


# GLP Requirements

- Related to an Environment with NMR Systems  
User Guide  
Version 003



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# 1 About

## 1.1 This Manual

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This manual enables safe and efficient handling of the device.

This manual is an integral part of the device, and must be kept in close proximity to the device where it is permanently accessible to personnel. In addition, instructions concerning labor protection laws, operator regulations tools and supplies must be available and adhered to.

**Before starting any work, personnel must read the manual thoroughly and understood its contents.** Compliance with all specified safety and operating instructions, as well as local accident prevention regulations, are vital to ensure safe operation.

The figures shown in this manual are designed to be general and informative and may not represent the specific Bruker model, component or software/firmware version you are working with. Options and accessories may or may not be illustrated in each figure.

## 1.2 Policy Statement

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It is the policy of Bruker to improve products as new techniques and components become available. Bruker reserves the right to change specifications at any time.

Every effort has been made to avoid errors in text and figure presentation in this publication. In order to produce useful and appropriate documentation, we welcome your comments on this publication. Support engineers are advised to regularly check with Bruker for updated information.

Bruker is committed to providing customers with inventive, high quality products and services that are environmentally sound.

## 1.3 Symbols and Conventions

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Safety instructions in this manual are marked with symbols. The safety instructions are introduced using indicative words which express the extent of the hazard.

In order to avoid accidents, personal injury or damage to property, always observe safety instructions and proceed with care.



**DANGER**

**Danger indicates a hazardous situation which, if not avoided, will result in death or serious injury.**

This is the consequence of not following the warning.

► This is the safety condition.

1. This is the safety instruction.

## **WARNING**



**Warning indicates a hazardous situation, which, if not avoided, could result in death or serious injury.**

This is the consequence of not following the warning.

- ▶ This is the safety condition.
- 1. This is the safety instruction.

## **CAUTION**



**Warning indicates a hazardous situation, which, if not avoided, may result in minor or moderate injury.**

This is the consequence of not following the warning.

- ▶ This is the safety condition.
- 1. This is the safety instruction.

## **NOTICE**

**NOTICE indicates a property damage message.**

This is the consequence of not following the notice.

- ▶ This is a safety condition.
- 1. This is a safety instruction.



**This symbol highlights useful tips and recommendations as well as information designed to ensure efficient and smooth operation.**

## 2 Introduction

### 2.1 Introduction

---

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.

#### 2.1.1 Who is Responsible for GLP?

---

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:

- Specifying test procedures
- Verifying that specifications are met
- Documentation of test results

## 2.2 Bruker's Role in GLP Qualification

---

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.

## 2.3 General Instrument Validation Tools

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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.

### 2.3.1 ATP

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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.

### 2.3.2 HWT Suite

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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.

### 2.3.3 SVT Software

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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

### 2.3.4 GLP Software

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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.**



# 3 Design Qualification

## 3.1 Introduction

---

**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 possess 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** directives, as well as received NRTL certification and bear the TÜV Rheinland sign:



Figure 3.1: The TÜV Rheinland Symbol

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.

## 3.2 Basic Steps for Design Qualification

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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.

### 3.3 Instrument Specifications

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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, specification sheets are available for Bruker spectrometers and magnets. These design specifications should be carefully compared with the user requirement specifications.

Check with your local Bruker representative for information on obtaining these files.

#### 3.3.1 Magnet Specifications

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Bruker magnet specification sheets are available to aid in setting the functional and performance specifications. Check with your local Bruker representative for information on obtaining these files.

For information on magnet accessories request the file "Overview of Bruker Accessories" from your local Bruker sales representative.

#### 3.3.2 Magnet Documentation

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The magnet manual is typically delivered with the magnet. Updated versions of the magnet manuals may also be available from Bruker. The latest version of the general parts of the current magnet manual, which can also be valuable for customers who have older magnet systems, may also be available.

Check with your local Bruker representative for information on obtaining these files.

#### Cryogen Refill Manuals

Cryogen refill manuals are available in five languages on the **Bruker Advanced Service Handbook (BASH) DVD**, or from Bruker.

### 3.4 Product Development and Evaluation

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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 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 production centers.

## 3.4.1 Magnet Development and Evaluation

Generally speaking, each magnet system is delivered with 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.

## 3.4.2 Bruker ISO 9001 Certification - Bruker BioSpin GmbH

The following is a list of ISO 9001 certifications available from Bruker that were available when this guide was prepared:

Certificate	Company Part
ISO Site Certificate	Bruker BioSpin GmbH
ISO Site Certificate	Bruker BioSpin GmbH - NMR Division
ISO Site Certificate	Bruker BioSpin GmbH - EPR/minispec Division
ISO Site Certificate	Bruker BioSpin GmbH - Magnet Division
ISO Certificate of Registration	Bruker BioSpin Corporation
ISO Certificate of Approval	U.E.S. Bruker (France)
ISO Certificate of Approval	Bruker BioSpin AG

*Table 3.1: List of Current ISO Certifications Available from Bruker*

Please contact your Bruker representative for an actual list of certifications.

## 3.4.3 Bruker ISO 9001 Certification - Magnet

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 which accompanies delivery of the magnet system.

## 3.4.4 Bruker CE Certification - Spectrometer

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 Spectrometer series 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 Z31812, Z31759, and Z31558) contain the individual Declaration of Conformity certificates (see the example in the following figure) for each respective AVANCE spectrometer. These manuals may be found on the BASH DVD. 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.**

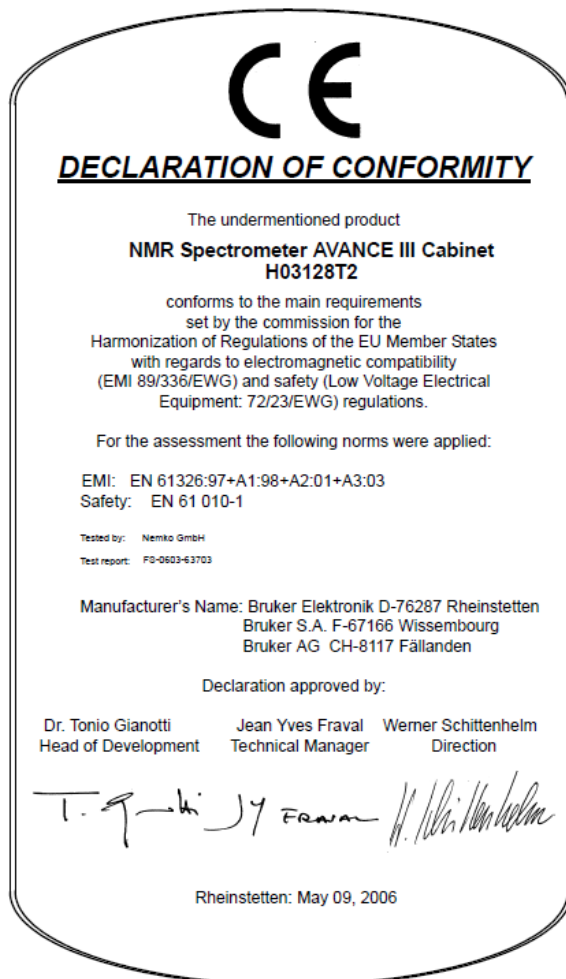


Figure 3.2: Example of an AVANCE Console Declaration of Conformity

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. These subunits received dedicated safety approval from third party testing agencies in accordance with requirements of the Low Voltage Directive 2006/95/EC and the Standard IEC/EN61010-1. Standalone units like the Sample Changer have separate CE-markings, Certificates of Conformity and Cer-

tification files and likewise received dedicated safety approval from third party testing agencies in accordance with requirements of the Low Voltage Directive 2006/95/EC and the Standard IEC/EN61010-1.

### 3.4.5 Bruker CE Certification - Magnet

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



Figure 3.3: Example of a Magnet CE Certificate

The Declaration of Conformity for the each individual Bruker Magnet System can be found in the NMR Magnet System manual that is delivered with the magnet.



# 4 Installation Qualification

## 4.1 Introduction

---

**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 noted 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 the site environment can change rapidly. Once the system is installed, laboratory conditions should be routinely monitored to ensure optimal performance.

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).

## 4.2 Site Planning and Preparation

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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. Bruker can review the site with the customer to ensure that it fulfills requirements.*

## 4.2.1 A Special Note about Safety

---

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 (e.g. EMF Directive 2004/40 or US -C95.6-2002, *Safety Levels with Respect to Human Exposure to Electromagnetic Fields*, 0-3 kHz, as well as current basic ICNIRP guidelines).
- It is generally accepted that stray fields are harmless below 0.5 mT (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 0.5 mT line with warning signs and to limit access to areas with more than 0.5 mT 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 5 to 10 mT. 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.**

## 4.2.2 Magnet Site Planning & Cryogenic Liquids Safety

---

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<sup>3</sup>/day (100-180 cubic feet/day) of nitrogen are evaporated, but during a quench 50-100m<sup>3</sup> (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 provides some of the key 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

Table 4.1: Table of Properties of Cryogenic Substances

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).

## 4.3 Factory Final Test

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.

### 4.3.1 Software Installation

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

## 4.3.2 Spectrometer Factory Final Test

---

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,
- Probe Test Results.

