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# An Overview on LC-MS Chromatography and its Qualification

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LCMS, Analytical Instrument Qualification, User requirement Specification.

## Abstract

Liquid chromatography and mass spectrometry (LC/MS) is a technique that couples the action of separation of analyte done by liquid chromatography subsequently analysis of separated analyte characteristics done by mass spectrometry. LC/MS is now being put forward by the analyst for the determination of identity, purity, quality, quantity, structural elucidation and molecular weight of unknown compounds. It is a powerful analytical technique that combines the resolution of liquid chromatography with the detection specificity of mass spectrometry. Liquid chromatography (LC) separates sample components and injects them into a mass spectrometer where MS align and detects charged ions. LC-MS also widely being used in evaluation and interpretation of bioavailability, bioequivalence and pharmacokinetic data in bioanalytical studies. LCMS is also playing an important role in the qualitative and quantitative determination of known pollutants, Food safety and development, product quality control such as the quantitation of residual veterinary drugs, food additives and the composition analysis of supplements and organic foods. This review focussed on the qualification of this analytical instrument LC-MS, where Analytical instrument qualification is collective document which provides evidence that instrument performs as per standards suitably for its intended application. Qualification of analytical instrument is usually done regularly on short term or long term to generate a validated data integrity. As AIQ is a continuous process over lifetime of instrument which comprises of DQ, IQ, OQ, PQ; on risk assessment analysis it provides information on requalification step. When an instrument meet standard, manufacturer functional and operational specification thereby it complies with User Requirement Specification, then an analytical instrument said to a qualified one.

## 1. Introduction:

In history of the analytical chemistry, there was relative incompatibility of existing MS ion sources with a continuous liquid stream. And the connection between MS and LC is an obvious continuation, but due to the development of various interfaces, the progress in this area has been limited for many years, and these have become incommodious and unreliable, so its preference was limited by some analytical laboratories[1]. As MS has higher sensitivity and high specificity compared with other chromatographic detectors, it has always been desirable to couple MS with liquid chromatographic methods. This combination of two selective techniques is widely for isolation and measurement of complex mixture. LCMS works on the principle of separation of compounds by their physicochemical properties in liquid chromatography and detection of compounds by their mass-to-charge ratio via mass detector. This dual sensitive selectivity makes LCMS a powerful analytical tool for an intended application. It can identify the substance corresponding to each

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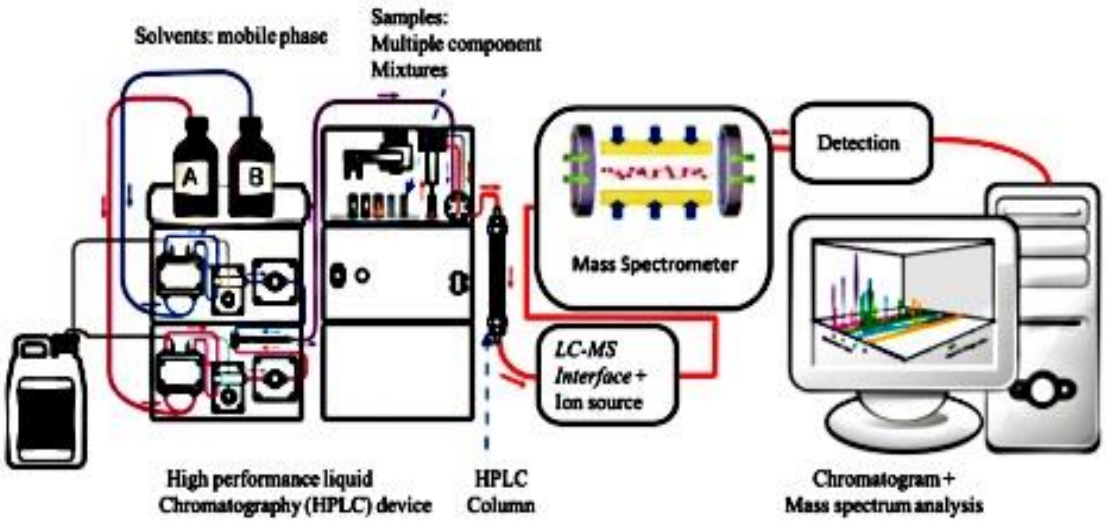
chromatographic peak from its unique mass spectrum [2].

