BioProfile® FLEX2 On-Line Autosampler

Analytical Comparability to Manual Sampling

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Data from a study done by a major pharmaceutical company

Abstract

This report summarizes linearity and comparability studies comparing the new BioProfile FLEX2 On-Line Autosampler to manual sampling. The study was done by a major pharmaceutical company as part of their internal validation for BioProfile FLEX2. Cell culture samples were analyzed both via the On-Line Autosampler and via manual sampling methods for all measurable parameters (pH, pCO_2, pO_2, glucose, lactate, glutamine, glutamate, ammonium, sodium, potassium, calcium, osmolality, cell density, and cell viability). BioProfile FLEX2 On-Line Autosampler provided representative cell culture samples to the FLEX2 for analysis and showed a high degree of accuracy and comparability against manual sampling methods.

Introduction

BioProfile FLEX was launched in 2008 as the world's first comprehensive analyzer for monitoring key cell culture attributes. FLEX incorporated Nova's decades of experience in biosensor technology for the measurement of critical cell culture analytes including pH, gases, nutrients, metabolites, and electrolytes, while combining other critical tests for cell density and osmolality into a single, compact-footprint device. FLEX has been widely adopted as the gold standard for cell culture monitoring and optimization for biotechnology and biopharmaceutical organizations throughout the world. With a focus on instrument consolidation, small sample volume requirements, full GMP compliance, and the easiest-to-use interface on the market, FLEX has become the leader in cell culture applications including cell line development, process development, pilot, and GMP commercial manufacturing.

Over the last several years there has been a dramatic shift in the cell culture market. Competition for therapeutics has hit an all-time high. New technologies for accelerated screening and optimization have been introduced to enable faster timelines and a new wave of miniaturized culture systems has provided tools that allow for a logarithmic increase in culture capacity without significant infrastructure changes. As a result, laboratory managers have had more pressure to improve workflow and efficiency. At the same time maximum product quality and consistency has not decreased.

To address these concerns, development efforts were initiated in 2013 for a new, automated FLEX cell culture analyzer. The goal for the product was to provide the best complement of cell culture tests and the fastest test times with the smallest possible sample volume for this increasingly demanding market. BioProfile FLEX2 provides measurement of 16 critical cell culture tests from a single sample, without any pre-sample preparation, in only four minutes. FLEX2's modular design makes it customizable for a broad range of cell culture applications and budgets. FLEX2 utilizes Nova's innovative MicroSensor Card™ technology, which provides maintenance-free chemistry biosensors on credit-card-sized cards that are replaceable in less than ten seconds. An intuitive user interface minimizes training requirements while 21CFR Part11 software features ensure compliance with all GMP manufacturing regulations.

BioProfile FLEX2 is the world's only comprehensive cell culture analyzer capable of sampling small volume culture systems. FLEX2 requires a low sample volume of 265 µL for all tests and provides a full panel of 16 assays in just over four minutes.

With the continued growth of Process Analytical Technologies (PAT) initiatives throughout the cell culture market, and the tremendous benefits automation contributes to accelerating product timelines and ensuring product quality, Nova recently launched BioProfile FLEX2 On-Line Autosampler (OLS). FLEX2 OLS is a modular system that connects as many as 10 bioreactors to one FLEX2 analyzer for fully automated sampling, analysis, and feedback control of key cell culture analytes—including pH, gases, metabolites, osmometry, cell density, and cell viability—with walkaway automation for up to three weeks and proven comparability to manual sampling.

With the OLS, FLEX2 uses a small 5.6 mL sample for more frequent sampling and a detailed look at culture performance: up to 24 samples per day per bioreactor can be analyzed in as fast as six minutes per sample. The OLS provides automated sampling, analysis, and feedback control of 10 bioreactors in as fast as one hour for chemistry results, with only 20 minutes needed for setup.

The OLS addition enables FLEX2 to deliver a number of cell culture analysis and automation advantages, including the unaided capture of key cell culture process attributes across 10 bioreactors, which allows the scientist to focus on other critical development processes; adherence to PAT initiatives; and freedom from after-hours monitoring.

To ensure samples analyzed by the FLEX2 On-Line Autosampler would report results comparable to those from traditional manual sampling methods, extensive testing has been performed as part of the final product validation. The results shown in this report summarize those findings from a major pharmaceutical company and verify comparability of FLEX2 On-Line autosampling to manual sampling methods. The real world results shown here are similar to Nova's in-house test results.

pH, pCO_2, and pO_2 Comparability

Figure 1 shows the graph of pH recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for pH between the two methods with a slope of 0.9587 and correlation coefficient of 0.938.