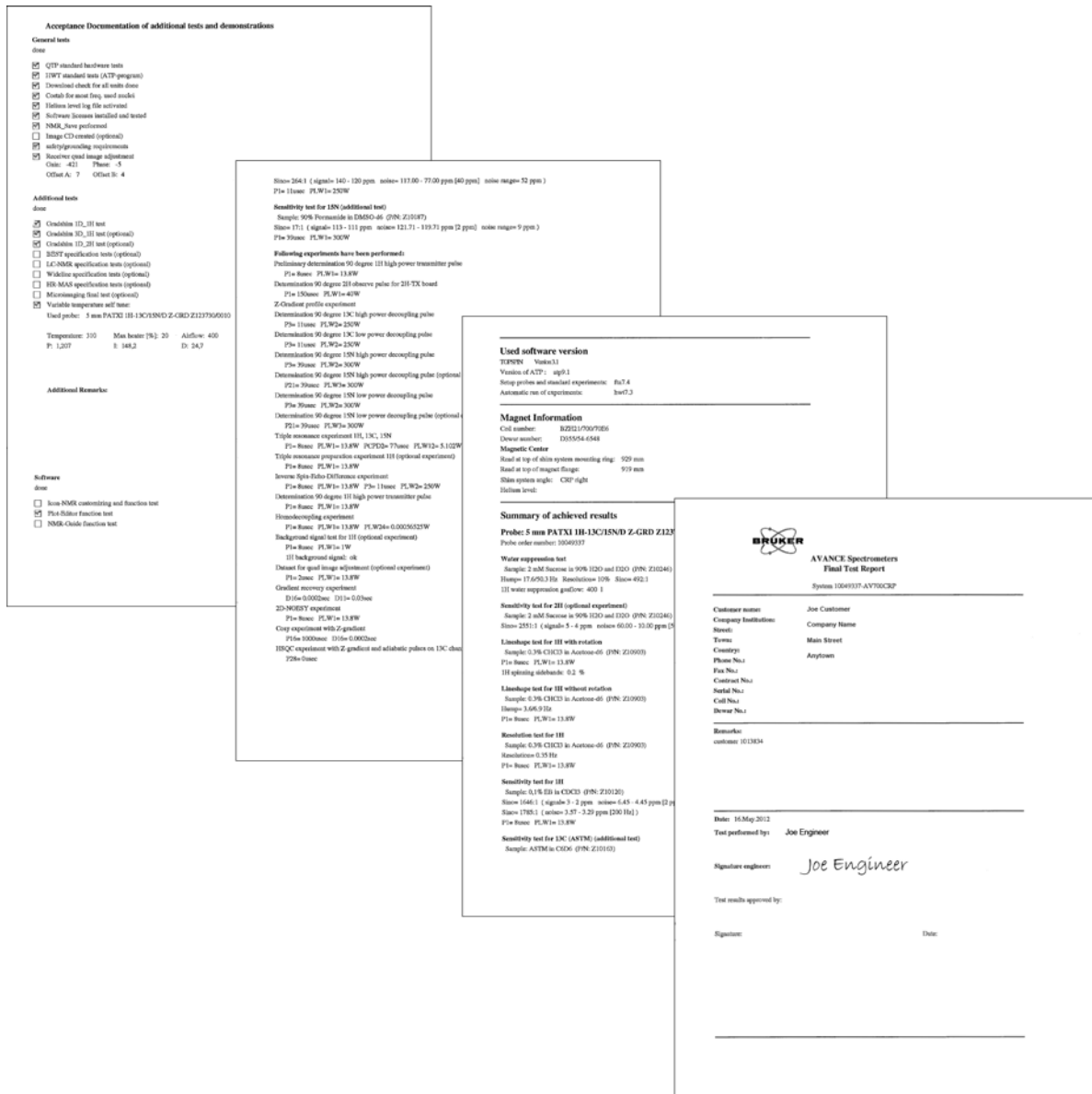


Figure 4.1: Sample Pages from a Spectrometer Final Test Report File

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 for more information.

### 4.3.3 Hardware Tests

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* [▶ 291](#).

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.

## 4.3.4 Magnet Factory Final Test

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 the figure below:

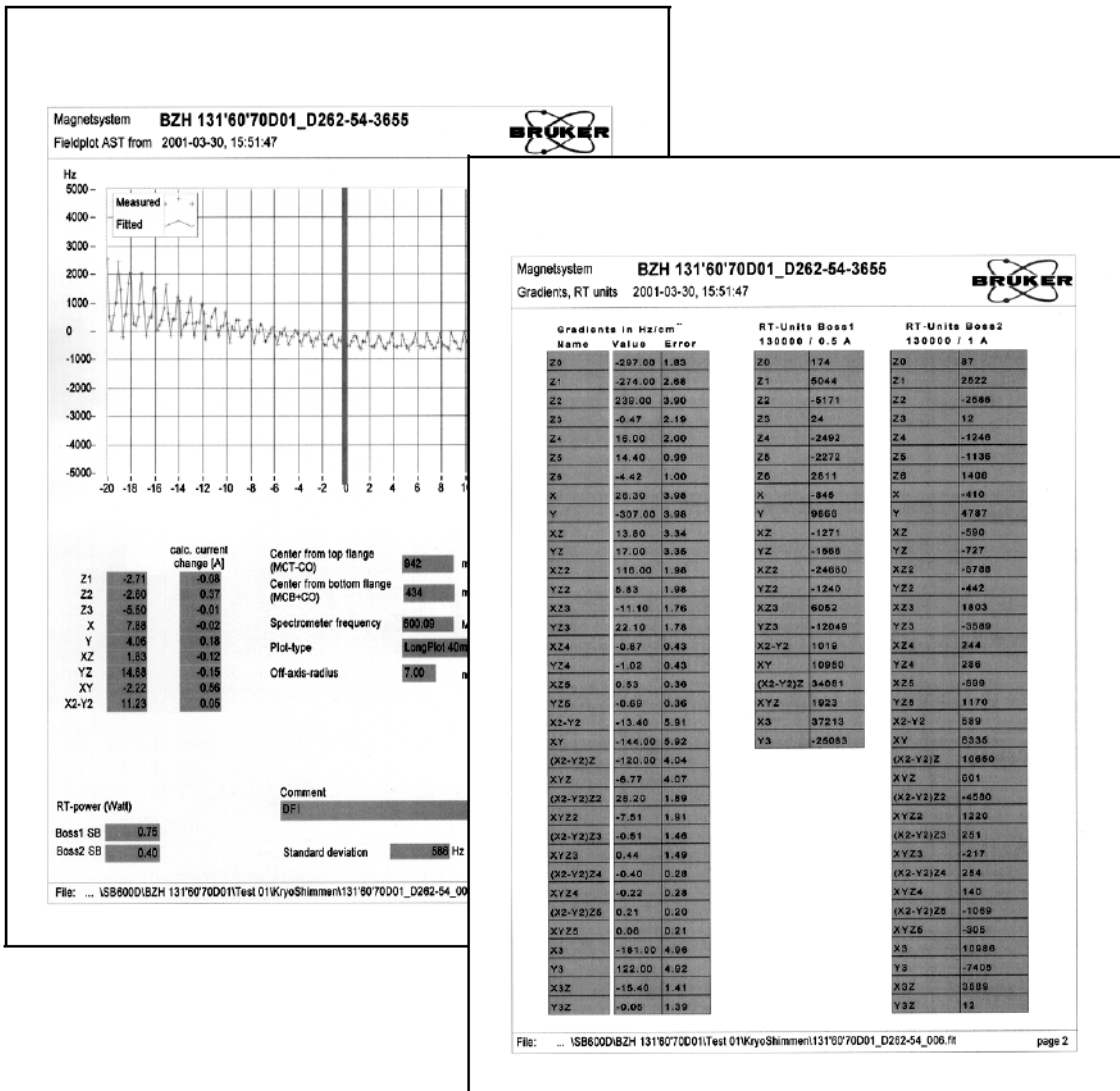


Figure 4.2: Example of a Magnet Field Plot

## 4.3.5 Factory Software Backup

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After the installation of the Windows or Linux based systems and the factory Final Test, Bruker makes a **complete backup** of the **entire installation** using Acronis backup software.

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.

## 4.4 Instrument Delivery and Installation

---

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 the figure below.
- 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.**

**Ascend 600/54 ULH Magnet System Packing List**

BZH .. 60 70H3 / D365 / 54 – 7....

Qty	Bezeichnung	Name	PN
1	Magnetsystem 600 MHz phasierbar	Magnetsystem 600 MHz load unalad	Z123788
1	Ventilkörper Vakuum Ventl KF40 Kpl	Sealing plug for vacuum valve KF40	Z56408
1	Sicherungsdeckel Vakuumventil	Security cover for vacuum valve	Z55553
1	N <sub>2</sub> Rohr (CU) ND54 D365	N <sub>2</sub> bore tube (CU) ND54 D365	Z57985
1	RT Rohr D365		
1	VPSM Zubehör und Flanschgut		
1	Blubberventil KF40 D370		
1	Deichtrenner HF Transderline		
1	RT - Flansch oben		
1	RT - Flansch unten		
2	RT - Dieffüllmische		
2	N <sub>2</sub> Kontaktflansch ND54 D3		
2	RS Reduzierflansch S8		
6	KS Lactem D3XX		
1	Aktivkohlebox set (2 Stück)		
1	Kartridgloss D3XX		
1	N <sub>2</sub> Rückschlagventil		
1	HE-Außenum Kessel		
1	He-Rückschlagventil		
1	Adapter Schlauchstoppel		
1	Adapter KF75		
1	Ladenumkopf ND10 Geperst		
1	Refillumkopf ND10 Geperst		
1	Zubehörsack		
1	Heliumrohr Resonator D30		
2	Ballfl Stab ND34		
1	N <sub>2</sub> Flowsystem D365		

Bruker BioSpin AG Magnetics Division  
 Tel: +41 (0)44 825 9111  
 Email: magnetics@bruker.ch



**Magnet System Packing List**

**ASCEND™ 600 MHz / 54 mm ULH**

<b>Part / Serial Number:</b>	Z123788 / 00.
<b>Coil / Dewar Number:</b>	BZH .. 60 70H3 / D 365/54 – 7...
<b>Ident Number:</b>	Z127017 / 010..
<b>Order Number:</b>	100.....



Dewar Number 7...

Z123788      Bruker BioSpin AG      0809      Trans 00 (rev. 18.10.2011)      1/1

Figure 4.3: Sample Magnet Packing and Shipping Container Contents Lists

## 4.5 Instrument/Hardware Setup

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.

## 4.6 Where does IQ end, and OQ begin?

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).

# 5 Operational Qualification

## 5.1 Introduction

---

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 Acceptance Test Protocol (ATP).

Before the Operational Qualification can be performed, the spectrometer, magnet, and any required software packages must be properly installed (refer to [Installation Qualification](#) [▶ 19](#)).

## 5.2 The ATP Acceptance Test

---

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](#) [▶ 30](#)).

**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

### 5.2.1 The Lineshape Test

---

This test is also commonly known as the Hump test. A <sup>1</sup>H or <sup>13</sup>C spectrum is acquired with one scan, typically on the CDCl<sub>3</sub> sample for <sup>1</sup>H and on the ASTM sample for <sup>13</sup>C. 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.

