Application Note

Pharmaceuticals

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Supporting Continuous Manufacturing of Drug Products with Transmission Raman Spectroscopy

Fast at-line analysis using an Agilent TRS100 adds analytical insight to existing in-line PAT

Author

Julia Griffen

Agilent Technologies, Inc.

Abstract

Continuous manufacturing (CM) of oral solid dosage forms is a growing trend in the pharmaceutical industry. Regulations and guidance documentation, such as ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products, have been developed to ensure quality control and rigorous analytical testing of tablets and capsules. This application note assesses the suitability of transmission Raman spectroscopy (TRS) for CM testing protocols. As an at-line technique, TRS enables fast, near real-time, high-throughput quantitative bulk analysis of oral solid dose forms. TRS complements existing inline sensors and probes, playing a vital role in supporting the development and deployment of CM of pharmaceutical drug products.

Introduction

TRS is a bulk analysis technique that uses a laser to irradiate one side of a sample, while the Raman signal is collected on the opposite side. Although the signal is obtained from the top surface of the sample, it provides a bulk representation of the entire sample (Figure 1). To address the high sample load of production-line testing, the Agilent TRS100 enables fast, non-destructive, automated analysis of large numbers of samples through a versatile tray system (Figure 2).

Pharmaceutical tests, such as assay and content uniformity (CU) measurements, are used to quantify the amount of drug in a dosage form and ensure uniformity across a batch. These tests are outlined in USP Chapter <905> Uniformity of Dosage Units.[1] Bulk sample analysis is a key factor when evaluating oral solid dose forms in accordance with USP <905>. From a quality perspective, it is essential for analysts to ensure that the analysis accurately reflects the finished dosage form that will be administered to patients.

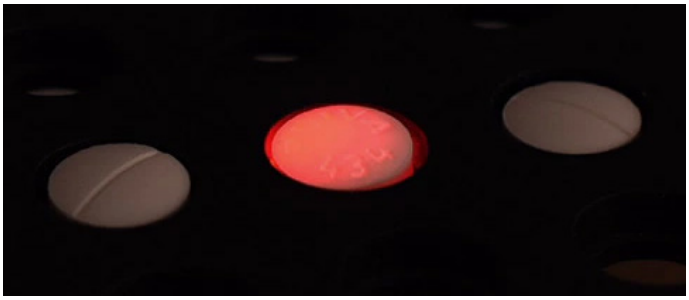

Figure 1. Transmission Raman illumination of a pharmaceutical tablet.

Surface-biased analysis techniques, such as conventional Raman and near infrared (NIR) spectroscopies with a backscatter geometry, where the laser and collection are on the same side (e.g., with a probe-based system), would result in sub-sampling that is non-representative of the entire sample. Figure 3 shows Monte Carlo mathematical simulations that demonstrate where the Raman signal would be collected in a backscatter and transmission configuration instrument, respectively.

Spectroscopic techniques, including TRS, have been used successfully to quantify the CU of oral solid dose (OSD) pharmaceuticals in batch manufacturing scenarios.[2] TRS, as an alternative to the traditional wet chemistry techniques such as HPLC, offers several advantages. These advantages include faster analysis times, increased throughput, and a reduction in required resources, solvents, and consumables, leading to greater efficiency and cost savings in analytical testing.[3]

CM of OSD forms has gained traction in recent years, becoming a prominent industry trend. Manufacturers are increasingly adopting CM to improve productivity and produce medications more efficiently. Since the first method was approved in 2015[4], many large pharmaceutical companies have introduced strategies to implement CM for OSDs.[5]

There is a regulatory need to conduct the CM of OSD forms in a controlled manner, ensuring patient efficacy and safety. The internationally harmonized guidance from ICH Q13, Continuous Manufacturing of Drug Substances and Drug Products[6], provides detailed requirements for this process. These guidelines emphasize the importance of at-line testing, an area where TRS adds significant value.

