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Small-volume continuous manufacturing of merestinib part II: technology transfer and cGMP manufacturing

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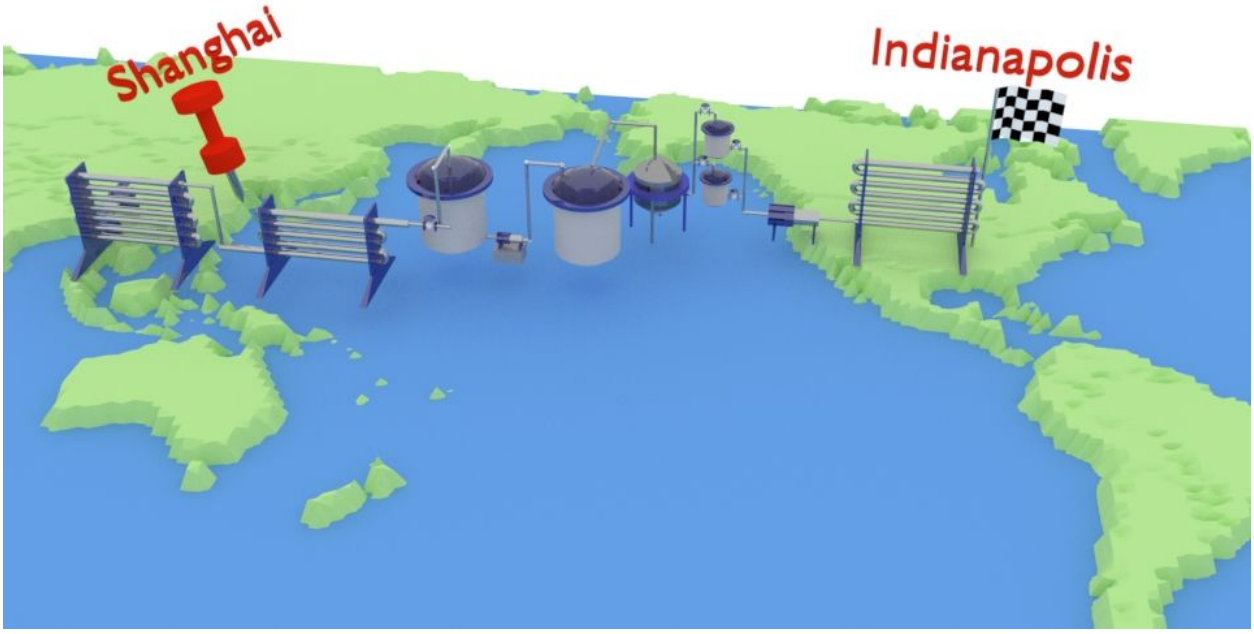
TOC GRAPHIC



ABSTRACT

Technology transfer of a small volume continuous (SVC) process and Current Good Manufacturing Practices (cGMP) manufacturing of merestinib are described. A hybrid batch-SVC campaign was completed at a contract manufacturing organization under cGMP. The decision process by which unit operations were selected for implementation in flow for the cGMP campaign is discussed. The hybrid process comprised a Suzuki-Miyaura cross-coupling reaction, a nitro-group hydrogenolysis, a continuous amide bond formation, and a continuous deprotection. A continuous crystallization using two mixed suspension, mixed product removal (MSMPR) crystallizers and a filtration with *in situ* dissolution were employed for purification between the two SVC steps. Impurity levels were monitored using both online process analytical technology (PAT) and offline measurements. The continuous processing steps operated uninterrupted for 18 days to yield in-solution drug substance at a throughput of 12.5 kg/day. Crystallization in batch mode afforded 183 kg of in-specification drug substance. Success of the campaign was attributed to robustness of the control strategy and to the multi-year partnership in continuous manufacturing between the development organization and the contract manufacturer. Key learnings are offered from the perspectives of both the development organization and the contract manufacturer.

