NMR in Pharma: Instrument Qualification

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Much has been written about the general objectives behind Instrument Qualification, as well as the detailed practical requirements to complete and maintain the collection of protocols designed to demonstrate that Qualification has been carried out appropriately, and in a timely manner. This document describes the general approach to Qualification from Bruker BioSpin, which in turn is designed to help customers achieve compliance.

It is noted that Qualification is a major subject area within the Pharmaceutical industry and this document describes only the detailed implementation associated with an analytical measurement system, intended for use in environments that are subject to "Good Laboratory Practice" (GLP) or "Good Manufacturing Practice" (GMP) regulations.

Annex 15 of the EU GMP Guidelines on Qualification and Validation[1] is a very useful document with multiple insights into the regulatory inspections over Qualification.

There is no doubt that the Qualification status of equipment, facilities and instrumentation etc. is frequently evaluated during regulatory inspections. A simple analysis of warning letters issued by the US Food and Drug Administration (FDA) held on their website shows that there is a strong focus on Qualification, with negative findings appearing regularly[2]. A few examples drawn from this source are shown below and on the following page – the calendar year is indicated in each document clip:

2018

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. The third-party review of your operation should comprehensively assess and assist with remediating your operations, including but not limited to: water system, process design and bioburden control, the laboratory system, equipment, facilities, microbiology specifications, qualification/validation program, and the quality unit.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

[1] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10_annex15.pdf. Retrieved January 2019
[2] https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm. Retrieved January 2019

2016

b. Laboratory data generated by the Karl Fischer autotitrator was not restricted. The program used to run your autotitrator, Tiamo™ 2.3 Light, is unable to record audit trails and cannot support accounts with unique user names and passwords for individual users. We acknowledge your commitment to upgrade to a compliant software package. However, your response is inadequate because you failed to provide an interim solution prior to its installation. In your response to this letter, provide a copy of the performance qualification and training activities associated with the newly purchased software.

2015

2. Failure to prevent unauthorized access or changes to data and to provide adequate controls preventing data omissions.

Our inspection noted that your firm did not retain complete raw data from testing performed to assure the quality of (b)(4), API. Specifically, our inspection revealed your firm did not properly maintain a back-up of HPLC chromatograms that form the basis of your product release decisions. Our inspection revealed discrepancies between the printed chromatograms and the operational qualification protocol for the High Performance Liquid Chromatography (HPLC) system, which is intended to demonstrate correct operation of the HPLC. These discrepancies included injection sequences and values to calculate relative standard deviation (RSD).

While investigating these discrepancies, our investigator requested the original electronic raw data. Your quality unit, after consulting with the Information Technology (IT) department, stated they were unable to retrieve the original electronic raw data because back-up discs were unreadable. Your quality unit then stated that back-up disks have been unreadable since at least 2013. Your HPLC system is used to test (b)(4), API for batch release. However, without complete, accurate, reliable, or retrievable raw data about the HPLC system's qualification, you lacked complete assurance that the system was operating as intended.

The process of Qualification has a logical flow and follows multiple standardised steps, which are described immediately below and shown in the following diagram:

URS (User Requirement Specification). A detailed specification of the instrumentation or equipment, written from the point of view of the required end-use. Note: Such a document is typically used throughout the life cycle of the instrument.

FDS (Functional Design Specification). A detailed specification of instrumentation or equipment written from the point of view of the vendor. This document is important if the requirements in the URS cannot be delivered using standard equipment.

DQ (Design Qualification). A document that describes how the design of the instrument or equipment is compliant with GMP principles. Note: Such a document is especially important if any new technology needs to be developed.

FAT (Factory Acceptance Tests) / SAT (Site Acceptance Tests). These describe the results of formal tests either on components, or on the complete system that may be completed at the site where the system is manufactured (FAT) or at the destination site (SAT).

