Content
July 9, 2018

PD2M Newsletter

A quarterly update for the Pharmaceutical Discovery, Development and Manufacturing Forum Members

Note from the editor

Carla Luciani
Pharmaceutical Discovery, Development and Manufacturing Forum, Newsletter Chair
Future Manufacturing Platforms Leader, Assoc. Engineer Advisor, Small Molecule Design and Development, Eli Lilly & Co.

Dear PD2M members,
After receiving an overwhelmingly positive feedback on the first issue of the PD2M Newsletter… we are back!
Firstly, I wanted to say thank you to the authors listed for their contribution with short articles. They made this second issue possible!

- *Jean Tom*, Bristol-Myers Squibb Company and *Cindy Starbuck*, Merck & Co and their tribute to Omar Davidson.
- *Melanie Dumarey*, GlaxoSmithKline, explains how GSK is using multivariate tools to accelerate continuous process development.

Secondly, for the next issue of the PD2M Newsletter, I am requesting a contribution that highlights The Future in Pharma. A few years ago, the discussion was about the application of continuous manufacturing and the use of modeling and simulation (see "What did we say about drug substance continuous manufacturing a few years ago?"). As we approach 2020, what is the new thing? Is it artificial intelligence? Virtual reality? New unit operations? Business models? If you are interested in contributing to this topic, please, contact me.

Following the great example by Jean Tom and Cindy Starbuck, we would like tributes to be a recurrent section of the PD2M Newsletter to highlight influential engineers in Pharma.
Summaries of recent or old publications of interest for PD2M members, upcoming events and/or learning opportunities, regulatory related news, etc. are also welcome (thanks Greg Frank for the idea).
Please, contact me if you want to contribute to any of the aforementioned sections.

Abstract

In celebration of what would have been Omar Davidson's 67th birthday on June 13, and 10 years after he passed away, we reflect on the legacy of his tenure as a leader and manager of the Chemical Engineering R&D group at Merck & Co. His influence shaped a generation of chemical engineers in process development across the pharmaceutical industry.

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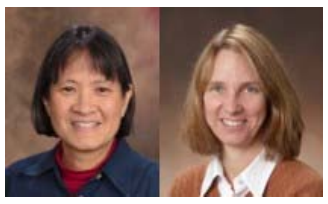
A Tribute to Omar Davidson



Jean Tom
Head - Development Engineering
Chemical & Synthetic Development, Bristol-Myers Squibb Company

Cindy Starbuck
Executive Director - Center for Materials Science & Engineering and Process Analytical Technology, Merck & Co.

Most individuals can point to a single manager or mentor who helped to shape his or her career. However, it is rare for one person to influence an entire generation of individuals. Omar A. Davidson was one such person – a chemical engineer at Merck who spent his entire career (1975-2005) in the same department. In his last position at Merck & Co., Inc., Omar served as the Executive Director of Chemical Engineering Research & Development (CERD), a group comprised of 186 employees, including the operations staff in four pilot plant facilities and a large process development group.

Omar was born in Jamaica as the oldest of the seven Davidson children. Omar excelled academically, and, upon completion of high school in Jamaica, came to the U.S. to study at Columbia University. Omar was a life-long Lion, receiving B.S. and M.S. degrees in Chemical Engineering in 1973 and 1975 and also a M.B.A. in 1988 while working full-time at Merck. Throughout his career, Omar implemented successful technology transfer and plant start-up projects for the active pharmaceutical ingredients (APIs) in many of Merck's major products. He was a pioneer in the field of pharmaceutical process economics, developing methodologies to combine cost evaluation and synthetic route selection to ensure that the lowest cost route was implemented. Omar also introduced new paradigms in process safety evaluation, intermediate sourcing, technology transfer, and crystallization research. While his technical accomplishments and impact on the commercial manufacturing processes for Merck's portfolio are quite notable, his influence in developing the next generation of leaders is the focus of this article.

Omar can be difficult to describe. Those who worked for him both feared and adored him. He had a strong will and tough exterior, but a heart of gold and a passion for instilling in new hires a practical approach to process development. He had both a bat and a tissue box in his office, and was not afraid to use either one. He was eccentric and unpredictable at times which kept people off-guard (and made many fear him), and he would willingly use this to his advantage to drive home points he wanted to make. Omar eschewed email and preferred the style of "management by walking around" – if you needed to talk to him you needed to either wait for his daily visit to your office, or you needed to find him. If you were in the middle of a crisis, you wanted Omar on your side. Omar defended his staff, but if and only if you were on solid technical ground. In short – Omar made all who worked with him a) accountable and b) better critical thinkers. With this picture of Omar, we can summarize his management style in five lessons below.

