

Mastersizer 2000 —

Validation and 21 CFR compliance
Questions and Answers



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This product support brochure applies to the
following Malvern Instruments products:
Mastersizer MS2000



Questions and Answers

Validation of analytical instruments is an issue that has always been important for pharmaceutical companies.

Now that the FDA has commenced its program to enforce the requirements laid down in 21 CFR Part 11 and has started to issue Form 483 Observation Notices for non-compliance, the emphasis on validation as a key activity is even greater.

As a market leader in particle sizing technology, Malvern Instruments has developed a reputation for being pro-active in addressing these concerns and is at the forefront in being able to assist its users both with validation and with 21 CFR compliance issues.

Who is responsible for the validation of the Mastersizer 2000?

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The short answer is that the final responsibility for the validation of any item of analytical equipment rests firmly with the user.

However, although many suppliers recognise that there is much that they can do to assist users with this onerous task, their levels of understanding of the requirements and their willingness to assist will vary considerably.

Since 1996, with the introduction of their QSpec validation contracts and the development of a quality system conforming to GAMP guidelines, Malvern Instruments has been pro-active in understanding validation issues. This has made a significant contribution to the reduction of Malvern users' validation workload and has led to an auditor's description of the Malvern quality system as "exemplary".

Who performs the validation?

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The user companies commonly employ an internal specialist validation department or a external consultancy to undertake all the tasks associated with the validation of analytical instruments and production processes.

What is validation?

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Validation is a high-level management process to provide on-going proof that a system or process is performing according to its initial specification.

This means that there are three essential ingredients. These are:

- Specification
- Performance
- Proof of performance

Is there a standard procedure that is followed by validators?

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Several types of procedure are followed but the most universally accepted takes the form of a series of validation steps known as "Qualifications" as outlined in the diagram below:

1) Design (Specification)

(Lifecycle Documentation)

SQ

Answers the Question:

Does the instrument fully satisfy the Market Requirements for which it was developed?

2) Construction

(Test Certificates)

CQ

Answers the Question:

Does the instrument exactly comply with the design specification?

3) Installation and Operation

(IQ/OQ Certificates)

IQ

OQ

Answers the Question:

Is the instrument exactly the same as when it left the factory?

4) Use (Performance)

Measurement of user's products and standards

PQ

Answers the Question:

Does the instrument do exactly what the purchaser intended?

The most readily understood of these qualification steps is the IQ/OQ since this is the one which most users see performed. In many cases, this is the only validation support offered by suppliers of analytical equipment.

The importance of Specification Qualification

From the definition of validation above, it follows that the foundation of a user company's validation activity is a specification against which the whole validation process can proceed.

According to best practice, the validation department should produce a validation plan that will set out the means by which any given instrument or process is to be validated.

This plan will include a Requirements Specification for the instrument in question. This will describe the functions to be performed by the instrument and set out the minimum performance specifications against which it should be tested. The specifications embodied in a well-designed Requirements Specification should all be verifiable by testing as far as possible. Selection of an appropriate instrument should also be made with reference to this Requirements Specification. When the Performance Qualification is finally performed, it should be specifically designed to test whether the system purchased meets the internal Requirements Specification. A well-designed Requirements Specification will feature specification points which can be explicitly tested to give a clear indication that a successful validation has been achieved.

To quote the FDA Guidance Document (21 CFR Part 11 - validation Guidance):

"Without first establishing end user needs and intended uses, we believe it is virtually impossible to confirm that the system can consistently meet them. Once you have established the end user's needs and intended uses, you should obtain evidence that the computer system implements those needs correctly and that they are traceable to system design requirements and specifications..."