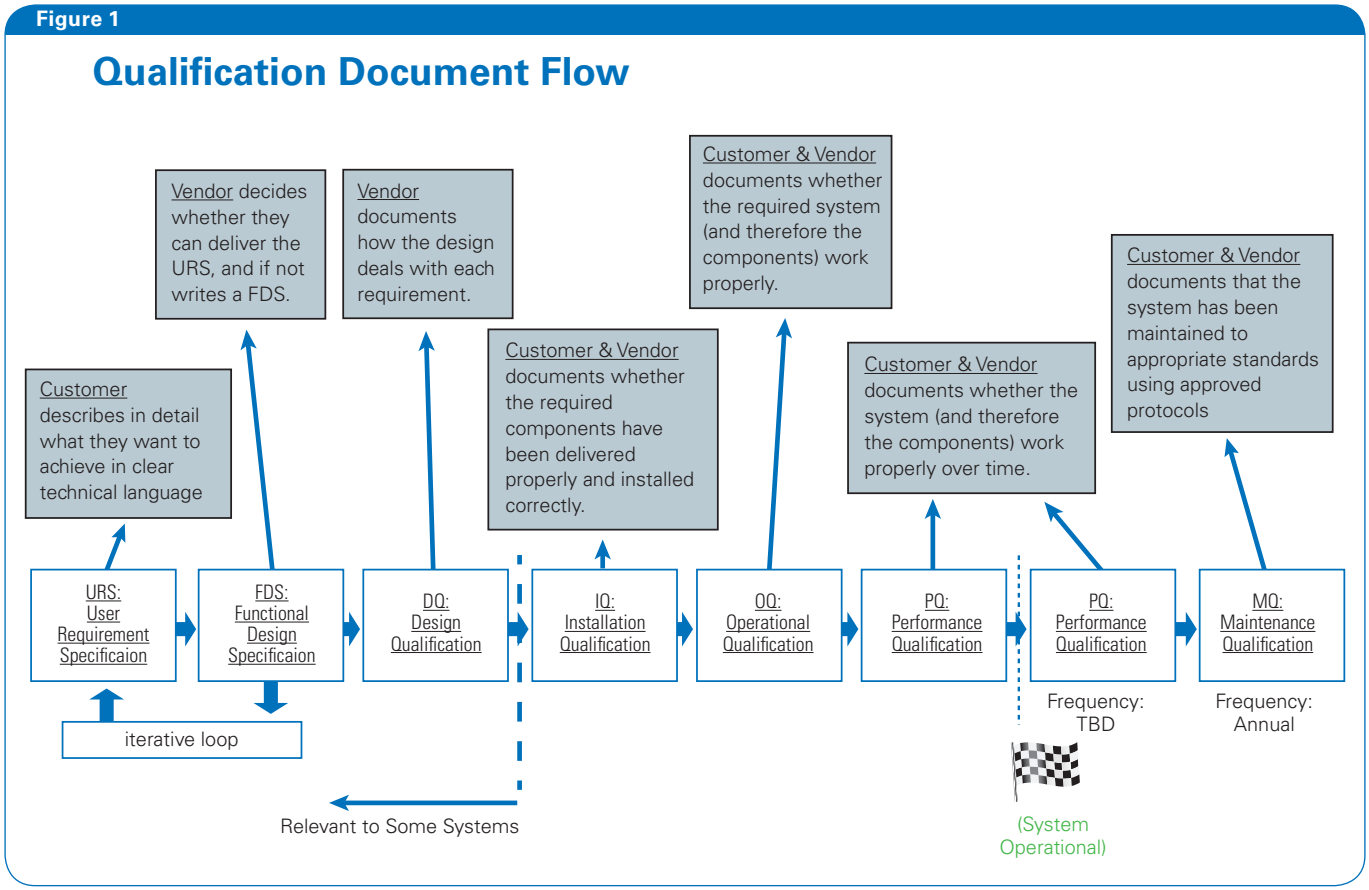
IQ (Installation Qualification). This qualification step documents that the system and all its components have been delivered correctly and installed properly.

OQ (Operational Qualification). This qualification step confirms that the system performs correctly and within the predetermined specification. It is often convenient to combine OQ with IQ.

PQ (Performance Qualification). This qualification step confirms that the system operates correctly but using materials and methods that are directly relevant to the process i.e. production material (or qualified substitutes). The PQ is performed following the installation of the system and at a frequency thereafter that varies between users and applications but an annual PQ is regarded as the minimum.

MQ (Maintenance Qualification). This describes and documents all maintenance activities performed on the instrumentation (both preventative maintenance – PM - and that in response to any failures), including the identity and qualification status of the service engineer(s). The minimum expected frequency of a PM visit is annual, and a PQ is typically performed upon its completion.