Lesson #1: Invest in your people -- develop a personal connection with your staff and show your human side. Omar especially loved to mentor new employees and he cared deeply about bringing out the best in his staff. He had a unique ability to develop a personal connection, regardless of a person's age, title or position. Omar had many interests outside of work – he was an avid reader of books and news, an investor, a food and culinary aficionado, a sports fan, a fisherman, and a boater – and was eager to dispense wisdom on all of these hobbies.

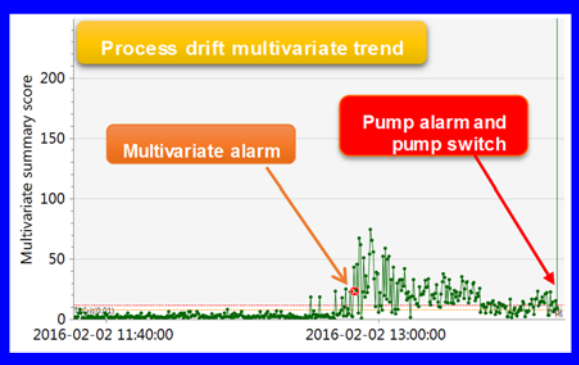
Lesson #2: To fail to prepare is to prepare to fail. Omar was a master of negotiation skills. He knew in advance of going into a meeting what he was willing to give up in order to get what he deemed was most important.

Lesson #3: Define the problem. Omar typically began any meeting with 'The problem is this…" He would then go on to define what he thought it was, in a very succinct and logical way. If everyone agreed on the problem definition, the solution quickly followed.

Lesson #4: Understand what your core job is and seek to develop differentiable skills. Omar did his best to shelter his staff from activities that he deemed superfluous, such as 'fly by night" initiatives, "slogans of the month" and the need to write "departmental mission statements". His motto was: do the job you were assigned to do, and to do it better than the person who had the job before you. Omar excelled at defining the role of engineers versus chemists, and no scale-up "issue" was beyond his ability to solve. Omar had zero tolerance for whiners: Omar believed that you owed the company superior engineering work, and, in return, the company owed you a paycheck – pure and simple.

Lesson #5: Enjoy what you do and when you stop enjoying it, do something else. Omar loved chemical engineering and developing elegantly simple engineering solutions to complex chemistry problems. He loved serving as a resource of facts, figures and experience to colleagues. He loved mentoring young engineers and encouraging them to step outside of their comfort zone. The fact that he enjoyed and loved what he did made his staff excited to work for him.

His lessons still resonate with many of his former staff, even now on the 10th anniversary of his passing. His influence continues not only at Merck but across the industry as former staff members have migrated to leadership positions across small and large Pharma. His lessons on process development made an entire generation of chemical engineers into technical leaders, while at the same time, compassionate and engaged managers.



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Multivariate monitoring for continuous API manufacturing

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Abstract

Real-time multivariate monitoring of a high number of process sensor readings during a continuous API synthesis enabled the identification of sources of high process variability and associated failure modes during late phase development. The potential for predictive maintenance during commercial manufacturing was also demonstrated.

