A REVIEW: QUALIFICATION OF ANALYTICAL INSTRUMENT

(DIFFRENTIAL SCANNING COLORIMETRY & GAS CHROMATOGRAPHY)

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INTRODUCTION:

Calibration and qualification of equipment are key requirements in GMP guidelines (EU GMP Guide, Annex 15 to EU GMP Guide, and FDA's Code of Federal Regulations, 21 CFR Part 211). These requirements also apply to instruments and systems in analytical laboratories of the pharmaceutical industry. Besides calibration and qualification, the validation of computerised systems is another key issue. The software components associated with the instruments and systems must be shown to be fit for their intended purpose. Computer validation requirements and guidances for the pharmaceutical industry are laid down, amongst others, by the EU (Annex 11 to EU GMP Guide, the PIC/S (Good Practices for Computerised Systems in Regulated "GXP" Environments"), GAMP® (Good Automated Manufacturing Practice), and FDA's Part 11.

The United States Pharmacopoeia (USP) has adopted ,**Analytical Instrument Qualification,** in 2008. This General Chapter has been updated in 2017 and a new version is coming up soon.

The pharmaceutical industry relies on the precision and accuracy of analytical instruments to obtain valid data for research, development, manufacturing, and quality control. Indeed, advancements in the automation, precision, and accuracy of these instruments parallel those of the industry itself. Through published regulations, regulatory agencies require pharmaceutical companies to establish procedures assuring that the users of analytical instruments are trained to perform their assigned tasks. The regulations also require the companies to establish procedures assuring that the instruments that generate data supporting regulated product testing are fit for use. The regulations, however, do not provide clear and authoritative guidance for validation/qualification of analytical instruments.

Consequently, competing opinions abound regarding instrument validation procedures and the roles and responsibilities of the people who perform them. On the latter point, many believe that the users (analysts), who ultimately are responsible for the instrument operations and data quality, were not sufficiently involved when the various stakeholders attempted to establish criteria and procedures to determine the suitability of instruments for their intended use. Therefore, the American Association of Pharmaceutical Scientists sponsored a workshop entitled, "A Scientific Approach to Analytical Instrument Validation," which the International Pharmaceutical Federation (FIP) and International Society for Pharmaceutical Engineering (ISPE) cosponsored. Held in Arlington, Virginia, on March 3-5, 2003, the event drew a crosssection of attendees: users, quality assurance specialists, regulatory scientists, validation experts, consultants, and representatives of instrument manufacturers.

The conference's objectives were these:

• Review and propose an effective and efficient instrument validation process that focuses on outcomes, and not only on generating documentation.

• Propose a risk-based validation process founded on competent science.

• Define the roles and responsibilities of those associated with an instrument's validation.

• Determine whether differences exist between validations performed in laboratories that adopt Good Laboratory Practice (GLP) regulations vs those that adopt Good Manufacturing Practice regulations (GMP).

• Establish the essential parameters for performing instrument validation.

• Establish common terminology.

• Publish a white paper on analytical instrument validation that may aid in the development of formal future guidelines, and submit it to regulatory agencies.

The various parties agreed that processes are "validated" and instruments are "qualified." This document, therefore, will use the phrase "Analytical Instrument Qualification (AIQ)," in lieu of "Analytical Instrument Validation." The term "validation" should henceforth be reserved for processes that include analytical procedures and software development.

DEFINATION OF QUALIFICATION:

Qualification is defined as an action of providing that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results.

Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

It is the entire process by which products are obtained from manufacturers or distributors, examined and tested, and then identified as a qualified products list.

COMPONENTS OF DATA QUALITY

Analytical instrument qualification helps justify the continued use of equipment, but it alone does not ensure the quality of data. Analytical instrument qualification is 1 of the 4 critical components of data quality. Figure 1 shows these components as layered activities within a Quality Triangle. Each layer adds to the overall quality. Analytical Instrument Qualification forms the base for generating quality data. The other essential components for generating quality data are the following: Analytical Methods Validation, System Suitability Tests, and Quality Control Checks.

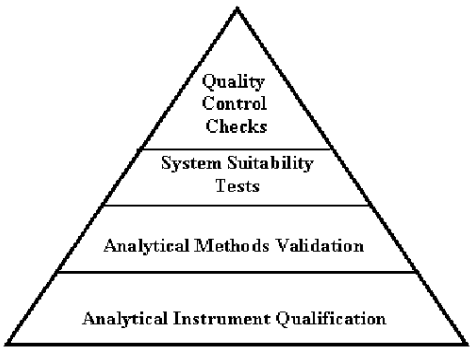


Figure 1. The Components of Data Quality

These quality components are described below.