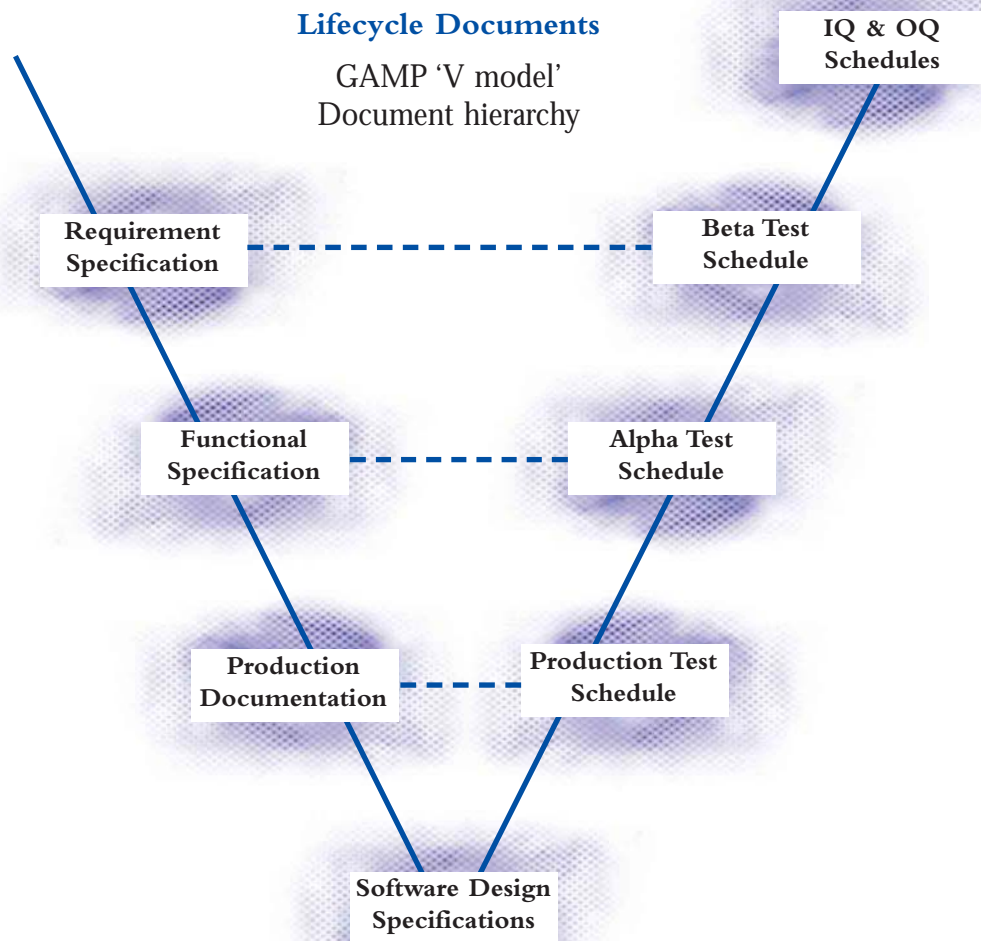
If the supplier has a Quality System which includes full documentation of design intentions and changes, this is a considerable validation resource which can benefit users in the pharmaceutical industry. Not only does it demonstrate that there is a quality infrastructure capable of delivering stability of performance allowing users in different operating divisions to have comparability of data but it also helps to satisfy the last point in the FDA guideline.

Users who can demonstrate access to such documentation are generally more likely to achieve a standard of system validation that will not be seriously challenged by the Regulatory Authorities.

What is lifecycle Documentation?

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The Lifecycle Documentation comprises all the supplier's project documentation relating to the development of the product. Malvern Instruments' Lifecycle Documentation is based on GAMP guidelines and is in close conformance to the well established "V" format as shown below:



These documents give auditors clear traceability of the design thoughts behind the equipment in question and allow them to check the inherent fitness for purpose of the instrument. They also provide documentary evidence that the design requirements have been satisfied in full. As can be seen, the right-hand arm of the "V" comprises a comprehensive series of tests to ensure that the specifications have been met at all levels– from the concepts described in the Requirements Specification through to the practical solutions contained in the functional specifications.

How can users get sight of the Lifecycle Documentation relating to the Mastersizer 2000?

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The Lifecycle Documentation relating to the Mastersizer 2000 is open to audit on a chargeable basis under the terms of a non-disclosure agreement.

Subscribers to Malvern's QSpec contract can obtain preferential audit rates.

Where is it held?

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Owing to the confidential nature of much of the documentation, it is retained at Malvern Instruments UK headquarters.

What is a QSpec contract and what does it provide?

