Improving Speed and Safety of Biopharmaceutical Manufacturing with HORIBA Analytical Solutions

Innovative spectroscopic (A-TEEM and Raman) and optical techniques (ViewSizer) offer faster, accurate and less costly alternatives to chromatographic quantitative analysis in biotechnology

迅速かつ安全なバイオ医薬品生産に貢献するHORIBAの分析ソリューション

クロマトグラフィに代わる革新的分光分析技術（A-TEEMおよびラマン）と光学技術（ViewSizer）による迅速・正確・低コスト分析手法

Linda Kidder YARLOTT
リンダ キダー ヤロー

Adam M. GILMORE
アダム M ギルモア

Sean TRAVERS
ショーン トラヴァース

The transition of biotechnologies from research project to pharmaceutical products requires analytical solutions that ensure safety and efficacy. In this paper we describe several innovative HORIBA products and highlight how these novel approaches rapidly deliver key information to accelerate processes in biopharmaceutical manufacturing. The HORIBA product portfolio can transform a variety of biopharmaceutical QC processes including the rapid characterization of cell culture media and viral vectors, vaccine manufacturing and analysis of components needed for cell and gene therapies.

Key words
Fluorescence Spectroscopy
EEM Fluorescence Spectroscopy
A-TEEM Fluorescence Spectroscopy

バイオ技術を用いて研究・開発された医薬品を量産する際には安全性と生産効率を確認するための分析技術が不可欠である。この論文ではいくつかの革新的なHORIBA製品について解説し，高度な分析技術を新たに適用することによってもたらされる医薬品の量産プロセス高速化のカギとなる情報を明らかにする。HORIBA製品によるポートフォリオを適用することによって，細胞培養培地やウィルスベクター（遺伝情報伝達核酸分子）の迅速な特性評価，ワクチンの製造，遺伝子細胞治療に必要な成分の解析など，さまざまな医薬品の品質管理のプロセスを変革することができる。

キーワード
蛍光分光分析　EEM分光　A-TEEM分光

Introduction

The publication of the human genome in February of 2001 was a tremendous achievement, and is just one of the multiple pieces of fundamental knowledge that has fueled the rapid pace of discovery and innovation in biotechnology. The tangible benefits to human health of this and other advances, like CRISPR-Cas9 gene editing, are just now being felt in the mainstream, as there is natural delay between discovery and commercialization. In many instances this transition to commercialization of transformative innovations is slowed by the lack of complementary analytical technologies to confirm safety and efficacy. The innovation of novel analytical tools (or repurposing of existing ones) to enable biopharmaceutical manufacturing may not receive the same recognition as the initial discoveries, but commercialization absolutely depends on it. In recognition of the need for innovations in analytical tools, governments around the world have created public-private partnerships to solve this problem.

NIIMBL (National Institute for Innovation in Manufacturing

Biopharmaceuticals)[1] in the US, for example, is focused on the development of "novel real-time analytical technologies for integrated continuous processing for process integration and intensification." Their goals are to enable "flexible and adaptive manufacturing, de-risk innovation, lower manufacturing costs and accelerate development and approval." NIIMBL want to speed commercialization of novel biopharmaceutical product categories, such as Cell and Gene Therapy, and also want to streamline processes for existing products that lack efficient analytical tools such as: monoclonal antibodies (mAbs), vaccines, antibody-drug conjugates (ADCs), bispecifics, and virus-like particles (VLPs). Another government funded consortia is the Cell and Gene Therapy Catapult (CGT Catapult) in the UK,[2] aimed at accelerating the development of process analytical technologies (PAT) for cell and gene therapy manufacturing. HORIBA has joined CGT Catapult with the purpose of assessing the A-TEEM fluorescence technology as a way of reducing batch failures and manufacturing costs.[3]

Traditional Analytical Approaches and Their Limitations

Chromatography is the workhorse in biotechnology, configurable with a wide range of detectors, stationary and mobile phase options, it is used to solve many analytical challenges. It is used for quantitative analysis, purification, classification, in R&D and for QA/QC. As omnipresent and useful as it is, separations techniques have drawbacks - chromatography is almost exclusively a lab-based technique. Although there have been attempts to make process-ready chromatography platforms, the challenges presented by these physical separations approaches are difficult to overcome robustly. Separations also tend to be quite expensive on a per-measurement basis, requiring solvents or gases for the mobile phase, columns and standards, and waste disposal fees for expended solvents. It is also slow compared to optical techniques - a fast chromatographic method typically takes tens of minutes to run compared to seconds-to-minutes for spectroscopy. Additionally, there are fundamental limitations in what chromatographic methods can detect, as they are limited to the chemistry exposed on the outside of molecules, with no visibility to what may be buried inside. Ultimately separations techniques confirm **expected** components, therefore, unexpected components often go unnoticed, being "invisible" to the developed chromatographic method.