## 5.2.2 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.

## 5.2.3 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.

## 5.2.4 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 a sensitivity calculation is done for this signal, similar to the one described in the sensitivity test.

## 5.2.5 Application Specific Experiments

---

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 <sup>13</sup>C high power decoupling pulse
- Determination of 90 degree <sup>13</sup>C low power decoupling pulse
- DEPT-90
- DEPT-135
- Inverse Spin-Echo Difference
- Determination 90 degree <sup>15</sup>N high power decoupling pulse
- Determination 90 degree <sup>15</sup>N low power decoupling pulse.

## 5.2.6 Probe Specifications

---

The probes that are used have a huge impact on the results achieved from an instrument. 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.

## 5.3 The Hardware Tests (HWT)

---

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.

### 5.3.1 Requirements for Running HWT Tests

---

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  $\pm 0.5\text{C}/\text{hour}$  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.

### 5.3.2 HWT General Tests

---

**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.

### 5.3.3 HWT Modulator Tests (shaped pulses)

---

**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.

## 5.3.4 HWT Tests using Gradients

---

### 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.

## 5.4 The Acceptance Test Protocol

---

The **Acceptance Test Protocol (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.

Resolution test for 13C  
Sample: ASTM in CDCl<sub>3</sub> (PN: Z10163)  
Resolution: 0.10 Hz  
P1= 15sec; PLW1= 15W PLW2= -0.34279W

Sensitivity test for 13C (ASTM)  
Sample: ASTM in CDCl<sub>3</sub> (PN: Z10163)  
Siso= 2811.3 (signal= 140 - 120 ppm noise= 119.50 - 79.50 ppm (40 ppm) noise range= 52 ppm)  
P1= 15sec; PLW1= 60W

Sensitivity test for 13C (BR)  
Sample: 100% Et<sub>2</sub>O in CDCl<sub>3</sub> (PN: Z10153)  
Siso= 3185.1 (signal= 140 - 120 ppm noise= 121.00 - 81.00 ppm (40 ppm) noise range= 44 ppm)

Sensitivity test for 15N  
Sample: 90% Freonamide in DMSO-d<sub>6</sub> (PN: Z10187)  
Siso= 342.1 (signal= 113 - 111 ppm noise= 117.92 - 115.92 ppm (2 ppm))  
P1= 15sec; PLW1= 60W

Following experiments have been performed:  
Preliminary determination 90 degree 1H high power transmitter pulse  
P1= 12sec; PLW1= 12W  
Determination 90 degree 2D observe pulse for 2D-TX board  
P1= 150sec; PLW1= 30W  
Z Gradient profile experiment (additional test)  
Determination 90 degree 13C high power decoupling pulse  
P1= 15sec; PLW2= 60W  
Determination 90 degree 13C low power decoupling pulse  
P1= 15sec; PLW2= 1.8W  
Determination 90 degree 15N high power decoupling pulse (optional)  
P1= 15sec; PLW2= 60W  
Determination 90 degree 15N low power decoupling pulse (optional)  
P1= 20sec; PLW2= 0.87W  
Determination 90 degree 15N high power transmitter pulse (optional)  
P1= 15sec; PLW1= 60W  
Determination of high power 1H decoupling pulse  
P1= 12sec; PLW1= 12W  
Determination 90 degree 1H low power decoupling (CPG) pulse  
P1= 70sec; PLW1= 0.13W  
DEPT 90 experiment  
P1= 15sec; PLW1= 50W P1= 12sec; PLW2= 15W PCFG2  
DEPT 135 experiment  
P1= 15sec; PLW1= 60W P1= 12sec; PLW2= 15W PCFG2

Determination 90 degree 13C low power decoupling pulse  
P1= 75sec; PLW2= 3.1W  
Determination 90 degree 15N high power decoupling pulse  
P1= 30sec; PLW2= 100W  
Determination 90 degree 15N low power decoupling pulse  
P1= 30sec; PLW2= 5.07W  
Inverse Spin-Echo Difference experiment  
P1= 8sec; PLW1= 13.8W P1= 11sec; PLW2= 250W  
Determination 90 degree 1H high power transmitter pulse  
P1= 8sec; PLW1= 13.8W  
Homonuclear coupling experiment  
P1= 8sec; PLW1= 13.8W PLW2= 0.0005625W  
2D-NOESY experiment  
P1= 8sec; PLW1= 13.8W  
Cosy experiment with Z gradient  
P1= 1000sec; D1= 0.0002sec  
HSQC experiment with Z gradient and adiabatic pulses on 13C channel  
P1= 8sec

Probe: 5 mm CPMX 13C/15N-HH-Z-GRD Z130738  
Probe serial number: 1069337

Water suppression test (additional test)  
Sample: 2 mM Sucrose in 90% H<sub>2</sub>O and D<sub>2</sub>O (PN: Z10246)  
Hump= 37.3714 Hz Resolution= 19% Siso= 844.1  
1H water suppression profile= 400.1

Lineshape test for 1H with rotation  
Sample: 0.3% CHCl<sub>3</sub> in Acetone-d<sub>6</sub> (PN: Z10903)  
Hump= 4.95.9 Hz  
P1= 12sec; PLW1= 12W  
1H opening sublevel= 0.3 %

Lineshape test for 1H without rotation (additional test)  
Sample: 0.3% CHCl<sub>3</sub> in Acetone-d<sub>6</sub> (PN: Z10903)  
Hump= 6.911.2 Hz  
P1= 12sec; PLW1= 12W

Resolution test for 1H  
Sample: 0.3% CHCl<sub>3</sub> in Acetone-d<sub>6</sub> (PN: Z10903)  
Resolution= 0.49 Hz  
P1= 12sec; PLW1= 12W

Sensitivity test for 1H  
Sample: 0.1% Et<sub>2</sub>O in CDCl<sub>3</sub> (PN: Z10120)  
Siso= 4066.1 (signal= 7 - 7 ppm noise= 7.00 - 5.00 ppm (2 ppm))  
Siso= 5138.1 (signal= 6.67 - 6.39 ppm (200 Hz))  
P1= 12sec; PLW1= 140W

Lineshape test for 13C with rotation  
Sample: ASTM in CDCl<sub>3</sub> (PN: Z10163)  
Hump= 1.24.1 Hz  
P1= 15sec; PLW1= 60W PLW2= -0.34279W  
13C opening sublevel= 0.1 %

Resolution test for 1H  
Sample: 0.1% Et<sub>2</sub>O in CDCl<sub>3</sub> (PN: Z10120)  
Siso= 1195.1 (signal= 3 - 2 ppm noise= 5.32 - 3.72 ppm (2 ppm))  
Siso= 1919.1 (signal= 4.72 - 4.43 ppm (200 Hz))  
P1= 8sec; PLW1= 13.8W

Following experiments have been performed:  
Determination 90 degree 2D observe pulse for 2D-TX board  
P1= 150sec; PLW1= 40W  
Determination 90 degree 13C high power decoupling pulse  
P1= 15sec; PLW2= 250W

Use software version  
TOPSPIN Version: 3.1  
Version of ATP: apl.1  
Setup probes and standard experiments: hpl7.4  
Automatic run of experiments: hpl7.3

Magnet Information  
Coil number: 82394/700701  
Driver number: 035554-7117  
Magnetic Center  
Read at top of shim system mounting ring: 929 mm  
Read at top of magnet flange: 919 mm  
Shim system angle: csp 481 out  
Helium level:

Summary of achieved results  
Probe: 5 mm PATXI 1H-13C/15N-Z-GRD Z1212  
Probe serial number: 1069337

Water suppression test  
Sample: 2 mM Sucrose in 90% H<sub>2</sub>O and D<sub>2</sub>O (PN: Z10246)  
Hump= 26.2674 Hz Resolution= 13% Siso= 457.1  
1H water suppression profile= 400.1

Lineshape test for 1H with rotation  
Sample: 0.3% CHCl<sub>3</sub> in Acetone-d<sub>6</sub> (PN: Z10903)  
Hump= 3.65.1 Hz  
P1= 8sec; PLW1= 13.8W  
1H opening sublevel= 0.3 %

Lineshape test for 1H without rotation  
Sample: 0.3% CHCl<sub>3</sub> in Acetone-d<sub>6</sub> (PN: Z10903)  
Hump= 3.65.4 Hz  
P1= 8sec; PLW1= 13.8W

Resolution test for 1H  
Sample: 0.3% CHCl<sub>3</sub> in Acetone-d<sub>6</sub> (PN: Z10903)  
Resolution= 0.42 Hz  
P1= 8sec; PLW1= 13.8W

Sensitivity test for 1H  
Sample: 0.1% Et<sub>2</sub>O in CDCl<sub>3</sub> (PN: Z10120)  
Siso= 1195.1 (signal= 3 - 2 ppm noise= 5.32 - 3.72 ppm (2 ppm))  
Siso= 1919.1 (signal= 4.72 - 4.43 ppm (200 Hz))  
P1= 8sec; PLW1= 13.8W

ACCEPTANCE FORM  
System: 1060337-AV700013X-CPFXD

Customer name:	Joe Customer	Broker engineer:	Mr. Broker
Operator name:	Company Name	Contract No.:	12345
Company:	Main Street	Serial Number:	001
Street:	Anytown	Call number:	CL234
Code/Zip:		Driver number:	DL567
Country:		Broker phone:	
Customer fax:		Broker fax:	
Customer e-mail:		Broker e-mail:	

Delivery date: 30.05.2012      Warranty begin: 03.06.2012

The installation was completed within specifications with appropriate training regarding instrument operation. Achieved specifications and spectra are attached.

Comments:

For the manufacturer:  
Date: 02.06.2012  
Name: N. Walnut

For the customer:  
Date: 02.06.2012  
Name:

Signature: *M. Broker*      Signature: *Dr. Joe Customer*

Figure 5.1: 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 [The ATP Acceptance Test](#) [▶ 271](#) more information on these tests and experiments.

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

## 5.5 Magnet Acceptance Test

---

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 re-fill.

