Migrating to Agilent Enterprise Edition: Enabling Significant Instrument Qualification Improvements

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Introduction

Agilent (at the time, HP Analytical) introduced Operational Qualification/ Performance Verification (OQPV) for our own LC and GC instruments in the early 1990's. Since then we have delivered well over 100,000 OQPV reports to customers around the world. Despite the undoubted success and acceptance of our original OQPV (called Classic Edition to distinguish from the new Enterprise Edition service) times have changed. Expectations and requirements of an OQ have shifted. The number and type of instruments and software used by our customers have increased. And of course we are immersed in the new world of computers and electronic media.

So Agilent set out with a team of international experts to create an upgraded compliance service that would meet the new demands while maintaining the critical requirements:

- Always pass US Food and Drug Administration (FDA) and national agency audits without over-testing or under-testing
- Challenge the analytical system with a scientifically sound methodology that provides valuable performance data
- Meet the quality needs of customers and the spirit and intention of the GLP & GMP laws
- Offer this service at a cost-effective price that makes it more than just worthwhile – it is the simplest and best qualification choice that a customer can make

What are the high-level changes in Enterprise Edition and what were the drivers for these changes?

The first big driver was the software environment. Many more chromatography data system (CDS) products now are available to control LC and GC systems. Agilent has OpenLAB CDS ChemStation and EZChrom Editions, MassHunter, and other specialist software. Our customers also use Empower, Chromeleon, Atlas, Turbochrom and many others. The Classic OQPV was a wonder of validated and almost fully automated OQ testing, but because it was built into the software these benefits were limited to Agilent instruments running on ChemStation. To provide all our customers – and customers of non-Agilent instruments – a single OQ solution as good or better than OQPV – it was clear we had to develop an automation tool independent of ChemStation and any other CDS.

The Agilent Automated Compliance Engine (ACE) is our new software tool that manages the workflow and protocols, calculates results and produces the reports. Naturally it is fully validated and tested. Authorized Service representatives carry "ACE laptops" in the same way that they carried "ChemStation laptops." Alternatively contract customers can have ACE software installed on their own laptops or with Agilent OpenLab networked CDS.

What are the high-level changes in Enterprise Edition and what were the drivers for these changes? (continued)

Another driver, somewhat related to the first, was the demand that Agilent perform the analytical instrument qualification using the customer CDS as controller. Theory and good practice in validation implies testing in the everyday operating conditions and using the full computer and instrument system in a 'holistic' manner. Classic OQPV did not allow this, but Enterprise Edition does. Additionally, our customers demanded the exact same OQ on their non-Agilent instruments. Sometimes called 'multi-vendor compliance,' this capability is fully realized in Enterprise Edition by virtue of:

- The independence of Agilent ACE software
- Extensive R&D to make test protocols that work on Agilent and non-Agilent systems as robust and reliable as old OQPV
- Training for our service engineers on both the hardware & software of the main non-Agilent systems

The third driver comes from shifts in typical instrument usage and the greater regulatory enforcement. Qualification today is a fairly mature subject. No longer are customers simply asked "do you perform qualification and calibration?" FDA and EU inspectors increasingly look deeper and check that an annual OQ adequately (within reason and practicality) tests the range of operational use of the systems. GMP and GLP guidelines have always stated this. There is no change in the regulations. It is the range of use that has shifted with regulatory enforcement.

For example, Classic OQPV tested HPLC pump flow rate performance at 1 and 2 ml/min set points (1.5ml/min flow rate is found in hundreds of analytical methods around the world.) Today customers run much lower flow rates and much higher flow rates and LC methods with elevated column temperatures. OQPV tested only at 40 °C. Most of the metrology tests in Enterprise Edition now allow a wider range of testing.

Our HPLC pump flow test in Enterprise Edition now defaults at the recommended 0.500 and 5.000 ml/min. The column compartment is tested at 40 °C and 80 °C.

