GLP Requirements

Related to an Environment with NMR Systems

User Guide
GLP Verification

Version 002

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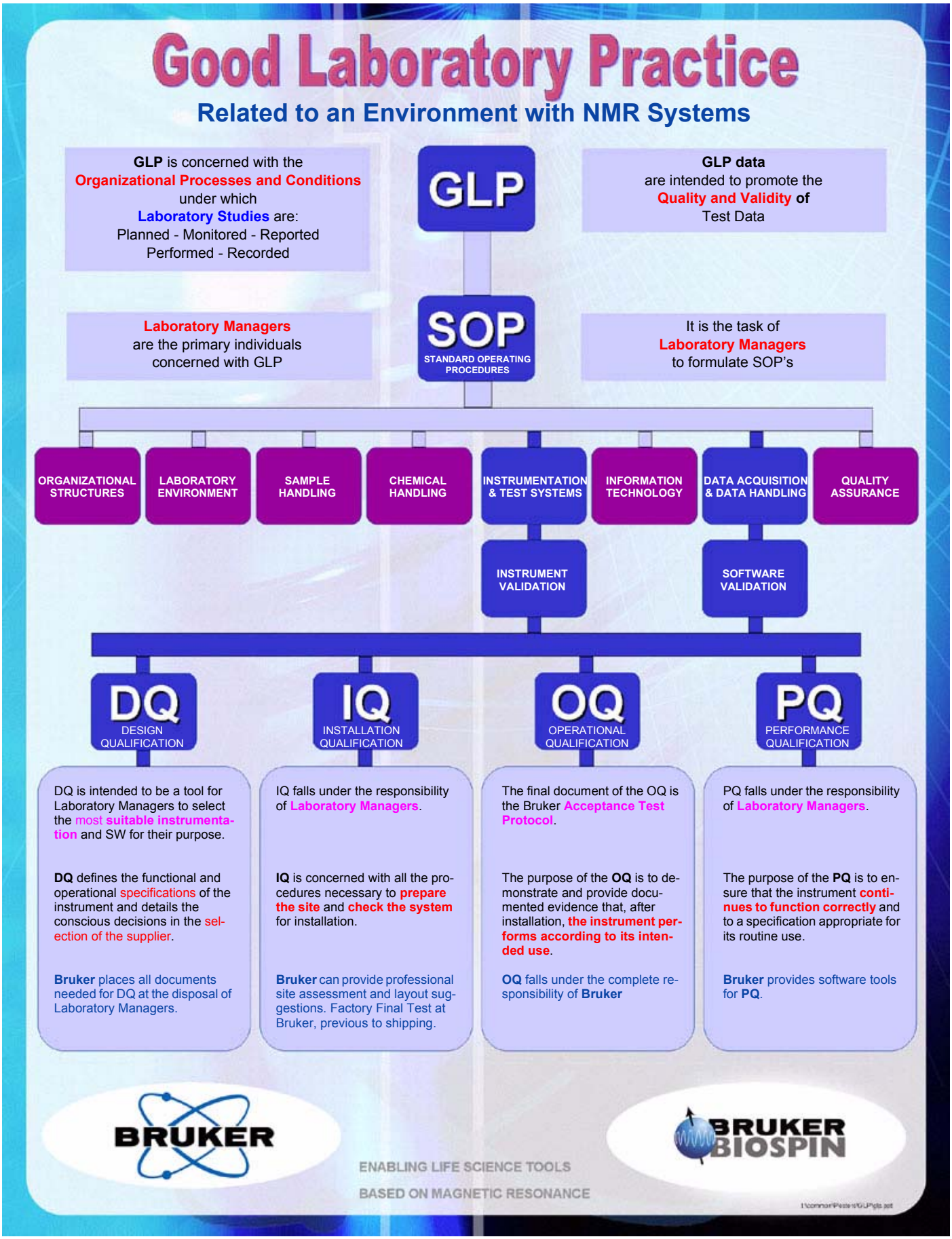

Good Laboratory Practice
Related to an Environment with NMR Systems
GLP is concerned with the Organizational Processes and Conditions under which Laboratory Studies are: Planned - Monitored - Reported Performed - Recorded
GLP
GLP data are intended to promote the Quality and Validity of Test Data
Laboratory Managers are the primary individuals concerned with GLP
SOP
STANDARD OPERATING PROCEDURES
It is the task of Laboratory Managers to formulate SOP's
ORGANIZATIONAL STRUCTURES
LABORATORY ENVIRONMENT
SAMPLE HANDLING
CHEMICAL HANDLING
INSTRUMENTATION & TEST SYSTEMS
INFORMATION TECHNOLOGY
DATA ACQUISITION & DATA HANDLING
QUALITY ASSURANCE
INSTRUMENT VALIDATION
SOFTWARE VALIDATION
DQ
DESIGN QUALIFICATION
IQ
INSTALLATION QUALIFICATION
OQ
OPERATIONAL QUALIFICATION
PQ
PERFORMANCE QUALIFICATION
DQ is intended to be a tool for Laboratory Managers to select the most suitable instrumentation and SW for their purpose.
DQ defines the functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier.
Bruker places all documents needed for DQ at the disposal of Laboratory Managers.
IQ falls under the responsibility of Laboratory Managers.
IQ is concerned with all the procedures necessary to prepare the site and check the system for installation.
Bruker can provide professional site assessment and layout suggestions. Factory Final Test at Bruker, previous to shipping.
The final document of the OQ is the Bruker Acceptance Test Protocol.
The purpose of the OQ is to demonstrate and provide documented evidence that, after installation, the instrument performs according to its intended use.
OQ falls under the complete responsibility of Bruker
PQ falls under the responsibility of Laboratory Managers.
The purpose of the PQ is to ensure that the instrument continues to function correctly and to a specification appropriate for its routine use.
Bruker provides software tools for PQ.
BRUKER
BRUKER BIOSPIN
ENABLING LIFE SCIENCE TOOLS
BASED ON MAGNETIC RESONANCE

Introduction 1

Introduction 1.1

Many chemical, pharmaceutical, biotech companies and laboratories must comply with regulatory requirements or are planning to organize their activity according to federal or international quality management standards. One of the best known standards is **GLP**, or **Good Laboratory Practice**.

In the U.S.A. GLP documents are issued by the Food and Drug Administration (FDA). The FDA GLP regulations are enforceable under the Federal Food, Drug and Cosmetic Act, and apply to non-clinical laboratory studies that are submitted to the FDA in support of an application for a research or marketing permit.

FDA regulations have also been taken on by the Council of the OECD countries, who then advised the corresponding health ministers to adopt GLP. Laws have then been formulated to cover this matter in each country, i.e., to regulate the way chemical substances are dealt with and with instrumentation in non-clinical laboratories.

Based on its official definition, GLP is concerned with the organizational processes and conditions under which laboratory studies are:

- **Planned**
- **Performed**
- **Monitored**
- **Recorded**
- **Reported**

GLP data are intended to promote the quality and validity of test data.

Who is Responsible for GLP? 1.1.1

Generally, **laboratory managers** (**LM**'s) are the primary individuals concerned with GLP, along with those people responsible in applying GLP principles to the above mentioned conditions.

It is the task of LM's to formulate **Standard Operating Procedures** (SOP's) which are adapted to the specific laboratory environment. SOP's on laboratory studies concern a whole range of activities and areas such as:

- Organizational structures
- Laboratory environment
- Sample handling
- Chemical handling
- **Instrumentation and test systems**

- Computer
- **Data acquisition and data handling (software)**
- Record keeping
- Quality Assurance (QA) in the laboratory

SOP's regarding **instrumentation** should focus on proving and maintaining the reliability of systems used in analytical measurements, as well as system:

- Maintenance
- Calibration
- Check-ups

The main requirement for GLP has come to be known under the term **Instrument Validation**.

The official **definition of Validation** is worded as follows:

„Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

The purpose of validation procedures is to make sure that equipment, such as spectrometers, perform reliably and remain suitable for their intended use.

In regards to Bruker NMR instruments this includes:

1. Specifying **test procedures**
2. Verifying that **specifications** are met
3. Documentation of **test results**

Bruker's role in GLP Qualification *1.2*

For Bruker NMR spectrometers, and for all other analytical equipment, GLP guidelines prescribe an **Instrument Validation** (**IV**), which is broken down into **four qualification steps**:

1. **Design Qualification** (**DQ**)
2. **Installation Qualification** (**IQ**)
3. **Operational Qualification** (**OQ**)
4. **Performance Qualification** (**PQ**)

Bruker can provide assistance in all four steps of instrument validation.

To meet this challenge of GLP qualification, Bruker spectroscopy systems have built-in **tools** to help comply with GLP regulations, meet inspectors' standards and, at the same time, increase throughput.

General Instrument Validation Tools 1.3

To assist in normal testing, calibration and validation of Bruker spectrometers and magnets, Bruker has developed an array of instrument validation tools which automate many of the validation procedures required for GLP qualification.

ATP 1.3.1

The *Automatic Test Procedure (ATP)* software package is a tool used by **Bruker engineers** to **define**, **store** and **execute** test experiments, and **report** and **archive** test measurements for AVANCE NMR spectrometers. The ATP package has been designed by Bruker for Bruker Test and Service Engineers to standardize the final test and acceptance procedures and documentation.

HWT Suite 1.3.2

The *Hardware Tests (HWT)* are a suite of tests primarily used in **Operational Qualification** (**OQ**) by **Bruker engineers** to demonstrate the hardware performance of our instruments. These tests are based on the tests compiled in an article by Joseph B.Vaughn and Philip L. Koons, in *Spectroscopy* 1995, 10(1) 36-40.

The hardware tests that you can perform using the HWT suite fall into three basic categories:

- General tests
- Modulator tests (shaped pulses)
- Tests using gradients

The HWT tests are commonly carried out as part of the ATP procedure, but can be run individually at any time during the lifetime of a spectrometer. Please note that HWT test should only be performed by specially trained laboratory personnel, Bruker service engineers, or Bruker application scientists.

SVT Software 1.3.3

The *Software Validation Test (SVT)* software, which is primarily used in **Operational Qualification** (**OQ**) is intended for **specially trained laboratory personnel** for the general hardware and software validation of Bruker NMR spectrometers. Some of the tests that you can perform using the SVT software include:

- Standard Line Shape, or Hump test for 1H or 13C
- Standard Resolution test for 1H or 13C
- Standard Sensitivity test for 1H or X-nuclei
- Standard Water Suppression test
- User defined tests

GLP Software *1.3.4*

The *Good Laboratory Practice (GLP) software*, which is primarily used in **Performance Qualification** (**PQ**) by **specially trained laboratory personnel**, performs tests which ensure continual and routine control of the spectrometer performance. The tests provide evidence that the instruments continue to function correctly.

The test must be adapted to:

- Instrument configuration
- Laboratory environment
- Laboratory task

It is the task of each Laboratory Manager to define the suitable GLP tests.

NMR-CHECK *1.4*

NMR-Check is a software package that among other features, allows Bruker service or trained laboratory personnel to remotely or locally check certain hardware components for faulty behavior. Once a problem has been identified as hardware oriented, NMR-Check will help in the precise diagnosis of the hardware fault and the identification of the effected hardware component. Therefore, NMR-CHECK is a valuable tool for reducing instrument downtime when hardware problems occur.

Design Qualification 2

Introduction 2.1

Design Qualification (DQ) defines the functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier.

Before a new system is purchased, DQ should ensure that the selected instruments posses all the necessary functions and performance criteria that will enable them to be successfully implemented for the intended application and to meet business requirements. Errors in setting the functional and operational specifications can have a negative technical and business impact. Therefore, a sufficient amount of time and resources should be invested in the DQ phase.

In order to meet the needs of our customers, Bruker has always committed itself to guaranteeing a continuously high standard in production, service and support. Bruker's ongoing commitment was reaffirmed in 1994 with the attainment of the **ISO 9001** certification for its Quality Management System. All AVANCE spectrometers and Bruker magnets fulfill all applicable safety requirements and comply with the **CE** norms. Hence, Bruker can provide the best evidence and support to Laboratory Managers to meet their requests for Design Qualification.

This chapter is an effort to provide assistance in setting the functional and operational specifications for our customers, as well as aiding in vendor qualification. For unique requirements or additional information on our spectrometer and magnet systems, feel free to contact your nearest Bruker sales or service representative.

Basic Steps for Design Qualification 2.2

While IQ, OQ and PQ are being performed in most regulated laboratories, DQ is a relatively new concept. DQ is unfortunately less often officially performed and documented, especially in those cases where the equipment is planned to be used for multiple applications.

The recommended steps for DQ cover:

- Description of the **analysis tasks**.
- Selection of the **analysis methods**.
- Description of the **intended use** of the instrumentation.
- Preliminary selection of functional and operational **specifications** (technical, environmental, safety).
- Preliminary **vendor qualification**.

- **Instrument tests** (if the technique is new).
- **Final selection** of the instrumentation.
- Documentation of the **final specifications**.

In the case when instruments are used for different applications with different functional or operational requirements, it is recommended to describe the most important intended applications and to specify the functional and performance specifications so that they meet the criteria for all applications.

Instrument Specifications *2.3*

Any validation should start with setting and documenting the specifications for user requirements, instrument functions and performance. To aid in setting the functional and performance specifications, the following specification sheets have been provided for Bruker spectrometers and magnets. These design specifications should be carefully compared with the user requirement specifications.

Table 2.1. AVANCE Spectrometer Specifications 200-400 MHz

BRUKER

AVANCE SERIES

BRUKER BIOSPIN

Technical Data

Specifications for Avance Spectrometers 200MHZ to 400MHZ		Standard	Options	Solids option *
Frequency Channels (SGU/FCU)	two channels, 6-440MHz each	2	upgrade up to 8 *	
	frequency resolution	< 0.005 Hz		
	phase resolution / min. event time	< 0.01° / 50 ns		
	amplitude resolution	< 0.1 dB		
	amplitude control, modulator / min. event time	96 dB / 50 ns		
	memory per channel e.g. for pulse shaping	1 MByte		
	phase accuracy over amplitude setting range	< 3°		
Timing Control Unit (TCU) with high-speed processor	memory	4 MByte		
	pulse sequence parameter calculation	in real time		
	timing resolution	12.5 ns		
	output bus for events and devices	3 x 32-bit		
Receiver Control Unit (RCU)	digitizer / max. oversampling rate	16-bit / 300kHz	16-bit / 2MHz	12-bit / 20MHz *
	data compression / digital filtering	on the fly		
Communication Processor (CCU)	memory	16 MByte		
	communication, protocol	Fast Ethernet TCP/IP™		
Host Computer	operating system	WINDOWS 2000™	UNIX™, LINUX™	

Quadrature Receiver	bandwidth (3dB)	1MHz		5MHz
	quadrature image peaks: - with phase cycle (1 transient/8 transients) - with Digital Quadrature Detection (DQD) using 16-bit/300kHz digitizer (SW < 25kHz) using 16-bit/2MHz digitizer (SW < 100kHz)	< 1% / < 0.2% 0%	 0%	< 1% / < 0.2%
			Options for CP/MAS	
Linear Amplifier #1 Selective output power at 1H / 19F frequency	max. output power (pulsed) 13C / 1H	150W / 50W	100W	1 kW / 150W **
	max. CW power	10W	25W	50W / 25W **
	max. duty cycle at full power	10%	25%	5%
	max. pulse length at full power	10 ms	500 ms	100 ms
	frequency range (BB at min. 125W) (1H/19F at min. 50W)	14 - 163MHz 188 - 400MHz	1H, 19F	1H, 19F
Linear Amplifier #2 Broadband output power at 13C frequency	max. output power (pulsed) 13C / 1H	150W / 50W	300W	1kW / 300W **
	max. CW power	10W	30W	50W / 30W
	max. duty cycle at full power	10%	10%	5% / 10%
	max. pulse length at full power	10ms	100ms	100ms
	frequency range (BB at min. 125W) (1H/19F at min. 50W)	14 - 163MHz 188-400MHz	BB	BB

Console	Dimensions & weights are approx.; voltage +10/-5% max. variation; 220V/50-60Hz; other line freq. & voltage upon request	MicroBay	OneBay	TwoBay Solids
Dimensions Electronic Cabinet	basic system (w x d x h)	0,63 x 0,83 x 0,96 m	0,69 x 0,83 x 1,30 m	1,31 x 0,83 x 1,30 m
Weight	ca. basic system, depending on options	> 150kg	> 260kg	> 380kg
Power Dissipation	ca. basic system, depending on options	> 1,2 kW	> 2,6 kW	> 9,6 kW

*** two-bay upgrade included**
**** power output for high resolution**
Technical specifications subject to change without notice

Table 2.2. AVANCE Spectrometer Specifications 500-600 MHz

BRUKER

AVANCE SERIES

BRUKER BIOSPIN

Technical Data

Specifications for Avance Spectrometer 500MHz to 600MHz		Standard	Options	Solids option *
Frequency Channels (SGU/FCU)	two channels, 6-643MHz each	2	upgrade up to 8 *	
	frequency resolution	< 0.005Hz		
	phase resolution / min. event time	< 0.01° / 50 ns		
	amplitude resolution	< 0.1 dB		
	amplitude control, modulator / min. event time	96 dB / 50 ns		
	memory per channel e.g. for pulse shaping	1 MByte		
	phase accuracy over amplitude setting range	< 3°		
Timing Control Unit (TCU) with high-speed processor	memory	4 MByte		
	pulse sequence parameter calculation	in real time		
	timing resolution output bus for events and devices	12.5 ns 3 x 32-bit		
Receiver Control Unit (RCU)	digitizer / max. oversampling rate	16-bit / 2MHz		12-bit / 20MHz
	data compression / digital filtering	on the fly		
Communication Processor (CCU)	memory	16 MByte		
	communication, protocol	Fast Ethernet, TCP/IP™		
Host Computer	operating system	WINDOWS 2000™	UNIX™, LINUX™	
Quadrature Receiver	bandwidth (3dB)	1MHz		5MHz
	quadrature image peaks: - with phase cycle (1 transient / 8 transients) - with Digital Quadrature Detection (DQD) using 16bit / 2MHz digitizer (SW < 100kHz)	< 1% / < 0.2% 0%		< 1% / < 0.2%
			Options for CP/MAS	
Linear Amplifier #1 Selective output power at 1H / 19F frequency	max. output power (pulsed)	40W	100W / 300W	1kW / 150W **
	max. CW power	12,5W	25W / 30W	> 50W / 25W **
	max. duty cycle at full power	25%	25% / 10%	5%
	max. pulse length at full power	10 ms	500ms / 100ms	100 ms
	frequency range	1H, 19F	1H, 19F	1H, 19F
Linear Amplifier #2 Broadband output power at 13C frequency	max. output power (pulsed)	300W	500W / 300W	1kW / 300W **
	max. CW power	25W	30W	50W / 30W
	max. duty cycle at full power	8%	6% / 10%	5% / 10%
	max. pulse length at full power	3 ms	60 ms / 100 ms	100 ms
	frequency range	BB	BB	BB
Console	Dimensions and weights are approximate; voltage +10/-5% max. variation; 220V/50-60Hz; other line freq. and voltage upon request	**OneBay**	**OneBay / TwoBay**	**TwoBay Solids**
Dimensions Electronic Cabinet	basic system (**w x d x h**)	0,69 x 0,83 x 1,30m	0,69 x 0,83 x 1,30m / 1,31 x 0,83 x 1,30m	1,31 x 0,83 x 1,30m
Weight	ca. basic system, depending on options	> 260kg	> 300kg / 320kg	> 380kg
Power Dissipation	ca. basic system, depending on options	> 2,6kW	> 3,5kW	> 9,6kW

*** two-bay upgrade included**
**** power output for high resolution**
Technical specifications subject to change without notice

Table 2.3. AVANCE Spectrometer Specifications 700-800 MHz

BRUKER

AVANCE SERIES

BRUKER BIOSPIN

Technical Data

Specifications for Avance Spectrometers 700MHz to 800MHz		Standard	Options	Solids option *
Frequency Channels (SGU/FCU)	three channels, 6-1070MHz each	3	upgrade up to 8 *	
	frequency resolution	< 0.005Hz		
	phase resolution / min. event time amplitude resolution	< 0.01° / 50 ns < 0.1 dB		
	amplitude control modulator / min. event time	96 dB / 50 ns		
	memory per channel e.g. for pulse shaping	1 MByte		
	phase accuracy over amplitude setting range	< 3°		
Timing Control Unit (TCU) with high-speed processor	memory	4 MByte		
	pulse sequence parameter calculation	in real time		
	timing resolution	12.5 ns		
	output bus for events and devices	3 x 32-bit		
Receiver Control Unit (RCU)	digitizer / max. oversampling rate	16-bit / 2MHz		12-bit / 20MHz
	data compression / digital filtering	on the fly		
Communication Processor (CCU)	memory	16 MByte		
	communication, protocol	Fast Ethernet, TCP / IP™		
Host Computer	operating system	WINDOWS 2000™	UNIX™, LINUX™	
Quadrature Receiver	bandwidth (3dB)	1MHz		5MHz
	quadrature image peaks: - with phase cycle (1 transient / 8 transients) - with Digital Quadrature Detection (DQD) using 16bit / 2MHz digitizer (SW < 100kHz)	< 1% / < 0.2% 0%		< 1% / < 0.2%
			Options for CP/MAS	
Linear Amplifier #1 **Selective output power at 1H / 19F frequency**	max. output power (pulsed)	100W	300W / 50W	1kW / 150W
	max. CW power	25W	30W / 10W	100W / 30W
	max. duty cycle at full power	25%	10% / 20%	5% / 20%
	max. pulse length at full power	500ms	100ms	100ms
	frequency range	1H, 19F	1H, 19F	1H, 19F
Linear Amplifier #2 **Broadband output power at 13C frequency**	max. output power (pulsed)	500W		1kW / 300W**
	max. CW power	30W		50W / 30W
	max. duty cycle at full power	6%		5% / 10%
	max. pulse length at full power	60ms		100ms
	frequency range	BB		BB
Linear Amplifier #3 **Broadband output power at 13C frequency**	max. output power (pulsed)	300W		
	max. CW power	30W		
	max. duty cycle at full power	10%		
	max. pulse length at full power	100ms		
	frequency range	BB		
Console	Dimensions and weights are approximate; voltage +10/-5% max. variation; 220V/50-60Hz; other line freq. and voltage upon request	**TwoBay**		**TwoBay Solids**
Dimensions Electronic Cabinet	basic system (**w x d x h**)	1,30m 1,31 x 0,83 x 1,30m		1,31 x 0,83 x 1,30m
Weight	ca. basic system, depending on options	> 320kg		> 380kg
Power Dissipation	ca. basic system, depending on options	> 3,5kW		> 9,6kW