KEYWORDS

continuous processing, small volume continuous, flow chemistry, continuous crystallization, scale-up, flow-NMR

INTRODUCTION

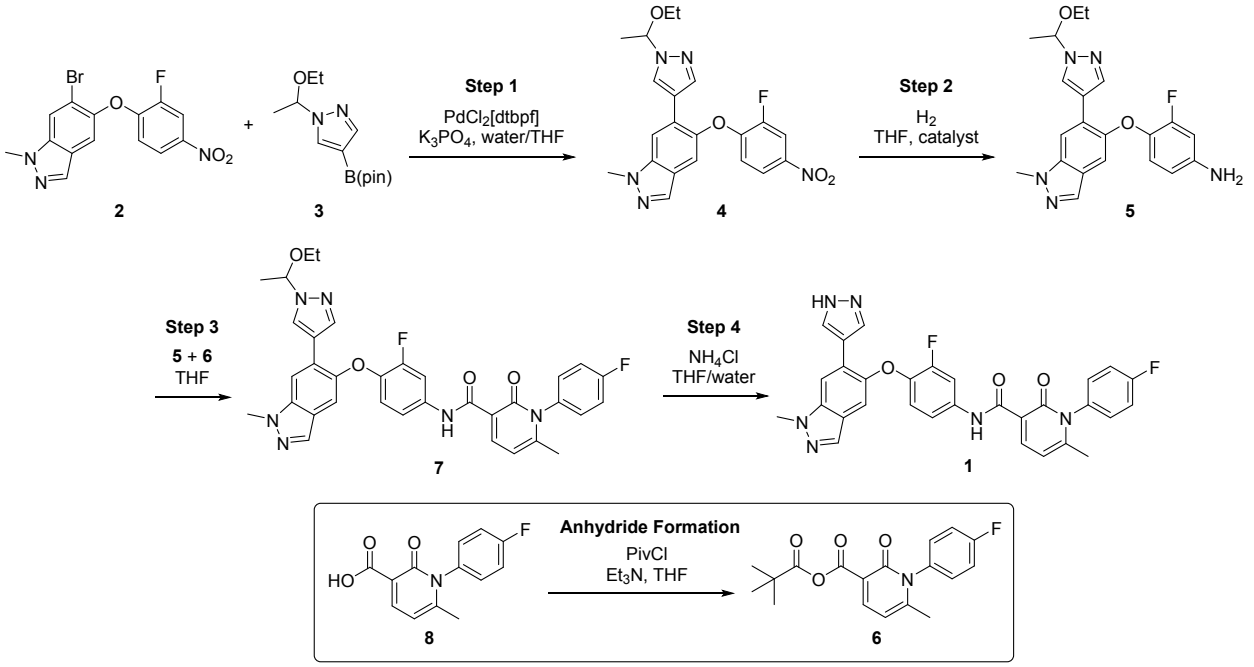
Continuous manufacturing (CM) is a maturing technology that is finding increased usage globally among pharmaceutical manufacturing organizations.[1,2,3,4,5,6,7] The transition toward CM has been motivated by the need to enable faster, more exothermic, and/or greener chemical transformations in pharmaceutical synthesis, by the ability to reduce process footprint using an emerging suite of intensified unit operations, and by the increased process insights brought about by more extensive use of process analytical technology (PAT) in the control of product quality.[8,9,10] As newer, 21st Century pharmaceutical manufacturing facilities are constructed, it is anticipated that there will be motivation to reduce capital costs by replacing larger equipment for batch processing with leaner, more modular equipment for CM.[11]

In the past 10–15 years, there has been a shift toward the broader use of contract manufacturing organizations (CMOs) in pharmaceutical manufacturing,[12] driven prominently by cost pressures in the pharmaceutical industry[13,14,15] and by the emergence of low cost cGMP manufacturing partners in India and in China.[16] Assuming that the trend toward increased utilization of CM technology in pharmaceutical syntheses continues, it is of growing importance that CMOs gain familiarity with CM technology. Since the manufacture of early developmental products is frequently outsourced, it is advantageous to be able to conduct flow unit operations at CMOs in order to install enabling chemistry or separations early in the product lifecycle. Having a CM-capable CMO network also helps sustain the global supply chain of pharmaceutical compounds and intermediates, lessening risk that compounds constructed from transformations that are unamenable to batch processing incur production delays when the demand for continuous processing technology exceeds internal capacity.