## 5.6 Software Backup and Computer Documentation

---

After the installation of the Windows or Linux based systems and the factory Final Test, Bruker makes a **complete backup** of the **entire installation** using Acronis backup software.

A list with a description of hardware, operating system software, and application software, etc. which was prepared at the factory before the instrument is shipped (see [Factory Software Backup](#) [▶ 25]), 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.

## 5.7 Checklist for an NMR Spectrometer Installation

The Checklist for an NMR Spectrometer Installation is provided by Bruker at the beginning of the installation, when GLP certification is required. Its purpose is to facilitate the check that all necessary documents are available for the final acceptance of the system.

### 1) Design Qualification

- Copy of specifications provided with the sales document

### 2) Installation Qualification

#### General Documents:

- Copy of the sales document.
- Shipping documents.

#### Documents from Final Test:

- QTP and ATP report from final test.
- Factory software backup (Disk Images).
- Probe test results (from production center).
- Magnet test report and magnet information in the magnet folder.
- Sample changer test protocol (e.g. SampleXpress Lite).
- Copies of CE certificates.
- Copies of the ISO certificates.

#### Documents from Site Planning:

- Copy of document from initial technical visit.
- Copy of completed site planning questionnaire.
- Copy of completed final check report with the customer upon arrival.

### 3) Operational Qualification

#### Documents from Acceptance Test:

- Magnet charging protocol/shim currents (added to the magnet folder).
- Acceptance tests (ATP) - signed by the customer/Bruker representative.
- Training in accordance with the list provided as part of ATP.

### 4) Performance Qualification 1 (if part of the contract)

- Run customer requirements specifications (includes definition of sample, sample preparation and measuring protocol).

### 5) Performance Qualification 2 (if part of the contract)

- VAQ Bruker standard visit.
- VAQ with customer samples and customer measuring protocol (see above).

Customer checklist approval: Date: \_\_\_\_\_ Name: \_\_\_\_\_

Bruker checklist approval: Date: \_\_\_\_\_ Name: \_\_\_\_\_

*Table 5.1: Checklist for an NMR Spectrometer Installation*



## 6 General Spectrometer/Magnet Maintenance

### 6.1 Introduction

---

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.

### 6.2 General Spectrometer Maintenance

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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.

#### 6.2.1 Spectrometer Service Intervals and Schedules

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##### **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.

##### **Automation**

Refer to the corresponding automation user manuals for corresponding maintenance schedules. The following is a list of user manuals for automation products available as of the publication date of this manual. Please contact your Bruker representative for other products not listed, or if the relevant documentation is lacking:

Description	Part Number
B-ACS 60/120	Z31597
B-ACS Sample Heater	Z31774
Bruker Sample Transport	Z31123
BSR Sample Rail	Z31571
MAS Rotor Test Station	Z31983
Preparation Gilson with SampleTrack	Z31695
PW5-30µl Level Converter	Z31902
NMR Case	B2926
SampleJet	Z31749
SampleMail	Z31931
SamplePro hr-MAS	Z31914
Sample Registration Unit	Z31954
SampleXpress	Z31900
SampleXpress Lite	Z31908

Table 6.1: List of Available Automation User Manuals

## 6.3 Maintenance Procedures for Cryo-Magnets

**Important:** When refilling cryogenic liquids the magnet should not be left unattended. Protective clothing, including safety gloves and eye protection should be worn 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.

### 6.3.1 Checking and Refilling Liquid Helium

The helium level should be checked weekly. These values should be recorded (see *Pertinent Magnet Information for SOP's* [▶ 44]). Additionally the helium flow can be measured by a helium flow meter or helium gas counter which is not a standard tool to a spectrometer. When the helium level does show the same level for more than week or when the boil off falls to zero for a period greater than 48 hours Bruker Service organization must be contacted. The tower tubes should be checked for the presence of ice. The procedure for checking the Helium towers and removing any ice blockage must be attempted only by 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 that is delivered with the magnet for details.

#### Guidelines for checking the Helium level

- Routinely (at least once per week) check the **helium level** with the help of the BSMS electronic measuring device.
- 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 *Pertinent Magnet Information for SOP's* [▶ 44].
- A **software tool** is also available, “helevtransfer” to automatically check and record the helium level.
- After the helium refill a check of the O-ring at the fill port is mandatory. A regular **greasing of the O-rings** at the nitrogen heat exchangers is recommended.
- Bruker's Magnet Information and Control Software (MICS) should be used to provide an overview of the helium and nitrogen level (standard only with Ascend magnets, optionally available for all other magnet systems). With USR magnets, the shield temperature etc. can be measured and displayed.

## Refilling Liquid Helium (LHe)

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

- **Safety 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 Refilling Procedures User Manual for UltraShield and Ascend NMR Magnet Systems for complete details on refilling and safety aspects when refilling!

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

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

Table 6.2: Nitrogen/Helium Refill Procedures

To obtain a copy of these manual 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.

### 6.3.2 Checking and Refilling Nitrogen

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The **nitrogen vessel** should be **checked weekly** 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 0.3 bar or less must be used!

Refilling Liquid Nitrogen

- **Safety gloves** and **eye protection** should be worn at all times.
- When refilling the LN2-dewars a **maximum pressure of 0.3 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 approx. 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 and Ascend NMR Magnet Systems (Nitrogen/Helium Refilling Procedures) for complete details on other safety aspects for refilling.

### 6.3.3 Moving an NMR Magnet System after Installation

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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!

## 6.4 Management Information and Control System

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The Magnet Information and Control System (MICS) supports the user to check the state of a magnet system and can give a reminder if a service operation is due (e.g. refill of cryogenic liquids).

## 6.4.1 Main Functions

### Overview

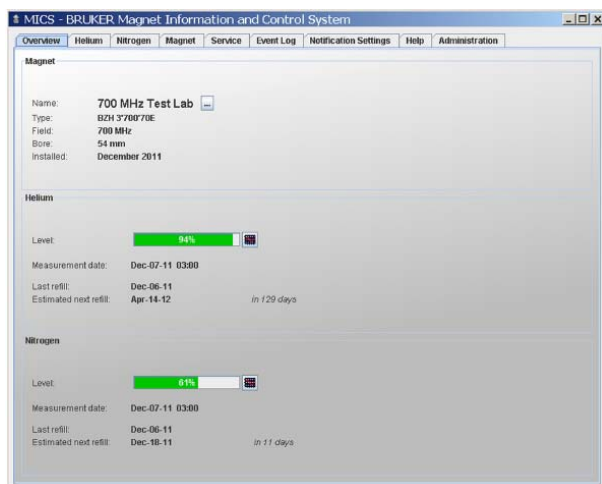


Figure 6.1: MICS Overview

The “Overview” tab displays basic magnet information and an overall status of the cryo-genic agents of the magnet system. It is possible to change the magnet name according to individual needs. This name will be used in e-mail notifications and other MICS messages.

### Helium

The “Helium” tab displays information about the current helium level, the refill history, the helium hold time and other important parameters related to the helium vessel of the magnet system.

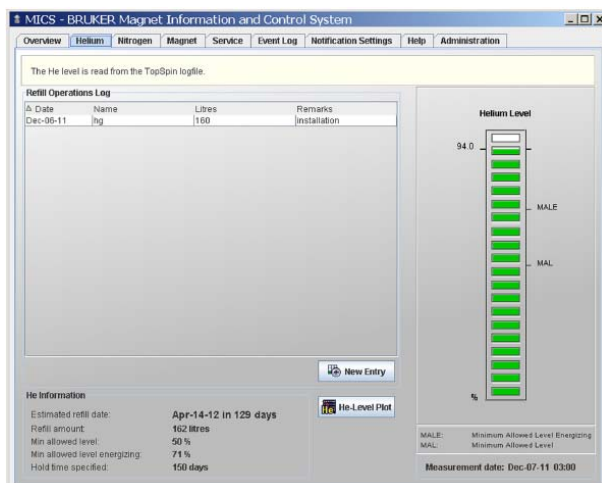


Figure 6.2: MICS Helium Tab

After helium refill, the refill information needs to be entered on the “Helium” tab. Press the button “New Entry” to access the editor and to enter the helium refill information.

Press the button “He-Level Plot” to display an updated plot of the helium level as a function of time. The next estimated refill date is calculated based on the present helium level and on previous helium levels. It is also displayed in the helium level plot.

# General Spectrometer/Magnet Maintenance

The helium level is measured automatically once a day (default 3:00 a.m.) and written in the helium log file. MICS does read always from the helium log file.

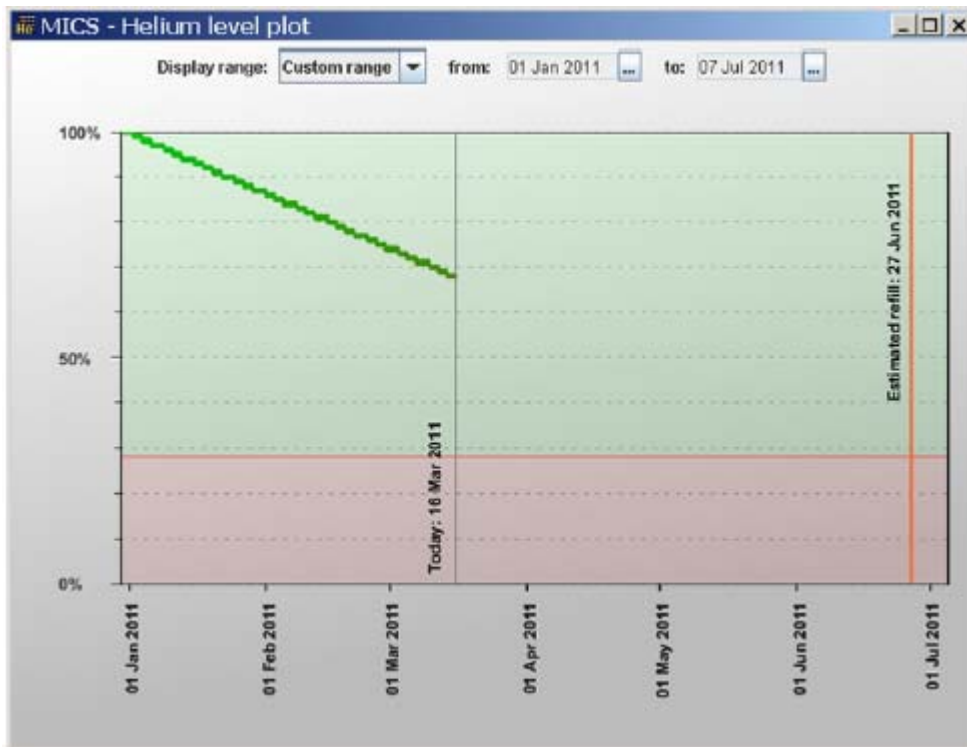


Figure 6.3: MICS Helium Level Plot

## Nitrogen

The “Nitrogen” tab displays information about the current nitrogen level (either calculated or measured), the refill history, the nitrogen hold time and the next scheduled nitrogen refill.