Figure 2. Examples of the various trays available for the Agilent TRS100 system.

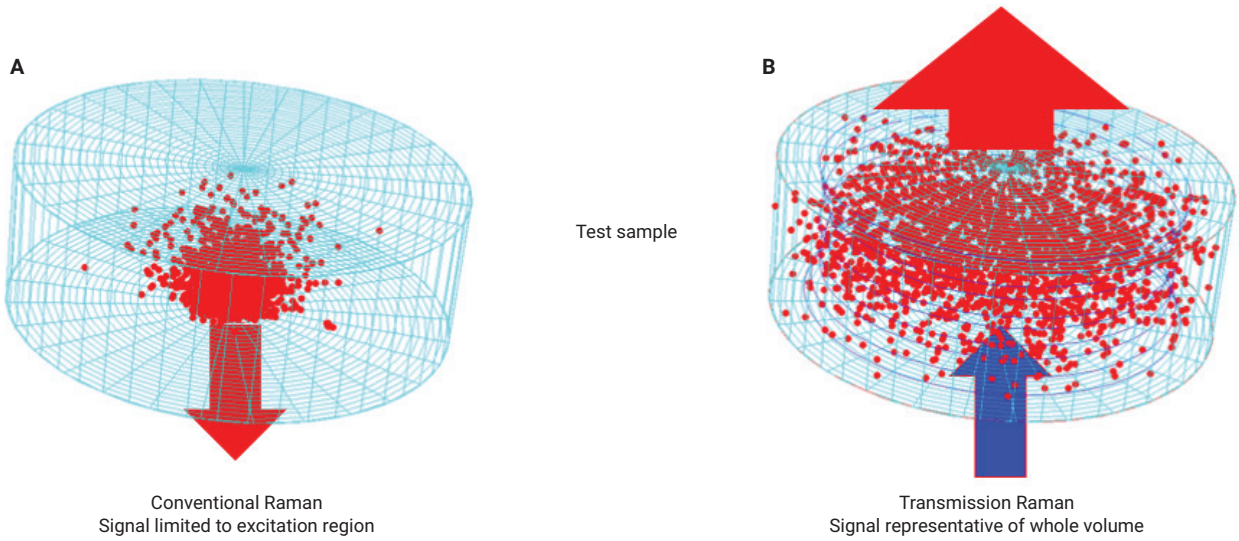

Figure 3. Monte Carlo simulations demonstrating the bulk sampling capabilities of TRS (A) compared to conventional Raman (B).[7]

Study outline and objectives

In this work, Agilent collaborated with the tablet press and CM equipment manufacturer Fette (Schwarzenbek, Germany)[8], in a joint demonstration of the capabilities of our respective at-line and in-line testing technologies.

The Fette continuous processing system (FE CPS) and tablet press (FE55) is a complete continuous direct compression (CDC) system. It applies fully-integrated in-line NIR blend uniformity (BU) of the powder and Tablet Uniformity (TU) sensors on the individual tablets that are pressed from the equipment. The CPS system features advanced in-line NIR process analysis technology (PAT), enabling continuous monitoring and direct adjustment of the production process.

Based on the guidance described in ICH Q13, a fast, at-line, bulk reference testing technique is also needed to validate and verify the PAT's performance and to verify that TU is equivalent to CU. To complement the in-line NIR PAT, the TRS100 was evaluated for CDC deployment, process optimization, process validation, and ongoing verification of the commercial process.

The objective of this study was to use the TRS100 to analyze tablet core samples produced by the FE55 and to compare the data to results obtained by the Fette in-line PAT (ePAT) and offline HPLC.

Experimental

The candidate OSD tablets, which were from a commercial pharmaceutical collaborator, had an active pharmaceutical ingredient (API) content of 85% w/w.