Figure 1: BioProfile FLEX2 Autosampler vs. manual for pH

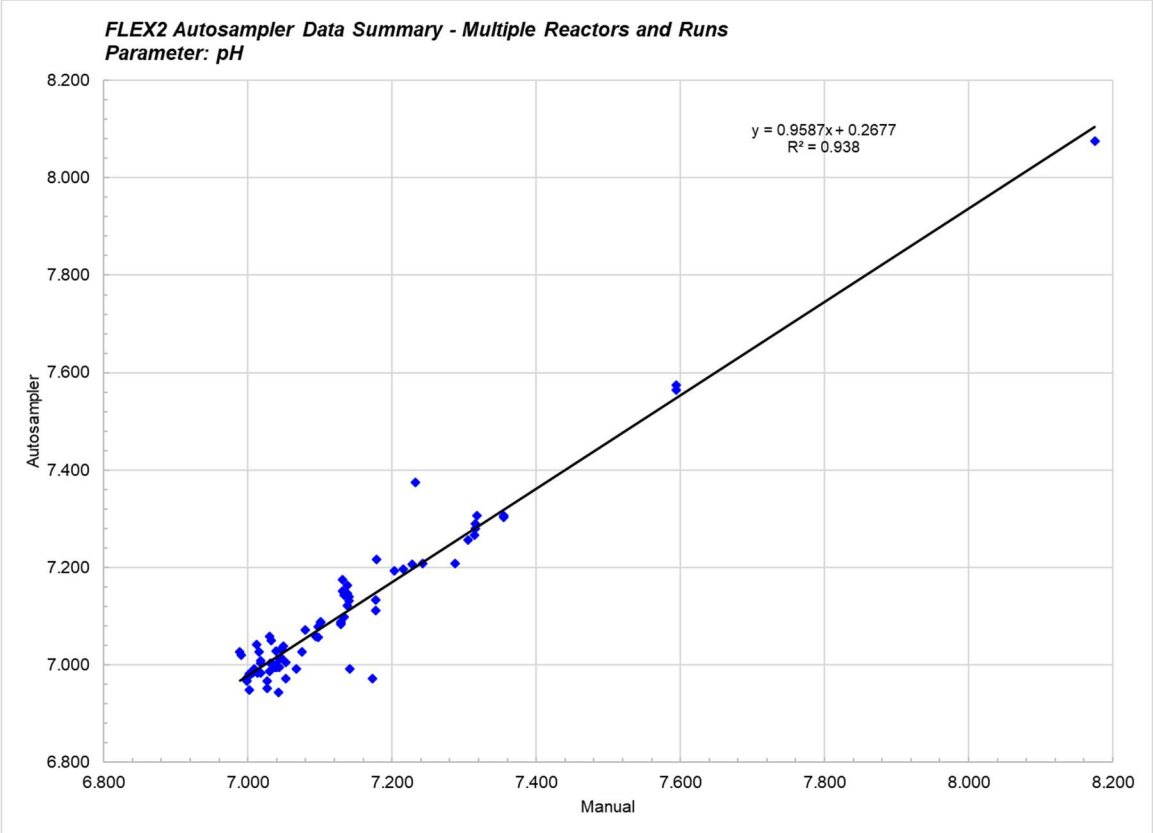


Figure 2 shows the graph of pCO_2 recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for pCO_2 between the two methods with a slope of 1.1582 and correlation coefficient of 0.8633.

Figure 2: BioProfile FLEX2 Autosampler vs. manual for pCO_2

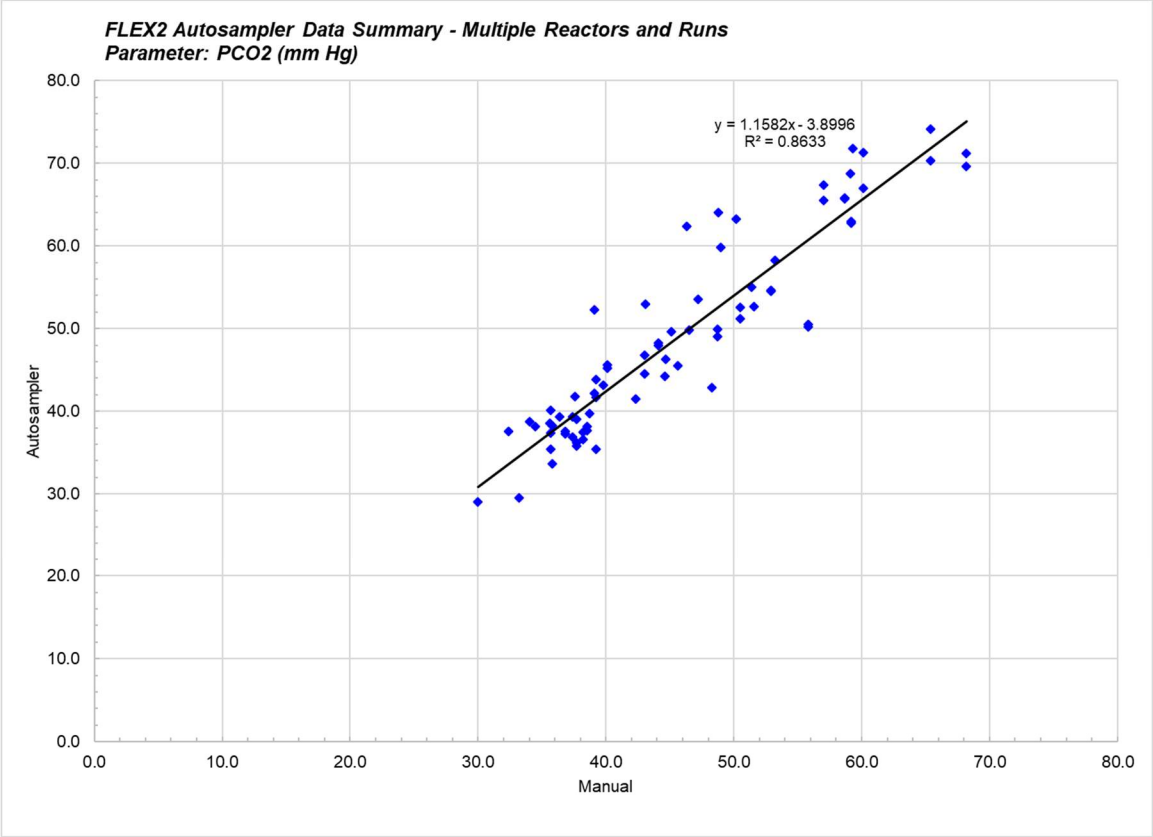
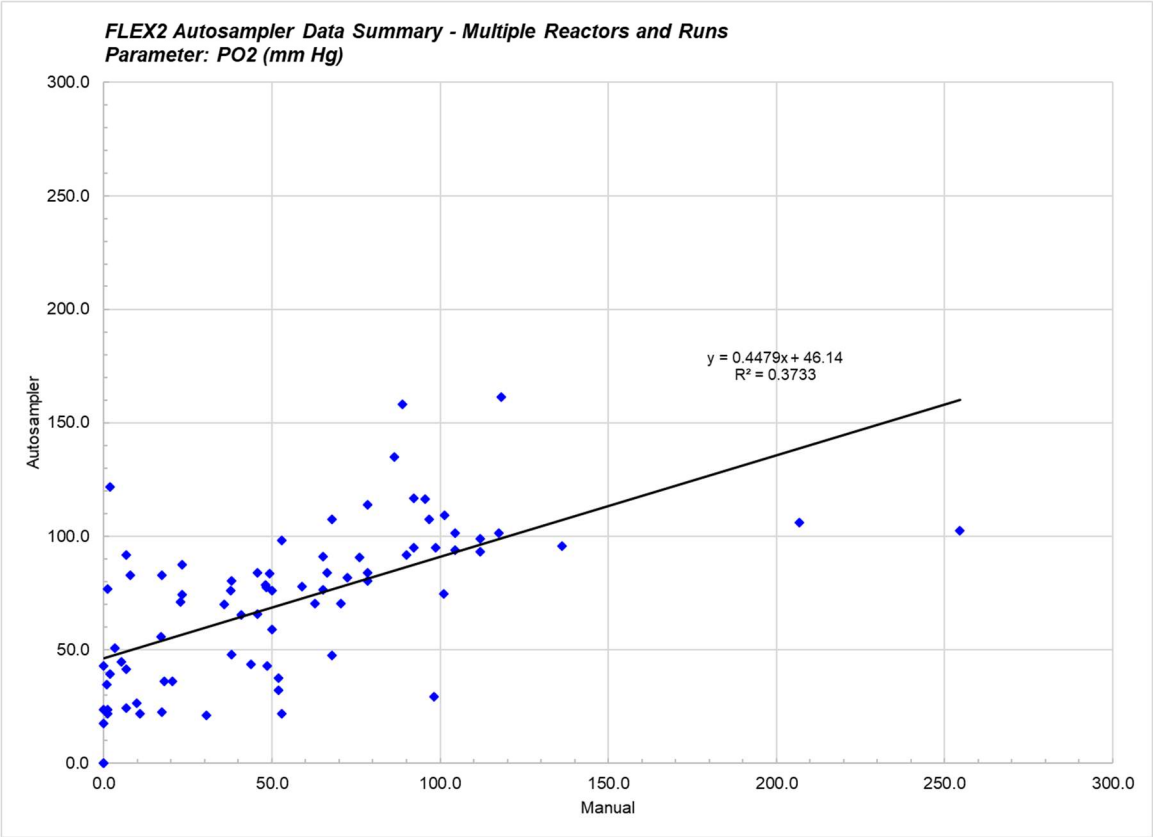


