

EFFICIENCY

Life Sciences Industry

Raylo Chemical Edmonton, Alberta,
Canada

Foxboro® 871 pH Sensor improves
Pharmaceutical Product, Process and Profits

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Background

Edmonton, Alberta, Canada

Raylo Chemical is a member of the Degussa Fine Chemicals Division, the world market leader in specialty chemicals. Raylo Chemical has a 40-year history of custom manufacturing active pharmaceutical ingredients and advanced intermediates for innovative pharmaceutical and biopharmaceutical companies. With extensive research, development and production capabilities, Raylo Chemical works closely with customers to provide high-value intermediate-form drugs and final-form drugs in quantities ranging from one gram up to multi-ton batches.

Complete control over its production process

As a custom manufacturer, Raylo is faced with developing and scaling a wide-range of chemistries and products and ultimately delivering them on a commercial basis.

“The compounds we produce are used in various human applications from cancer treatments to antivirals. Processes have to be controlled tightly in order to ensure quality and consistent high yields. While our products are generally high-value, it is a competitive industry, so delivering high yield to the customer is a must,” said Rob Pastushak, Senior Technical Supervisor of Pharmaceutical Manufacturing.

Another critical and ongoing challenge facing Raylo is demonstrating to its clients and the U.S. Food and Drug Administration (FDA) that the company has complete control over its production process. The Raylo Edmonton facility is Current Good Manufacturing Practices (cGMP) certified, which is a quality standard to ensure that quality and repeatability are built into their production process. All of the company’s production equipment must be tested and certified, which involves a strict qualification process for regulatory compliance, and regular audits by the FDA. Raylo must document its process and ability to consistently deliver quality ingredients in the high volumes required.

According to Pastushak, “The majority of our business involves exports to the United States. If we don’t receive FDA approval, we will go out of business. We must clearly demonstrate that we control every aspect of our manufacturing process at all times, and that our instruments are properly calibrated on a regular basis. Given the value of the drugs we produce, our clients rightfully demand we work closely with them to develop cost-effective manufacturing processes that produce consistent yields.”

“Crystallization is critical and pH is king. When the chemical composition of a drug falls outside of the correct pH range, quality and yield suffer because maximum crystallization fails to occur.”



Goals

- Improve process efficiency and batch yields
- Reduce equipment and maintenance costs
- Improve pH measurement accuracy

Challenges

- Improve the efficiency of the manufacturing process, specifically pH measurement within caustic solutions, without impacting the company bottom line

Solutions & Products

- Foxboro® Measurement & Instruments

Results

- Accurate pH measurement in demanding application, accurate to ± 0.03 pH units
- cGMP and FDA regulatory standards compliance and certification
- Less time for pH adjustment, three hours rather than the 18 to 24 hours it previously took
- Less sampling - no longer have to take 40 samples to the lab to confirm measurement accuracy — only one is needed now, as a matter of quality assurance protocol

Problems with pH Measurement

To assure consistent product quality and maximize batch yields, Raylo launched an effort to improve the efficiency of its manufacturing process. Pastushak focused on pH measurement.

“Measuring pH was a problem at that time because of the unreliability of our pH sensors. They simply could not hold up under aggressive chemicals that we use, such as hydrobromic acid. The organic solvent constituent caused the probe’s O-rings to degrade during the most critical point of the process. In many cases, three probes, at approximately \$600 per probe, would fail during processing just one batch,” said Pastushak.

Once the O-ring degraded, the pH probes no longer provided accurate readings, which presented another problem for Raylo. The process calls for two phases of crystallization, each of which requires pH measurement with tight tolerances of plus or minus 0.1 of the target value.

Because of the unreliability of these devices, Raylo was forced to confirm pH measurements on a benchtop meter in its lab.