Analytical Instrument Qualification :

Analytical Instrument Qualification (AIQ) is documented evidence that an instrument performs suitably for its intended purpose and that it is properly maintained and calibrated. Use of a qualified instrument in analyses contributes to confidence in the veracity of generated data.

Analytical Methods Validation:

Analytical methods validation is documented evidence that an analytical method does what it purports to do and delivers the required attributes. Use of a validated method should instill confidence that the method can generate test data of acceptable quality.

Various user groups and regulatory agencies have defined procedures for method validation. Specific requirements regarding methods validations appear in many references on the subject. Among some common parameters generally obtained during method validations are the following:

• precision.

• sensitivity

• specificity

• repeatability

• linearity

• analyte

System Suitability Tests

Typically conducted before the system performs samples analysis, system suitability tests verify that the system works according to the performance expectations and criteria set forth in the method, assuring that at the time of the test the system met an acceptable performance standard.

Quality Control Checks

Most analyses are performed using reference or calibration standards. Single- or multipoint calibration or standardization correlates instrument response with a known analyte quantity or quality. Calibrators/standards are generally prepared from certified materials suitable for the test. Besides calibration or standardization, some analyses also require the inclusion of quality control check samples, which provide an in-process assurance of the test's performance suitability.

In summary, AIQ and analytical method validation assure the quality of analysis before conducting the tests. System suitability tests and quality control checks assure the high quality of analytical results immediately before or during sample analysis.

Qualification phases:

Qualification of instruments is not a single, continuous process but instead results from many discrete activities. For convenience, these activities have been grouped into 4 phases of qualification.

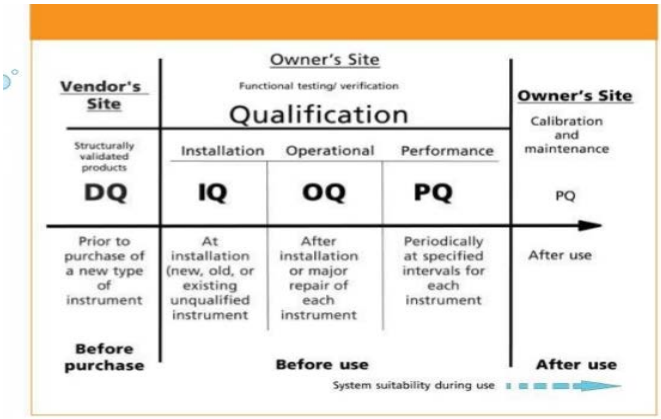
- ✓ Design Qualification (DQ)
- ✓ Installation Qualification (IQ)
- ✓ Operational Qualification (OQ)
- ✓ Performance Qualification (PQ)

Design qualification:

The AIQ process timeline begins with the DQ phase at the vendor's site, in which the instrument is developed, designed, and produced in a validated environment according to good laboratory practices (GLP), current good manufacturing practices (CGMP), and ISO 9000 standards. Users should ensure that the instrument is fit for their intended use and that the manufacturer has adopted a quality system for development, manufacturing, and testing and has adequate support for installation, service, and training. Vendor supplied documentation and consumer audits of the vendor are usually sufficient to satisfy users' DQ requirements. Design qualifications are the specifications a manufacturer uses to describe a device or equipment. It seeks to demonstrate that the requirements detailed in the User Requirements Specifications (URS) are all going to be executed satisfactorily before a new design can be authorized.

Since the instrument design is already in place for the commercial off-the-shelf (COTS) systems, the user does not need to repeat all aspects of DQ. However, users should ensure

that COTS instruments are suitable for their intended applications and that the manufacturer has adopted a quality system for developing, manufacturing, and testing.



Installation Qualification:

Qualification is a documented collection of activities needed to install an instrument in the user's environment.

System Description: Provide a description of the instrument, including its manufacturer, model, serial number, software version, etc. Use drawings and flowcharts where appropriate. Instrument Delivery: Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Utilities/Facility/Environment: Verify that the installation site satisfactorily meets vendor-specified environmental requirements. A commonsense judgment for the environment suffices; one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.

Network and Data Storage: Some analytical systems require users to provide network connections and data storage capabilities at the installation site. If this is the case, connect the instrument to the net-work and check its functionality.

Assembly and Installation: Assemble and install the instrument and perform any initial diagnostics and testing. Assembly and installation of a complex instrument are best done by the vendor or specialized engineers, whereas users can assemble and in-stall simple ones. For complex instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance.

Installation Verification: Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and (when present) the installing engineer should con-firm that the installation was successful before proceeding with the next qualification phase.