Instrumentation and acquisition settings

The Agilent TRS100 system was used to acquire the transmission Raman spectra using the following settings: 0.65 W laser power, 4 mm spot size, medium optics, and a 10-second scan time (1 second exposure × 10 accumulations).

All samples were placed into a tray system that had a maximum capacity of 100 samples. The tablets were analyzed using the TRS100 in sub-lots of up to 100 samples.

The calibration samples (61 individual tablets), which varied in concentration of API, excipients, and other factors (full details not provided), were supplied after off-site preparation. Figure 4 shows the resulting Raman spectra of these samples.

First-run production samples (6 samples × 5 repeats = 30 spectra) were included with the calibration samples to account for any tablet relaxation and changes arising from the tablet press.

CM samples from the Fette CDC system (333 spectra), 71 of which were sent for HPLC analysis to verify API content, were further split into 48 calibration and 23 validation samples for method development. The remaining 262 spectra were used for validation.

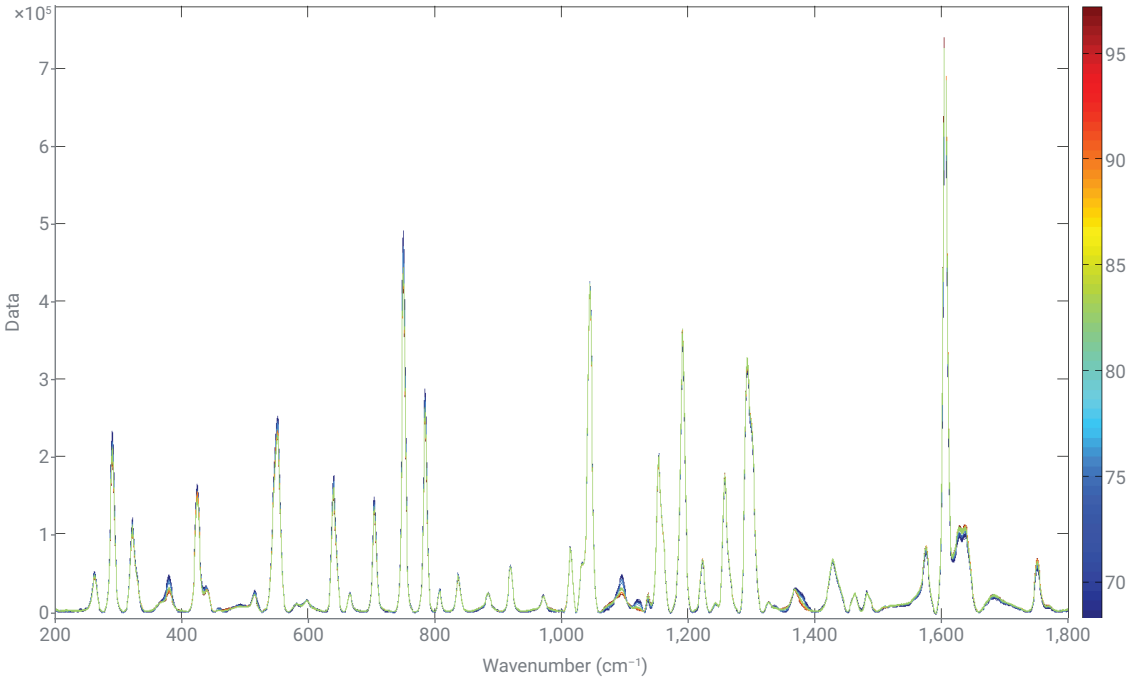

Figure 4. Spectra of calibration samples, color-coded according to API % w/w, obtained using the Agilent TRS100. The high-quality spectra show spectral variation that trends with changes in concentration.

Software

All Raman spectra were acquired using the Agilent ContentQC analysis and management software for the TRS100. Chemometric model building was performed in Solo by Eignevector,[9] which is supplied with the TRS100. Solo generates real-time results within the ContentQC software. Postrun analysis and calculations of individual sample results were compared in Microsoft Excel.