The fourth driver follows from the third. **One-size OQ may not fit all needs.** Enterprise Edition services allow customers to have an OQ protocol made especially for their set points and add extra tests not in OQPV. Agilent provides a standard protocol – the Agilent-recommended Equipment Qualification Plan (EQP) – which is the simplest choice and should meet most requirements. But now it is possible for customers to make set point changes in a *Variance to Standard EQP,* a selection page in the Standard EQP Review Document. For changes deeper than set points (such as extra tests, limit changes, custom forms etc.) **a customer-configured EQP can be produced on demand.** Customers simply make change requests through their Agilent representative or email: Enterprise_Edition@agilent.com

Are there any other practical or process changes in Enterprise Edition?

Yes. Approval of the protocol (called EQP) before execution of the OQ is greatly simplified, regardless of the complexity and type of analytical equipment. Customers need only sign a single recommended EQP that can cover all systems and configurations of analytical instruments in their lab. There is no need for individual protocols to be created before each scheduled OQ or sent by mail as a paper document for approval. The same simple process is followed for all major chromatography and spectroscopy techniques, including LC, GC, MS, UV-Vis, Dissolution, SFC, AA, and ICP-MS. Approval of the Global EQP also covers the hardware installation qualification (IQ) protocol and any software IQ and OQ ordered at time of new instrument purchase. All the tests & checks in our standard hardware and software IQ & OQ are listed in the Agilent-recommended EQP for each technique – or you may have a single EQP that includes them all under a single set of signatures.

Approval of the reports, called Equipment Qualification Reports (EQR), is the biggest change. The standard deliverable is a CD disk with links to the IQ and/or OQ report(s) plus raw data and other supporting information. The EQR is a secure Adobe Acrobat document with a single page for customer approval signatures. Compare this to over 80 pages in OQPV that needed both the service engineer and customer to sign and date at the bottom of each page. This is all made possible by the technology of secure and active Adobe Acrobat forms – fully proven electronic media that are 100% acceptable to the FDA and national agencies, 21 CFR Part 11 compliant records that may be printed as paper copies if desired.

This design meets the Agilent commitment to follow FDA GMPs for the 21st Century initiative, world-wide environmental concerns over excessive paper usage and many customer strategies to move towards paperless laboratories.

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Diving into the details – how do the protocols and tests in Enterprise Edition compare to Classic?

The answer is multi-dimensional. We already mentioned single protocols, pdf reports, customer-selectable set points, functionality on non-Agilent instruments and software as well as enhancements. It is also worth noting that Agilent carried out a full analysis of our OQ test design for LC, GC and MS systems. The goal was an ideal OQ – avoid over-testing or under-testing; to align with current literature and international norms but without significantly deviating from the Classic OQPV given its international gold-standard status. Agilent hired internationally recognized experts into the development team and used the input of independent advisors (including customers and agency representatives) to assess what changes and additions should be made to Classic OQPV.

Concepts that have not changed include:

- Always perform direct metrology for temperature and flow using the best calibrated test equipment. Indirect measurement of flow and temperature found in competitor protocols were considered susceptible to error caused by variation in columns, ambient conditions, etc. Regardless of purported design elegance, the inferred final results can never be as absolute or comparable as direct metrology.
- In LC tests, avoid the variable contribution to system performance of the analytical column, by eliminating a test column. OQ aims to test only the hardware, not hardware plus an arbitrary choice of analytical column.
- Caffeine is still used as the chemical reference standard for LC precision, carry-over, linearity and UV detector wavelength accuracy tests. It is a representative sample, has continuity with OQPV, and matches international standards and published literature. It is accepted by auditors, is safe, stable, easy to use, low-cost, and readily available in accurate, pre-made solutions. And the fact that caffeine has a nice spectral maximum at 205 nm makes it the best choice for low UV verification.

The names of the tests are similar or identical to OQPV.

- All the calculation formulas remain the same where the test design is unchanged.
- The standard OQ suite of tests for GC is kept the same in terms of operator procedure and limits.
- All service engineers must be trained and certified before they can deliver the service.
- The software tool and the test designs are fully validated and maintained for quality by a large support team following Agilent ISO-approved life-cycle methodology.

IQ checks are the same in Enterprise Edition as in Classic.