Operational qualification (OQ): After a successful IQ the instrument is ready for OQ testing. The OQ phase may consist of these test parameters:

Fixed Parameters: These tests measure the instrument's non changing, fixed parameters such as length, height, weight, etc. If the vendor-supplied specifications for these parameters satisfy the user, he or she may waive the test requirement. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument and therefore never need re determining.

Secure Data Storage, Backup, and Archive: When required, secure data handling, such as storage, backup, and archiving should be tested at the user site according to written procedures.

Instrument Functions Tests: Test important instrument functions to verify that the instrument operates as intended by the manufacturer and required by the user. The user should select important instrument parameters for testing according to the instrument's intended use. Vendor supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor and user specifications.

The extent of OQ testing that an instrument undergoes depends on its intended applications. We therefore offer no specific OQ tests for any instrument or application. Nevertheless, as a guide to the type of tests possible during OQ, consider these, which apply to a high performance liquid chromatography (HPLC) unit:

- pump flow rate
- gradient linearity
- detector wavelength accuracy
- detector linearity
- column oven temperature
- peak area precision
- peak retention time precision

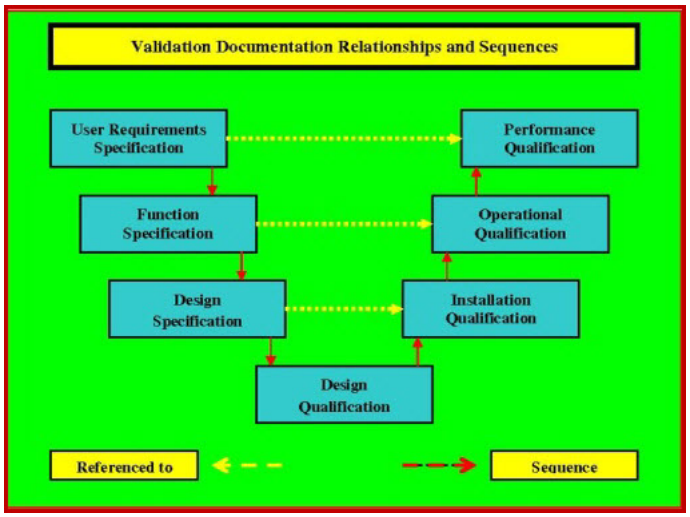
Performance qualification (PQ):

Once an IQ and an OQ have been performed, PQ testing is conducted. PQ testing should be performed under the actual running conditions across the anticipated working range. PQ testing should be repeated at regular intervals; the frequency depends on such parameters as the ruggedness of the instrument and the criticality and frequency of use. PQ testing at periodic intervals also can be used to compile an instrument performance history.

Performance Checks: Set up a test or series of tests to verify an acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications. Some tests may resemble those performed during OQ, but the specifications for their results can be set differently if required. PQ tests are performed routinely on a working instrument, not just on a new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications. Nevertheless, user specifications for PQ tests should evince trouble free instrument operation vis-à-vis the intended applications.

Preventive Maintenance and Repairs: When PQ tests fail to meet specifications, the instrument requires maintenance or repair. For many instruments a periodic preventive maintenance may also be recommended. Relevant PQ test should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

Standard Operating Procedure for Operation, Calibration, and Maintenance: Establish standard operating procedures to maintain and calibrate the instrument. Use a logbook, binder, or electronic record to document each maintenance and calibration activity.



Performance Qualification Relationships

Instrument Categories:

Modern laboratories typically include a suite of tools. These vary from simple spatulas to complex automated instruments.

Group A Instruments

Conformance of Group A instruments to user requirements is determined by visual observation. No independent qualification process is required. Example instruments in this group include light microscopes, magnetic stirrers, mortars and pestles, nitrogen evaporators, ovens, spatulas, and vortex mixers.

Group B Instruments

Conformance of Group B instruments to user requirements is performed according to the instruments' standard operating procedures. Their conformity assessments are generally unambiguous. Installation of Group B instruments is relatively simple and causes of their failure readily discernable by simple observations. Example instruments in this group include balances, incubators, infrared spectrometers, melting point apparatus, muffle furnaces, pH meters, pipettes, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, vacuum ovens, and viscometers.

