GxP Requirements

A Bruker BioSpin guide related to an environment in regulated markets with NMR floor-standing systems

User Guide
Version 006

Innovation with Integrity

NMR

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1 Introduction

Many companies and laboratories in regulated markets, such as chemical, pharmaceutical, biopharmaceutical, biotech, cosmetics, forensics and others must comply with regulatory requirements or are planning to organize their activities per international quality management standards and good practices guidelines.

One of the best known GxP standards is GLP, or Good Laboratory Practice, but there are several other Good Practice procedures defined today, these are often referred to as GxP regulations, requirements, or processes. Since Bruker's NMR spectrometers are often installed in laboratory environments, this manual will primarily refer to GLP, even though all topics also apply to GMP or other GxP processes.

In the U.S.A. GxP guiding 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 (see FDA: "21 CFR part 58" GLP regulation) that are submitted to the FDA in support of an application for a research or marketing permit.

FDA regulations have also been adopted by the Council of the OECD countries and documents on their website at *www.oecd.org* are updated on a regular basis. They advise the corresponding health ministers to adopt principles for Good Laboratory Practice.

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.

1.1 Who is Responsible for GLP?

Today, everyone is concerned with GLP, but it is the task of the Quality Assurance (QA) to decide on GLP/GMP requirements for specific circumstances, and it is mostly the task of the laboratory manager (LM) to ensure compliance with such requirements. These requirements can include general policies and Standard Operating Procedures (SOP's) concerning a whole range of activities and areas including the following:

- Organizational structures.
- Laboratory environment sample handling.
- Chemical handling.
- Instrumentation and test systems.
- Computer: Ensuring that computerized systems are suitable for their intended purposes.
- 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:

- Calibration
- Maintenance
- Check-ups

1.2 Bruker's Role in GLP Qualification

The FDA defines validation that is used in the Life Sciences industry as:

„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.

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

- Design Qualification (*DQ*)
- Installation Qualification (*IQ*)
- Operational Qualification (*OQ*)
- Performance Qualification (*PQ*)

All systems, including purchased systems, need to be tested and evaluated by the regulated user. It is the regulated user's responsibility to decide on the depth and breadth of the testing efforts.

Bruker can provide assistance in all four steps of instrument validation. A list of documents that is required to verify the qualification steps outlined above is provided in the section *Checklist for an NMR Spectrometer Installation [▷ 25]*.

Bruker spectroscopy systems have built-in **tools** to help comply with GLP regulations, meet inspectors' standards and overall meet the challenge of GLP qualification.

This manual is intended to address cryogenically cooled magnet systems.

1.3 General Instrument Validation Tools

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.

1.3.1 Installation (IQ) and Operational (OQ) Qualification Protocol

Bruker provides two IQ/OQ protocols (P/N H165691 for AVANCE III HD and P/N H168890 for AVANCE NEO) outlining all the steps of the installation and operational qualification procedure during the course of a spectrometer installation. This protocol is completed by the installing Bruker engineer together with customer representatives. All installation steps are validated with the appropriate documents and signed by the named responsible persons.

An additional computer system validation protocol (P/N H166444) is provided for **21 CFR Part 11** compliance.

1.3.2 NMRPT

The **NMR P**roduct **T**est (NMRPT) 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 NMRPT package has been designed by Bruker for Bruker Test and Service Engineers to standardize the final test and acceptance procedures including the probe tests and documentation.

The NMRPT manual (P/N ZUEP0102) describes the test procedure and contains a list of all possible experiments.

1.3.3 Assure-SST Software

The **Assure-S**ystem **S**uitability **T**est (Assure-SST) software performs tests which ensure continual and routine control of the spectrometer performance. This software is primarily used by specially trained laboratory personnel to assist with **Performance Qualification** (PQ).

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

This is particularly useful for, but not limited to, spectrometers installed in a GLP regulated environment.

The tests must be adapted to:

- Instrument configuration
- Laboratory environment
- Laboratory task

It is the task of each Laboratory Manager (LM) to decide and define the suitable AssureSST tests for PQ. Bruker can assist with the definition of tests for the individual spectrometer configuration and the specifications that should be achieved on a long-term basis.

Introduction

2 Design Qualification

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 (instrument) is purchased, functional and operational specifications should be set during the DQ to 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, sufficient time and resources should be invested in the DQ phase.

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 since 1994 with the attainment of the ISO 9001 certification and later-on integration of ISO 13485 for its Quality Management System.

All Bruker AVANCE spectrometers and magnet systems fulfill all needed applicable safety requirements and comply with the European Directives (CE marking) and with international safety standards (CB scheme or *NRTL*).

Thus, Bruker can provide the best evidence and support to Laboratory Managers to meet their requests for Design Qualification. This chapter provides 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.

2.1 Basic Steps for Design Qualification

The recommended steps for DQ include:

- 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**.

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.

The scope of the Design Qualification must include (but is not limited to) verification that:

- The design will achieve the User Requirements Specification **URS** (**validation**).
- The design conforms with cGMP (see FDA: 21 CFR part 211), and where software is used, conforms to the Life Cycle Model requested in the verification process and is e.g. detailed in the good automated manufacturing practice for GAMP4 level (software life cycle).

  Note: GAMP guidelines are published via ISPE: *http://www.ispe.org/gamp-resources*.
- The design complies with the Validation Plan/VP (**validation**).
- The required utility services are available and validated (**validation**).
- All the required support documentation is specified (**documentation**).
- The system can be calibrated **(operation/performance**).
- The system can be maintained (**service**).
- Operation staff training requirements are defined (**training**).
- The system will operate in a manner safe to both product and staff (**safety**).
- The system conforms to all applicable national standards and guidelines (**regulatory**).

2.2 Instrument Specifications

Any validation process should start with setting and documenting the specifications for user requirements (URS), 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 specification sheets.

2.2.1 Magnet Specifications

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, or go to *www.bruker.com*.

2.2.2 Magnet Documentation

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 manuals.

Cryogen Refill Manuals

Cryogen refill manuals are available in five languages on the **B**ruker **A**dvanced **S**ystem **H**andbook (*BASH*) DVD, or from Bruker.

In addition, Bruker provides movies (see *www.bruker.com*) showing in detail the correct refilling procedures both for liquid nitrogen (LN_2) as well as for liquid helium (LHe).

2.3 Product Development and Evaluation

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 to ISO 9001 certified process requirements and through Bruker's internal quality systems.

All source code and documentation for customer-released software and hardware are archived with all necessary version control information at a Bruker BioSpin R&D facility.

Documentation for error reports and error report management are retained at the Bruker production centers.

2.3.1 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 is linked via a Production Planning System (PPS) 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 PPS.

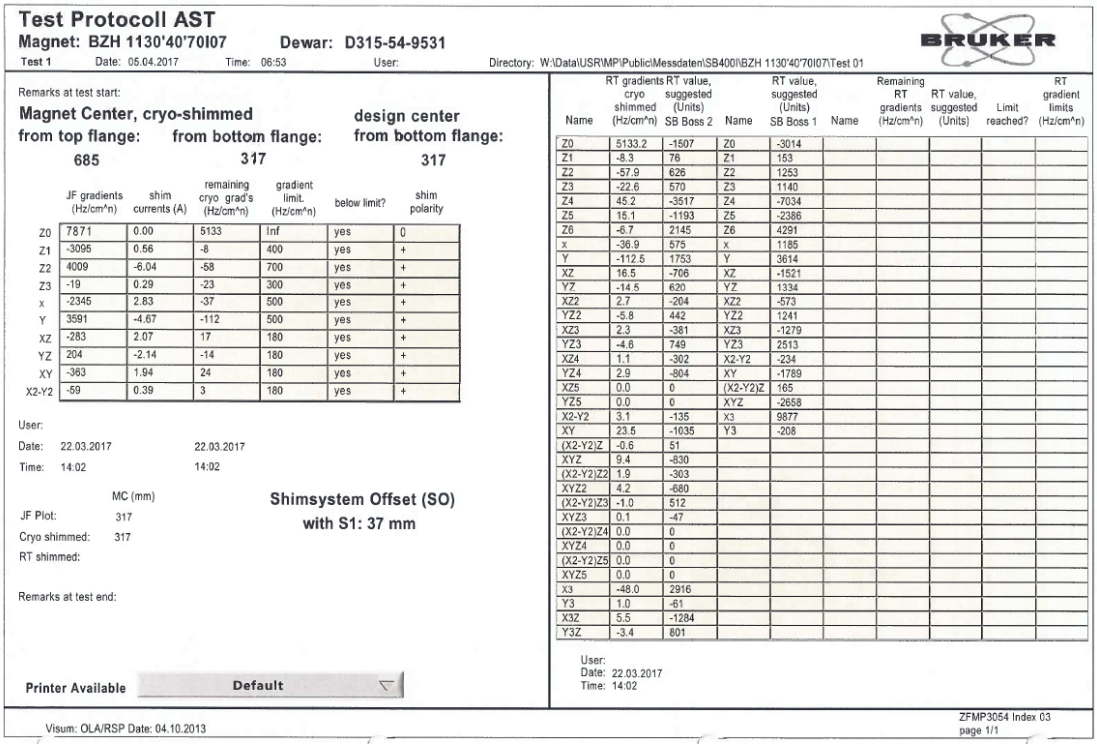
The document parts lists are created and maintained in our Cryo Construction Department. All documents dealing with the manufacturing and testing of a magnet system are mentioned in the Operations Plan (OP) along with the appropriate work procedures.

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, 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 Bruker's Magnet Test Department.

One example page from such a report is given below:



Test Protocoll AST

Magnet: BZH 1130'40'70I07 **Dewar: D315-54-9531**

Test 1 Date: 05.04.2017 Time: 06:53 User: Directory: W:\Data\USR\MP\Public\Messdaten\SB400\BZH 1130'40'70I07\Test 01

Remarks at test start:

Magnet Center, cryo-shimmed

from top flange: 685 **from bottom flange: 317** **design center from bottom flange: 317**

	JF gradients (Hz/cm^n)	shim currents (A)	remaining cryo grad's (Hz/cm^n)	gradient limit. (Hz/cm^n)	below limit?	shim polarity
Z0	7871	0.00	5133	Inf	yes	0
Z1	-3095	0.56	-8	400	yes	+
Z2	4009	-6.04	-58	700	yes	+
Z3	-19	0.29	-23	300	yes	+
X	-2345	2.83	-37	500	yes	+
Y	3591	-4.67	-112	500	yes	+
XZ	-283	2.07	17	180	yes	+
YZ	204	-2.14	-14	180	yes	+
XY	-363	1.94	24	180	yes	+
X2-Y2	-59	0.39	3	180	yes	+

User:

Date: 22.03.2017 22.03.2017

Time: 14:02 14:02

MC (mm)

JF Plot: 317

Cryo shimmed: 317

RT shimmed:

Shimsystem Offset (SO) with S1: 37 mm

Remarks at test end:

Printer Available Default

Name	RT gradients cryo shimmed (Hz/cm^n)	RT value, suggested (Units) SB Boss 2	Name	RT value, suggested (Units) SB Boss 1	Name	Remaining RT gradients (Hz/cm^n)	RT value, suggested (Units)	Limit reached?	RT gradient limits (Hz/cm^n)
Z0	5133.2	-1507	Z0	-3014					
Z1	-8.3	76	Z1	153					
Z2	-57.9	626	Z2	1253					
Z3	-22.6	570	Z3	1140					
Z4	45.2	-3517	Z4	-7034					
Z5	15.1	-1193	Z5	-2386					
Z6	-6.7	2145	Z6	4291					
X	-36.9	575	X	1185					
Y	-112.5	1753	Y	3614					
XZ	16.5	-706	XZ	-1521					
YZ	-14.5	620	YZ	1334					
XZ2	2.7	-264	XZ2	-573					
YZ2	-5.8	442	YZ2	1241					
XZ3	2.3	-381	XZ3	-1279					
YZ3	-4.6	749	YZ3	2513					
XZ4	1.1	-302	X2-Y2	-234					
YZ4	2.9	-804	XY	-1789					
XZ5	0.0	0	(X2-Y2)Z	165					
YZ5	0.0	0	XYZ	-2658					
X2-Y2	3.1	-135	X3	9877					
XY	23.5	-1035	Y3	-208					
(X2-Y2)Z	-0.6	51							
XYZ	9.4	-830							
(X2-Y2)Z2	1.9	-303							
XYZ2	4.2	-680							
(X2-Y2)Z3	-1.0	512							
XYZ3	0.1	-47							
(X2-Y2)Z4	0.0	0							
XYZ4	0.0	0							
(X2-Y2)Z5	0.0	0							
XYZ5	0.0	0							
X3	-48.0	2916							
Y3	1.0	-61							
X3Z	5.5	-1284							
Y3Z	-3.4	801							

User:
Date: 22.03.2017
Time: 14:02

Visum: OLA/RSP Date: 04.10.2013

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Figure 2.1: Example Page from of a Test Protocol

2.3.2 Bruker ISO 9001 Certification - Bruker BioSpin GmbH

The following is a list of ISO 9001 Management System (MS) certifications available from Bruker when this guide was prepared:

ISO Certificate	Company Site	
ISO MS Multisite Certificate No. 12 100 56571 TMS via TÜV SÜD Management Service.	Bruker Switzerland AG	Switzerland/CH
	Bruker BioSpin GmbH	Germany/DE
	Bruker BioSpin MRI GmbH	Germany/DE
	Bruker France S.A.S.	France/FR
	Bruker BioSpin Corporation	United States of America/US

Table 2.1: Listed Sites of Bruker BioSpin in the Relevant ISO Certification Document

Please contact your Bruker representative for provision of an actual Bruker BioSpin ISO multisite certificate, or see section Bruker BioSpin in *https://www.bruker.com/about-us/who-we-are/whoweare/quality.html*.