Molecular spectroscopy approaches like Fluorescence, Raman, near-infrared (NIR) and Fourier-transform infrared spectroscopy (FT-IR), on the other hand, are green, rapid, robust, and non-destructive technologies that can sit near-, at-, or even in-line. These techniques are sensitive to molecular environment in total, not just the molecules exposed on the exterior of a molecule, and spectroscopic libraries can be used to identify "unexpected" components. These attributes have contributed to molecular spectroscopy approaches, largely Raman and NIR, being incorporated as standard Process Analytical tools (PAT).

There is however a continuum of capability across these optical techniques, and some struggle to detect low concentration components, or to easily distinguish very similar components. Vaccines, ADCs, bispecifics, Adeno-Associated Virus (AAV) characterization (serotype differentiation, full vs. empty capsid) are all samples that require the highest level of specificity and sensitivity, so that even Raman cannot always reliably provide the detailed characterizations needed. Multidimensional excitation-emission matrix (EEMs) fluorescence should be the technique of choice based on its sensitivity and specificity. However, standard EEM implementations have struggled with repeatability and reproducibility. HORIBA has solved this with a patented 2-in-1 approach to multidimensional fluorescence spectroscopy called Absorbance, Transmittance and Excitation Emission Matrix (A-TEEM).[4] Table 1 compares A-TEEM with other optical spectroscopy techniques.

Summarizing, we find that in support of biopharmaceutical manufacturing, standard separations approaches,

Table 1 Comparison of Molecular Spectroscopy Analytical Techniques for Biopharmaceutical Analysis

Technique	Sensitivity	Selectivity	Comments	LOD (PPM)
A-TEEM (2-in-1) Fluorescence	↑	↑	UV/Vis & Fluorescence, Quantitative across broad concentration range	<0.001
2D/EEM Fluorescence	↑	↑	Poor analytical quantification, molecular fingerprint is concentration dependent	<0.1
Raman	○	○	Struggles with low concentrations	25-150
FTIR	○	○	Water interferes with molecular fingerprint	100-2000
UV/VIS	○	↓	Low selectivity Low information content	0.3
NIR	↓	↓	Struggles with low concentrations Low selectivity	0.1-1

although effective, are slow and mostly confined to the laboratory, and unable to characterize unexpected sample components, or differentiate samples based on non-surface characteristics. Vibrational spectroscopic techniques such as Raman, NIR, and FT-IR, are rapid and effective for many samples, able to operate on the manufacturing line, and can characterize samples on overall molecular environments, not just surface variations; but have constraints for low concentrations or highly similar samples. Fluorescence A-TEEM shares the speed and efficiency of Raman, adds the high specificity and sensitivity of fluorescence EEMs, and finally implements reproducibility and repeatability that transform it into a true analytical tool. We'll go into a bit more detail about A-TEEM implementation and applications in the next section.

Fluorescence spectroscopy progression - from EEM to A-TEEM™

Fluorescence spectroscopy is an exceptionally sensitive tool. In some sense this sensitivity presents challenges for its adoption as a routine analytical tool, as clearly assigning a spectral change to a corresponding sample change can be quite complicated. There have been several advances though, that have enabled even complex fluorescence profiles to be converted into actionable information. Multivariate analysis and fluorescence Excitation Emission Matrix (EEM) spectroscopy taken together have advanced the use of fluorescence spectroscopy for routine use. An EEM is a 3D scan, resulting in a contour plot of excitation wavelength vs. emission wavelength vs. fluorescence intensity. EEMs are used for a variety of applications and, coupled with chemometrics, have shown success in monitoring batch endpoint and quality of final product in a bio-fermentation process.[5]

Fluorescence EEM spectroscopy unites the sensitivity of chromatography with the attributes of spectroscopic implementation, such as speed, robustness, low cost of measurement, and is effective for low concentration samples, and in looking for very slight environmental or molecular structural changes.