As the reliance on CM increases, the success of chemistry, manufacturing, and controls development for pharmaceutical production will be contingent on delivery of a control strategy that leverages the strengths of CM, while accounting for the challenges added by process intensification. The U.S. Food and Drug Administration has commented on the role of CM in implementation of a control strategy, citing the importance of understanding process dynamics in the ability to control quality attributes.[17] These challenges associated with the dynamics of the process include design for startup and shutdown operations, mitigation of process disturbances, and the need for

material diversion strategies. For manufacturing organizations entering into CM, addressing these technical challenges may introduce additional operational challenges, including the need to manage and monitor richer sets of process data, the need for around-the-clock campaign staffing, and the need for real-time or nearly real-time analytical feedback to confirm that the process is in a state of control. Collaboration between development and manufacturing organizations is imperative to ensure successful technology transfer and product quality throughout production.[12]

In Part I of this publication, Lilly described development of a process for the small volume continuous (SVC) manufacturing of merestinib (**1**, LY2801653, Scheme 1).[18] In the route presented in Part I (Scheme 1), the Suzuki-Miyaura cross-coupling between bromide **2** and pyrazole **3** generated nitro-compound **4** (Step 1), which underwent hydrogenolysis to afford the aniline **5** (Step 2). Addition of mixed anhydride **6** to aniline **5** afforded the amide **7** (Step 3), which finally underwent deprotection in a heated flow reactor to afford **1** (Step 4).



Scheme 1. Synthesis of merestinib.

Following a successful 20 kg process demonstration, a team of Lilly chemists and engineers was afforded approximately six months to orchestrate technology transfer of the continuous process to a CMO for delivery of more than 125 kg cGMP drug substance (DS) suitable for Phase 3 clinical trials. Given the abbreviated timeline for technology transfer, the Lilly team elected to adapt the demonstrated fully continuous process to operate as a hybrid batch-continuous process at the CMO. Summarized in Table 1, the team's decisions to convert CM unit operations to batch mode were made based upon the intended process control strategy for the cGMP campaign and the robustness of the unit operations at this stage of process development. Step 1, which was operated during the CM demonstration in a repeating batch mode for the Suzuki-Miyaura cross-coupling reaction, was readily converted to a fully batch process, which reduced the overall technological and logistical complexity of implementing the cGMP sequence at the CMO. Perceived challenges in delivering aniline **5** from the hydrogenolysis reaction in a continuous reactor within an abbreviated timeline contributed to the team's decision to also execute the Step 2 hydrogenolysis in batch mode. Discussed in Part I,[18] these challenges associated with continuous hydrogenolysis technology at the time included lack of development time to characterize catalyst bed life, the high dilution required to achieve a homogeneous feed stream, the criticality of adjusting process conditions to control for purity, and occasional episodes of reactor fouling. Operation in batch mode also decoupled the process cycle time for Step 2 from the throughput of the downstream continuous unit operations, and thus the hydrogenolysis reaction time could be lengthened on the basis of in-process control (IPC) sampling.

Table 1. Chosen modes of operation for cGMP campaign.