The LC/MS interface can implement three processes, such as the evaporation of liquid and analyte molecules into vapor, the ionization of uncharged analyte molecules in the gas phase or the desorption of analyte ions from the liquid phase, and the extraction of a strong gas flow to maintain a high vacuum on the mass spectrometer. Basic instrumental parts of the LCMS are Chromatograph, Ion source, Mass analyser, Detector. There are different types of instruments available based on the types of mass spectrometry. They are Single Quadrupole, Triple Quadrupole, Ion Trap (low resolution), TOF (high resolution), Ion Trap (high resolution), TOF (high resolution) [3].

There are series of stages takes place during the quantitative analysis of the sample. They are as follows:

- Sample collection
- Calibration and quality control samples
- Sample preparation and extraction
- Analysis Calibration standards
- Data processing
- Reporting Most modern quantitation [4]




**Flowchart 1:** Instrumentation of LC-MS Chromatography

In the most important step, LCMS works on the basis of column elution under pressure whereas the mass measurement unit works in vacuum. The mass spectrometer cannot directly detect continuous flow, they need liquid through the interface. This interface moves the mobile phase used in the chromatographic step and transfers the analyte to the mass detection unit for measurement [5]. There can be different types of interfaces, but the most commonly used ionization sources are electrospray ionization systems (ESI), atmospheric pressure chemical ionization systems (APCI), or atmospheric pressure photoionization systems (APPI), which nebulize the liquid into a fine spray, ionized and then transferred to the mass detector. The mass detector measures the mass-to-charge ratio of the ions by exposing the ions to a magnetic or electric field that can change the movement of the ions, thereby classifying the ions according to their mass [6]. The detector can then measure and amplify the ion current to determine the number of ions classified. The mass-spectrometer detector transmits the mass-charge data to the computer, and the computer displays the information in the form of a mass spectrum. The mass spectrum of a sample can be used to determine the concentration of known or unknown compounds, determine the concentration of impurities, and obtain information about its chemical structure. There are pros and cons in LCMS technique. Some of the benefits, such as selectivity, speed and sensitivity. Every technique has their own hindrance and they are Expense, Complexity, Limited dynamic range, Excessive selectivity [7].

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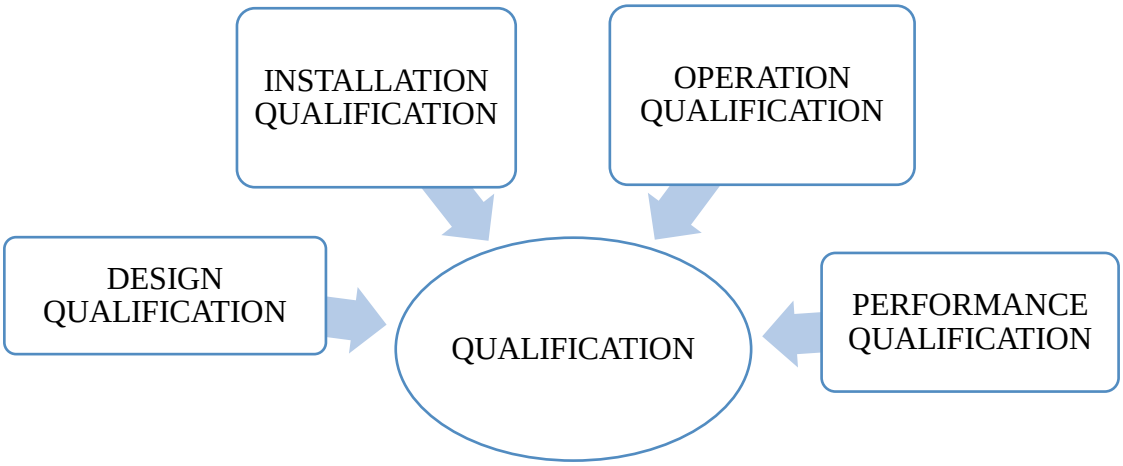
LCMS has unique application has its own. LCMS is used in many industries, such as pharmaceuticals and biopharmaceuticals industry. LCMS is widely used to analyze drugs, vitamins and minerals in whole blood, plasma, serum and urine as well as metabolomics, proteomics and genomics research. The use of LCMS in the biopharmaceutical discipline enables the bioassay and characterization of antibody-based drugs. With high sensitivity and detection selectivity, MS provides the flexibility of simultaneous multi-component analysis and improves the accuracy, reliable and efficiency of HPLC analysis in these applications [8].

