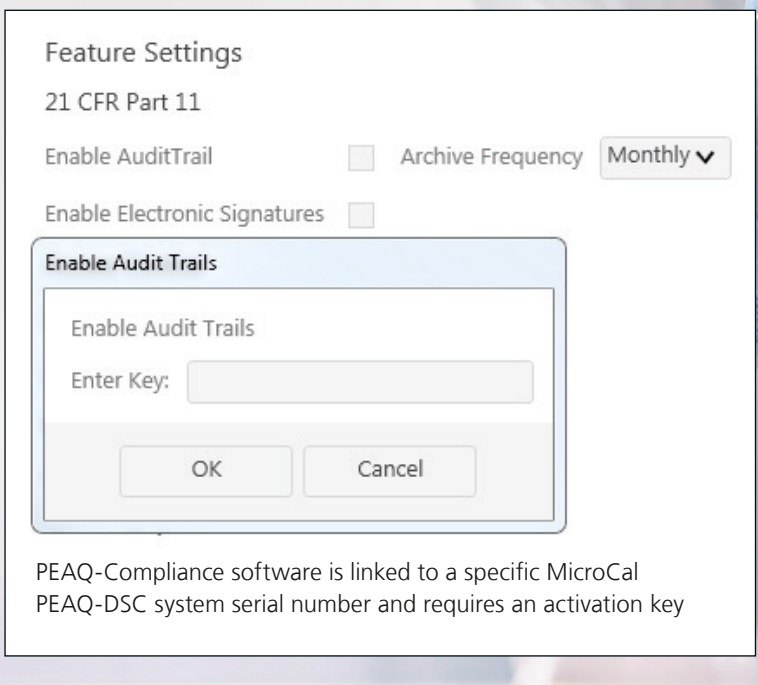
21 CFR Part 11 and Annex 11 Compliance software: DSC for the regulated environment

The all-new MicroCal PEAQ-DSC software is available with an optional 21 CFR Part 11 compliance module. This makes both MicroCal PEAQ-DSC systems perfect for QC-type work, including root cause analysis and in-process measurements.

Malvern has a wealth of experience working in cGxP environments. We understand the need for easy-to-use analytical systems that enable robust method development and transfer, with the support of 21 CFR Part 11 and also Annex 11 compliance tools and full lifecycle documentation.

PEAQ-Compliance enables the control of electronic records via an audit trail and the logging of key events such as the creation and modification of records. Central to the security of this system is the control and traceability of user interaction with the system and software. Both PEAQ-DSC and PEAQ-Compliance software require user log-in credentials, allowing electronic signatures for records. Metadata, including User ID, date and time logging, instrument information and ID, and method parameters, are saved to electronic records, and all copies or modifications of these records retain the original associated metadata.

Access to electronic records is controlled by the Malvern-Access Configurator (MAC) via Microsoft Windows' security system, and security access levels can be configured to suit each organisation's particular requirements.



PEAQ-Compliance software is linked to a specific MicroCal PEAQ-DSC system serial number and requires an activation key

KEY FEATURES:

- Electronic records from MicroCal PEAQ-DSC include metadata:
  - User ID, date and time, instrument type, method parameters, etc.
- Copy/modified electronic records retain all original metadata
- Electronic records include audit trail and log events
- PEAQ-DSC and PEAQ-Compliance software require user log-in to provide electronic signatures for electronic records
- Access to electronic records is controlled using Malvern Access Configurator (MAC). Security access levels can be configured as required

PEAQ-PERFORMANCE

Keep your system performing perfectly

A further requirement for analysis in a regulated environment is instrument Performance Qualification (PQ), which includes regular checks on the system to ensure that it is performing within defined acceptance criteria. PEAQ-Performance, part of the MicroCal PEAQ-DSC software, is a new feature specifically designed to simplify these performance checks.

Even if 21 CFR Part 11 compliance is not required for your DSC data, it is useful to frequently perform DSC analysis of a protein with a well-characterized DSC thermogram as a validation of instrument performance. Regular validation increases confidence in the reliability and reproducibility of your data, eliminating the need for analysis replication which can waste precious sample.