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Introduced in 1996 in support of the Mastersizer S and Mastersizer X, the QSpec validation contract provides users with a framework to make their validation tasks simpler. When the Mastersizer 2000 was launched in late 1998, it was launched with full QSpec support. As part of the original QSpec project, Malvern's quality documentation system was revised to conform exactly to GAMP guidelines in order to simplify audits and validation generally. To help users get the best from this development, the QSpec concept of validation contract was devised to provide the following benefits to subscribers:

- Rights to view the Lifecycle Documentation relating to the software and hardware development.
- Details of the performance of the numerical validation of the software together with a right to view this validation being performed.
- A right to view the software source code.
- Provision of a Logbook to house all the validation documentation including the IQ/OQ certification relating to the instrument.
- The provision of user training records for ease of reference by auditors.
- A specimen standard operating procedure.
- An Escrow Licence agreement entitling the subscriber to access to the software source code and the development tools in the (unlikely) event of the inability of Malvern Instruments to continue to offer support.
- A manual describing the Malvern Instruments approach to validation. This is a very useful tool to help auditors understand the thoroughness of the QSpec concept and Malvern's Quality documentation hierarchy which is summarised in the diagram shown on page 7.

The Total Validation Scheme

Validation requirement:

Lifecycle Documentation

- Alpha Test
- Beta Test
- Change History

SQ

Satisfied by:

- QSpec Contract
- Rights to View Documentation

Manufacture

- Test Schedule
- Test Results

CQ

- Test Certificates
- including OQ results at manufacture (QSpec-Rights to View)

Installation

- IQ/OQ Specs
- Test Latices
- Quality Audit Standards

IQ

OQ

- OQ Test pre-defined
- for Optical System
- for Sample Handling Units (With clear test procedures and clear pass-fail criteria)

User's responsibility, but Malvern supplies:

- Paid analysis
- Advice on:
 - Sample Handling
 - SOP development
 - Method development

PQ

- Achieved by testing on 'Real' Materials looking at:
 - Sampling method
 - SOP for measurement
 - Performance

Is an annual OQ enough to assure users and Regulatory Authorities of the continued integrity of the system?

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This question is best answered by considering the implications of the failure of an annual OQ. When did the instrument drift out of specification? Was it the day after the performance of the previous year's OQ or was it the day before the failed OQ? Will a product recall be required?

If the answers to these questions suggest that a failure would present users with a problem, then regular use of the Quality Audit Standards and latices used in the OQ is strongly recommended.

Does Malvern Instruments provide a means whereby an instrument's performance can be checked on a regular basis?

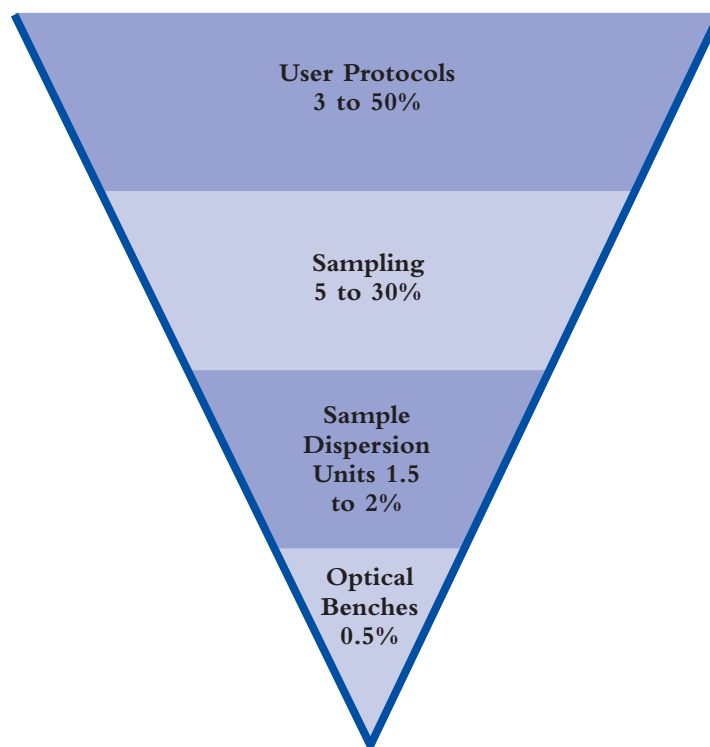


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Up until 1998, latex standards and a reference reticle provided the main tools for checking the performance of a Mastersizer system. From 1998, latex standards became the preferred means of checking the integrity of the optical system of a sizer. The success of these has been such that it is now commonplace for the optical bench of a Mastersizer to be accurate to better than 1% on the Dv50 of the latices used for the performance of OQs.