The Limitation of Standard EEM Spectroscopy

The molecular identification capabilities of a standard EEM spectroscopy has some fundamental limitations. The inner filter effect (IFE) distorts the measured fluorescence spectrum of a molecule due to re-absorption that occurs at higher concentrations. The standard correction protocol uses a secondary measurement from a different absorbance spectrometer to adjust the measured fluorescence signal. But as the measurement does not occur simultaneously and with the same exact volumes, this approach doesn't provide a perfect correction. The imperfect match between data and correction means that an EEM for a single component won't necessarily be reproducible, and this severely limits the ability of a traditional EEM for robust component identification as well as quantification.

A-TEEM™ Spectroscopy Overcomes These Limitations

To overcome this limitation, HORIBA Scientific developed a new technology, called A-TEEM™ spectroscopy,[4] giving a spectrofluorometer the ability to simultaneously acquire Absorbance, Transmittance and a fluorescence Excitation Emission Matrix (A-TEEM) of a particular sample. Because the absorption spectra used for IFE correction are collected at the same time on the same sample as the fluorescence measurement, the correction is reproducible, and the A-TEEM data can be used for accurate sample ID as well as highly sensitive and specific component quantification.

A-TEEM provides ***true and accurate representations of fluorescent molecules over a broad concentration range*** (typically up to ~2 absorbance units). Additionally, absorbance and color information for all molecules, including non-fluorescent ones, is acquired and can be used in multivariate methods for comprehensive multi-component molecular identification. Interestingly, color can be a very sensitive indicator of protein product quality, and this information is acquired as part of the measurement. The A-TEEM method is a robust and extremely sensitive analytical technique, comprising the best attributes of both molecular spectroscopy (speed, low per measurement cost, lab-to-line placement) and chromatography (sensitivity and selectivity). A-TEEM therefore has the potential to replace traditional instruments like HPLC, GC, LCMS, and GCMS as a simpler, and faster analytical tool, with significantly lower per-sample measurement costs. A-TEEM is also a green approach to quantification compared to chromatography, as the need for a mobile phase goes away. Based on simultaneous use of fluorescence and absorbance spectroscopy, A-TEEM is validatable using the standard approaches for these two techniques.[6] A-TEEM molecular fingerprints are extremely information-rich, and multivariate analysis techniques are used to simplify the data and answer specific questions, providing direct and unambiguous results.

The A-TEEM fluorescence method provides a complete and traceable optical fingerprint of liquid samples, overcoming limitations that previously hampered adoption of fluorescence EEMs. This technique is well suited to the characterization of vaccines and other biopharmaceutical samples, with not only the sensitivity and specificity comparable to chromatographic methods, but also the speed, cost savings, and reproducibility of vibrational spectro-

scopic approaches.

Cell Culture Media - Where Bioproducts Begin

The fundamental process in creating biopharmaceutical products is the growth of cells in bioreactors, fed by cell culture media, a specially formulated broth which contains a balance of nutrients to optimize cell productivity. The cost of the media itself is a small fraction of the value of the final product, therefore assessing its quality prior to the start of a bio-fermentation is a cost-effective way to ensure end-product quality and quantity. Standard approaches to perform this critical QC step are chromatography and mass spectrometry, making these measurements time consuming, expensive, and designed only to confirm what is expected, not to detect the unexpected. There is a growing interest in the use of molecular spectroscopic approaches for media QC, and both Raman and EEMs have been tested.[7,8] As is often the case, the combination of these two spectroscopic approaches may be the best way to cover the breadth of components that need to be characterized for this application.

As expected, A-TEEM provides a robust approach to assess the quality of cell culture media prior to the addition of cells.[9] We investigated eight different commercially available cell culture media samples, with the goal to differentiate between them, and also to study the sensitivity of the technique to detect environmental degradation. A more in-depth analysis of specific cell media components is a topic for future studies, and not addressed in this overview. Five samples from each of the eight types of media were analyzed, each sample was measured in triplicate resulting in 120 measurements, and each measurement took ~60 seconds. All cell culture media was stored at 4°C before testing and allowed to equilibrate to ambient laboratory temperature prior to analysis. The PCA showed clear differentiation between the different categories of media. To explore the specificity of the technique, a separate analysis including data

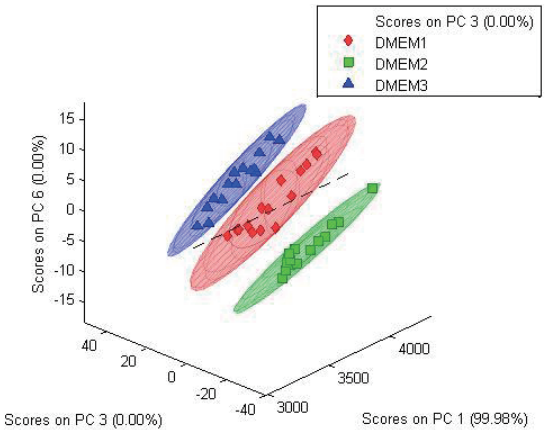

Figure 1 3D principal component scores plot showing ability of A-TEEM to differentiate within a cell culture category. DMEM samples of varying composition (types 1-3) were analyzed.