## 2. 2.Steps Involved in Qualification of Instrument:

Qualification is not a single step process, a part of validation. Qualification of instrument is the act of documenting that equipment is designed as per user specification, installed properly at buyer's site with utility required by manufacturer, check whether it operates correctly according to instruction manual and guide documents provided by manufacturer and performs actual process which may lead to the expected results[9].




**Flowchart 2:** Steps in Qualification process

### 2.1. Design Qualification:

Design Qualification (DQ) is the process of documenting all aspects of a specific equipment design, from selecting qualified suppliers to meeting the final system requirements by comparing specifications with user needs. [10]


**Flowchart 3:** Requirements in Design qualification [11]

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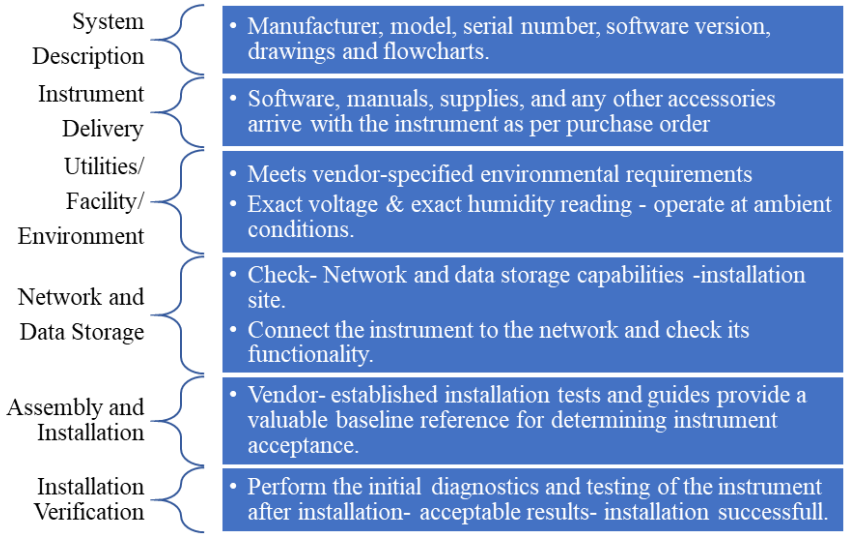
### 2.2. Installation Qualification:

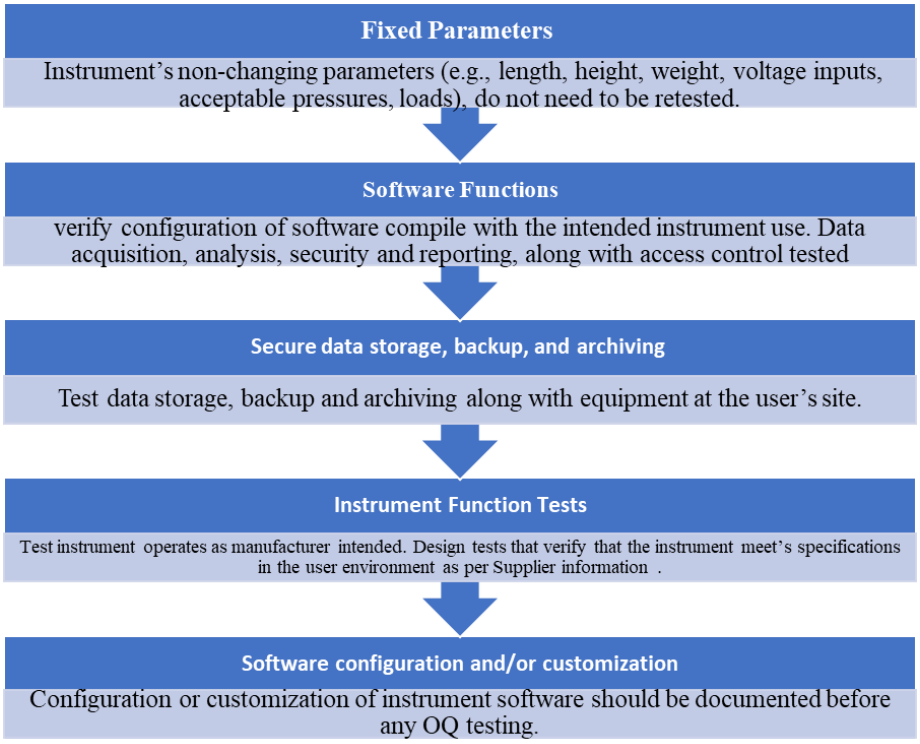
Installation Qualification (IQ) is the process of documenting all protocols and specifications required to install an equipment in a specific environment. Installation Qualification provides evidence that installed equipment's design and intended application meet user needs at their environment [12].




