CE and the SCIEX BioPhase 8800 in Precision Medicine

An interview with Mani Krishnan, Vice President & General Manager, SCIEX CE & BioPharma

Introduction

As readers of this Journal know, precision medicine products – therapeutics and diagnostics – are highly dependent on reproducible processes to sustain quality healthcare applications. Precisely made products are acutely crucial for the development of biologic therapeutics, which are sensitive to reproducible processes, rigorously controlled supply chains, and highly trained personnel.

High-quality equipment is needed for these precision processes. In this regard, we had the opportunity to pose questions to Mani Krishnan on the BioPhase 8800 CE system1 and related platform technologies.

Q. What science and technology issues led SCIEX to develop the BioPhase 8800 system?

A. When SCIEX set out to develop the next evolution in capillary electrophoresis (CE), we interviewed hundreds of scientists and leading innovators in biotherapeutic development. First, we heard about the need to make confident decisions faster and earlier in development with answers that they can rely on. They also told us that the industry is transitioning from standard monoclonal antibodies to more complex antibodies and new genomic medicines. Not only are these molecules becoming more complex, but the

requirement to understand molecular biology and the need to close the developability gap in a much shorter time frame has created tremendous pressure on scientists.

In short, samples are getting more complex, more numerous, and results are required in less time. At that time, scientists using CE systems for purity analysis had to choose between high throughput screening with low resolution, or highly sensitive, single sample analysis.

With this in mind, we combined insights from our customers, the latest technology advancements, and our experience with the PA 800 Plus – the Gold standard for capillary electrophoresis sodium dodecyl sulfate (CE-SDS) analysis – and today you have the BioPhase 8800 system (see **Figure 1**), an entirely new CE platform designed to enable parallel processing of up to eight samples, including different molecules for different applications, simultaneously on a single platform using CE-SDS and capillary isoelectric focusing (CIEF) with ultra-violet (UV) or laser-induced fluorescence (LIF) detection.

"The industry is transitioning from standard monoclonal antibodies to more complex antibodies and new genomic medicines."

Q. In follow up to Q1, how does the improved technology of the BioPhase 8800 system advance precision medicine in pharma's development pipeline?

A. Parallel processing combined with high resolution separation, detection flexibility and validated kits accelerates method optimization and analysis (see **Figure 2**). For the first time, it is possible to quickly develop methods for screening and characterizing traditional and newly engineered molecules for use across the development continuum from discovery to development, manufacturing and QC/QA. This newly engineered system accelerates analysis and dramatically shortens new therapy development timelines while providing the sensitive, high-resolution data expected in the biopharma industry. As a result, biologic drug developers are able to maximize efficiencies, and accelerate time to market.

Q. A quick search shows that you worked with filtration technologies for sample preparation in general and virus removal in particular. Can you comment on the current state of sample preparation, for example, removing viral contamination – virus, viral proteins, RNA or DNA?

A. My experience has been more on creating a viral barrier and enabling viral clearance from bioprocesses – how to minimize adventitious viral contamination and how to clear adventitious and endogenous viruses from biopharmaceuticals. While the focus was on viral barrier/clearance, demonstrating and validating the effectiveness of barrier or clearance technologies requires samples to be adequately prepared and tested.

Sample preparation requirements differ widely depending on the nature of the sample, the analytical methods and the specific application – characterizing novel drug candidates at the discovery phase, monitoring cell-culture during manufacturing, and testing for final product release (see **Figure 3**). In all cases, simplifying sample preparation and reducing sample preparation time helps streamline workflows, minimize errors, and ensure consistency and quality.