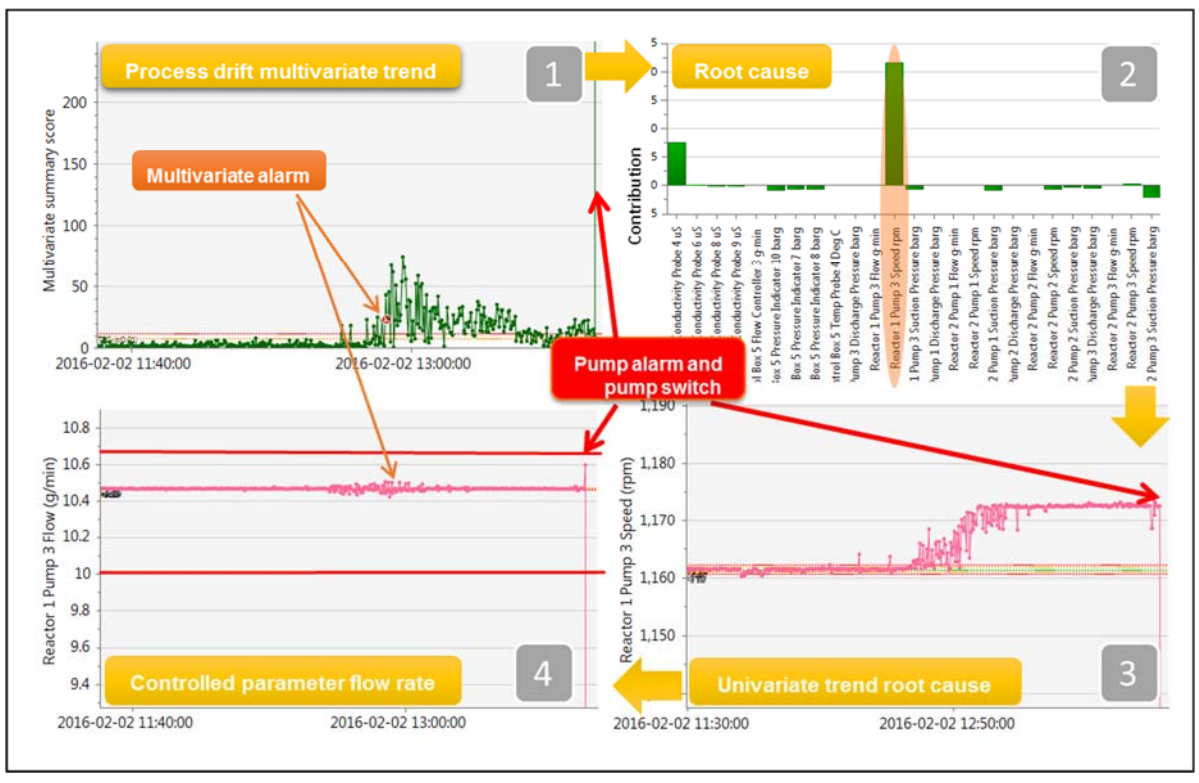
Acknowledgements

The author would like to thank Martin Hermanto, Malcolm Berry, Hannah Robinson, Pete Shapland, Peter Hamilton, Christian Airiau and Simeone Zomer (GSK).

GSK's commitment to innovative manufacturing to produce high quality medicines resulted in the successful implementation of continuous processes for the syntheses (partial or end to end) of selected active pharmaceutical ingredients (API's). Highly consistent API was produced by controlling important parameters such as flow rate and temperature via feedback loops, and implementing an appropriate divert to waste strategy based on univariate alarms, which prevented the collection of material produced outside the accepted ranges. These innovative processes all demonstrated the expected benefits: a footprint reduction of the manufacturing facilities and a decreased consumption of energy and solvents.

Currently, GSK is investigating the use of multivariate tools to accelerate continuous process development at R&D and further enhance process performance during commercial API manufacture. The applied multivariate statistical process control (MSPC) tools enabled the visualization of a high number of sensor readings (>50) for both controlled process parameters (e.g. flow rate, temperature) and non-controlled process attributes (e.g. pump speed, conductivity, pressure) in few trends resulting in a more holistic, real-time overview of the process performance. In late phase development, these process trends successfully identified sources of high process variability and corresponding failure modes, i.e. pump and reagent supply blockages. Additionally, they enabled rapid root cause analysis for a recurrent failure mode, which highlighted instability in one reagent (gas) supply and prompted a small equipment adjustment.

The multivariate monitoring approach was then successfully transferred to the manufacturing site providing a real-time visualization of process performance. In the figure below it is shown how the MSPC tool detected an excursion from steady state (1) and correctly identified the source of process drift, i.e. increased pump speed (2). This observation revealed that the pump had to work harder (3) to maintain the flow rate within the accepted ranges (4) indicating a pump blockage. This hypothesis was confirmed by the increased flow rate variability eventually resulting in the flow rate exceeding the accepted ranges (red lines in figure 4 below) approximately one hour after the multivariate alarm was flagged. Similar observations at both the pilot and manufacturing plant demonstrated that multivariate trends generally detected process disruptions earlier than the established univariate control systems and therefore can be used to trigger corrective actions for known failure modes before the process exceeds accepted ranges and thus preventing divert to waste events.