**Flowchart 4:** Requirements in Installation qualification [13]

### 2.3. Operational Qualification:

Operation Qualification (OQ) is the process of documenting that specific equipment design operates as per the user requirement and intended use. Operational qualification tests performed to ensure selected qualified equipment meet the final system requirements by comparing specifications with user needs. [14].




**Flowchart5:** Requirements in Operational qualification [15]

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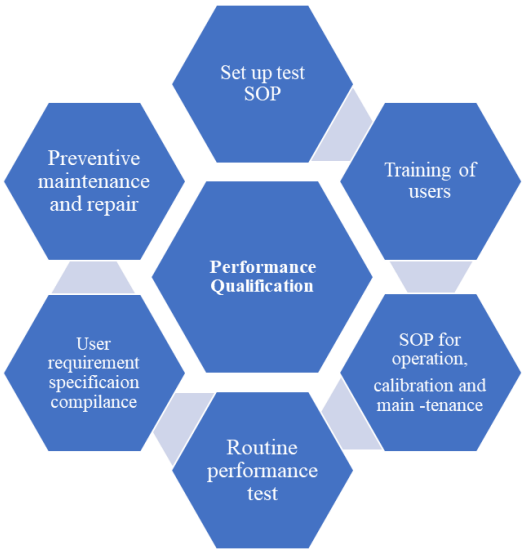
### 2.4. Performance Qualification:

Performance Qualification (DQ) is the process of documenting performance of all aspects of a specific equipment, by conducting a series of test to ensure that equipment meets the intended system requirements by comparing specifications with user needs. [16].




**Flowchart 6:** Requirements in Performance qualification [17]

## 3. 3. Procedure Involved in Qualification of Lc Ms:

### 3.1. Installation Qualification (IQ)

Before the installation qualification begins, First fill out the Form to identify that both the performer and reviewer are qualified enough to perform installation and to acknowledge the successful completion of the installation qualification. Complete two steps involved in the Preliminary IQ Procedure such as describing the details of received system instruments by their equipment name, serial numbers, installation date and location for correctness and verify against purchase order for compliance. Confirm receipt of the instrument documents required for qualification such as system guide and qualification workbook including OQ/PQ/maintenance procedure [18,19].

**Steps to be followed to complete the installation qualification procedure:**

Confirm installation site that suits the system and its operation. Confirm that all materials required for installation are present such as binary solvent manager, column heater, autosampler, pneumatic tubing to flow control and sensor switch cables.

Confirm that the following ethernet cable, leak sensor installed, input/output and power connections are being made.

Confirm that the following fluid connections are being made such as inlet supply lines for different solvent reservoir, Seal Wash solvent line, purge line port on degasser and Pump Outlet to port on inject valve. Confirm that the following waste connections are being made such as tygon tubing is connected from waste outlet to a waste container and the degasser vent tube is connected to an exhaust system.

Confirm that the following signal and power connections are being made such as leak sensors, column heater, AC power cable and analog I/O terminal strip.