With Ascend magnet systems the Nitrogen Level Sensor is standard, with all other magnets it is available as an option.



The “Nitrogen” tab does not exist for nitrogen free systems and for magnet systems equipped with a Bruker Nitrogen Liquefier (BNL).

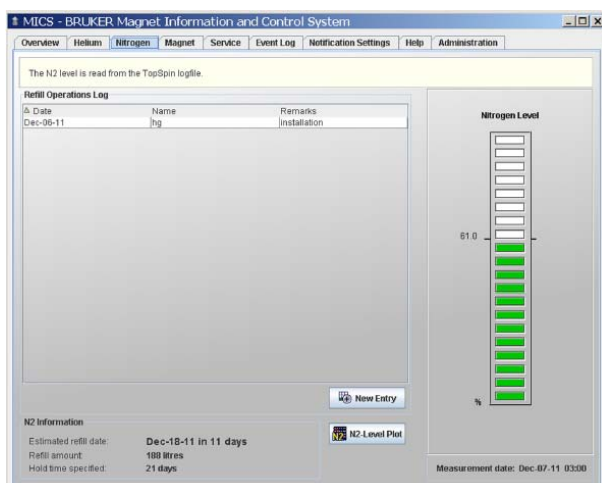


Figure 6.4: MICS Nitrogen Tab

Each time after refilling nitrogen, it is important to enter this information in MICS. Start MICS and select the “Nitrogen” tab. Update the refill table by pressing “New Entry”. This is particularly important if the magnet system is not equipped with a nitrogen level measurement device (see information below).



The nitrogen level displayed in the “Nitrogen” tab is a measured value only if the magnet system is equipped with a nitrogen level sensor. In magnet systems, that are not equipped with a nitrogen level sensor, the nitrogen level as well as the next pending refill date is a calculated value. It is based on the last refill date and on the known nitrogen loss rate of the cryostat.

For complete information on MICS refer to the MICS User Manual P/N Z33037.

## 6.5 Adjustments

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

### 6.5.1 Frequent Routine Adjustments

#### 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 <sup>1</sup>H and one for <sup>13</sup>C in a dual <sup>1</sup>H/<sup>13</sup>C probe; one for <sup>1</sup>H 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.

## 6.5.2 Long Term Adjustments

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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** for details:

Title	Part Number
Avance Beginners Guide (English)	Z31633e
Avance Beginners Guide (German)	Z31633d
Avance Beginners Guide (French)	Z31633f
Avance Beginners Guide (Spanish)	Z31633s
Avance Beginners Guide (Italian)	Z31633i
Solids Experiments Manual	H9321

Table 6.3: Part Number for Reference Manuals

## 6.6 Software Maintenance

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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* [▶ 57](#).

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 *GLP Tests* [▶ 53](#) for details.

# 7 SOP's, Data Security and More

## 7.1 Standard Operating Procedures

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**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 list:

- 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.

## 7.1.1 Level of Detail in SOP's

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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.

## 7.1.2 Pertinent Magnet Information for SOP's

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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** that is delivered with the magnet.

### Charging Record SC Magnet System

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

### Function Control Form for the Cryo Magnet System

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

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.

## 7.1.3 Emergency Plan for NMR Systems

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Due to the strong magnetic fields and presence of cryogenics when using NMR systems, it is important to define and communicate what to do 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:

- Emergency list of contacts.
- Instructions for employees and external workers.
- Instructions on Fire Department notification.
- 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 should not be accessible to the public. Make sure access is **restricted to authorized and 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, floor-taping 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 (see table below) 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 such as a 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:

Name	Bureau/Department	Travel Time	Phone
In case of problems or emergency's <b>DURING WORKING HOURS</b> advise the following personnel:			
In case of problems or emergency's <b>DURING NIGHT, WEEKEND OR HOLIDAYS</b> advise the following personnel:			
FIRE DEPARTMENT			
POLICE			
TECHNICAL SERVICES			

*Table 7.1: Example of an Emergency List of Contacts*

### Instructions for Employees and External Workers

As noted previously NMR laboratories should not be accessible to the public, thus access must be restricted to authorized and 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 magnet's sphere of influence metallic parts, tools, cleaning equipment and other objects (keys, eyeglass frames) made of metal can develop 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  $-196^{\circ}\text{C}$  and  $-269^{\circ}\text{C}$  respectively. Skin contact with these liquids can lead to **severe cold burns**; eye contact could result in **blindness** (first aid measures must be established).
- 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 **displace 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 respected and to ensure that the area around the vicinity 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 achieved 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 technical 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, fiberglass) 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 cryogenes come in contact with the eyes, rinse thoroughly 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.

### 7.1.4 Other Pertinent Information for SOP's

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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) DVD.
- 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.

## 7.2 Data Security, Integrity and Traceability

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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:

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

For most analytical work points 1 and 2 apply, so the open question is only with reference to point 3. Laboratories can decide to do signatures on paper, but they have no choice on records. The records must be kept electronically. Refer to the following link on current information regarding this requirement:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>.

## 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 identification codes and passwords as a basis for 'legally' binding signatures may have to be changed.
- New specialists, for example 'electronic archivist', may be required.

## 7.2.1 System Validation

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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 in a timely manner.

### 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.”*

## 7.2.2 Bruker TopSpin and 21 CFR 11 Compliance

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TopSpin is a software package for the control of Bruker NMR Spectrometers, for data manipulation, analysis and presentation. It can be used in direct connection with the spectrometer or as a stand alone "data station" version.

Spectrometers running TopSpin as their spectrometer software may be used in companies/institutions that are legally bound to quality regulations, such as 21 CFR Part 11. The document „**TopSpin: 21 CFR Part 11 Compliance Document**“, available from Bruker, provides a comprehensive overview of how the requirements of 21 CFR Part 11 are supported by TopSpin and to assist companies in the validation of their systems.

The document is also a part of the TopSpin documentation delivered with every TopSpin installation on a Bruker spectrometer.



# 8 Performance Qualification

## 8.1 Introduction

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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.

## 8.2 GLP Tests

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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.

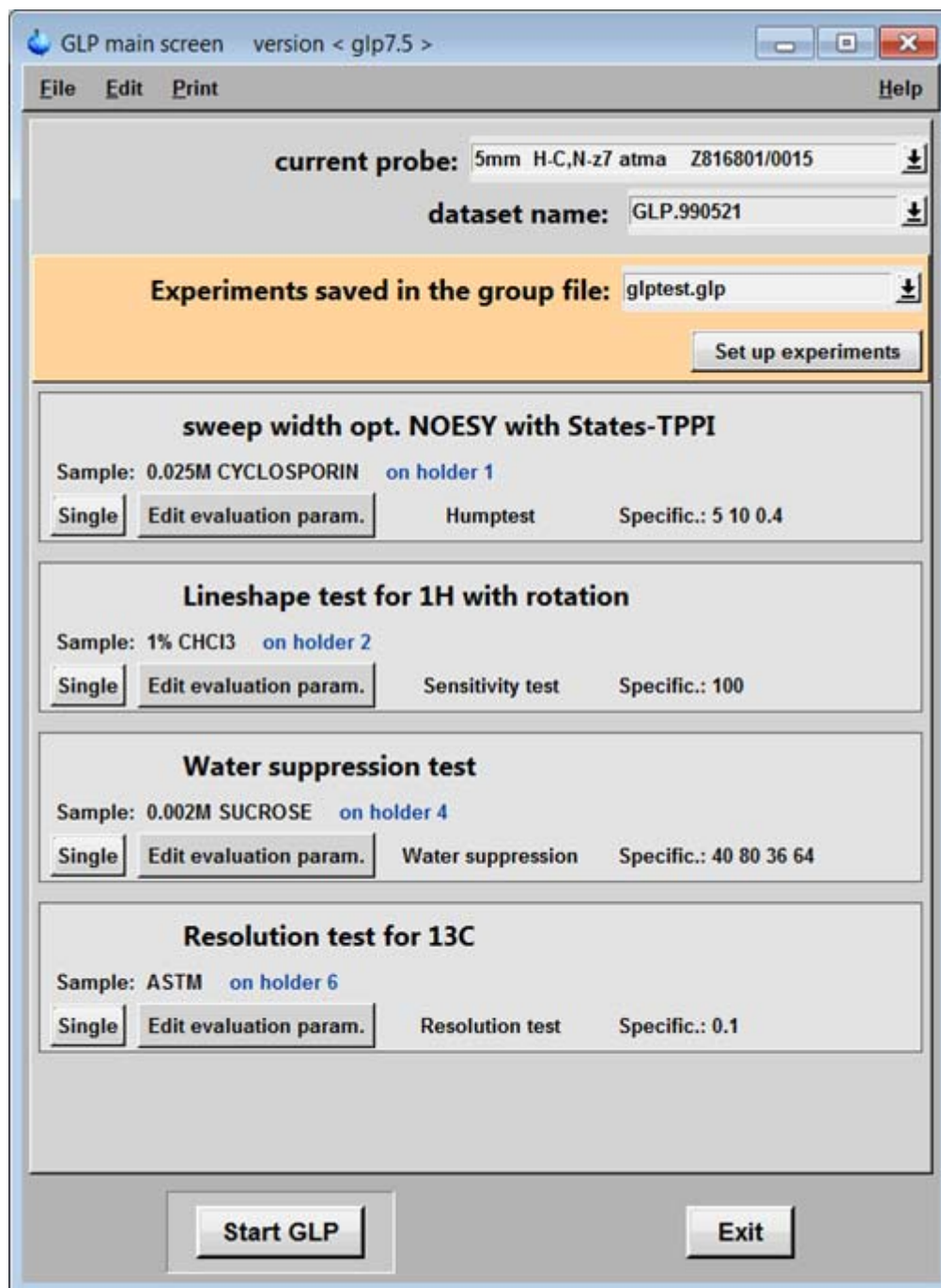


Figure 8.1: The GLP Test Software

## 8.2.1 Standard GLP Tests

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.