Multivariate calibration

Two partial least squares (PLS) chemometric methods were used to develop calibration models for the prediction of the concentration of the API in the CM tablets. The methods included:

1. A "Quick" method based on the assumed gravimetric values of the API % w/w content of the calibration and first-run samples (Figure 5). This method allowed the TRS100 system to be used in real time for the entire collection of the CM data set over two days. Data for this predictive method was collected and the model was built within a 3-hour window. Samples: Calibration + first-run samples = 91 spectra. Preprocessing: Smoothing, Baseline (Automatic Whittaker Filter), MSC, Mean Center. Spectral Range: 219 to 823 and 1,014 to 1,421 cm^{-1}. Y values: % w/w gravimetric values.

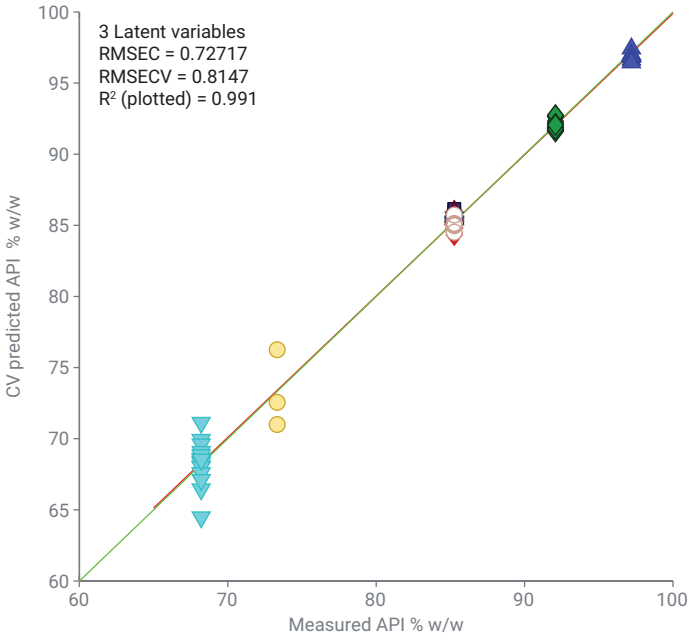

Figure 5. PLS model of the quick calibration method.

2. A "Fine-tuned" method using the calibration + first-run + CM data set using a mix of HPLC and gravimetric values (Figure 6). This method allowed for fine-tuning of the analytical method using the HPLC values for the samples, which were assumed to improve the accuracy of performance. Samples: Calibration 61 + first-run samples 30 + 48 robustness run = 139 spectra. Preprocessing: Smoothing, Baseline (Automatic Whittaker Filter), MSC, Mean Center. Spectral Range: 170 to 774 and 965 to 1,372 cm^{-1}. Y values: HPLC weight corrected except for density.

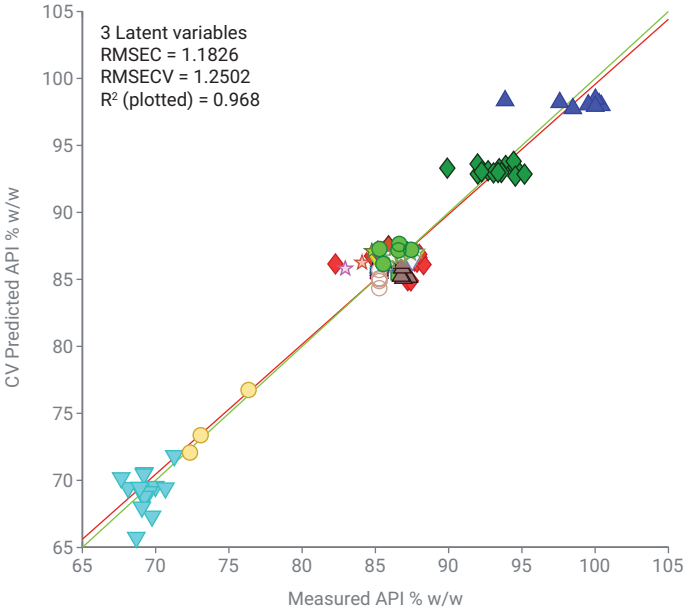

Figure 6. PLS model of the fine-tuned calibration method.