Figure 3 shows the graph of pO_2 recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a correlation for pO_2 between the two methods with a slope of 0.4479 and correlation coefficient of 0.3733. It should be mentioned that the results for pO2 comparability are not unexpected. Since the samples used for these measurements were cell culture samples, oxygen was being depleted continuously via cell respiration. With a controller setpoint of 30% air saturation and PID control, frequent sparging was necessary to maintain O2 setpoint. For statistical confidence in the data, the same analyzer was utilized for both manual and autosampler

samples. Since the autosampler needed to complete analysis before manual samples could be analyzed, there was a minimum of 8 minutes between autosampler draws and manual draws. With high oxygen consumption rates of the CHO cells used in this study as well as the high cell densities observed, it was impossible to achieve comparable samples and therefore comparable results were not expected. It should be noted that is inherent in the operation of the bioreactor and not indicative of a design flaw of the autosampler.

Figure 3: BioProfile FLEX2 Autosampler vs. manual for pO_2



General Chemistry Comparability

Figure 4 shows the graph of glutamine recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for glutamine between the two analyzers with a slope of 0.9896 and correlation coefficient of 0.9951.

Figure 4: BioProfile FLEX2 Autosampler vs. manual for Glutamine

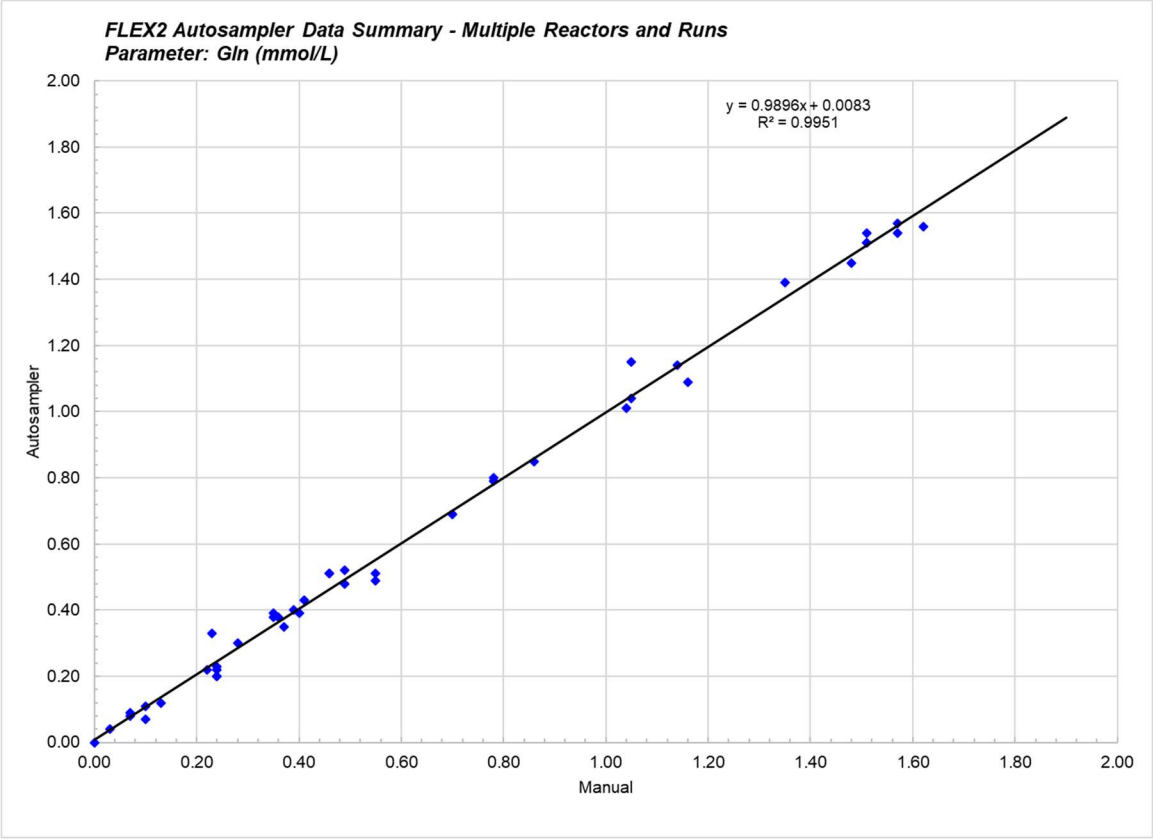


Figure 5 shows the graph of glutamate recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for glutamate between the two analyzers with a slope of 1.0006 and correlation coefficient of 0.9763.