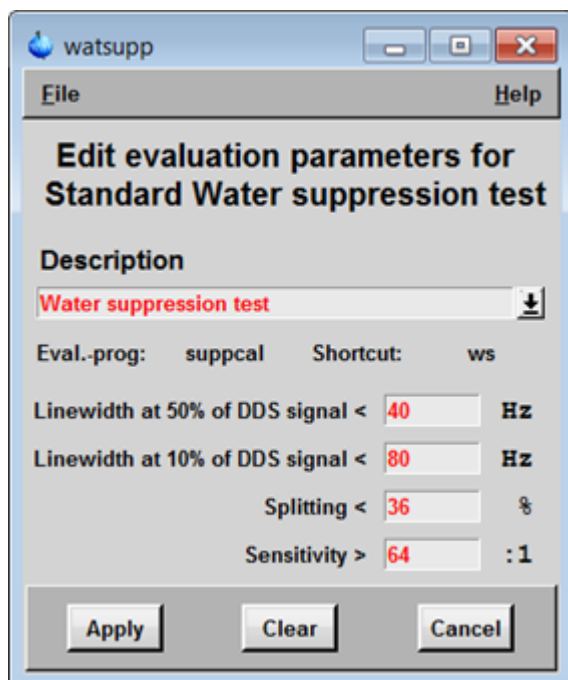


Figure 8.2: Example for Setting Specifications for GLP Water Suppression Test

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.

**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:**  
**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% CHCl<sub>3</sub>

**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: \_\_\_\_\_

Figure 8.3: Sample GLP Report

## 8.2.2 Recommended Samples for Use with GLP

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](#) [58] for a complete list of samples for use with SVT or GLP.

### 8.2.3 Values for GLP Sensitivity Test

---

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.

## 8.3 The SVT Software Package

---

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 customer's 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).

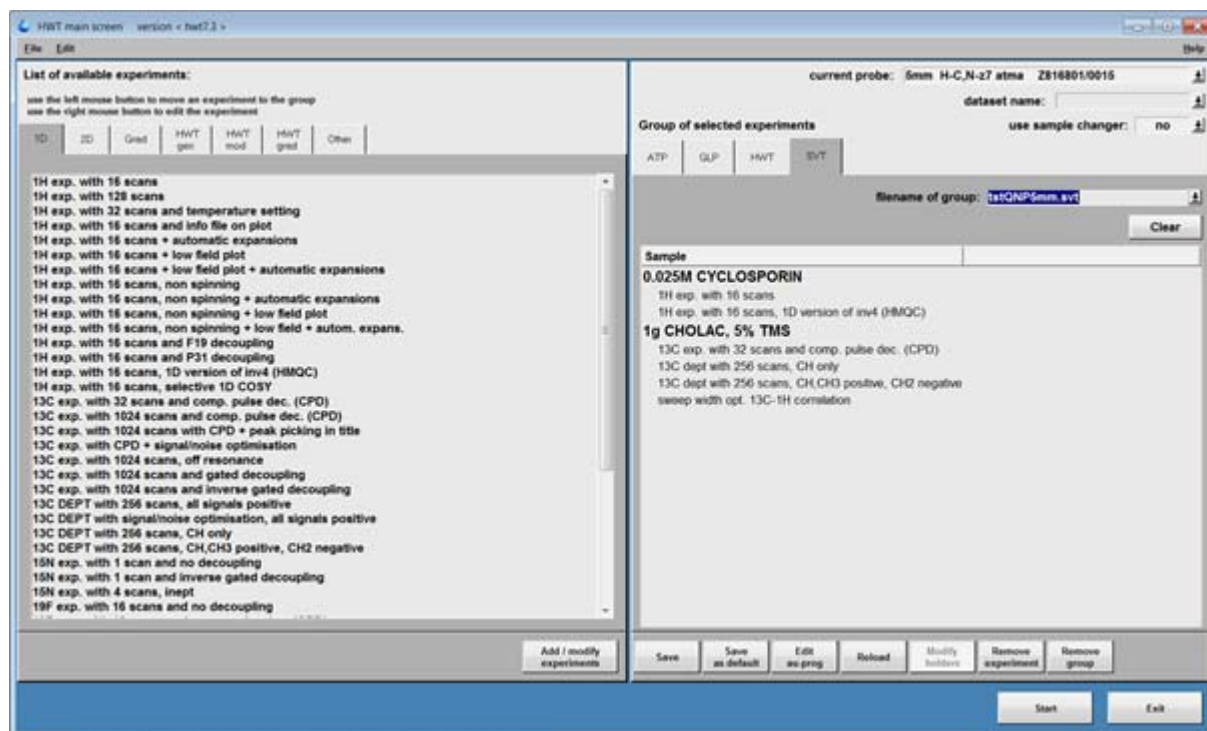


Figure 8.4: The SVT Test Software

## 8.3.1 Standard Tests Performed Using the SVT Software

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

## 8.3.2 Recommended Samples for Use with SVT

For a list of recommended samples for use in connection with the GLP and SVT tests, please contact your local Bruker representative.

## 8.4 Assure Software Package

The Assure software package has two automation modules: Assure – *System Suitability Test* (SST) and a screening module named Assure - *Raw Material Screening* (RMS). The SST module is designed to monitor and maintain instrument performance. The RMS module assists in the quality control of materials, ingredients and components used in a wide range of products.

Assure-SST and Assure-RMS were designed to be used in a production or research facility. As a result, many of the features incorporated allow use of this software by non-NMR spectroscopists and on NMR spectrometers in GLP environments.

## 8.4.1 Assure – System Suitability Test (SST)

---

### Summary of Features

- Automated System Suitability Test includes acquisition and analysis of NMR standards <sup>1</sup>H lineshape, <sup>1</sup>H sensitivity, <sup>13</sup>C sensitivity, <sup>19</sup>F sensitivity, <sup>31</sup>P sensitivity, and temperature calibration.
- To reduce routine maintenance of the spectrometer shims, shim sets from successful <sup>1</sup>H lineshape experiments are stored and recalled as a starting shim set for queued raw material samples.
- Automated 'Stop' criteria to halt acquisition upon specification failure.
- Automated PDF report generation of SST results.

### Software Design

The Assure-SST module was designed to work as a means of monitoring instrument performance on a regular basis. This is achieved via IconNMR which monitors the performance and temperature of the system according to an interval selected by the user. Assure-SST module can work either in a standalone mode where the user can use the normal IconNMR submission interface or in parallel with the Assure-RMS module. If Assure-SST determines the system to be out of specifications then general sample submissions through IconNMR or Assure-RMS will halt until all specifications are achieved.

## 8.4.2 Assure - Raw Material Screening (RMS)

---

### Summary of Features

- Utilization of Assure-SST for instrument performance check.
- Automated data acquisition using IconNMR using user defined parameter sets.
- Automated qualitative analysis of spectra using a supplied or generated NMR spectral database.
- Handling of calculations requiring multiple spectra averages.
- Absolute or Relative concentration determination.
- Quantification on supported nuclei (<sup>1</sup>H, <sup>2</sup>H, <sup>13</sup>C, <sup>19</sup>F, <sup>31</sup>P).
- Automated report generation including a summary Quality Control Report (QCReport.pdf) which reports a 'pass' or 'fail' report (or numerical) and a detailed Expert Report (ExpertReport.pdf) which outlines the total analysis.
- Flexible report generation.
- GLP compatible.
- Customizable security features.

## Software Design

The Assure software utilizes four software components: (1) pre-existing components of TopSpin, (2) new features in IconNMR, (3) NMR spectral databases (SBASE), and (4) the Assure software as summarized in the figure below. Successful completion of a System Suitability Test releases IconNMR for general sample submission. Submitted raw materials are collected with the acquisition and processing functions of TopSpin. The raw material spectrum (or spectra) is then passed to the Assure-RMS software for evaluation and generation of reports.



Figure 8.5: Assure-RMS Software Package Overview Diagram

## Workflow

The system is designed for sample submission by a novice user. The user should be able to prepare a sample and submit it via the Assure-RMS IconNMR interface. The figure below shows the progression of sample.