Process Step	*Implementation for cGMP Campaign*	*Rationale*
Step 1	Batch	Ease of implementation of existing process in batch mode
Step 2	Batch	Complexity of rapid transfer of continuous reactor to CMO Ability to extend reaction time in batch mode based on IPC

Step 3	Continuous	Demonstration of impurity control strategy under cGMP
Step 4	Continuous Reaction	High temperature / pressure needed to enable reaction.
	Batch Crystallization	Insufficient capacity for CM crystallization at CMO
	Batch Isolation	Preference for clearly delineated batch size, quantity

Critical to the process impurity control strategy was suppression in the DS of process intermediates **4** and **5**, as well as the many process impurities potentially introduced during hydrogenolysis. Design of the batch process for Step 2 was conducted with the goal of controlling for indazole **4** and any hydrogenolysis impurities in the resulting aniline **5**. Control of the aniline **5** was then dependent on the process design in Step 3, namely assurance of near-complete consumption of **5** in the Step 3 reaction and precise control over the Step 3 crystallization to afford consistent rejection of any unreacted **5**. The opportunity presented by CM to minimize process variability in the unit operations in Step 3 motivated the Lilly team's decision to operate this step fully in continuous mode. The Step 4 deprotection reaction was designed to operate at high temperature and pressure[19] and was also operated in continuous mode. For the DS crystallization, impurity rejection was shown in the earlier process demonstration to be comparable between batch and continuous modes; however the DS crystallization kinetics were slow such that long processing times were necessary to achieve high product yields. In lieu of installing more and/or larger crystallization vessels for the CM process, the DS workup and crystallization were chosen to operate in batch mode. This decision also allowed for clear delineation of DS batches from the hybrid batch/continuous process.

STA Pharmaceutical was selected for cGMP production of **1** using the hybrid process. In advance of this selection, Lilly had partnered with STA for approximately three years to strengthen STA's position in CM. This collaboration included visits of STA scientists to Lilly to

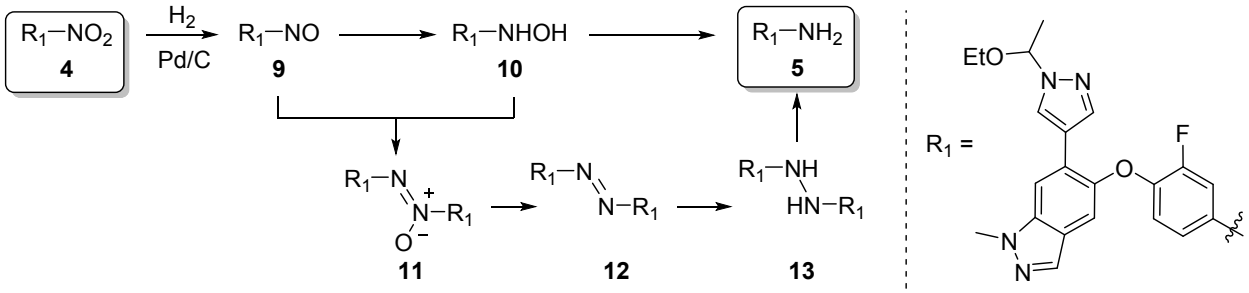
learn and train on the use of CM equipment at both development and commercial manufacturing scale, and led to the development of subject matter experts in flow chemistry and engineering at STA that communicated regularly with Lilly scientists on CM. Lilly also sited multiple early-phase projects at STA that leveraged CM. Even with these prior successes, the installation of a multi-step continuous process at STA was found to require even more dedication and collaboration between Lilly and STA to ensure that the project would be staffed by trained personnel for several weeks of around-the-clock operation, including both preparation and campaign activities. Activities also included installation of PAT and process automation when deemed most critical, configuration of new equipment, and development of a control strategy and batch record consistent with STA's quality system.

This publication summarizes the development activities at Lilly and STA that culminated in the organizations' collective ability to deliver cGMP material suitable for Phase 3 clinical trials. Technology transfer of a hybrid batch/continuous version of the process to STA was completed to produce 183 kg of **1** under cGMP manufacturing, including operation of the two continuous steps for 18 days at a throughput of 12.5 kg DS/day (prior to batch crystallization of the DS). Conclusions cite learnings from both Lilly and STA regarding the successful transfer of a multi-step continuous process.