Pastushak said, “When you process 3,000 to 5,000 liters and add five to ten kilos of caustic solution at a time, it might take 20 to 40 lab tests to ensure the pH is right during pH adjustment. Going to the lab so often to confirm pH just killed production efficiency, but it was a necessary evil to comply with the strict quality control standards that are essential to our business.”

Pastushak points out that given the competitive nature of the custom manufacturing business and the tight margins that exist in the industry, even a one or two percent variance in yield can have a huge impact on the bottom line. “A small one or two percent increase in the target commercial yield is translated as 100 percent pure profit,” he said. “Likewise, a consistent loss of one or two percent of the commercial target yield translates as lost profit. You don’t stay in business long with this type of performance.”

Solution

To resolve the pH measurement issue, Pastushak researched several probes and decided to test the Foxboro 871PH Series sensor. The 871 is a rebuildable pH probe that incorporates patented technology from the award-winning Foxboro DolpHin™ pH sensor line.

According to Pastushak, “The 871’s Ryton® polymer plastic construction is compatible with all the materials in our process and is just what the doctor ordered for our demanding application.”

Foxboro worked closely with Raylo to fully understand the requirements of the application and provide a solution tailored for Raylo’s process requirements.

“Foxboro offered the technical expertise and production capabilities to modify the 871 sensors to include O-rings made out of Kalrez, which was a big factor in our choosing them over their competitors. The other units we considered were only available as is, off-the-shelf. We needed a durable pH sensor with Kalrez O-rings, and Foxboro was able to deliver the solution,” said Pastushak.

The 871PH rebuildable sensor includes a robust and continuously reusable sensor body with a field-replaceable measuring electrode, reference junction and electrolyte. When immersed into the process solution, the measuring electrode produces an electrical signal proportional to the hydrogen ion activity. The reference electrode provides a stable basis for comparison and completes the circuit. These two electrodes constitute an electrolytic cell with a millivolt output that is proportional to the pH of the solution.

The measuring electrode is the “business” area of the sensor and includes glass that comes in contact with the media being measured. The 871PH features a patented glass formulation that improves measurement stability, accuracy and service life in high-temperature applications, up to 250°F. The glass also increases response speed up to five times compared with conventional sensors, and allows longer duty cycles.

Proven in Process

To ensure the sensor met quality standards, Raylo put the Foxboro 871PH through extensive testing before integrating the unit into the manufacturing process. Raylo utilizes the Foxboro 871PH probe in conjunction with two 7,600-liter reactor vessels stationed side-by-side with a shared condenser. One vessel serves as a reaction vessel and the other as a dissolute receiver, quench reactor or work-up reactor. When mixing organic reagents, acidic or basic byproducts are often generated with potential impact to the product because of the changing pH.

To ensure that the product comes out of solution with the proper pH, Raylo typically dilutes the organic mixture with water. This mixture must then be measured for pH and adjusted until the right balance is achieved. To adjust the pH, Raylo pump-circulates the solution through the bottom of each vessel to the top, where the 871 sensor measures pH in a slurry loop. Based on signals from the 871 sensor, a pre-made caustic or acid solution is added until the right level is achieved. If the pH remains stable for two minutes, the pH test for any secondary crystallization level ensues. The 871 provides reactive, real-time pH measurements, which are key to reducing cycle time.

“We can now complete a pH adjustment in three hours rather than the 18 to 24 hours it previously took. And we no longer have to take 40 samples to the lab to confirm measurement accuracy — we only take one, as a matter of quality assurance protocol. Previously, every time we grabbed a lab sample, we had to put the process on hold until we got the results back. This is significant when you consider not only the yield impact but the cost of a process hour,” said Pastushak.

This reduction in the number of confirmation measurements also improved personnel safety. The fewer the confirmation measurements, the less number of times the technicians need to open the line to manually obtain samples. This fits in line with Raylo’s strong commitment to implementing the highest precautions with all of its safety controls.

“We found many vendors that offered quality sensors, but Foxboro was the only one that could provide a robust design that could stand up to all the reagents and solvents in our solutions.”

