Applying Quality by Design Principles to the Migration of a Compendial Method between Multiple HPLC Systems

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PURPOSE

Within the pharmaceutical industry, compendial LC methods are used to assess whether the regulatory specifications for raw materials or finished products are met. Analytical laboratories are often required to migrate these methods to different laboratories or different models of LC instrumentation. The methods may be migrated without revalidation, however equivalent performance must be demonstrated.

Method migration can be challenging. Differences across HPLC systems can impact method performance. A plan designed to identify and control how method performance is affected by differences in instrumentation is a valuable tool in obtaining a successful outcome.

Quality by Design (QbD) Principles were incorporated in the development of a plan to migrate the USP Ibuprofen Tablets Organic Impurities method from a legacy HPLC system (originator system) to two modern HPLC systems (receiver systems) from different instrument vendors.

METHOD(S)

Migration Plan

Utilizing QbD principles, a migration plan was developed. This involved a three-step process:

1. System Comparison
2. Risk Assessment
3. Control Strategy

Migrated Method

The USP Ibuprofen Tablets Organic Impurities method was migrated from a legacy HPLC system to two receiver systems. The method parameters are in Table 1.

METHOD: USP Ibuprofen Assay & Organic Impurities (Isocratic Reverse Phase Separation)	
Mobile Phase	4 g/L chloroacetic acid in 40:60 Water:Acetonitrile, pH 3
Flow Rate	2.0 mL/min (isocratic)
Run Time	10 minutes
Injection Volume	10.0 µL
Column Temperature	Ambient
Sample Temperature	15.0 ºC
Column	XBridge™ C18 column: 4.6 x 250 mm, 5 µm (P/N 186003117)
Detector	UV: λ = 254 nm
Seal Wash	10:90 Acetonitrile: Water
Needle Wash	90:10 Methanol: Water
Purge Solvent	60:40 Acetonitrile: Water

Table 1: Migrated HPLC Method

RESULT(S)

MIGRATION PLAN:

1. **System Comparison:** A review of each of the HPLC systems was conducted. Each of the receiver systems was compared against the legacy system to understand similarities and identify any differences that might impact method performance.

2. **Risk Assessment:** Identified system differences were examined to assess the risk posed to method migration. This assessment assigned a risk level to each identified parameter. Injector carryover, detector noise, and tubing dimensions were identified as the parameters presenting the highest risk to successful method migration.

3. **Control Strategy:** A control strategy was devised for the parameters having the highest risk. The control strategy included defining the needle wash composition and number of washes to control carryover, ensuring an adequate lamp warm up time, defining the sampling rate and degassing the mobile phase to reduce noise, and adhering to the vendor recommended tubing dimensions for each system.

	Legacy System	Receiver System 1, (Vendor 1)	Receiver System 2 (Vendor 2)
Pump Type	Quaternary	Quaternary	Quaternary
Pump Mixer	None	Standard (675 µL)	None
Pump Compressibility Compensation	Automatic and continuous	Automatic and continuous	User defined
Autosampler Injection Type	Flow through needle with split injection	Flow through needle	Flow through needle
Autosampler Needle Wash	Pre aspirate, post inject	Pre inject and/or post Inject	Pre inject
Autosampler Temperature Control	Installed	Installed	Installed
Column Compartment Preheater/Heat Exchanger	Passive heating	Passive heating	Passive heating
Detector Type	VWD	VWD	VWD
Detector Flow Cell Pathlength	10 mm	10 mm	10 mm
Detector Flow Cell Volume	16.3 µL	16.3 µL	14 µL
Tubing Injector to Column	0.009"	0.005"	0.005"
Tubing Column to Detector	0.005"	0.005"	0.007"

Table 2: System Comparison

Parameter	Potential Impact	Control
Injector Carryover	Signal to Noise Ratio, Precision, Accuracy	Define appropriate needle wash composition and number of washes in protocol.
Detector Noise	Signal to Noise Ratio, Precision, Accuracy	Ensure adequate lamp warm up time. Define sampling rate in protocol. Degas mobile phase.
Tubing Dimensions	Retention time, Resolution, Signal to Noise Ratio, Tailing	Adhere to the vendor's recommended tubing dimensions.

Table 3: Risks and Control Strategy

METHOD MIGRATION:

With the control strategy in place, the method was run on both receiver systems. Each of the systems met the pre-defined acceptance criteria for successful method migration, specifically the USP system suitability requirements for relative standard deviation, resolution, and signal to noise ratio. In addition to meeting the acceptance criteria, the two receiver systems showed improved peak area precision (%RSD) and increased sensitivity (higher signal to noise value) compared with the legacy HPLC system.