CONTROL STRATEGY DEVELOPMENT

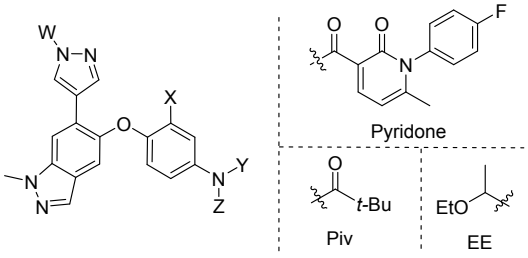
The control strategy for the hybrid cGMP process considered development knowledge acquired before and during the SVC process demonstration (discussed in Part I)[18] in concert with the introduction of batch processes for Steps 1 and 2. As discussed in Part I, the placement of the hydrogenolysis step in the synthetic route in Scheme 1 necessitated significant modifications to the process control strategy in preparation for the cGMP campaign. Most noteworthy were the many impurities to be controlled at or prior to the DS. Reduction of **4** to the aniline **5** was known to proceed through the pathway in Scheme 2, generating intermediates nitroso **9**, hydroxylamine **10**, azoxy **11**, azo **12**, and hydrazo **13**.[20,21,22] Other process impurities generated during the hydrogenolysis or in forward processing of hydrogenolysis intermediates to the amide bond formation step are listed in Table 2. Under certain processing conditions,

reduction leading to loss of the fluoro substituent (**14**) and/or the ethoxy-ethyl protecting group (**15**) on **5** were observed. Importantly, process intermediate **5** and process impurity **15** were potential genotoxic impurities (GTIs) and were controlled to a target of less than 80 ppm in the DS for the hybrid cGMP campaign. Additional hydrogenolysis impurities included ethyl-adduct **16**, which formed from reaction of **5** with acetaldehyde from the cleaved ethoxy-ethyl protecting group, and hydroxybutyl adduct **17**, which formed as a byproduct with the use of tetrahydrofuran (THF) as the solvent. Forward processing of hydroxylamine **10** was observed to generate the hydroxamic acid **18**. Likewise, forward processing of **14** afforded defluorinated amide impurity **19**. Impurity **15** had the potential to undergo a second amide bond formation reaction in Step 3 to generate either the bisamide **20** or the pivaloyl-adduct **21**. Pivalamide **22** was a potential byproduct from reaction of **5** with anhydride **6** or acid **8**.



Scheme 2. Hydrogenolysis intermediates and process impurities.

Table 2. Other key process impurities.



Process Impurity	*Formation Conditions*	*W*	*X*	*Y*	*Z*

14	Defluorination of **5**	EE	H	H	H
15	EE deprotection during hydrogenolysis	H	F	H	H
16	Reductive amination (**5** + acetaldehyde)	EE	F	H	CH_2CH_3
17	Reaction in presence of THF	EE	F	H	$(CH_2)_4OH$
18	Acylation of **10**	EE	F	OH	Pyridone
19	Amidation of **14**	EE	H	H	Pyridone
20	Di-acylation of **15**	Pyridone	F	H	Pyridone
21	Di-acylation of **15**	Piv	F	H	Pyridone
22	Pivalamide formation	EE	F	H	Piv