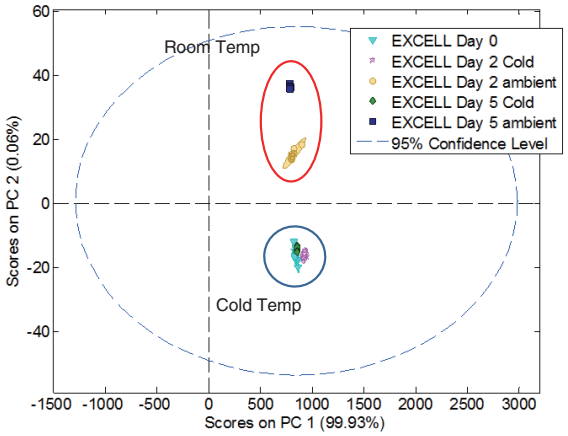

Figure 2 A-TEEM characterization of fresh from degraded cell culture media samples

from only a single category of media was performed. Figure 1 shows three different DMEM samples with slight compositional differences were easily distinguishable.

The final test for A-TEEM characterization of cell culture media was to compare fresh samples with those degraded through exposure to light, and elevated (room) temperature. A-TEEM was able to track the degree of degradation over a period of 5 days, as shown in Figure 2. A-TEEM provides a rapid approach to differentiating eight commercial cell media formulations, classifying three similar formulations, and tracking degradation of a cell media sample against adverse storage conditions.

Viral Vectors Characterization

Researchers have turned to nature to understand how to deliver genetic material into human cells, and viruses provide a perfect mechanism. Several specific viruses, Adeno-Associate Virus (AAV) and lentivirus, for example, have been found to have appropriate characteristics, allowing scientists to manipulate them for the purpose of delivering genetically engineered payloads into human cells. These so-called viral vectors are the work horses of cell and gene therapy, and are making inroads into other applications, such as vaccines. In developing and deploying viral vectors, there are multiple parameters that are important to characterize for a complete picture of product quality. Measurements need to discriminate: 1) whole, broken, empty, aggregates, and infectious or non-infectious viruses; 2) empty from full capsids; and 3) vector serotypes. We'll present results from HORIBA's multi-laser Nanoparticle Tracking Analysis (NTA) approach using the ViewSizer 3000™ technology showing how it can be used to determine infectious titer, and then briefly touch on as-yet unpublished results from the A-TEEM method on its ability discriminate empty from full capsids and discriminate between vector serotypes.

Infectious Titer Determination with ViewSizer 3000

The ViewSizer 3000 is a nano-particle tracking (NTA) platform that incorporates three lasers to collect the most accurate distribution and concentration data across a wide range of sample sizes. The point of the three lasers is to compensate for a variety of known problems when looking at a polydisperse sample: large particles scatter too much light and will saturate the detector from one laser, whereas small particles will only weakly scatter, and will be hard to detect. With three different lasers with independent power control, particles size can be determined across a very broad range, with scattering signals optimized to provide the most accurate distribution and concentration results.

The Viral Plaque Assay is the most robust approach to determine Infectious Titer, and it is highly manual and very time consuming. Viral preparations are serially diluted and allowed to grow on the planar surface of cell culture monolayer. Over a period of time (hours to weeks) the viral cells proliferate, infecting the confluent cells and destroying them. Regions of dead cells appear as empty patches on the culture surface, and these regions or "plaques" are then manually counted to determine the number of Plaque Forming Units (PFU) in a given dilution. Multiplying the PFUs by the dilution factor determines the final infectious titer of the parent stock, expressed in PFU/mL.

