Pharma

Maximizing laboratory productivity: How modernizing an instrument park leads to significant reduction in system suitability failures

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Thermo Fisher Scientific Pharma Service Group (PSG, also known as Patheon) provides industry-leading pharma service solutions in drug development, clinical trials logistics, and commercial manufacturing. With more than 55 locations worldwide, expertise in chemical and biotherapeutic molecule drug substances, and drug products across the product lifecycle, the Pharma Service Group is well regarded as a leader in pharmaceutical services. Addressing such a wide range of drug substances and products, as well as demanding timelines and operating in a cGMP environment, PSG needs to be flexible and have streamlined processes while continuing to be compliant with regulatory agency requirements.

To meet the growing demands for a variety of projects, PSG has recently embarked on a technology refresh program to replace aging analytical equipment with a more modern liquid chromatography platform. The new platform must be compatible with their existing IT infrastructure (Waters™ Empower™ 3 Chromatography Data System), suitable for the analysis of both chemical and biologic molecules, and compatible with legacy HPLC methods as well as modern UHPLC assays. Meeting all requirements, the Thermo Scientific™ Vanquish™ UHPLC platform was adopted across the PSG network.

The transition to this platform presented some hesitancy for analysts familiar with other technologies as well as clients who had developed their methods on other vendor LC systems. However, greater flexibility, ease-of-use, enhanced robustness, and serviceability leading to improved day-to-day operations, significantly outweighed these challenges.

> "Even though the Vanquish systems are used much more than other systems, they have significantly fewer instrument-related failures."

System suitability failures

"System suitability tests (SST) verify that the system will perform in accordance with the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test."[1]

In other words, the system must meet the requirements for a particular method such as reproducibility (% RSD), resolution between certain peaks, sensitivity (S/N ratio), etc. to be deemed acceptable to run actual samples. When these requirements are not met, there is a system suitability failure leading to an investigation. Although investigations do not necessarily lead to out of specification (OOS) or out of trend (OOT) outcomes, which can have significant impacts with regulatory agencies, they are still of concern as they disrupt daily lab operations. However, failure to routinely assess systems suitability can lead to deviation as seen in a recent warning letter from the FDA.[2]

It should be noted that System Suitability Tests are not the same as analytical instrument qualification (AIQ). "AIQ is the collection of document evidence that an instrument performs suitably for its intended purpose. Use of a qualified instrument in analyses contributes to confidence in the validity of generated data."[1] In relation to liquid chromatography, we can say that a qualified (U)HPLC system is fit for its intended purpose, operating as intended by the instrument manufacturer within the operating ranges define by the lab, for example within a certain flow rate, with a particular detector, or column temperature range, etc. Although instrument qualification is essential to a laboratory working in a GMP environment, having a qualified instrument does not guarantee system suitability as this is tied to a specific method. Even though the instrument meets the general specifications, there are many different factors that can lead to a system suitability failure (SSF) (i.e., not meeting the requirements of the method). Such factors include mistakes during sample preparation, column degradation, or lack of robust method and instrument performance. In an ideal world, sample preparation should not be a source of error, the LC column should be changed regularly and have robust LC system performance, but in the fast-paced cGMP laboratory many things can happen that are difficult to predict. Modernizing an analytical instrument park with state-of-the-art technology can assist in eliminating instrument-related SSF, such as the ones associated with pump failures, autosampler errors, or inconsistent detector performance.

Analytical procedure lifecycle: the impact of ICH Q14

The ICH Q14 guidance on Analytical Procedure Development (currently under review within the industry) provides general recommendations for analytical procedure development and lifecycle management. In short, the goal of development is to obtain an analytical procedure fit for its intended purpose and two approaches—minimal and enhanced analytical method development—should be considered. Table 1 shows the main difference between the two approaches.

Table 1. Minimal vs. enhanced approach to analytical method development

Minimal approach (validatable)	Enhanced approach (optimized through AQbD)
• **Identify attributes to be tested** by the analytical procedure • Select **appropriate analytical technology** • **Conduct appropriate development studies** to evaluate analytical procedure performance characteristics • Define **appropriate analytical procedure description including control strategy**	• **Evaluate sample properties and expected variability** based on the manufacturing process • Define **analytical target profile** (ATP) • **Conduct risk assessment and evaluate prior knowledge** • Conduct **uni- or multi-variate experiments** • Define an **analytical procedure control strategy based on enhanced procedure understanding** • Define a **lifecycle change management plan**

Although, the minimal approach is acceptable in most cases, the enhanced approach is ideal to support development and lifecycle management of analytical procedures by offering a systematic way of developing and refining knowledge of analytical procedures. The analytical product lifecycle comprises several elements including analytical procedure development, validation, and change management, which are interrelated as shown in Figure 1.