Crystallization for impurity control at Step 2 was avoided because of the containment needed for isolation of the potential GTI **5**. Likewise, prior development work indicated that a single crystallization of the amide **7** would be sufficient to achieve impurity targets, and thus it was preferred to use crystallization at Step 3 as the primary rejection point for all hydrogenolysis-derived impurities. This necessitated extensive fate and purge experiments for Step 3, as well as the DS crystallization at Step 4. Impurity purge data from the Step 3 and Step 4 crystallizations informed the Step 2 end-of-reaction targets for all hydrogenolysis-derived impurities and the nitro intermediate **4**. A set of preliminary batch crystallization studies explored the rejection of potential Step 2 and Step 3 process impurities. These impurities were spiked into the Step 3 crystallization in batch mode in three experiments to confirm that the rejection of the impurities was constant in the region of interest. The experiments included (i) a seeded isothermal batch crystallization at 20 °C, (ii) a seeded isothermal batch crystallization at 50 °C, and (iii) a final seeded isothermal batch crystallization at 50 °C, wherein the impurity levels were adjusted to satisfy proposed impurity tolerance levels and to account for any reduced rejection efficiency in the multi-component mixture. The spiked impurity levels are provided in Figure 1a. As shown in Figure 1b, rejection efficiencies of the tested

impurities did not vary significantly with temperature or with the change in initial concentration at 50 °C. Rejection efficiencies in excess of 60% were observed for all impurities except **18**, **19**, **20**, and **21**.

Crystallization of an impurity-rich Step 3 reaction solution was repeated in continuous mode using a series of two 250 mL baffled mixed suspension, mixed product removal (MSMPR) crystallizers. This laboratory-scale MSMPR crystallization system has been described previously.[23] The same three impurity-rich product solutions prepared for the batch crystallization studies were assessed in these studies. The antisolvent (cyclohexane) and solution of the intermediate **7** were each fed to the first of the two MSMPR crystallizers. Isothermal crystallization conditions, with both MSMPR crystallizers operating at 20 °C and with 4 h mean residence time, were originally selected because a continuous cooling crystallization was known to introduce additional risk of solids fouling in the transfer lines between crystallizers. As shown in Figure 1c, the isothermal procedure resulted in relatively poor rejection of many impurities in comparison to batch mode. Upon increase of the temperature of the first MSMPR crystallizer to 50 °C (while maintaining a temperature of 20 °C in the second crystallizer), impurity rejection was observed to greatly improve. Use of a combined antisolvent and cooling continuous crystallization afforded high rejection efficiency for many significant process impurities, including >90% rejection of the aniline **5**. Similarly to the results in batch mode, poorer rejection efficiencies were observed for **18**, **19**, **20**, and **21**. Further repetition of the cooling crystallization procedure with adjusted impurity levels revealed all rejection efficiencies to be nearly unchanged at the spiking level of interest. (Note that impurities **13** and **18** were not included in this final experiment.) Based on these extensive impurity rejection studies, it was decided for the cGMP campaign to operate the Step 3 continuous crystallization under non-isothermal conditions despite the added risk of solids fouling in the transfer lines between the two MSMPR crystallizers. Re-dissolved Step 3 intermediate **7** obtained from the spiking study was forward processed through the final deprotection step to confirm acceptable purity of the DS following a batch workup and isolation procedure. Based on the collective results of these fate-and-purge studies, in-process limits for key impurities were established for the cGMP campaign.

