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Transferring methods onto a new UHPLC platform:

How Sanofi increased productivity and reduced costs and solvent usage

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Sanofi is one of the largest multinational pharmaceutical companies headquartered in Paris, France. It has operations in over 170 countries and focuses on the research, development, manufacturing and marketing of a wide range of pharmaceutical products, including prescription drugs, vaccines and consumer healthcare products. Sanofi's mission to improve the health and well-being of people worldwide aligns with Thermo Fisher Scientific's Mission to enable customers to make the world healthier, cleaner and safer.

As both companies have a shared focus on advancing healthcare and providing innovative solutions to address global health challenges, in 2021, they embarked on a partnership to modernize Sanofi LC instruments with cutting-edge technologies from Thermo Fisher Scientific. Both parties have benefited from this partnership, Sanofi by improving productivity and reducing cost, and Thermo Fisher Scientific by learning first-hand how their instruments perform daily in R&D to QC laboratories.

To improve lab productivity and streamline day-to-day operations, Sanofi Compiègne has replaced a portion of their aging high-performance liquid chromatography (HPLC) systems with the Thermo Scientific™ Vanquish™ Flex Ultra-High-Performance Liquid Chromatography (UHPLC) systems and took this opportunity to modernize some high-volume methods. In addition to the above benefits, this initiative aligns with the push from regulatory bodies to get liquid chromatography users to modernize their instruments and have a proper method lifecycle management process.

As such, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q14 guidance on Analytical Procedure Development[1] (adopted in November 2023) provides general recommendations for analytical procedure development and lifecycle management. Amongst other matters, the ICH recommends continual improvement of the analytical procedure, which can

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"By dramatically reducing analytical time and minimizing solvent use, the Thermo Scientific Vanquish Flex UHPLC sets a new standard for efficiency, sustainability and safety in the lab."

—**Xavier Lelièvre**, Head of Analytical Development, CHC Development Center, Sanofi

be achieved by modernizing instrumentation and transferring analytical methods to the latest technologies to enhance specificity, precision and accuracy.

In addition, there have been updates to the United States Pharmacopeia (USP) Chapter <621>[2], allowing more flexibility to update compendial gradient liquid chromatography methods. This update gives users more flexibility to change column dimensions, flow rate and other parameters for both isocratic and gradient methods without needing to revalidate.

Instrument and method modernization: Significant benefits justifying the effort

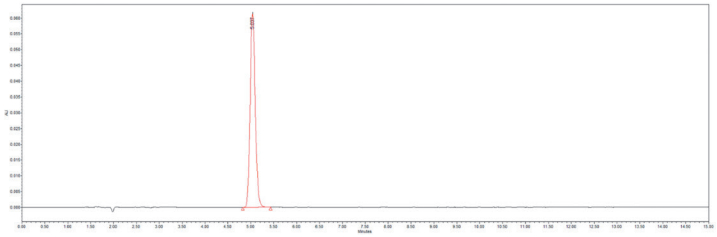
The Sanofi Compiègne Development Center Analytical team, which operates under the Sanofi Consumer Healthcare branch, manufactures over-the-counter drugs for allergies, pain management and digestive health. They produce nearly four billion tablets, capsules and powders, of which 60% are exported.

The team's development center supports product development for their own production as well as other manufacturing sites. Due to country-specific requirements, the final product can come in different formats, necessitating liquid chromatographic methods that can be easily implemented across manufacturing sites and for different drug products.

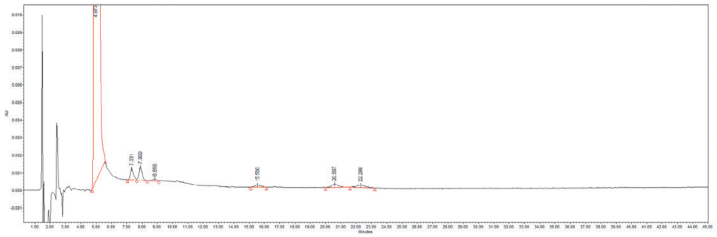
Exporting products to different regions poses an additional challenge, as it requires the submission of drug packages to the regulatory bodies of each market. The complexity of these processes, along with the significant paperwork and approvals needed from multiple stakeholders, often creates bottlenecks in method modernization. However, for high-volume products, the effort is justified.