In the future, the potential of multivariate modelling for predictive maintenance will be explored to enhance performance of continuous syntheses during commercial manufacture. Routine implementation will require an operational framework based on standardized procedures and workflows for operators, which minimize interactions and ensure that data-driven decisions are compliant with the quality management system. Secondly, an efficient model maintenance plan will be required to ensure that a fit for purpose model is in place at all times. Lastly, it will be explored how multivariate monitoring approaches can complement more established tools as PAT or off line testing within the control strategy.

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What did we say about drug substance continuous manufacturing (CM) a few years ago?

Carla Luciani
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Future Manufacturing Platforms Leader, Assoc. Engineer Advisor, Small Molecule Design and Development, Eli Lilly & Co.

Abstract

Study the Past if You Would Define the Future – Confucius.

This short article summarizes what companies said a few years ago about drug substance continuous manufacturing.

A few years ago, the result of a survey was published on the status of implementation of drug substance continuous manufacturing (CM) in the pharmaceutical industry (Poechlauer et al. *Org. Proc. Res. Dev*. 2012, 16, 1586). Within the members of the ACS GCI Pharmaceutical Roundtable, 15 corporations were asked questions about drug substance CM. Both questions and collective answers are roughly summarized below:

- Does your company investigate, develop, or use continuous processes?

  Yes. All the companies answered they had experience.

- If your company has investigated CM, at which stage of the product life has been used and why?

  The answer to this question depended on the stage of the development cycle:

  - At early stages of the development cycle: Increase speed, simplify scale-up, increase throughout and manufacturing flexibility, improve safety and enable chemistry.
  - At later stages of the development cycle: avoid process changes, minimize investment, improve process control, reduce cost and waste.

- In which production stage you use CM?

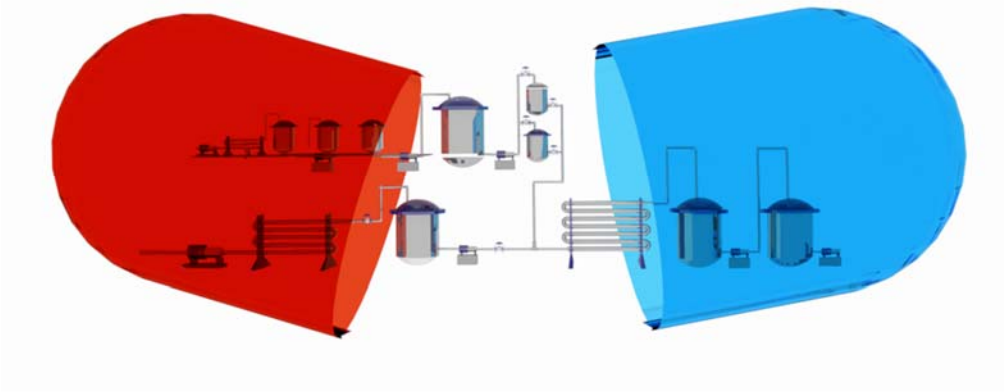
  Both c-GMP and non c-GMP for both primary and secondary manufacturing.

- What are the biggest hurdles that you have experienced or expect in the implementation of a continuous process?

  Major investment in new technology while sufficient capacity of batch plants is available. Lack of personnel with adequate competencies to develop and implement continuous processes. Technical maturity and lack of equipment at different scale.

- Have regulatory authorities such as FDA discussed with you or audited the implementation of continuous process under cGMP conditions? Results?

  About one third of the companies discussed continuous processes with regulatory authorities as FDA. They reported a supportive behavior in discussions.



About 6 years later … some things have changed for sure. Several examples of fully continuous drug substance processes have been published, CM plants have been built, groups within R&D & manufacturing organizations have been created to be specifically focused on CM, existing collaborations between academia and industry in the field of CM continued growing, and new collaborations were born.

Should we consider performing a similar survey again? What questions should we reiterate? What new questions should we ask? For instance, are contract manufacturing organizations (CMOs) broadly adopting CM? How do concepts such as design space, proven acceptable ranges, and critical process parameters apply to CM? Are process system engineers influencing the change?
This article is not only a summary of what we thought about CM a few years ago… it is also an open request to thought leaders to tell us their opinion about the future!

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Important Links

For Updated Information about AICHE Annual Meeting, visit:
https://www.aiche.org/conferences/aiche-annual-meeting/2018.
The final program will be posted the week of July 9th.

Visit PD2M Website
https://www.aiche.org/community/sites/divisions-forums/pharmaceuticaldiscovery-development-and-manufacturing-forum-pd2m