2.3.3 Bruker EU Declaration of Conformity and CE Marking - 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 as conforming to the European Regulations and Directives.

The conformity to the respective European Directives is covered by appropriate CE-marking on the instrumentation. The CE-marking also implies that compliance to the requirements has been accordingly documented.

All Bruker spectrometer series are independently tested by third parties (where appropriate and applicable) to satisfy the occupational health & 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 for each respective AVANCE spectrometer. The figure below shows the CE certificate for the most recent AVANCE NEO spectrometer generation.

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 declaration and CE marking can be checked by Inspecting Authorities for GLP certification.

EU Konformitätserklärung
EU-Declaration of Conformity
Declaration de Conformité – UE
Bruker BioSpin Group

BRUKER

Der Unterzeichner, der den nachstehenden Hersteller vertritt:
The undersigned, representing the following manufacturer:
Le signataire, qui représente le producteur suivant:

Hersteller / Manufacturer / Producteur:
Anschrift / Address / Adresse:

Bruker BioSpin AG
Industriestraße 26, 8117 Fällanden, Switzerland

erklärt hiermit, dass die... / herewith declares that... / déclare par la présente que le ...

Produkt Serie / Product Series/ Série de Produit

AVANCE NEO – OneBay
Spectrometer Systems
300 ... 850 MHz

CE

Produkt ID - Auftrags Nr. / Product ID – Order No. /
ID de Produit – Numéro d'Ordre:

H031280B - H031280BX

...in Übereinstimmung mit den Bestimmungen der nachstehenden EU-Richtlinien (einschließlich aller zutreffenden Änderungen) ist.
...is in conformity with the provisions of the following EU directives (including all applicable amendments).
...est conforme aux dispositions des directives d'union européennes suivantes (y compris tous les amendements applicables).

2014/35/EU

Europäische Richtlinie **Niederspannungsrichtlinie (NS-RL)** betreffend...	European Directive **Low Voltage Directive (LVD)** to...	Directive européen **Directive Basse Tension (DBT)** au...
Elektrische Betriebsmittel zur Verwendung innerhalb bestimmter Spannungsgrenzen Electrical equipment designed for use within certain voltage limits Matériel électrique destiné à être employé dans certaines limites de tension	(Neufassung) (recast) (refonte)	(früher 2006/95/EG) (former 2006/95/EC) (avant 2006/95/CE)

Angewandet harmonisierte / Applied harmonized standards / Suite à des normes harmonisées applicables:

EN 61010-1:2010 / **IEC 61010-1** (3rd Edition)	**EN 61010-2-081:2015 /** **IEC 61010-2-081** (2nd Edition)		

2014/30/EU

Europäische Richtlinie **Elektromagnetische Verträglichkeit (EMV)** betreffend...	European Directive **Electromagnetic Compatibility (EMC)** to...	Directive européen **Compatibilité Electromagnétique (CEM)** concernant...
...die elektromagnetische Verträglichkeit ...Electromagnetic compatibility ...la Compatibilité Électromagnétique	(Neufassung) (recast) (refonte)	(früher 2004/108/EG) (former 2004/108/EC) (avant 2004/108/CE)

Angewandte harmonisierte Normen / Applied harmonized standards / Suite à des normes harmonisées applicables:

EN 61326-1:2013 / **IEC 61326-1** (2nd Edition)	**EN 61000-3-2:2014 /** **IEC 61000-3-2** (4th Edition)	**EN 61000-3-3:2013 /** **IEC 61000-3-3** (3rd Edition)	

Für das dazugehörige Magnetsystem der Produktserie.../ for the appropriate magnet system of product series.../ pour le système magnétique correspondant de série de produits...
(siehe zugehörige EU KE (EU DoC) des Magnet Systems / see appropriate EU DoC of Magnet System / voir la DdC UE (EU DoC) de systéme d'aimant adéquate)

Fällanden, 02. May 2017
Schweiz / Switzerland / Suisse

Pietro Lendi
Komponenten Manager / Component Manager / Responsable de Composants
Avance Systems / R&D Organisation – Bruker BioSpin Group

Figure 2.2: Example of an AVANCE NEO Console Declaration of Conformity

For Europe: Each instrument or system (NMR spectrometer) carries CE-marking and has an EU Declaration of Conformity. Subunits, assemblies or components receive (in general) dedicated safety approval from third party testing agencies in accordance with requirements to the Low Voltage Directive 2014/35/EU and the Product Safety Standard IEC/EN 61010-1 for laboratory testing equipment.

Standalone units, assemblies or components like the Sample Changer carry their own CE-marking, EU Declaration of Conformity and certification (in general), likewise receive dedicated safety approval from third party testing agencies in accordance with requirements of the Low Voltage Directive 2014/35/EU and the Product Safety Standard IEC/EN 61010-1 for laboratory testing equipment.

2.3.4 Bruker EU Declaration of Conformity and CE Marking - Magnet

All Bruker magnet system series (except cryogen-free magnets) are inspected by third party testing agencies to satisfy the specific safety requirements of the European Union for pressure equipment and therefore qualify for carrying the CE-marking provided by the notified body (CE 0036).

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

TÜV SÜD Industrie Service

ZERTIFIKAT

gültig bis: 31.12.2020

CERTIFICATE

valid until: 31.12.2020

Interne Fertigungskontrolle mit überwachten Druckgeräteprüfungen in unregelmäßigen Abständen (Modul A2) nach Richtlinie 2014/68/EU

Internal production control plus supervised pressure equipment checks at random intervals (module A2) according to Directive 2014/68/EU

Zertifikat-Nr.: *Certificate No.:* **Z-EU-CH-WAL-20-01-2722764-24074004**

Name und Anschrift des Herstellers: *Name and address of manufacturer:*
Bruker Switzerland AG
Industriestrasse 26
CH-8117 Fällanden

Der Hersteller ist nach Prüfung der Voraussetzungen berechtigt, die von ihm im Rahmen des Geltungsbereichs hergestellten Druckgeräte mit unserer Kennnummer gemäß dem abgebildeten CE-Kennzeichen zu kennzeichnen:

The manufacturer is - after examination of the prerequisites - authorised to provide his pressure equipments manufactured within the scope of the examination with our identification number to the CE-marking as illustrated:

CE 0036

Prüfbericht Nr.: *Evaluation report No.:* **P-EU-CH-WAL-20-01-2722764-24074004**

Geltungsbereich: *Scope of examination:*
Kryostat zu Magnetsystem für Spektroskopie der Kategorie I und II

Cryostat to Magnetsystem for Spectroscopy of category I and II

Fertigungsstätte: *Manufacturing plant:*
Bruker Switzerland AG
Industriestrasse 26
CH-8117 Fällanden

Mannheim, 31.01.2020
(Ort, Datum)
(Place, date)

TÜV SÜD Industrie Service GmbH
Zertifizierungsstelle für Druckgeräte
Ralf Brinkmann

Echtheitsprüfung durch App TÜV SÜD Verify
Verification of Certificate by TÜV SÜD App Verify

TÜV SÜD Industrie Service GmbH 09 36 Notified Body

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Notified Body, No. 0036
TÜV SÜD Industrie Service GmbH
Westendstr. 199
80686 München
GERMANY

Dokument ID: 2722764Yfb667

Seite 1 zum Zertifikat Nr. / Page 1 of the certificate No. Z-EU-CH-WAL-20-01-2722764-24074004

Figure 2.3: Example of a Magnet CE Certificate

The Declaration of Conformity for each individual Bruker Magnet System can be found in the NMR Magnet System manual that is delivered with the magnet. This certificate is renewed on an annual basis.

3 Installation Qualification

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 user's site, up to and including its response to the initial application of electrical power.

Important: It is the responsibility of the Laboratory Manager to make sure that the prerequisites for IQ are being fulfilled.

Upon request, **Bruker may assist** 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.).

Sites are subject to continual changes in factors that affect performance. Once the system is installed, laboratory conditions should be routinely monitored and documented 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 provide safety information relating to the operation of the instrument (ambient conditions, handling of cryogenic equipment).

3.1 Site Planning and Preparation

To help determine whether a site is suitable for locating a Bruker spectrometer, Bruker has prepared a corresponding Site Planning guide for your system line, which can lead you through this process.

In these Site Planning guides a variety of aspects are covered including:

- Safe cabinet and magnet positioning.
- Adequate ceiling height.
- Electromagnetic interference.
- Service access and vibrations.

Aspects regarding the actual installation are also dealt with briefly.

The latest versions of the Site Planning guides are available on the Bruker Advanced System Handbook (BASH) DVD, 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 will also work with you individually on answering any specific questions that may arise during the site planning and preparation process.

3.1.1 A Special Note about Safety

Safety is at the heart of GLP and occupational health and safety 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 the system owner to ensure safety in their NMR laboratories or environments and to comply with local and international safety regulations (e.g. for Europe: EMF Directive 2013/35/EU, for the US C95.6-2002, *Safety Levels with Respect to Human Exposure to Electromagnetic Fields*, 0-3 kHz, as well as current basic ICNIRP guidelines, see *www.icnirp.org*).
- It is generally accepted that stray fields are harmless below 0.5 mT (5 Gauss) (ten times the earth magnetic field). Stronger stray fields closer to the NMR magnet system may disturb heart pacemakers, erase magnetic cards and storage devices, and adversely affect watches and micro mechanical devices.
- It is strongly recommended that you mark the 0.5 mT (5 Gauss) line and the 3 mT (30 Gauss) line with warning signs and to limit access to areas with more than 0.5 mT field to trained and qualified 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 for the horizontal ones. 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 3 mT (30 Gauss) to 10 mT (100 Gauss). Massive iron objects such as pressurized gas cylinders are extremely dangerous in the vicinity of a superconducting NMR magnet system. They should be mounted very close to the door and away from the NMR magnet system, or preferably outside the magnet room. Inside the magnet room a wall mounted gas distribution system is recommended.
- The laboratory room must be technically equipped, so that even with a magnet *quench* no excess pressure in the room occurs, whereas the windows and doors may burst.
- Personnel should always be protected from any danger resulting from any escaping nitrogen or 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 especially considered. An oxygen warning device and adequate ventilation must be provided.

The safety notes found in the Magnet System manual, which is delivered with each magnet, should always be read before operating the system.

Also, be sure to review the Site Planning and any relevant system/component manuals, for safety aspects of Bruker instrumentation.

Bruker provides dedicated General Safety Considerations User Manuals, which are available in several languages on the Bruker Advanced System Handbook (BASH) DVD.

Title	Part Number
AVANCE NEO General Safety Considerations User Manual (English)	H171764
AVANCE NEO General Safety Considerations User Manual (Chinese)	H171764CN
AVANCE NEO General Safety Considerations User Manual (French)	H171764F
AVANCE NEO General Safety Considerations User Manual (German)	H171764D
AVANCE NEO General Safety Considerations User Manual (Italian)	H171764IT
AVANCE NEO General Safety Considerations User Manual (Japanese)	H171764JP
AVANCE NEO General Safety Considerations User Manual (Polish)	H171764PL
AVANCE NEO General Safety Considerations User Manual (Portuguese)	H171764PT
AVANCE NEO General Safety Considerations User Manual (Russian)	H171764RU
AVANCE NEO General Safety Considerations User Manual (Spanish)	H171764S
AVANCE General Safety Considerations User Manual (English)	Z31836
AVANCE General Safety Considerations User Manual (Chinese)	H156875
AVANCE General Safety Considerations User Manual (German)	Z31836D
AVANCE General Safety Considerations User Manual (French)	Z31836F
AVANCE General Safety Considerations User Manual (Spanish)	Z31686S
AVANCE General Safety Considerations User Manual (Japanese)	H156876
AVANCE General Safety Considerations User Manual (Portuguese)	H156877
AVANCE General Safety Considerations User Manual (Italian)	H154614
Fourier Systems General Safety Considerations Manual	Z33049
Note: Other languages can be provided upon request.	