For example, Compiègne and another Sanofi manufacturing site collectively produce 300 lots of a specific drug per year, manufactured under four different dosage strengths. Each batch requires liquid chromatography testing for assay and impurity analysis. Some of these lots also need to be tested for content uniformity. Consequently, a significant number of analyses need to be conducted, and there is an extensive amount of required sample preparation.

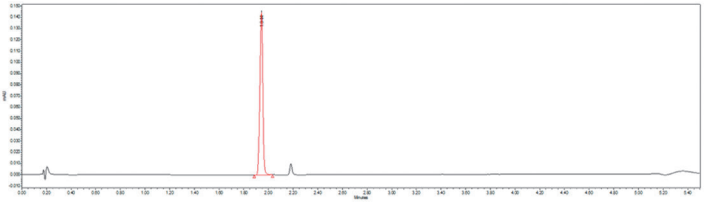
Figure 1.



Legacy assay method



Legacy impurity method



New combined assay/impurity method

To reduce the analytical burden associated with this large volume of analysis, the Compiègne Analytical Development group developed brand-new assay and impurity methods for the Vanquish Flex UHPLC system, enabling both assays and impurity analyses to be performed in the same analytical run. Figure 1 compares chromatography from the previous methods to the new one. The use of the Vanquish Flex UHPLC system resulted in a substantial decrease in total run time, from one hour to just five and a half minutes, saving approximately 54 minutes and reducing the analytical run time by 91% (Table 1).

Table 1. Legacy versus Vanquish Flex method run time

Legacy method run time (min)		**Vanquish Flex UHPLC method run time** (min)
Assay	**Impurity**	**Assay/impurity**
15	45	5.5

Table 2. Analysis time and solvent consumption savings from moving onto the Vanquish Flex UHPLC

	Comparative study[1]		
	Legacy method	**Vanquish Flex method**	**Savings**
LC analysis time (hr)	13 hr 35 min	2 hr 57 min	10.6 hr
Solvent consumption (mL)	1222 mL	133 mL	1089 mL

[1]Based on comparative study of three lots and 10 content uniformity

Adoption of the Vanquish Flex UHPLC and implementing the new methods resulted in efficiency gains:

Legacy method

- The analysis time required for a comparative study of three lots at four dosages, one of which required content uniformity testing, was 13 hours and 35 minutes of instrument run time
- Used 1222 mL of mobile phase

Vanquish Flex method

- The overall run time was reduced to two hours and 57 minutes
- The overall run time for the same number of lots and content uniformity tests consumed 133 mL of solvent
- Represents a significant reduction of 78% (equivalent to 10.6 hours) in instrument run time and an 82% reduction (equivalent to 1.09 L) in solvent consumption

The impressive productivity gains achieved through instrument and method modernization also resulted in substantial cost savings for Sanofi, considering that this method supports the release of up to 300 batches annually.

- Saves 106 days of analysis time
- Reduces solvent usage by 109 liters
- Saves approximately $7,070 per year in labor costs and solvent consumption/disposal (as indicated in Table 4)

These savings further demonstrate how the modernization efforts financially benefit Sanofi.

The re-optimization of the analysis that accompanied the transition to the Vanquish Flex UHPLC also resulted in significant improvements in sample preparation. During the development, the impurity and assay methods were consolidated, leading to not only reduced analysis time but also a decrease in the time and solvent required for sample preparation.

> "The impressive productivity gains achieved through instrument and method modernization also resulted in substantial cost savings for Sanofi."

Previously, the method involved the preparation of multiple mobile phases to accommodate various methods, dilutions and long agitation times. In addition, the initial method required the preparation of four test solutions of different concentrations for each lot (two for assay and two for impurities) due to sensitivity needs for impurities at the detector wavelength.

