Efficient and economical HPLC Performance Qualification
Consensus paper of the Working Group Drug Quality Control / Pharmaceutical Analytics of the German Pharmaceutical Society (DPhG), in collaboration with the Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik (APV; engl.: International Association for Pharmaceutical Technology)

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A proposal is made how an innovative concept of continuous Performance Qualification can improve Analytical Instrument Qualification (AIQ) considerably. It reduces time and effort during routine Operational and Performance Qualification (OQ / PQ) on the one hand and provides high quality data which allows for demonstrating system qualification to all parties involved in GMP auditing, on the other.

The discussion started in October 2007 during the annual symposium of the Working Group Drug Quality Control / Pharmaceutical Analytics of the German Pharmaceutical Society (DPhG). The Working Group Analytics and Quality Assurance of the Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik (APV) supported and substantially contributed to the concept. Eventually the conclusion of the discussions, presentations and evaluations was submitted as a draft paper [1] in June 2009 and accepted in August 2009. Meanwhile the concept is also supported by the Bundesverband der Arzneimittelhersteller (BAH).

1. Introduction

Manufacturing and quality control of pharmaceutical products are subject to restrictions of a highly formalized environment. This, of course, is very reasonable and important since pharmaceuticals are goods of exceptional quality which must be standardized worldwide and surveyed on highest level. The triangle of data quality [Fig.1] with the AIQ at its basis displays the parts of this quality survey.

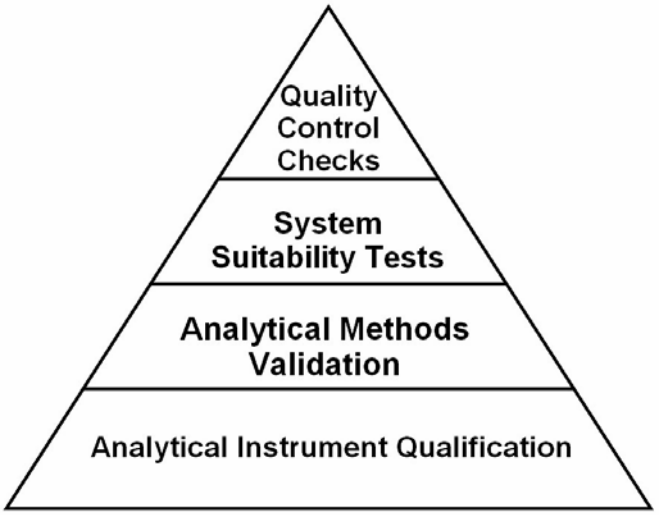

Figure 1: data quality triangle according to USP <1058> [2]

2. Analytical Instrument Qualification vs. Equipment Qualification/Validation

Standardized nomenclature is of great importance in a regulated environment. However, it was not until the approval of the USP general chapter <1058> in 2008, that the nomenclature became consistent. Since then the term *validation* is used for analytical methods and software, while *qualification* is reserved for hardware. The general term *equipment* had also been replaced by the more precise term *analytical instrument.*

2.1. USP general chapter <1058> AIQ

Although, General Chapters with numbers larger than <999> are only recommendatory in nature, this monograph was well received by the pharmaceutical industry as it forms an official regulatory basis for the qualification of equipment in pharmaceutical quality control.

The General Chapter proposes three different categories of instruments with differing qualification effort to be applied:

Group A (simple equipment like stirrers)
Group B (e.g. thermometers, pH meters, refractometers)
Group C (sophisticated, mostly computer-based devices like HPLC, GC, NIR, etc.)

In addition it recommends following the well-established qualification phases also for analytical instrument qualification:

- Design Qualification
- Installation Qualification
- Operational Qualification
- Performance Qualification

These qualification phases are exhaustively discussed in the literature [1-5].

3. Classic Performance Qualification and System Suitability Test

Performance Qualification is not a one time exercise. In fact it includes the periodic checks of the instrument like regular calibration activities, preventive maintenance and necessary repairs over the whole life cycle of the individual piece of equipment. However, it only provides a snapshot of system performance as it is performed periodically.

System Suitability Tests are generally performed directly before and between routine analytical series. They are method specific and based on the concept that the equipment (including software and analytical procedures) constitutes an integral system that can be evaluated as such.
Up to now it was not believed that SSTs could substitute PQ to a major extent.

4. Proposal of the Working Groups for a <u>new</u> concept of a continuous (ongoing) Performance Qualification

Continuous PQ is an innovative and beneficial concept which allows for a thorough instrument qualification by spending less time and effort but obtain even higher data quality at the same time. Therefore it combines a straightforward parameters list [Tab.1] with the fact that under certain circumstances SSTs provide data of comparable informative value as PQs do [1].