3.1.2 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, if adequate ventilation is provided to prevent suffocation. During normal operation, only 3-5m^3/day (100-180 ft^3/day) of nitrogen are evaporated, but during a *quench* 50-100m^3 (1800-3600 ft^3) of helium are produced within a short time. Windows and doors are normally sufficient for ventilation even after a quench.

Here are some general ventilation guidelines for siting a magnet system:

- NMR magnet systems should never be set up in an airtight room.
- The magnet location should be selected so 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 (N_2)	Helium (He)
Characteristics	inert (gas); refrigerated (liquid)	inert (gas); refrigerated (liquid)
CAS No.	7727-37-9	7440-59-7
EINECS No.	231-783-9	231-168-5
UN No.	1977	1963
Molecular weight	28	4
Melting point @ 1 atm	-210.0°C / 63.05°K / -346.0°F	-272.2°C / 0.95°K / -452.1°F
Boiling point @ 1 atm / @ 367 psia	-195.8°C / 77.15°K / - 320.5°F	-268.9°C / 4.15°K / - 459.7°F
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
GHS code	GHS 04	GHS 04
Hazcode	2.2	2.2
Color (liquid)	none	none
Color (gas)	none	none
Odour (gas)	none	none
Taste (gas)	none	none
Flammability – NFPA rating	non flammable – 0	non flammable – 0
Health hazard – NFPA rating	Can cause rapid suffocation – 3	difficulty breathing – 1
Reactivity – NFPA rating	none – 0	none – 0
Disposal	only vent to atmosphere in a well-ventilated place	
Toxicity	non toxic	non toxic
Ecological	no known damage	no known damage
Explosion hazard with combustible material	non hazardous	non hazardous
Fire hazard: liquefies oxygen and promotes ignition	yes	yes
Fire hazard: combustible	no	no
Fire hazard: promotes ignition directly	no	no
Pressure rupture: if liquid or cold gas is trapped	yes	yes

Table 3.1: Table of Properties of Cryogenic Substances

Refer to the section *Emergency Plan for NMR Systems* [▶ 50] for more information about magnet system safety and information that should be included in organization Standard Operating Procedures (SOP's).

Special precautions need to be observed if the NMR system is used with a Prodigy CryoProbe. These probes use liquid nitrogen for cooling and evaporate nitrogen gas into the NMR laboratory. Sufficient air circulation is required when using them. Consult the order information manual (P/N Z33045) for instructions on the correct installation of Prodigy CryoProbes and observe the safety instructions provided in this manual.

3.2 Factory Final Test

All Bruker instruments and their components 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. The customer certificates for the system and its components are delivered with the system documentation.

3.2.1 PC Preparation and Software Installation

As part of the factory final test, the computer software is installed on the Bruker supplied computer system **according to Bruker definitions, recommendations** and the system configuration requirements.

Several certificates result from the Bruker internal validation tests. Two are listed as an example below:

- TopSpin<version>_ validation_certificate (<version> = installed TopSpin version)
- TopSpin<version>_GAMP-5_certificate (<version> = installed TopSpin version)

3.2.2 Spectrometer Console Factory Final Test

Before the instrumentation is shipped from the factory, Bruker spectrometer consoles undergo thorough final testing using the **NMR Product Test** (NMRPT) software suite, the results of which are recorded in the Customer Certificate.

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 Customer Certificate also records key information concerning the instruments, such as:

- System Information
- Software and Service Tools Installed
- Workstation Information
- Spectrometer Configuration
- Hardware Configuration
- List of Measured Experiments

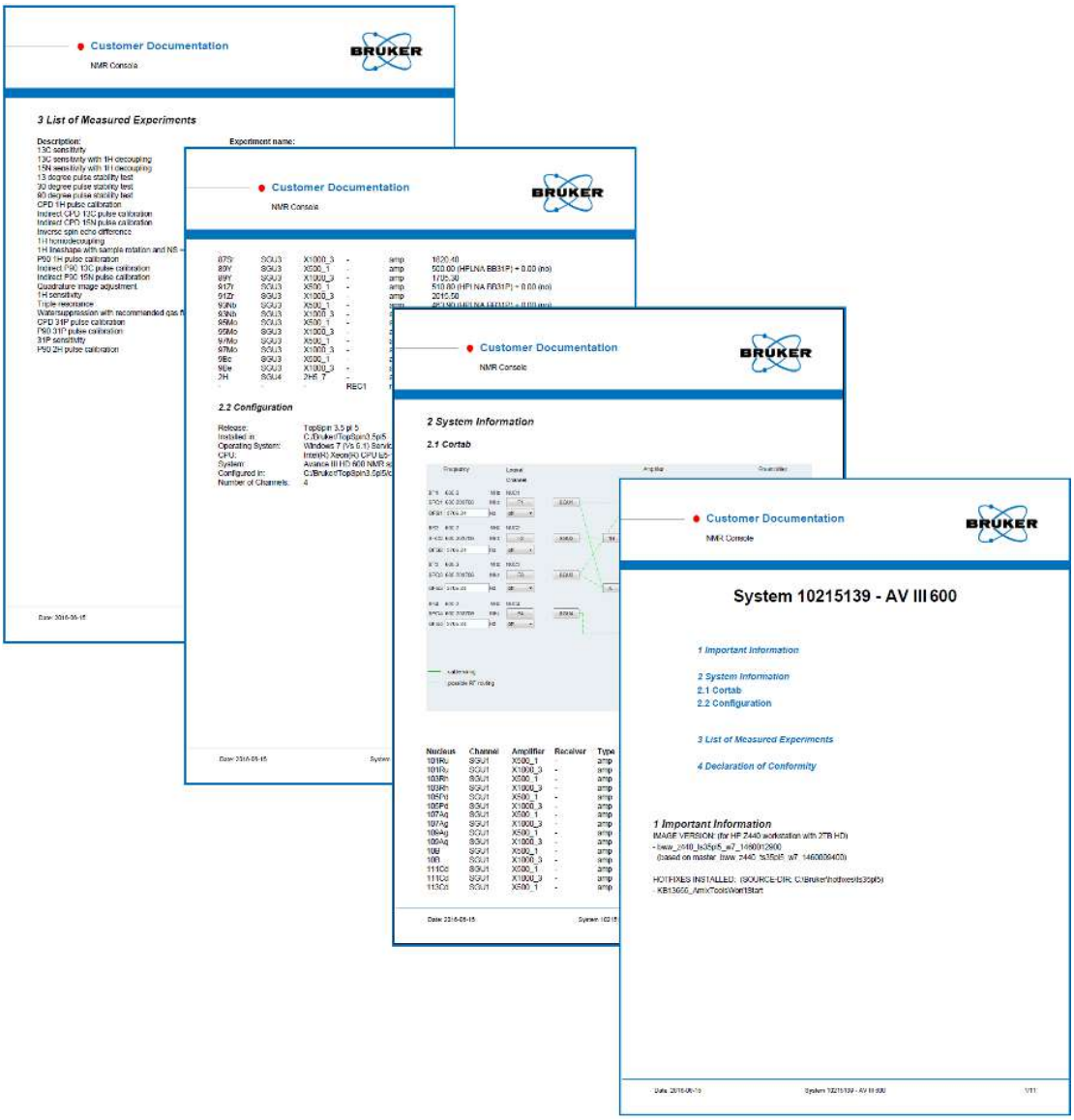


Figure 3.1: Sample Pages from a Spectrometer Console Customer Certificate

This preliminary factory final test is very thorough. Parts of these tests are repeated and documented under the NMRPT procedure during the **Operational Qualification**.

Refer to the section the Acceptance Test Protocol for more information.

3.2.3 Probe Tests

Stringent tests to prove the NMR performance of all probes delivered with the system are also accomplished through the NMRPT procedure. These tests are described in the Acceptance Test Procedure Manual ZUEP0102.

Depending on the design of the probe, some experiments cannot be run on every probe. The NMRPT software autonomously determines the complete list of possible tests.

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

3.2.4 Magnet Factory Final Test

Magnet systems undergo a complete system test before they are delivered to customers.

The tests are carried out based on Quality Management Procedures (ISO 9001) and Bruker's 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:

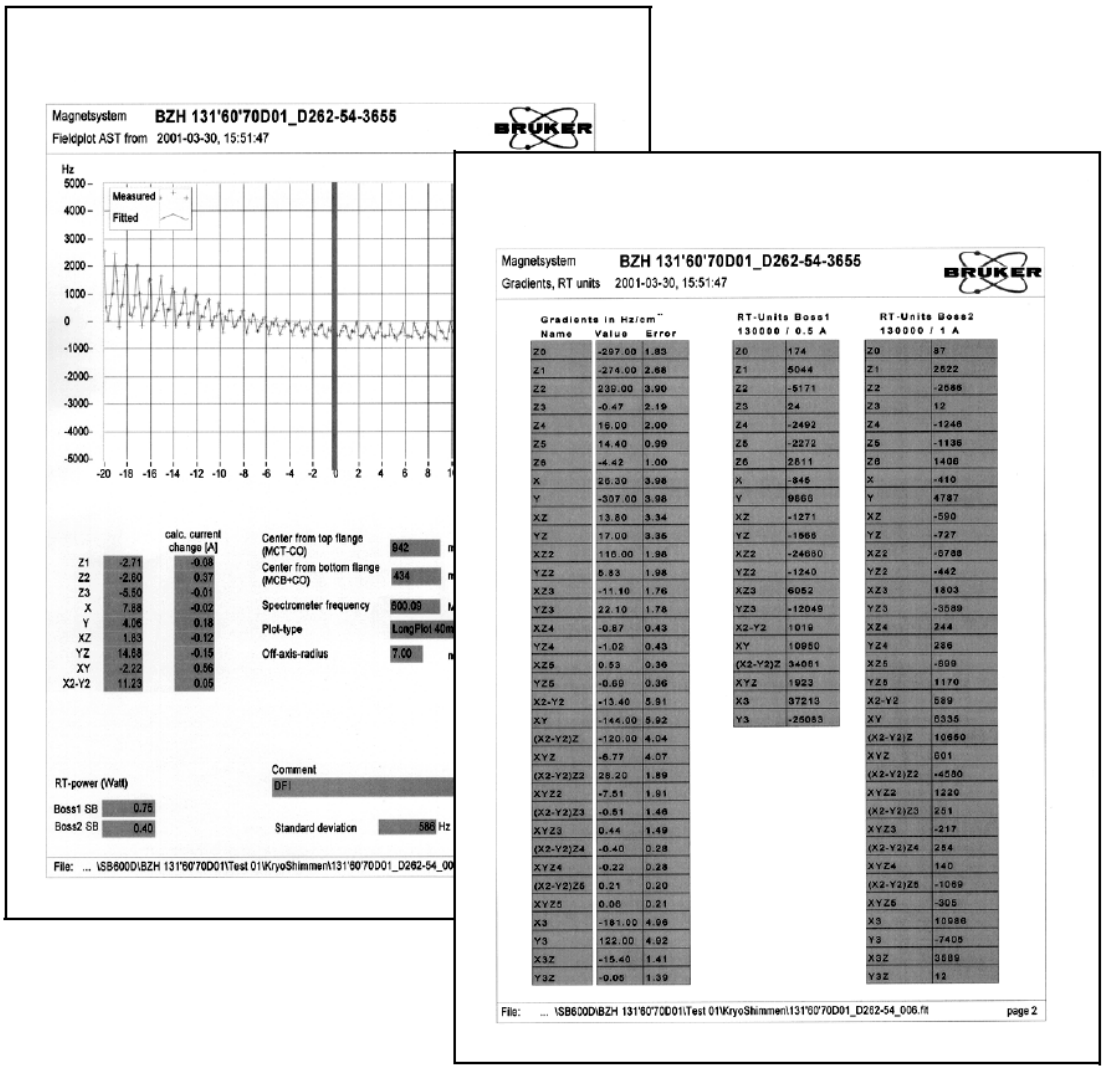


Figure 3.2: Example of a Magnet Field Plot

3.2.5 Factory Software Backup

Bruker PCs are delivered with the most recent version of Windows or Linux supported by Bruker. Bruker provides a **complete backup** of the **entire installation** on a USB device located in the **computer housing**. This image can be installed, if necessary, with a software backup tool also provided on the USB device.

A list (uxnmr.info) 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. All configuration files for the specific console are stored on a USB device located in the **console housing**. 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.