The new method uses the same sample solutions for assay and impurities that are simultaneously read at two different wavelengths, giving an appropriate response for each determination. The combination of two methods into one led to an additional savings of approximately $12,188 due to improved sample preparation, as summarized in Table 5.

Moreover, having a single method with simplified sample preparation significantly reduces the risk of user errors, thereby further enhancing productivity improvements. This consolidation of methods not only streamlines operations but also contributes to cost savings and better overall efficiency.

The Vanquish Flex UHPLC has additional benefits, such as improving overall laboratory productivity. The feedback from the

Table 3. Estimated laboratory cost (major contributors) of running an HPLC

Description/parameter	**Amount** (USD)
Full time employee (FTE) labor costs, covering salary, benefits, facilities and taxes (daily)[1]	$190
Cost per liter of HPLC solvent	$20
Cost per liter of solvent disposal	$10

[1]Based on a 7.5-hour work day

Table 4. Estimated yearly savings from moving the HPLC methods to the Vanquish Flex UHPLC

	Yearly savings[1]
LC analysis time (working day)	20
Solvent consumption (L)	109
Labor (USD)[2]	$3,800
Solvent (USD)	$3,270

[1]Yearly savings from 300 lots
[2]Assuming a 7.5-hour work day and only 25% of daily activities associated with HPLC

Table 5. Estimated yearly savings from sample preparations from moving the HPLC methods to the Vanquish Flex UHPLC

	Savings[1]		
	Comparative study	**Yearly estimate**	**Yearly estimate** (USD)
Sample preparation time	2 hr 30 min	33 days	$6,188
Solvent consumption	2 L	200 L	$6,000

[1]Based on a 7.5-hour work day

laboratory is that the systems are an easy-to-understand flow path, making the systems simple to use and easy to learn. They have benefited from using Thermo Scientific™ Viper™ Fingertight Fittings for easy, tool-free column installations that provide reliable, leak-free connections.

Vanquish Flex systems have proven to be robust and have not led to any system suitability failures since they started using them. The system also shows improved reproducibility of <1% over their legacy LC, which can have an impact on analytical results.

The autosampler capacity (216 x 2 mL vials) of the Vanquish Flex is also seen as a major advantage, as it can run every sample from a dissolution profile study on one system versus being split over two systems when using another vendor. The time needed to inject is reduced by 60% compared to another vendor. Interacting with Vanquish Flex systems gave the users the impression that they were working in a "high-end/modern" lab.

Finally, the system needed to be operated under Empower, and the Vanquish Flex integration was seamless. The instrument method creation is intuitive, and the audit trail is detailed.

In addition to the quantifiable benefits mentioned, there are other advantages that are more challenging to measure but align with the corporate social responsibilities of both Sanofi and Thermo Fisher Scientific. These include reducing environmental footprint and energy consumption and improving population health.

Reducing method length and using energy-efficient systems leads to lower energy consumption. Reducing chemical usage and waste disposal contributes to environmental preservation. Moreover, minimizing exposure to solvents enhances the well-being of analysts and reduces the risk of work-related health issues and accidents.

Conclusion

While modernizing HPLC instruments and methods may initially appear as a significant challenge, the recent technological advancements and regulatory expectations for proper analytical procedure lifecycle management have prompted companies to upgrade their instrument fleets.

> "Vanquish Flex systems have proven to be robust and have not led to any system suitability failures."

The partnership between Sanofi and Thermo Fisher Scientific, which involves replacing legacy HPLC systems with Vanquish Flex UHPLC systems, demonstrates the benefits laboratories can achieve through this transformation. These benefits include enhanced environmental health and safety and reduced instrument occupancy, solvent consumption, sample preparation time and environmental footprint. Ultimately, the significant cost savings, productivity gains and how this partnership supports meeting sustainability requirements greatly justifies the effort required.

Footnotes

1. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (2022). Analytical Procedure Development Q14 draft version.
2. Thermo Fisher Scientific (2023). Allowable adjustments of chromatographic conditions: United States Pharmacopeia USP chapter <621>.

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