However good an optical bench is, a successful measurement will ultimately depend on the good performance of the sample dispersion unit. This unit must evenly disperse the particles in a sample, keep them in a homogeneous dispersion without agglomeration and pass them through the laser beam of the sizer without bias or distortion.

Differences in the efficiencies of air regulators in Dry Powder Feeders and variations in stir speeds, circulation pump speeds and efficiencies in wet sample dispersion units can all give rise to differences in measurement performance of the whole system. All these factors serve to explain why there can be greater variation between sample dispersion units than optical systems. Control and monitoring of these factors can have a greater impact on the accuracy of a particle size measurement than small imperfections in optical systems.



The Sources of Result Variation in the field.

To challenge sample dispersion units but ensure that any variations noted are due to differences between units and not differences in the samples, Malvern introduced their Quality Audit Standards– riffle split soda glass bead samples which meet the following key requirements:

Broad size distribution	The material has a size distribution from 20 to 120 µm.
Sealed one-shot bottles eliminate sampling variations and give unlimited storage life	No need for batch numbering of samples associated with shorter shelf-life samples such as latex.
Spherical	Simplifies inter-instrument comparisons– recommended in ISO 13320
Relatively Low Cost	Important to encourage regular use.
Supply not likely to be quickly exhausted	250 Kg master batch– the largest quantity ever produced to create a standard sample material. This gives dependability of test protocols and avoids the need for regular re-characterisation of fresh batches associated with short production runs of samples.
Well-characterized and repeatable	A statistically significant sample of the whole bulk was measured and an uncertainty of only 0.75% was established on the dv50. This means that if differences are noted, they are due to the unit and not the sample.
Optically representative of real world samples	Soda glass has a refractive index of 1.53– this compares favourably with the following common excipients and additives: Calcium Carbonate 1.53; Sugar and Talc 1.51; Magnesium Stearate 1.43; Lactose 1.34.

Note: Sample materials with higher refractive indices are atypical and likely to be misleading in terms of the ability of a system to measure real-world samples.

How are the Quality Audit Standards supplied?

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All Quality Audit Standards are supplied in packs of ten sealed bottles complete with measurement protocols, pass/fail criteria and Certificates of Conformance. The following standards are available:

For MS1, DIF2021, Hydro 2000S and Hydro 2000SM: QAS2001

For MS15, DIF2012, Hydro 2000G, Hydro 2000M and Hydro 2000MU: QAS2002

For MAM2460, MAM2461 and Scirocco 2000 Dry Powder Feeders and the Autosampler 2000: QAS2003

For Hydro 2000 μ P Micro Precision sample dispersion unit: QAS2005

For Micro and Microplus Particle Size Analyzers using a 1000ml beaker: QAS2006

There is also a "Saver" pack, Part no. QAS2004, comprising one ten-pack each of QAS2001, QAS2002 and QAS2003.