Parameter	Acceptance Criteria	Legacy LC System	LC System Vendor 1	LC System Vendor 2
%RSD Peak Area				
Related Comp J	NMT 6.0%	2.1%	0.1%	0.1%
Ibuprofen	NMT 6.0%	4.9%	1.1%	0.6%
Related Comp C	NMT 6.0%	2.4%	0.1%	0.1%
%RSD Retention Time				
Related Comp J	NMT 6.0%	0.2%	0.1%	0.1%
Ibuprofen	NMT 6.0%	0.2%	0.1%	0.1%
Related Comp C	NMT 6.0%	0.2%	0.1%	0.0%
Resolution				
Related Comp J – Ibuprofen	NLT 2.5	12.4	14.0	11.0
Ibuprofen - Related Comp C	NLT 2.5	7.5	8.6	7.2
Signal to Noise				
Ibuprofen	NLT 10	11	49	49

Table 4: Method Migration Experimental Results
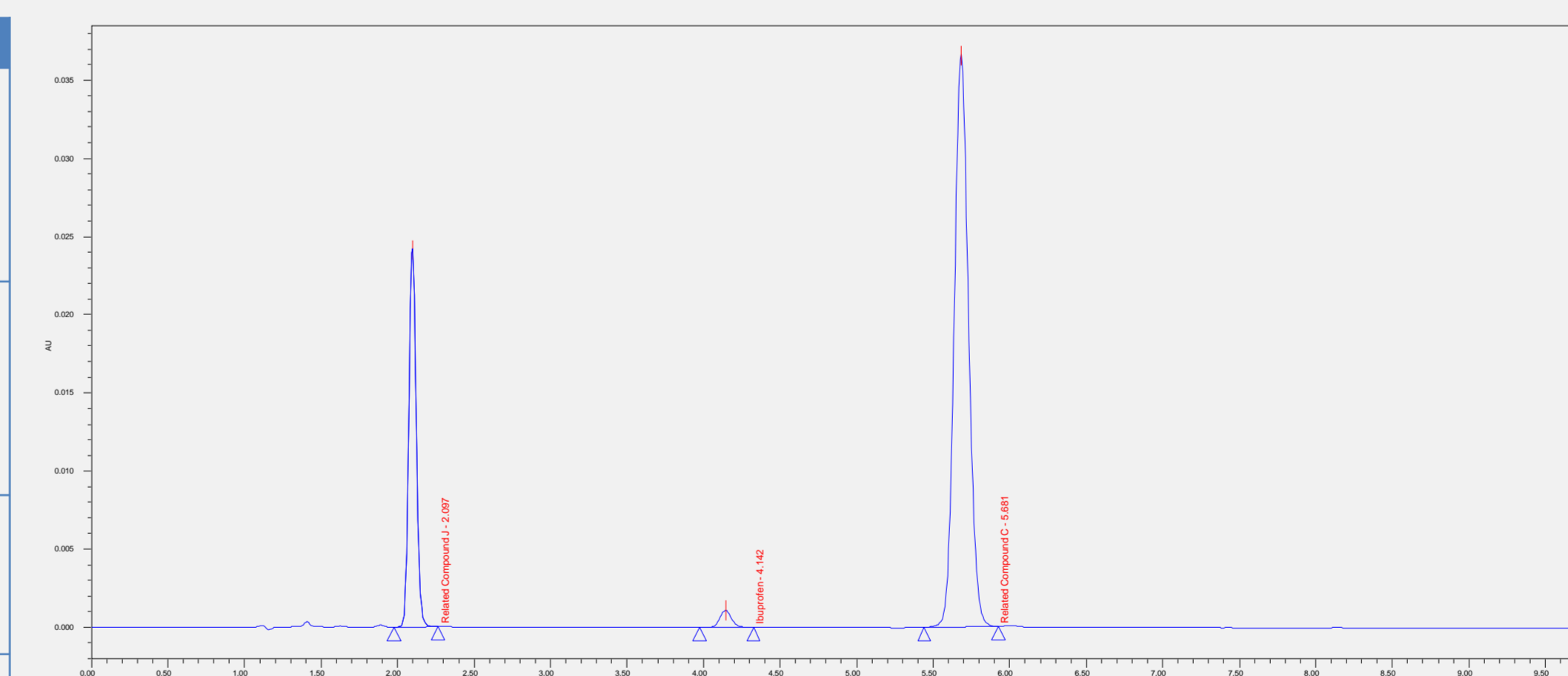

