Process Analytical Tools for Flow Analysis: A Perspective

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1. Introduction

Continuous-flow manufacturing is an attractive alternative to traditional batch processes as it affords the potential for a more flexible approach to manufacturing. This is particularly relevant in the pharmaceutical industry where the increased potency of new active pharmaceutical ingredients (APIs) means that smaller quantities of drug are required to deliver the desired therapeutic outcome [1]. In addition, continuous manufacturing limits the risk of large batch failures and opens up the possibility of just-in-time manufacturing for compounds that have a limited shelf life [2]. Just-in-time manufacturing could significantly reduce production costs for APIs and is expected to make continuous manufacturing an attractive alternative for drug manufacturing. The focus of this article is to review the present and future roles of flow analysis for reaction control and monitoring in small molecule fine chemical synthesis.

At present, pharmaceuticals are largely manufactured in batch reactors. Stringent rules are in place to regulate all manufacturing practices ranging from the synthesis of the API to the formulation of pills. Regulatory agencies (e.g., the United States Food and Drug Administration [USFDA], Pharmaceuticals and Medical Devices Agency [PMDA], Health Canada, and others) continue to provide valuable guidelines to ensure that the manufacturing methods do not adversely impact the ultimate pharmaceutical product. There has been a paradigm shift in pharmaceutical drug manufacturing in the current decade towards cleaner and more efficient manufacturing processes. In 2015, Vertex pharmaceuticals received the first new drug application (NDA) approval for using continuous manufacturing technology for the preparation of Orkambi™, a mixture of lumacaftor and ivacaftor (Figure 1) [3]. Soon after, Janssen, a pharmaceutical company of Johnson & Johnson, was awarded with the first NDA supplement approval for switching from batch production to continuous manufacturing for Prezista®/darunavir, a USFDA-approved drug for human immunodeficiency virus (HIV) treatment (Figure 1) [4]. Fundamentally, the expectations from batch and continuous productions have not changed; both production methods are required to deliver APIs in their purest possible form. However, continuous manufacturing, which is based on dynamic flow technology, must be subjected to continuous monitoring to ensure that the production conditions are not compromised over time.

There have been significant advancements in the area of flow analysis research [5]; however, there is a disconnect between integration of the best-suited flow analysis technologies with the best available flow reactor technologies. For example, reactor technologies that primarily deal with the flowability of matter under harsh reaction conditions have evolved significantly. It is now possible to conduct flow reactions under very high temperature and pressure [6–10] with and without introducing restrictive flow-path technologies, both of which have noteworthy merits based on the nature of the flow application [11]. Almost all sources of radiative and convective energy have been applied to flow reactors, delivering fast and efficient access to a wide range of reaction conditions [12–14]. Depending on the intensity of the supplied energy, phase transitions (e.g., liquid to gas or solid to gas) are possible in the reactor and so high-pressure flow reactors were introduced to prevent reagents undergoing undesirable phase transitions during heating. Conversely, the vast majority of advanced flow analysis technologies are still suited to ambient temperature and pressure conditions. Most analytical samplers, which bridge the fluidic gap between the reactor and the analytics, are not compatible with reaction matrices that may contain solids or gases, common by-products of typical organic reactions. Therefore, an effective overlap between flow reactor technology and flow analysis is a necessity, especially when the regulatory agencies are seemingly urging inventors to come up with new technologies for better control of continuous manufacturing. To achieve this, in 2004, the USFDA introduced the Critical Path Initiative, which was designed to monitor existing and emerging technologies in manufacturing sectors and to identify areas of product development in need of improvement. Process analytical technology (PAT), which is defined as "a system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality," was proposed by the USFDA soon after [15]. In essence, PAT aims to establish a standard for product quality by careful regulation of manufacturing standards to eliminate preventable risks in pharmaceutical products originating from the manufacturing conditions. PAT-enabled tools are defined as tools that allow process understanding for scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. The guidance for pharmaceutical development in ICH Q8 (International Conference on Harmonization of technical requirements for drugs) calls for continuous process verification wherein manufacturing process performance is continuously monitored and evaluated as opposed to full-scale singular batch verification methods, which are essentially treated as pass-fail qualifiers for an entire batch of API. In continuous format, the risk of losing an entire batch due to a single failure is somewhat mitigated as the effluents in the flowed format are tested at regular intervals to monitor a compartmentalized portion of the production stream over a time period. Real-time release testing (RTRT), which is also included in ICH Q8(R2) [16], was proposed to evaluate the quality of in-process and/or final product from continuous manufacturing and to ensure that the quality standards are met during a production run [17]. The ultimate goal for a RTRT-enabled PAT tool is to reliably extract and analyze a sample from flow reactors in order to ascertain that the process parameters that are critical to the fate of the product (critical process parameters; CPP) are kept unchanged over a selected period of time during a production run. According to document 21 CFR 210.3, the current definition of a "lot" is "a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit time or quantity in a manner that assures its having uniform character and quality within specified limits." [17] Identification of CPP for a process (batch or continuous)