Group C Instruments

Conformance of Group C instruments to user requirements is highly method specific, and the conformity bounds are determined by their application. Examples are as follows:

- Atomic absorption spectrometers
- Differential scanning calorimeters
- Densitometers
- Diode-array detectors
- Electron microscopes
- Elemental analyzers
- Flame absorption spectrometers
- Gas chromatographs
- High-pressure liquid chromatographs
- Inductively coupled argon plasma emission spectrometers
- Mass spectrometers
- Micro-plate readers

QUALIFICATION OF GC EQUIPMENT

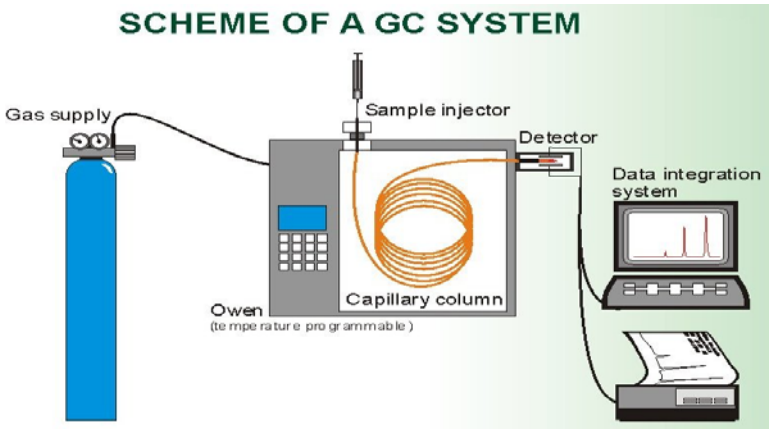
Introduction

The present document is the second Annex of the core document "Qualification of Equipment", and it should be used in combination with it when planning, performing and documenting the GC equipment qualification process.

The core document contains the general introduction and the Level I and II of qualification, common to all type of instruments, and the present annex contains GC instrument-related recommendations on parameters to be checked and the corresponding

typical acceptance limits, as well as practical examples on the methodology that can be used to carry out these checks.

The tests proposed in the Level III and IV of qualification are based on an overall approach, in which several parameters are checked at the same time in a combined test procedure, to obtain information on the overall system performance (e.g. peak area precision, retention time precision, temperature program reproducibility etc). Nevertheless, it should be noted that it is also acceptable to check these parameters individually by using other well defined procedure.



LEVEL I

Selection Of Instruments & Suppliers

At level I of the qualification of a gcequipment(selection of instruments and suppliers). It is recommended to select a manufacture of gc that can satisfy the needs of the laboratory and works under ISO 9001 certification.

Level II

Equipment Qualification:

Installation and release for use.

It is recommended to check all requirements set during the selection of the instrument, and calibration should be performed before putting into service by an accredited external service supplier, or Internally by appropriately qualified personnel, using certified reference buffers according to an approved procedure.

Level III

Periodic and motivated instrument

Checks Examples of requirements for GC instruments with FID.

Instrument Module	Parameters to be checked	Typical tolerance limit
1.Inlet System	1.1 Injector leak test 1.2 Pressure Flow accuracy and stability 1.3 Repeatability of Injection (overall test 1) -In Split Mode -In Split less Mode 1.4 Injector temperature stability and accuracy 1.5 Carry over (Overall test-3)	Pressure drop <kPa within 5 minutes covered by overall test 1 RSD < 3.0% RSD < 3.0% Covered by overall test 2 <0.2%
2.Oven	2.1 Repeatability of oven temperature characteristics	Covered by overall test 2
3. FID Detector	3.1 Lenearity 3.2 Constant detector response 3.3 Noise 3.4 Draft	R 2> 0.999 Covered by overall test 1 or 2 See annex 1 See annex 1

Practical examples of tests and their associated tolerance limits for several parameters related to the performance of the different modules of a GC are presented below.

These examples can be considered by the OMCLs as possible approaches to perform the Level III of the equipment qualification process: “Periodic and motivated instrument checks”.

Several tests are proposed to check various parameters at the same time (overall tests).

In order to run the tests in a more economical way, other suitable solutions can be used, as for example, the “Grob Test” mixture, available from different suppliers (e.g. Alltech, Sigma, Thames Restek).

This commercial solution should be appropriate to the column material used. It is recommended to run the overall tests by using always the same test column, exclusively dedicated to qualification purposes, to guarantee reproducible conditions.

1. INLET SYSTEM

The following tests are proposed for the periodic and motivated check of the GC Inlet System.

1.1. INJECTOR LEAK TEST

Method:

If not otherwise specified by the instrument manufacturer, the leak test is carried out according to the procedure laid down in the instrument manual or by the built in automatic leak check procedure of the instrument.

Otherwise use the test described below:

 Disconnect the column from the injector and close the injector outlet with a sealed cap. Close the septum purge and the bypass.

 Adjust the flow and pressure controller to the maximal possible value of the pressure gauge.

 Adjust the flow controller to zero.

 Read the pressure after 1 minute and record the value.

 Record the pressure after 5 minutes.