*** two-bay upgrade included**

**** power output for high resolution**

Technical specifications subject to change without notice

Table 2.4. AVANCE Spectrometer Specifications 900 MHz

BRUKER

AVANCE SERIES

BRUKER BIOSPIN

Technical Data

Specifications for Avance Spectrometers 900 MHz		Standard	Options	Solids option *
Frequency Channels (SGU/FCU)	three channels, 6 - 1070MHz each	3	upgrade up to 8 *	
	frequency resolution	< 0.005Hz		
	phase resolution / min. event time	< 0.01° / 50ns		
	amplitude resolution	< 0.1 dB		
	amplitude control, modulator / min. event time	96 dB / 50ns		
	memory per channel e.g. for pulse shaping	1 MByte		
	phase accuracy over amplitude setting range	< 3°		
Timing Control Unit (TCU) with high-speed processor	memory	4 MByte		
	pulse sequence parameter calculation	in real time		
	timing resolution output bus for events and devices	12.5 ns 3 x 32-bit		
Receiver Control Unit (RCU)	digitizer / max. oversampling rate	16-bit / 2MHz		12-bit / 20MHz
	data compression / digital filtering	on the fly		
Communication Processor (CCU)	memory	16 MByte		
	communication, protocol	Fast Ethernet, TCP / IP™		
Host Computer	operating system	WINDOWS 2000™	UNIX™, LINUX™	
Quadrature Receiver	bandwidth (3dB)	1MHz		5MHz
	quadrature image peaks: - with phase cycle (1 transient / 8 transients) - with Digital Quadrature Detection (DQD) using 16-bit/2MHz digitizer (SW<100kHz)	< 1% / < 0.2% 0%		< 1% / < 0.2%
			Options for CP/MAS	
Linear Amplifier #1 **Selective output power at 1H / 19F frequency**	max. output power (pulsed)	100W	300W / 50W	1kW / 150W
	max. CW power	25W	30W / 10W	100W / 30W
	max. duty cycle at full power	25%	10% / 20%	5% / 20%
	max. pulse length at full power	500ms	100ms	100ms
	frequency range	1H, 19F	1H, 19F	1H, 19F
Linear Amplifier #2 **Broadband output power at 13C frequency**	max. output power (pulsed)	1kW / 300W **	500W	
	max. CW power	50W / 30W	30W	
	max. duty cycle at full power	5% / 10%	6%	
	max. pulse length at full power	100ms	60ms	
	frequency range	BB	BB	
Linear Amplifier #3 **Broadband output power at 13C frequency**	max. output power (pulsed)	1kW / 300W **	300W	
	max. CW power	50W / 30W	30W	
	max. duty cycle at full power	5% / 10%	10%	
	max. pulse length at full power	100ms	100ms	
	frequency range	BB	BB	
Console	Dimensions and weights are approximate; voltage +10/-5% max. variation; 220V/50-60Hz; other line freq. and voltage upon request	**TwoBay**		
Dimensions Electronic Cabinet	basic system (**w x d x h**)	1,30m 1,31 x 0,83 x 1,30m		
Weight	ca. basic system, depending on options	> 380kg		
Power Dissipation	ca. basic system, depending on options	> 9,6kW		

*** two-bay upgrade included**
**** power output for high resolution**
Technical specifications subject to change without notice

Magnet Specifications 2.3.1

The following table lists the Bruker magnet specification sheets that were available at the time this guide was published. Check with your local Bruker representative for information on obtaining these files.

Table 2.5. UltraShield Magnet Specifications

UltraShield Magnets		
NMR Frequency	**Standard Bore**	**Wide Bore**
300 MHz (low loss)	30us232d.pdf	30ws205c.pdf
300 MHz 1 year (ultra low loss)	30us207d.pdf	n.a.
400 MHz (low loss)	40us207c.pdf	40ws245c.pdf
400 MHz 1 year (ultra low loss)	40us241c.pdf	n.a.
400 MHz OEM	ts1114a.pdf	ts1117a.pdf
500 MHz	50us221c.pdf	50ws360e.pdf
500 MHz OEM	ts1057c.pdf	ts1011c.pdf
600 MHz	60us262d.pdf	60ws372b.pdf
600 MHz OEM	ts1054a.pdf	n.a.
700 MHz	70us372b.pdf	n.a.

Table 2.6. UltraStabilized Magnet Specifications

UltraStabilized Magnets		
NMR Frequency	**Standard Bore**	**Wide Bore**
750 MHz	n.a.	75w2289b.pdf
800 MHz	80s2254e.pdf	n.a.
900 MHz	90s2254b.pdf	n.a.

For information on magnet accessories request the file “Overview of Bruker Accessories“ from your local Bruker Sales Representative.

Magnet Documentation 2.3.2

The latest version of the manuals listed in this section are always available at our Switzerland Website: ***http://www.bruker.ch/magnetics.html***.

The latest version of the general parts of the current magnet manual, which can also be valuable for customers who have older magnet systems, are available on the Bruker Switzerland Website:

Magnet System Manual - English (.pdf)

Cryogen Refill Manuals

Cryogen refill manuals are available in five languages at ***http://www.bruker.ch/magnetics.html***.

Product Development and Evaluation *2.4*

For Laboratory Managers it is essential to obtain evidence that any development, any production, any test and any installation step of the instrumentation they intend to acquire, is **retraceable** and internally supported with Standard Operating Procedures (SOP's).

Bruker software, spectrometers and magnets have been developed and evaluated in accordance with ISO 9001 certified practices and through Bruker's internal quality systems. Bruker has been ISO 9001 certified since 1994.

All source code and documentation for customer-released software and hardware are permanently archived with all necessary version control information at the Bruker Germany facility.

Documentation for error reports and error report management are retained at the Bruker Germany facility.

Magnet Development and Evaluation *2.4.1*

Generally speaking, each magnet system has its own individual technical documentation. However, certain documents apply to all systems of a specific type, or even to all magnet systems. The appropriate technical documentation for a magnet system are linked via a Production, Planning and Control System (PPCS) at Bruker.

Development documents, calculations, manuals and sales information are entered in a document parts list (similar to a material parts list). These documents are also entered and administered in the PPCS.

The document parts lists are created and maintained in our Cryo Construction Department. All documents dealing with the manufacturing and testing of a magnet system are mentioned in the Operations Plan (OP) along with the appropriate work procedures. The OP is created and maintained by our Magnet Construction Planning Office.

All inspection and manufacturing reports, along with any support documents are archived in paper form, or are summarized as a printout in the OP, which is located in the magnet system book. These documents are created by our Magnet Construction, Dewar Construction and Magnet Test departments. The documents are assembled, and archived by our Magnet Test Department.

Figure 2.1. ISO Certificate of Approval - Bruker BioSpin GmbH

Certificate of Approval

Awarded to

Bruker BioSpin GmbH
NMR Division
76287 Rheinstetten, Germany

Bureau Veritas Quality International certify that the Quality Management System of the above supplier has been assessed and found to be in accordance with the requirements of the quality standards detailed below

QUALITY STANDARDS

DIN EN ISO 9001:1994

SCOPE OF SUPPLY

Design, development, application, marketing and sales, production, delivery, installation and customer service of analytical instruments and process control systems.

Original approval date: **13 October 1994**

Subject to the continued satisfactory of the operator's Quality Management System, this Certificate is valid for a period of three years from:

07 December 2000 / Valid until: 07 December 2003

Date: **22 January 2002**

For Bureau Veritas Quality International (Germany) GmbH
Sachsenfeld 4, Haus 5
D – 20097 Hamburg

Certificate No: **73878**

Figure 2.2. ISO Certificate of Registration - Bruker BioSpin Corporation

CERTIFICATE OF REGISTRATION

MOODY INTERNATIONAL CERTIFICATION

This is to certify that the Quality Management Systems of:

Bruker BioSpin Corporation

19 Fortune, Manning Park
Billerica, MA 01821

has been assessed by AOQC Moody International, Inc. in respect of their Quality Management System and found to comply with ANSI/ISO/ASQC Q9001: 1994

ISO 9001

Approval is hereby granted for registration providing the rules and conditions relating to certification are observed at all times.

Certification Scope: **Design, manufacture, and distribution of life science systems, QA/QC systems and analytical instruments based on magnetic resonance core technology.**

Registration Number: **9806038**

Date of Issue: **7 August 2001** **Valid Until:** **15 December 2003**

Thomas W. Harris

Thomas W. Harris
Managing Director
signed for and on behalf of
AOQC Moody International

ANSI-RAB ACCREDITED QMS

AOQC ISO 9001

24900 Pitkin Road • Suite 200 • The Woodlands, Texas 77386

Figure 2.3. ISO Certificate of Approval - U.E.S. Bruker (France)

Certificate of Approval

Awarded to

U.E.S. BRUKER

34 Rue de l'Industrie, 67166 WISSEMBOURG Cedex
3 Avenue du Général de Gaulle, 91090 LISSES
FRANCE

Bureau Veritas Quality International certify that the Quality Management system of the above supplier has been assessed and found to be in accordance with the requirements of the quality standards detailed below :

NF EN ISO 9001 : 1994

SCOPE OF SUPPLY

DEVELOPMENT, MANUFACTURING, SALES, MAINTENANCE AND SERVICE OF SCIENTIFIC AND MEDICAL RESEARCH SYSTEMS.

Original approval date 31 October 1994

Subject to the continued satisfactory operation of the supplier's Quality Management System, this certificate is valid for a period of three years from :

13 March 2001

The present certificate is valid on behalf of COFRAC accreditation until the 15th December 2003

Issue date 11 April 2001

Philippe POULIN
BVQI FRANCE S.A. Managing Director

Bureau Veritas Quality International

Certificate N° 81095

BVQI France - Le Guillaumet 1133/2L - 685
92046 PARIS LA DEFENSE CEDEX (France)

Bruker ISO 9001 Certification - Magnet *2.4.3*

Every Bruker Magnet System is designed, produced and tested in accordance with established quality standards, verified by our ISO 9001 certification. A copy of the ISO certification covering magnet production is delivered in the Magnet System Manual (***Table 5.1.***) which accompanies delivery of the magnet system. The following figure is an example of the certificate issued by magnet manufacturing at Bruker BioSpin AG in Switzerland, one of the sites where Bruker magnets are manufactured.

Figure 2.4. ISO Certificate of Approval - Bruker BioSpin AG

BVQI

Certificate of Approval

BRUKER BIOSPIN AG
CH-8117 FÄLLANDEN / SWITZERLAND

Bureau Veritas Quality International (BVQI) certify that the Quality Management System of the above supplier has been assessed and found to be in accordance with the requirements of the quality standards detailed below:

SN EN ISO 9001 : 1994
SN EN 46001 : 1996
SN EN ISO 13485 : 1996

SCOPE OF SUPPLY

DESIGN, PRODUCTION AND SALES OF SCIENTIFIC AND ELECTRONIC MEDICAL EQUIPMENT FOR ANALYTICAL PURPOSES

Original approval date: **29TH SEPTEMBER 1994**

Subject to the continued satisfactory operation of the supplier's Quality Management System, this Certificate is valid for a period of three years from:

23RD NOVEMBER 2000

Zurich: **7TH DECEMBER 2001**

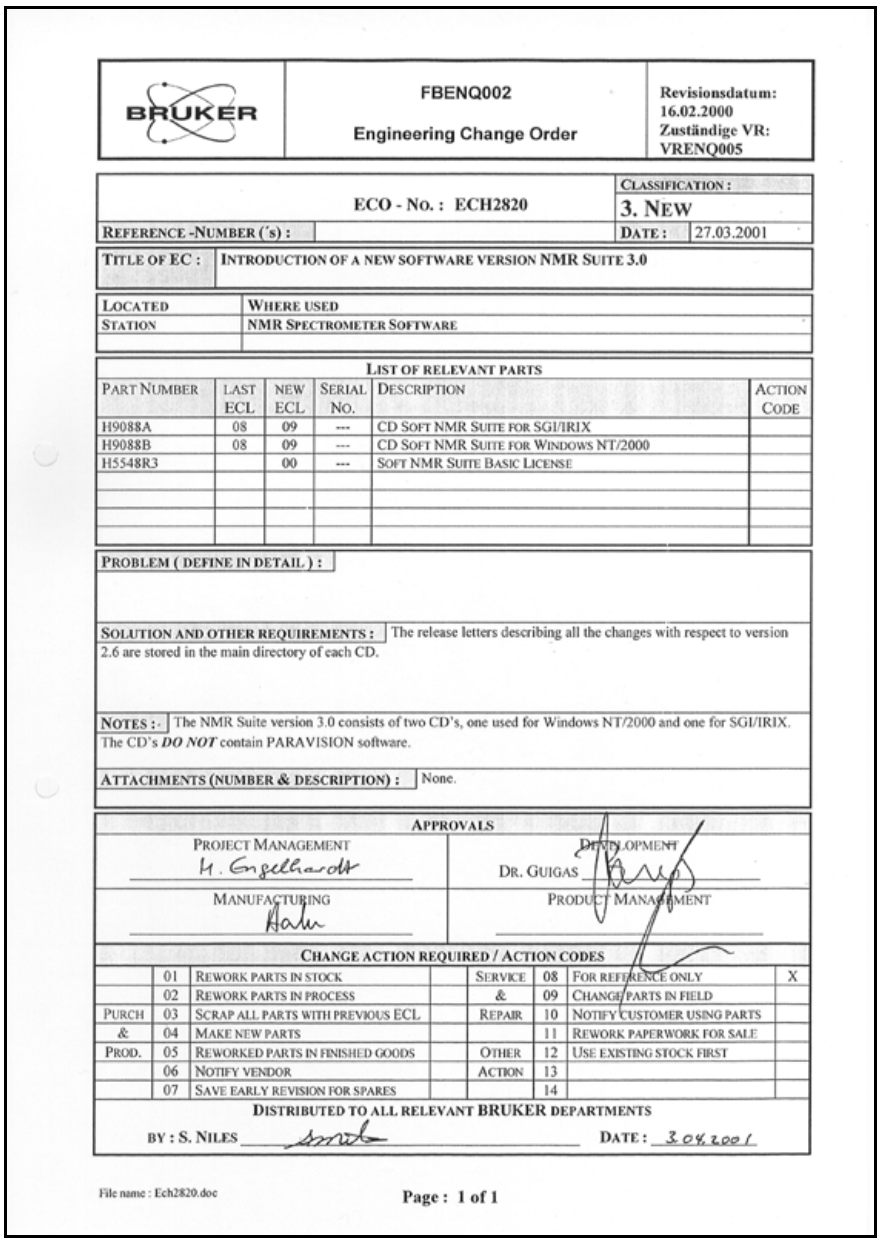
SWISS CERTIFICATION

For Bureau Veritas Quality International

Certificate No: **75961/A / 2ND EDITION** Swiss Certification Service 003

SF06/J3

Figure 2.5. Example: Official Release Documentation FBENQ002



BRUKER

FBENQ002

Engineering Change Order

Revisionsdatum: 16.02.2000
Zuständige VR: VRENQ005

ECO - No. : ECH2820

CLASSIFICATION : 3. NEW

REFERENCE -NUMBER (´s) :

DATE : 27.03.2001

TITLE OF EC : INTRODUCTION OF A NEW SOFTWARE VERSION NMR SUITE 3.0

LOCATED STATION	WHERE USED
	NMR SPECTROMETER SOFTWARE

LIST OF RELEVANT PARTS

PART NUMBER	LAST ECL	NEW ECL	SERIAL NO.	DESCRIPTION	ACTION CODE
H9088A	08	09	---	CD SOFT NMR SUITE FOR SGI/IRIX	
H9088B	08	09	---	CD SOFT NMR SUITE FOR WINDOWS NT/2000	
H5548R3		00	---	SOFT NMR SUITE BASIC LICENSE	

PROBLEM (DEFINE IN DETAIL) :

SOLUTION AND OTHER REQUIREMENTS : The release letters describing all the changes with respect to version 2.6 are stored in the main directory of each CD.

NOTES : The NMR Suite version 3.0 consists of two CD's, one used for Windows NT/2000 and one for SGI/IRIX. The CD's ***DO NOT*** contain PARAVISION software.

ATTACHMENTS (NUMBER & DESCRIPTION) : None.

APPROVALS

PROJECT MANAGEMENT M. Engelhardt

DEVELOPMENT DR. GUIGAS

MANUFACTURING

PRODUCT MANAGEMENT

CHANGE ACTION REQUIRED / ACTION CODES

	01	REWORK PARTS IN STOCK	SERVICE & REPAIR	08	FOR REFERENCE ONLY	X
	02	REWORK PARTS IN PROCESS		09	CHANGE PARTS IN FIELD	
PURCH & PROD.	03	SCRAP ALL PARTS WITH PREVIOUS ECL		10	NOTIFY CUSTOMER USING PARTS	
	04	MAKE NEW PARTS		11	REWORK PAPERWORK FOR SALE	
	05	REWORKED PARTS IN FINISHED GOODS	OTHER ACTION	12	USE EXISTING STOCK FIRST	
	06	NOTIFY VENDOR		13		
	07	SAVE EARLY REVISION FOR SPARES		14		

DISTRIBUTED TO ALL RELEVANT BRUKER DEPARTMENTS

BY : S. NILES DATE : 3.04.2001

File name : Ech2820.doc

Page : 1 of 1

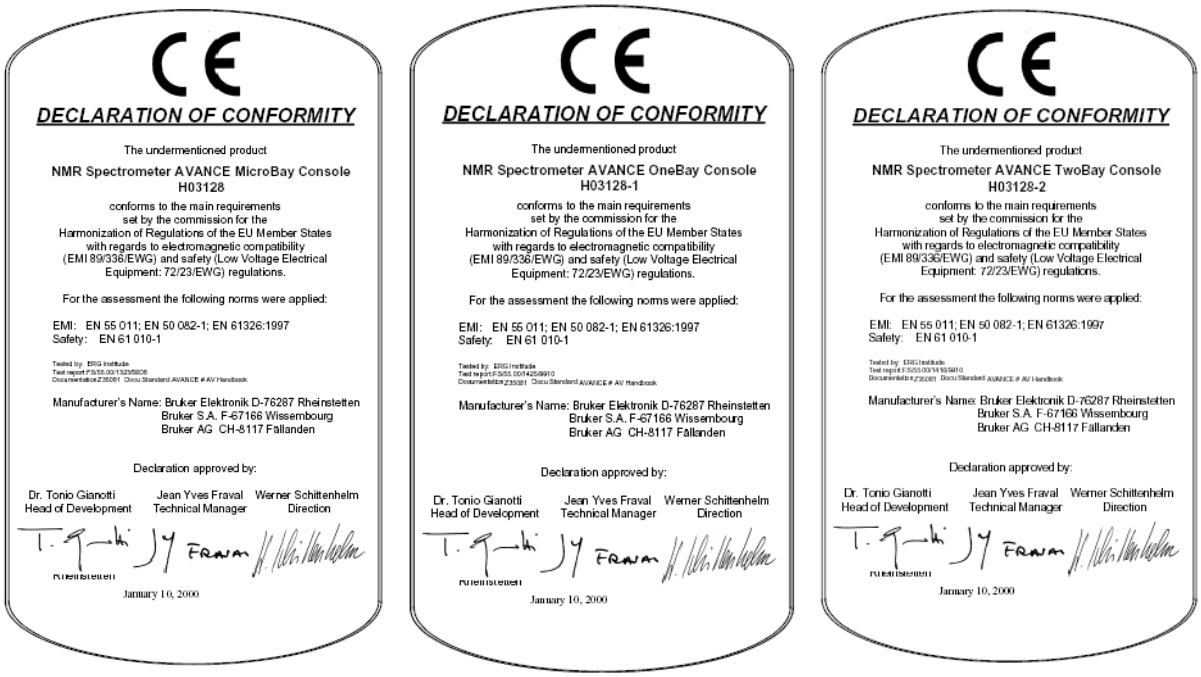
Bruker CE Certification - Spectrometer *2.4.4*

Instrumentation manufactured or imported into the European Union must satisfy a wide range of health and safety requirements. Instrumentation satisfying these requirements are certified Conform to the European Regulations. The Conformity to the European Regulations is stressed by a CE-MARKING on the instrumentation. The CE-marking also implies that compliance to the requirements has been documented.