Changes:

- Now called OQ not OQPV to align with literature and current guidance nomenclature for GMP/GLP.
- *Wander* was a unique Agilent proprietary algorithm. It was removed to align with literature and other comparable protocols.
- The holmium oxide internal test was considered a pre-OQ diagnostic or calibration check and is not reported in Enterprise Edition OQ. This check is performed in Agilent Preventive Maintenance (PM) service prior to the OQ.
- All precision tests (flow precision, injection precision and temperature stability over time) use six readings to align with the latest literature & guidance and allow statistically comparable RSD results.

None of the changes affect the regulatory compliance status.

Enhancements and Additions:

- The Gradient Performance test has been re-designed and enhanced. A different gradient slope is used that tests and challenges more aspects of gradient performance and provides some additional, very useful information.
- The Column Compartment Temperature test now uses a special T-piece that allows measurement of the temperature of the water flowing out of the thermal exchange blocks.
- A Signal-to-Noise test has been added to ensure cell cleanliness (in LC), replace absolute area check (in GC), harmonize with MS qualifications that require signal-to-noise checks, provide comparable sensitivity results and thereby provide more system performance data.
- The response linearity test now adds Response Factor (R/F) Precision aligned with current literature and provides a more sensitive measure of linearity.
- For labs that run non-Agilent CDS such as Waters Empower, we can control the instrument during OQ, collect the digital signal data, and calculate the results in ACE. This provides a full 'holistic' OQ that simultaneously qualifies the instrument hardware and the Empower control and data acquisition functions.
- Two-Limit feature: each test's final result can be calculated against two limits if required. This allows the customer-configured OQ to report against a User Limit (limit1) and the Agilent-recommended Limit (limit2) simultaneously. Or, as is common in process instrument calibration, a *Warning Limit* and *Action Limit* may be applied. Lab workers are familiar with Upper and Lower Limits in their control chart procedures, but Two-Limit reporting is new to LC and GC qualification. The Agilent-recommended EQPs have both limit1 & limit2 values set the same – effectively de-activating this feature.

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List of Enterprise Edition OQ tests for 1100/1200 LC versus Classic OQPV tests for 1100 LC

Test Name in Enterprise Edition	Set Point / Parameter in Enterprise Edition for 1100/1200 series LC	Limits in Enterprise Edition A.01.60	Difference from Classic OQPV
Pump Flow Accuracy and Precision	Flow rate 1 = 0.500 ml/minute	Accuracy ≤ 5.00%	Same limits.
	Flow rate 2 = 5.000 ml/minute	Precision ≤ 0.50%	Set points widened from previous 1ml/min and 2ml/min
Column Temperature Accuracy and Stability	Temperature 1 = 80.0 °C*	Accuracy ≤ 3.0 °C	Same limit for the 40 °C set point as OQPV. Stability was only measured at 40 °C with 0.5 °C limit in OQPV.
	Temperature 2 = 40.0 °C	Accuracy ≤ 2.0 °C	
	For any temperature	Stability ≤ 1.0 °C	Test design is enhanced to measure flow temperature in Enterprise Edition whereas OQPV tested the thermal block temperature.
Wavelength Accuracy (UV-Vis)	Wavelength 1 =205 nm [Maximum] Wavelength 2 =245 nm [Minimum] Wavelength 3 =273 nm [Maximum]	≤ 2 nm	Same limit and set point
Wavelength Accuracy (FLD)	Wavelength 1=350 nm [Maximum] Wavelength 2=397 nm [Maximum]	≤ 3 nm	Same limit and set point
Signal Noise and Drift (UV-Vis)	Noise	Noise VWD (0.04), DAD/MWD (0.05).	Same limits (mAU and mAU/hr)
	Drift	Drift VWD (0.5), DAD/MWD (5.0)	The proprietary and unique *Wander* calculation in OQPV is removed.
Signal Noise and Drift (RID)	Noise	≤ 10.000 nRIU	Same limit and set point
	Drift	≤ 400.000 nRIU/hour	Same limit and set point
Signal to Noise (UV-Vis)	Signal to Noise	≥ 3000	New test
Signal to Noise (RID)	Signal to Noise	≥ 2000	New test
Signal to Noise (FLD)	Signal to Noise	≥ 400	New test
Injection Precision (UV and RID)	Height RSD	≤ 2.00 %	Same limit and set point
	Area RSD	≤ 1.00 %	Same limit and set point
Injection Carry Over (UV-Vis and RID)	Height Carry Over	≤ 0.40 %	Same limit and set point
	Area Carry Over	≤ 0.20 %	Same limit and set point
Response Linearity (UV-Vis)	Coefficient of Determination (r2)	≥ 0.99900	Same limit and set poin
	R/F Precision	≤ 5.00 %	New parameter and limit
Response Linearity (RID)	Coefficient of Determination (r2)	≥ 0.99500	OQPV limit is 0.9990. Injection volume was 2 uL in OQPV; this is now 5 uL
	R/F Precision	≤ 10.00 %	New parameter and limit