Part of change management is continual improvement of the analytical procedure, which can be achieved by modernizing instrumentation and transferring analytical methods to the latest technologies for improved specificity, enhanced precision, and accuracy. In other words, modernizing an instrument fleet is strongly encouraged as it can lead to overall lab efficiency gains through failed assays.

Vanquish UHPLC systems significantly reduce instrument-related system suitability failures

The Patheon Toronto facility has modernized its UHPLC instrument park by converting 48% of the instrument fleet to Thermo Scientific UHPLC systems — mostly Thermo Scientific Vanquish Flex UHPLC systems. Replacing aging liquid chromatography systems has led to obvious benefits like reducing instrument downtime, easier access to routine consumables, and providing state of the art technology to build newer/faster methods. It also led to a significant reduction in system suitability failures. In fact, from July 2020 to June 2022, as the Vanquish footprint was increased from 18% to 47% of the LC fleet, system suitability failures were decreased by 34% overall.

As mentioned before, SSF can be unrelated to instrumentation. A review of sources of the SSF from selected manufacturing sites within the PSG network indicates that, on average, 80% of SSF are unrelated to instrument failures. For that matter, a more thorough analysis has been done by investigating instrument related system suitability failures for 6 months. This was done by reviewing the root causes of failures logged in the quality management software. Only the ones that could be tied directly to instrument failures (such as pump failures, leaks, etc.) were taken into account. For example, if an instrument failure was reported, but a failing column was behind the root cause, this was not considered.

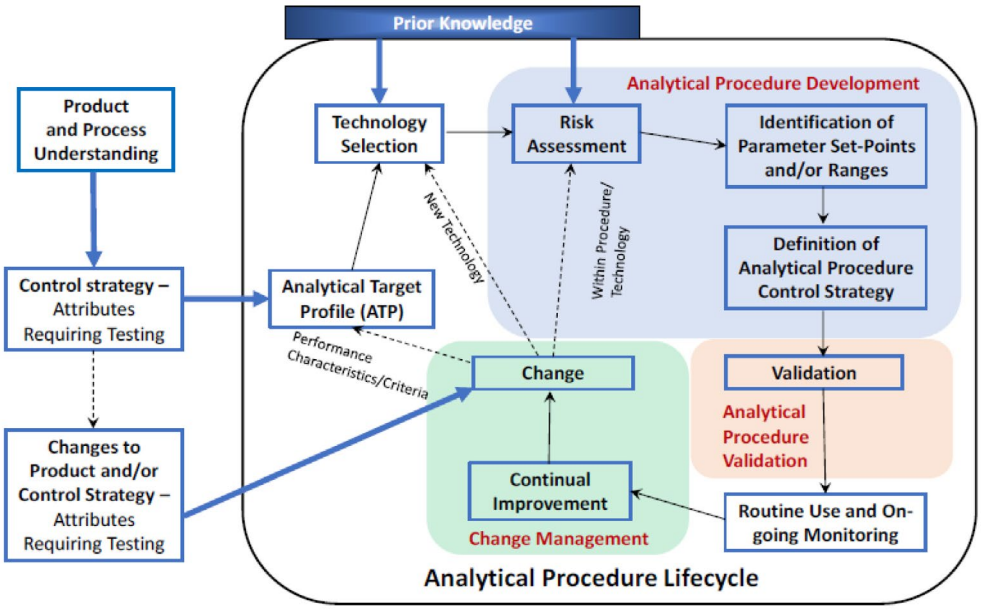

Figure 1. Analytical procedure lifecycle[3]

When comparing SSF on Vanquish UHPLC systems vs. other LC systems we see that, on average, Vanquish UHPLCs account for ~24% of LC instrument-related SSF (by logged incident). It is important to stress that even though the Toronto LC fleet comprises 48% Vanquish systems, these systems represent on average 63% of the total hourly LC usage monthly. Therefore, even though the Vanquish systems are used much more than other LCs, they have significantly fewer instrument-related failures. Figure 2 compares the number of days per month the Vanquish LC fleet and other vendor LCs are used before leading to an instrument SSF. Although the monthly numbers of hours vary greatly due to variable instrument use, the Vanquish LC instrument uptime always exceeds that of competitors systems averaging at 6 times more usage.