Figure 5: BioProfile FLEX2 Autosampler vs. manual for Glutamate

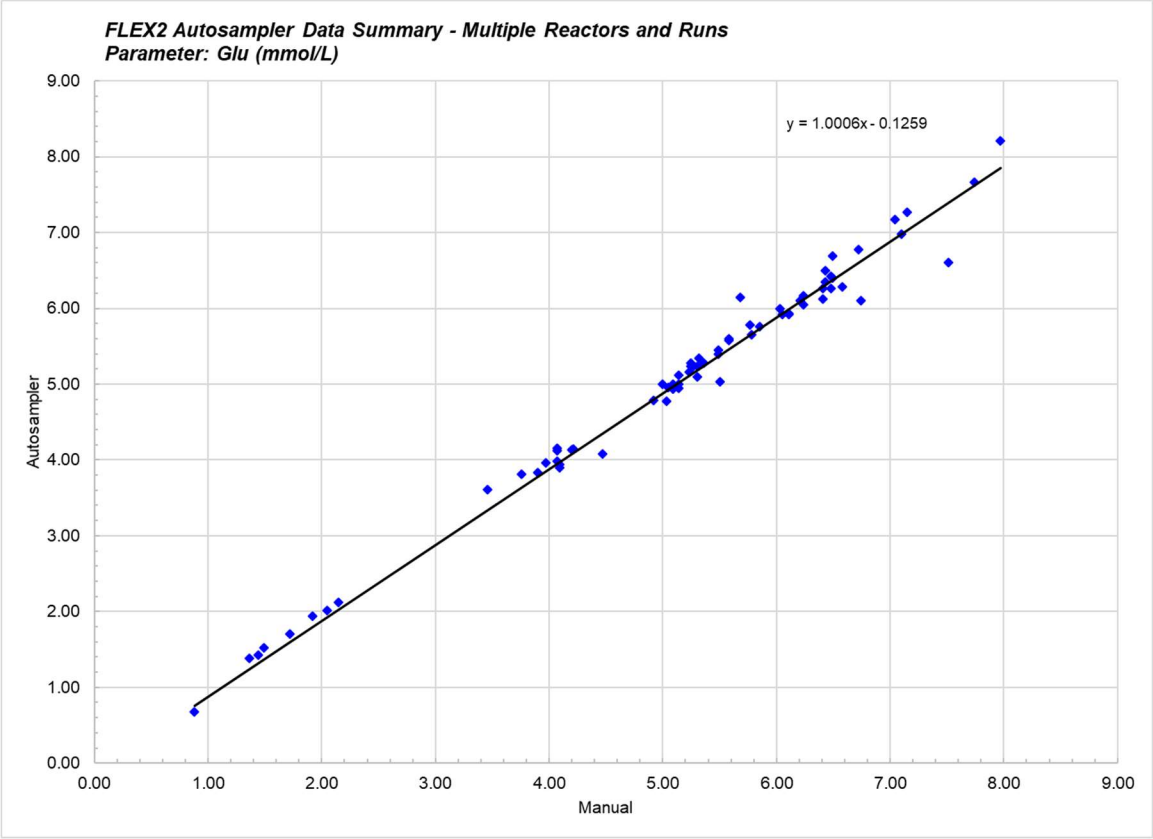


Figure 6 shows the graph of lactate recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for lactate between the two analyzers with a slope of 0.9445 and correlation coefficient of 0.9902.

Figure 6: BioProfile FLEX2 Autosampler vs. manual for Lactate

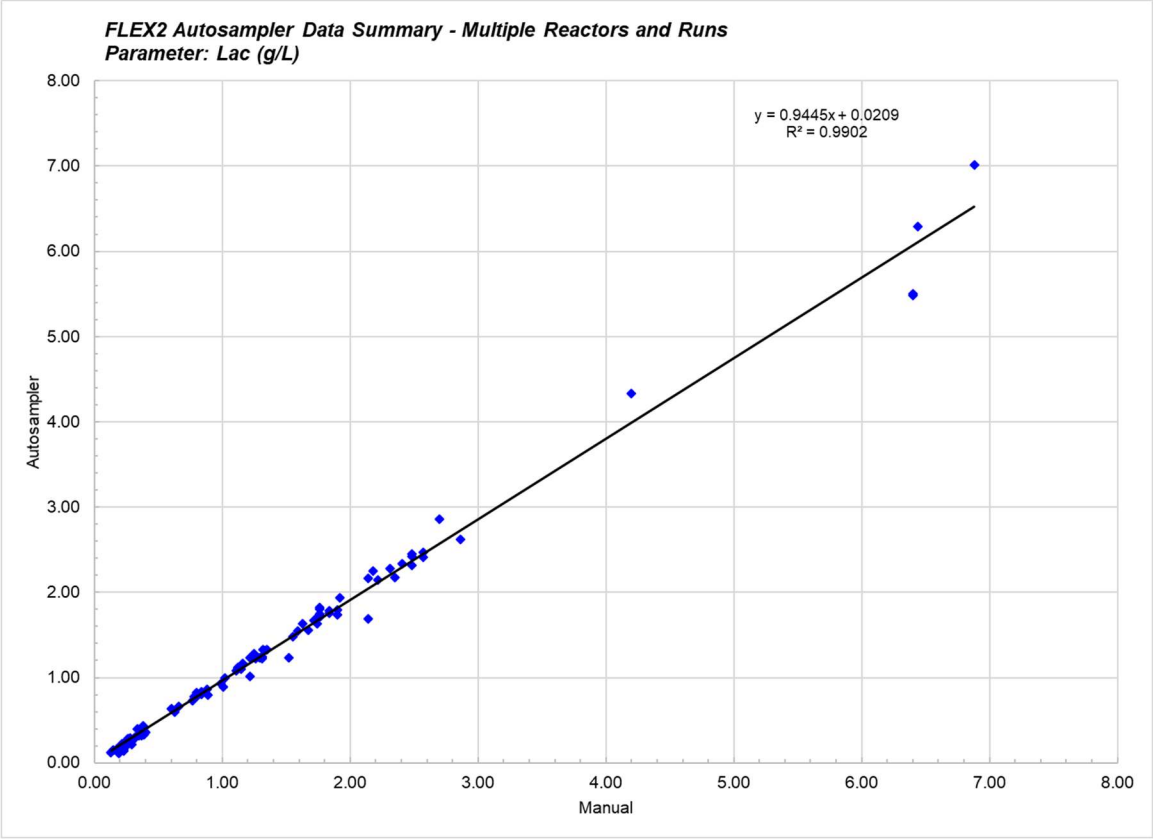


Figure 7 shows the graph of glucose recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for glucose between the two analyzers with a slope of 0.9831 and correlation coefficient of 0.9979.