3.3 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 the 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 the 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 DVD's).
- Prepare any required installation reports.
- Use the IQ/OQ Protocol document (P/N H165691 for AVANCE III HD and P/N H168890 for AVANCE NEO) to protocol the complete installation qualification procedure.

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*	*P/N*	
1	**Magnetsystem 600 MHz plombiert**	**Magnetsystem 600 MHz lead sealed**	**Z123788**	❑
1	Ventilkörper Vakuum Ventil KF40 Kpl	Sealing plug for vacuum valve KF40	Z56408	❑
1	Sicherungsdeckel Vakuumventil	Security cover for vacuum valve	Z55552	❑
1	N_2 Rohr (CU) ND54 D365	N_2 bore tube (CU) ND54 D365	Z57985	❑
1	RT Rohr D365			
1	VPM Zubehör und Flanschgar			
1	Blubbersonde KPL D370			
1	Dichtscheibe HE Transferline			
1	RT - Flansch oben			
1	RT - Flansch unten			
2	RT – Dichtflansche			
2	N2 Konataktflansch ND54 D3			
2	RS-Reduzierflansch SB			
6	RS-Laschen D3XX			
1	Aktivkohlenbox set (2 Stück)			
1	Kurzschluss D3XX			
1	N2 Rückschlagventil			
1	HE-Aufbauten Kompl.			
1	He-Rückschlagventil			
1	Adapter Schlauchnippel			
1	Adapter KF25			
1	Ladeturmkopf ND30 Gepresst			
1	Refillturmkopf ND30 Gepress			
1	Zubehörsack			
1	Helmholtz Resonator D30			
2	Baffel Stab ND24			
1	N2 Flowsystem D365			

ZXKV0089

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

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

Dewar Number 7…

ZXKV0089 Bruker BioSpin AG BBIO Stand: 00 vom 18.10.2011 1 / 3

Figure 3.3: Sample Magnet Packing and Shipping Container Contents Lists

3.4 Instrument/Hardware Setup

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

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

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

3.5 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).

3.6 Checklist for an NMR Spectrometer Installation

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

Type of System and System Owner Information

Customer Name: _____

Company: _____

Address: _____

Postal Code / City / Country: _____

Order No.: _____

System Type: _____

1) Design Qualification

- Copy of specifications provided with the sales document (typically probe and magnet sales specification data sheets).
- Copies of CE certificates (*).
- Copies of the ISO certificates (**).
- TopSpin<vers.>_validation_certificate (<vers.> = installed TopSpin version).
- AssureNMR<vers.>_validation_certificate (<vers.> = installed Assure version).
- TopSpin<vers.>_GAMP-5_certificate (<vers.> = installed TopSpin version).

2) Installation Qualification

General Documents:

- Copy of the sales document.
- Shipping documents.
- Installation and operational qualification protocol (P/N H165691 for AVANCE III HD and P/N H168890 for AVANCE NEO).
- Installation and acceptance test description (P/N ZUEP0102).

Documents from Final Test:

- Customer certificate from console final test (from production center).
- Factory console configuration backup (on USB device in console).
- Factory computer software backup (disk image on USB device in computer).
- Customer Certificate from probe final test (from production center).
- Magnet test report and magnet information in the magnet folder.

- Sample changer test protocol (e.g. SampleXpress Lite).

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.

Documents Specific to the Computer Installation (*)

- 21 CFR Part 11 document (P/N H152957).
- Computer system validation protocol (P/N H166444).
- GxP requirements document (P/N Z31619).

3) Operational Qualification

Documents from Acceptance Test:

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

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

- Run customer defined instrument performance qualification tests (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).

6) Planned Maintenance Checklist Documentation (if part of the contract) (*)

- Description for Planned Maintenance Checklist (P/N H160159).
- Planned Maintenance Checklist (P/N H160158).

7) Executive Summary/Comments

_____

_____

_____

_____

Customer checklist approval: Date: _____ Name: _____

Bruker checklist approval: Date: _____ Name: _____

(*) Documents available from Bruker internal SharePoint server.

(**) Documents available from Bruker Internet homepage *www.bruker.com*

Table 3.2: Checklist for an NMR Spectrometer Installation

4 Operational Qualification

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 per its **intended use** and/or **intended purpose**.

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

The final document of the OQ is the Acceptance Protocol.

Before the Operational Qualification can be performed, the spectrometer console and its peripherals, magnet, and any required software packages must be properly installed (refer to *Installation Qualification* [▶ 15]).

Use the IQ/OQ Protocol document (P/N H165691 for AVANCE III HD and P/N H168890 for AVANCE NEO) to protocol the complete operational qualification procedure.

4.1 Magnet Acceptance Test

The magnet is required for the Spectrometer Acceptance Test, thus the performance of the magnet is proven through the successful completion of the NMR Product Test (NMRPT).

The Magnet Acceptance Test results are integrated and maintained in the Acceptance Protocol. Additional results from cryo-shimming and room temperature shimming are summarized in the magnet installation protocol.

Magnet Acceptance Test notes

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

4.2 The NMR Product Test (NMRPT)

The NMR Product tests are carried out to demonstrate and document that the spectrometer and magnet are performing per their intended use. These tests vary based on the hardware configuration and probes that are used.

The probes that are used have a significant impact on the results achieved by an instrument. The range of probes available is quite large and new probes are constantly being introduced, so it is important to check with Bruker BioSpin for current specifications on the probes that apply to your specific applications.

The NMRPT manual (P/N ZUEP0102) describes the test procedure and contains a list of all possible experiments. To standardize the acceptance procedures and documentation, the software suite NMRPT has been designed by Bruker for Test and Service Engineers.

In principle, the NMRPT software follows the same pathway during the Factory Final Test and the Acceptance Test (OQ) procedures. Nevertheless, a focus is made on demonstrating that the **Operational Qualification** (OQ) of the instrument is met. In particular, additional NMR device experiments (Hardware tests) are also performed during this test. At the end of the NMRPT, the customer confirms that the instrument meets the standards that they have established by signing the Acceptance Protocol, together with the Bruker Service Engineer (refer to *The Acceptance Protocol [▶ 29]*).

The customer certificate with the specification for the individual probe is always delivered together with the probe. The tests outlined below must meet the specifications stated in the customer certificate.

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

- The Pulse Calibration Experiments.
- The Lineshape Test.
- The Resolution Test.
- The Sensitivity Test.
- The Water Suppression Test (not possible for all probe types).
- Application Specific Experiments.

4.2.1 The Pulse Calibration Experiments - Probe

The Pulse Calibration Experiments are performed in accordance with the capabilities of the probe. Specifications are provided on the customer certificate delivered with the probe.

4.2.2 The Lineshape Test

The Lineshape Test is also commonly known as the Hump Test. A ^{1}H or ^{13}C spectrum is acquired with one scan, typically on the $CDCl_3$ sample for 1H and on the ASTM sample for ^{13}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.

4.2.3 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.

4.2.4 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.

4.2.5 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, similarly to the one described in the sensitivity test. This test is not performed for all probes, because some probes are not suitable for running this test.

4.2.6 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 ^{1}H pulse.
- Determination of 90 degree ^{13}C pulse.
- Determination of 90 degree ^{15}N pulse.
- DEPT-90.
- DEPT-135.
- Inverse Spin-Echo Difference.
- Hardware tests (i.e. gradient profile and recovery, B1 homogeneity etc.).

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 originally based on the tests compiled in an article by Joseph B. Vaughn and Philip L. Koons, in Spectroscopy 1995, 10(1) 36-40.

The temperature stability in your laboratory and the temperature stability of your spectrometer have a significant impact on the quality of the hardware tests.

A maximum variation of the room temperature of +/-0.5 °C/hour is about the highest tolerance one should allow before running these hardware tests.

4.3 The Acceptance Protocol

The **Acceptance Protocol** 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.

Upon completion of the NMRPT procedure both the Bruker engineer and an authorized customer representative sign the final Acceptance Protocol form.

One copy of the complete NMRPT results remains with the customer, and another copy is kept at Bruker.

A computerized summary of the results is also saved to the host computer into a special location reserved for the NMRPT results.

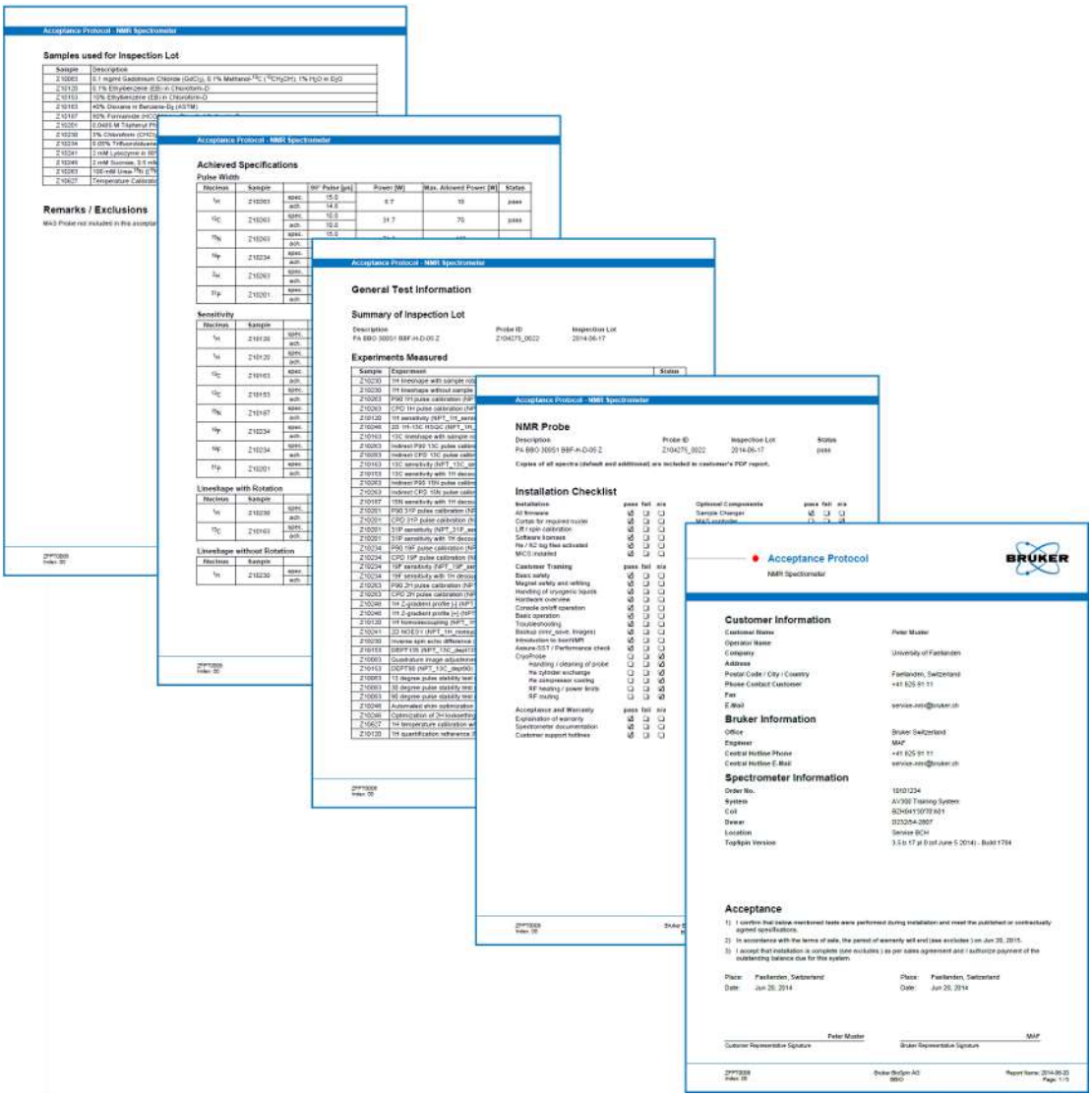


Figure 4.1: Sample Pages from an Acceptance Protocol

Refer to *The NMR Product Test (NMRPT) [▷ 27]* for more information on these tests and experiments. The exact tests and results that are maintained depend on the system configuration and probe being used.

4.4 Software Backup and Computer Documentation

After the completion of the NMRPT procedure, Bruker makes a **complete backup** of the **entire installation** using backup software.

The list (uxnmr.info) with a description of hardware, operating system software, and application software, etc. which was prepared at the factory before the instrument was shipped (see *Factory Software Backup [▷ 23]*), is updated if any changes have taken place. This list aids in verifying GLP requirements as well as handling any computer problems.

All relevant **computer system** information, including the installed software versions are captured in this backup file. In addition, the TopSpin software offers a command **nmrsave** to periodically archive all important system information to a central storage location.

It is recommended that the system owner keeps a copy of this archive on an independent computer system.