All Bruker Magnets and Spectrometers are checked by external inspectors to satisfy the safety requirements of the European Union and therefore qualify for carrying the CE-marking.

Our AVANCE Console Wiring Manuals (P/N Z31226, Z31228, and Z31558) contain the individual Declaration of Conformity certificates (see the following figures) for each respective AVANCE spectrometer. These manuals may be found on the Bruker Automated Service Handbook (BASH) CD. The conformity test procedures and results are kept in Certification files which are kept at our manufacturing site. **The CE files can be checked by Inspecting Authorities for GLP certification.**

Figure 2.6. AVANCE Consoles Declaration of Conformity



CE

DECLARATION OF CONFORMITY

The undermentioned product

NMR Spectrometer AVANCE MicroBay Console
H03128

conforms to the main requirements set by the commission for the Harmonization of Regulations of the EU Member States with regards to electromagnetic compatibility (EMI 89/336/EWG) and safety (Low Voltage Electrical Equipment: 72/23/EWG) regulations.

For the assessment the following norms were applied:

EMI: EN 55 011; EN 50 082-1; EN 61326:1997
Safety: EN 61 010-1

Manufacturer's Name: Bruker Elektronik D-76287 Rheinstetten
Bruker S.A. F-67166 Wissembourg
Bruker AG CH-8117 Fällanden

Declaration approved by:

Dr. Tonio Gianotti, Head of Development
Jean Yves Fraval, Technical Manager
Werner Schittenhelm, Direction

January 10, 2000

CE

DECLARATION OF CONFORMITY

The undermentioned product

NMR Spectrometer AVANCE OneBay Console
H03128-1

conforms to the main requirements set by the commission for the Harmonization of Regulations of the EU Member States with regards to electromagnetic compatibility (EMI 89/336/EWG) and safety (Low Voltage Electrical Equipment: 72/23/EWG) regulations.

For the assessment the following norms were applied:

EMI: EN 55 011; EN 50 082-1; EN 61326:1997
Safety: EN 61 010-1

Manufacturer's Name: Bruker Elektronik D-76287 Rheinstetten
Bruker S.A. F-67166 Wissembourg
Bruker AG CH-8117 Fällanden

Declaration approved by:

Dr. Tonio Gianotti, Head of Development
Jean Yves Fraval, Technical Manager
Werner Schittenhelm, Direction

January 10, 2000

CE

DECLARATION OF CONFORMITY

The undermentioned product

NMR Spectrometer AVANCE TwoBay Console
H03128-2

conforms to the main requirements set by the commission for the Harmonization of Regulations of the EU Member States with regards to electromagnetic compatibility (EMI 89/336/EWG) and safety (Low Voltage Electrical Equipment: 72/23/EWG) regulations.

For the assessment the following norms were applied:

EMI: EN 55 011; EN 50 082-1; EN 61326:1997
Safety: EN 61 010-1

Manufacturer's Name: Bruker Elektronik D-76287 Rheinstetten
Bruker S.A. F-67166 Wissembourg
Bruker AG CH-8117 Fällanden

Declaration approved by:

Dr. Tonio Gianotti, Head of Development
Jean Yves Fraval, Technical Manager
Werner Schittenhelm, Direction

January 10, 2000

AVANCE MicroBay ***AVANCE OneBay*** ***AVANCE TwoBay***

Each instrument or complete system (e.g. spectrometer) carries one CE-marking only. Subunits of a CE-certified system (e.g. BSMS, BLA, etc.) do not need CE-Markings. Standalone units like the Sample Changer have separate CE-markings, Certificates of Conformity and Certification files.

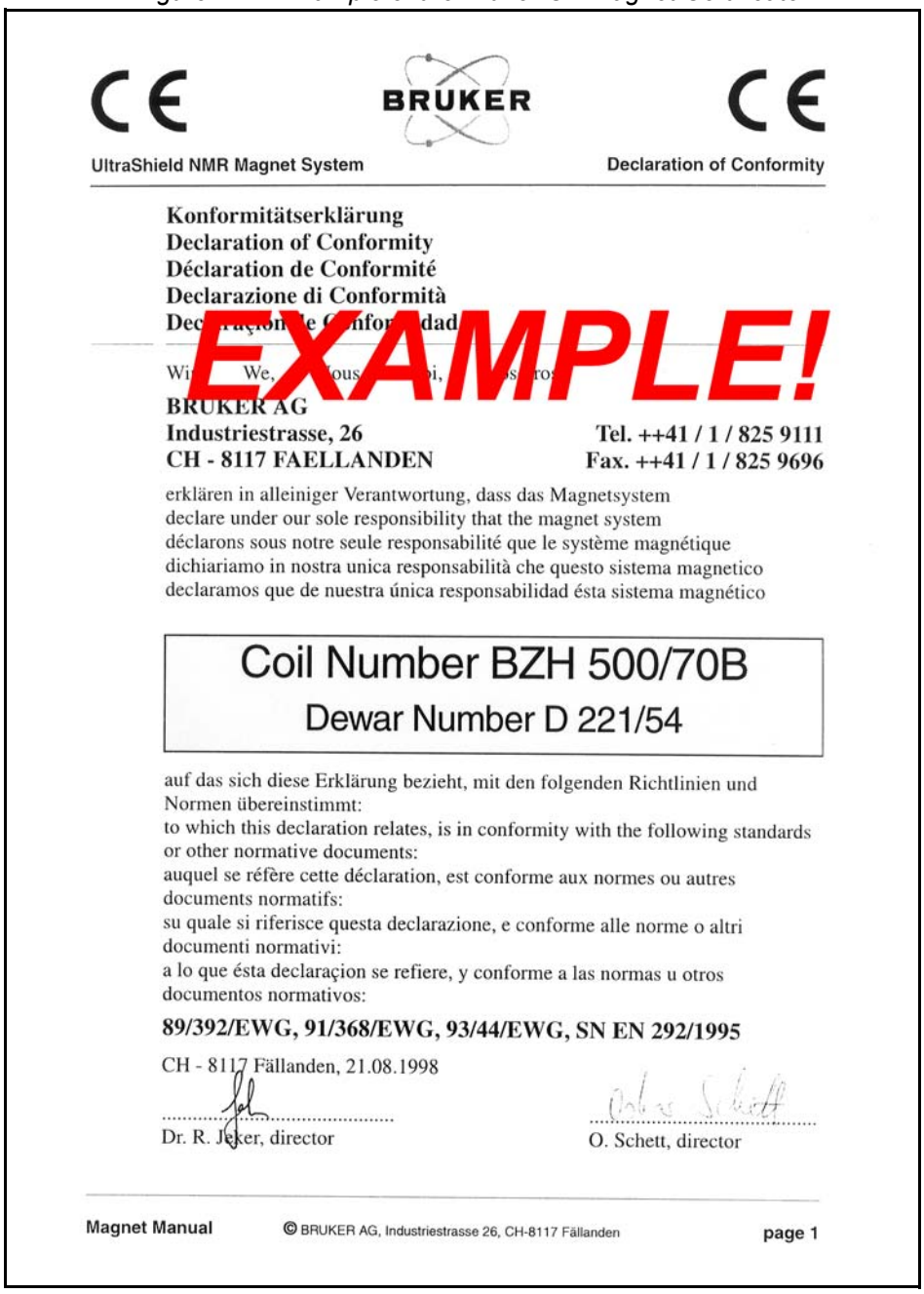
Bruker CE Certification - Magnet *2.4.5*

Every Bruker magnet system conforms to the following standards or other normative documents:

89/392/EWG, 91/368 EWG, 93/44/EWG, SN EN 292/1955

The Declaration of Conformity for the each individual Bruker Magnet System can be found in the NMR Magnet System manual (***Table 5.1.***) that is delivered with the magnet. An example of this Declaration of Conformity certificate is shown below:

Figure 2.7. Example of the Bruker CE Magnet Certificate



CE BRUKER CE

UltraShield NMR Magnet System — Declaration of Conformity

Konformitätserklärung
Declaration of Conformity
Déclaration de Conformité
Declarazione di Conformità
Dec[illegible]dad

EXAMPLE!

Wi[illegible] We, [illegible]ous [illegible]i, [illegible]ros

BRUKER AG
Industriestrasse, 26 **Tel. ++41 / 1 / 825 9111**
CH - 8117 FAELLANDEN **Fax. ++41 / 1 / 825 9696**

erklären in alleiniger Verantwortung, dass das Magnetsystem
declare under our sole responsibility that the magnet system
déclarons sous notre seule responsabilité que le système magnétique
dichiariamo in nostra unica responsabilità che questo sistema magnetico
declaramos que de nuestra única responsabilidad ésta sistema magnético

Coil Number BZH 500/70B
Dewar Number D 221/54

auf das sich diese Erklärung bezieht, mit den folgenden Richtlinien und Normen übereinstimmt:
to which this declaration relates, is in conformity with the following standards or other normative documents:
auquel se réfère cette déclaration, est conforme aux normes ou autres documents normatifs:
su quale si riferisce questa declarazione, e conforme alle norme o altri documenti normativi:
a lo que ésta declaraçion se refiere, y conforme a las normas u otros documentos normativos:

89/392/EWG, 91/368/EWG, 93/44/EWG, SN EN 292/1995

CH - 8117 Fällanden, 21.08.1998

Dr. R. Jeker, director — O. Schett, director

Magnet Manual © BRUKER AG, Industriestrasse 26, CH-8117 Fällanden page 1

Installation Qualification

3

Introduction 3.1

The Installation Qualification (IQ) is concerned with all procedures necessary to prepare the site and check the system for installation.

IQ covers the installation of the instrument at the users site up to and including its response to the initial application of electrical power.

It is the responsibility of the Laboratory Manager to take care of the IQ. Bruker may assist, if requested, by providing professional site assessment and layout suggestions, as well as certifying that the instrument is properly connected and placed (site planning, vibrations, external magnetic influences, air conditioning, electrical and gas supply, etc.). It should be notes however, that our site analysis is **not a guarantee that the system will meet specifications** and perform without a problem at all times. Sites are subject to continual changes in factors that effect performance, thus a the site environment can change rapidly. Laboratory conditions should be routinely monitored to ensure optimal perforance.

IQ also involves formal checks to confirm that the instrument and its components have been supplied as ordered and that the instrument is properly installed in the selected environment.

Bruker can also provide Safety information relating to the operation of the instrument (ambient conditions, handling of cryogenic equipment).

Site Planning and Preparation 3.2

In order to determine whether a site is suitable for locating a Bruker spectrometer, **Bruker provides several Site Planning guides** which will lead you through this determination. In these guides, which are available from Bruker upon request, a variety of aspects are covered including: **safety, cabinet and magnet position, ceiling height, electromagnetic interference, service access and vibrations**, to name a few. Aspects regarding the actual installation are also dealt with briefly.

The latest version of the Site Planning guides are always available on the Bruker Automated Service Handbook (BASH) CD-ROM, or through your nearest Bruker representative.

The recommendations regarding site planning that are found in these guides are based on the experience of Bruker engineers accumulated through the years. Every effort has been made to make the site requirements realistic and readily achievable. Although the guides have been written to help you plan the site, predicting NMR performance is complicated by the fact that every site is unique, thus

Bruker also will work with you individually on answering any unique questions that may arise during the site planning and preparation process.

For fulfilling requirements for GLP certification it is important to document that the site does indeed fulfill our recommendations, particularly regarding utilities such as electricity, air conditioning, water and gases, as well as safety issues such as the hazards of superconducting magnets, emergency exhaust systems for the event of a magnet quench etc.

A Special Note about Safety *3.2.1*

Safety is at the heart of GLP and safe working procedures should always be addressed in site planning, as well as in formulating documentation, SOP's etc. Some of the key safety considerations with spectrometers and magnets include:

- **Superconducting NMR magnet systems** cause potential **safety hazards** due to their extended magnetic stray field, their **large attractive forces** on ferromagnetic objects and their **large content of cryogenic liquids**. It is the sole responsibility of our customers to ensure safety in their NMR laboratories and to comply with local safety regulations.
- It is generally accepted that stray fields are **harmless below 5 Gauss** (ten times the earth magnetic field). Stronger stray fields closer to the NMR magnet system may disturb heart pacemakers, erase magnetic cards and storage devices, and adversely affect watches and micro mechanical devices.
- It is recommended that you **mark the 5 Gauss line with warning signs** and to limit access to areas with more than 5 Gauss field to NMR staff only. Be aware that a magnetic stray field extends in all three dimensions and is not blocked by the walls, floor or ceiling. For vertical NMR magnet systems **the vertical extension is even larger than the horizontal one**. High fields will also affect the rooms above and below the magnet.
- Strong attraction of ferromagnetic objects may occur at close distances to the magnet, where the magnetic field is above 50 to 100 Gauss. Massive iron objects such as **pressurized gas cylinders**, are extremely dangerous in the vicinity of a superconducting NMR magnet system. They should be mounted very close to the door and away from the NMR magnet system, or preferably outside the magnet room. Inside the magnet room a wall mounted gas distribution system is recommended.
- The laboratory room must be technically equipped, so that even with a **magnet quench** no excess pressure in the room occurs, whereas the windows and doors may burst.
- Personnel should always be protected from any danger resulting from any escaping helium gas during refill (refer to the respective magnet manual or the Avance Beginners Guide for details).

- **When magnet systems are placed in a pit**, the danger of suffocation must be particularly taken into account. An **oxygen warning device** and adequate ventilation must be provided.

Always read the Safety notes found in the Magnet System Manual, which is delivered with each Magnet, before operating the system. Also be sure to review the Site Planning and Spectrometer User Manuals for all safety aspects of Bruker instrumentation.

Magnet Site Planning & Cryogenic Liquids Safety *3.2.2*

Superconducting magnets use liquid nitrogen and liquid helium as cooling agents. These liquids expand their volume by a factor of 700 when they are evaporated and then allowed to warm up to room temperature.

The gases are nontoxic and completely harmless as long as an adequate ventilation is provided to prevent suffocation. During normal operation only 3-5m^3/day (100-180 cubic feet/day) of nitrogen are evaporated, but during a quench 50-100m^3 (1800-3600 cubic feet) of helium are produced within a short time. Windows and doors are normally sufficient for ventilation even after a quench. Always make sure that the **NMR magnet systems are never located in an airtight room**.

The magnet location should be selected such that the door and the ventilation can be easily reached from all places in the room. The doors should always open to the outside. The air conditioning system should draw the air out of the room, not just recirculate the air within the room. The room layout, ceiling clearance and magnet height should provide for the easy transfer of liquid nitrogen and helium. This will considerably reduce the risk of accidents.

The following ***Table 3.1.*** provides some of the key properties of cryogenic substances:

Table 3.1. Table of Properties of Cryogenic Substances

Properties	Nitrogen	Helium
Molecular Weight	28	4
Normal boiling point	-196°C / 77°K	-269°C / 4.2°K
Approximate expansion rate (volume of gas at 15°C and atmospheric pressure produced by unit volume of liquid at normal boiling point)	680	740
Density of liquid at normal boiling point [kg m^{-3}]	810	125
Color (liquid)	none	none
Color (gas)	none	none
Odor (gas)	none	none
Toxicity	very low	very low
Explosion hazard with combustible material	no	no
Pressure rupture if liquid or cold gas is trapped	yes	yes
Fire hazard: combustible	no	no
Fire hazard: promotes ignition directly	no	no
Fire hazard: liquefies oxygen and promotes ignition	yes	yes

Refer to the section ***"Emergency Plan for NMR Systems"*** for more information about magnet system safety and information that should be included in organization Standard Operating Procedures (SOP'S).

Factory Final Test *3.3*

All Bruker instruments undergo a Final Test at the factory before being shipped to the final destination. A copy of the **Final Test Report** is kept on file by Bruker, and is available to GLP inspectors upon request.

Software Installation *3.3.1*

Prior to the factory final test, the computer software is installed by Bruker service engineers **according to Bruker recommendations** and the system configuration requirements.

Spectrometer Factory Final Test *3.3.2*

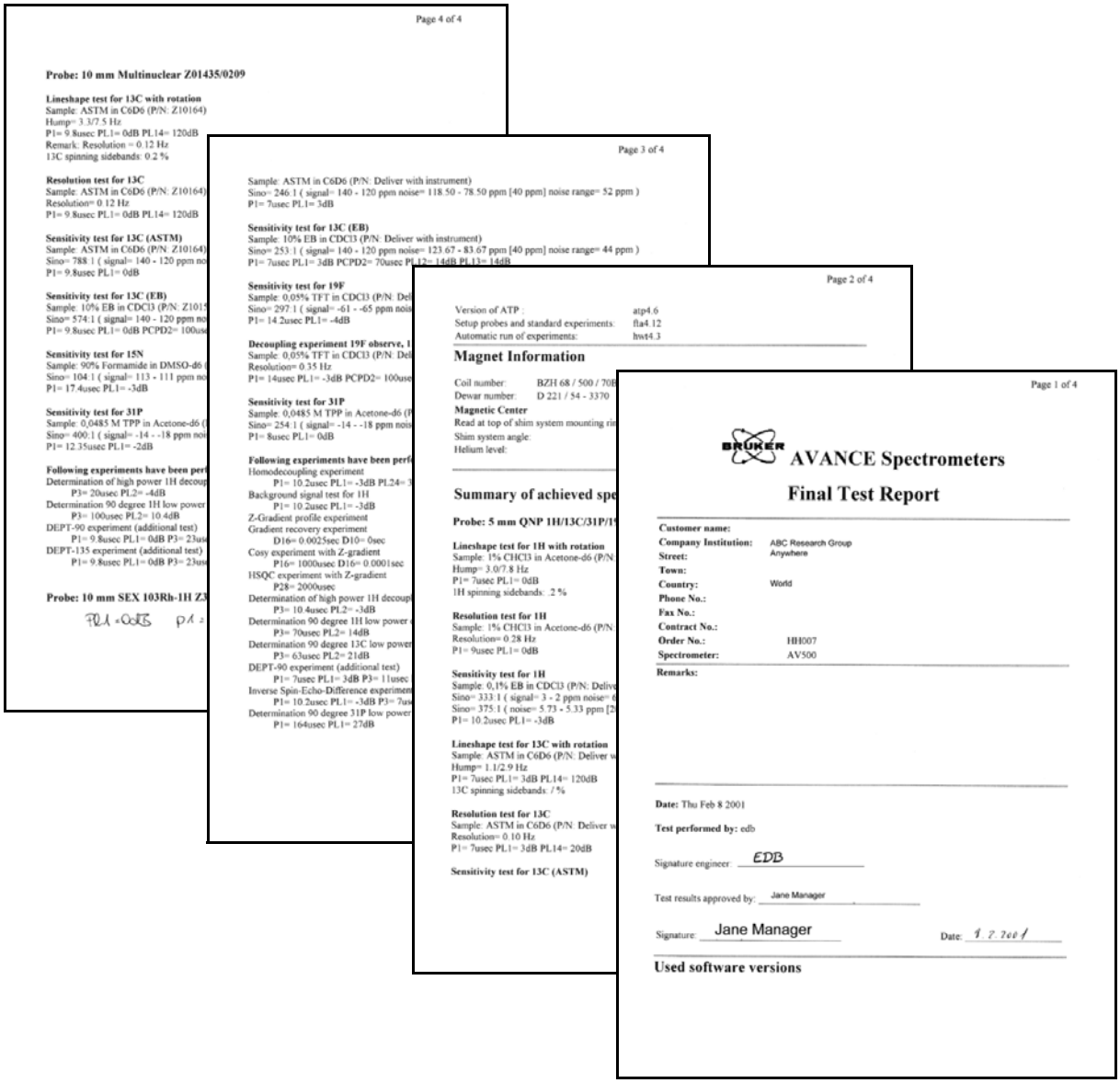
Before the instrumentation is shipped from the factory, Bruker spectrometers undergo thorough final testing using the **Acceptance Test Protocol** (ATP) software suite, the results of which are recorded in the **Final Test Report**. Some of the tests that are completed during the Final Test procedure include:

- Lineshape Test,
- Resolution Test,
- Sensitivity Test,
- Water Suppression Test,
- A variety of other experiments that establish the validity of the instrument

In addition, the Final Test Report also records key information concerning the instruments, such as:

- System Information,
- Customer Information,
- Software and Service Tools Installed,
- Workstation Information,
- Disk Partition Information if applicable,
- Hardware Inventory,
- Network Information,
- Printer/Plotter Information if applicable,
- Software License Information,
- Spectrometer Configuration,
- Hardware Configuration,
- Probes Test Results.