Figure 7: BioProfile FLEX2 Autosampler vs. manual for Glucose

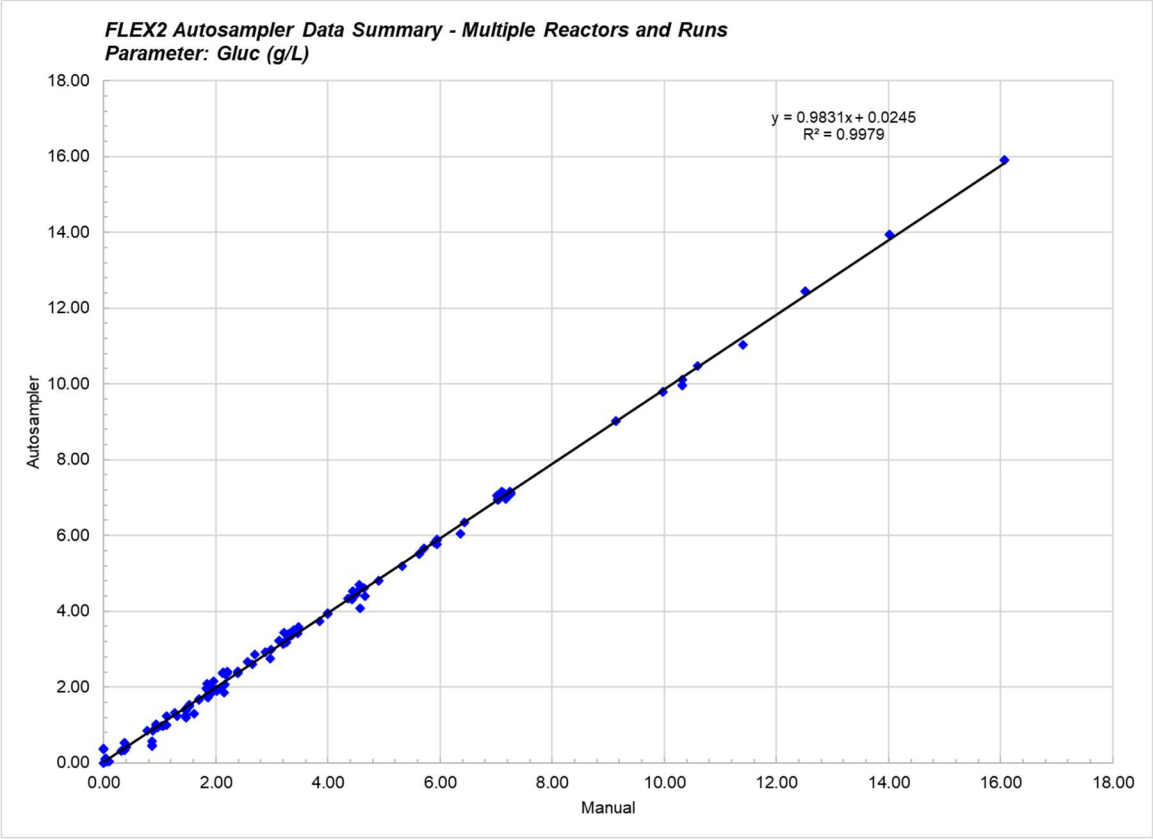


Figure 8 shows the graph of ammonium recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for ammonium between the two analyzers with a slope of 0.9813 and correlation coefficient of 0.9994.

Figure 8: BioProfile FLEX2 Autosampler vs. manual for Ammonium

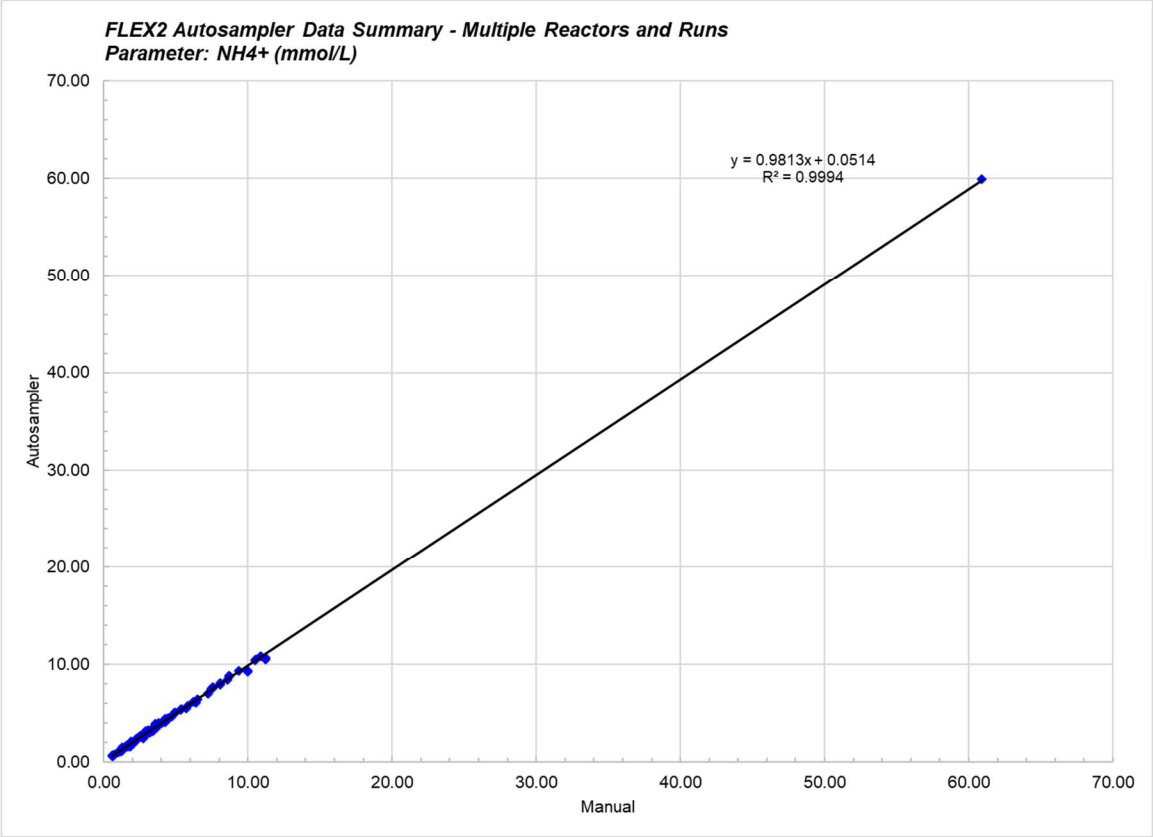


Figure 9 shows the graph of sodium recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for sodium between the two analyzers with a slope of 0.9971 and correlation coefficient of 0.9977.