To determine the utility of the ViewSizer 3000 approach, the following protocol was followed: samples were transferred to the ViewSizer 3000 cuvette, fitted with a magnetic stir bar, and twenty-five video segments were collected, with five seconds of stirring in between each to ensure completely independent sets of particles in each video. The measurements were recorded with the following parameters: frame rate: 30 frames/second; exposure: 15 ms; gain: 30; blue laser power: 210 mW; green laser power: 12 mW; and red laser power: 8 mW; temperature control: active, 22°C. Each run took between 15-20 minutes. Multiple users independently analyzed the samples using the same measurement and acquisition parameters described above. The data were then processed and plotted using the same settings. Particle sizes ranged from 50 nm to 1000 nm, with a significant enrichment of particles around 200 nm, as shown in Figure 3. The total viral particle concentration within the sample was 1.6 x 107 particles/mL. The distribution tailing towards 1000 nm suggests the existence of host cell debris or other background particles contained within the cell culture growth media. The image extracted from the video recordings further validated the presence of larger viral aggregates.

Infectious titer data from multiple assay replicates performed by independent analysts were plotted as a function of measured particle concentration from the ViewSizer 3000 and fitted with a result shown in Figure 4. The result indicates an excellent R^2 value of greater than 0.9. When the results are analyzed using only data from one of the three lasers available, correlation dropped to an R^2 value of 0.6 because of its inability to properly count the aggregates. By using three lasers, all particles were counted and the improved correlation is presumably because infectious aggregates contribute to the titer and were quantified along with single virus particles. This result indicates that over the course of multiple experiments, the ViewSizer 3000 accurately and reproducibly determined the viral titer within a heterogeneous sample.

This demonstrates the ViewSizer 3000's ability to assess not only intact viral particles and aggregates, but also potential cell debris and background noise generated during upstream processing. Since downstream processing depends strongly on the removal of these impurities to minimize further aggregation, quantifying infectious viruses reliably depends on understanding both the purity of the upstream sample and the downstream analytical precision. The ability to detect these aggregates and cell

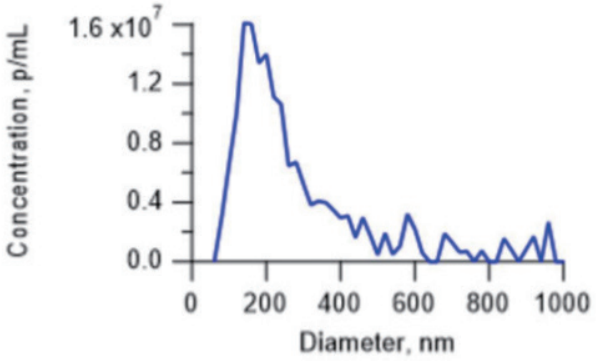

Figure 3 Measurement result of a human viral vector sample. Note the distribution tailing towards 1000 nm suggests the presence of host cell debris and aggregates.

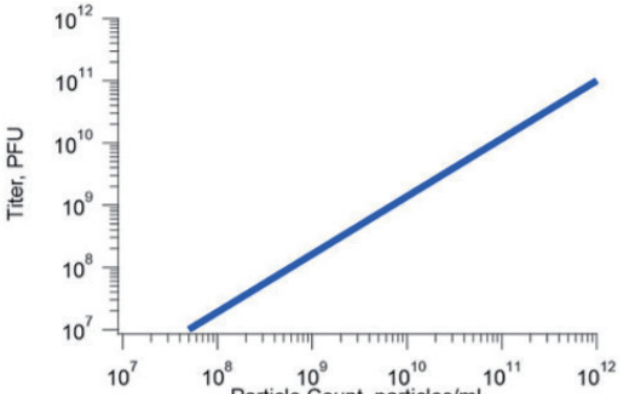

Figure 4 R^2 value of > 0.9 was achieved between titer and data collected from the ViewSizer 3000.

debris is also critical when examining the stability of the final product over time. As we saw with the roll out of Coronavirus vaccines, the stability of biologic preparations within a freezer is a crucial factor to understand. With Viewsizer we are able to compare fresh preparations of a sample to ones that have been in the freezer for a number of weeks. By monitoring the increasing number of aggregates/cell debris that are present in the stored samples versus time, it is possible to gain an understanding of how long a sample is stable in a freezer. Utilizing the multiple lasers of the system is a crucial factor in these studies, as the particles of interest are usually. around 80-120 nm, while aggregates and debris can appear all the way up to a micron; suggesting that the ability to measure across that entire size range is an indispensable tool in understanding the stability of these biologic preparations.

In addition to the applications described above, there are several unpublished studies that point towards other very interesting applications of A-TEEM, including the differentiation of AAV serotypes (AAV2 from AAV9), and quantification of empty vs full capsid ratio.