At the current Vanquish system footprint, we can estimate a 52% reduction of instrument-related system suitability failures, which can be directly tied to significant annual savings associated with unproductive work. For example, if a laboratory had ~150 instrument-related system failures and replaced their aging instrumentation to meet the same productivity gain as in our case study, they would now have ~72 SSF/year (Figure 3). By industry standards, an investigation can take up to 20 hours, and each hour of investigation could represent $200 of cost/loss of revenue, this would lead to $300K annual savings.

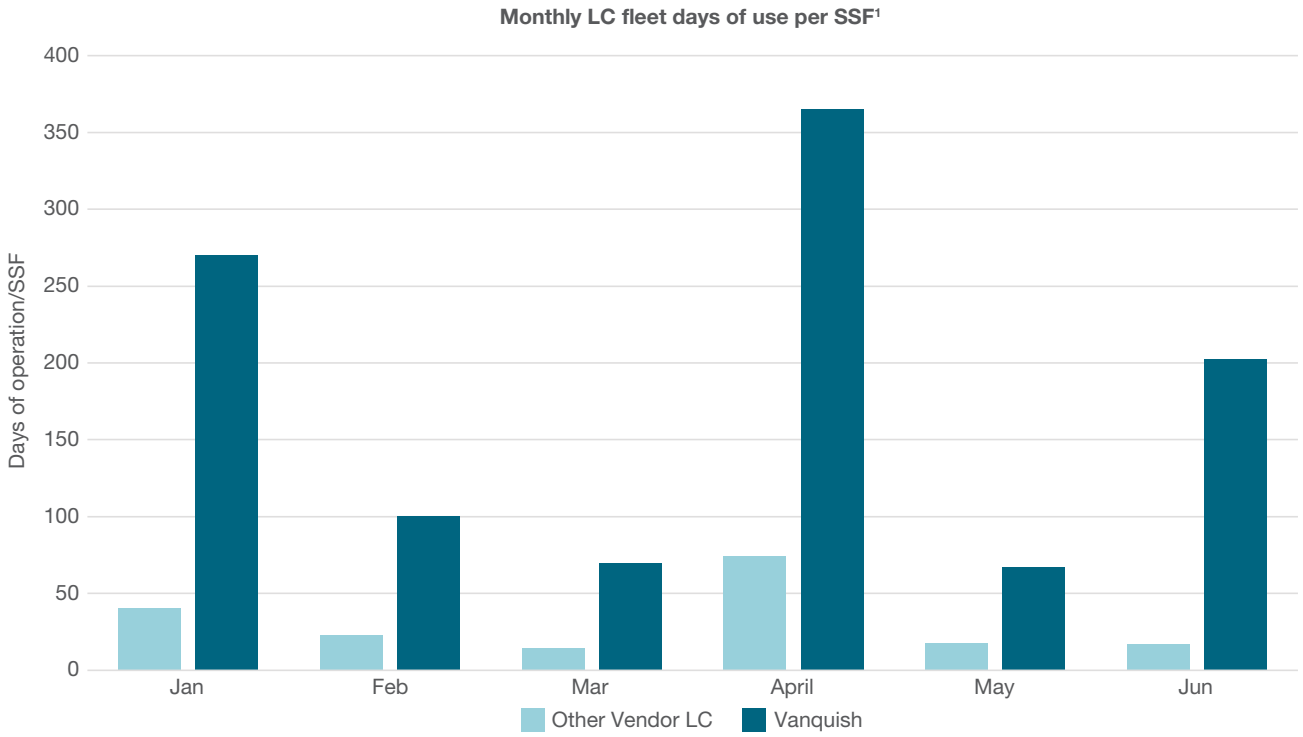

Figure 2. Daily usage of Vanquish system and combined other vendor LC systems broken down by month, per SSF, highlighting the Vanquish system runs for much longer without incident

> "We estimate a 52% reduction of instrument-related system suitability failures, which can be directly tied to significant annual savings associated to unproductive work."

Fewer instrument-related system suitability failures due to improved robustness of the Vanquish systems as indicated above represent just a portion of the SSF reductions associated with modernizing the LC instrument fleet. In fact, transferring methods onto the Vanquish platform has led to method improvement and longer column lifetime. As seen in Table 2, a UHPLC of another brand was very close to the tailing factor SST requirements of the method, which lead to frequent failures. Fortunately, transferring the method to a Vanquish Flex system reduces the tailing factor, and the method meets system suitability criteria more consistently. This improvement also led to improved column lifetime by providing a larger operating range, which allowed a safety buffer due to the column performance.

As seen in Table 3, transferring methods to the Vanquish Flex system also proved beneficial in improving the signal-to-noise ratio (method sensitivity). As indicated, the S/N ratio for the method was very close to the allowed limit, which resulted in several system suitability failures during operation on older HPLC systems.