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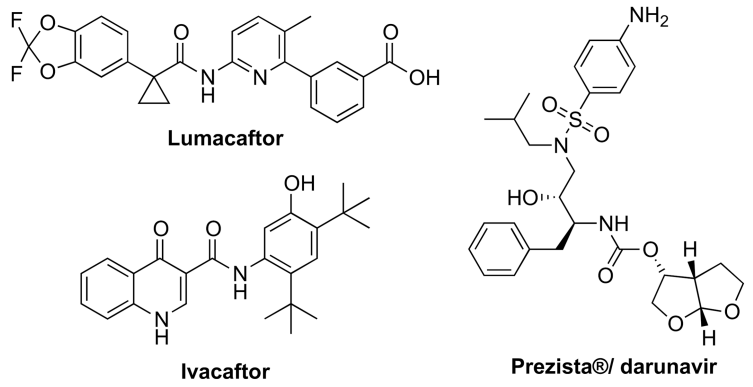

Figure 1. Structure of lumacaftor/ivacaftor (Orkambi™) and Prezista®

relies on the ability to measure certain critical quality attributes (CQA). For continuous-flow formats, the measurements of CQAs are expected to occur in real time as per the suggested guidelines for RTRT. It is important to note that the ultimate objective of including PAT in flow analysis is to transform continuous-flow chemistry from a cutting-edge research science to an alternative production platform for industrial applications. The objectives can be summarized in 5 steps:

- Development of on-line, in-line, and at-line measurement tools to improve production quality and consistency. This could be achieved using an automated sample withdrawal mechanism using either an array of fluid diverting devices [18–23], or by directly inserting an analytical probe in the reactor flow-path [24–28]. A PAT tool that includes a fluid diversion mechanism could be used to extract a sample for analysis at the completion of a flow experiment either from an offline analytical setup or at-line using a local analytical instrument. Manual interference is needed in both which may also include a sample preparation step prior to the analysis. The fluid diverting device can be also placed between the flow reactor and a bulk product collection vessel, so a sample can be analyzed in-line. Alternatively, a detector probe can be placed directly in the flow-path of the reaction mixture to obtain reaction information real-time.
- Development of real-time release testing (RTRT) to ensure the quality of in-process and/or the final product. The strategy currently relies on the ability to communicate with all analytical tools from a single platform or software. Inline strategies, when integrated to a suitable controller for automations, can qualify as an online PAT tool for flow analysis. A universal online PAT-enabled flow-analysis tool, in theory, could allow flow analysis to be free from human errors and traceable in accordance with the guidelines of data integrity by the USFDA. Introduction of online flow-analysis strategies would also allow computer scheduling of high frequency sampling thereby drastically increasing overall sensitivity in the purity measurement of the bulk product. For example, an increase in sampling frequency could allow production scientists to detect traces of impurities at an early stage and reject non-conforming materials which can be temporarily held in compartmentalized confinement (e.g., a loop) until an analytical confirmation is received from the computer-controlled analytical platform [29].
- To prevent or limit rejects and batch re-processing. Online feedback in continuous flow could help to prevent contamination of an entire batch by simply diverting the contaminated reactor stream into a different flow path. Additionally, small segments of effluent stream could be isolated and assayed in a "pre-lot" before they are added to the main reactor output, if the desired analytical purity is achieved [20].
- Another aspect of PAT-enabled inline or online tools lies in the ability to perform multi-variate analysis of multiple quality attributes in parallel. For example, information on reactor performance and product stability could be obtained in parallel thereby lowering the risk of pursuing an undesirable design space during the early phase of the drug discovery. Quality-by-design (QbD), which is gaining widespread popularity in current manufacturing practices, would be ideally included in the campaign for online PAT strategies for flow analysis [17].
- Increase the use of automation to improve operator safety. Two key advantages in flow chemistry lie in the ability of the reaction format to give products just in time and on-demand. Online automated analysis technologies, which would eliminate the need for human interference, would enable scientists to synthesize chemical entities that are challenging to prepare under current manufacturing practices.