5 Performance Qualification

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

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

For **laboratory personnel**, Bruker has designed the AssureSST software to assist in their PQ's. Laboratory managers should formulate appropriate SOP's for PQ.

Bruker has designed a powerful software tool known under the name of **NMR Product Test** (NMRPT) for **Bruker service personnel** to aid in service aspects of PQ.

5.1 AssureSST Tests

The *AssureSST* software tool is primarily used for tests in Performance Qualification (PQ). The purpose of these GLP tests is to document the long-term stability of the NMR spectrometer.

The basic idea of the software package is to establish lists of experiments that are performed at standard intervals, for example, every day, or every Monday, or once every month. If all the experiments run without a problem, a protocol will be printed with observed results 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, the supervisor should take corrective action (e.g. re-shim, tune, change hardware, re-calibrate pulses and/or power levels etc.). When coupled with AssureNMR to run samples for material validation, the instrument in a GLP facility is configured to stop all acquisitions until AssureSST passes successfully.

The AssureSST tests provide documented evidence that the instruments are functioning correctly.

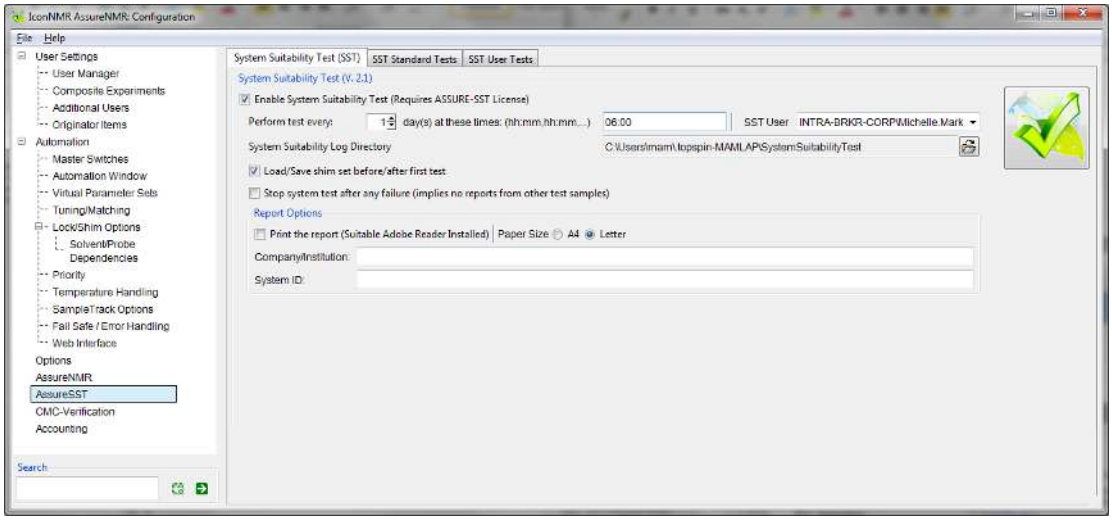


Figure 5.1: The Start Page of AssureSST Software Interface

5.1.1 Standard AssureSST Tests

The basic idea behind the AssureSST tests is to keep things as simple as possible. Therefore, only a **very limited**, but **extremely effective**, number of **tests** are offered, including:

- Standard Lineshape, or Hump test for ^{1}H or ^{13}C.
- Standard Resolution test for ^{1}H or ^{13}C.
- Standard Sensitivity test for ^{1}H or X-nuclei (nuclei other than ^{1}H).
- Temperature test.
- Any user defined tests. The Standard Water Suppression test is commonly selected as a test in this category.

The Lineshape Test

This test is also commonly known as the **Hump test**. A ^{1}H or ^{13}C spectrum is acquired with one scan, typically on the $CDCl_3$ sample for ^{1}H and on the ASTM sample for ^{13}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. The resulting shim set is saved.

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 Temperature Test

The Temperature test is performed on the appropriate sample for the probe and application, i.e. 99.8% methanol-d, or 4% methanol, or 80% glycol. This test measures the distance between peaks in the sample and calculates the temperature from this difference.

If needed, the software adjusts the probe temperature until the desired value is reached.

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.

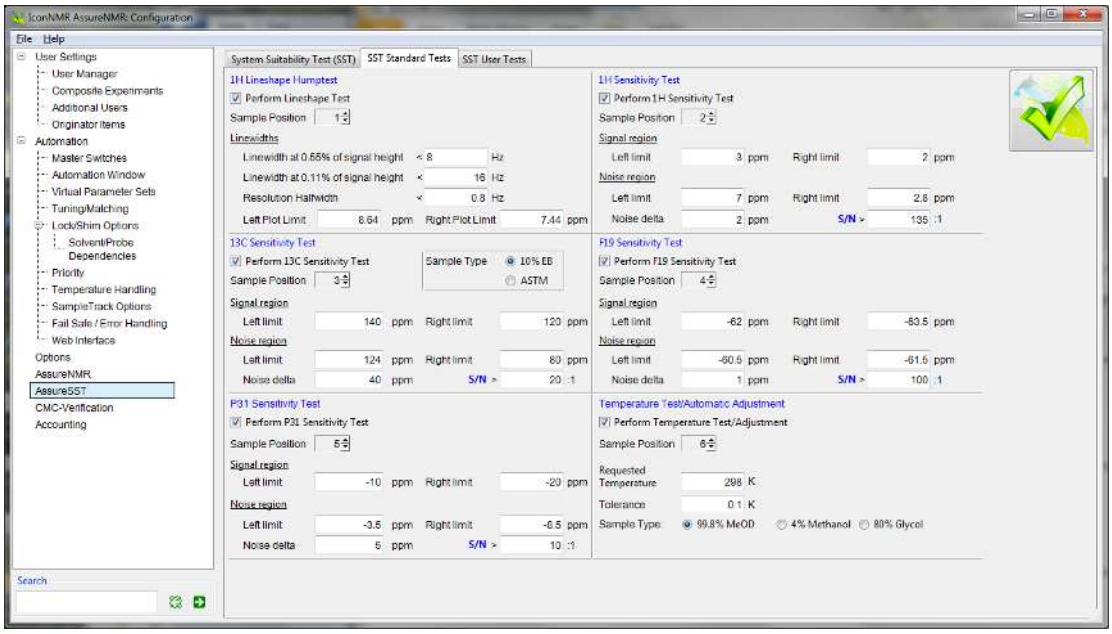
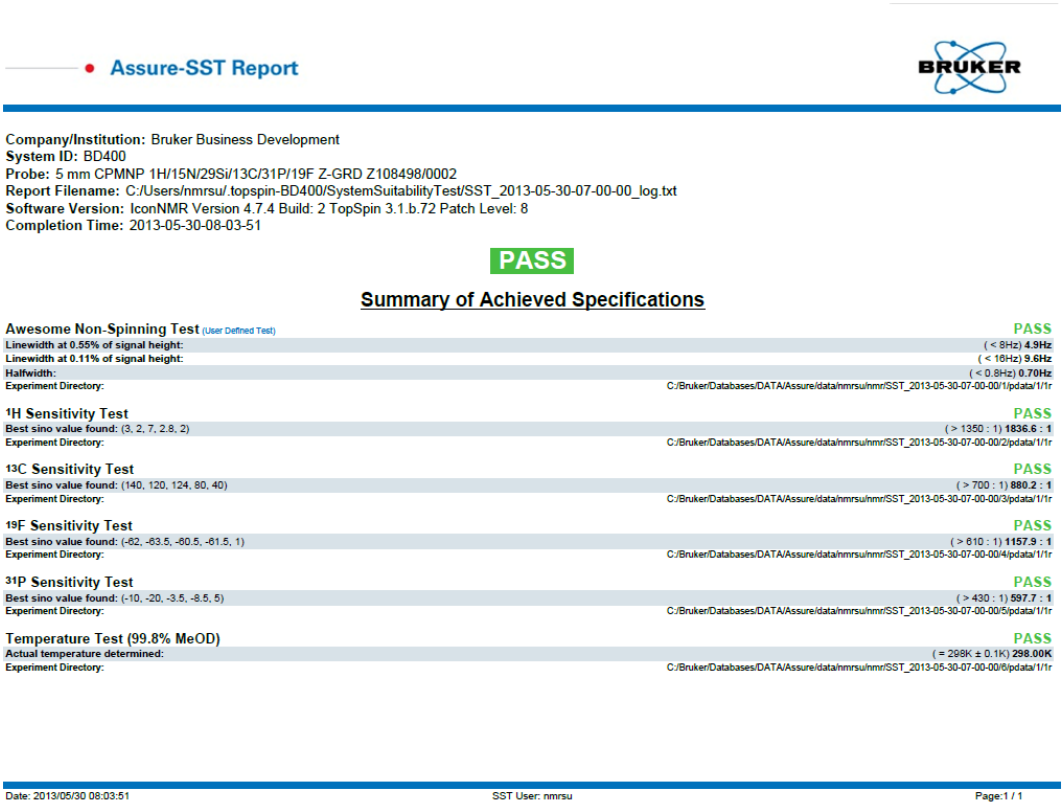


Figure 5.2: Example of Setting Specifications for Assure-SST Tests

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

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



Assure-SST Report

BRUKER

Company/Institution: Bruker Business Development
System ID: BD400
Probe: 5 mm CPMNP 1H/15N/29Si/13C/31P/19F Z-GRD Z108498/0002
Report Filename: C:/Users/nmrsu/.topspin-BD400/SystemSuitabilityTest/SST_2013-05-30-07-00-00_log.txt
Software Version: IconNMR Version 4.7.4 Build: 2 TopSpin 3.1.b.72 Patch Level: 8
Completion Time: 2013-05-30-08-03-51

PASS

Summary of Achieved Specifications

Awesome Non-Spinning Test (User Defined Test) — PASS
Linewidth at 0.55% of signal height: (< 8Hz) 4.9Hz
Linewidth at 0.11% of signal height: (< 16Hz) 9.6Hz
Halfwidth: (< 0.8Hz) 0.70Hz
Experiment Directory: C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2013-05-30-07-00-00/1/pdata/1/1r

^{1}H Sensitivity Test — PASS
Best sino value found: (3, 2, 7, 2.8, 2) (> 1350 : 1) 1836.6 : 1
Experiment Directory: C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2013-05-30-07-00-00/2/pdata/1/1r

^{13}C Sensitivity Test — PASS
Best sino value found: (140, 120, 124, 80, 40) (> 700 : 1) 880.2 : 1
Experiment Directory: C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2013-05-30-07-00-00/3/pdata/1/1r

^{19}F Sensitivity Test — PASS
Best sino value found: (-62, -63.5, -60.5, -61.5, 1) (> 610 : 1) 1157.9 : 1
Experiment Directory: C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2013-05-30-07-00-00/4/pdata/1/1r

^{31}P Sensitivity Test — PASS
Best sino value found: (-10, -20, -3.5, -8.5, 5) (> 430 : 1) 597.7 : 1
Experiment Directory: C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2013-05-30-07-00-00/5/pdata/1/1r

Temperature Test (99.8% MeOD) — PASS
Actual temperature determined: (= 298K ± 0.1K) 298.00K
Experiment Directory: C:/Bruker/Databases/DATA/Assure/data/nmrsu/nmr/SST_2013-05-30-07-00-00/6/pdata/1/1r

Date: 2013/05/30 08:03:51 SST User: nmrsu Page:1 / 1

Figure 5.3: Example of a Sample AssureSST Report

5.1.2 Recommended Samples for Use with AssureSST

The recommended samples for use with AssureSST tests are the same as for NMRPT, although, for practicality, fewer samples will be used with AssureSST (see also *Application Specific Experiments* [▷ 29]).

For a list of recommended samples, please contact your local Bruker representative.

5.1.3 Values for AssureSST Test Specifications

The probes that are used have a huge impact on the results achieved from an instrument. Probe performance is 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 most laboratories 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% compared to the specifications provided on the customer probe certificate.

5.2 AssureNMR Software Package

The AssureNMR software package has two automation modules: *Assure – System Suitability Test* (AssureSST) and a material screening module named AssureNMR.

- The AssureSST module is designed to monitor and maintain instrument performance.
- The AssureNMR module assists in the quality control of materials, ingredients and components used in a wide range of products.

AssureSST and AssureNMR were designed to be used in a production or research facility. Thus, many of the features incorporated allow use of this software by non-NMR spectroscopist and on NMR spectrometers in GLP environments.

AssureSST is included with AssureNMR or is also available as a standalone package.

5.2.1 Assure – System Suitability Test (AssureSST)

Summary of Features

- Automated System Suitability Test includes acquisition and analysis of NMR standards ^{1}H lineshape, *1H* sensitivity, *13C* sensitivity, *19F* sensitivity, *31P* sensitivity, and temperature calibration.
- To reduce routine maintenance of the spectrometer shims, shim sets from successful ^{1}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 AssureSST module was designed 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 based on an interval selected by the user.