Confirm that the following TUV, PDA, or PDA detector signal and power connections are being made such as Ethernet cable, leak sensor and I/O terminal signal; Detector fluid connection such as flow cell, column outlet to detector inlet and back pressure regulator to flow cell.

Power-on all system instruments. Adjust the pressure regulator, if necessary. Set the X-axis - Transfer Shuttle flow controls and Y-axis Transfer

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Shuttle hard stops. Install the sample organizer shelves. Launch the MassLynx software. Record the firmware and software version numbers of the system instruments and devices [20].

### 3.2. Operational And Performance Qualification (OQ&PQ)

Similarly Fill out the Form to identify that both the performer and reviewer are qualified enough to perform and to acknowledge the successful completion of the operational and performance qualification.

Confirm that recommended materials used for performing the operational and performance qualification including hardware, chemicals, labware, test solution and calibration information for the test equipment are present.

**Steps to be followed to prepare mobile phase:**

Measure 700 mL acetonitrile and 300 mL water, and then transfer to a 1000-mL reservoir bottle. Cap the reservoir bottle, and then shake to mix. Label the reservoir bottle: “acetonitrile: water, 70:30”.

Perform an instrument resolution setup and calibration for unit mass resolution mode in both positive and negative ion polarity using the IntelliStart software.

**Steps to be followed for performing calibration of mass spectrometer:**

Ensure a bottle of solution is placed on reservoir and purged. In the MassLynx main window, click MS Console. Click on Xevo TQ-XS MS Detector on the left to release the drop-down menu > select IntelliStart. From the Type of Analysis menu, select Unit Mass Resolution. Select “show instrument set-up options”. In the IntelliStart page, ensure the check boxes for Instrument Resolution, (Positive and Negative) and Instrument Calibration, are selected. Clear the Pre-checks check box. From the icon list on the right-hand side of the MS Console, click Start.

Ensure the procedure ends successfully. Record the pass/fail result, “Resolution and calibration results”, of the operational qualification results. Save and print the resolution reports [21,22].

## 5. SYSTEM OPERATIONAL QUALIFICATION (OQ): MASS SPECTROSCOPIC DETECTOR

### 5.1. MS Detector Linearity

The MS detector linearity test uses a series of six standards at different concentrations with constant injection volume to determine whether the detector response is linear over the sample concentration range. The sample concentrations are plotted against the sample amount and the coefficient of determination ($R^2$) is applied to determine the linearity of the detector's response.

In the main MassLynx window, click Open Sample List. Select MS Detector Linearity.spl. Highlight all the samples in the list, and then click Run. From the Start Sample List Run window, select Acquire Sample Data, and then click OK. When acquisition is complete, select the sample list injections (sample list lines 2 through 7) in MS Detector Linearity.spl.

In the TargetLynx software, select Process Samples, using ESI_Positive_Detector_Linearity_Area.mdb method, then select Integrate samples, Calibrate standards, and Quantify samples. Click OK. Select File > Apply Layout > Acquity_QWB_Linearity.qlt. Verify that all peaks are correctly integrated in TargetLynx. Save the TargetLynx data set. Print the summary report. Examine the summary report, and record the $R^2$ value, “System OQ: MS chromatographic test results” of the system operational qualification results document associated with this workbook. **Requirement:** The $R^2$ value must be greater than or equal to 0.990.

### 5.2. MS Injector Linearity and Accuracy

The MS injector linearity and accuracy test determines whether a delivered injection volume is linear within specified criteria.The system uses the same sample vial to inject different injection volumes with the same sample concentration. The software plots the peak area versus the injection volume to determine the injector linearity and accuracy.

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From the main MassLynx window, click Open Sample List. Select MS Injector Linearity and Accuracy.spl. Select lines 1 to 5 configurations in the list and then click Run. When acquisition is complete, select the sample injections sample list lines 2 through 5 in Injector Linearity and accuracy.spl. In the TargetLynx software, select Process Samples, using the Injector_Linearity_Area.mdb method, and then select Integrate Samples, Calibrate Standards, and Quantify Samples. Click OK. Click File > Apply Layout > Acquity_QWB_Linearity.qlt. Save the TargetLynx data set and Print the summary report.