2. The Current State: Flow Chemistry and Flow Analysis

Conducting a flow reaction under high pressure or using a multiphase reaction mixture is viewed as difficult, but attainable. As previously outlined (vide supra), flow reactor technologies have advanced considerably in the last decade to allow the application of forcing reaction conditions to flow streams. However, the scarcity of suitable PAT tools for pharmaceutical processing that are operational under the reaction conditions and reliably provide information on the state of matter inside the flow reactor is a significant drawback for flow chemistry as a routine process development platform. There are examples of high-pressure and high-temperature sampling tools that are capable of handling challenging conditions in other sectors (e.g., petrochemicals [30]). However, because the pharmaceutical industry typically utilizes a significantly larger range of functional groups, and a wide variety of organic and inorganic reagents, there is still a need to develop a universal PAT solution for pharmaceutical manufacturing.

Recently, there have been enormous advances in the availability of emerging analytical technologies from injections [31] to detection [5]. Sensitivity and resolution of analytical data originating from modern analytical instruments has reached a level where it is possible to detect chemicals at very low concentrations meaning higher purity products and safer chemical processes. However, analytical products evolved independently of PAT and so a disconnect remains between the analytical technologies available to a researcher and PAT enabled tools. One of the primary criteria of qualifying a technology as a PAT tool for flow-analysis lies in its ability to tolerate a wide range of chemicals and also function in the presence of all phases (i.e., solids, liquids, gases and mixtures). There are up to two crucial steps for the analysis of a sample from a flow reactor, namely, sampling and analysis. For flow experiments where analysis is performed directly using an inline probe at the flow-path of the reactor, a sampling step is not necessary. However, this strategy requires

complete compatibility between the detector and the reaction matrices. Various detection techniques (e.g., near infrared [NIR], infrared [IR], Raman) are on-hand to do RTRT using this option [25–27, 32, 33]. Inclusion of high-definition detectors, which would not only quantitate a target analyte, but also confirm the identity of the chemical, are feasible, but not popularly applied. For example, mass spectrometric or nuclear magnetic resonance spectroscopic techniques have been reported, but the analytical samples must be treated under specific conditions to remove interference from undesirable entities in order for the techniques to provide optimal, and in some cases even meaningful, results. On the other hand, a fluid diverting device could be placed in the flow-path of the reactor to extract a portion of the stream from the reactor. The entire event is commonly termed as sampling. The sample is then subjected to analysis, often by a chromatographic technique. The results from such techniques do not strictly qualify for RTRT. However, isolation of the analyte in a post-sampling path allows users to do various sample preparatory operations in order to obtain a high-resolution analytical dataset (e.g., a chromatogram). The ability to conduct sample preparation prior to the analysis is a powerful tool that opens up the opportunity to treat the analyte using common sample cleaning techniques, making the strategy widely applicable. For example, if the analyte from a specific flow experiment contains solids and the detector chosen for the same experiment is sensitive to solid particulates, automated but offline filtration (commercially developed by Gerstel Maestro, application note: 5/2008) can be performed prior to the analysis. However, the issue of analytical tools being unable to handle multi-phase reaction mixtures remains. In this case, the sampling mechanism, which acts as the bridge between the reaction and the analysis, is expected to remain functional in the presence of the multi-phase reaction matrices or under harsh reaction conditions. For example, if the analytical sample contains a mixture of liquids and gases, the fluid diverting device, which is typically a rotary valve, may not be able to reliably isolate a known volume of one of the two phases. That said, Ley and coworkers from the University of Cambridge reported a novel membrane-based device that allows the gases to permeate through the membrane thereby separating the liquids from the gases for possible individual quantifications [34]. The development of such a capability is significant for the integration of PAT tools into the flow path of a prospective universal flow reactor. Another important hurdle in handling the flow reactor output stems from reactions that generate solid particulates as they proceed (e.g., salts or insoluble biological matter). The presence of insoluble matter drastically narrows down the options for analytical detectors or chromatographic techniques. The sampling device, which also comprises of delicate movable flow-paths, is likely to become blocked or restrict reagent flow when slurries are present. We recently reported a unique multi-position valve-based sampling strategy that shows preliminary promise towards separating solids from liquids in a continuous manner [19]. Previously, we also demonstrated that the sampling valves used in our flow experiments are suitable for isolating a flowed reaction mixture from a high-pressure flow reactor without altering the process pressure or the flow rate during the sampling event [18, 35].