Figure 3.1. Sample pages from a Spectrometer Final Test Report File



Page 4 of 4

Probe: 10 mm Multinuclear Z01435/0209

Lineshape test for 13C with rotation
Sample: ASTM in C6D6 (P/N: Z10164)
Hump= 3.3/7.5 Hz
P1= 9.8usec PL1= 0dB PL14= 120dB
Remark: Resolution = 0.12 Hz
13C spinning sidebands: 0.2 %

Resolution test for 13C
Sample: ASTM in C6D6 (P/N: Z10164)
Resolution= 0.12 Hz
P1= 9.8usec PL1= 0dB PL14= 120dB

Sensitivity test for 13C (ASTM)
Sample: ASTM in C6D6 (P/N: Z10164)
Sino= 788:1 (signal= 140 - 120 ppm no
P1= 9.8usec PL1= 0dB

Sensitivity test for 13C (EB)
Sample: 10% EB in CDCl3 (P/N: Z1015
Sino= 574:1 (signal= 140 - 120 ppm no
P1= 9.8usec PL1= 0dB PCPD2= 100us

Sensitivity test for 15N
Sample: 90% Formamide in DMSO-d6
Sino= 104:1 (signal= 113 - 111 ppm no
P1= 17.4usec PL1= -3dB

Sensitivity test for 31P
Sample: 0,0485 M TPP in Acetone-d6
Sino= 400:1 (signal= -14 - -18 ppm noi
P1= 12.35usec PL1= -2dB

Following experiments have been per
Determination of high power 1H decoup
P3= 20usec PL2= -4dB
Determination 90 degree 1H low power
P3= 100usec PL2= 10.4dB
DEPT-90 experiment (additional test)
P1= 9.8usec PL1= 0dB P3= 23us
DEPT-135 experiment (additional test)
P1= 9.8usec PL1= 0dB P3= 23us

Probe: 10 mm SEX 103Rb-1H Z3

Page 3 of 4

Sample: ASTM in C6D6 (P/N: Deliver with instrument)
Sino= 246:1 (signal= 140 - 120 ppm noise= 118.50 - 78.50 ppm [40 ppm] noise range= 52 ppm)
P1= 7usec PL1= 3dB

Sensitivity test for 13C (EB)
Sample: 10% EB in CDCl3 (P/N: Deliver with instrument)
Sino= 253:1 (signal= 140 - 120 ppm noise= 123.67 - 83.67 ppm [40 ppm] noise range= 44 ppm)
P1= 7usec PL1= 3dB PCPD2= 70usec PL12= 14dB PL13= 14dB

Sensitivity test for 19F
Sample: 0,05% TFT in CDCl3 (P/N: Del
Sino= 297:1 (signal= -61 - -65 ppm nois
P1= 14.2usec PL1= -4dB

Decoupling experiment 19F observe, 1
Sample: 0,05% TFT in CDCl3 (P/N: Del
Resolution= 0.35 Hz
P1= 14usec PL1= -3dB PCPD2= 100use

Sensitivity test for 31P
Sample: 0,0485 M TPP in Acetone-d6 (P
Sino= 254:1 (signal= -14 - -18 ppm nois
P1= 8usec PL1= 0dB

Following experiments have been perf
Homodecoupling experiment
P1= 10.2usec PL1= -3dB PL24=
Background signal test for 1H
P1= 10.2usec PL1= -3dB
Z-Gradient profile experiment
Gradient recovery experiment
D16= 0.0025sec D10= 0sec
Cosy experiment with Z-gradient
P16= 1000usec D16= 0.0001sec
HSQC experiment with Z-gradient
P28= 2000usec
Determination of high power 1H decoup
P3= 10.4usec PL2= -3dB
Determination 90 degree 1H low power
P3= 70usec PL2= 14dB
Determination 90 degree 13C low power
P3= 63usec PL2= 21dB
DEPT-90 experiment (additional test)
P1= 7usec PL1= 3dB P3= 11usec
Inverse Spin-Echo-Difference experiment
P1= 10.2usec PL1= -3dB P3= 7us
Determination 90 degree 31P low power
P1= 164usec PL1= 27dB

Page 2 of 4

Version of ATP: atp4.6
Setup probes and standard experiments: fla4.12
Automatic run of experiments: hwt4.3

Magnet Information

Coil number: BZH 68 / 500 / 70
Dewar number: D 221 / 54 - 3370
Magnetic Center
Read at top of shim system mounting ri
Shim system angle:
Helium level:

Summary of achieved spe

Probe: 5 mm QNP 1H/13C/31P/1

Lineshape test for 1H with rotation
Sample: 1% CHCl3 in Acetone-d6 (P/N
Hump= 3.0/7.8 Hz
P1= 7usec PL1= 0dB
1H spinning sidebands: .2 %

Resolution test for 1H
Sample: 1% CHCl3 in Acetone-d6 (P/N
Resolution= 0.28 Hz
P1= 9usec PL1= 0dB

Sensitivity test for 1H
Sample: 0,1% EB in CDCl3 (P/N: Deliv
Sino= 333:1 (signal= 3 - 2 ppm noise=
Sino= 375:1 (noise= 5.73 - 5.33 ppm [2
P1= 10.2usec PL1= -3dB

Lineshape test for 13C with rotation
Sample: ASTM in C6D6 (P/N: Deliver w
Hump= 1.1/2.9 Hz
P1= 7usec PL1= 3dB PL14= 120dB
13C spinning sidebands: / %

Resolution test for 13C
Sample: ASTM in C6D6 (P/N: Deliver w
Resolution= 0.10 Hz
P1= 7usec PL1= 3dB PL14= 20dB

Sensitivity test for 13C (ASTM)

Page 1 of 4

AVANCE Spectrometers

Final Test Report

Customer name:
Company Institution: ABC Research Group
Street: Anywhere
Town:
Country: World
Phone No.:
Fax No.:
Contract No.:
Order No.: HH007
Spectrometer: AV500
Remarks:

Date: Thu Feb 8 2001

Test performed by: edb

Signature engineer: EDB

Test results approved by: Jane Manager

Signature: Jane Manager Date: 9.7.2001

Used software versions

This preliminary factory Final Test is very thorough. Parts of these tests are repeated and documented under the ATP during the **Operational Qualification**. Refer to the section ***"The Acceptance Test Protocol" on page 42*** for more information.

Hardware Tests *3.3.3*

Stringent tests to prove the NMR performance of all hardware components are accomplished through the HWT tests. These tests are described in ***"Requirements for Running HWT Tests" on page 41***,

These tests are initially executed during the Final Test and the Acceptance Test, but many of the tests can be performed at any time, e.g., as part of Performance Qualification.

Magnet Factory Final Test *3.3.4*

Before magnet systems are delivered to customers, they undergo a complete system test. All the tests are carried out based on Quality Management Procedures (ISO 9001) and our internal test regulations.

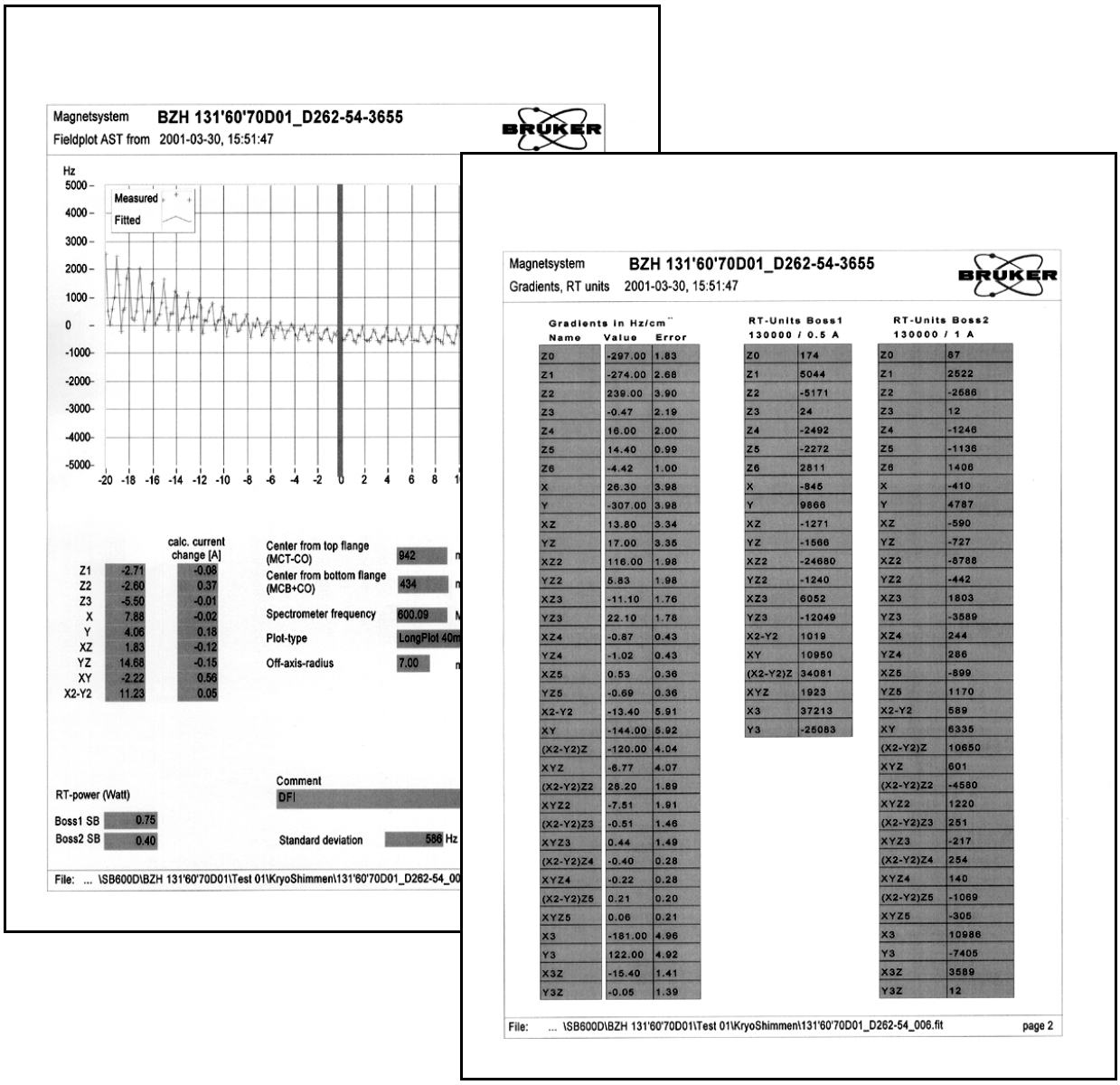
All customer relevant specifications are verified and appropriately archived, including:.

- Helium and Nitrogen boil off rate
- Homogeneity of the magnet field
- Drift rate

A complete **Final Test Report**, including a summary of achieved specifications and other documentation recording the magnet Final Test results are maintained at the Bruker manufacturing site.

An example of one of the documents archived during this test phase is the **field plot**, an example of which is shown in ***Figure 3.2.***.

Figure 3.2. Example of a Magnet Field Plot



Factory Software Backup *3.3.5*

After the installation of the PC, Linux or UNIX-based systems and the factory Final Test, Bruker makes a **complete backup** of the **entire installation** using Disk Imaging software (PC) or respective backup software (Linux, UNIX).

A list with a description of all hardware, operating system software, and application software, including drawings when appropriate, is prepared at the factory before the instrument is shipped. If any **additional software** is installed on the system, for example in **other phases of GLP**, this should also be **added to the list**. This will aid in verifying GLP requirements, as well as in handling any subsequent computer problems.

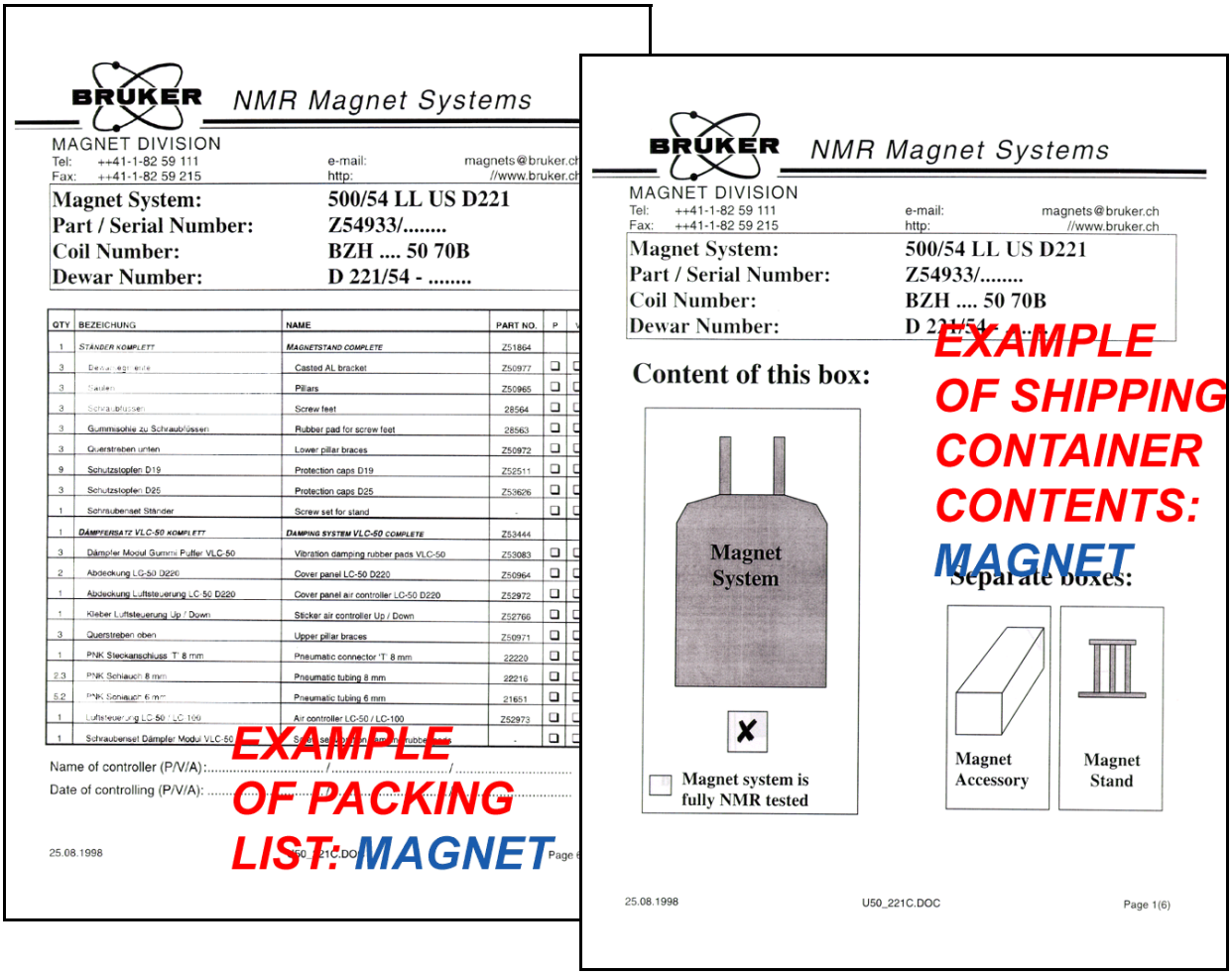
Instrument Delivery and Installation *3.4*

Steps for IQ include activities during and following the delivery of the instrument. When the instruments arrive at the customer site it is **recommended that the following steps be carried out**:

- **Compare equipment, as received, with purchase order** (including software, hardware, and accessories). For magnets, the contents of the shipping containers, as well as a detailed packing list are included in the Appendix section of the Magnet System Manual. A sample of these documents can be found in ***"Sample Magnet Packing & Shipping Container Contents Lists" on page 36***.
- **Check documentation for completeness** (operating manuals, maintenance instructions, test protocols, safety, and validation certificates). As Bruker service personnel install the instruments, some of these documents will be filled out with the service representative.
- Prepare a list of **equipment manuals** and **documentation** (including any CD-ROM's).
- Prepare any required **installation reports**.

Check equipment and packaging for any damage. Any indication of transportation damages must be reported immediately to the transport company and to Bruker.

Figure 3.3. Sample Magnet Packing & Shipping Container Contents Lists



Instrument/Hardware Setup 3.5

Bruker spectrometers and magnets are installed by qualified Bruker service representatives, according to documented guidelines and procedures.

The NMR console is assembled by a Bruker Engineer according to documented guidelines and procedures. During the assembly phase all components are carefully checked for their electric and electronic functionality.

The result of the instrument setup is a fully functional spectrometer.

Where does IQ end, and OQ begin? 3.6

Although it may seem illogical to stop IQ at this point, in the middle of the customer installation, it is nevertheless the right point with respect to GLP conventions.

The second part of the customer installation deals with acceptance testing of the system, which has solely to do with the operational performance of the instrumentation. By definition this is grouped under Operational Qualification (OQ).

Operational Qualification

4

Introduction 4.1

The purpose of the Operational Qualification (OQ) is to demonstrate and provide documented evidence that, after installation, the instrument performs and will continue to perform according to its intended use.

For NMR-spectrometers and magnets **this step falls under the complete responsibility of Bruker personnel**.

The final document of the OQ is the **A**cceptance **T**est **P**rotocol (**ATP**).

Before the Operational Qualification can be performed, the spectrometer, magnet, and any required software packages must be properly installed (refer to ***"Installation Qualification" on page 27***.

The ATP Acceptance Test 4.2

The tests that are carried out, to demonstrate and document that the spectrometer and magnet are performing according to their intended use, vary according to the hardware configuration and probes that are used.

In order to standardize the acceptance procedures and documentation, the software suite ATP has been designed by Bruker for Test and Service Engineers.

In principle, the ATP software follows the same pathway during the Final Test (IQ) and the Acceptance Test (OQ) procedures. Nevertheless, a focus is made on demonstrating that the **Operational Qualification (OP)** of the instrument is met. In particular, additional NMR device experiments ('HWT' tests) are also performed during this test. At the end of the ATP, the customer verifies that the instrument meets the standards that they have established by signing the Acceptance Test Protocol, together with the Bruker Service Engineer (refer to ***"The Acceptance Test Protocol" on page 42***).

Typical acceptance tests that are performed during the Operational Qualification, using the ATP software suite include:

- The Lineshape Test
- The Resolution Test
- The Sensitivity Test
- The Water Suppression Test
- Application Specific Experiments

The Lineshape Test *4.2.1*

This test is also commonly known as the **Hump test**. A 1H or 13C spectrum is acquired with one scan, typically on the CDCl3 sample for 1H and on the ASTM sample for 13C. The **width of the reference signal at 0.55% height and 0.11% height** is calculated with a double exponential fit along the left and right side of the signal. These values are compared with the listed specifications and marked accordingly.

The Resolution Test *4.2.2*

The Resolution Test checks the **width of the referred signal at half height**. The test is passed if the width is equal or better than the specified value.

The Sensitivity Test *4.2.3*

The Sensitivity Test can be performed for all standard nuclei. The **height of the largest signal** between the signal limits is calculated. A predefined noise window is shifted in 25 steps along the spectrum between the noise limits. Each time, the noise value is determined and the signal-to-noise ratio is calculated with respect to the height of the largest signal. The best value must meet or exceed the specification.

The Water Suppression Test *4.2.4*

The Water Suppression Test is performed on the sucrose sample. The **width of the water signal at 50% and 10% of the height** of the DDS signal is determined. In addition, the **line splitting of the anomeric proton** at ca. 5.25 ppm is evaluated and a sensitivity calculation is done for this signal, similar to the one described in the sensitivity test.

Application Specific Experiments *4.2.5*

Typical experiments that might be performed, **depending on the configuration** and intended use, include:

- 2D-NOESY
- COSY with Z-gradient
- HSQC with Z-gradient
- Determination of 90 degree 13C high power decoupling pulse
- Determination of 90 degree 13C low power decoupling pulse
- DEPT-90
- DEPT-135
- Inverse Spin-Echo Difference
- Determination 90 degree 15N high power decoupling pulse

- Determination 90 degree 15N low power decoupling pulse.

Probe Specifications *4.2.6*

The probes that are used have a huge impact on the results achieved from an instrument. In the following tables are examples of specifications for some of the most popular Bruker BioSpin 5 mm probes. As the range of probes that are available is quite large and new probes are constantly being introduced, please check with Bruker BioSpin for current specifications on the probes that apply to your specific applications.