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List of Enterprise Edition OQ tests for 1100/1200 LC versus Classic OQPV tests for 1100 LC (continued)

Test Name in Enterprise Edition	Set Point / Parameter in Enterprise Edition for 1100/1200 series LC	Limits in Enterprise Edition A.01.60	Difference from Classic OQPV
Gradient Composition	Composition Accuracy, Composition Noise, Composition Drift	≤ 2.00 %	New test design, new parameters.
	High Coefficient of Determination (r2)	≥ 0.99900	New parameter and limit. This tests linearity at start of gradient.
	Mid Coefficient of Determination (r2)	≥ 0.99900	New parameter and limit. This tests linearity at the 50:50 zone.
	Low Coefficient of Determination (r2)	≥ 0.99900	New parameter and limit. This tests linearity at end of gradient.
Sample Temperature Accuracy	Set point 4 °C	≥ –2.0 °C to ≤ 5.0 °C	Same limit and set point
	Additional Set point is Selectable	± 3.0 °C setpoints >10 °C	Choice not available in OQPV
Injection Linearity (UV-Vis only)	Coefficient of Determination (r2)	≥ 0.999000	New optional extra test – choice not available in OQPV
	R/F Precision	≤ 5.00 %	
Injection Response (UV-Vis)	For a known injection vol. / conc. / path length, the peak area is predictable (within a range.)	≥ 1,200,000 to ≤ 1,800,000 counts (std cell path length)	This is a new semi-quantitative test of Injection Accuracy - choice not available in OQPV

*For routine qualification of installed base 1050, 1090 LC systems the column temperature set point recommendation is 60 °C limit ± 3 °C
The new instruments – LCMS, ELSD, CTC etc. never were covered by Classic OQPV so are not listed here.

Injection Linearity and Injection Response are only available with a Custom EQP.

For GC there are no significant changes to set points and limits in the core OQ tests. The main changes are:

- The signal-to-noise test replaces the old absolute area test and oven temperature now is measured directly with calibrated probe and meter.
- The harmonized look and feel of the reports (EQR) is an improved and cleaner presentation of the Classic reports which were different for different GC models.
- The thermal qualification and response linearity tests that were separate services now are simply optional extra tests in Enterprise Edition. This further harmonizes the look and feel of GC reports.

How are Equipment Qualification Reports (EQR) different from OQPV Reports?

The easiest way to check is simply to look at the extract of a sample hardware OQ report provided in an EQP attachment. The main differences are:

- A report (plus all raw data) is delivered to a customer as a single, secure pdf on a dedicated CD disk. View it on your computer using the freely available program, Acrobat Reader™.
- It has a color front page and one click to the back page shows a summary of results that can be used as your Qualification Certificate. Print only these 4 or 5 pages for your paper copy to save paper, while providing all the summary information required. You may keep the pdf records on the disk and/or on your own network storage system for fully auditable electronic records.

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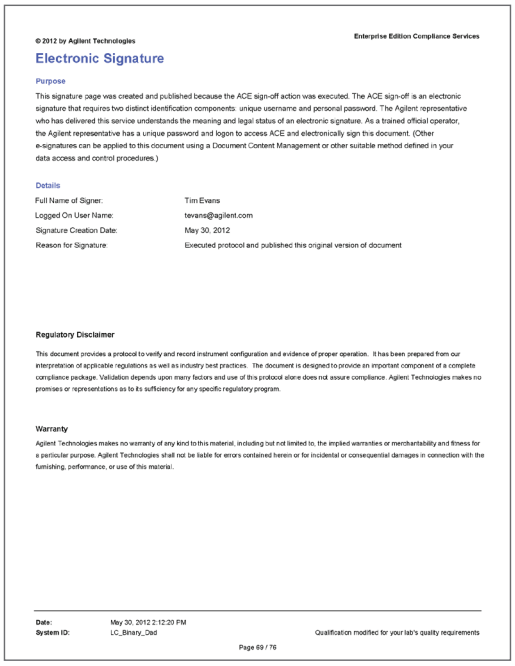