3. Future Direction for Flow Analysis: An Outlook

As of 2014, no specific FDA regulations or guidance exist about continuous manufacturing, other than the definition of "lot." [36] Continuous manufacturing is not in conflict with the USFDA guidance, but consistent with USFDA's efforts on promoting QbD to manage risks. USFDA and others recognize that the measurement of CQA and the control of CPP are likely to come from designs different from those for batch sampling. This is to be expected given the science of flow chemistry, by definition, depends on the flow-rate, a critical process parameter irrespective of the nature of the chemistry in question. The sampling and analytical design must not interfere with the flowability of matter inside the reactor. Additionally, reaction kinetics are expected to be fast given the residence time is short inside a flow reactor. This calls for raising the temperature which, in turn, would likely cause phase transition of the matters inside the reactor. Thus, the sampler is expected to be pressure tolerant. Once a sampler fitted with analytics that does not interfere with the flowability of matter and reliably samples at any time interval irrespective of the process temperature and pressure, one can determine when to collect "good" product and when to stop during a flow run. Control strategies are different. In batch mode, a singular sampling and analysis can render a batch successful. Time is a CPP in flow. Flow format gives an opportunity to "virtually" stop a portion of a "traditional" batch reaction and separate that portion from the rest depending on the outcome from the analysis of that portion. That is a significant advancement in the ability to make products from a chemical reaction without having to lose an entire reactor-full of materials. However, the strategy of validating an entire batch in portions is only feasible when analytics, which may or may not include a sampler, are ready for a wide range of flow reactions including the ones that require high temperature, pressure, and the mixtures that may contain solids or gases. Flow chemistry and fluid dynamics are two fundamental science streams that are building a case for a shift in how commodities can be manufactured in the future. Current research on flow chemistry is expected to not only develop science using applications where the chemistry is robust for continuous manufacturing, but also to reinvent itself to fill missing links (e.g., the development of a multi-purpose sampler, robust RTRT analytical techniques, AI-based human-free controller software, etc.), so continuous manufacturing can be applied beyond the scope of present applications. Diversification of continuous manufacturing, however, is easier said than done especially when diversity of reaction conditions of chemical syntheses is taken into account. At present, flow chemistry is mostly considered an option for chemical processes that demonstrate fast reaction kinetics. A plethora of energy sources (from microwave [10] to high intensity photochemical sources [37]) are being experimented on to accelerate chemical reactions that are currently deemed as too sluggish for the flow format. Technologies (e.g., Coflore, http://www.amtechuk.com/) are on-hand to undertake complex fluid dynamics and (e.g., slurry flow [38], pressurized supported catalyst column [39], Ley's liquid–gas flow [34], Lilly's solid pumping for formulation [40], etc.) to overcome issues arising from flowability of matter. However, analysis in real-time is critical for the constant verification of the state of matters, which often undergo highly complex, sometimes risky high energy treatments, inside the reactor. RTRT has long been recognized as an essential tool in process manufacturing, but continuous-flow manufacturing, wherein time is a default CPP, shifted the importance of analysis from a preferred option to a requirement. The need for robust and reliable sampling and analytical devices, which can handle complex fluidic matter encourages chemists and chemical engineers to work hand in hand toward developing devices with superior capabilities (e.g., semi-porous membranes flow path for liquid–gas mixtures [34], multi-position valve technologies for solid–liquid mixtures [19], microfluidic chip distillation for liquid–liquid separation [41], etc.). Necessity, which ultimately drives scientific discovery, could come from diverse areas of fundamental and applied science research as the popularity of continuous manufacturing continues to grow. For example, in continuous-flow biosynthesis, which comprises complex multi-phase complex mixtures [42], the sensitivity of protein-based material to