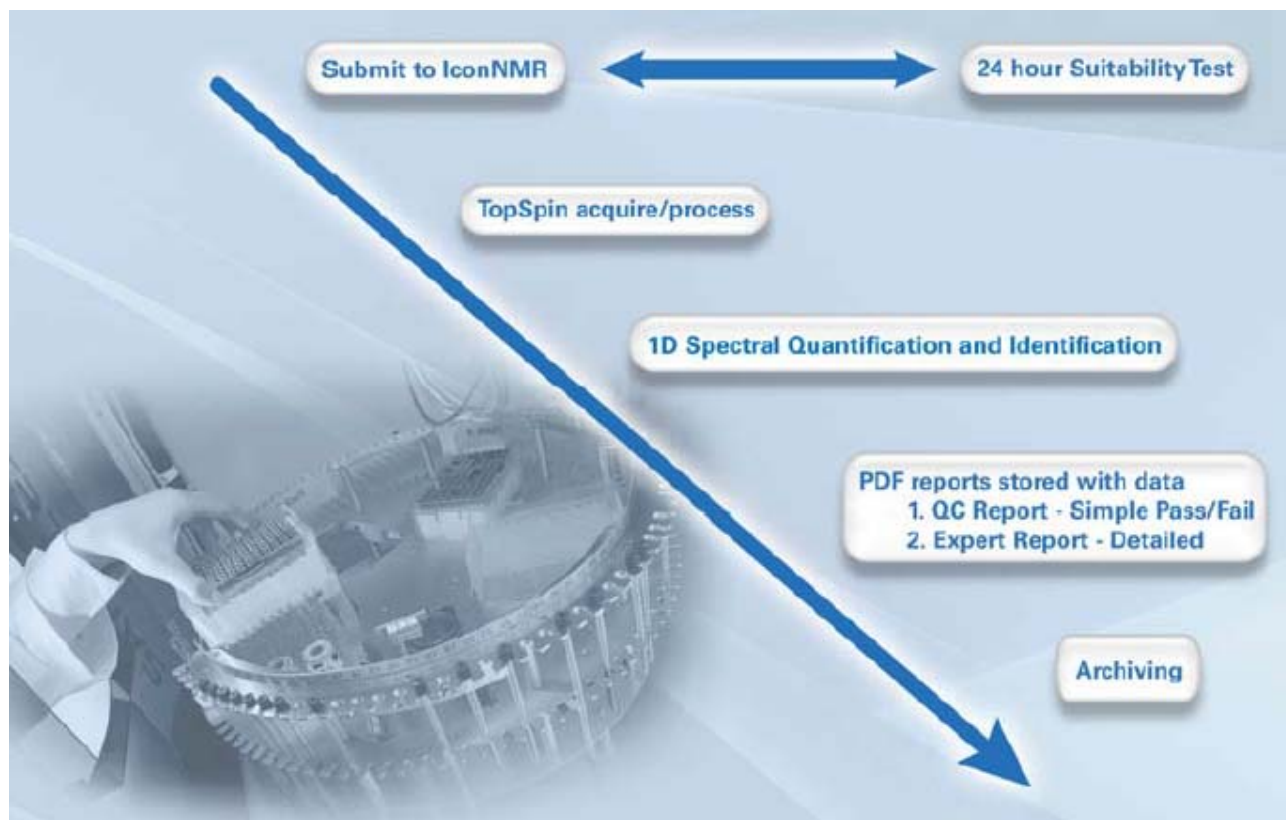


Figure 8.6: Workflow of Assure-RMS Software Diagram

## GLP Requirement

GLP software package (see [GLP Tests](#) / [5.31](#)) is not required to be installed for the Assure software. Additional GLP configuration of the report layout can be done. Instructions can be found in the GLP manual or by typing 'help glp' in the TopSpin command line.

Although components of the GLP package are used, the default installation and a successful System Suitability Test is not a de facto GLP validation. In order for the instrument to be brought to full GLP compliance, contact Bruker to arrange for instrument validation by a certified GLP engineer.

### 8.4.3 Assure - Report Examples

#### Example Log File from System Suitability Tests

```

Filename: SystemTest_2010-01-7-15-16-36_log.txt
### System Suitability Report ###
###
### RESULT: PASSED ###
###
#
# Output of System Tests Follows: #
GLP procedure: This is GLP
Experiment: Data Set: SystemTest_2010-01-07-15-16-36 1 1
C:\Bruker\TOPSPIN_Screener
    
```

Specification result of humpcal: ok

Line width at 0.55% of signal height = 5.0 Hz (< 20Hz) ok

Line width at 0.11% of signal height = 10.8 Hz (< 30Hz) ok

Half width = 0.54 Hz (< 5Hz) ok

#

GLP procedure: This is GLP

Experiment: Data set: SystemTest\_2010-01-07-15-16-36 2 1

C:\Bruker\TOPSPIN\_Screener Specification result of sinocal: ok

Best sino value found = 443.8 :1 (> 20:1) ok

#

GLP procedure: This is GLP

Experiment: Data set: SystemTest\_2010-01-07-15-16-36 4

C:\Bruker\TOPSPIN\_Screener

Specification result of sinocal: ok

Best sino value found = 25.8 :1 (> 20:1) ok

#

Data set: SystemTest\_2010-01-07-15-16-36 3 C:\Bruker\TOPSPIN\_Screener

Experiment: Experiment: Temperature test for Methanol-d4 99.8% atom%d

Specification result of temperature: ok

Actual temperature determined to be 300 on 2010-01-07-15-30-19 during system suitability test

## Example Results of a System Suitability Test

### Assure-System Suitability Test



**Company/Institution:** Bruker BioSpin  
**System ID:** 12345678  
**Report Filename:** C:/Users/nmrsu/.topspin-spect/SystemSuitabilityTest/SST\_2011-01-01-12-00-00\_log.txt  
**Software Version:** IconNMR Version 4.6.2 Build: 38.9  
**Completion Time:** 2011-07-28-01-06-34

**PASS**

#### Summary of Achieved Specifications

##### **<sup>1</sup>H Lineshape**

Specification result of humpcal:	ok
Linewidth at 0.55% of signal height:	3.3 Hz
Linewidth at 0.11% of signal height:	7.4 Hz
Halfwidth	0.23 Hz
Experiment Directory:	C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2011-01-01-12-00-00/1/pdata/1/1r

##### **<sup>1</sup>H Sensitivity**

Specification result of sinocal:	ok
Best sino value found:	275.7 :1
Experiment Directory:	C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2011-01-01-12-00-00/2/pdata/1/1r

##### **<sup>13</sup>C Sensitivity**

Specification result of sinocal:	ok
Best sino value found:	232.2 :1
Experiment Directory:	C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2011-01-01-12-00-00/3/pdata/1/1r

##### **<sup>19</sup>F Sensitivity**

Specification result of sinocal:	ok
Best sino value found:	528.3 :1
Experiment Directory:	C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2011-01-01-12-00-00/4/pdata/1/1r

##### **<sup>31</sup>P Sensitivity**

Specification result of sinocal:	ok
Best sino value found:	111.3 :1
Experiment Directory:	C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2011-01-01-12-00-00/5/pdata/1/1r

##### **Temperature Test (99.8% Methanol-d4)**

Specification result of temperature:	ok
Actual temperature determined:	298.00 K
Experiment Directory:	C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2011-01-01-12-00-00/6/pdata/1/1r

Figure 8.7: Example Results of a System Suitability Test

## Example of a QC Report

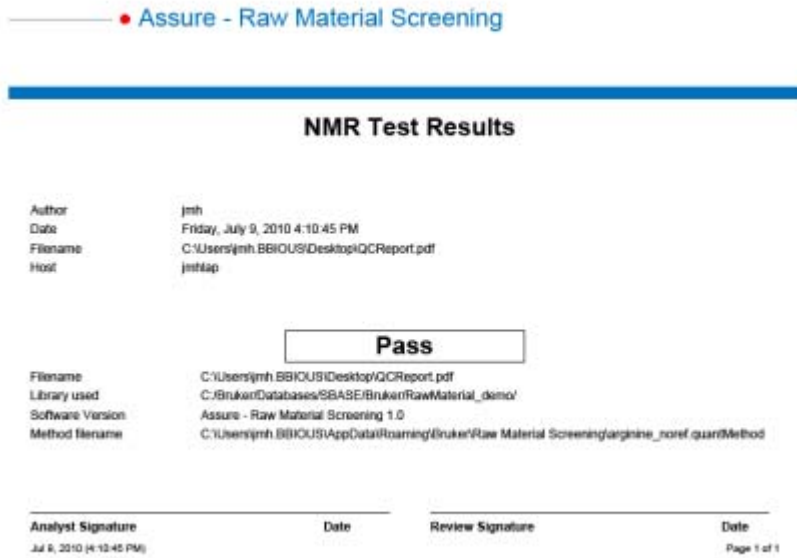


Figure 8.8: Example of a QC Report

# 9 Summary of General Instrument Validation Tools

## 9.1 ATP

---

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.

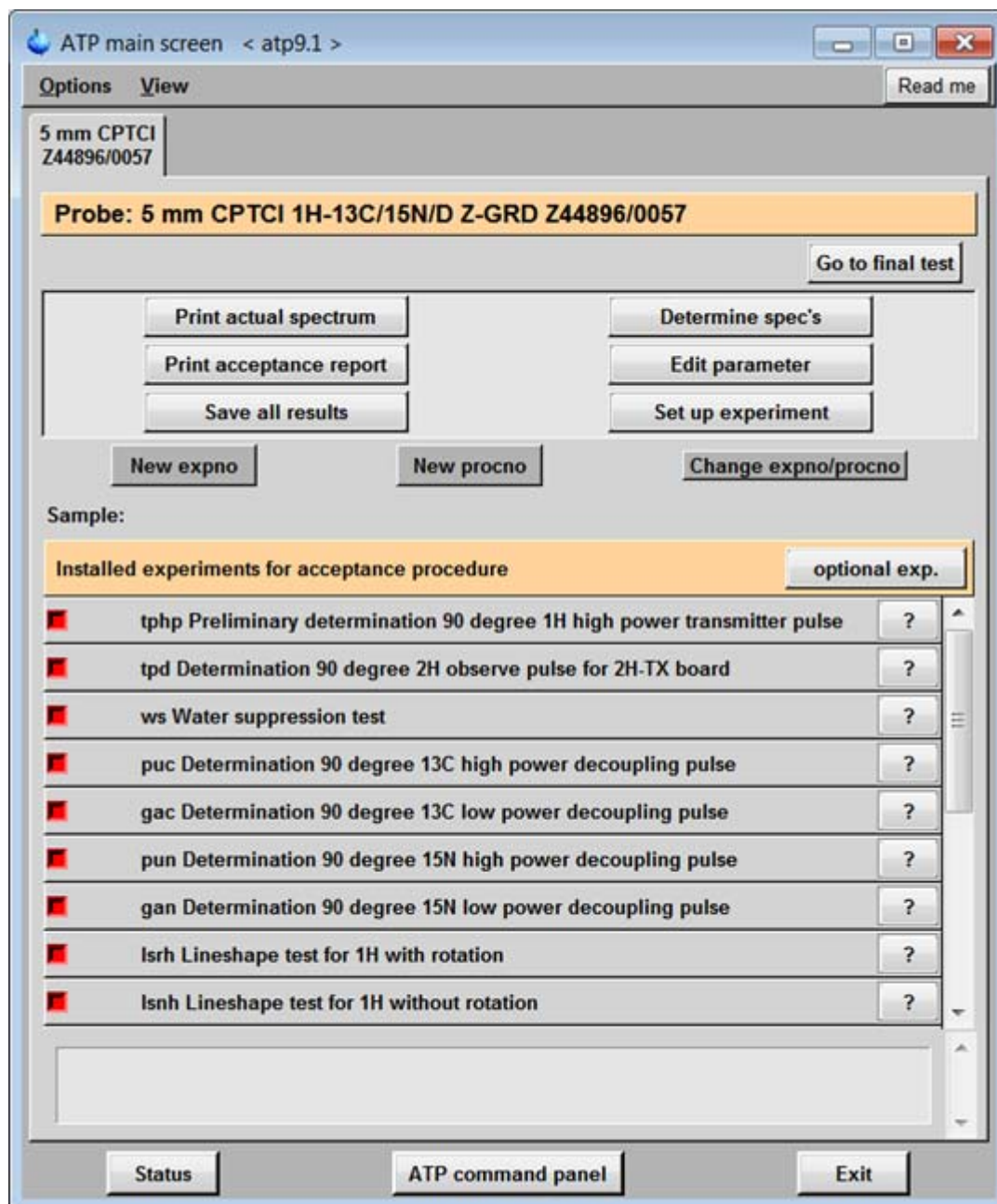


Figure 9.1: The ATP Software Package

## 9.2 The HWT Software Package

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.