Limits:

 Pressure drop ≤ 15 kPa within 5 minutes.

1.2. INLET PRESSURE/FLOW ACCURACY AND STABILITY

A direct measurement of these parameters was not deemed practical or necessary, but the optimal conditions of flow/pressure can be verified by the overall test 1.

Limits: Refer to overall test 1.

1.3. REPEATABILITY OF INJECTION

The verification of this parameter is covered by the overall test 1.

This test is to be performed in both split and split less mode.

Limits: Refer to overall test 1.

1.4. INJECTOR TEMPERATURE ACCURACY AND STABILITY

Due to the fact that the temperature cannot be reliably measured without opening and modifying the system and due to the difficulties of introducing a probe inside this module, the verification of this parameter is considered to be covered by the overall test 2.

Limits: Refer to overall test 2.

1.5. INJECTOR CARRY OVER

After having injected the solutions for the linearity test of the FID detector, in increasing order, inject the blank and measure the peaks that correspond to the major peaks (= analytes) in the linearity solutions.

The verification of this parameter is covered by the overall test 3.

Limits: Refer to overall test 3.

2. OVEN

2.1. REPEATABILITY OF THE OVEN TEMPERATURE CHARACTERISTICS

Due to the fact that the temperature cannot be reliably measured without opening and modifying the system conditions and that even when introducing a probe inside the oven, its location would not reflect the real temperature conditions at all points, the verification of this parameter is covered by the overall tests 2A and 2B.

Limits: Refer to overall test 2.

3. FID DETECTOR

The following tests are proposed for the periodic and motivated check of the GC FID detector.

3.1. FID DETECTOR LINEARITY

Increasing amounts of analyte are injected and a linear response should be obtained. The verification of this parameter is covered by the overall test 3.

Limits: Refer to overall test 3.

3.2. CONSTANT FID DETECTOR RESPONSE

The proper and reproducible functioning of the FID can be demonstrated by checking the peak areas obtained from a predefined standard solution.

The verification of this parameter is covered by the overall test 1 or 2.

Limits: Refer to overall test 1 or 2.

3.3. FID DETECTOR NOISE AND DRIFT

If the instrument has a built-in automatic system for the verification of the noise and drift, follow the manufacturer's instructions and apply the defined acceptance criteria.

Otherwise, use the test described below:

Settings:

- Column installed
- Suitable flow, depending on column length/diameter
- No injection
- Oven temperature: 40°C
- Detector on and heated at working temperature (270- 300°C)

Method:

- After stabilisation of the system, record the signal for 15 minutes.
- Noise: evaluate 10 periods of 1 minute and calculate the mean value.
- Drift: Evaluate the slope of the baseline over the 15 minutes.

Limits:

- The acceptance criteria for these parameters have to be chosen in accordance with the instrument vendor's instructions and the intended use of the instrument.
- If no instructions are given, the user has to pre-define these acceptance criteria by taking into account the previous experience and the intended use of the instrument.
- No fixed values can be pre-defined in this guideline due to the high variety of integration systems used and consequently the acceptance criteria may be expressed in different units (voltage, current, arbitrary units per time).

OVERALL TEST 1

The overall test 1 covers the following parameters:

- Pressure/flow accuracy and stability in the inlet system.

Retention time repeatability

- Repeatability of injection: peak area precision

- In split mode

- In split less mode

The test may be combined with overall test 3.

Split mode: Test solution: 1-octanol in n-hexane 1% (v/v).

Settings:

- Column: SPB-1 (30m x 0.32mm ID x 0.25µm film)

- Carrier gas: He
- Velocity: 25cm/sec
- Split: 1:100
- Injection: 1µl
- Injector temperature: 220°C
- Oven temperature: 100°C isotherm
- Detector temperature: 300°C
- Runtime: 8 min
- Retention time of 1-octanol: about 5 min

Split less mode:

- Stock solution: 1-octanol in n-hexane 1% (v/v)
- Test solution: Dilute 10 ml of the stock solution with nhexane to 100 ml (corresponds to 1µl/ml of 1-octanol in nhexane)
- Settings:
- Column: SPB-1, 30m, 0.32mm ID, 0.25µm film
- Carrier: He
- Velocity: 30cm/sec
- Split less injection: purge valve closed during 2 min
- Injection: 0.2µl of the test solution
- Injector Temperature: 220°C
- Oven Temperature: Initial 60°C for 4 min, 15°C/min. up to 135°C, final time 1min
- Detector temperature: 300°C
- Runtime: 9.5 min
- Retention time of 1-octanol: about 8 min

Method:

Carry out 6 consecutive injections of the test solution and calculate the RSD of the different peak areas and retention times.