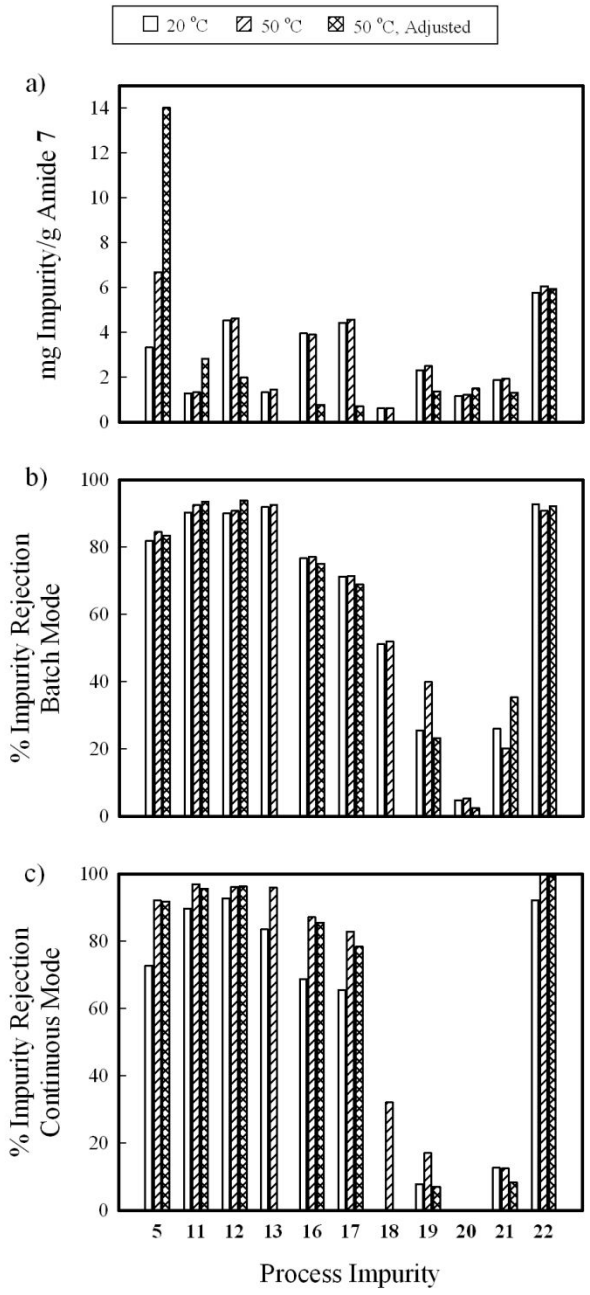


Figure 1. Impurity rejection study for Step 3 crystallization development. (a) Impurity spiking levels relative to amide **7**. (b) Percent impurity rejection for seeded, isothermal batch crystallization. (c) Percent impurity rejection for continuous crystallization with the first MSMPR crystallizer at 20 °C or 50 °C and the second MSMPR crystallizer at 20 °C.

Development for the hydrogenolysis focused on identification of batch processing conditions that would deliver aniline intermediate **5** with all Step 2 impurities controlled to below their target levels. Initial batch hydrogenolysis screening experiments were conducted at 250 mg scale with a Biotage® Endeavor using 5% Pd/Al_2O_3 (Johnson Matthey® A-302099-5 and A-302011-5), 5% Pd/C (Johnson Matthey® A503023-5 and A405028-5), and 5% Pd(S)/C (Johnson Matthey® A103023-5) catalysts. Promising screening conditions were then tested at a 5 g scale in a Parr® autoclave (results in Table 3). The THF charge was limited to 50 mL for the scale-up experiments (compared to approximately 150 mL for full solubility of **4** at room temperature); consequently the potential for formation of solvent-related impurities was proportionally reduced relative to the continuous process. From Table 3, hydrogenolysis conditions employing 5% Pd/C (A503023-5) were found to promote the greatest selectivity toward aniline **5** while offering acceptable control of defluorinated **14** and the hydrogenolysis intermediates, with the exception of hydroxylamine **10**. As a reaction intermediate, control of **10** could be facilitated in batch mode by extending the Step 2 reaction time (if necessary) based on IPC end-of-reaction results.

Table 3. UHPLC analysis of Step 2 hydrogenolysis reaction conducted at 5 g scale in Parr® autoclave. All experiments were conducted at 8 bar and in 50 mL THF. N.D. = not detected by UHPLC (LOQ 0.05%).