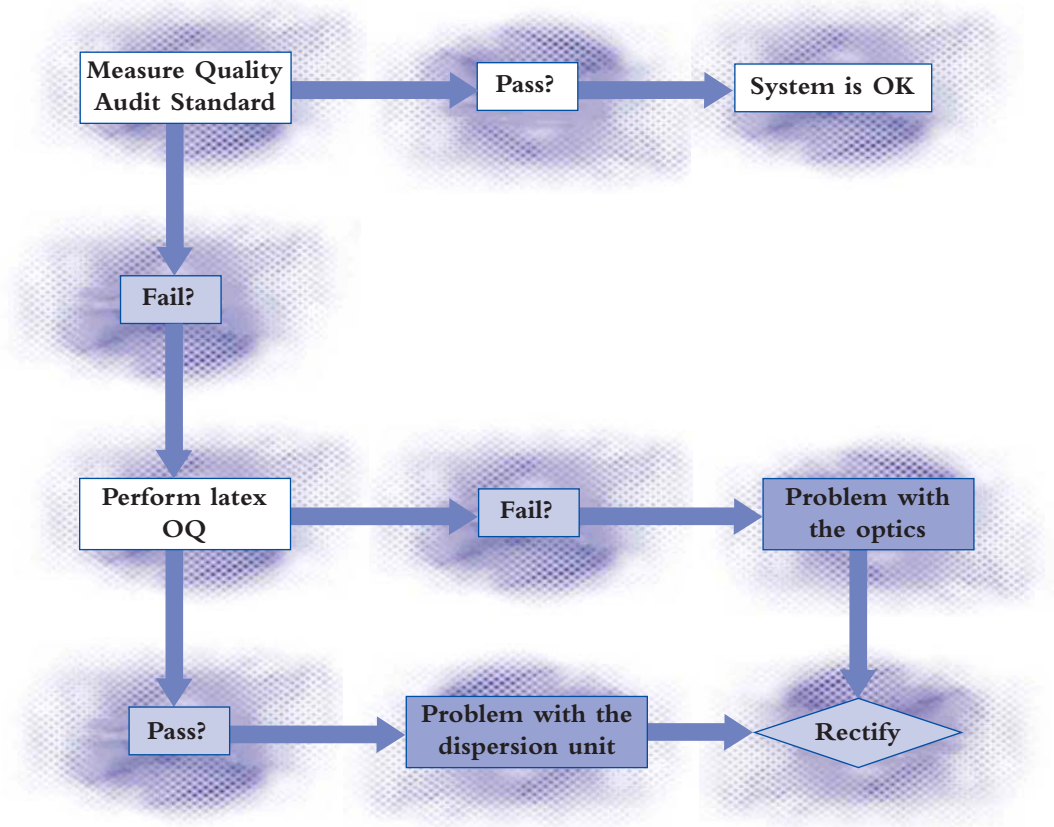
Quality Audit Standards also form an important part of the Consumable Parts kits now available for the dispersion units of the Mastersizer 2000.

When should we use latex and when should we use a Quality Audit Standard to check our instruments?



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Because the Quality Audit Standard is a sample with a broad distribution, it will check the performance of the sample dispersion unit as well as the sizer. Because latices have very narrow size distributions, the results that are obtained will not be affected by differences in sample dispersion units but will be very sensitive to differences in the performance of the optics. This means that the two types of material can be used together to home in on the cause of any loss of integrity in the complete system as shown in the diagram below:





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Software validation is often regarded as being different from system validation with users talking about systems having "validated software" as if this was a stand-alone activity in which they do not participate.

In fact, the final responsibility for software validation does actually rest with the user but the user needs to make sure that certain important criteria have been met by the supplier.

The first and most obvious of these criteria is that there is evidence that the supplier has carried out functional testing. (Referred to in FDA Guidelines as "Black Box" testing.) The second of these is that the supplier has followed "contemporary quality standards" in the development of the software.

According to FDA Guidelines, Malvern is strictly speaking an external Third Party supplier of software. This means that end users should create their own internal Requirements Specification as discussed earlier. However, the guidelines also state that the end user should, if possible, obtain a copy of the developer's Requirements Specifications for comparison.

Owing to the fact that Malvern has followed GAMP guidelines in the creation of its quality system relating to software and hardware, the Company is able to provide rights to view the Requirements Specification relating to the software as well as the results of the Functional Testing of the software. There is also an ultimate right to view the source code and development documentation. End users can, if they wish, also become Escrow Licensees.

In addition to the Functional Tests, Malvern's documentation and change control system ensures the continued integrity of the software and provides traceability of changes made.

When users have validated all their methods on an existing version of software, upgrading to a new version of software may not be entirely straightforward. A very important part of Malvern's software change process is to inform users of the nature of the changes introduced in the software so that a proper assessment of the impact of a change can be made.

What about 21 CFR 11 compliance?