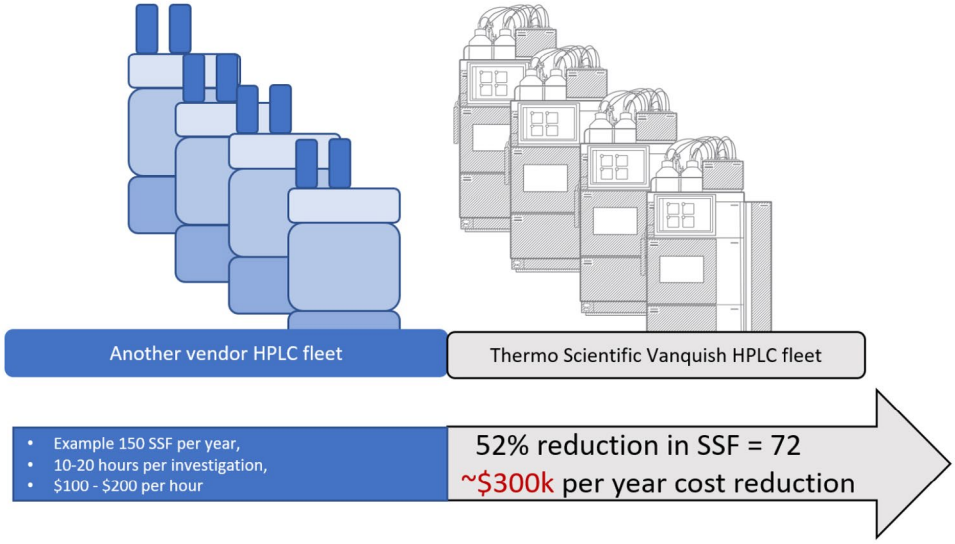

Figure 3. Example of how an HPLC fleet with 150 SSF per year would have significant cost savings by replacing with Vanquish systems

Table 2. Improved tailing factor, peak area, and RT precision and resolution compared to original method

Parameter	Criteria	Vanquish Flex UHPLC	UHPLC A
No significant interference at RT of active and impurities in blank injection	NMT 0.1% of active area in 1st standard injection	No interference	No interference
USP S/N of sensitivity	NLT 10	31	35
Theoretical plates (n=5)	NLT 10,000	52444	55713
Tailing factor (n=5)	**NMT 2.5**	**2.1**	**2.4**
% RSD of active peak area (n=5)	NMT 2.0%	0.0	0.2
% RSD of active peak area (n=all)	NMT 2.0%	0.1	0.4
% RSD of active RT (n=5)	NMT 2.0%	0.0	0.1
% RSD of active RT (n=all)	NMT 2.0%	0.0	0.1
Check standard (% Recovery)	98.0–102.0 %	99.7	100.4
Resolution between impurity A and active peak	NLT 1.0	**1.2**	**1.1**

Table 3. Improved peak shape can influence sensitivity when it really counts

Parameter	Criteria	Vanquish Flex UHPLC	UHPLC A
USP S/N of sensitivity	**NLT 10**	**17**	**12**
Tailing factor (n=5)	NMT 2.0	1.0	1.1
% RSD of active peak area (n=5)	NMT 2.0%	0.0	0.1
% RSD of active peak area (n=all)	NMT 2.0%	0.1	0.3
% RSD of active RT (n=all)	NMT 2.0%	0.0	0.0
Check standard (% Recovery)	98.0–102.0 %	100.1	100.0
Resolution between impurity A and active peak	NLT 1.0	2.1	2.1

Conclusion

Modernizing an instrument park can be seen as a significant investment, not only from a monetary perspective, but also in terms of time and labor. However, rather than just replacing with like-for-like new systems, choosing to replace with industry proven, robust Vanquish UHPLC platforms can have significant advantages, especially for improving daily operations by reducing system suitability failures. This far outweighs the drawbacks associated with fleet replacement. Moreover, with the ICH Q14 currently under review, it is expected that cGMP laboratories have proper analytical procedure lifecycle strategy in place. Modernizing instrumentation is a straightforward and futureproof way to meet current and future regulatory guidance and can lead to significant cost savings.

References

1. USP <1058> Analytical Instrument Qualification.
2. U.S. Food and Drug Administration Warning Letters. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/shandong-analysis-and-test-center-524254-06222017; https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/international-trading-pharm-lab-inc-598537-04242020
3. ICH Q14 – Analytical Procedure Development, Draft Version, Endorsed on 24 March 2022, ICH 2022. https://database.ich.org/sites/default/files/ICH_Q14_Document_Step2_Guideline_2022_0324.pdf

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