Results and discussion

Testing the quick and fine-tuned calibration models

HPLC reference data were available for 23 of the CM samples, so these tablets were used to test the quick and fine-tuned TRS100 methods. The control limits used for the validation process (shown in Figure 7) are defined in Table 1. As summarized in Table 2, the TRS results performed similarly to the offline HPLC results of the same samples. However, both result-sets of Raman data were within a tighter range and had lower relative standard deviations (RSDs) than the HPLC results, suggesting better precision.

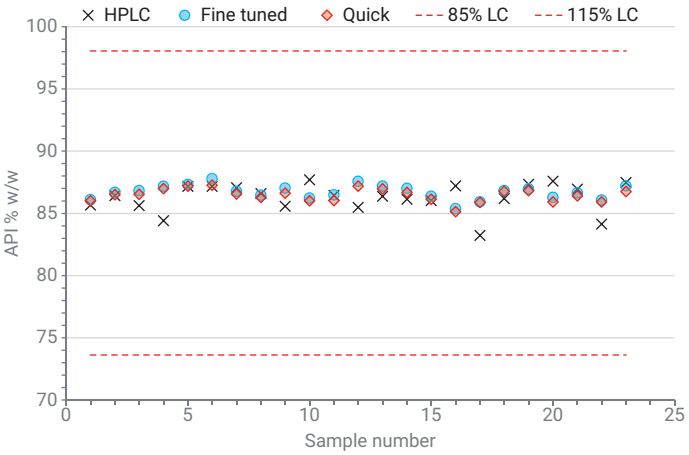

Figure 7. Results of the 23 validation samples acquired using the two TRS methods (quick and fine-tuned) compared to HPLC values.

Table 1. Control limit definitions.

Lower Control Limit (LCL) 85% LC	Lower Alarm Limit (LAL)	Target API	Upper Alarm Limit (UAL)	Upper Control Limit (UCL) 115% LC
72.47% w/w	73.62% w/w	85.26% w/w	96.9% w/w	98.05% w/w

Table 2. Summary of results of the 23 validation samples.

	HPLC	Quick Model	Fine-Tuned Model
Mean	86.29	86.20	86.44
Minimum	83.23	85.48	85.58
Maximum	87.70	86.84	87.10
Range	4.47	1.36	1.51
Standard Deviation (SD)	1.15	0.39	0.40
Relative %RSD	1.33	0.45	0.46

Applying the quick and fine-tuned calibration methods to CM samples

To assess the consistency in the CM process and the predictive performance of the analytical methods, the two calibration models were used to predict the API % w/w value of the remaining 262 CM samples. The narrow range and low RSDs of the results presented in Figure 8 and Table 3 show the highly consistent predictive performance of both TRS methods. The results confirm the suitability of the technique for at-line testing of OSD forms and for verifying the performance of the in-line NIR PAT.

Table 3. Summary of results of the remaining 262 continuously manufactured samples.

	Quick Model	Fine-Tuned Model
Mean	86.12	86.36
Minimum	85.34	85.58
Maximum	86.98	87.21
Standard Deviation (SD)	0.31	0.30
Relative %RSD	0.36	0.35