Table 4.1. Sensitivity and Pulse Width without Gradient / with Z-gradient Selected 5 mm Probes

Probe	Type	Nucleus	Sample	300	400	500	600 +	90º PW
Selective	SEL	^{1}H	0.1% EB	240:1	630:1*	900:1*	1150:1*	≤ 8 μs
Broadband Inverse	BBI	^{1}H ^{31}P ^{13}C ^{15}N	0.1% EB TPP ASTM Urea	220:1	600:1*	900:1*	1000:1*	≤ 8 μs ≤ 25 μs ≤ 15 μs ≤ 30 μs
Triple Res. Inverse	TXI	^{1}H ^{13}C ^{15}N	0.1% EB ASTM Urea	220:1 ≤ 15 μs ≤ 40 μs	600:1* ≤ 15 μs ≤ 40 μs	900:1* ≤ 12 μs ≤ 33 μs	1100:1* ≤ 12 μs ≤ 37 μs	≤ 8 μs
Dual ^{13}C / ^{1}H	DUL	^{13}C ^{13}C ^{1}H	ASTM 10% EB 0.1% EB	100:1 80:1 135:1	160:1 120:1 220:1	220:1 180:1 330:1	290:1 240:1 370:1	≤ 10 μs ≤ 10 μs ≤ 15 μs
Broadband Observe	BBO	^{31}P ^{13}C ^{13}C ^{15}N ^{1}H	TPP ASTM 10% EB 90% Form. 0.1% EB	90:1 100:1 80:1 15:1 135:1	135:1 160:1 120:1 20:1 220:1	120:1 220:1 160:1 32:1 330:1	160:1 280:1 210:1 40:1 370:1	≤ 15 μs ≤ 10 μs ≤ 10 μs ≤ 15 μs ≤ 15 μs
Quattro Nucleus	QNP	^{19}F ^{31}P ^{13}C ^{13}C ^{1}H	TFT TPP ASTM 10% EB 0.1% EB	140:1 100:1 100:1 80:1 135:1	150:1 150:1 150:1 120:1 220:1	220:1 200:1 200:1 150:1 330:1		≤ 20 μs ≤ 10 μs ≤ 10 μs ≤ 10 μs ≤ 15 μs
Quattro Nucleus	QNP	^{31}P ^{13}C ^{13}C ^{15}N ^{1}H	TPP ASTM 10% EB 90% Form. 0.1% EB	65:1 100:1 80:1 14:1 135:1	100:1 160:1 120:1 20:1 220:1	140:1 220:1 160:1 25:1 330:1	150:1 240:1 210:1 30:1 370:1	≤ 10 μs ≤ 10 μs ≤ 10 μs ≤ 15 μs ≤ 15 μs
Quattro Inverse ^{1}H / ^{31}P-^{13}C / ^{15}N	QXI	^{1}H ^{31}P ^{13}C ^{15}N	0.1% EB TPP ASTM Urea			750:1*	800:1*	≤ 10 μs ≤ 40 μs ≤ 15 μs ≤ 45 μs

Table 4.1. Sensitivity and Pulse Width without Gradient / with Z-gradient Selected 5 mm Probes

Triple Res. Inverse ^{1}H / ^{13}C-BB	TBI	^{1}H ^{13}C(fixed) ^{31}P(BB) ^{13}C(BB) ^{15}N(BB)	0.1% EB ASTM TPP ASTM Urea		500:1*	750:1*	850:1*	≤ 10 µs ≤ 20 µs ≤ 25 µs ≤ 15 µs ≤ 30 µs
Notes: *These sensitivity values are over 200 Hz noise; all other 1H sensitivity values are over 2 ppm noise. 1H sensitivity values apply for new AVANCE spectrometers only. Probes fitted with an XYZ gradient may hav a performance 10% lower than the above values. EB = ethylbenzene, TPP = 0.0485 M triphenylphosphate, ASTM = 60% C_6D_6 in dioxane, TFT = 0.05% 1,3,5-trifluorotoluene, Form. = formamide (^{1}H decoupling without NOE), Urea = 100mM urea, 100mM methanol in DMSO-d6. **Technical data and specifications subject to change without notice.**								

Table 4.2. 1H Resolution and Lineshape - Selected 5 mm Probes

SEL, BBI, TXI		300	400	500	600 +	MHz
BOSS 1	Resolution spinning Spinning sidebands Lineshape spinning Lineshape non-spinning	0.45 ≤ 1 5 / 10 8 / 14	0.45 ≤ 1.5 5 / 9 6 / 12			Hz % Hz Hz
BOSS 2	Resolution spinning Spinning sidebands Lineshape spinning Lineshape non-spinning			0.45 ≤ 2 5 / 10 7 / 14	0.45 ≤ 2 5 /10 6 / 12	Hz % Hz Hz
Notes: 3% $CHCl_3$ sample for 200-400 MHz, 1% $CHCl_3$ sample for 500-600 MHz. Resolution at 50% level. Lineshape at 0.55% / 0.11% levels. **Technical data and specifications subject to change without notice.**						

Table 4.3. 13C Resolution and Lineshape - Selected 5 mm Probes

DUL, BBO, QNP		300	400	500	600	MHz
BOSS 1	Resolution spinning Spinning sidebands Lineshape spinning	0.2 ≤ 1 2 / 4	0.2 ≤ 1 2 / 4	0.2 ≤ 1 3 / 5	0.2 ≤ 1 4 / 8	Hz % Hz
Notes: ASTM sample. Resolution at 50% level. Lineshape at 0.55% / 0.11% levels. **Technical data and specifications subject to change without notice.**						

Table 4.4. Water Suppression - Selected 5 mm Probes

Probe		300	400	500	600	
SEL BBI, TXI SEL, BBI, TXI SEL, BBI, TXI	S/N S/N Lineshape Splitting	33:1 25:1 50 / 100 ≤ 40	60:1 55:1 50 / 100 ≤ 40	110:1 95:1 50 / 100 ≤ 40	160:1 150:1 75 / 130 ≤ 40	 Hz %
Notes: 2 mm Sucrose sample. Lineshape non-spinning with BOSS shim system at 50% / 10% levels of DSS signal. **Technical data and specifications subject to change without notice.**						

The Hardware Tests (HWT) 4.3

The *Hardware Tests (HWT)* are a suite of tests primarily used in Operational Qualification (OQ) to demonstrate the hardware performance of our instruments. These tests are based on the tests compiled in an article by Joseph B.Vaughn and Philip L. Koons, in *Spectroscopy* 1995, 10(1) 36-40.

The chief operator of the NMR system should be the primary person that performs these tests and procedures, however, anyone with a sound knowledge of the hardware and software installed should be able to run all the tests successfully.

The Hardware tests that you can perform using the HWT suite fall into three basic categories:

- General tests
- Modulator tests (shaped pulses)
- Tests using gradients

For complete instructions on the use of this software refer to the manual 'HWT Installation and User Manual' part number H9532.

Requirements for Running HWT Tests 4.3.1

The temperature stability in your laboratory and the temperature stability of your spectrometer have a significant impact on the quality of the HWT tests. A maximum variation of the room temperature of +/-0.5C/hour is about the highest tolerance you should allow before running these hardware tests. Please get in touch with a Bruker applications representative if you have further questions regarding general laboratory requirements.

HWT General Tests 4.3.2

Selected Examples:

- **180 degree test** - Demonstrates phase settling speed, five repetitions of a 180 degree pulse executed at different phase angles are performed.
- **RF Homogeneity test** - Demonstrates the homogeneity of the rf field generated in the observe coil. 100 experiments with an incremented pulse length from p1/10 to 10*p1 microseconds are performed. This test is used to determine the 810/90 degree pulse width ratio.
- **Amplitude stability test** - Demonstrates the overall amplitude stability of the system. The results of 32 experiments are presented as a spectrum and as table of intensities with statistical analysis. This test can be performed with different pulse width, generally a pulse width of 30 and 90 degrees is used.

HWT Modulator Tests (shaped pulses) 4.3.3

Selected Examples:

- **Modulator linearity test** - Using square pulses with different peak amplitudes the linearity of the modulators is tested.
- **Shaped pulse amplitude linearity test** - The amplitude linearity test based on 6dB amplitude changes and pulse doubling from the HWT general tests section is repeated with gaussian shaped pulses.
- **Shaped pulse amplitude stability test** - The amplitude stability test from the HWT general tests section is repeated with gaussian shaped pulses.

HWT Tests using Gradients *4.3.4*

Selected Examples:

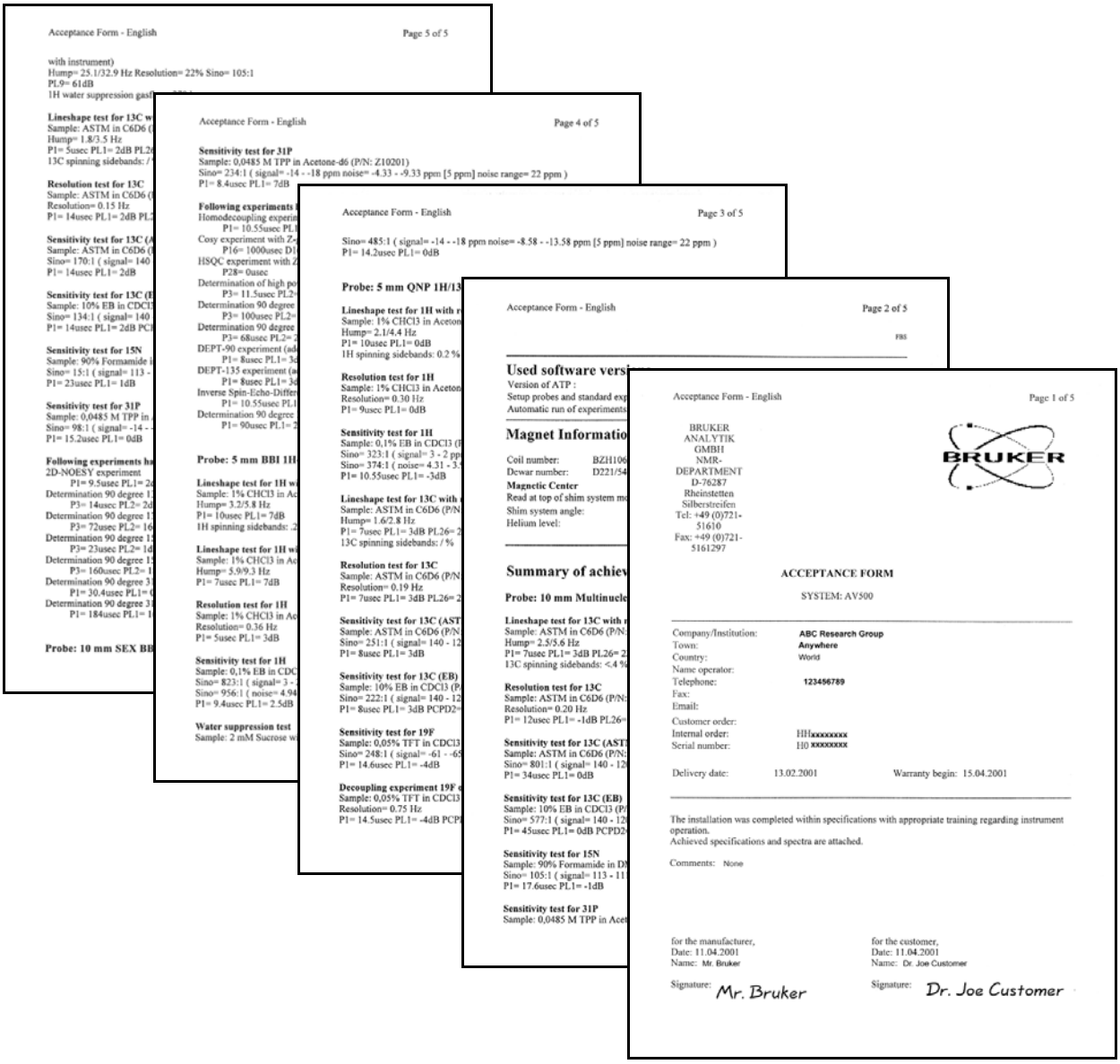
- **Amplitude stability after gradient echo** - Demonstrates stability of the gradient amplifiers. A pair of gradients with opposite amplitudes follows an rf pulse. The amplitude of the resulting signal is analyzed for amplitude variation.
- **Amplitude stability after gradient pulse** - The amplitude stability test from HWT general test section is repeated. Before the rf pulse, a gradient is applied and the test is run three times with different gradient durations and strengths.
- **Gradient recovery test** - The recovery of the signal after a gradient is recorded from 10 microseconds to 100 microseconds.

The Acceptance Test Protocol *4.4*

The **A**cceptance **T**est **P**rotocol (**ATP**) is a series of standardized forms, test protocol and other support documents that provide a history of the acceptance tests results, and of the final acceptance of the instruments by the customer.

The ATP sequence is carried out by the installation/service engineer during acceptance testing. Upon completion of all the testing both the Bruker engineer and an authorized customer representative sign the final Acceptance Protocol form. The original copies of the complete ATP results are kept at Bruker. A computerized summary of the results are saved to the host computer.

Figure 4.1. Sample pages from an Acceptance Test Protocol



Some of the documents that result from the ATP testing which are maintained by Bruker include:

- Lineshape Test for 1H with and without rotation
- Resolution Test for 1H
- Sensitivity Test for 1H
- Water Suppression Test
- Sensitivity Test for 13C
- The various experiments that have been performed (e.g. 2D-NOESY, Cosy experiment with Z-grad., HSQC experiment with Z-grad, etc.).

Refer to section ***4.2*** for more information on these tests and experiments.

The exact tests and results that are maintained depend on the system configuration and probe being used.

Magnet Acceptance Test 4.5

As the magnet is required for the Spectrometer Acceptance Test, the performance of the magnet is proved through the successful completion of the ATP testing. The Magnet Acceptance Test results are integrated and maintained in the Acceptance Test Protocol (ATP).

Magnet Acceptance Test notes

- Due to a long settling time, the magnet system reaches its **final drift** and **loss rates** after several days or weeks, depending on the magnet model.
- The **field homogeneity** can only be verified with a NMR lineshape test. When the specifications for the lineshape, resolution and S/N are reached, the field homogeneity specifications are also reached.
- The **helium holding time** of the system can first be determined after the second helium refill.

Software Backup and Computer Documentation 4.6

After the installation of the PC, Linux, or UNIX-based systems and the factory Final Test, Bruker makes a **complete backup** of the **entire installation** using Disk Imaging software (PC) or respective backup software (Linux, UNIX).

The list of hardware, operating system software, and application software, etc. which was prepared at the factory before the instrument is shipped (see ***"Factory Software Backup" on page 34***), is updated if any changes have taken place. This list aids in verifying GLP requirements as well as handling any computer problems.

Computer systems should be well documented with **model number**, **serial and revision numbers** and the software should be labeled with model and revision numbers. Documentation should include items like size of the hard disk, internal memory (RAM), installed type and version of operating software, standard application software and user contributed software, for example MACRO programs. This information is important because all items can influence the overall performance of a computer system. The information should be readily available when a problem occurs with the computer system.

General Spectrometer/ Magnet Maintenance

5

Introduction 5.1

For all practical purposes, maintenance and adjustments can be considered part of Performance Qualification (PQ). The purpose of the PQ is to ensure that the instrument continues to function correctly and to a specification appropriate for its routine use. Regular maintenance and periodic adjustments ensure that this goal is achieved.

General Spectrometer Maintenance 5.2

The service intervals and schedules for the maintenance of the Bruker magnets and spectrometers are based on the results of Bruker's continuous research in this area.

Spectrometer Service Intervals and Schedules 5.2.1

Console:

Requirements for exchanging the filter matting in the floor plates or doors are different for the different console types.

Routinely check the functionality of the air filters and ventilation fans in the complete units.

Sample Changer

The Sample Changer horizontal and vertical cylinders should be cleaned and greased **annually**. The following grease should be used:

Horizontal cylinder:	Silicon Grease	Part Number H5043
Vertical cylinder	Graphite Grease	Part Number H5042

Maintenance Procedures for Cryomagnets 5.3

Important: When refilling cryogenic liquids the magnet should not be left unattended. Protective clothing, including leather or PVC gloves and eye protection should be warn at all times. Liquid Nitrogen (LN2) spilling out of the magnet filling ports could fall onto the top or bottom magnet flange. The risk is that of the O-rings freezing and the vacuum level decreasing to the point of a magnet quench, making a new installation of the magnet necessary.

Checking and Refilling Liquid Helium 5.3.1

The **Helium vessel** should be **checked weekly** for boil off and helium level. Use a helium flow meter or a helium gas counter. These values should be recorded (see ***"Magnet Refill Record" on page 55***). If the boil off falls to zero for a period greater than 24 hours, the tower tubes should be checked for the presence of ice. The procedure for checking the tower tubes and removing any blockage should be attempted only by a trained technician with considerable experience on cryogenic systems.

It is recommended that you refill the helium vessel within the specified hold time period and certainly before the level falls below the allowed minimum level. Refer to the Magnet System User Manual (***Table 5.1.***) that is delivered with the magnet for details.

Guidelines for checking the Helium level

- Routinely (at least once per week) check the **helium level gauge** with help of the B-SN 18, BSMS or BSMS/2 electronic measuring devices.
- When the electronic measurement is not possible due to a malfunction, you can check the helium level with help of the **dipstick** or otherwise contact the nearest Bruker Service Representative.
- The measured value should be recorded in a table or graph, for example ***"Magnet Refill Record" on page 55***.
- A **software tool** is also available, “**helevtransfer**” to automatically check and record the helium level.
- A regular **greasing of the O-rings** at the LHe refill neck tube is recommended.

Refilling Liquid Helium (LHe)

When refilling liquid helium the following safety points should be observed:

- Leather or PVC **gloves and eye protection** should be worn at all times.

- The **refill opening** of the helium dewar **should not be left open** for extended periods of time, as this may result in excessive icing of the magnet dewars.
- When refilling the He-dewars a ***maximum*** **pressure of 0.25 bar** should be used.
- During the transfer the **helium transfer line should not be allowed to ice up**, as then only helium gas will reach the magnet, which may result in a magnet quench. When the transfer line begins to ice up, the refill must immediately be stopped and the transfer line evacuated or exchanged.
- The **O-ring** sealing the syphon entry port should be checked approximately 10-20 minutes after every transfer, once the ice buildup on the towers has defrosted. The **helium vessel should never be left open** to atmosphere for more than 5 seconds.
- Check that there is a gas flow through the flow meter after the refill of helium.

Refer to the Users Manual for UltraShield NMR Magnet Systems (Table 5.1.) for complete details on refilling and safety aspects when refilling!

The LN2 and LHe refill procedures are the same for Standard and UltraShield Magnets.

Table 5.1. Nitrogen/Helium Refill Procedures

Refill Procedure	Document	Part Number
Liquid Nitrogen LN2	Users Manual for UltraShield NMR Magnet Systems	Z31326 (English) Z31320 (German) Z31366 (French) Z31367 (Italian) Z31368 (Spanish)
Liquid Helium LHe	Users Manual for UltraShield NMR Magnet Systems	Z31326 (English) Z31320 (German) Z31366 (French) Z31367 (Italian) Z31368 (Spanish)

To obtain a copy of these manual please visit our Switzerland Website at ***http://www.bruker.ch/magnetics.html*** or contact your nearest Bruker Service Representative for a copy of these manuals.

The transfer of cryogenic liquids should be stopped immediately when the vessel is full. Failure to observe this can lead to the freezing of O-rings and a subsequent vacuum loss of the NMR magnet system, which may result in a magnet quench.

Checking and Refilling Nitrogen *5.3.2*

The **Nitrogen vessel** should be **checked daily** for boil off and nitrogen level. These values should be recorded. If the boil off drops to zero, the filling and exhaust ports should immediately be checked for the presence of ice.

The Nitrogen vessel will normally need to be **refilled every 7-10 days**. When the vessel is being refilled, liquid nitrogen should not be allowed to spill onto the room temperature bore closure flange. Use teflon tubes on the nitrogen filling ports during refill.

Over-pressured LN2 should never be used for refilling nitrogen. A maximum pressure of 0.5 bar or less must be used!

Refilling Liquid Nitrogen

- Leather or PVC **gloves and eye protection** should be worn at all times.
- When refilling the LN2-dewars a ***maximum*** **pressure of 0.5 bar** should be used.
- Generally, liquid nitrogen should be filled **once a week.** This will enable you to experience on how long each refill takes.
- After the refill, check that the nitrogen filling ports are free of ice.

When you notice that the refill takes longer than normal it is quite possible that an **ice stricture has formed in the LN2 refill neck**. This stricture can be removed quite easily with a 6 mm diameter plastic or fiberglass rod. This rod should be ap-

prox. 50 cm long and must be secured to prevent it falling into the N2 dewar. The rod should be inserted deep into the stricture until it begins to enter the N2 dewar.

Refer to the Users Manual for UltraShield NMR Magnet Systems (***"Nitrogen/Helium Refill Procedures"***) for complete details on other safety aspects for refilling.

Moving an NMR Magnet System after Installation 5.3.3

Do not shift or transport the NMR magnet system after installation! Transportation without a transport fixture may lead to damage or even destruction of the NMR magnet system!

Adjustments 5.4

The following are adjustments that may need to be made **periodically** to optimize instrument performance.

Frequent Routine Adjustments 5.4.1

Locking and Shimming

Before running an NMR experiment, it is necessary to optimize the homogeneity of the magnetic field. This is done by a procedure commonly referred to as "**locking and shimming**". Refer to the **Avance Beginners Guide** (P/N Z31633) for instructions on how to perform locking and shimming.

Tuning and Matching

Each probe is fitted with as many resonant circuits as there are nuclei indicated on the probe label (e.g., one for 1H and one for 13C in a dual 1H/13C probe; one for 1H and one for a wide range of nuclei in BBO or BBI probes). A resonant circuit for the lock nucleus is also fitted, even though the standard user will never need to adjust it. Each of the circuits has a frequency at which it is most sensitive (the resonance frequency). **Once the sample is inserted, the probe should be**

tuned and matched for these individual frequencies. Refer to the **Avance Beginners Guide** for details.

Long-term Adjustments *5.4.2*

The following adjustments normally need to be carried out only when spectrometer performance is no longer optimal.

Pulse Length

- Pulse length calibration is done by inspecting the spectra resulting from experiments while sequentially increasing a defined pulse length. The pulse program required and the optimal spectrum depends on the kind of pulse which is to be optimized. Refer to the **Avance Beginners Guide** or the **Solids Experiments Manual** (P/N H9321) for details.