The AssureSST module can work either in a standalone mode where the user can use the normal IconNMR submission interface, or in parallel with the AssureNMR module.

If AssureSST determines the system to be out of specification, then general sample submissions through IconNMR or AssureNMR will stop until all specifications are achieved.

The use of AssureSST to support the use of the NMR spectrometer in a GLP environment is outlined in the section *AssureSST Tests [▶ 31]*.

5.2.2 AssureNMR - for Material Screening

Summary of Features

- Utilization of AssureSST 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 (^{1}H, ^{2}H, ^{13}C, ^{19}F, ^{31}P).
- Automated analysis and 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 AssureNMR software utilizes four software components:

- Pre-existing components of TopSpin.
- New features in IconNMR.
- NMR spectral databases (SBASE).
- The AssureNMR software as summarized in the figure below. Successful completion of a System Suitability Test releases IconNMR for general sample submission.

The NMR method for validating the material is defined in AssureNMR. When development of the method is complete, it is then ‘released’ for use in IconNMR to initiate an analysis.

A released method cannot be modified. Submitted materials for screening using the AssureNMR method are collected with the acquisition and processing functions of TopSpin.

The material spectrum (or spectra) is then passed to the AssureNMR software for evaluation and generation of reports.

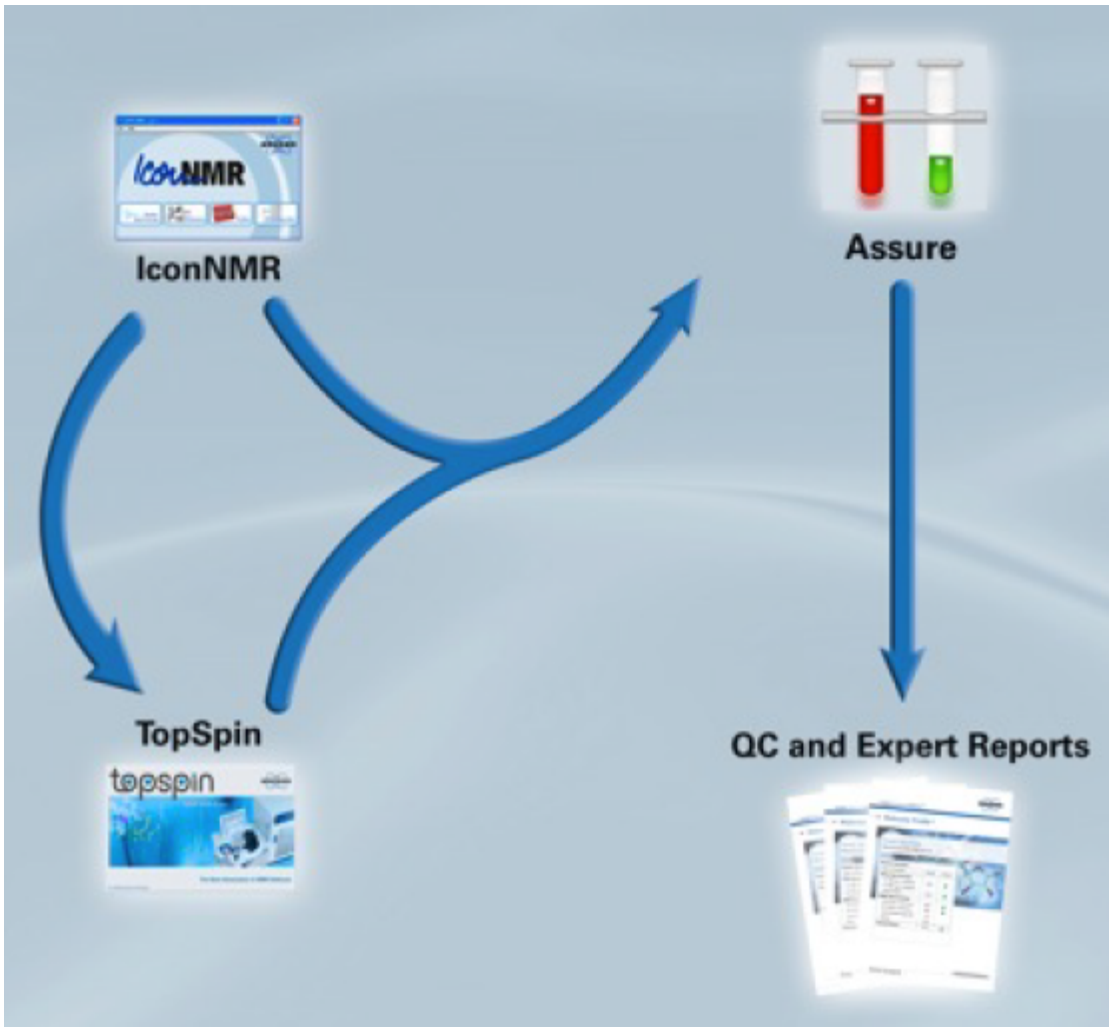


Figure 5.4: AssureNMR Software Package Overview Diagram

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 AssureNMR IconNMR interface.

The figure below shows the progression of sample.

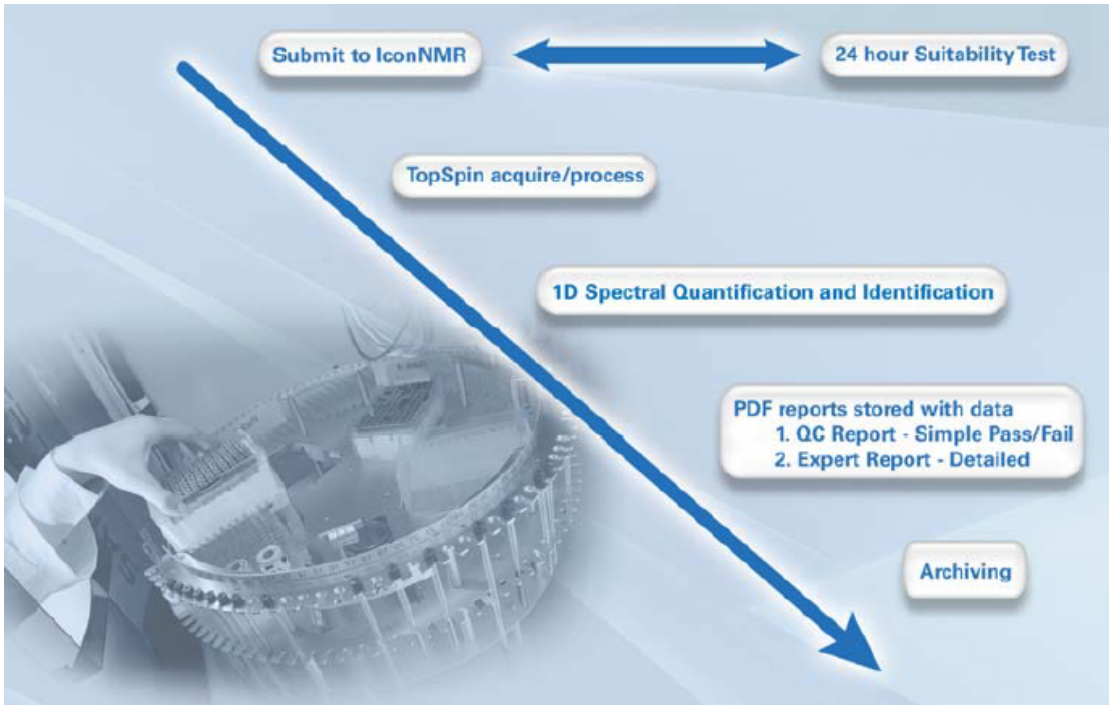
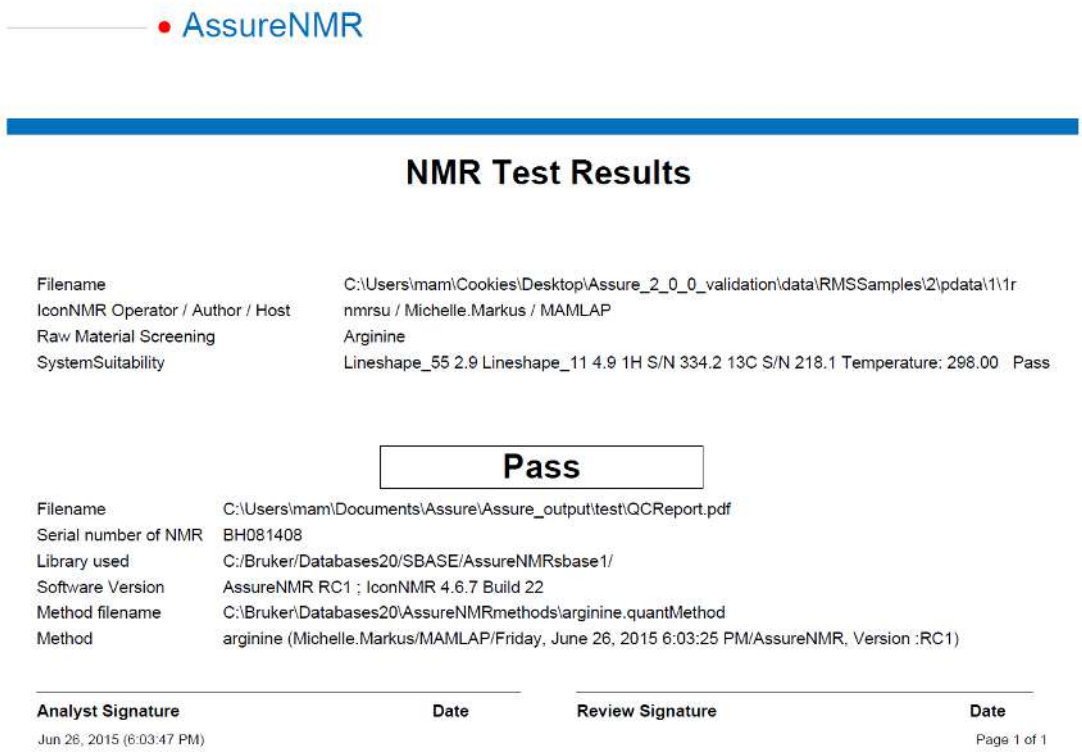


Figure 5.5: Workflow of AssureNMR Software Diagram

5.2.3 Assure - Report Examples

Example of a QC Report for PQ activities



AssureNMR

NMR Test Results

Filename	C:\Users\mam\Cookies\Desktop\Assure_2_0_0_validation\data\RMSSamples\2\pdata\1\1r
IconNMR Operator / Author / Host	nmrsu / Michelle.Markus / MAMLAP
Raw Material Screening	Arginine
SystemSuitability	Lineshape_55 2.9 Lineshape_11 4.9 1H S/N 334.2 13C S/N 218.1 Temperature: 298.00 Pass

Pass

Filename	C:\Users\mam\Documents\Assure\Assure_output\test\QCReport.pdf
Serial number of NMR	BH081408
Library used	C:/Bruker/Databases20/SBASE/AssureNMRsbase1/
Software Version	AssureNMR RC1 ; IconNMR 4.6.7 Build 22
Method filename	C:\Bruker\Databases20\AssureNMRmethods\arginine.quantMethod
Method	arginine (Michelle.Markus/MAMLAP/Friday, June 26, 2015 6:03:25 PM/AssureNMR, Version :RC1)

Analyst Signature **Date** **Review Signature** **Date**

Jun 26, 2015 (6:03:47 PM)

Page 1 of 1

Figure 5.6: Example of a QC Report

6 General Spectrometer/Magnet Maintenance

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.

6.1 General Spectrometer Maintenance

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.

6.1.1 Spectrometer Service Intervals and Schedules

Console

Requirements for exchanging the filter matting in the floor plates or doors are different for the different console types and depend on the laboratory conditions.

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 missing:

Description	Part Number
B-ACS 60/120	Z31597
B-ACS Sample Heater	Z31774
Bruker Sample Transport	Z31123
MAS Rotor Test Station	Z31983
PW5-30µl Level Converter	Z31902
SampleMail / SampleCase	Z31972
SampleJet	Z31749
SamplePro hr-MAS	Z31914
SamplePro Tube	Z33091
Sample Registration Unit	Z31954
SampleXpress	Z31900
SampleXpress Lite	Z31908

Table 6.1: List of Available Automation User Manuals

Bruker offers a variety of service contracts that cover all aspects of planned maintenance (see *www.bruker.com\LabScape*). The planned maintenance checklist (P/N H160158) is used to document all steps of the planned maintenance visit. The description of the performed tests is provided with the document P/N H160159.

6.2 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 (LN_2) 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.