Vaccine Characterization and Manufacturing QC

The NIIMBL Vaccines roadmap[10] noted that vaccine product release time is on the scale of weeks to months, rather than the one to two days that might be possible with the right analytical tools. Vaccines have historically been relatively simple formulations, with one or multiple vaccine component (live-attenuated vaccines, subunit, polysaccharide, conjugate, or toxoid) with a diluent, and perhaps an adjuvant (a component that enhances the immune response). With the events of the last 18 months, vaccine technology has made huge advances in the fight against the Coronavirus pandemic, and mRNA vaccines, and the use of viral vectors has proliferated. The ViewSizer has been used as an analytical tool in the analysis of adjuvants.[11] However, the focus of this section will be on describing an approach for QC for vaccine manufacture that might meet the NIIMBL goal of one to two days for product QC.

One of the struggles for standard vibrational spectroscopic approaches is that vaccines tend to be formulated at very low concentrations. Raman spectroscopy without resonant enhancement struggles to characterize protein samples under ~1 mg/ml. Although Surface Enhanced Raman (SERS) can be used to enhance signals, it is challenging to fully characterize the impact that SERS substrates might have on the vaccine components. A-TEEM has been shown to have very low limits of detection, recently calculated to be ~0.15 µg/mL for a well-characterized vaccine formulation.[12] For these same low concentration vaccine samples, A-TEEM has shown the ability to readily detect post-translational modifications, as well as differentiate between samples with simple amino acid substitutions, even those of non-fluorescent amino acids. In addition to the low limits of detection, A-TEEM has also been shown to characterize complex mixtures, differentiating and quantifying components against strong backgrounds, most notably in wine.[13]

To demonstrate the suitability of A-TEEM to the analysis of vaccines, we tested four over-the-counter multicomponent canine vaccine products. We used the SOLO-JEC brand multi-component canine vaccines (Table 2) from Boehringer Ingelheim VetMedica that were available at a local retail store (Tractor Supply Store). We tested SOLO-JEC 5 ("protection against five common canine infectious diseases"); SOLO-JEC 6 ("delivers the same protection as SOLO-JEC 5 plus additional protection against coronavirus); SOLO-JEC 9 ("delivers additional protection against four types of leptovirus that are known to infect dogs"; and SOLO-JEC 10 ("delivers the same protection as SOLO-JEC 9 plus additional protection against coronavirus")..

The vaccines were reconstituted according to the package directions, diluted with distilled water in a ratio of 1:61 and added to a cuvette for measurement. To ensure repeatability, six individual measurements were collected for each vaccine, and this was done on two separate days. The calibration data set therefore consists of 48 measurements. To test reproducibility, a third unique set of validation samples were collected on a different instrument by a different operator, with 5 repeat measurements for each vaccine formulation, resulting in a validation set with 20

Table 2 OTC multicomponent vaccine products tested for this study

	Basic Program Solo-Jec 5&6		Lepto Included Solo-Jec 9&10	
Disease	Solo-Jec 5	Solo-Jec 6	Solo-Jec 9	Solo-Jec 10
Distemper	●	●	●	●
Hepatitis		●	●	●
Adenovirus 1	●			
Adenovirus 2	●	●	●	●
Coronavirus		●		●
Parainfluenza	●	●	●	●
Parvovirus	●	●	●	●
Lepto (4 types)			●	●
Gentamicin	●	●	●	●
Amphotericin 8	●			
Thimerosal		●	●	●
Adjuvant	●	●	●	●

Table 3 Samples used for Calibration and Validation

Vaccine	Calibration set (n=48)	Validation set (n=20)
Spectra 5	S5	U5
	S-5	
Spectra 6	S6	U6
	S-6	
Spectra 9	S9	U9
	S-9	
Spectra 10	S10	U10
	S-10	

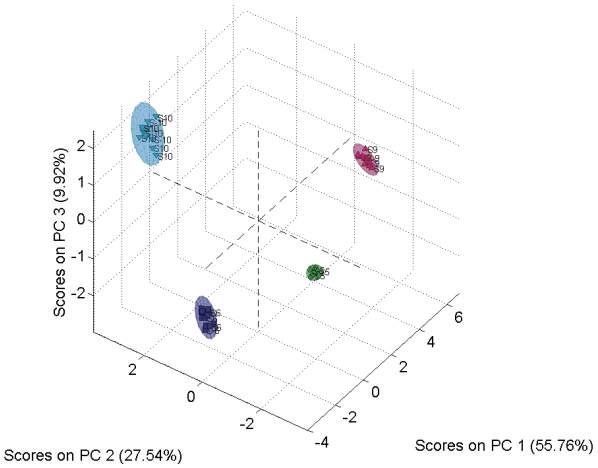

Figure 5 PCA scores scatter plot showing clear differentiation between 4 vaccine products, and excellent reproducibility for multiple measurements of a single vaccine type.