DC Offset

- The acquired FID can be DC offset adjusted via the RS485 Interface. Two different commands for each channel are implemented. The two offset adjustments can be done using the RX22 Service Tool. A DC-Offset voltage is added to the NF amplifier in the AF-Section. This adjustment can be done individually for each channel A and B. Refer to the **RX Receiver Manual** (P/N Z31189) for details.

Quad Image

- The quadrature imagine adjustment can be set via the RS485 Interface. Two different commands for gain adjust and phase adjust are implemented. These two adjustments can be done using the **RX22 Service-Tool**. With the Gain Adjustment the gain difference between the in-phase and quad-phase channel is altered. With the Phase Adjustment, the phase difference between this two channels is set. Refer to the **RX Receiver Manual** (P/N Z31189) for details.

Software Maintenance *5.5*

In case of software updates on an otherwise fully functional spectrometer, a Software Validation Test (SVT) should be performed. This is typically done with the Bruker SVT package, which is described in the section ***"The SVT Software Package" on page 75***.

Detailed software update information is provided for every software version in the form of an installation guide. This guide is delivered with every new software version.

Periodical checks of the basic spectrometer functionality are ideally executed with the GLP Software package. See ***"The GLP Software Package" on page 76*** for details.

SOP's, Data Security and More

6

Standard Operating Procedures 6.1

Standard Operating Procedures (**SOP's**) are written procedures for a laboratory's program. They define how to carry out protocol-specified activities, and are often written in a chronological listing of action steps as shown in the following table:

Table 6.1. Suggested Standard Operating Procedure Contents

SOP's should be established for at least the following:

- Routine inspection, cleaning, maintenance, calibration and standardization of instruments.
- Actions to be taken in response to equipment failure.
- Analytical methods.
- Definition of raw data.
- Data handling, storage, and retrieval.
- Qualification of personnel.
- Health and safety standards.
- Authorized access to equipment.
- Receipt, identification, storage, mixing, and method sampling of test and control articles.
- Record keeping, reporting, storage, and retrieval of data.
- Coding of studies, handling of data, including the use of computerized data systems.
- Operation of quality assurance personnel in performing and reporting study audits, inspections, and final study report reviews.

SOP's should be preferably be written by key laboratory personnel who are close to the instrument, such as the Laboratory Manager. It should also be thoroughly reviewed by the instrument's operators. SOP's should be written on how the procedures *actually* work, not just how they are supposed to work under ideal conditions.

This ensures that the information is adequate and that the document invites rather than discourages routine use.

For easy reference the SOP should contain:

- A unique identification and revision number,
- Page numbers and total number of pages,
- For equipment testing: performance acceptance criteria, recommended corrective actions, and a template for continuous entries of test results and corrective actions,
- A history of revisions.

Be sure to place copies of the SOP's close to the instruments to provide easy accessibility for operators.

Any deviations from SOP's must be authorized by the study director and significant changes in established SOP's must be authorized by management.

Level of Detail in SOP's *6.1.1*

How specific should a SOP be or how general can it be? If written too restrictively, SOP's will frequently need revising. On the other side, if the details are insufficient, instructions will fail to provide adequate direction for personnel. SOP's should be detailed enough to provide meaningful direction for personnel. The level of detail depends mainly on the education, training, and experience of personnel. Things that may change frequently, for example the suppliers of materials should not be specified in a SOP.

Pertinent Magnet Information for SOP's *6.1.2*

The following collection of forms aid in recording some of the standard control and maintenance functions for the magnet, which is one of the requirements for instrumentation under GLP.

It is highly recommended that these or similar localized forms be created and their usage be defined and documented in the instrument SOP.

Printed copies of these forms, which may be copied as required, are available in the **Bruker Magnet System Manual** (***Table 5.1.***) that is delivered with the magnet.

Charging Record SC Magnet System

Figure 6.1. Charging Record SC Magnet System

BRUKER

Form — Magnet Test

BZH	D
CHARGING RECORD SC MAGNET SYSTEM	

Cryo Power Supply #		Main Coil Switch Test	A
Main Coil Heater	mA	Shim Coil Heaters	mA

Date	Time	Remarks		Sense mV	Current-Current A - A		Helium %
		Start with	A				

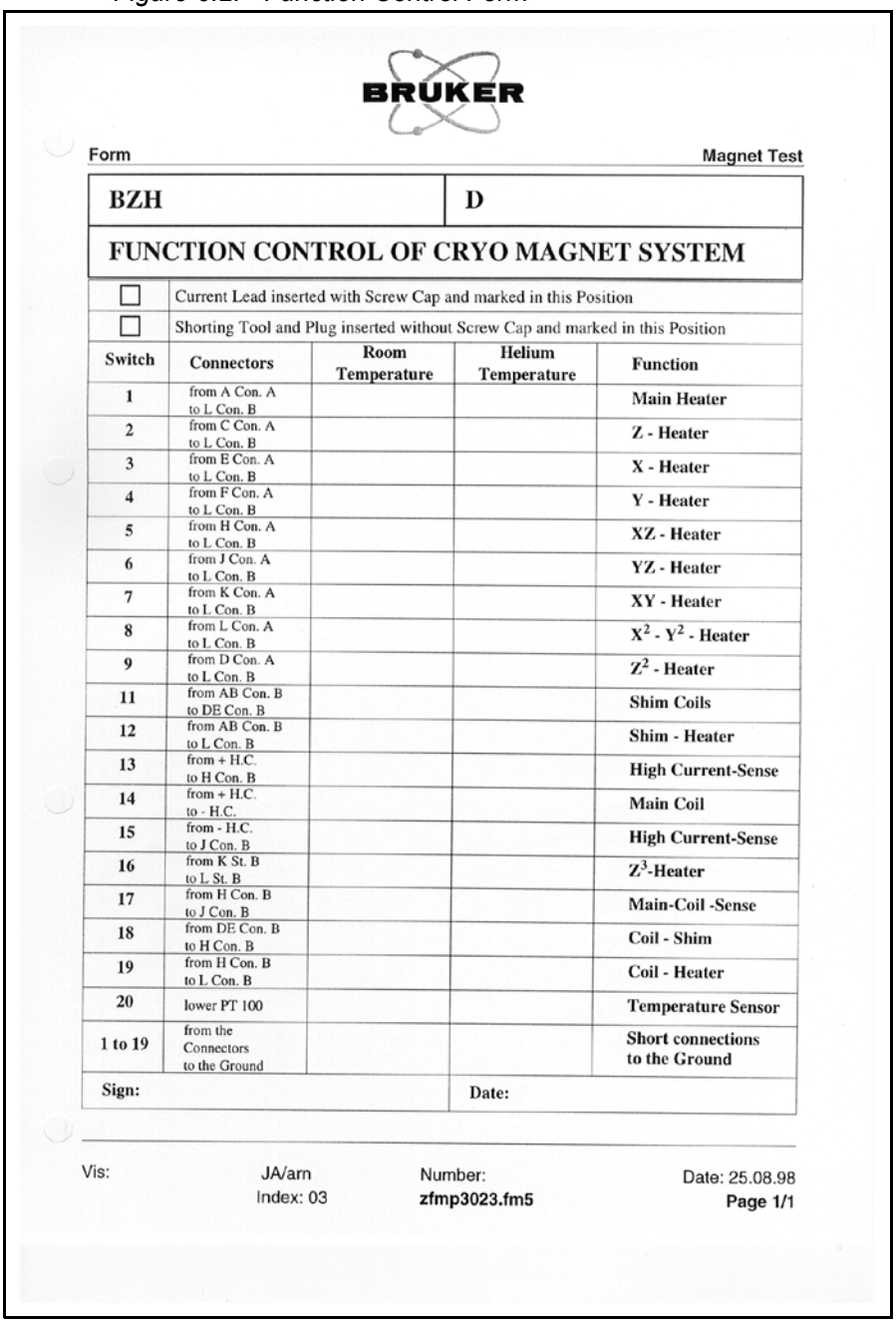
Date:	Vis:

Vis: JA/arn Index: 03 Number: **zfmp3022.fm5** Date: 25.08.98 **Page 1/1**

This form is used to record the charging of the magnet coil.

Function Control Form for the Cryo Magnet System

Figure 6.2. Function Control Form



BRUKER

Form Magnet Test

BZH	D

FUNCTION CONTROL OF CRYO MAGNET SYSTEM

☐ Current Lead inserted with Screw Cap and marked in this Position

☐ Shorting Tool and Plug inserted without Screw Cap and marked in this Position

Switch	Connectors	Room Temperature	Helium Temperature	Function
1	from A Con. A to L Con. B			Main Heater
2	from C Con. A to L Con. B			Z - Heater
3	from E Con. A to L Con. B			X - Heater
4	from F Con. A to L Con. B			Y - Heater
5	from H Con. A to L Con. B			XZ - Heater
6	from J Con. A to L Con. B			YZ - Heater
7	from K Con. A to L Con. B			XY - Heater
8	from L Con. A to L Con. B			X^2 - Y^2 - Heater
9	from D Con. A to L Con. B			Z^2 - Heater
11	from AB Con. B to DE Con. B			Shim Coils
12	from AB Con. B to L Con. B			Shim - Heater
13	from + H.C. to H Con. B			High Current-Sense
14	from + H.C. to - H.C.			Main Coil
15	from - H.C. to J Con. B			High Current-Sense
16	from K St. B to L St. B			Z^3-Heater
17	from H Con. B to J Con. B			Main-Coil -Sense
18	from DE Con. B to H Con. B			Coil - Shim
19	from H Con. B to L Con. B			Coil - Heater
20	lower PT 100			Temperature Sensor
1 to 19	from the Connectors to the Ground			Short connections to the Ground
Sign:			Date:	

Vis: JA/arn Number: Date: 25.08.98

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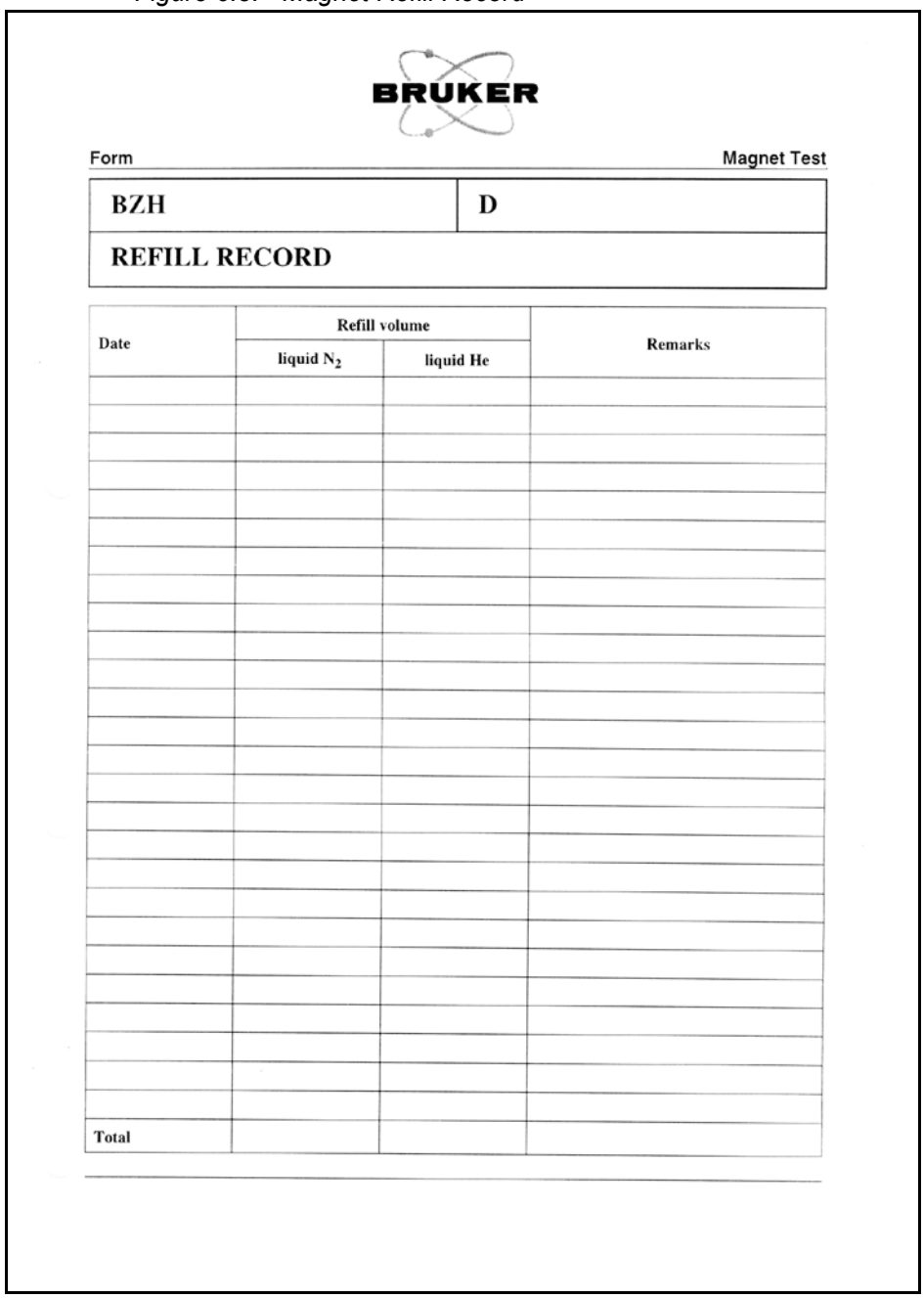
This form may be used to record the measured resistances of the magnet coil before the installation at room temperature and after the cool down procedure.

Magnet Nitrogen/Helium Refill Record

Figure 6.3. Magnet Refill Record



BRUKER

Form Magnet Test

BZH	D
REFILL RECORD	

Date	Refill volume		Remarks
	liquid N_2	liquid He	
Total			

The Refill Record should be used to record the helium level and the nitrogen level. This form should also be used to record the refills of liquid helium and of liquid nitrogen.

Emergency Plan for NMR Systems *6.1.3*

Due to the strong magnetic fields and presence of cryogens when using NMR systems, it is important to define and communicate what to due in case of problems or an emergency. An **Emergency Plan** can be defined as a documented set

of instructions on what to do if something goes wrong. Emergency Plans are often defined as part of the SOP, or as a stand-alone document. In any case every NMR laboratory should have an Emergency Plan in effect in case of problems or emergencies.

The Emergency Plan should be made up of **at least** the following sections:

1. Emergency list of contacts.
2. Instructions for employees and external workers.
3. Instructions on Fire Department notification.
4. Information on handling medical emergencies.

As every organization has its own policies and procedures, as well as varying laboratory layouts, an Emergency Plan should be individually defined for each laboratory as appropriate. Some general safety guidelines that should be included in an emergency plan include:

- NMR laboratories must not be accessible to the public. Make sure access is **restricted to qualified employees only**.
- Instruct your employees regularly on safety procedures, including what to do in the event of an emergency.
- Strong magnetic fields involve various hazards. The danger zone should be **labeled as precise and clearly as possible** by use of barriers, tape on the floor or other visual warning devices. Consult your safety manual for specific information concerning the danger zone (0.5 mT line).
- Complete the Emergency List of Contacts (***Table 6.2.***) and **keep it up to date**. Hang the list in obvious places, so when an emergency occurs the appropriate people/organizations can be notified immediately.
- Mark the paths to available **emergency exits** clearly.
- Strictly **enforce the smoking ban** during refilling procedures.
- If your magnet system is installed in a small room or a confined space (e.g. pit), it is **highly recommended** that you wear or install **oxygen warning devices**.

Emergency List of Contacts

The Emergency List of Contacts is nothing more than a list of people and/or organizations (e.g. fire department) to notify in the event of an emergency. The following table is an example of Bruker's minimum recommendations:

Table 6.2. Emergency List of Contacts

In case of problems or emergency's **DURING WORKING HOURS** advise the following personnel:

Name	Bureau/Department	Phone

In case of problems or emergency's **DURING NIGHT, WEEKEND OR HOLIDAYS** advise the following personnel:

Name	Bureau/Department	Travel Time	Phone

FIRE DEPARTMENT	
POLICE	
MEDICAL SERVICES	
TECHNICAL SERVICES	

Instructions for Employees and External Workers

As noted previously NMR laboratories must not be accessible to the public, thus access must be restricted to qualified employees only. Strong magnetic fields involve various hazards. The danger zone should be labeled as clearly as possible by the use of barriers or other visual warning devices (Consult your safety manual for specific information concerning the danger zone - 0.5 mT line).

Employees should be regularly informed of the potential hazards within the laboratory. Ideally, this should include all the employees that work in the area, but specifically laboratory personal and external workers, such as cleaning and service personnel, who may have access to the laboratory (especially the magnet room). This information should be documented in a laboratory SOP, and routine and new employee briefings should take place.

At a minimum employees and external workers should be informed of the following dangers:

- Magnet systems **attract metals** made from iron, steel, or nickel.
- The magnet system creates a very strong magnetic field. In a magnets sphere of influence metallic parts, tools, cleaning equipment and other

objects (keys, eyeglass frames) made of metal can develope strong, even **uncontrollable forces** and turn into **dangerous projectiles**.

- Persons carrying **pacemakers and/or medical implants** are not permitted, ***under any circumstances***, in the proximity of magnet systems.
- Watches, electric and electro-mechanical devices, as well as credit cards and other magnetic storage media may be damaged or malfunction if brought inside the labeled magnetic field area (refer to the Bruker Site Planning Manual for details).
- If an object does get drawn and sticks to the magnet, immediately inform the responsible individual. ***Never*** try to remove the object by force, as this may result in further damage to the magnet, the object or to yourself.
- Magnet systems are cooled by use of liquid nitrogen and helium. In liquid state, these gases have a temperature of -196°C and -269°C respectively. Skin contact with these liquids can lead to **severe cold burns**; eye contact could result in **blindness**.
- Persons should never touch any super-cooled metal parts, as there is a danger of **skin adhesion**.
- Always wear **protective clothing and goggles** when coming in direct contact with the system.
- **Nitrogen** is colorless and odorless, and has a higher density than air. In a closed room nitrogen will **settle to the floor**.
- **Helium** is also colorless and odorless, but has a lower density than air, so will **rise to the ceiling**. When in contact with moist air, the production of a fog may be observed. A high concentration of helium in the surrounding air can be observed by a significant raise of the voice.
- In a gaseous state both substances **deplace oxygen**. A sudden discharge of gas from the system in a closed or insufficiently ventilated room may result in **suffocation**. It is therefore compulsory to provide adequate ventilation (a room volume exchange of 3-5 times/hour).
- In case of a **sudden discharge of gas** from the magnet system, immediately open all available windows and doors and exit the room without delay.
- When working in the magnet room always keep the location of the **nearest exit** in mind. When escaping gases mix with ambient air a fog may form, blocking the exits from view.
- During a quench liquid oxygen may be produced. It will drip from the top of the towers of the magnet. If liquid oxygen comes in contact with oil or grease, **spontaneous combustion** may occur. It is essential that the smoking ban is repected and to ensure that the area around the vincinity of the magnet system is clean and free from clutter.
- Never step or climb on a magnet system.
- Release of the stored energy in a magnet can be acheived through use of the emergency switch. However, be aware that **the magnetic field remains!!!**

Instructions on Fire Department Notification

Procedures for contacting the local Fire Department should be annotated in the SOP and posted near the entrance of the magnet room (preferably near a telephone). Any employee or external worker working near the magnet system should be informed on what to do in an emergency.

It is also recommended that the magnet operator introduce the **fire department and/or local authorities** to the magnet site. It is important that these organizations be informed of the potential risks of the magnet system, i.e. that much of the magnetic rescue equipment (oxygen-cylinders, fire extinguishers, axe's etc) can be hazardous close to the magnet system. Of course, their expertise and experience can be invaluable in creating an emergency plan.

Other key points that should be addressed in an SOP regarding fire department notification and handling of an emergency include:

- Helium gas escaping from the system should not be mistaken for smoke. Instruct the fire department and technial service not to „extinguish" the magnet system with water. The outlet valves could freeze over and generate excess pressure within the system.
- NMR laboratory windows which are accessible during an emergency should be clearly marked with warning signs, visible from the outside.
- Within an NMR laboratory CO2 non-magnetic fire extinguishers (aluminum, fiberglas) should be used.
- Breathing equipment which uses oxygen tanks made out of magnetic material can be life threatening when used close to a magnet system that still has a magnetic field present.

Information for Handling Medical Emergencies

Procedures for handling medical emergencies should also be discussed in the SOP and posted near the entrance of the magnet room. Employees and local emergency medical personnel should be informed of the potential risks and special procedures required when respond to a medical emergency in the magnet system area. Key points that should be addressed include:

- Medical treatment should not take place close to a magnet system.
- Contact with cooling liquids, gases or vapors can lead to skin irritations similar to burns. The severity of the burn depends on the temperature and exposure time. In the case where liquid cryogens come in contact with the eyes, rinse thoruoughly with clear water and seek immediate ophthalmologic advice.

It is also highly recommended that the procedures for **First Aid for Cold Burns** be posted at a key point near the magnet room entrance:

First Aid for Cold Burns:

- Get the injured into a warm room (ca. 22°C).
- Loosen all clothing which could prevent blood circulation of the affected parts.
- Pour large quantities of warm water over the affected parts. (***Never use hot water or dry heat!***).
- Cover the wound with dry and sterile gauze. **Do not apply too tightly** as to impair blood circulation!