Table 1: 12 parameters which are necessary to qualify an HPLC instrument thoroughly. In case one or more of the suggested procedures are not realizable due to an inapt SST, one should choose an appropriate SST (if possible) or revert to the classic PQ for this instrument. Tolerance values were chosen according to [1]. This table complies with the EDQM specifications [8]

Module	Parameter	Procedure	Tolerance
Injector	Precision of injection volume	Can be determined by measuring the RSD% of peak areas	<1.0% RSD
	Linearity of injection volume	Can be determined by stepping up the injection volume successively (1,10,20,50,100µl) and measuring the increase of the peak areas	$R^2 \geq 0.999$
	Injection Carryover	Can be determined by running a blank test directly after an analysis and measuring possible absorption	method specific
Autosampler	Thermostatting precision	Measurement of temperature over a set period of time. *only suitable for autosamplers with temperature control*	±2°C
Solvent delivery system	Flow rate accuracy	Can be determined by measuring the volumetric flow rate of mobile phase through the column over a set period of time. (1.0 ml/min for 10 min, 2.0 ml/min for 5 min and 2.5 ml/min for 10 min)	expected volume ± 3%
	Mobile phase proportioning	Can be surveyed continuously with the aid of retention times and their RSD%. If unexpected discrepancies occur a classic gradient test is advisable.	
	Flow rate precision	Can be determined by measuring the RSD% of retention times	<1.0% RSD

Detector	Wavelength accuracy	Can be determined by measuring the spectrum of one substance of the test sample	specific maxima ± 2 nm
	Noise	Can be determined by carrying out a dynamic measurement with mobile phase for 15 min	$< 1 \cdot 10^{-3}$ AU (for dynamic noise)
	Drift	Can be determined by carrying out a dynamic measurement with mobile phase for 1 h	$< 5 \cdot 10^{-3}$ AU/h
	Linearity of detector response	Can be determined in the same manner as linearity of injection volume	$R^2 \geq 0.999$
Column oven	Thermostatting precision of column oven	Can be determined by measuring the RSD% of retention times	<1.0% RSD

Maintaining the consistency of nomenclature, these Working Groups recommend using the term *continuous* instead of *ongoing* to avoid confusion with different meanings of "ongoing PQ" in the literature [5].

Concluding, these Working Groups propose that this concept becomes an accepted standard procedure for Performance Qualification.

5. How to employ continuous PQ to a particular analytical instrument or analytical laboratory?

The Working Groups suggest the following course as a possible example:

1. Examine the SST of your method. If there are multiple methods running alternately on the system, take the simplest one(s). Make sure that the respective standard substances are well defined.
2. Look for a well separated peak (you should find at least one as this is typically claimed for an SST [6,7])
3. Create and validate a spreadsheet, which calculates RSD% for the peak area and retention time of the selected peak.
4. Run your analysis series, which by default may be structured as followed:
    a. 1 x Blank injection (determination of baseline noise or drift)
    b. $3 \leq n \leq 6$ x Standard [6] (determination of all AUC or t_R dependant parameters)
    c. 1 x Blank injection (determination of baseline noise or drift)
    d. 1 x Impurity (only if testing for impurities is demanded in the SOP → The tolerance value is method / substance specific)
    e. 5-10 x Sample (the actual analysis)
    f. 1 x Standard (determination of AUC drift)

5. Since there is a validated spreadsheet, the determination of all AUC and t_R related parameters is done automatically whenever the analysis series is performed. It is recommendable to collect these data in a control chart in order to establish a performance history of the instrument in terms of a lifecycle management.
6. The parameters not related to AUC or t_R can be controlled with a little extra effort using the routine analysis data. Depending on the applications, these parameters should be checked at appropriate intervals, for example as defined in the classic PQ [1].

6. What to do when an SST is inapt? – Limitations of this concept.

Not all SSTs are capable of providing all necessary performance information. In this case three scenarios can be differentiated.

Scenario I:
Multiple methods are run alternately on one instrument. The SST of the most appropriate method can be selected. Hence the instrument will be qualified whenever this method is in use.

Scenario II:
One method is run on the instrument and not all parameters can be determined using the SST. In this case these particular parameters must be determined as they were during classic PQ. If e.g. a compound with poorly defined UV – maxima is analyzed wavelength accuracy cannot be checked properly. In that case it is unavoidable to test wavelength accuracy traditionally with $HoClO_4$ or caffeine.

Scenario III:
One method is run on the instrument and the SST is completely unsuitable to provide PQ relevant data. In that case the concept of continuous PQ cannot be applied. Classic PQ must be carried out as before.

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7. References

[1] Kaminski et al., *J Pharm Biomed Anal,* accepted for publication

[2] USP, United States Pharmacopoeia 31 NF-26 S1 General Chapter <1058> (2008) Analytical Instrument Qualification.

[3] S.K. Bansal, T. Layloff, E.D. Bush, M. Hamilton, E.A. Hankinson, J.S. Landy, S. Lowes, M.M. Nasr, P.A. St Jean, V.P. Shah, *AAPS PharmSciTech* 5 (2004) E22.

[4] V. Grisanti, E.J. Zachowski, *LC-GC NA* 20 (2002) 356 – 362.

[5] P. Bedson, D. Rudd, *Accred Qual Assur* 4 (1999) 50 – 62.

[6] Ph.Eur., European Pharmacopoeia 6.4. Chapter 2.2.46 (2009) Chromatographic separation techniques.

[7] USP, United States Pharmacopoeia 31 NF-26 S1 General Chapter <621> (2008) System Suitability.

[8] http://www.edqm.eu/medias/fichiers/Annex_1_Qualification_of_HPLC_Equipment.pdf