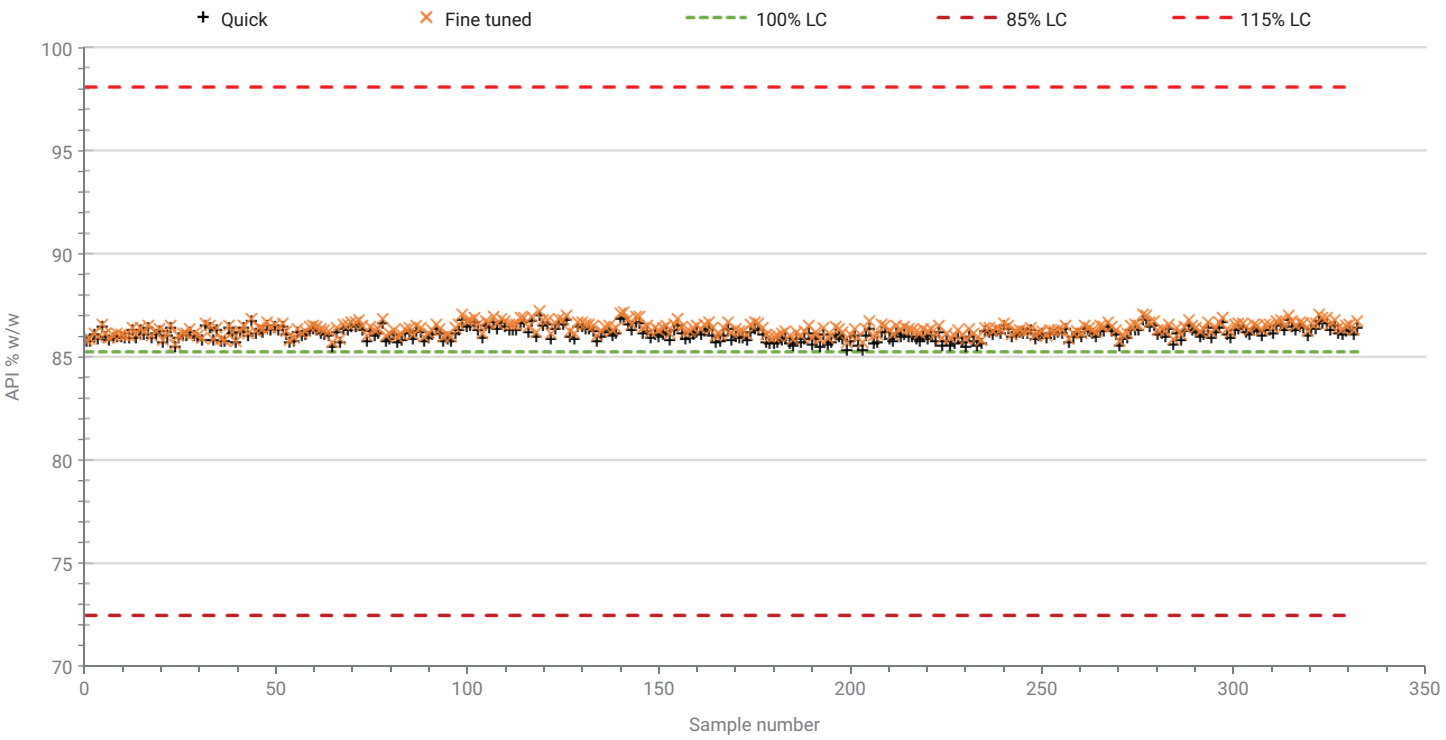

Figure 8. Validation results of the remaining 262 continuously manufactured samples.

Comparison of TRS and PAT data

A final comparison of the TRS data from the fine-tuned model with the Fette inline TU sensor of the CDC system, measuring every single tablet produced during the 24-hour continuous run, is shown in Figure 9. The results show that the performance of the TRS closely aligns with that of the Fette NIR TU sensor in a consistent manner with low variation. Greater variation in the data acquired using the Fette NIR ePAT sensors is expected due to faster acquisition times of 3.8 ms for each tablet, resulting in 4,197,271 concentration points (Figure 9). The tighter clustering of the TRS data is expected due to the longer, 10-second, acquisition times and transmission measurements through the sample volume reducing sub-sampling.