- Immobilize the concerned body part.
- Seek immediate medical assistance.

Other Pertinent Information for SOP's *6.1.4*

The following information has a significant impact on the results obtained from the instrumentation, thus it should be considered for inclusion in the laboratory SOP.

Sample Preparation

The sample quality can have a **significant impact on the quality of the NMR spectrum**. The following is a brief list of suggestions to ensure high sample quality:

- Always use clean and dry sample tubes to avoid contamination of the sample.
- Always use high quality sample tubes to avoid difficulties with shimming.
- Filter the sample solution.
- Always use the same sample volume or solution height (recommended values: 0.6 ml or 4 cm of solution for 5 mm sample tubes, 4.0 ml or 4 cm of solution for 10 mm sample tubes). This minimizes the shimming that needs to be done between sample changes.
- Use the depth gauge to position the sample tube in the spinner. This is discussed further in Chapter 5 'Sample Positioning' of the BSMS User's Manual and on the Bruker Automated Service Handbook (BASH) CD-ROM.
- Check that the sample tube is held tightly in the spinner so that it does not slip during an experiment.
- Wipe the sample tube clean before inserting it into the magnet.
- For experiments using sample spinning, be sure that the spinner, especially the reflectors, are clean. This is important for maintaining the correct spinning rate.

Data Security, Integrity and Traceability *6.2*

Protecting the integrity, security, and traceability of electronic records is most critical for any business and regulatory environment. Success in complying with new regulations such as the FDA's 21 CFR Part 11 (electronic signatures and records) hinges on securing the authenticity and integrity of data you generate.

Since the mid 1990's the FDA has paid a lot of attention to data integrity and authenticity. Several warning letters have even been issued regarding this topic. Data integrity became even more important in 1997 when 21 CFR Part 11 was issued. With this regulation, electronic records and signatures can be equivalent to paper records and handwritten signatures. The regulation applies to all industry segments regulated by the FDA that includes Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and current Good Manufacturing Practice (GMP).

Who has to comply to 21 CFR Part 11?

Laboratories have to comply with Part 11 when three criteria are present:

1. When computers are used to create, modify, maintain, archive, retrieve, or transmit data.
2. When at any time electronic records hit a durable storage device.
3. When the laboratory intends to create records that are intended to be submitted to or required by the FDA.

For most analytical work numbers 1 and 2 apply, so the open question is only with reference to number 3. Laboratories can decide to do signatures on paper, but they have no choice on records. They must be kept electronically. (Status as of January 2000).

Primary requirements of 21 CFR Part 11

The primary requirements of the regulation for analytical laboratories are:

- Limited system access to authorized individuals.
- Use of validated existing and new computer systems.
- Secure retention of electronic records to instantly reconstruct the analysis.
- User independent computer generated time-stamped audit trails.
- Ensure system and data security, data integrity and confidentiality through limited authorized system access.
- Use of secure electronic signatures for closed and open systems.
- Use of digital signatures for open systems.

Implementing the new rule will have a significant impact on the instrumentation, the work processes and on the people in analytical pharmaceutical laboratories:

- The current process of generating signatures should be evaluated (who has to sign what and when?).
- New procedures have to be developed in the company and in the laboratory for limited authorized access to systems and data (who can do what?).
- Computerized systems used for implementation must be updated or replaced to ensure correct functionality.
- The manner of using and handling I.D. codes and passwords as a basis for ‘legally’ binding signatures may have to be changed.
- New specialists, for example ‘electronic archivist’, may be required.

System Validation *6.2.1*

All computer systems used to generate, maintain and archive electronic records must be validated to ensure accuracy, reliability, consistent independent performance and the ability to discern invalid or altered records.

This holds true for new as well as existing systems. It is basically nothing new for laboratories using computers in a regulated environment. In validating computer

systems, the problem lies not as much with new or fairly new systems, but more with the older systems. They require a formal evaluation and a statement on their validation status. If they cannot be validated they cannot be used under 21 CFR Part 11.

Procedures should be in place to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Records must be protected to enable their accurate and ready retrieval throughout the records retention period.

The FDA expects final results to be kept with the original data and the procedures for processing the data („meta data"). The FDA wants to be able to trace the final results back to the raw data using the same tools as the user when the data was generated. This is probably one of the most difficult requirements to implement. Knowing that they are subject to the predicate rule, the records must be kept for ten years or more, and computer hardware and software have a much shorter lifetime, one can anticipate problems with this paragraph.

One problem is to decide exactly which records should be logged and retained. The situation is most complex for quantitative chromatographic analyses. Usually in chromatography data acquisition, evaluation and printout is done automatically using pre-programmed methods. However, occasionally the pre-programmed integration method can be inappropriate which becomes obvious on the chromatogram and peak baseline printout. In this case analysts have to work with the raw data and adjust parameters to generate more appropriate measurements of peak integrations. This is a manual iterative process, which frequently is subjective to the user. A few years ago it was sufficient to keep the original data and the final results together with the final method used to develop the final results. Now, the expectation is to keep all integration methods in between as well.

A second problem is the availability of the records throughout the retention period. The problem is not so much the durability of storage devices such as CD-ROM's but more the computer hardware, operating systems and application software that is required to reconstruct the analysis. If all this was available, it would be difficult to find the people who could operate this old equipment. The FDA does not necessarily expect companies to save computer hardware and software for the sole purpose of recreating events, rather the expectation is that data and 'meta data' should be able to be accurately converted to future systems.

Limited System Access

Procedures should be in place to limit the access to authorized user. This can be ensured through physical and/or logical security mechanisms. Most companies already have such procedures in place. Typically users have to log on to a system with user I.D. and password. Problems have been reported with practical implementation in analytical laboratories when computer controlled systems are collecting data over time, especially when more than one person operates a computer at similar times using different applications and during a shift change in a routine lab. Group users I.D.s. and passwords can be used to log on the system, but unique identification through individual application specific passwords must be available for binding signatures with records.

Audit Trails and Electronic Signatures

Procedures should be available to use secure, computer generated, time-stamped audit trails to independently record the date and time of operator entries

and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information.

When using electronic signatures for closed and open systems it is important that written policies are established, and adhered to, which hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to determine record and signature falsification.

In general, personnel in the lab should be trained on 21 CFR Part 11 and on the meaning of electronic signatures. The training should be documented and after the training attendees should sign a paragraph stating, for example: „I understand that electronic signatures are legally binding and have the same meaning as handwritten signatures“.

Part 11 does not mandate electronic signatures. Signatures can still be made on paper. Such systems are called hybrid systems. Companies should inform the FDA when they intend using electronic signatures with a letter like:

“This is to certify that ’My Company’ intends that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.”

To comply with some of the fundamental regulations specified by rule 21 CFR Part 11, Bruker has implemented Audit Trails in NMR Suite 3.1 and beyond.

Performance Qualification 7

Introduction 7.1

The purpose of the Performance Qualification (PQ) is to ensure that the instrument continues to function correctly and to a specification appropriate for its routine use. PQ provides the continuing evidence of control and of acceptable performance of the instrument during its routine use.

PQ's have to be carried out **regularly**, and following any maintenance intervention on the instrument. Routine, frequent minimized PQ's can be carried out by the laboratory personnel. Less frequent, detailed PQ's should be carried out by Bruker service personnel.

For **laboratory personnel**, Bruker has designed the SVT and GLP tools to assist in their PQ's. It is the task of **laboratory managers** to formulate SOP's for PQ.

For **Bruker service personnel**, Bruker has designed a powerful software tool presently known under the name of „Automatic Test Procedures," (ATP) to aid in service aspects of PQ.

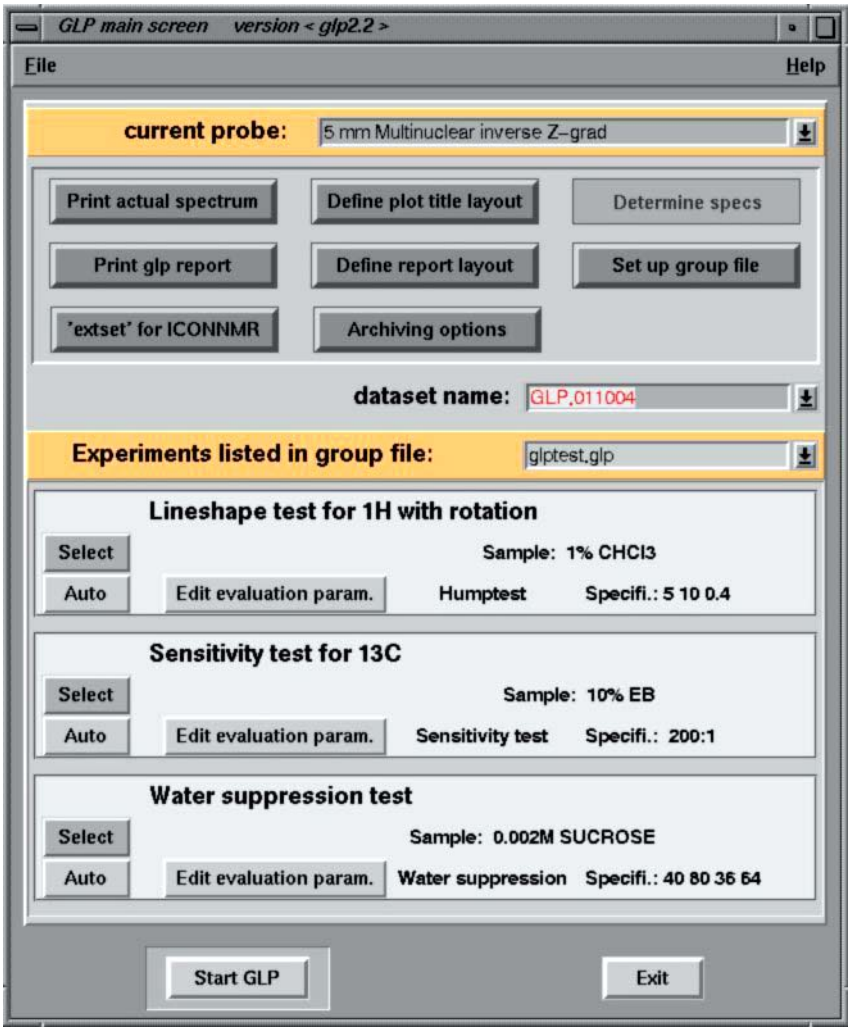
GLP Tests 7.2

The *Good Laboratory Practice* (GLP) software is primarily used for tests in Performance Qualification (PQ). The purpose of the GLP tests are to document the long-term stability of NMR spectrometer.

The basic idea of the software package is to establish lists of experiments that are performed at standard intervals, for example every Monday and once every month. If all the experiments run without a problem, a GLP protocol will be printed and this protocol becomes part of the general GLP documentation of the laboratory. In contrast to this, if one or more of the tests fail, it is up to the supervisor to take action (e.g. re-shim, tune, change hardware, re-calibrate pulses and/or power levels etc.).

The tests provide documented evidence that the instruments continue to function correctly.

Figure 7.1. The GLP Test Software



Standard GLP Tests *7.2.1*

The general idea behind the GLP tests is to keep things as simple as possible. Therefore, we offer only a **very limited**, but **extremely effective**, number of **tests**, including:

- Standard Lineshape, or Hump test for 1H or 13C
- Standard Resolution test for 1H or 13C
- Standard Water Suppression test
- Standard Sensitivity test for 1H or X-nuclei
- Any user defined tests

The Lineshape Test

This test is also commonly known as the **Hump test**. A 1H or 13C spectrum is acquired with one scan, typically on the CDCl3 sample for 1H and on the ASTM

sample for 13C. The **width of the reference signal at 0.55% height and 0.11% height** is calculated with a double exponential fit along the left and right side of the signal. These values are compared with the listed specifications and marked accordingly.

The Resolution Test

The Resolution test checks the **width of the referred signal at half height**. The test is passed if the width is equal or better than the specified value.

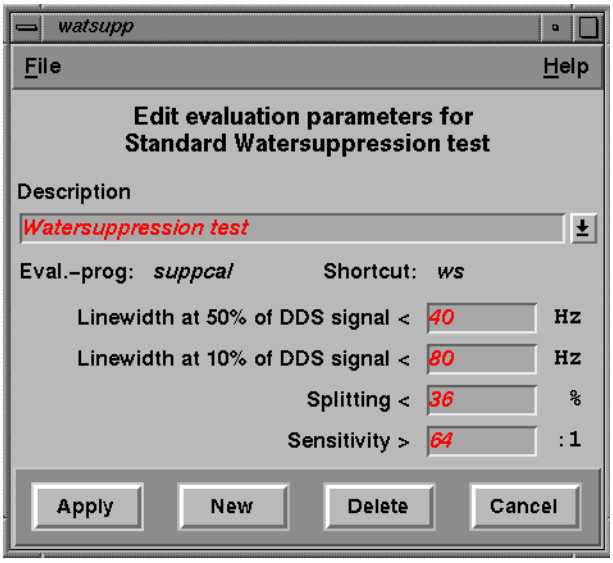
The Sensitivity Test

The Sensitivity test can be performed for all standard nuclei. The **height of the largest signal** between the signal limits is calculated. A predefined noise window is shifted in 25 steps along the spectrum between the noise limits. Each time, the noise value is determined and the signal-to-noise ratio is calculated with respect to the height of the largest signal. The best value must meet or exceed the specification.

The Water Suppression Test

The Water Suppression test is performed on the Sucrose sample. The **width of the water signal at 50% and 10% of the height** of the DDS signal is determined. In addition, the **line splitting of the anomeric proton** at ca. 5.25 ppm is evaluated and for this signal a sensitivity calculation is done similarly to the one described in the sensitivity test.

Figure 7.2. Example for Setting Specifications for GLP Water Suppression Test



The GLP software will allow you to run the test manually or automatically.

For complete instructions on the GLP software, refer to the GLP Installation and User Manual that is delivered with the software package.

For an example of the GLP Test Report print-out refer to the figure below.

Figure 7.3. Sample GLP Report

GLP TEST REPORT
BRUKER ANALYTIK GmbH, NMR-DEPARTMENT
Silberstreifen, D-76287 Rheinstetten
Tel: +49 (0)721-51610, Fax: +49 (0)721-5161297

Company/Institution:	Bruker Analytik GmbH
Name customer:	Marcel
Street:	Silberstreifen
Town:	Rheinstetten 76287
Country:	Germany
Name operator:	Mike
Phone (Lab):	0721-5161 XXX
Fax:	0721-5161 XXX
ISDN:	
Email:	
Spectrometer type:	AVANCE400
System order #:	HH001234
Contact Bruker-Spectrospin:	Mike
Phone Bruker-Spectrospin:	07243-504 XXX
Fax Bruker-Spectrospin:	07243-504 XXX
Email Bruker-Spectrospin:	
Email Bruker-Spectrospin:	
ISDN Bruker-Spectrospin:	
Sales contract #:	
Service contract #:	

Summary of achieved specifications

Result of loop over all experiments	
Lineshape test for 1H with rotation	OK
Resolution test for 13C	OK
Water suppression test	OK
Dataset name: GLP.980626 1 1 v demo	
Experiment: Lineshape test for 1H with rotation	
Sample: 1% CHCl3	
Specification result of humpcal:	**OK**
Linewidth at 0.55% of signal height = 7.2 Hz (< 10Hz)	OK
Linewidth at 0.11% of signal height = 18.7 Hz (< 20Hz)	OK
Halfwidth = 0.31 Hz (< 0.4Hz)	OK
Dataset name: GLP.980626 2 1 v demo	
Experiment: Resolution test for 13C	
Sample: ASTM	
Specification result of hwcal:	**OK**
Half width = 0.08 Hz (< 0.1Hz)	OK
Dataset name: GLP.980626 3 1 v demo	
Experiment: Water suppression test	
Sample: 0.002M SUCROSE	
Specification result of suppcal:	**OK**
Linewidth at 50% of DDS signal = 38.3 Hz (< 40Hz)	OK
Linewidth at 10% of DDS signal = 75.1 Hz (< 80Hz)	OK
Splitting = 32 % (< 36%)	OK
Sensitivity = 86.20 :1 (64:1)	OK

Remarks: _____
Date:
Test performed by:
Test results approved by: _____
Signature: _____ Date: _____

Recommended samples for use with GLP *7.2.2*

The recommended samples for use with GLP tests are the same as for SVT, although, for practicality, fewer samples will be used in the lab. Refer to ***"Recommended Samples for use with SVT" on page 72*** for a complete list of samples for use with SVT or GLP.

Values for GLP Sensitivity Test *7.2.3*

The probes that are used have a huge impact on the results achieved from an instrument. Probe performance has been measured and specified by Bruker under the condition that magnets have been perfectly shimmed, and that the spectrometer environment meets all requirements concerning magnetical and mechanical stability, as well as air conditioning. In reality, normal laboratory conditions are not usually so ideal that top probe specifications can be reached at all times and under any circumstances. This is the reason why for GLP assessment of the Performance Qualification, it makes sense to **scale down the threshold passed/failed in sensitivity by ~20%.**

In the following tables are examples of what can be reasonably considered for GLP sensitivity tests with some of the most frequently used Bruker 5 mm probes.

Table 7.1. Sensitivity and Pulse Width without Gradient / with Z-gradient Selected 5 mm Probes

(values scaled down by ~20% - read paragraph above for details)

Probe	Type	Nucleus	Sample	300	400	500	600 +	90º PW
Selective	SEL	^{1}H	0.1% EB	190:1	500:1*	720:1*	920:1*	≤ 8 µs
Broadband Inverse	BBI	^{1}H ^{31}P ^{13}C ^{15}N	0.1% EB TPP ASTM Urea	175:1	480:1*	720:1*	800:1*	≤ 8 µs ≤ 25 µs ≤ 15 µs ≤ 30 µs
Triple Res. Inverse	TXI	^{1}H ^{13}C ^{15}N	0.1% EB ASTM Urea	175:1 ≤ 15 µs ≤ 40 µs	480:1* ≤ 15 µs ≤ 40 µs	720:1* ≤ 12 µs ≤ 33 µs	880:1* ≤ 12 µs ≤ 37 µs	≤ 8 µs
Dual ^{13}C / ^{1}H	DUL	^{13}C ^{13}C ^{1}H	ASTM 10% EB 0.1% EB	80:1 60:1 105:1	125:1 95:1 175:1	1750:1 140:1 260:1	230:1 190:1 295:1	≤ 10 µs ≤ 10 µs ≤ 15 µs
Broadband Observe	BBO	^{31}P ^{13}C ^{13}C ^{15}N ^{1}H	TPP ASTM 10% EB 90% Form. 0.1% EB	70:1 80:1 60:1 10:1 105:1	105:1 125:1 95:1 15:1 175:1	95:1 175:1 125:1 25:1 260:1	125:1 220:1 165:1 30:1 295:1	≤ 15 µs ≤ 10 µs ≤ 10 µs ≤ 15 µs ≤ 15 µs
Quattro Nucleus	QNP	^{19}F ^{31}P ^{13}C ^{13}C ^{1}H	TFT TPP ASTM 10% EB 0.1% EB	110:1 80:1 80:1 60:1 105:1	120:1 120:1 120:1 95:1 175:1	175:1 160:1 160:1 120:1 260:1		≤ 20 µs ≤ 10 µs ≤ 10 µs ≤ 10 µs ≤ 15 µs
Quattro Nucleus	QNP	^{31}P ^{13}C ^{13}C ^{15}N ^{1}H	TPP ASTM 10% EB 90% Form. 0.1% EB	50:1 80:1 60:1 10:1 105:1	80:1 125:1 95:1 15:1 175:1	110:1 175:1 125:1 20:1 260:1	120:1 190:1 165:1 20:1 295:1	≤ 10 µs ≤ 10 µs ≤ 10 µs ≤ 15 µs ≤ 15 µs
Quattro Inverse ^{1}H / ^{31}P- ^{13}C / ^{15}N	QXI	^{1}H ^{31}P ^{13}C ^{15}N	0.1% EB TPP ASTM Urea			600:1*	640:1*	≤ 10 µs ≤ 40 µs ≤ 15 µs ≤ 45 µs

Table 7.1. Sensitivity and Pulse Width without Gradient / with Z-gradient Selected 5 mm Probes

(values scaled down by ~20% - read paragraph above for details)

Triple Res. Inverse ^{1}H / ^{13}C-BB	TBI	^{1}H ^{13}C(fixed) ^{31}P(BB) ^{13}C(BB) ^{15}N(BB)	0.1% EB ASTM TPP ASTM Urea		400:1*	600:1*	680:1*	≤ 10 µs ≤ 20 µs ≤ 25 µs ≤ 15 µs ≤ 30 µs

Notes: *These sensitivity values are over 200 Hz noies; all other 1H sensitivity values are over 2 ppm noise.
1H sensitivity values apply for new AVANCE spectrometers only.
Probes fitted with an XYZ gradient may hav a performance 10% lower than the above values.

EB = ethylbenzene, TPP = 0.0485 M triphenylphosphate, ASTM = 60% C_6D_6 in dioxane, TFT = 0.05% 1,3,5-trifluorotoluene, Form. = formamide (^{1}H decoupling without NOE), Urea = 100mM urea, 100mM methanol in DMSO-d6.
Technical data and specifications subject to change without notice.