Figure 9: BioProfile FLEX2 Autosampler vs. manual for Sodium

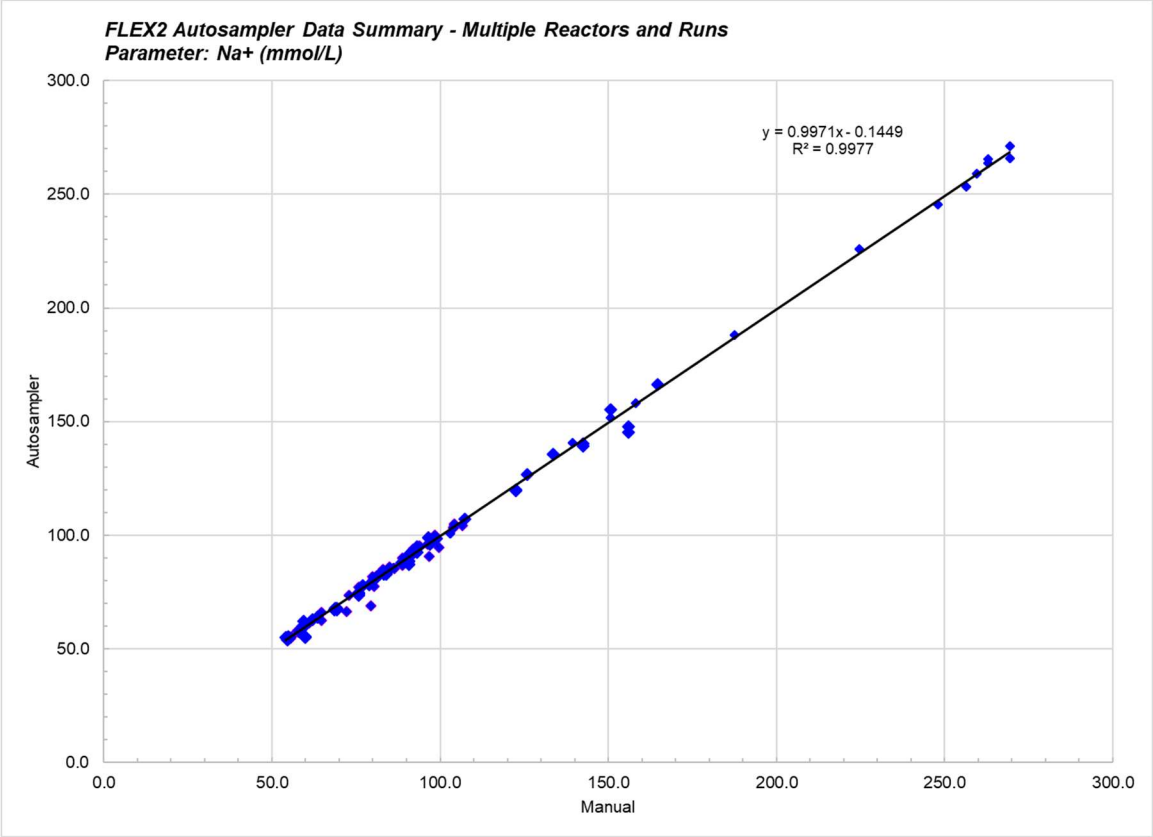


Figure 10 shows the graph of potassium recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for potassium between the two analyzers with a slope of 0.9832 and correlation coefficient of 0.9968.

Figure 10: BioProfile FLEX2 Autosampler vs. manual for Potassium

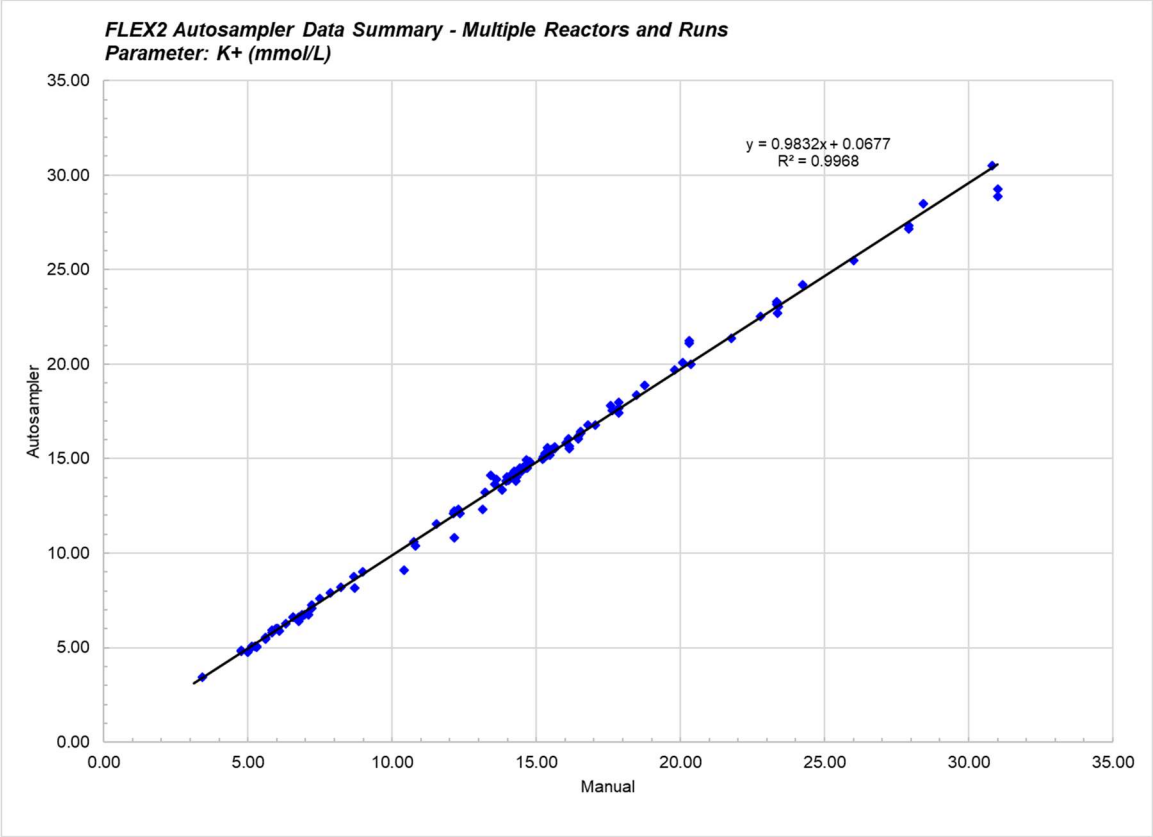


Figure 11 shows the graph of osmolality recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for osmolality between the two analyzers with a slope of 1.0027 and correlation coefficient of 0.9976.