Limits:

Retention time repeatability: the RSD of the retention times should be ≤ 2.0%.

Peak area precision (split and split less mode): the RSD of the peak areas should be ≤ 3.0%

OVERALL TEST 2

The overall test 2 covers the following parameters:

-Injector, oven and detector temperature accuracy and stability, retention time repeatability - Two alternative tests are proposed

1.Overall test 2

A Test solution:

- 0.035 ml 1-octanol
- 0.035 ml 2-octanone
- 0.035 ml 2,6-dimethylanilin
- 0.035 ml n-tridecane
- 0.035 ml n-tetradecane
- 35 mg n-eicosane

Dissolved in 50 ml Dichloromethane

Settings:

- Column: SPB-1 (30m x 0.32mm ID x 0.25µm film)
- Carrier gas: Helium
- Velocity: 25 cm/s
- Split: 1:100
- Injection volume: 1 µl
- Injector temperature: 220°C
- Detector: FID
- Detector temperature: 300°C
- Gradient programme: 60°C (4 min), 5°C/min, 270°C (3 min)

Method:

Inject the solution twice and calculate the relative retention times in relation to n-eicosane (RRT = 1)

Limits:

The RSD of each RRT from two consecutive injections should be ≤ 1.0%2.Overall test 2B

Test Solution:

1.0% (W/W) n-Nonane and Hexadecane in Tetradecane.

Settings:

- Column: Ultra-1 (25m x 0.32mm ID x 0.52µm film)
- Injection volume: 1 µl

- Solvent: Tetradecane
- Oven temperature: 110°C
- Gradient programme: 110°C, 20°C/min, 180°C (final time: 3.5 min)
- Detector temperature: 250°C
- Injector temperature: 200°C
- Detector: FID
- Flow rates: Carrier gas (Helium): 2 ± 0.2 ml/min Hydrogen: 30 ± 1.0 ml/min
- Air: 400 ± 20.0 ml/min
- Makeup (Nitrogen): 28 ± 1.0 ml/min
- Split ratio: 15
- Split vent: 30 ± 3.0 ml/min
- Septum purge: 3-5 ml/min

Method:

Allow the system to equilibrate

- Injection sequence:

1) Blank (Tetradecane)

2) 6 replicates of the test solution. Calculate the mean of the retention times and peak areas and the relative standard deviation of n-Nonane and n-Hexadecane

Limits:

- Retention time repeatability: RSD of the peak retention times of the 6 replicates ≤ 2%
- Retention time (Rt) accuracy; Nevertheless, individual ranges should be predefined by the laboratory depending on the column used (e.g. Rt ± 0.2 min).

OVERALL TEST 3

This test is a modified version of the overall test 1 to be used for the verification of:

- Detector linearity: linearity of the areas recorded

- Injector carry-over: area recorded in the blank run

It is described for both split and split less mode and may be combined with overall test 1.

Split mode:

- Test solution: 1-octanol in n-hexane 1% (v/v)
- Prepare further reference solutions by diluting the test solution as described below.

Settings:

see overall test 1

Injection sequence:

- 5.0 ml of the test solution diluted to 25.0 ml with n-hexane (2 µl/ml): 2 injections
- 10.0 ml of the test solution diluted to 25.0 ml with nhexane (4 µl/ml): 2 injections
- 15.0 ml of the test solution diluted to 25.0 ml with n-hexane (6 µl/ml): 2 injections
- 20.0 ml of the test solution diluted to 25.0 ml with n-hexane (8 µl/ml): 2 injections
- If combined with overall test 1 for repeatability: test solution (10 µl/ml): 6 injections n-hexane as blank (carry over)

Split less mode:

- Stock solution: 1-octanol in n-hexane 1% (v/v)
- Test solution: Dilute 10 ml of the stock solution with nhexane to 100 ml (corresponds to 1µl/ml of 1-octanol in nhexane).
- Prepare further reference solutions by diluting the test solution with n-hexane.

Settings:

see overall test

Injection sequence:

- 5.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.2 µl/ml): 2 injections
- 10.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.4 µl/ml): 2 injections
- 15.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.6 µl/ml): 2 injections
- 20.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.8 µl/ml): 2 injections

If combined with overall test 1 for repeatability: test solution (1 µl/ml): 6 injections n-hexane as blank (carry over)

Limits:

- Linearity: coefficient of correlation of the calibration line obtained with the reference solutions and the test solution: $r\,2 \geq 0.999$.
- Carry-over: the percentage of the peak area corresponding to the analyte in the blank solution should be $\leq$ 0.2% of the peak area of this analyte in the chromatogram obtained with the solution with the highest concentration within the sequence.

Level IV.