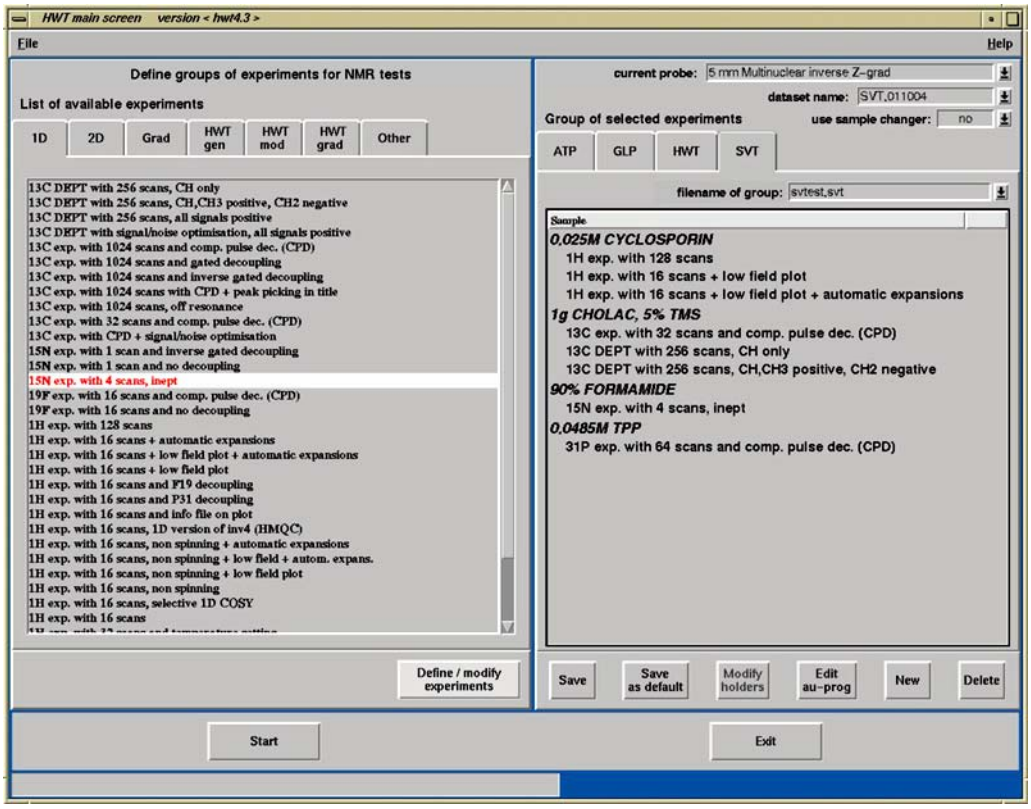
The SVT Software Package *7.3*

The *Software Validation Test (SVT)* software is intended for laboratory personnel for the general hardware and software validation of Bruker NMR spectrometers. As with the HWT software, the chief operator of the NMR system should be the primary person that performs these tests and procedures, however, anyone with a sound knowledge of the hardware and software installed should be able to run all the tests successfully.

The quality of the results obtained from ATP, HWT, SVT and GLP tests depend on the general conditions within a NMR laboratory. The reproducibility of the tests will improve if the temperature and humidity in the laboratory are stable. However, more important are good matching, tuning and shimming of your probe in connection with a good overall maintenance of the spectrometer and adjustment of the pulses and power levels for the various nuclei. For questions regarding general laboratory requirements contact your Bruker service engineer or application specialist.

The SVT tests are part of Bruker's own in-house testing procedures. They can be used at a customers laboratory to verify that a particular software version is compatible with an existing spectrometer configuration and its hardware components. As such, SVT is equally important in all phases of GLP (DQ, IQ, OQ and PQ).

Figure 7.4. The SVT Test Software



Standard Tests performed using the SVT Software 7.3.1

Some of the standard SVT tests that you can perform using the SVT software package include:

- Standard 1H acquisition
- Standard 13C acquisition
- Standard 15N acquisition
- Standard COSY acquisition
- Standard NOESY acquisition
- Standard HMBC acquisition
- Standard HSQC acquisition

Recommended samples for use with SVT 7.3.2

The following table lists the recommended samples for use in connection with the GLP and SVT tests. You can also use your own samples, but for reproducibility, especially of the GLP tests, we strongly recommend standardized Bruker test samples. For a complete list of all Bruker samples please contact your local Bruker representative.

Table 7.2. Recommended Samples for use with SVT

Sample	Diameter	P/N
1% CHCI3 in Acetone-d6	5	Z10248
1% CHCI3 in Acetone-d6	10	Z10250
0.1% EB in CDCI3	5	Z10120
0.1% EB in CDCI3	10	Z10121
ASTM in C6D6	5	Z10163
ASTM in C6D6	10	Z10164
10% EB in CDCI3	5	Z10153
10% EB in CDCI3	10	Z10154
1g Cholesteryl acetate in CDCI3	5	Z10161
1g Cholesteryl acetate in CDCI3	10	Z10162
0.1M Urea 15N, 0.1 CH3OH 13C in DMSO-d6	5	Z10263
0.1M Urea 15N, 0.1 CH3OH 13C in DMSO-d6	10	Z10265
0.05% TFT in CDCI3	5	Z10234
0.05% TFT in CDCI3	10	Z10235
90% Formamide in DMSO-d6	5	Z10187
90% Formamide in DMSO-d6	10	Z10188
85% Hexamethyldisiloxane in C6D6	5	Z10209
2mM Sucrose with 0.5nM DSS, 2nM NaN3 in 10% D2O and 90% H2O	5	Z10246
2mM Sucrose with 0.5nM DSS, 2nM NaN3 in 10% D2O and 90% H2O	10	Z10268
50mM Cyclosprin in CDCI3	5	Z10092
25mM Cyclosprin in CDCI3	10	Z10086
25mM Cyclosprin in CDCI3	5	Z10093

Summary of General Instrument Validation Tools

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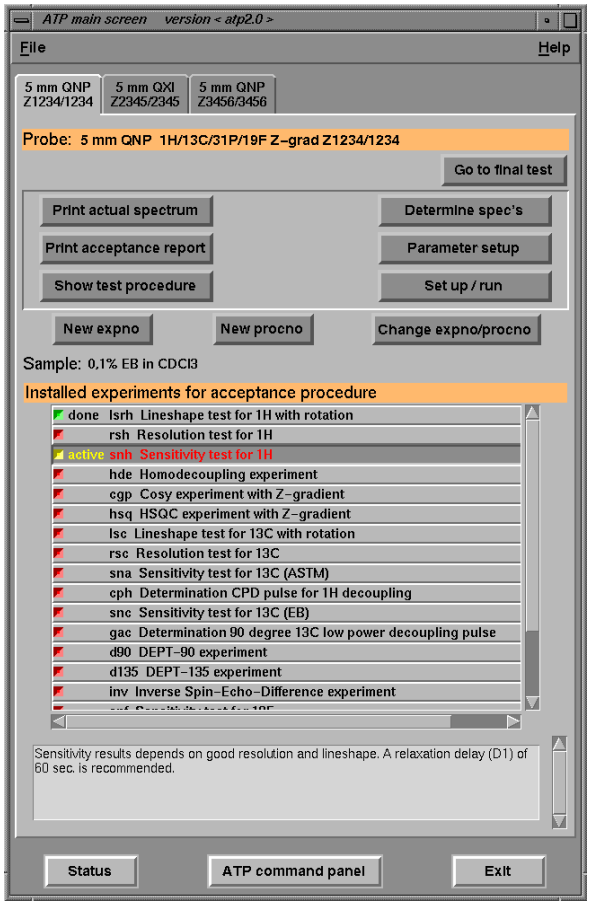
ATP 8.1

The *Acceptance Test Procedures (ATP)* software package has been designed by Bruker for Bruker Test and Service Engineers to standardize the final test and acceptance procedures and documentation.

In principle, the ATP software follows the same pathway during the Final Test (IQ) and the Acceptance Test (OQ) procedures. Nevertheless, a focus is made on demonstrating that the **Operational Qualification (OP)** of the instrument is met. In particular, additional NMR device experiments ('HWT' tests) are also performed during this test. At the end of the ATP, the customer verifies that the instrument meets the standards that they have established by signing the Acceptance Report, together with the Bruker Service Engineer.

Figure 8.1. The ATP Software Package



The HWT Software Package *8.2*

The *Hardware Tests (HWT)* are a suite of tests primarily used in Operational Qualification (OQ) to demonstrate the hardware performance of our instruments. These tests are based on the tests compiled in an article by Joseph B.Vaughn and Philip L. Koons, in *Spectroscopy* 1995, 10(1) 36-40.

The chief operator of the NMR system should be the primary person that performs these tests and procedures, however, anyone with a sound knowledge of the hardware and software installed should be able to run all the tests successfully.

The Hardware tests that you can perform using the HWT suite fall into three basic categories:

- General tests
- Modulator tests (shaped pulses)
- Tests using gradients

For complete instructions on the use of this software refer to the manual 'HWT Installation and User Manual' part number H9532.

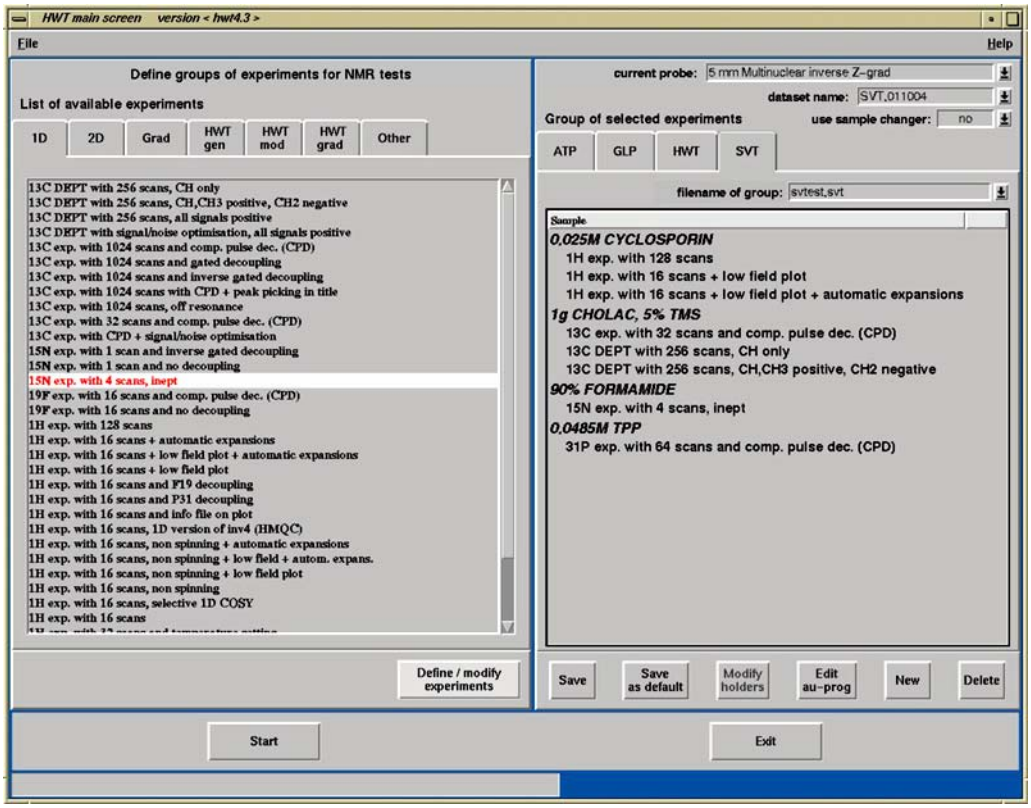
The SVT Software Package 8.3

The *Software Validation Test (SVT)* software is intended for laboratory personnel for the general hardware and software validation of Bruker NMR spectrometers. As with the HWT software, the chief operator of the NMR system should be the primary person that performs these tests and procedures, however, anyone with a sound knowledge of the hardware and software installed should be able to run all the tests successfully.

The quality of the results obtained from ATP, HWT, SVT and GLP tests depend on the general conditions within a NMR laboratory. The reproducibility of the tests will improve if the temperature and humidity in the laboratory are stable. However, more important are good matching, tuning and shimming of your probe in connection with a good overall maintenance of the spectrometer and adjustment of the pulses and power levels for the various nuclei. For questions regarding general laboratory requirements contact your Bruker service engineer or application specialist.

The SVT tests are part of Bruker's own in-house testing procedures. They can be used at a customers laboratory to verify that a particular software version is compatible with an existing spectrometer configuration and its hardware components. As such, SVT is equally important in all phases of GLP (DQ, IQ, OQ and PQ).

Figure 8.2. The SVT Test Software



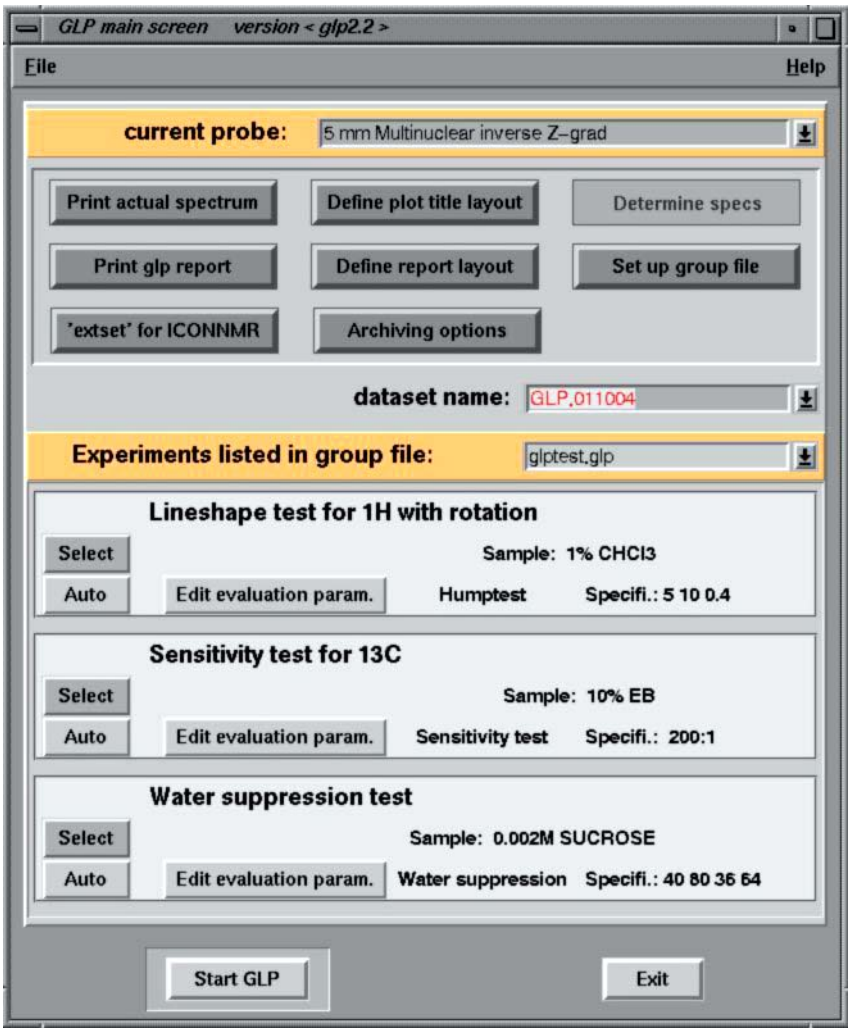
The GLP Software Package 8.4

The *Good Laboratory Practice* (GLP) software is primarily used in Performance Qualification (PQ). The purpose of the GLP tests is to document the long-term stability of NMR spectrometer.

The basic idea of the software package is to establish lists of experiments that are performed at standard intervals, for example every Monday and once every month. If all the experiments run without a problem, a GLP protocol will be printed and this protocol becomes part of the general GLP documentation of the laboratory. In contrast to this, if one or more of the tests fail, it is up to the supervisor to take action (e.g. re-shim, tune, change hardware, re-calibrate pulses and/or power levels etc.).

The tests provide documented evidence that the instruments continue to function correctly.

Figure 8.3. The GLP Test Software



The GLP software will allow you to run the test manually or automatically.

For complete instructions on the GLP software, refer to the GLP Installation and User Manual that is delivered with the software package.

NMR-CHECK 8.5

NMR-Check is a Software-Package that allows Bruker service or application personnel to remotely log into customer systems for troubleshooting, application or training. The concept thereof is a shared session of XWINNMR, that allows both the customer and the local Bruker representative to watch and influence the contents of the screen. The application chemist can use it to check on spectra taken by the customer, which may look unsatisfactory.

Used as a service tool at the UNIX level, NMR-Check helps Bruker engineers to analyze a problem on a distant spectrometer, with all the known software tools as if he were on site. Hence, this kind of diagnose is quicker, more accurate and cheaper for the customer. If a service visit is still required, the engineer, due to prior knowledge of the problem, can bring the relevant tools and parts with him.

Standard Magnet Validation Tests 8.6

Consumption Test

The exhaust rate can be determined using a gas meter or calibrated flow meter.

Drift Test

The drift rate can be determined using a lineshape sample and switch lock. The atmospheric pressure must be observed when testing the drift rate.

Homogeneity Test

The homogeneity can be determined by performing a lineshape test.

Summary of General Instrument Validation Tools

Glossary

Accreditation	The procedure by which an authoritative body gives formal recognition that a body is competent to carry out specific tasks.
Accuracy	The degree of agreement of a measured value with the actual expected value.
AOAC	Association of Offcial Analytical Chemists
Astm	American Society for Testing and Materials
BASH	Bruker Automated Service Handbook. A collection of Bruker hardware and application User and Service manuals distributed on CD-ROM in PDF format.
Calibration	The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by material measure and the corresponding values of the measurand.
CITAC	Co-Operation on International Traceability in Analytical Chemistry. A forum for worldwide cooperation and collaboration on the mechanisms needed to ensure the validity and comparability of analytical data on a global basis.
cGMP	Current Good Manufacturing Practice.
CFR	Code of Federal Regulations. Collection of all regulations issued by U.S. government agencies. The individual titles making up the regulations are numbered the same way as the federal laws on the same topic. For example, the Federal Food, Drug, and Cosmetic Act is found in Title 21 of United States Code and the companion regulations implementing the law are found in 21 CFR.
Computer System	A system composed of computer(s), peripheral equipment such as disks, printers and terminals, and the software necessary to make them operate together (ANSI/IEEE Standard 729-1983).
Computerized System	A system that has a computer as a major, integral part. The system is dependent on the computer software to function.
EPA	Environmental Protection Agency of the United States Government. A regulatory body who develops and enforces all aspects of environmental monitoring. This includes development of analytical methods.
EP	European Pharmacopeia, Official compendium of the member states of the Council of Europe, which includes all EC and EFTA countries.
FDA	Food and Drug Administration, U.S. agency, part of the Department of Health and Human Services, responsible for regulating clinical research and approval of marketing permits for food, drugs, medical devices and cosmetics in the U.S.
GALP	Good Automated Laboratory Practice
GAMP	Good Automated Manufacturing Practice
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
ILAC	International Laboratory Accreditation Cooperation. Working for international acceptance of data generated by accredited organizations. Developed the ISO Guide 25.
Installation Qualification	Documented verification that all key aspects of hardware installation adhere to appropriate codes and approved design intentions and that the recommendations of the manufacturer have been suitably considered.
ISO	International Organization for Standardization. Agency responsible for developing international standards; over 160 technical committees, 650 sub-committees and 1500 working groups; more than 6000 ISO standards published; represents more than 90 countries. Founded in 1947.
JP	Japanese Pharmacopeia, Official pharmacopoeia of Japan.
LOD	Limit of detection.
LOQ	Limit of quantification.
NIST	National Institue for Standards and Technology in the United States.
OECD	Organization for Economic Cooperation and Development.
Operational Qualification	Documented verification that the equipment related system or subsystem performs as intended throughout representative or anticipated operating ranges.
Performance Verification	A service offered by Bruker support organizations. It verifies that the system at the user's site performs according to the specifications as agreed between the vendor and the purchaser.
Performance Qualification	Documented verification that the process and/or the total process related system performs as intended throughout all anticipated operating ranges.
PIC	Pharmaceutical Inspection Convention, a multinational organization (primarily of European countries) whose members have agreed to mutual recognition of facility inspections for good manufacturing practice.
PMA	Pharmaceutical Manufacturers Association in the United States. A trade association that represents more than 100 firms, collectively producing more than 90 percent of American prescription drugs.
Qualification	Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.
Reference Material	A material or substance, one or more properties of which are sufficiently well established to be used for calibrating an apparatus, assessing a measurement method or for assigning values to materials.
Retrospective validation	Establishing documented evidence that a system does what it purports to do based on review and analysis of historic information.
Ruggedness	An indication of how resistant the process is to typical variations in operation, such as those to be expected when using different analysts, different instruments and different reagent lots.

Source code	An original computer program in a legible form (programming language), translated into machine-readable form for execution by the computer.
Study director	Person in the laboratory responsible for the outcome of the GLP validation.
USP	United States Pharmacopeia
Warning Letter	Letter issued by U.S. Food and Drug Administration to manufacturer containing adverse findings and giving the manufacturer 15 days in which to reply. It replaced the Regulatory Letter and the Notice of Adverse Findings.
Validation	Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.
Verification	Confirmation by examination and provision of evidence that specified requirements have been met.

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