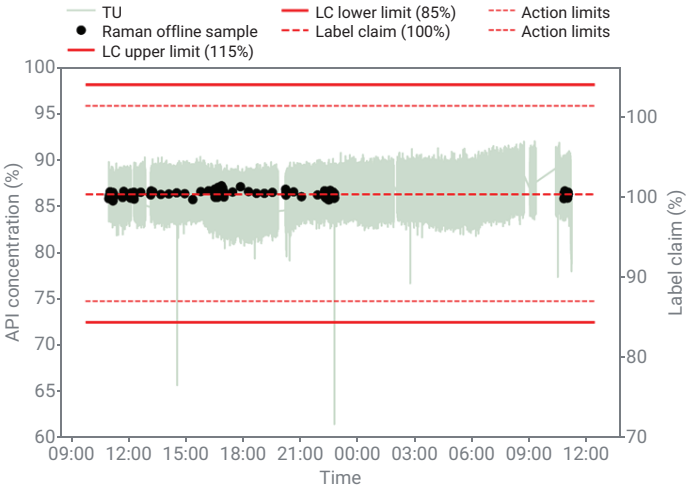

Figure 9. Comparison of API concentration data acquired using the at-line TRS100 method and the inline ePAT NIR sensors of the Fette CDC system.

Conclusion

This study demonstrates the effectiveness of the Agilent TRS100 as an at-line analytical technique for bulk predictive sampling of oral solid dose forms, supporting continuous direct compression (CDC) in pharmaceutical manufacturing.

The quantitative data produced by the TRS100 also confirmed the performance of the Fette inline process analysis technology (ePAT) system. Using an at-line method to validate and verify the PAT system is faster and more cost-effective than traditional offline wet chemistry techniques, which are performed in a separate QC laboratory.

The TRS100 showed that tablet uniformity (TU)—obtained through inline diffuse reflectance NIR of the PAT—is equivalent to content uniformity (CU), as determined using offline transmission Raman spectroscopy.

TRS adds value by supporting the CDC process development and enhancing process understanding, even with rapid calibration methods developed in less than three hours. It also demonstrates consistent results on the whole sample, compared to inline measurements that only analyze a subsample of a tablet.

References

1. United States Pharmacopeia Chapter <905> Uniformity of Dosage Units Stage 6, **2011**.
2. Teva Uses the Agilent TRS100 to Achieve Regulatory Milestone for Content Uniformity Testing with the FDA, https://www.agilent.com/about/newsroom/presrel/2022/05jul-ca22025.html (accessed September 2024)
3. Römer, M. Transmission Raman Spectroscopy–Implementation in Pharmaceutical Quality Control, In Solid State Development and Processing of Pharmaceutical Molecules: Salts, Cocrystals, and Polymorphism, Gruss, M. Ed.; Wiley-VCH GmbH, *79*, **2021**, 165–184
4. Vertex Pharmaceuticals, FDA Approves Orkambi, Press Release, July 2, **2015**.
5. Markarian, J.; Adopting Continuous Manufacturing for Solid-Dose Drug Products, **2021**, *45*, 10, 34–37. https://www.pharmtech.com/view/adopting-continuous-manufacturing-for-solid-dose-drug-products (accessed September 2024)
6. ICH Guideline Q13 on Continuous Manufacturing of Drug Substances and Drug Products - Scientific Guideline. database.ich.org/sites/default/files/ICH_Q13_Step4_Guideline_2022_1116.pdf (accessed September 2024)
7. Everall, N.; *et al.* Temporal and Spatial Resolution in Transmission Raman Spectroscopy, *Appl. Spectrosc.* **2010**, *64*, 52.
8. Fette Compacting, https://www.fette-compacting.com/en/products-technologies/continuous-manufacturing/fe-cps (accessed September 2024).
9. Eigenvector Research, Inc, https://eigenvector.com/software/solo/ (accessed September 2024).

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