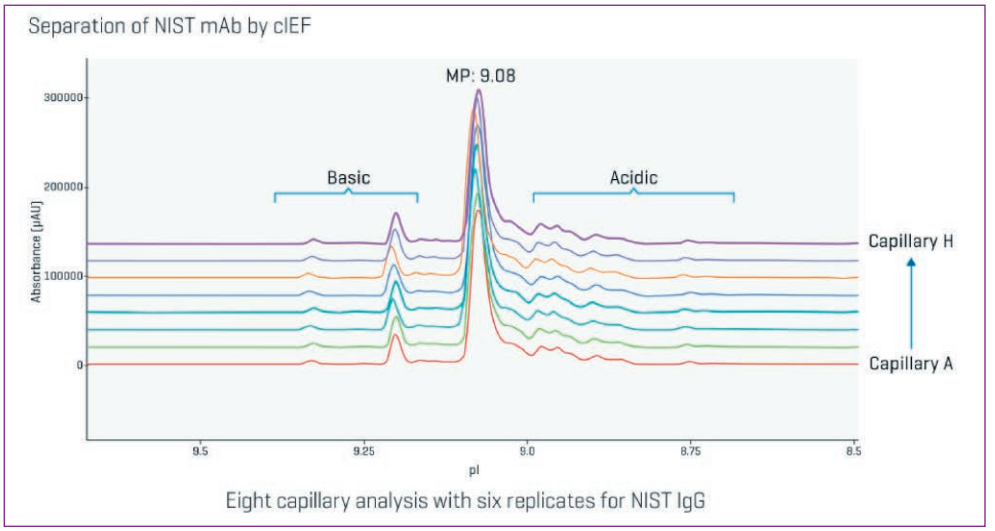


Figure 1: The BioPhase 8800 System. Repeatable and sensitive cIEF analysis on the BioPhase 8800 system shows eight capillary analysis with six replicates for NIST IgG.

"Sample preparation requirements differ widely depending on the nature of the sample"

That is always the focus at SCIEX – to facilitate highly sensitive, accurate analyses with a minimum of sample preparation. We invest significant time in developing improved, simpler preparation protocols and in many cases offer specially designed kit-based assays containing all of the necessary reagents for particular analyses on particular SCIEX instruments.

Q. Has SCIEX investigated using CE to develop COVID treatments – e.g., vaccine or biologics development? Quality control of processes?

A. The BioPhase 8800 system is uniquely suited for use in the analysis of antibody therapeutics,

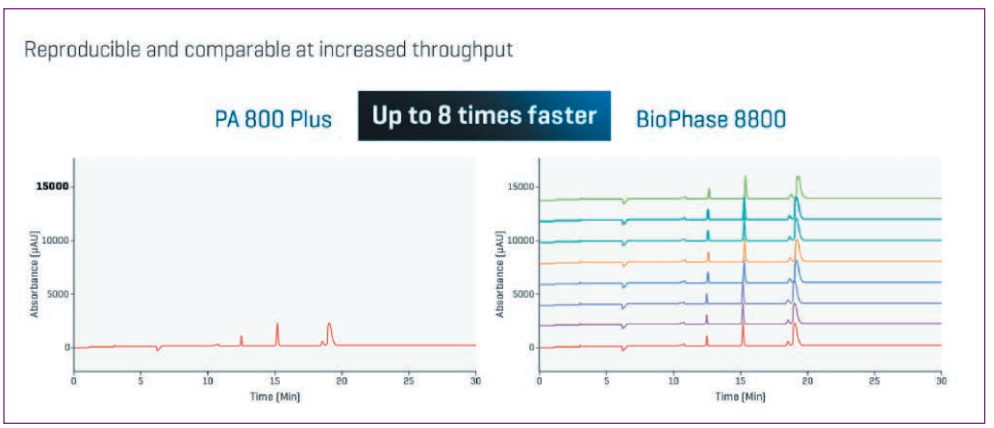


Figure 2: Processes Eight Samples in Parallel. Comparative of SDS-CGE separations of the reduced mAb sample on the multi-capillary BioPhase 8800 system and the single capillary PA 800 Plus Pharmaceutical Analysis system.

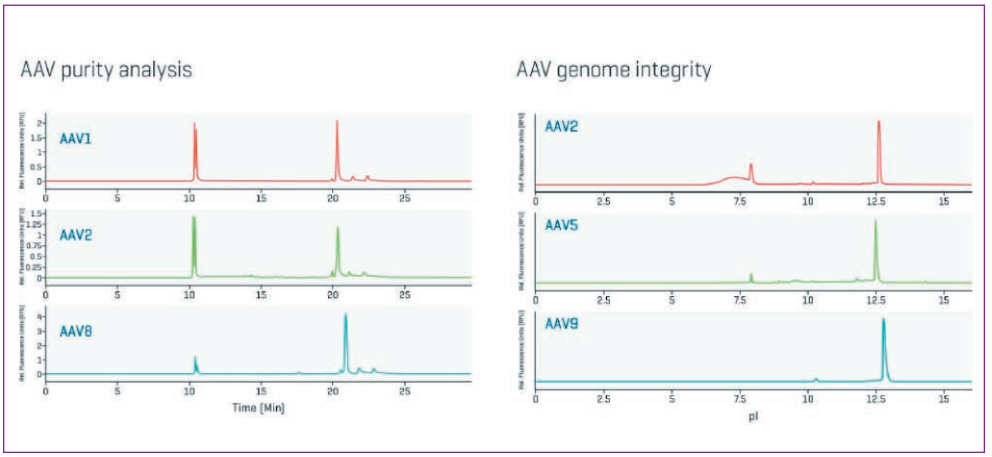


Figure 3: Assess Genomic Medicines More Quickly. Evaluate AAV purity and genome integrity on the BioPhase 8800 system.