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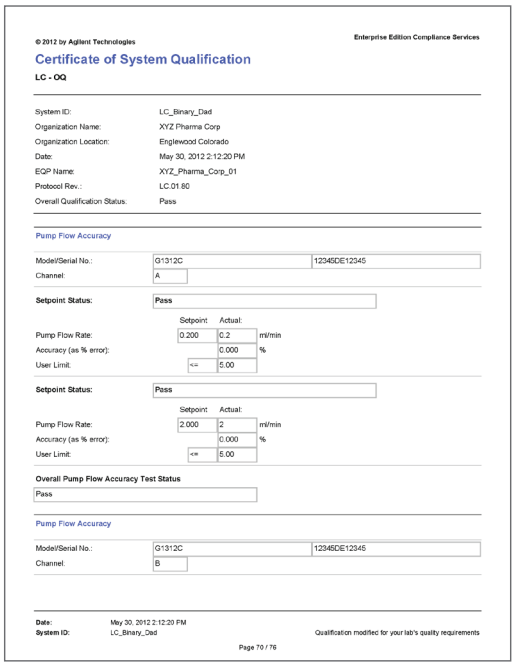

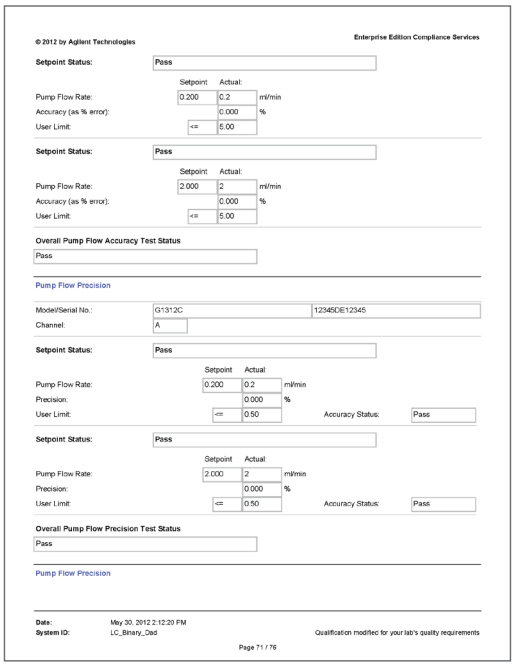

Certificate of System Qualification – at customer-selected location

- The major sections of the Equipment Qualification Report (EQR) include:
  - All the details and descriptions of the tests and the system being tested
  - A detailed test summary section that shows pass/fail per test, the number of times each test was run and overall OQ status
  - The raw values and calculated results for each test run plus pass/fail status and chromatograms
  - Data integrity and audit log pages to ensure trustworthiness and allow easy traceability to raw data
  - Copies of certificates for the equipment, chemical standards and service engineer training
  - Sections with general information, glossary, list of formulas, etc. You can request that these not be included in future EQRs to receive shorter reports if multiple OQs are delivered.

What should I do if I want to move my annual OQ service from Classic to Enterprise Edition?

The simplest answer is – just download and approve one of the published Agilent-recommended EQPs for the appropriate techniques, and order the service contract as usual. However, some customers have situations that require slightly more complex actions.

If a lab has a calibration/qualification that references the Agilent OQPV by name or even copies out the OQPV tests and limits — we need to ensure the new service does not conflict with the SOP. Check carefully the words in your SOP for any exception phrases such as "...or approved alternative" or "... or following Agilent's current recommended procedures." Many customers have simply made their old SOP obsolete– the EQP approval substitutes for an SOP.

Some firms have an efficient SOP deviation process where the QA Manager/Director can issue a simple form that states that the Agilent Enterprise Edition service and the signed EQP(s) are an approved alternative to the current local Qualification SOP. This allows instant use of Enterprise Edition and provides you time to consider whether or how to make a new SOP.