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With the issue of V 5 software for the Mastersizer 2000, Malvern offers the highest potential for compliance available from a laser diffraction particle size analyser today.

Surely you either comply or you don't?

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In the same way that validation is the responsibility of the user, compliance is also ultimately dependent on the user. Incorrect user procedures can undermine the compliance of any system.

It follows that the intrinsic compliance of a system is a matter of degree that will depend on how well that system complies without reliance on user procedures.

There are two approaches to making software compliant.

The Mastersizer 2000 approach to providing compliance is to control user access so that only authorised personnel can perform edits and deletions and the reasons for such actions are recorded. An audit trail is provided which logs all such actions. The security features and authority checks are all built into the Mastersizer 2000 software itself so that even if unauthorised users can get past the front door provided by Windows NT security, they will be barred from using the Mastersizer 2000 software itself.

Provision has been made for the software to import Mastersizer S and Mastersizer X results as read-only files in order to provide comparability of results as well as continuity of viewing ability.

The second approach to achieving compliance is one of prohibition of all activities which would change any data stored on the system. By this means, the need for the provision of audit trails is removed.

This approach is more appropriate to well-established software and systems (so-called "legacy systems") which were in existence before Part 11 came into force in 1997.

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The requirements relating to electronic signatures are met by printing result reports to Adobe® PDF files using Adobe Acrobat®. These documents can then be digitally signed and stored. The PDF file format is currently supported by all major agencies and is the preferred submission medium of the FDA.

(See <http://www.adobe.com/epaper/features/govtandpdf/reviews.html> for further details of the use of Acrobat to expedite new drug applications and reviews.)

The act of saving a result as an Acrobat file is one of "printing". Acrobat is specified as the printer for the results and the result is then automatically compiled as a pdf file for digital signing.

The Mastersizer 2000 V5 software allows automatic generation of pdf files of measurement results for review and signature.

Version 5 of Adobe Acrobat provides a simple Public Key Infrastructure (PKI) system that supports all electronic signature requirements such as multiple signings and digital representation of signatures. Signatures are automatically validated using PKI.

More sophisticated PKI certificate options can readily be added to enhance the basic Adobe solution.

There are numerous third party packages available from all the major players in the PKI market, such as Entrust, VeriSign, and PenOp. Further details are available from the Adobe® web site at the following URL:
<http://www.adobe.com/epaper/tips/acrsignatures/main.html>



Example of a double signature. One is a representation of the user's actual script signature, the other is purely digital. Both have legal force.

For a person to be able to sign a document, details of that user must be known to the system. The "Self-sign" feature provided with Adobe Acrobat uses this information to generate a digital identifier for that user and a certificate to identify that user from the digital identifier. These credentials are stored in a centralised directory that is secured using the operating system's security.

In situations where several people may be required to sign documents and all the signatures need to be verified, certificates can be e-mailed to other signatories so that they can verify all the signatures on a document. Two 32-digit alphanumeric security codes can be used to check that certificates have not been tampered with.

Does upgrading to Version 5 software automatically give me 21 CFR compliance?

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No. The user still needs to implement an archive and storage solution. The security system needs to be configured correctly and SOPs need to be created to control its use and administration.

If Electronic Signatures are to be implemented, the user needs to create SOPs to regulate the use of the self-sign features of Acrobat. These will include providing the FDA with notification of their intent to use Electronic Signatures together with evidence of signers' identities tied to their Electronic Signatures.

The user also needs to have installed a feature key to enable the particular features which bring the software into compliance. This key was originally offered with Version 3.2 software and users who purchased it then will find that the 21 CFR compliant features in Version 5 are automatically available as soon as it is installed. Other users wishing to achieve compliance can follow a simple procedure to purchase and install this feature key which will ensure that their systems can access the 21 CFR compliant features in version 5 software and all later versions as they are issued.

I am only interested in the Electronic Records aspects of compliance. Do I still need a Feature Key?

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Yes. Everyone using an electronic records system to store data required by the FDA must comply with the ER part of 21 CFR. Most of the significant coding effort that has gone into providing 21 CFR compliance in the Mastersizer 2000 software has addressed the Electronic Records aspects of compliance.

spectris

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