PEAQ-Performance automatically ensures that your instrument is performing at an optimum level, which translates directly to excellent, reliable data, enabling you to make decisions with absolute confidence. Performance checks can be incorporated into the experimental sets, and the software automatically analyzes this data, comparing it to expected results and sending an alert if it encounters a failure – giving the user the ability to stop the instrument and avoid loss of time or sample. PEAQ-DSC's user-friendly guided workflows with embedded help videos empower any level of user to generate high quality data.

KEY FEATURES:

- Automatic system-ready and baseline stability check before starting a run
- Removes subjectivity and simplifies operation
- Saves time and maximizes data utility
- Built-in automated cleaning protocols

PEAQ-Performance check

PEAQ-SMART

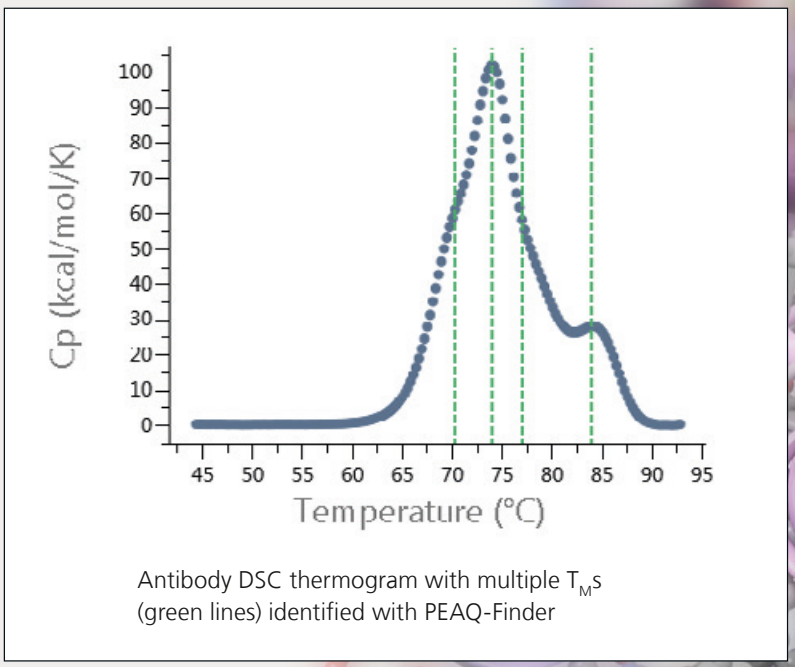
Easy experimental set-up, fast and intuitive data analysis and report generation

PEAQ-Smart provides new and improved control and data analysis for faster experimental design and implementation. Embedded videos are included to give a visual overview of DSC experimental design and also guide maintenance of the system – these help users of every level proceed with confidence. In addition, a new PEAQ-Smart report designer is included.

An SOP-Builder is built-in, to guide and accelerate experimental set-up and provide the capability to perform rescans and downscanning for reversible denaturation studies.

PEAQ-Smart provides a wide range of options for choosing buffer-buffer scans for automated subtraction from sample data. The software also offers automated creation and subtraction of the integration baseline, with improved functionality for manual adjustment of pre- and post-transition ranges, and a choice of integration baseline options: spline, progress, or linear. Furthermore, fitting of data to different unfolding models comes as standard.

Finally, PEAQ-Smart contains PEAQ-Finder, which enables the automated T_M determination of multiple thermograms. PEAQ-Finder offers automatic peak selection, with improved ability to resolve overlapping transitions. This tool resolves even very minor peak shoulders, allowing for non-subjective T_M picking and the identification and analysis of peaks which were previously undetectable.
This all results in faster, more accurate and objective DSC data analysis.