Figure 1



The flow of Qualification documents

Two additional features in this diagram are worthy of note:

- There can be an iterative loop between the URS and FDS steps because an end user may request a feature or behavior from an instrument that is not technically feasible, or not available at a reasonable cost within a given time frame. This loop is essentially a negotiation between the user and vendor over scope, cost and time to supply.

- URS, FDS and DQ are not applicable to all systems simply because the end user could purchase a NMR system that is an assembly of existing components i.e. it is COTS. In such situations, it is often sufficient to state this directly in correspondence between the customer and the vendor (this correspondence should be kept on file and perhaps backed up by an inspection of the manufacturer and / or examination of their conformance with standards such as ISO 9001 or ISO 13485).

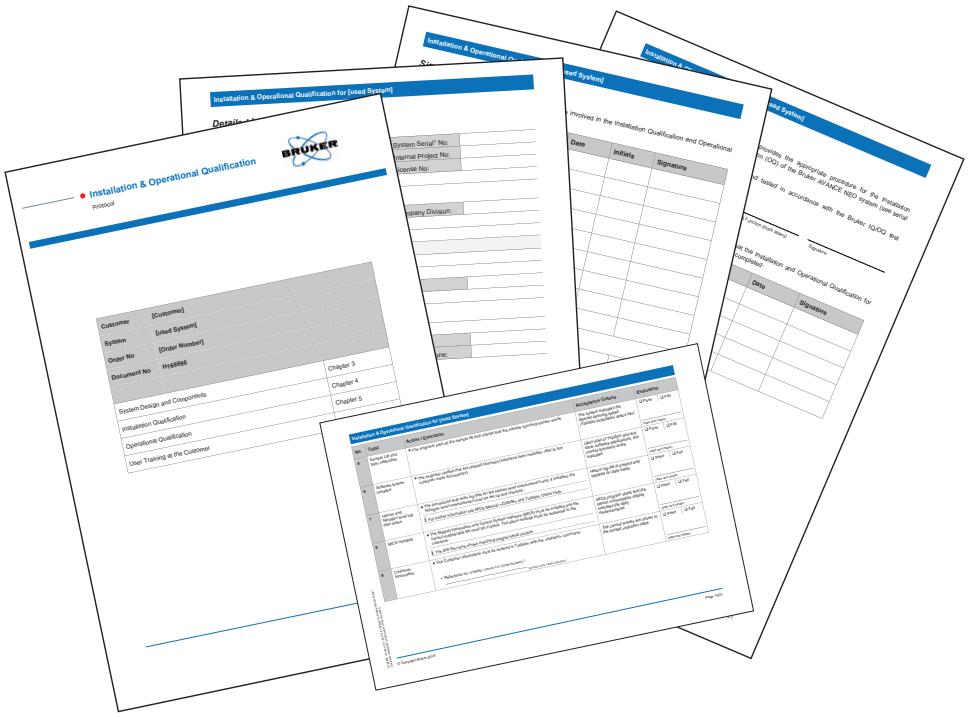
Bruker BioSpin is able to support customers with Qualification in a number of ways i.e. during manufacture, components are tested on multiple occasions, using standard materials or protocols, the test results are provided within the documentation pack on receipt of the system.

Additionally, IQ and OQ protocols are available and these are completed by a fully qualified service engineer during installation and testing of the system, working in close collaboration with the team at the receiving site. Once completed, reviewed and "signed off" by various customer representatives, these protocols form part of the package of documents that help to show that a system is compliant.

For instrumentation, PQ is typically performed by a customer using their own materials although Bruker Biospin also supplies software that supports PQ (Assure SST, AutoCalibrate).

The Qualification documents provided by Bruker Biospin are applicable to new systems, but can also be applied to existing systems if required, for example, by a change control review.

Figure 2



Example pages from the IQ / OQ protocols

Abbreviations

COTS	Commercial-off-the-shelf	GMP	Good Manufacturing Practice
cGMP	Current Good Manufacturing Practice (FDA regulations)	IQ	Installation Qualification
EU	European Union	MQ	Maintenance Qualification
FAT	Factory Acceptance Test	OQ	Operational Qualification
FDA	Food and Drug Administration	PM	Preventative Maintenance
FDS	Functional Design Specification	PQ	Performance Qualification
GLP	Good Laboratory Practice	URS	User Requirements Specification
		SAT	Site Acceptance Test

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