measurements, as shown in Table 3. A simple principal component analysis (PCA) was able to easily differentiate between the 4 vaccine products, with tight clustering of the calibration data.

In order to classify "unknowns" from the validation samples, a discriminant analysis model was created using Extreme Gradient Boost - Discriminant analysis. A-TEEM was able to identify and validate "unknown" samples with 100 percent certainty, as shown in Figure 6.

A-TEEM is the only spectroscopic approach that can perform this level of analysis on low concentration and complex vaccine formulations. Standard chromatographic QC approaches for vaccine batch analysis take days to complete. The results presented here demonstrate the potential for an on-line, rapid, sensitive and reproducible spectroscopic approach for vaccine QC, offer a potential solution to meet the goals for vaccine release that NIIMBL has set.

Conclusion - The Future of Biopharma Characterization

HORIBA Instruments Inc. has a unique portfolio of analytical solutions that offer rapid, cost-efficient alternatives to chromatography, manual titer, qPCR, Analytical Ultra Centrifugation and other traditional analytical approaches. From A-TEEM to ViewSizer and with Raman as a complementary approach, these tools have the potential to

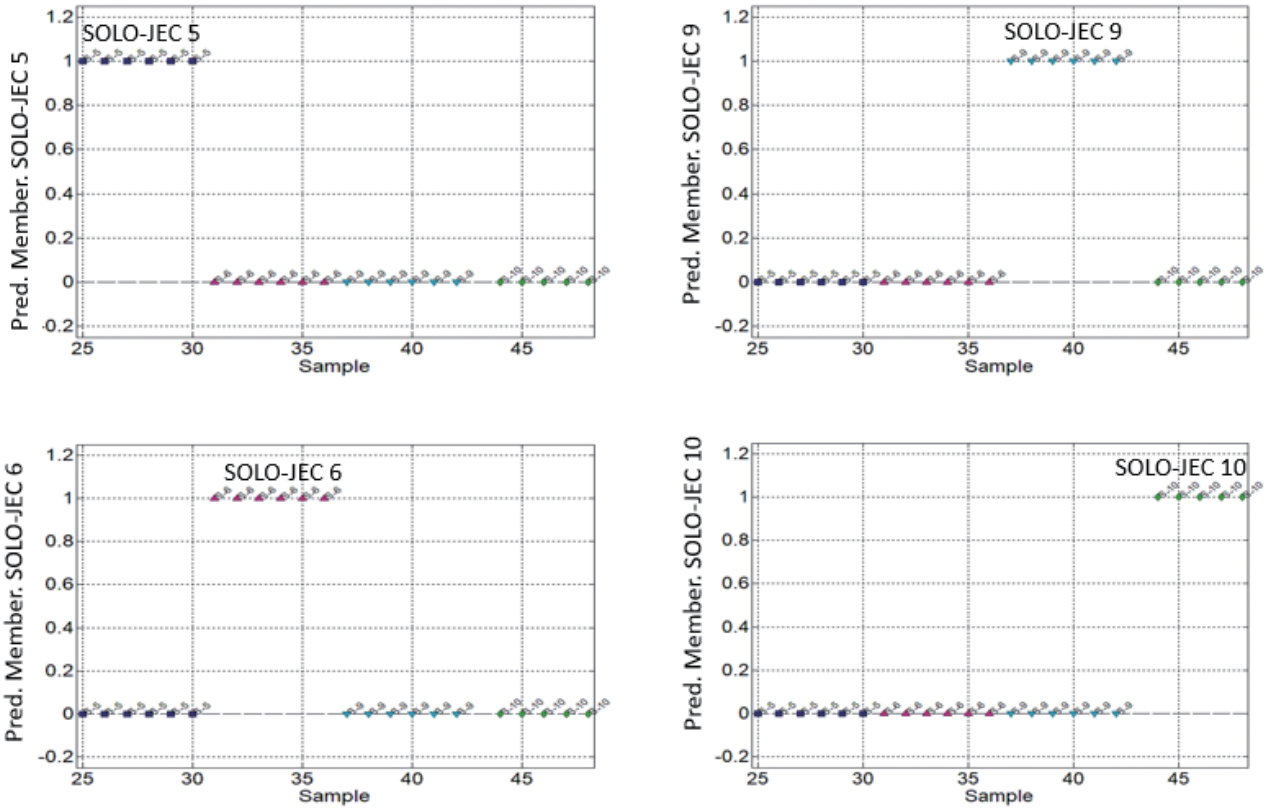

Figure 6 100% success in correctly identifying the vaccine product for unknown samples