iron is an inherent problem. Consequently, manufacturers of analytical instruments have drawn expertise from the field of materials science to build flow paths suitable for biological assays (for example, the Thermo Scientific™ UltiMate™ 3000 BioRS System). RTRT strategies, which rely on how quickly analytical conditions (e.g., tuning of mass spectrometric conditions) can be toggled for simultaneous monitoring of multiple chemical entities from a single chromatographic run (for example, in a multiple reaction monitoring [MRM] setting), require sophisticated electronics, which are developed by members of the electronic and electrical engineering communities (for example, Agilent Technologies 5973 Inert Performance Electronics, application note: 5989 1574EN). Vast improvements in the field of chromatographic separation (e.g., UHPLC, SFC developed by Waters corporation) open new avenues for fast and simultaneous multi-channel chromatographic analysis and make inclusion of high-resolution analysis a future milestone in RTRT. Research is currently underway to stretch the capability of online PAT tools from a process development tool to monitoring of continuous manufacturing processes in real-time so that batch failures may be averted. The ability to save a batch through online RTRT is not just another economic advantage of continuous manufacturing. On-demand and just-in-time aspects of flow manufacturing allow scientists to make compounds that are either extremely hazardous or made via intermediates not synthesized in a laboratory beyond a few milligrams at a time [43]. The "Safety Research Interest Group" (SRIG), which was established by the Centre for Drug Evaluation and Research (CDER) in 2011, recognizes the need for improving "product quality and design, manufacturing processes, and product performance related to safety" as one of the seven major areas of safety-related needs. Just-in-time and on-demand aspects of continuous manufacturing are very much in agreement with this initiative from the USFDA [44]. Information feed-back loops through online PAT tools could enable scientists to undertake hazardous chemical experiments without an onsite human presence. In the burgeoning area of automation, the coupling of different mathematical models, algorithms, and cloud-based programs (Ley-lab example [45], GSK [46], Jensen [28, 35, 47]) has been used to attempt to control and manage continuous-flow processes. Integrating these powerful computing devices and PAT-enabled devices has great potential for streamlining manufacture of hazardous and high-potency compounds [48]. Indeed, the "Holy Grail" in continuous-flow manufacturing would be to link PAT-enabled devices into artificial intelligence software that could not only monitor reaction and process parameters, but also control and optimize conditions when problems with purity or yield are detected. Advancements are however needed in "feed-forward" controls [36] which would alert process scientists before a process failure has actually taken place. This is a superior strategy as the information relayed from a feedback mechanism is received after a batch failure has taken place. Some research has been performed to show how the outcome from a reactor can be temporarily stored until the controller software receives the feedback information, so the main batch can be saved during a process failure [20]. However, the benefits from the information relay loops can be expanded beyond just saving a batch to keeping a continuous manufacturing process uninterrupted by taking advance corrective measures. When a system breach happens somewhere in the flow path of a continuous manufacturing plant, reversal of the failed component is not always hands-free (e.g., a clogged valve). In many cases, these terminal events are preventable if detected in advance. Research is underway to empower feed-forward mechanisms with sophisticated near-future predicting algorithms to prevent such terminal interruptions. More attention should be paid to developing robust analytical devices that can handle all three states of matters and mixtures without failure. Efforts in building such devices with a high degree of chemical tolerance would help increase the chance for the acceptance of such flow-analysis devices as universal PAT tools. A concerted effort from all areas of science and technology could make such a mammoth task, which would truly save a batch before a failure occurred and deliver promised economic profits to the investors in the technology, a reality.