"Rapid and reproducible detection, separation and sizing of mRNA an be achieved using the BioPhase 8800 CE-LIF"

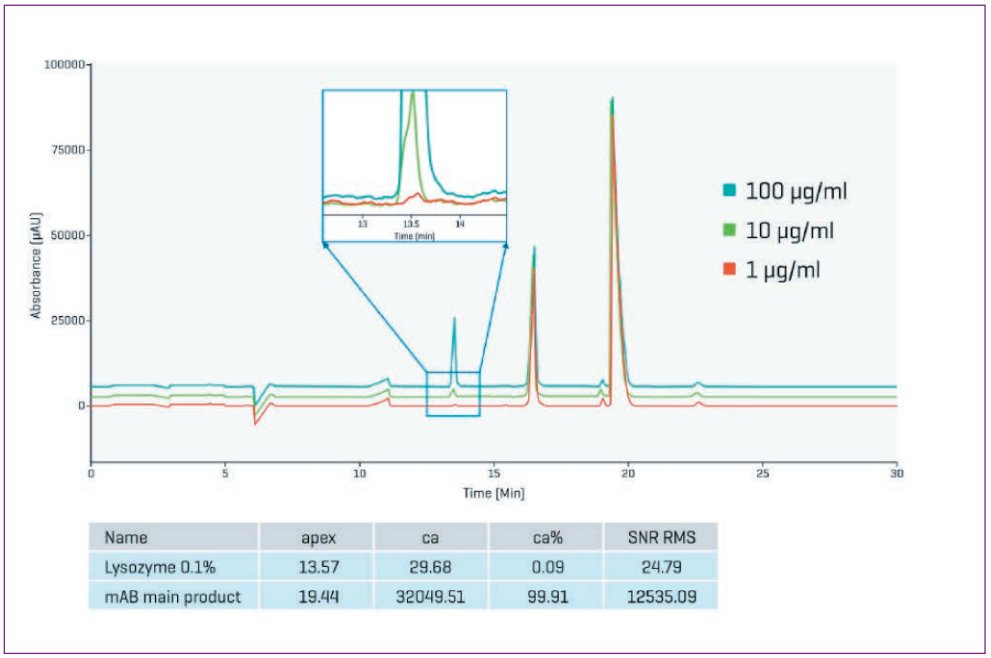
nucleic acid based products, vaccines, and other biologic treatments.

For monoclonal antibody therapies, variations in low-level impurities with therapeutic proteins is a common challenge that can adversely impact efficacy and safety (see **Figure 4**). CE-SDS analysis provides automated, quantitative purity data on both intact and reduced monoclonal antibodies. Only the BioPhase 8800 offers sensitive CE-SDS analysis combined with the speed of a multi-capillary system.

For viral-vector based products, the BioPhase 8800 system, using CE with laser-induced fluorescence detection (CE-LIF) provides rapid, repeatable and accurate determination of the size and purity of adeno-associated virus (AAV) capsids and are capable of detecting intact and partial AAV genome as well as smaller impurities. Purity analysis of AAV capsids using CE-SDS, meanwhile, offers improvements over the traditional SDS-PAGE (polyacrylamide gel electrophoresis) method. Plasmid DNA (pDNA) is used as a precursor for both viral vectors and RNA-based molecules. With CE-LIF detection in the BioPhase 8800, one can run an automated method for quantitative analysis of pDNA isoforms.

In addition, rapid and reproducible detection, separation and sizing of mRNA can be achieved using the BioPhase 8800 CE-LIF with single-base resolution down to 15 nucleotides. CE-LIF can also provide high-resolution analysis of 5' RNA fragments of 5-40 bases and 3' RNA fragments with poly adenosine fragments from approximately 0 to 200 bases because these SCIEX methods are known to be effective for analyzing synthetic antisense oligonucleotides.

These examples are just a few ways in which the BioPhase 8800 CE system can support the development of COVID-19 vaccines and therapeutics.



Name	apex	ca	ca%	SNR RMS
Lysozyme 0.1%	13.57	29.68	0.09	24.79
mAB main product	19.44	32049.51	99.91	12535.09

Figure 4: Sensitive Quantitation. Regulators commonly require quantitation down to 0.1% for impurities. The BioPhase 8880 system with UV detection detects 0.1% lysozyme spiked into 1000 ug/ml of IgG.