- Rob Pastushak
Senior Technical Supervisor of
Pharmaceutical Manufacturing

Results

During an initial one-month test, Raylo discovered that the 871pH allowed them to control pH faster by adjusting to solution changes over a shorter period of time.

“The results have been consistent from batch to batch. As soon as we add a solution to adjust pH, the probe responds immediately and provides the new pH reading. We’ve found it to be accurate to ± 0.03 pH units, which are well within our target limits,” Pastushak said.

The Foxboro 871pH sensor’s fast response, coupled with the sensor’s long reliable duty cycle and the elimination of 40 grab samples, also allows Raylo to produce more batches in the same period of time. The faster, real-time readings have helped Raylo reduce manufacturing cycles by up to 20 percent, which increases capacity and competitiveness.

“Overall, yields have increased and cycle times have been shortened. When you add in the increase in quality, the improved pH readings by one sensor can be worth hundreds of thousands of dollars per year,” said Pastushak.

According to Pastushak, the 871pH sensor is also very durable. “The one we deployed two years ago looks like it did the day we bought it. All we do is clean it after each use. The Ryton bodies are holding up extremely well. They display no degradation, pitting or corrosion even though we run the gamut of pH ranges, solvents and aggressive conditions,” he said.

Durability is critical in a chemical processing plant such as Raylo’s, where one delay can cause cascading impacts to the schedule. “When a day is lost in manufacturing, you lose it forever. A one day delay can cause a backlog that snowballs from days to weeks to months for future batches,” Pastushak said.

The Foxboro 871pH probe helps Raylo show its clients and the FDA just how much the company is dedicated to improving process control and product quality.

During the past two years, Raylo has replaced three legacy probes within its manufacturing process and plans to replace three more. Raylo also has a second manufacturing facility with 15 probes that will eventually be swapped out as well.

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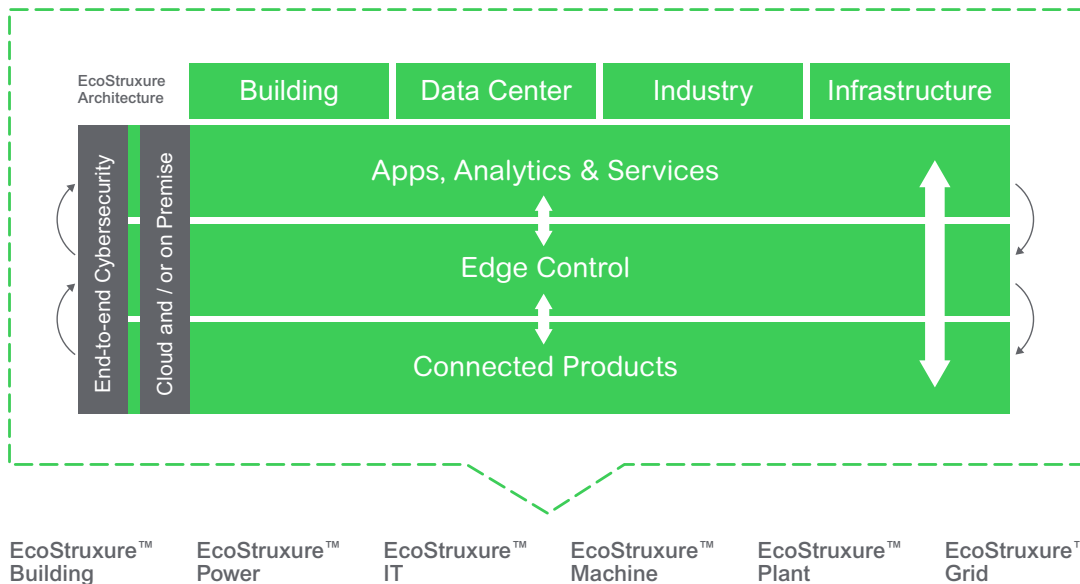
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