References

1. Bormett, D. High-Potency APIs: Containment and Handling Issues, *Pharm. Technol.* (Sept. 2008, Issue 4), http://www.pharmtech.com/high-potency-apis-containment-and-handling-issues (accessed 21/10/2017).
2. Subramanian, G. *Continuous Processing in Pharmaceutical Manufacturing*; Wiley-VCH: Weinheim, 2015.
3. FDA News Release, *FDA Approves New Treatment for Cystic Fibrosis* (July 2nd 2015), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453565.htm (accessed 21/10/2017).
4. Pharmaceutical Technology Editors, FDA Approves Tablet Production on Janssen Continuous Manufacturing Line, *Pharm. Technol.* (April 12 2016), http://www.pharmtech.com/fda-approves-tablet-production-janssen-continuous-manufacturing-line (accessed 21/10/2017).
5. Trojanowicz, M.; Kołacińska, K. *Analyst* **2016**, *141*, 2085–2139.
6. Sipocz, T.; Lengyel, L.; Sipos, G.; Kocsis, L.; Dormán, G.; Jones, R. V.; Darvas, F. *J. Flow Chem.* **2016**, *6*, 117–122.
7. Negus, M. P.; Mansfield, A. C.; Leadbeater, N. E. *J. Flow Chem.* **2015**, *5*, 148–150.
8. Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *European J. Org. Chem.* **2009**, *3*, 1321–1325.
9. Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15*, 1456.
10. Organ, M. G.; Sauks, J. M.; Mallik, D.; Lawryshyn, Y.; Bender, T. P. *Org. Proc. Res. Dev.* **2013**, *18*, 1310–1314.
11. Trojanowicz, M. *Talanta* **2016**, *146*, 621–640.
12. Estel, L.; Poux, M.; Benamara, N.; Polaert, I. *Chem. Eng. Process. Process Intensif.* **2017**, *113*, 56–64.
13. Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.* **2016**, *116*, 10276–10341.
14. Kim, H.; Dixit, S.; Green, C. J.; Faris, G. W. *Opt. Express* **2009**, *17*, 218–227.
15. U.S. Department of Health and Human Services Food and Drug Administration, *Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (Sept. 2004), https://www.fda.gov/downloads/drugs/guidances/ucm070305.pdf (accessed 21/10/2017).
16. U.S. Department of Health and Human Services Food and Drug Administration. *Development, Pharmaceutical Guidance for Industry Q8(R2)*, **2009**.
17. Moore, C. M. V. *AAPS Annu. Meet.* **2011**.
18. Somerville, K.; Tilley, M.; Li, G.; Mallik, D.; Organ, M. G. *Org. Process Res. Dev.* **2014**, *18*, 1315–1320.
19. Kwak, J. S.; Zhang, W.; Tsoy, D.; Hunter, H. N.; Mallik, D.; Organ, M. G. *Org. Process Res. Dev.* **2017**, *21*, 1051–1058.
20. Tilley, M.; Li, G.; Savel, P.; Mallik, D.; Organ, M. G. *Org. Process Res. Dev.* **2016**, *20*, 517–524.
21. Mcmullen, J. P.; Jensen, K. F. *Org. Process Res. Dev.* **2010**, *14*, 1169–1176.
22. McMullen, J. P.; Jensen, K. F. *Org. Process Res. Dev.* **2011**, *15*, 398–407.
23. Reizman, B. J.; Jensen, K. F. *Acc. Chem. Res.* **2016**, *49*, 1786–1796.
24. Newton, S.; Carter, C. F.; Pearson, C. M.; De, L. Alves, C.; Lange, H.; Thansandote, P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 4915–4920.
25. Carter, C. F.; Lange, H.; Ley, S. V.; Baxendale, I. R.; Wittkamp, B.; Goode, J. G.; Gaunt, N. L. *Org. Process Res. Dev.* **2010**, *14*, 393–404.
26. Mitic, A.; Cervera-Padrell, A. E.; Mortensen, A. R.; Skovby, T.; Dam-Johansen, K.; Javakhishvili, I.; Hvilsted, S.; Gernaey, K. V. *Org. Process Res. Dev.* **2016**, *20*, 395–402.
27. Foley, D. A.; Doecke, C. W.; Buser, J. Y.; Merritt, J. M.; Murphy, L.; Kissane, M.; Collins, S. G.; Maguire, A. R.; Kaerner, A. *J. Org. Chem.* **2011**, *76*, 9630–9640.
28. Fabry, D. C.; Sugiono, E.; Rueping, M. *React. Chem. Eng.* **2016**, *1*, 129–133.
29. U.S. Department of Health and Human Services Food and Drug Administration Guidance for Industry. *Data Integrity and Compliance with CGMP Guidance for Industry*, **2016**.
30. *Siemens Application Note-91819 Petrochemical Industry Ethylene Plant*, **2016**.