Figure 11: BioProfile FLEX2 Autosampler vs. manual for Osmolality

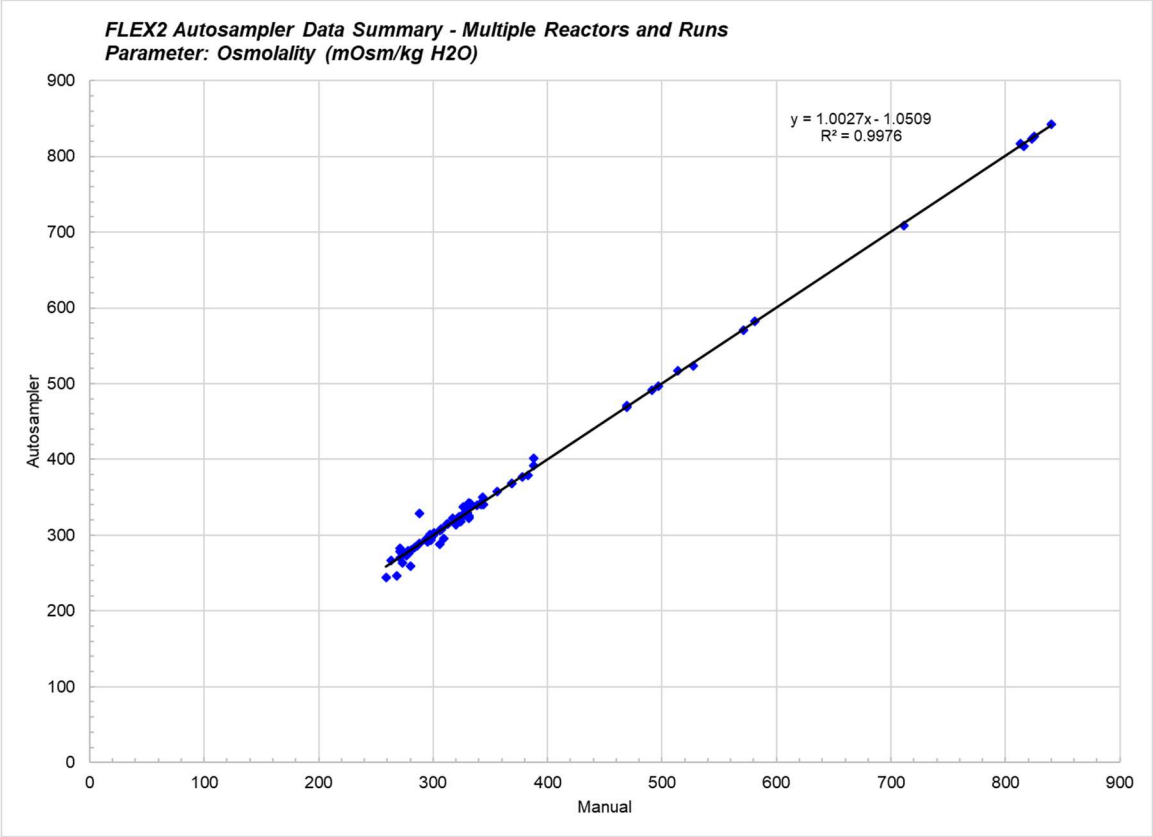


Figure 12 shows the graph of total cell density recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for total cell density between the two analyzers with a slope of 0.9667 and correlation coefficient of 0.9719.

Figure 12: BioProfile FLEX2 Autosampler vs. manual for total cell density

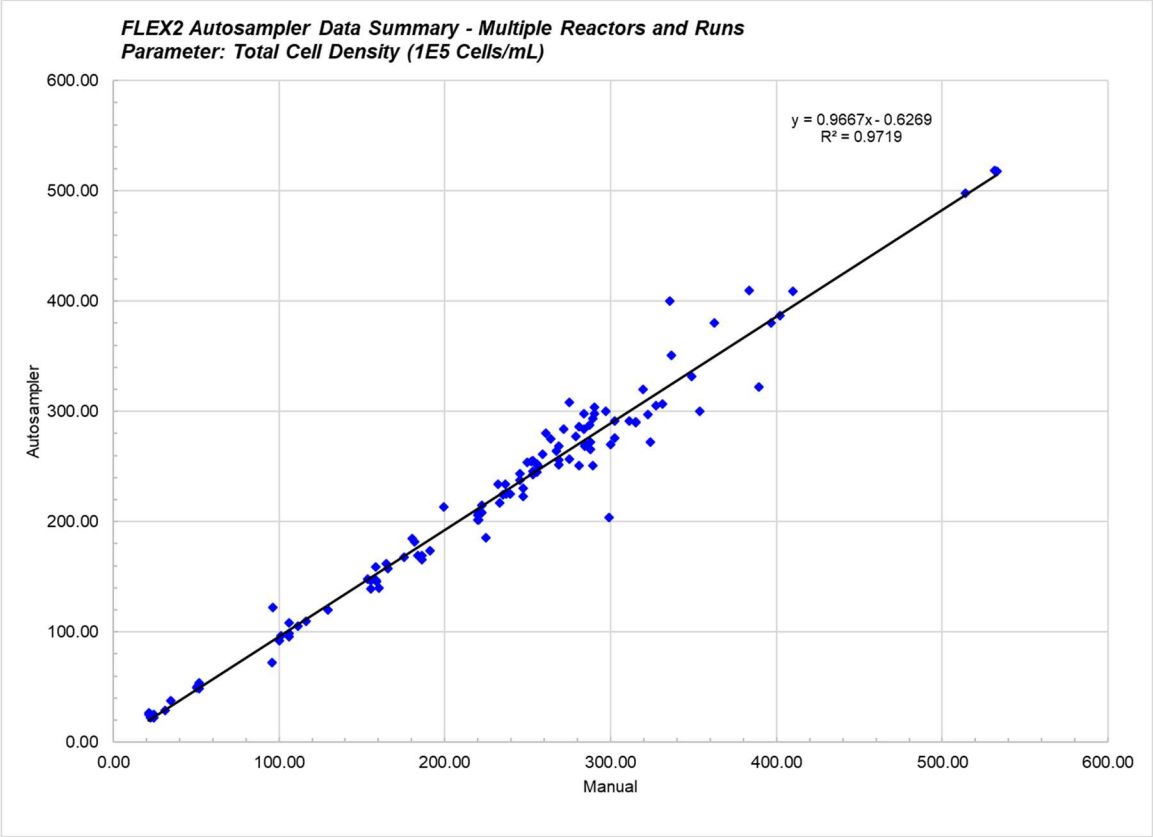


Figure 13 shows the graph of viable cell density recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for viable cell density between the two analyzers with a slope of 0.963 and correlation coefficient of 0.9732.