Antibody DSC thermogram with multiple T_Ms (green lines) identified with PEAQ-Finder

KEY FEATURES:

- SOP-Builder
- Automated data analysis
- PEAQ-Finder: Multi-peak ID and analysis – ideal for multi-domain proteins, including antibodies
- Report designer

PEAQ-COMPARE

Directly compare DSC thermograms, between molecules and between batches

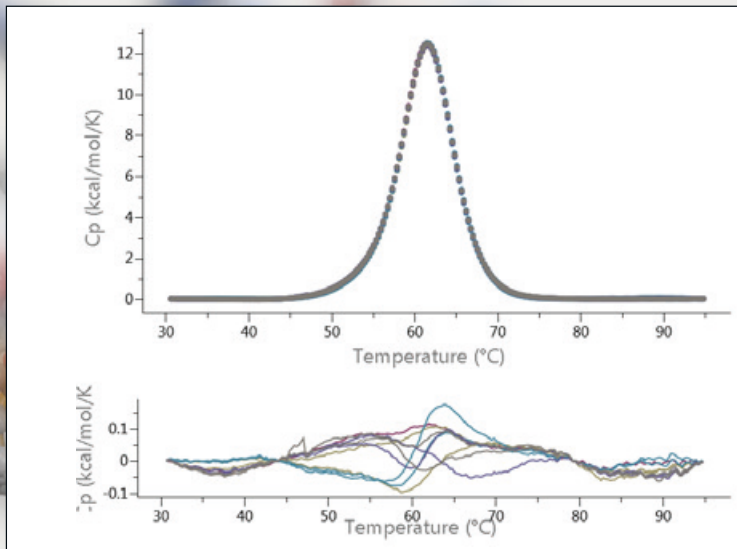
DSC has excellent utility as a biophysical and higher order structure (HOS) analysis technique to investigate the comparability of protein samples. This has obvious value when comparing a biosimilar to a reference protein, but it is also very useful in establishing the comparability of batches of the same protein.

For example, when substantial changes are made to the manufacturing process, a comparability exercise must be conducted to evaluate the impact of the change(s) on the product's critical quality attributes. DSC is commonly used as a HOS biophysical assay to show that the proteins in two compared samples have highly similar DSC profile 'fingerprints'.

MicroCal PEAQ-DSC Automated systems include PEAQ-Compare, a new software tool which performs rapid data analysis and evaluation on a set of DSC thermograms, and provides an objective, quantitative similarity comparison. PEAQ-Compare evaluates several DSC parameters in order to determine and rank-order comparability, and provides detailed information on residual data.

KEY FEATURES:

- Biosimilarity
- Batch-to-batch comparison
- Comparability rank-ordering



PEAQ-Compare assesses the comparability of 9 samples of ribonuclease. Residual data is shown at the bottom.

SPECIFICATION COMPARISON SUMMARY

Parameter	MicroCal PEAQ-DSC Automated	MicroCal PEAQ-DSC (Manual system)
Technology	Differential Scanning Calorimetry	Differential Scanning Calorimetry
Measurement parameters	Temperature midpoint T_M Enthalpy ΔH Heat capacity change ΔC_p	Temperature midpoint T_M Enthalpy ΔH Heat capacity change ΔC_p
Cell type	Capillary	Capillary
Cell material	Tantalum	Tantalum
Working cell volume	130 µL	130 µL
Sample capacity	288 (6 x 96-well plates)	N/A
Sample volume (minimum in well)	325 µL	250 µL (manual filling)
Typical sample concentration[1]	0.01 mg/mL - 10 mg/mL	0.01 mg/mL - 10 mg/mL
Sample throughput	≤50 samples / day	≤6 samples / 8h
Sample storage temperature	4°C - 40°C	N/A
Noise[2]	0.05 µCal/°C	0.05 µCal/°C
Baseline repeatability[2]	1 µCal/°C	1 µCal/°C
Response time[2]	5s	5s
Measurement repeatability[3]	0.2 µCal/°C	0.2 µCal/°C
Measurement reproducibility[4]	<0.08°C St.Dev. T_M and <2% RSD on ΔH	<0.08°C St.Dev. T_M and <2% RSD on ΔH
System reproducibility[4]	<0.1°C St.Dev. T_M and <5% RSD on ΔH	<0.1°C St.Dev. T_M and <5% RSD on ΔH
Multiple feedback modes	Yes (passive, high gain, low gain)	Yes (passive, high gain, low gain)
Temperature Range[2,5]	2°C to 130°C	2°C to 130°C
Maximum scan rate	240°C/h	240°C/h
Reverse scanning	Yes	Yes
Pressure perturbation calorimetry (PPC)	N/A	Optional
Cleaning routines	3 pre-programmed routines	N/A (manual cleaning device)
Cleaning solvents	Water and detergent as standard	Water and detergent as standard
21 CFR Part 11-ready	Yes, with PEAQ-Compliance software option	Yes, with PEAQ-Compliance software option
Network ready	Yes, with email alert capability	Yes, with email alert capability
Operating temperature	+10°C to +28°C	+10°C to +28°C
Storage temperature	-20°C to +50°C	-20°C to +50°C
Humidity range	10% to 70%, non-condensing (10% to 90% for storage)	10% to 70%, non-condensing (10% to 90% for storage)
Ingress protection	IP21	IP21
Power requirements	100-240V AC; 50/60Hz, 70W (cell), 400W (max, autosampler), PC as supplied	100-240V AC; 50/60Hz, 70W (cell), PC as supplied
Certification	CE (EN61010-1), EMC (EN61326-2-1, EN61326-1, FCC, ICES, VCCI), ISO9001:2008	
Dimensions (W x H x D)	101 cm × 70 cm × 68 cm	20 cm × 19 cm × 44 cm
Weight	Approx. 25 kg	8.2 Kg