31. Smith, D.; Španěl, P. *Mass Spectrom. Rev.* **2005**, *24*, 661–700.
32. Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; et al. *Science (80-.)* **2016**, *352*, 61–67.
33. Cardoso, F. S. P.; Mickle, G. E.; Da Silva, M. A.; Baraldi, P. T.; Ferreira, F. B. *Org. Process Res. Dev.* **2016**, *20*, 306–311.
34. Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**, *48*, 349–362.
35. Sans, V.; Cronin, L. *Chem. Soc. Rev.* **2016**, *45*, 2032–2043.
36. Woodcock, J. *MIT-CMAC Int. Symp. Contin. Manuf. Pharm*. **2014**.
37. Lévesque, F.; Seeberger, P. H. *Org. Lett.* **2011**, *13*, 5008–5011.
38. Cole, K. P.; Groh, J. M.; Johnson, M. D.; Burcham, C. L.; Campbell, B. M.; Diseroad, W. D.; Heller, M. R.; Howell, J. R.; Kallman, N. J.; Koenig, T. M.; et al. *Science (80-.)* **2017**, *356*, 1144 LP-1150.
39. (a) Price, G. A.; Hassan, A.; Bogdan, A. R.; Djuric, S. W.; Organ, M. G. *Angew. Chem., Int. Ed.* **2017**, *56*, 13347–13350; (b) Price, G. A.; Bogdan, A. R.; Aguirre, A. L.; Iwai, T.; Djuric, S. W.; Organ, M. G. *Catal. Sci. Technol.* **2016**, *6*, 4733–4742.
40. Cole, K. P.; Campbell, B. M.; Forst, M. B.; McClary Groh, J.; Hess, M.; Johnson, M. D.; Miller, R. D.; Mitchell, D.; Polster, C. S.; Reizman, B. J.; Rosemeyer, M. *Org. Process Res. Dev.* **2016**, *20*, 820–830.
41. Lam, K. F.; Cao, E.; Sorensen, E.; Gavriilidis, A. *Lab Chip* **2011**, *11*, 1311–1317.
42. Feist, P.; Hummon, A. B. *Int. J. Mol. Sci.* **2015**, *16*, 3537–3563.
43. Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.
44. U.S. Department of Health and Human Services Food and Drug Administration Drug Safety Priorities Initiatives and Innovation, **2015**.
45. Fitzpatrick, D. E.; Battilocchio, C.; Ley, S. V. *Org. Process Res. Dev.* **2016**, *20*, 386–394.
46. Keles, H.; Susanne, F.; Livingstone, H.; Wade, C.; Bourdon, R. E.; Rutter, A. *Org. Prep. Proced. Int.* **2017**, 10.1021/ac, DOI 10.1021/acs.oprd.7b00245.
47. Reizman, B. J.; Jensen, K. F. *Org. Process Res. Dev.* **2012**, *16*, 1770–1782.
48. Thomson, N. M.; Singer, R.; Seibert, K. D.; Luciani, C. V.; Srivastava, S.; Kiesman, W. F.; Irdam, E. A.; Lepore, J. V.; Schenck, L. *Org. Process Res. Dev.* **2015**, *19*, 935–948.