Examine the summary report, and record the R2 value, "System OQ: MS chromatographic test results" of the system operational qualification results are documented. Requirement: The R2 value must be greater than or equal to 0.990[23].

### 5.3. MS Flow Rate Linearity

The MS flow rate linearity test determines whether the solvent manager flow rate is linear. The Xevo TQ-XS is used as a detector. The system injects samples using a constant injection volume and different flow rate. Each retention time is normalized using the flow rate in µL as the multiplication factor. The standard deviation of the normalized product must be less than or equal to 60 µL.

In the main MassLynx window, click Open Sample List. Select MS Flow Rate Linearity.spl. Change the MS Tune file in the sample list to the amended SYSTEM_DDMMMYYYY.ipr with the date created. Select all the samples in the list, and then click Run. From the Start Sample List Run window, select Acquire Sample Data, and then click OK. When acquisition is complete, select sample list lines 1 through 4 in Flow Rate Linearity.spl. In the MassLynx window, click the Chromatogram tab. Print the chromatograms. Examine the chromatograms, and record the retention times in minutes for each chromatogram, "System OQ: MS chromatographic test results" of the system operational qualification results are documented [24].

### 5.4. MS Injector Carryover

The MS injector carryover test determines the presence of sample carryover from one injection to the next. The Xevo TQ-XS is used as a detector. A pre-blank injection is performed to determine whether the system is ready to measure carryover. A standard sulfadimethoxine injection at a concentration of 0.5 pg on column is made, which corresponds to 0.005% of the challenge injection concentration of 10 ng on column. The standard injection is followed by a challenge injection, which is followed by three post-blank injections. The first post-blank injection must be less than or equal to 0.005% of the challenge injection[25].

In the main MassLynx window, click Open Sample List. Select MS Injector Carryover.spl. Change the MS Tune file in the sample list to the amended SYSTEM_DDMMMYYYY.ipr with the date created. Select all the samples in the list and click Run. When the acquisition is complete, select sample lines 3 through 8 in MS Injector Carryover.spl. In the TargetLynx software, select Process Samples, using the Carryover_Area.mdb method, and then select Integrate Samples, Calibrate Standards, and Quantify Samples. Click OK. Click File > Apply Layout > Acquity_QWB_Carryover.qlt. Save the TargetLynx data set by clicking File > Save As, and then enter an appropriate file name, for example, Carryover_Area_DDMMMYYYY_01. Print the TargetLynx summary report. Examine the summary report, and record the "% of Stock solution" value for the Carryover_PostBlank_test_01 sample, "System OQ: MS chromatographic test results" of the system operational qualification results are documented. Requirement: The "% of Stock solution" value must be less than or equal to 0.005% [26].

## 4. Conclusion:

As we know that Analytical instrument deliver a data set that provide level of assurance in the identity, quality, purity, integrity of the drug product and hence this can be achieved only through well-established analytical instrument qualification. Analytical instrument qualification is an important part of validation protocol in a regulated industries to ensure finished product quality and safety reaching end user. If AIQ fails to qualify instruments properly then it may result in poor quality product, increased batch failure and also industry may face serious consequences on not compiling the standard

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regulations. There should be Validation Master Plan (VMP) in place describing the analytical instrument qualification protocol on compliance with user requirement and manufacturer specification before the commencement of DQ/IQ/OQ/PQ and requalification. Procedures for using equipment should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.Major critical steps to be followed to bring out good quality product, increase profitability, reduce product recall and gain custom compliance such as developing a VMP covering all aspect of qualification, implementing through trained validation team, requalification program for significant instruments once a year, well-established SOPs and documentation of test reports. Requalification can be performed at long term intervals ( i.e annually or every two or three years) or if there is any modification in instrument, change in instrument setup and change in location should be performed on short term intervals (i.e daily, weekly, monthly), if not analytical instrument qualification may deteriorate from standard compliance. The analytical equipment must be certified to prove its suitability for the intended use. Although equipment certification is nothing new and the company spends a lot of time, such deviations are often mentioned in FDA inspection observations and warning letters.

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