Figure 1: Ibuprofen Tablets Organic Impurities Standard Solution
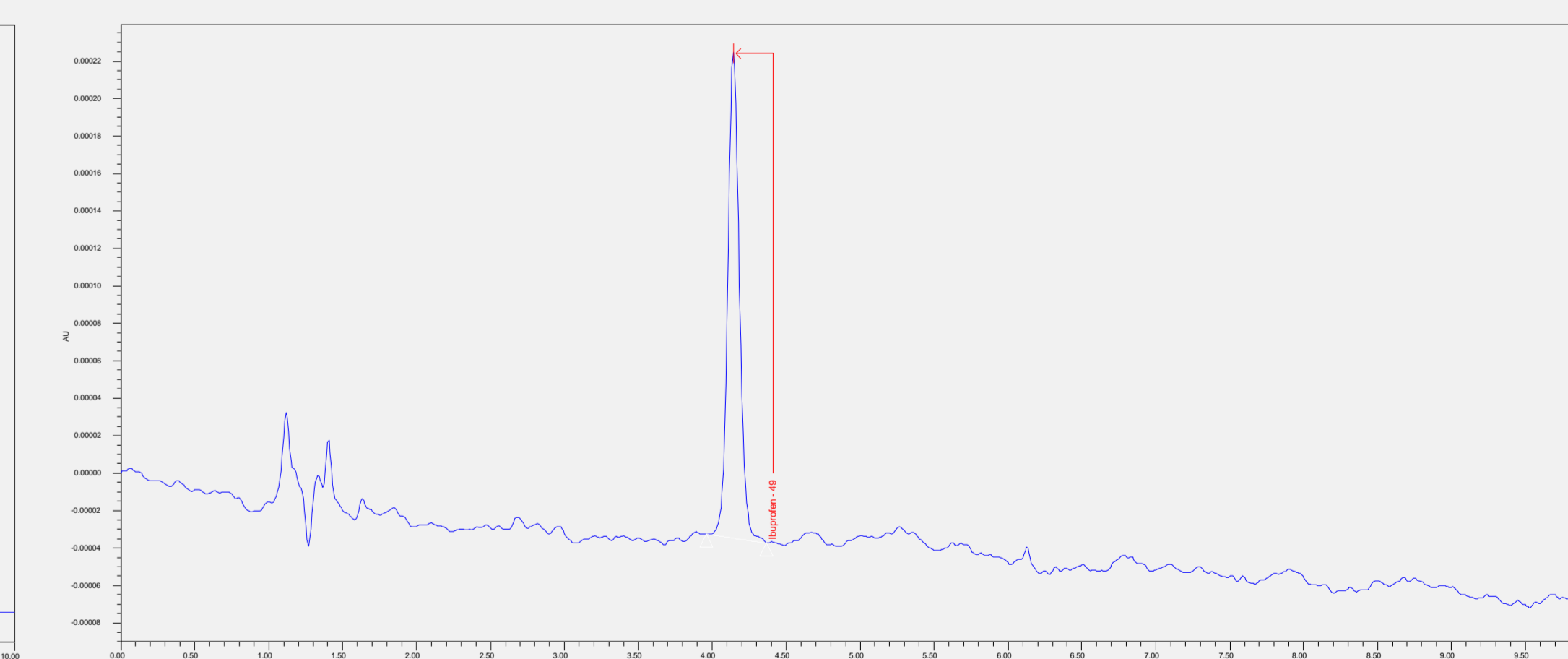

Figure 2: Ibuprofen Tablets Organic Impurities Sensitivity Solution

CONCLUSION(S)

Quality by Design principles were utilized for the development and implementation of a plan for the migration of the USP Ibuprofen Tablets Organic Impurities method between a legacy HPLC system and two modern HPLC systems from different instrument vendors. The approach identified each system's performance capabilities and provided an understanding of how different instrument parameters could affect method performance. Using this information, potential risks to a smooth method migration were identified, and a control strategy devised and implemented. The results obtained met acceptance criteria. Overall, the risk-based approach provided a proactive and successful strategy for method migration and the exercise demonstrated the performance benefits of keeping instrumentation assets up to date.

REFERENCES

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