shorten manufacturing times, and improve product safety with the ability to identify unknown components. The applications presented here are not meant to be an exhaustive compilation of the value that HORIBA tools provide to life science, but to highlight how spectroscopic and optical approaches offer a robust solution, as biopharmaceutical production methods scale to meet growing demand, and more information is needed more quickly. Starting with cell culture media, the fundamental raw material for all bioprocessing, both Raman and A-TEEM have proven utility in characterizing the quality of this material. Viral vectors are used to deliver novel vaccines and the components that make cell and gene therapies successful; ViewSizer and A-TEEM can be used to speed up analytical characterization steps that are needed in their manufacture. Finally, vaccines production has taken on new urgency, and A-TEEM has the potential to reduce QC time from weeks to hours. Other contributions in this version of Readout will explore other aspects and applications, including characterization of up-and-coming biotechnologies, like exosomes, and how HORIBA technologies are critical for the characterization of bioprobes.

* Editorial note: This content is based on HORIBA's investigation at the year of issue unless otherwise stated.

References

[1] NIIMBL. https://niimbl.force.com/s/about-niimbl.

[2] About Cell and Gene Therapy Catapult. https://ct.catapult.org.uk/about-us.

[3] Editors, B. P. I. (2021, June 18). Horiba Joins CGT Catapult Consortium to Accelerate Development of PAT. BioPharm International. https://www.biopharminternational.com/view/horiba-joins-cgt-catapult-consortium-to-accelerate-development-of-pat.

[4] Gilmore, A. M. & Tong, X. (2014, December 2). System and Method for Fluorescence and Absorbance Analysis, US Patent 8,901,153.

[5] Peter P. Mortensen; Rasmus, Bro. Real-time monitoring and chemical profiling of a cultivation process. Chemometrics and Intelligent Laboratory Systems, Volume 84, Issues 1-2, 1 December 2006, Pages 106-113.

[6] Adam M. Gilmore. How to Collect National Institute of Standards and Technology (NIST) Traceable Fluorescence Excitation and Emission Spectra. National Center for Biotechnology Information. March 27, 2014.

[7] Li et al., "Fluorescence Excitation-Emission Matrix (EEM) Spectroscopy for Rapid Identification and Quality Evaluation of Cell Culture Media Components," Applied Spectroscopy volume 65, Issue 11, 2011.

[8] Li et al., "Rapid Characterization and Quality Control of Complex Cell Culture Media Solutions Using Raman Spectroscopy and Chemometrics." Biotech & Bioeng. Volume 2, Issue 107, 2010.

[9] Alvin Togonon, Adam Gilmore, Ben Yang, Karoly Csatorday and Marinella Sandros. Monitoring Cell Culture Media Variability using A-TEEM™

[10] The National Institute for Innovation in Manufacturing Biopharmaceuticals Vaccines Roadmap

[11] P. Singh et al., "Particle size analyses of polydisperse liposome formulations with a novel multispectral advanced nanoparticle tracking technology", International Journal of Pharmaceutics, Vol. 566, 2019, pp 680-686.

[12] Unpublished results

[13] R. K. R. Ranaweera, "Authentication of the geographical origin of Australian Cabernet Sauvignon wines using spectrofluorometric and multi-element analyses with multivariate statistical modelling", Food Chemistry 335 (2021) 127592

Linda Kidder YARLOTT, Ph. D.
リンダ キダー ヤロー
HORIBA New Jersey Optical Spectroscopy Center
HORIBA Instruments Incorporated

Adam M. GILMORE, Ph. D.
アダム M ギルモア
HORIBA New Jersey Optical Spectroscopy Center
HORIBA Instruments Incorporated

Sean TRAVERS, Ph. D.
ショーン トラヴァース
Technical Sales Representative and Consultant for HORIBA Scientific
Anatom Technology