Figure 13: BioProfile FLEX2 Autosampler vs. manual for viable cell density

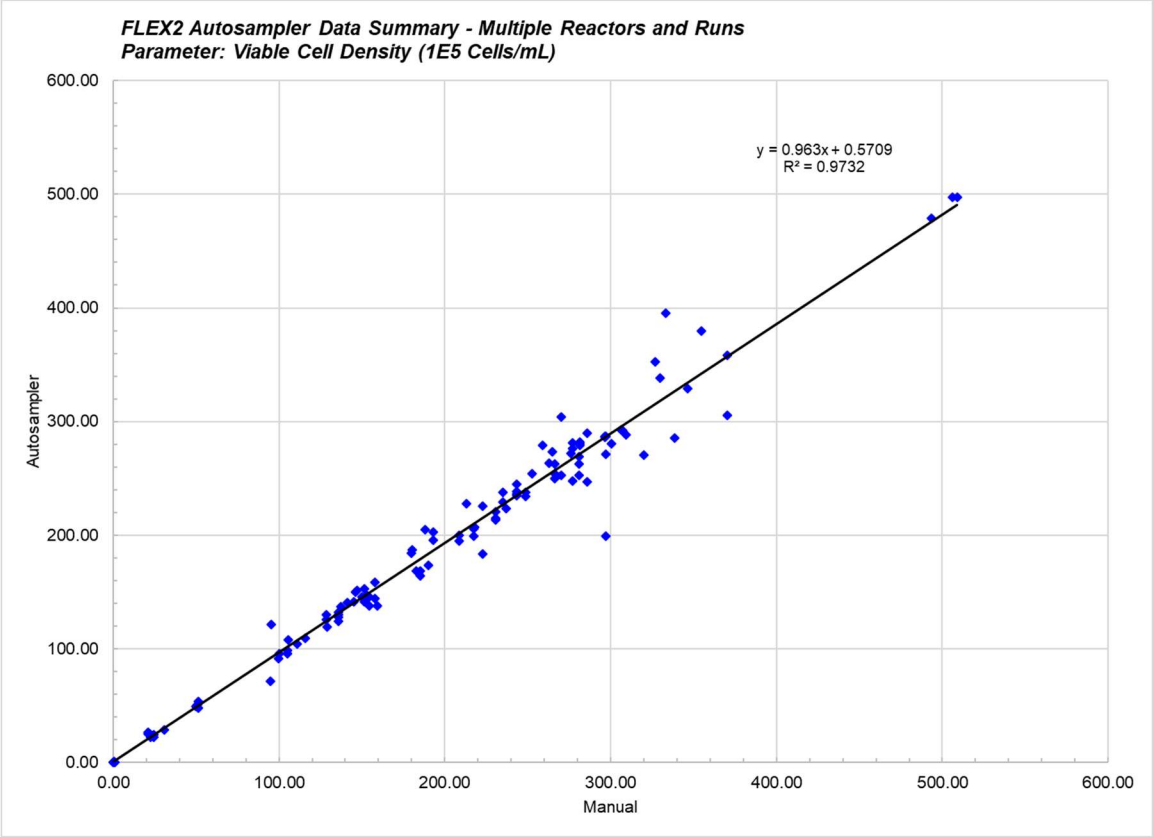
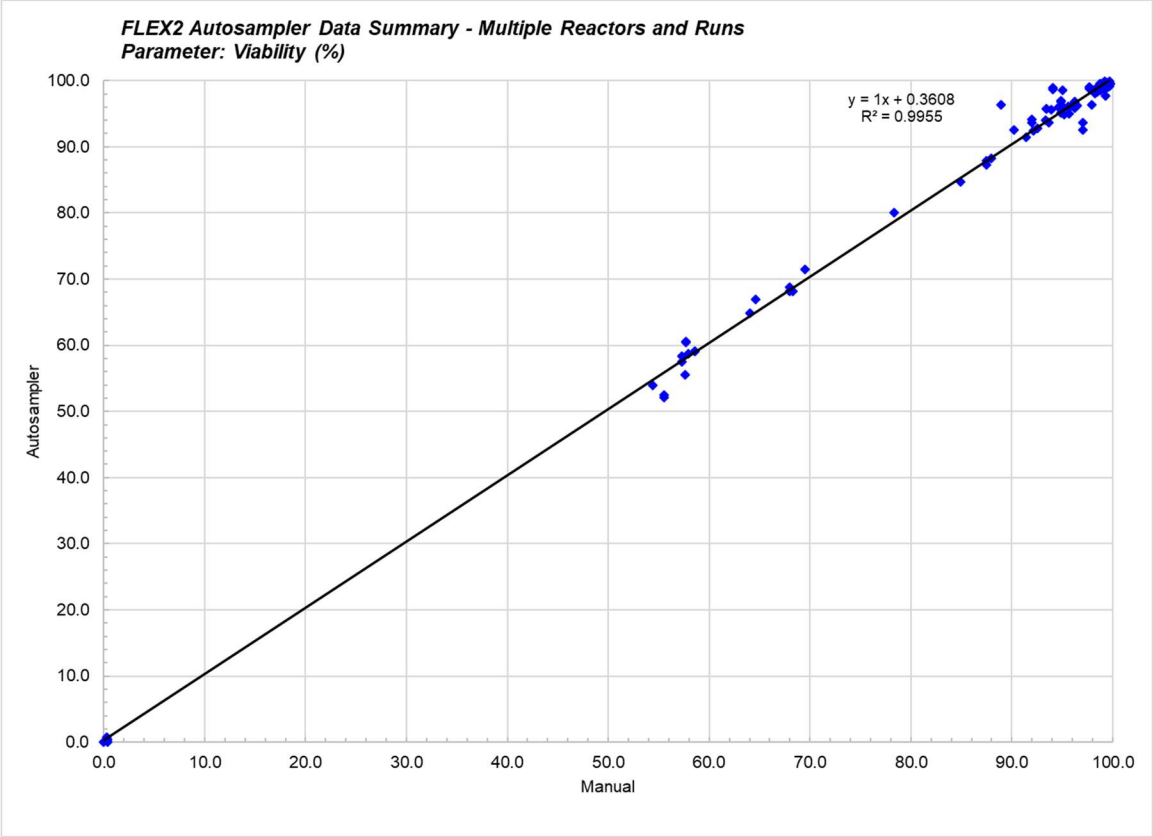


Figure 14 shows the graph of viability recovery for samples taken via the FLEX2 On-Line Autosampler compared to manual sampling method. Results show a strong correlation for viability between the two analyzers with a slope of 1 and correlation coefficient of 0.9955.

Figure 14: BioProfile FLEX2 Autosampler vs. manual for viability



Conclusion

BioProfile FLEX2 On-Line Autosampler was developed to provide fully automated sampling from up to 10 bench scale bioreactors. As part of the validation plan, BioProfile FLEX2 OLS was tested against manual sampling methods for linearity and comparability. FLEX2 OLS met all the product validation requirements.