Note: For safe handling of the cryogenic (refrigerated) liquids, please always also review the latest *MSDS* from your supplier!

Bruker offers a wide range of services to support customers with the maintenance for their systems. This includes a refill service for liquid helium and liquid nitrogen.

For further information, visit Bruker's homepage website at *www.bruker.com\LabScape* or contact your local office!

6.2.1 Checking and Refilling Liquid Helium

The helium level should be checked weekly. These values should be recorded (see *Pertinent Magnet Information for SOP's* [▶ 50]). 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 [50]*.
- 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 always be worn.
- 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 helium dewars a **maximum pressure of 0.1 bar** must 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 LN_2 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.

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.

6.2.2 Checking and Refilling Nitrogen

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.

The liquid cryogen transport dewars used to refill the magnet must be of the low pressure type. **Never use high pressure gas-packs.**

Refilling Liquid Nitrogen

- **Safety gloves** and **eye protection** should always be worn.
- When refilling the liquid nitrogen dewars a **maximum pressure of 0.3 bar** must 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 liquid nitrogen 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 nitrogen dewar.

The rod should be inserted deep into the stricture until it begins to enter the nitrogen dewar.

Refer to the User Manual for UltraShield and Ascend NMR Magnet Systems (Nitrogen/ Helium Refilling Procedures) for complete details on other safety aspects for refilling.

6.2.3 Moving an NMR Magnet System after Installation

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! Magnets may only be relocated by trained Bruker personnel.

Revalidation of the NMR Magnet system is required after the relocation.

Also check safety requirements for the NMR system in the corresponding user manual.

6.3 Magnet Information and Control System

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

6.3.1 Main Functions

Overview

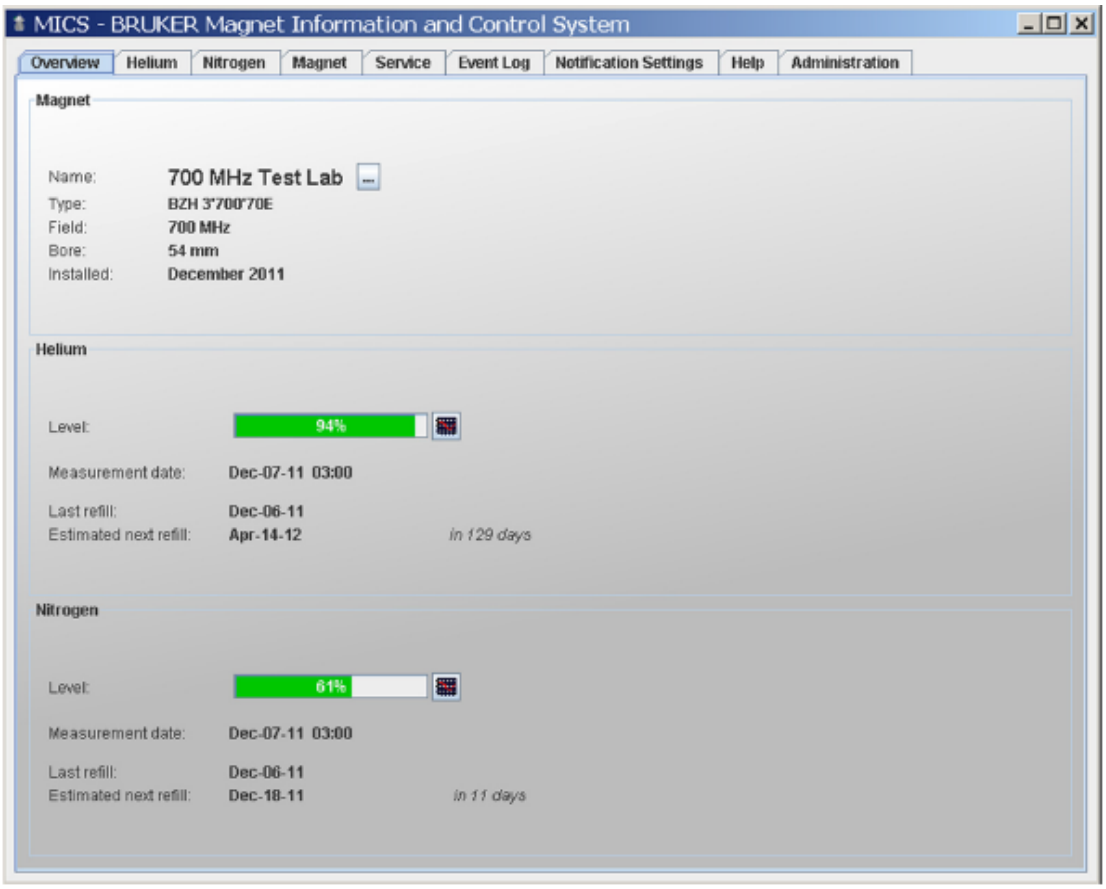


Figure 6.1: MICS Overview

The **Overview** tab displays basic magnet information and an overall status of the cryogenic agents of the magnet system. It is possible to change the magnet name based on individual requirements. 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.

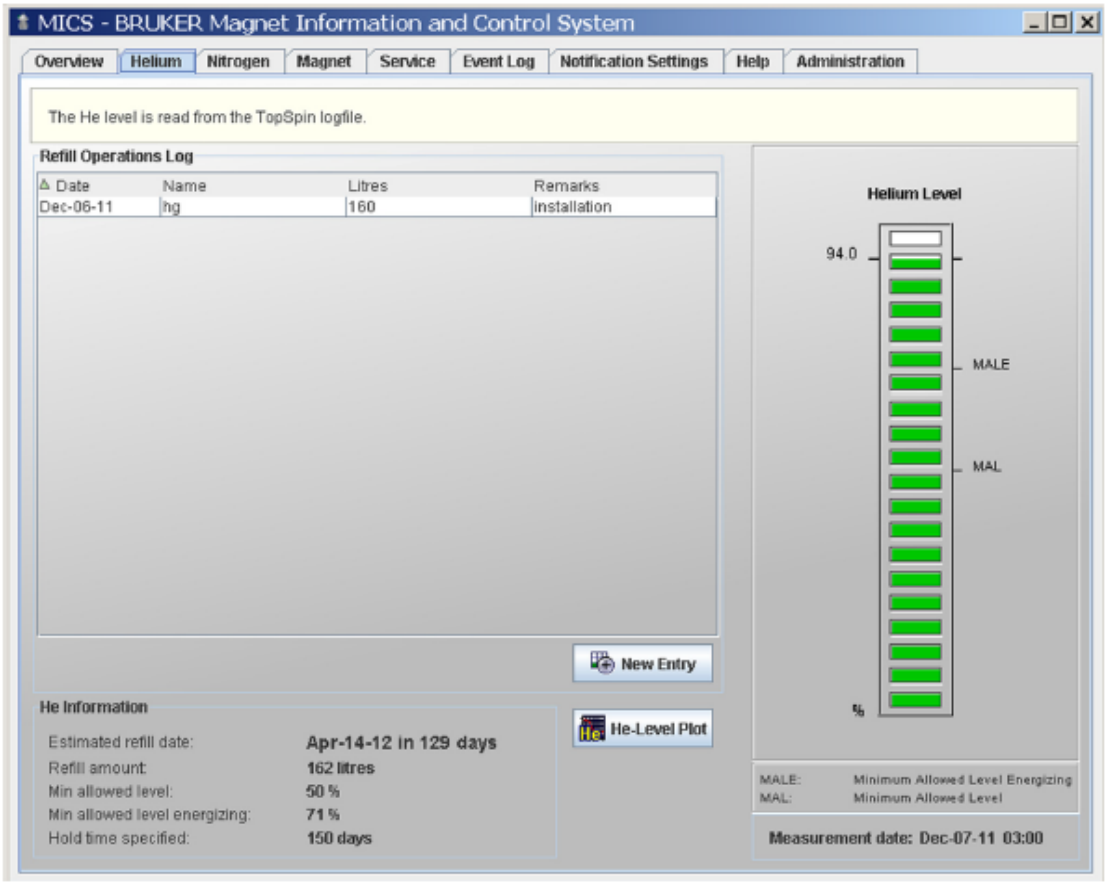


Figure 6.2: MICS Helium Tab

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.

The helium level is measured automatically once a day and written in the helium log file.

By default, MICS reads the last measured value directly from the BSMS and keeps track of these values.

Alternatively, MICS can also be configured to read from the helium log file.

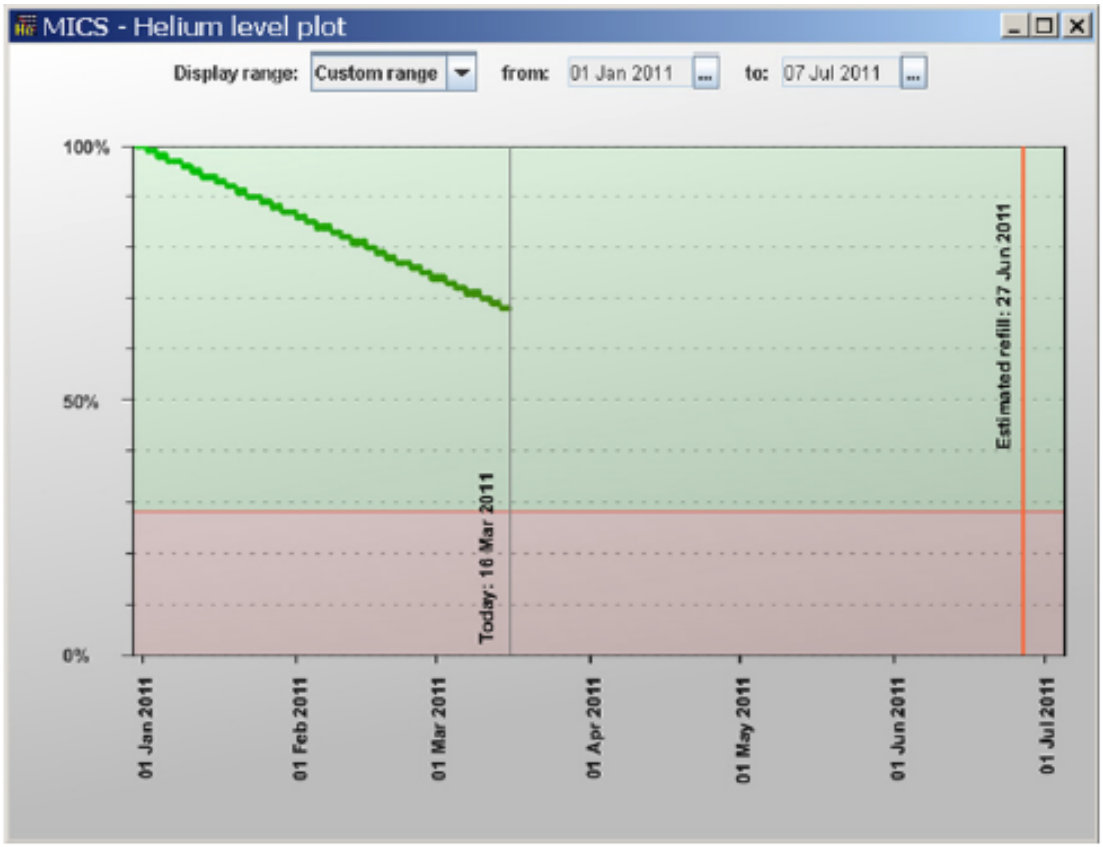


Figure 6.3: MICS Helium Level Plot

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 part of a standard delivery, 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).