"A key challenge is that the current high throughput CE techniques do not provide the necessary resolution"

Q. An area of interest in bioprocessing has been in-line and on-line monitoring of products. What can you say about using the BioPhase 8800 for such applications? For example, will the 8800 be connected for bioassay follow-up? Or MS analysis?

A. During clone selection and process development, a large number of samples must be screened. A key challenge is that the current high throughput CE techniques do not provide the necessary resolution and consequently requires scientists to perform assay bridging studies from the current high throughput techniques to the more high-resolution CE systems used downstream. The BioPhase 8800 eliminates the need to do assay bridging studies as it provides the high-resolution data required downstream in a high throughput system (see Figure 5). The BioPhase 8800 enables the consistent delivery of accurate, comparable data from discovery labs to process development, the manufacturing floor, and QA/QC, thereby simplifying and facilitating tech transfer across the development continuum. And we have already demonstrated that the CE-SDS and CIEF results obtained with the BioPhase 8800 are comparable to those obtained on our well-established PA 800 Plus system.

We work very closely with our customers and are developing and exploring additional applications for the BioPhase 8800. We are excited to share them as they become available.

Q. Can you tell us about the underlying software of the 8800 system, especially as it relates to creating a database for clinical validation or in clinical laboratory practices? That is, how might this system be used in clinical applications?

Figure 5: Multiplying Results from a Single Run. Eight parallel capillaries run more samples and molecules.

A. The reimagined software designed for the BioPhase 8800 makes getting results quick and easy. The intuitive software interface, including touchscreen instrument control, places system set up and monitoring literally at the user's fingertips. Simple drag-and-drop functionality for method and sequence creation complements innovative data analysis for accelerated characterization. Specifically, in the BioPhase 8800, the new software makes it possible to multiplex data integration from the multiple channels, thereby decreasing time for data processing and potentially freeing resources for other activities.

At this time, the BioPhase 8800 system has not been designed for use in clinical laboratories. It is a system developed for research use only and intended to support the development and validation of biologics drug manufacturing processes and the product release of biologics drug products.

Q. Thank you for your replies to our questions. Do you have any final thoughts you would like to share?

A. The PA 800 system was developed after recognizing the unique ability of this technology to solve critical questions for biopharma, and that system (the PA 800) transformed the way scientists analyze biologics. Today, purity analysis for virtually every biologic drug in the market and those undergoing clinical trials is conducted on our "We never stopped listening, learning, and experimenting to really understand the challenges our customers face" PA 800 system, which is a tremendous honor and responsibility for SCIEX.

"We never stopped listening, learning, and experimenting to really understand the challenges our customers face"

Even so, we never stopped listening, learning, and experimenting to really understand the challenges our customers face. Today, biopharmaceutical drug developers are working with increasingly complex molecules. At the same time, they need to understand molecular liabilities much sooner in order to close the developability gap and ensure the manufacturability of robust, stable molecules prior to clinical trials. Existing approaches to detect and characterize changes during drug development take too long.

Our customers told us about the challenges of transitioning to more innovative biologics. They told us they needed faster analysis and confident results, and we listened. As our customers face the adoption of evolving challenges presented by novel technologies and the new paradigms in biologic development they are creating, we are always innovating, striving to answer the questions they bring to us – hence, our development and release of the BioPhase 8800. JoPM

About SCIEX

SCIEX delivers solutions for the precision detection and quantification of molecules, empowering our customers to protect and advance the wellness and safety of all. We have led the field of mass spectrometry for 50 years. From the launch of the first ever commercially successful triple quadrupole in 1981, we have developed groundbreaking technologies and solutions that influence life-changing research and outcomes.

Today, we continue to pioneer robust solutions in mass spectrometry and capillary electrophoresis. Our customers are able to quickly respond to environmental hazards, better understand biomarkers relevant to disease, improve patient care in the clinic, bring relevant drugs to market faster and keep food healthier and safer. That's why thousands of life science experts around the world choose SCIEX to get the answers they can trust to better inform critical decisions that positively impact lives.

Mani Krishnan

Mani is the Vice President & General Manager of the CE & BioPharma Business Unit. A proven leader, Mani brings more than 25 years of strong business, technical and leadership experience in life sciences and the BioPhama industry to guide his global team. Mani holds a Bachelor of Technology in Chemical Engineering from the Indian Institute of Technology, Madras, India and a Master of Science in Chemical Engineering, from the University of Calgary in Calgary, AB, Canada.

References

1. SCIEX presents industry first multi-capillary system for CE-SDS, the BioPhase 8800 system, https://sciex.com/about-us/press-releases/2021/sciex-presents-industry-first-multi-capillary-system-for-ce-sds-the-biophase-8800-system