For thorough QA review and approval we provide a description of the service in the EQP Review Documents (with more information on the Agilent web site under the Compliance Services section), a Part 11 Conformance document, and other examples as attachments to each EQP and this document.

If a vendor audit is deemed appropriate by your QA department, Agilent can provide a Validation binder with Agilent's lifecycle documentation showing the full testing and validation of Enterprise Edition and ACE. An electronic copy of the Validation binder is available to QA auditors upon receipt of a signed confidential disclosure agreement. These electronic documents have saved firms the expense of on-site audit visits to our offices in Delaware, USA or Waldbronn, Germany.

What are the main risks of migrating to Enterprise Edition and how can they be avoided?

We do not believe that there are any regulatory compliance risks in using Enterprise Edition – in fact we are confident that it is the safest, most sustainable and convenient option for firms large and small. However, the previous section mentioned the need to ensure that your own SOPs align with (or at least do not conflict with) the Enterprise Edition protocols. Keeping a copy of the signed approval of your EQP(s) is an expectation. Keeping copies of the reports and your approvals is essential. The CD and report format make that easier and more convenient than paper reports when searching for past records and performance data. Ink signatures on the print-out of the secure pdf report and/or on the EQR CD disk are both 21 CFR Part 11 compliant "hybrid ink on paper signatures linked to an electronic record."

As you may see, there are some first-time preparation steps to complete prior to the first ACE delivery. After that the automated Enterprise Edition OQ typically takes less time to deliver than Classic OQPV. ***A pre-approved EQP is essential to ensure an expeditious and efficient delivery of the service without last-minute adjustments.*** Pre-approval of the EQP is therefore checked by our schedulers when they call to arrange a time for the PM and OQ service. To ensure that any Agilent service engineer scheduled to arrive on-site will execute the customer-configured EQP you approved, keep a CD copy handy in the lab, just in case your regular engineer, who is familiar with your requirements and has your EQP in his ACE laptop, is not available. Agilent engineers save a copy of the approved EQP on every report CD – so once the first one is completed there is always a copy for any other Agilent service engineer to access.

Once the first couple of OQ deliveries are completed in a lab contract and you gain familiarity with the new report style, the benefits and efficiency gains are fully enjoyed. We can reduce the size of reports by turning off the repetitive text sections. The first time you need to electronically forward a copy of an OQ report for remote review (because the usual approver is out of office) or have to search and compare instrument performance data across multiple makes of LCs in your lab, or have an external audit of your lab qualification system – you'll appreciate that your organization has invested in Agilent Enterprise Edition compliance services.

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Summary of high-level differences between Enterprise and Classic Edition Compliance Services

Table: List of Characteristics of an Analytical Instrument Qualification (AIQ) Program and comparison between Enterprise and Classic Edition OQ services

Characteristic	Enterprise Edition OQ	Classic Edition OQPV
Meets the letter, spirit and intent of cGMP and GLP regarding Equipment Qualification	Yes	Yes
Acceptable to (and used by the Labs of) International Agency auditors	Yes	Yes
QA-approved system in major Pharmaceutical firms	Yes	Yes
Compatible with Agilent LC, LC/MS and GC, GC/MS instruments	Yes	Yes
Compatible with leading non-Agilent LC and GC instruments and suitable for use as an Enterprise-wide program	Yes	No
Compatible with Agilent ChemStation CDS	Yes	Yes
Compatible with all Agilent CDS and most non-Agilent CDS (for example, OpenLab, EZChrom, MassHunter, Empower)	Yes	No
Adequate for compliance without delivering "over-testing"	Yes	Yes
Provides a protocol with fixed recommended tests and limits	Yes	Yes
Provides customer selectable setpoints and then a fixed protocol for future use that contains these tests and limits	Yes	No
Comprehensive final report with automated results calculation and pass/fail status reporting	Yes	Yes
Flexible-sized final report in secure pdf format that can be printed to paper in full, or in part (to save paper)	Yes	No
Final report in secure pdf format with a single signature	Yes	No
Reports with searchable electronic data and results	Yes	No

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