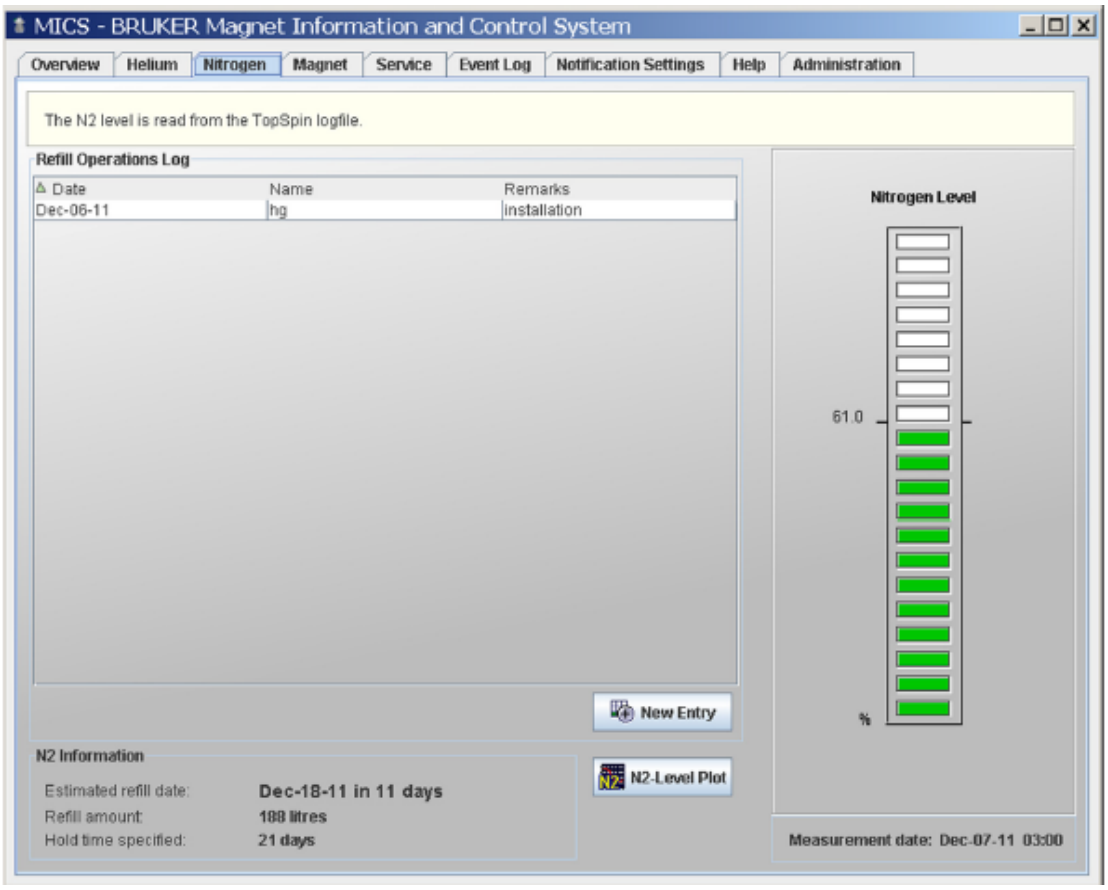


Figure 6.4: MICS Nitrogen Tab

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.

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).

Bruker offers a remote monitoring service to support customers with the maintenance for their systems. For further information, visit our website at *www.bruker.com\LabScape* or contact your local office!

6.4 Adjustments

The following adjustments can be made **periodically** to optimize instrument performance.

6.4.1 Frequent Routine Adjustments

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 ^{1}H and one for ^{13}C in a dual $^{1}H/^{13}C$ probe; one for ^{1}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 rarely 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 (P/N Z31633) for details.

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.

6.4.2 Long Term Adjustments

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 that is required and the optimal spectrum depends on the kind of pulse which is to be optimized.

Refer to the **AVANCE (NEO) Beginners Guide** or the **Solids Experiments Manual** for details:

Title	Part Number
AVANCE NEO Beginners Guide (English)	H171804E
AVANCE NEO Beginners Guide (Chinese)	H171804CN
AVANCE NEO Beginners Guide (German)	H171804D
AVANCE NEO Beginners Guide (French)	H171804F
AVANCE NEO Beginners Guide (Italian)	H171804IT
AVANCE NEO Beginners Guide (Polish)	H171804PL
AVANCE NEO Beginners Guide (Portuguese)	H171804PT
AVANCE NEO Beginners Guide (Spanish)	H171804S
AVANCE Beginners Guide (English)	Z31633E
AVANCE Beginners Guide (Chinese)	H3163CN
AVANCE Beginners Guide (German)	Z31633D
AVANCE Beginners Guide (French)	Z31633F
AVANCE Beginners Guide (Spanish)	Z31633S
AVANCE Beginners Guide (Polish)	Z31633PL
AVANCE Beginners Guide (Portuguese)	H156878
AVANCE Beginners Guide (Italian)	Z31633I
Solids Experiments Manual	Z31848
Other language versions of the Beginners Guide can be provided upon request.	

Table 6.3: Part Number for Reference Manuals

6.5 Software Maintenance

When software updates are available on an otherwise fully functional spectrometer, the basic TopSpin configuration steps must be performed. This is typically followed by an operational check using AssureSST. See *AssureSST Tests [▶ 31]* for details.

Detailed software update information is provided for every software version in the Bruker Release Letter.

The Release Letter is shown during the installation of the software update, is available through the TopSpin help menu, and can also be downloaded from the Bruker homepage *www.bruker.com*.

7 SOP's, Data Security and More

7.1 Standard Operating Procedures

Standard Operating Procedures (SOP's) are written procedures for a laboratory's program. They should 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 preferably be written by key laboratory personnel who are close to the instrument, such as the Laboratory Manager, often also identified as the system owner.

It should also be thoroughly reviewed by the instrument's operators to verify that the procedure can be followed by the intended operator.

SOP's should be written on how the procedures actually are to be followed, 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 ideally contain:

- A unique identification and revision number.
- Page numbers and total number of pages.
- Purpose, background and flow chart.
- 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

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.

The use of specific tools and/or working details should be documented in a working instruction, rather than in a standard operating procedure.

7.1.2 Pertinent Magnet Information for SOP's

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 used in a GLP environment.

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 Super Conducting 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

Due to the strong magnetic fields and presence of cryogens 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 standalone 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 unauthorized members of staff. 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 (5 Gauss/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 **DURING WORKING HOURS** advise the following personnel:			
In case of problems or emergency's **DURING NIGHT, WEEKEND OR HOLIDAYS** 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 unauthorized members of staff, 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 using barriers or other visual warning devices. Consult your safety manual for specific information concerning the danger zone – 0.5 mT (5 Gauss) and 3 mT (30 Gauss) lines.

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 (a suitable *Figure 7.1: [▶ 53]* for room entrance areas is available at Bruker under P/N H179657):

- Magnet systems **attract metals** made from iron, steel, or nickel.
- The magnet system creates a very strong magnetic field. Under the influence of the magnets sphere, 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 yourself.
- Magnet systems are cooled by use of liquid nitrogen and helium. In liquid state, these gases have a temperature of -196 °C and -269 °C respectively. Skin contact with these liquids can lead to **severe cold burns**; eye contact could result in **blindness** (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**!!!

Figure 7.1: Example of a Multi-Lingual Warning Plate for Room Entrance Areas with High EMF

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 CO_2 non-magnetic fire extinguishers (aluminum, fiberglass) should be used.
- Breathing equipment which uses oxygen tanks made from magnetic material can be life threatening when used close to a magnet system that still has a magnetic field present.

Information for Handling Medical Emergencies

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

Key points that should be addressed include:

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

It is also 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:

Always refer to local occupational health and safety regulations and available instructions.

- Seek immediate first aid.
- Get the injured into a warm room (ca. 22 °C/72 °F).
- 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

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 System 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

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.

TopSpin is a Bruker 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 standalone “data station” version.

TopSpin is compliant with 21 CFR Part 11. This is documented in the *TopSpin: 21 CFR Part1 11 Compliance Document* (P/N H152957).

Use the **Bruker Computer System Validation Protocol** (P/N H166444) for a 21 CFR Part 11 validation procedure if this should be required.

8 Summary of General Instrument Validation Tools

8.1 NMRPT

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

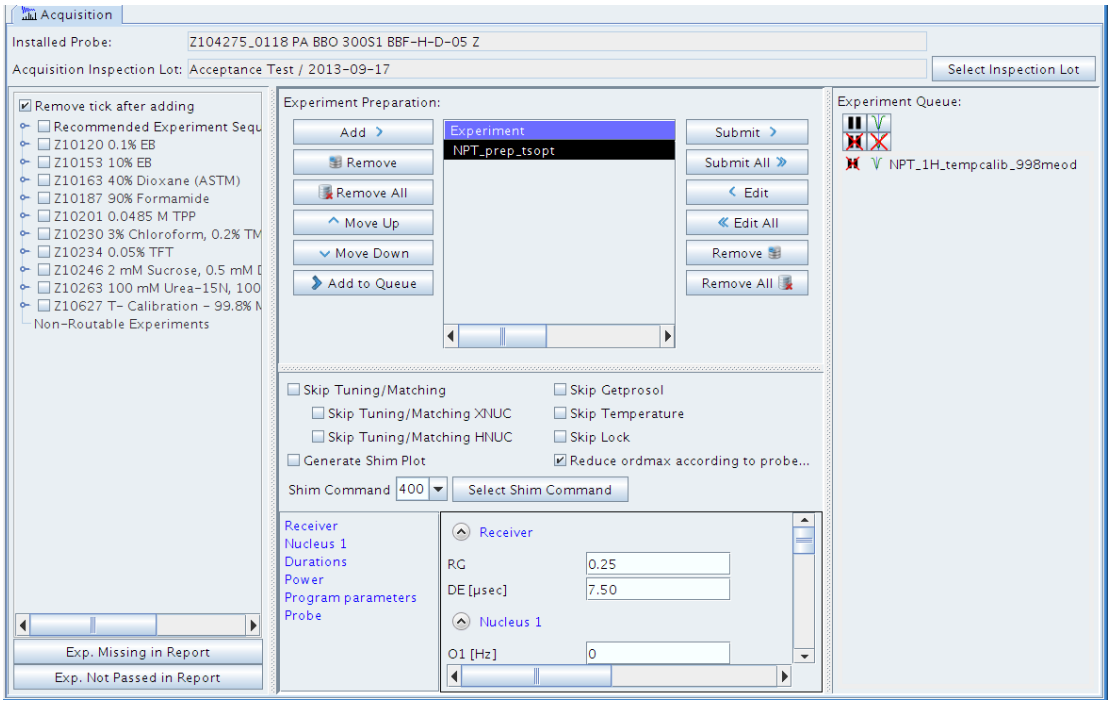


Figure 8.1: The NMRPT Software Interface

8.2 Assure – System Suitability Test (AssureSST)

Summary of Features

- Automated System Suitability Test includes acquisition and analysis of NMR standards ^{1}H lineshape, *1H* sensitivity, *13C* sensitivity, *19F* sensitivity, *31P* sensitivity, and temperature calibration.
- To reduce routine maintenance of the spectrometer shims, shim sets from successful ^{1}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 AssureSST module was designed 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 based on an interval selected by the user.

The AssureSST module can work either in a standalone mode where the user can use the normal IconNMR submission interface, or in parallel with the AssureNMR module.

If AssureSST determines the system to be out of specification, then general sample submissions through IconNMR or AssureNMR will stop until all specifications are achieved.

The use of AssureSST to support the use of the NMR spectrometer in a GLP environment is outlined in the section *AssureSST Tests [31]*.

8.3 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 *Magnet Information and Control System [43]*.

9 Contact

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WEEE DE43181702

Bruker BioSpin Hotlines

Contact our Bruker BioSpin service centers.

Bruker BioSpin provides 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 service center or hotline you wish to contact from our list available at:

https://www.bruker.com/service/information-communication/helpdesk.html

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Glossary

13C

Carbon-13 (13C) is a natural, stable isotope of carbon and one of the environmental isotopes.

19F

Fluorine-19 nuclear magnetic resonance is an analytical technique used to identify fluorine-containing compounds. 19F is one of the most important nuclei for NMR spectroscopy.

1H

1H, a number of chemical compounds with one hydrogen atom.

31P

Phosphorus-31 NMR spectroscopy (NMR stands for nuclear magnetic resonance) is an analytical technique. Solution 31P-NMR is one of the more routine NMR techniques because 31P has an isotopic abundance of 100% and a relatively high magnetogyric ratio.

BASH

Bruker Advanced Service Handbook

DQ

Design Qualification (DQ): Documented verification that the proposed design is suitable for the intended purpose (GAMP5).

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.

IQ

Installation Qualification (IQ): Documented verification that a system is installed according to written and pre-approved specifications (GAMP5).

MSDS

Material Safety Data Sheet

NRTL

NRTL: Nationally Recognized Testing Laboratory. Workplace product safety is a critical component of workplace safety and both the construction and general industry OSHA electrical standards contain requirements for certain products to be tested and certified by an NRTL. NRTLs are private sector organizations that are recognized by OSHA to perform this certification (extract from: https://www.osha.gov/dts/otpca/nrtl/).

OQ

Operational Qualification (OQ): Documented verification that a system is operated according to written and pre-approved specifications throughout specified operation ranges (GAMP5).

PQ

Performance Qualification (PQ): Documented verification that a system is capable of performing the activities of the processes it is required to perform, according to written pre-approved specifications, within the scope of the business process and operating environment (GAMP5).

Quench

A magnet quench is the breakdown of superconductivity in a partially or fully energized magnet. The stored field energy is transformed into heat, leading to a fast evaporation of liquid helium. During a quench, an extremely large quantity of helium gas (i.e. 43 m3 to 595 m3 depending on the magnet type) is produced within a short time. Although these gases are inert, if generated in large enough quantities, they can displace the oxygen in the room causing potential danger of suffocation.

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