## 9.3 The SVT Software Package

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 customer's 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).

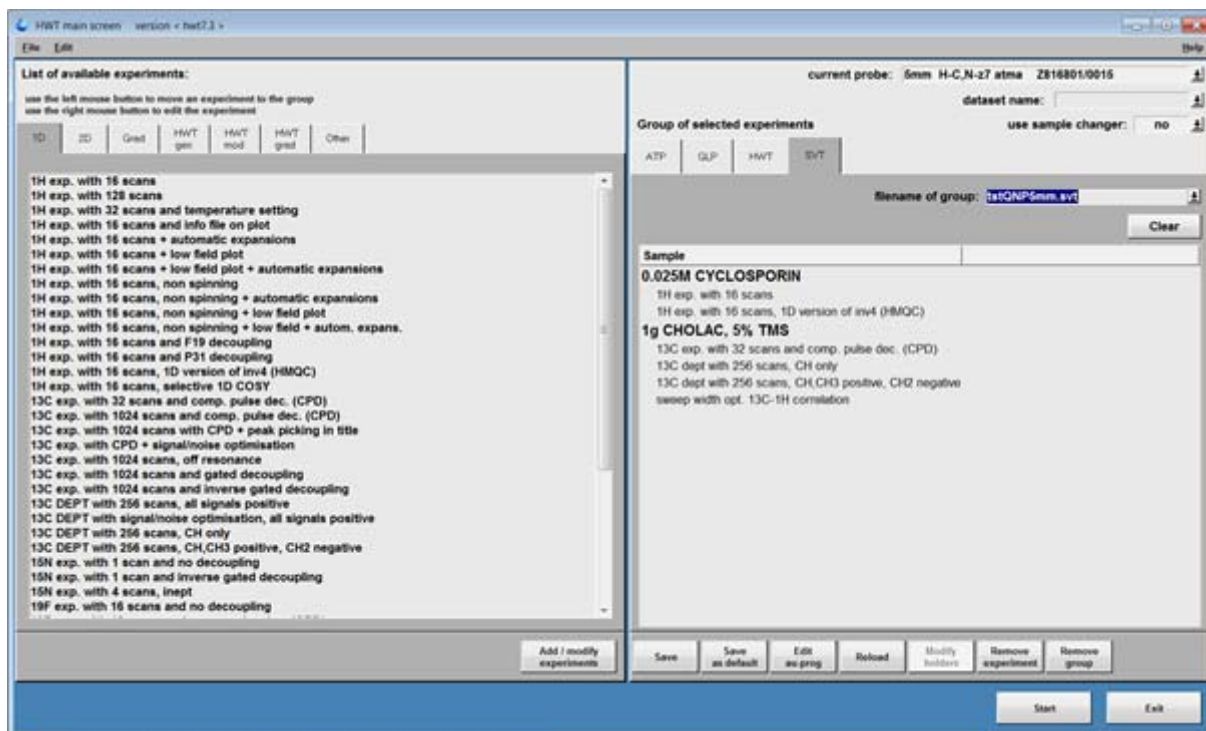


Figure 9.2: The SVT Test Software

## 9.4 The GLP Software Package

---

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.

# Summary of General Instrument Validation Tools

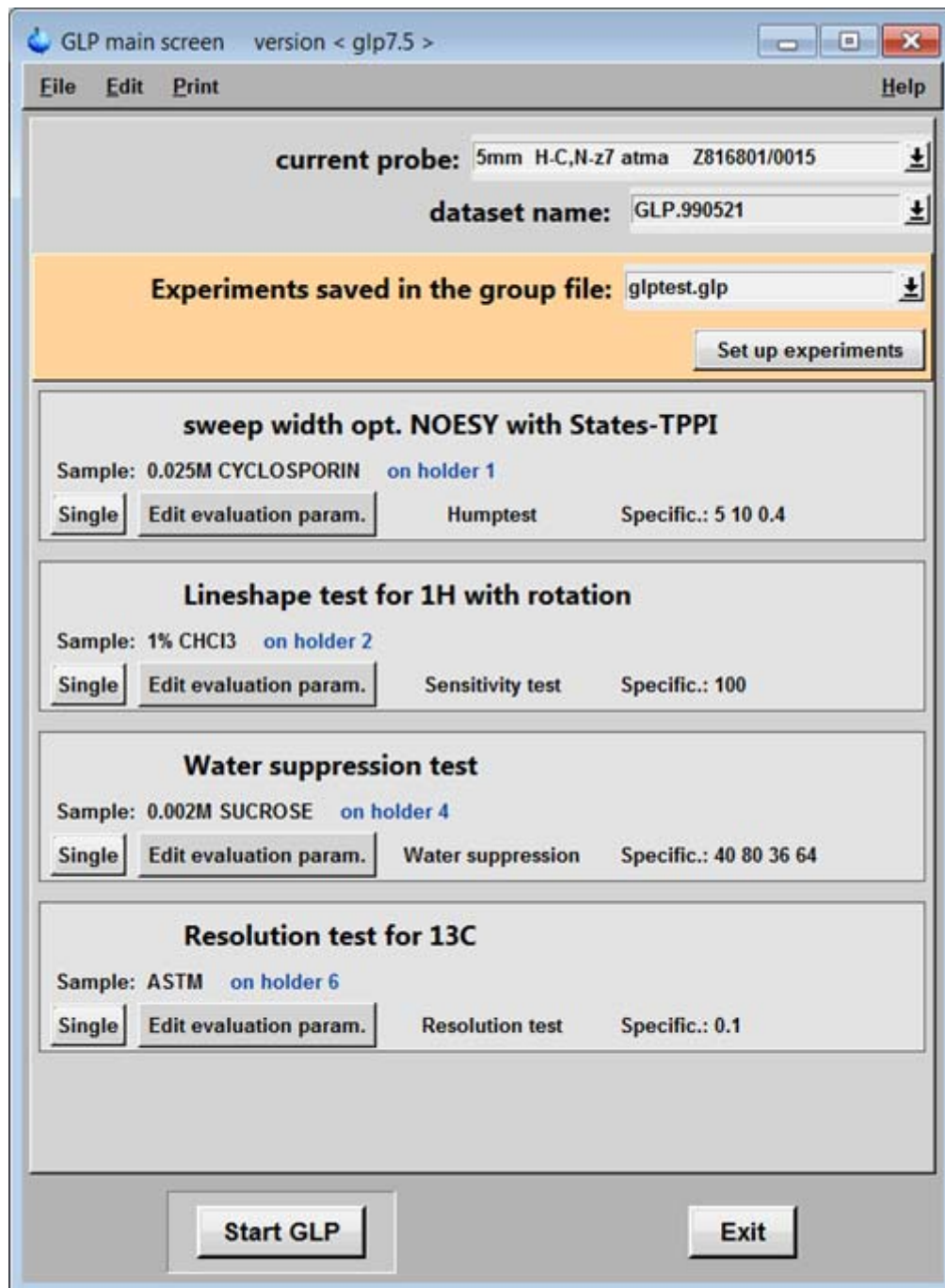


Figure 9.3: The GLP Test Software

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.

## 9.5 Assure – System Suitability Test (SST)

---

### Summary of Features

- Automated System Suitability Test includes acquisition and analysis of NMR standards 1H lineshape, 1H sensitivity, 13C sensitivity, 19F sensitivity, 31P sensitivity, and temperature calibration.
- To reduce routine maintenance of the spectrometer shims, shim sets from successful 1H lineshape experiments are stored and recalled as a starting shim set for queued raw material samples.
- Automated 'Stop' criteria to halt acquisition upon specification failure.
- Automated PDF report generation of SST results.

### Software Design

The Assure-SST module was designed to work as a means of monitoring instrument performance on a regular basis. This is achieved via IconNMR which monitors the performance and temperature of the system according to an interval selected by the user. Assure-SST module can work either in a standalone mode where the user can use the normal IconNMR submission interface or in parallel with the Assure-RMS module. If Assure-SST determines the system to be out of specifications then general sample submissions through IconNMR or Assure-RMS will halt until all specifications are achieved.

## 9.6 Standard Magnet Validation Tests

---

### 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.

See also *Management Information and Control System* ▶ [38](#).

# 10 Contact

**Manufacturer:**

Bruker BioSpin NMR  
Silberstreifen  
D-76287 Rheinstetten  
Germany  
Phone: +49 721-5161-6155  
<http://www.bruker-biospin.com>

**NMR Hotlines**

Contact our NMR service centers.

Bruker BioSpin NMR provide dedicated hotlines and service centers, so that our specialists can respond as quickly as possible to all your service requests, applications questions, software or technical needs.

Please select the NMR service center or hotline you wish to contact from our list available at:

[http://www.bruker-biospin.com/hotlines\\_nmr.html](http://www.bruker-biospin.com/hotlines_nmr.html)



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# Glossary

## **BASH**

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Bruker Advanced Service Handbook

## **closed system**

---

Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

## **digital signature**

---

Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

## **electronic record**

---

Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

## **electronic signature**

---

Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

## **handwritten signature**

---

Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

## **open system**

---

Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.



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