[1]Sample dependent; [2]Typical results for ribonuclease (RNase) in 50 mM KAc buffer at pH 5.5, at 60°C/h with passive feedback; [3]Rescans of a stable buffer;
[4]Using ribonuclease (RNase); [5]Range may be extended down to -10°C upon request.

VALIDATION AND SUPPORT

Malvern's materials characterization technology and expertise enables scientists and engineers to understand and control properties of dispersed systems.

Malvern's instruments are used to measure particle size, particle shape, zeta potential, molecular weight, size and conformation, rheology and for stability assessment and chemical identification.

This information helps accelerate R&D, enhance product quality and optimize process efficiency.

Areas we work in:

- ACADEMIC BIOCHEMICAL RESEARCH
- BIOSCIENCE
- FOOD AND DRINK
- ASPHALT
- (BIO) PHARMACEUTICALS
- COSMETICS AND PERSONAL CARE
- CHEMICALS
- MINING AND MINERALS
- POWER GENERATION
- CEMENT
- METAL POWDERS
- PLASTICS AND POLYMERS
- SURFACE COATINGS
- ELECTRONICS
- CERAMICS
- ADHESIVES AND SEALANTS

Excellence through experience

Many Malvern systems are used in highly regulated environments, and product validation and R&D traceability are priorities for our customers. Operating to ISO9001: 2000 with TickIt accreditation for software development, Malvern is a major supplier to the highly demanding (bio) pharmaceutical and chemical industries. Malvern's products play pivotal roles in high quality research and manufacturing throughout the world.

As a global supplier, we understand our responsibility to minimize the impact we have on the environment, and operate to both ISO14001 and OHSA18001.

Validation

To help our customers comply with the requirements of the Regulatory Authorities, such as the US Food and Drugs Administration (FDA) and the Medicines and Healthcare products Regulatory Agency (MHRA), Malvern provides a comprehensive range of validation tools.

These aids follow a user's validation process through from Installation and Operational Qualification (IQ/OQ) to the maintenance phase with annual OQ renewals.

World-class service and support

Malvern offers professional support at all levels. Our intention is to increase your laboratory's productivity through the creation of a working relationship for the lifetime of your instrument, providing service, support, training and information.

- Global network of fully-trained service personnel
- Worldwide coordination for multinational companies
- Technical support from the Malvern Helpdesk via telephone or email
- Range of maintenance contracts and service agreements to cover all requirements
- Validation support
- Consultancy-based onsite training courses
- e-Learning training courses
- Classroom training courses
- Web seminars
- Sample and application consultancy

No other company offers more

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