In-use instrument checks Examples of requirements for GC instruments with FID.

Parameter to be checked	Typical Tolerence limit
1.System suitability check for method	According to Ph,Eur,or MAH validated in house method
2. Peak area precision	RSD < 3.0% Unless or otherwise priscribed
3.Retention time repeatability	RSD < 2.0%
4.Sensitivity	According to Ph,Eur,or MAH validated in house method

QUALIFICATION OF DSC (DIFFERENTIAL SCANNING CALORIMETRY) EQUIPMENT;

Differential scanning calorimetry

The technique was developed by E.S. Watson and M.J. O'Neill in 1960, and introduced commercially at the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy in 1963.

This technique is used to study what happens to polymers/samples upon heating

• It is used to study thermal transitions of a polymer/sample (the changes that take place on heating)

– For example:

• The melting of a crystalline polymer

• The glass transition

• The crystallization

Principle

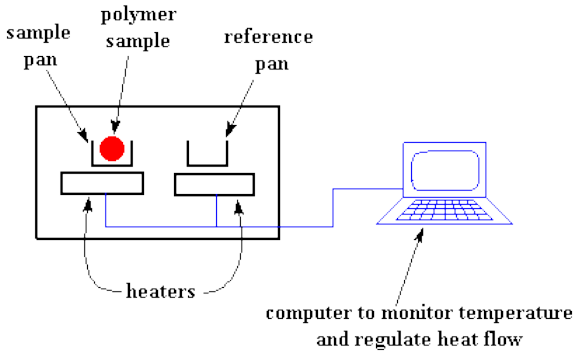
• The sample and reference are maintained at the same temperature, even during a thermal event in the sample

• The energy required to maintain zero temperature difference between the sample and the reference is measured

• During a thermal event in the sample, the system will transfer heat to or from the sample pan to maintain the same temperature in reference and sample pans.

How studied what happens to a polymer when heated?

The polymer is heated in a device that looks something like this:



There are two pans, In sample pan, polymer is added, while the other, reference pan is left empty

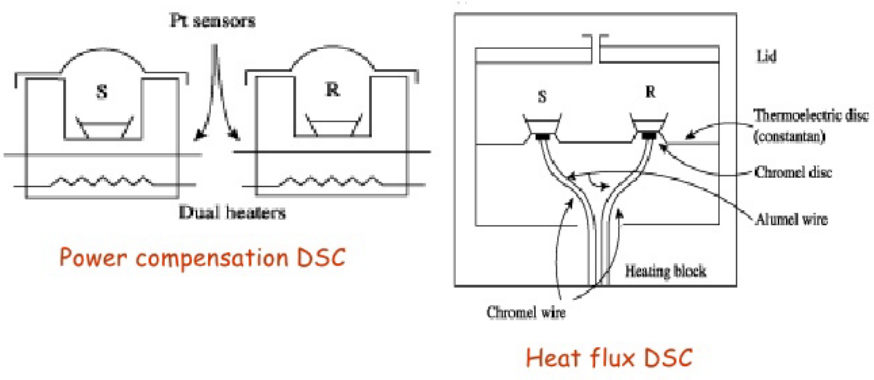
• Each pan sits on top of heaters which are controlled by a computer

• The computer turns on heaters, and let them heat the two pans at a specific rate, usually 10oC/min.

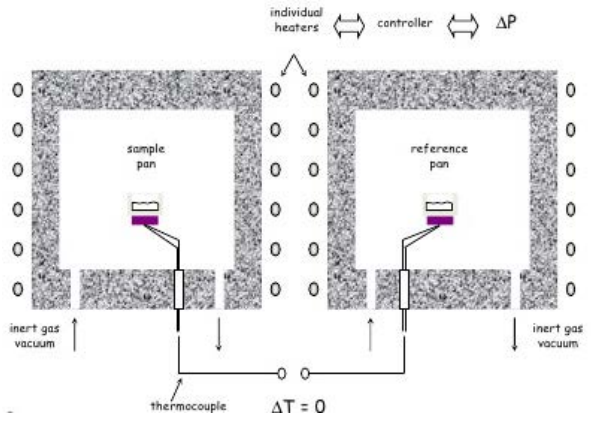
• The computer makes absolutely sure that the heating rate stays exactly the same throughout the experiment.

Differential Scanning Calorimetry Instrument

Two basic types of DSC instruments: power compensation DSC and heat-flux DSC.



Power Compensation DSC



Sample holder

• Aluminum or Platinum pans

Sensors

• Platinum resistance thermocouples

• Separate sensors and heaters for the sample and reference

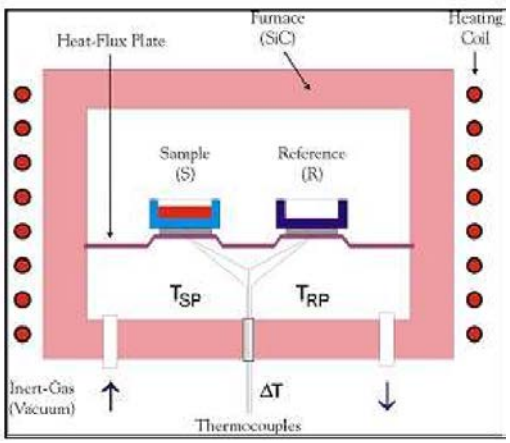
Furnace

• Separate blocks for sample and reference cells

Temperature controller

• Supply the differential thermal power to the heaters to maintain the temperature of the sample and reference at the program value

Heat Flux DSC



Sample and reference holders

• Al or Pt pans placed on constantan disc

• Sample and reference holders are connected by a low-resistance heat flow path

Sensors

• Chromel® (an alloy made of 90% nickel and 10% chromium)-constantan area thermocouples (differential heat flow)

Chromel®-alumel (an alloy consisting of approximately 95% nickel, 2% manganese, 2% aluminium and 1% silicon) thermocouples (sample temperature) Thermocouple is a junction between two different metals that produces a voltage due to a temperature difference .

Furnace

• One block for both sample and reference cells

Temperature controller

• The temperature difference between the sample and reference is converted to differential thermal power, which is supplied to the heaters to maintain the temperature of the sample and reference at the program value.

DESIGN SPECIFICATIONS OF DSC;

Principle	Heat Flux Type
Heat Flow Range	+40µW
Hold Time	0-99 min,hour
Noise Level	1µW
Size(mm)	300Wx 490Dx 290H
Temperature range	-150 TO 000^0c
Program Rate	0-99^0K/hour
Cooling time	About 6 min from 600^0c to 400^0c
Atmosphere	Inert gas or air
Power Supply	100/120 VAC 800AV

INSTALLATION QUALIFICATION

The DSC should be:

IN

• A temperature-controlled area(15°C to 30°C is recommended).

• A clean environment.

• An area with ample working and ventilation space.

ON

• A stable, heat-resistant, and fire-resistant work surface. INSTALLATION QUALIFICATION

Near

- A power outlet (120 Vac, 50 or 60 Hz, 15amps). A step up/down line transformer may be required if the unit is operated from a higher or lower line voltage.
- Your controller.
- A compressed lab air and purge gas supply for use during cooling, sub ambient, and high temperature experiments.

Away from

- Dusty environments.
- Exposure to direct sunlight.
- Direct air drafts (fans, room air ducts).
- Poorly ventilated areas.
- Flammable materials

PERFORMANCE QUALIFICATION

The most common procedure is to run an indium standard under the normal test conditions and measure the heat of fusion value and melting onset temperature.

• These values are then compared with literature values and a check made against accepted limits.

• For many industries limits of—

- ✓ +0.5 ◦C for temperature or 1% for heat of fusion may be accepted, though tighter limits of •+0.3 ◦C and 0.1% may also be adopted. ⎫
- ✓ The choice of limits depends on how accurate you need to be.
- ✓ Indium is the easiest standard to use because of its stability and relatively low melting point of 156.6 ◦C, which means it can often be reused, provided it is not heated above 180◦C.

SUMMARY;

The purpose of the use of analytical instruments is to generate reliable data. Instrument qualification helps fulfill this purpose. No authoritative guide exists that considers the risk of instrument failure and combines that risk with users' scientific knowledge and ability to use the instrument to deliver reliable and consistent data. In the absence of such a guide, the qualification of analytical instruments has become a subjective and often fruitless document-generating exercise. Taking its cue from the new FDA initiative, "Pharmaceutical GMP's for the 21st Century," an efficient, science- and risk-based process for AIQ was discussed at a workshop on analytical instrument qualification. This report represents the distillate of deliberations on the complicated issues associated with the various stages of analytical instrument qualification. It emphasizes AIQ's place in the overall process of obtaining quality reliable data from analytical instruments and offers an efficient process for its performance, one that focuses on scientific value rather than on producing documents. Implementing such a process should remove ambiguous interpretations by various groups.

Data quality is built on the foundation of method and software validation, AIQ, and system suitability. Each of these components plays a significant role in the process of validation. In a regulated laboratory, instruments must produce reliable data, and only a proper AIQ process can fulfill this mission. During all phases of clinical development, including the use of small scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use. Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination. So validation and calibration is very important for analytical instruments.

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