Experiment	*1*	*2*	*3*	*4*	*5*
Catalyst	A503023-5 (Pd/C)	A302011-5 (Pd/Al_2O_3)	A302099-5 (Pd/Al_2O_3)	A302011-5 (Pd/Al_2O_3)	A302011-5 (Pd/Al_2O_3)
Catalyst Loading	5 wt%	5 wt%	5 wt%	5 wt%	1 wt%
Temperature	50 °C	50 °C	30 °C	30 °C	30 °C
Product Purity	99.65%	99.10%	99.50%	99.50%	98.24%
Impurities					
10	0.05%	0.09%	0.08%	0.09%	N.D.
11	N.D.	0.12%	N.D.	N.D.	N.D.
12	N.D.	N.D.	N.D.	N.D.	0.38%

13	N.D.	N.D.	0.08%	N.D.	0.81%
14	0.09%	0.16%	0.10%	0.10%	0.07%
15	0.08%	N.D.	0.08%	0.11%	0.05%

For the 5% Pd/C catalyst system, the impact to changes in processing parameters was investigated *via* in-process monitoring with the use of ^{1}H and ^{19}F NMR. Information on the NMR experimental configuration can be found in the Supporting Information, as well as in previous publications that have described the in-process NMR method and its application to measurement of mass transfer rates.[24,25] Manipulated conditions in the in-process NMR experiments included changes to catalyst loading, pressure, temperature, reaction concentration, catalyst lot, reaction additives, oxygen levels, and agitation rate. Impurities **14** and **15** were found to be well-controlled within the range of conditions tested. Impurities **12** and **13** formed more prominently under low mass transfer or low catalyst loading conditions, where the primary pathway to aniline formation became disfavored. Residual sulfur, which could enter into Step 2 from the palladium removal unit operation in Step 1, was confirmed as a catalyst poison and also resulted in formation of higher levels of **12** and **13** due to higher *in situ* content of hydroxylamine **10**. Longer reaction times and lower concentrations of **4** led to more elevated levels of the hydroxybutyl adduct impurity **17**.

Using the NMR data, a kinetic model was developed that allowed for selection of suitable processing conditions that would control the defluorinated impurity **14** and hydrogenolysis intermediates to acceptable levels. The model included catalyst deactivation kinetics and was used to understand the feasible operating region, normal operating ranges and proven acceptable ranges, and to assess criticality. To lessen the risk of generating impurities **12** and **13**, the optimized cGMP process was designed to produce **5** in 30 kg batches at 45 °C and 8 bar, using 3 wt% Pd/C (5%, A503023-5). The optimized batch process afforded the aniline **5** in ≥99.7% purity in lab-scale

demonstrations, with process impurity **14** controlled to ≤0.05 area% and all hydrogenolysis reaction intermediates controlled to the limit of quantitation (LOQ) of 0.05 UHPLC area%.

The aniline intermediate **5** was to be controlled by ensuring sufficient conversion in the Step 3 amide bond formation reaction, such that any unreacted **5** would be purged to an acceptable level in the Step 3 crystallization. Kinetics for the consumption of aniline **5** in the amide bond formation reaction were determined in batch mode.[26] In comparison to the non-GMP CM demonstration campaign,[18] the robustness of the Step 3 reaction in suppressing the impurity **5** was improved by increasing the target feed stoichiometry of the anhydride **6** to 1.10 equiv. (justified by the crystallization fate-and-purge results for the acid **8** and the anhydride **6**) and by extending the reaction time in the PFR to 140 min. The cGMP Step 3 reactor was divided into two stages: a 9 L segment and a 5 L segment, corresponding to 90 min and 50 min residence time, respectively, at the intended cGMP campaign flow rates. Acceptable progress of the reaction after 90 min was assessed using online HPLC, installed between the two PFR stages. At 60 °C, a reaction time of 90 min was sufficient to achieve less than 0.1 HPLC area% of **5** in the product stream. The second, 5 L stage of the Step 3 reactor was sized to account for a lag period of 50 min to allow time for material diversion in response to the HPLC analysis prior to the crystallization.

The robustness of the Step 4 deprotection reaction was evaluated in laboratory flow reactor experiments using a 2.5 mL PFR heated inside of a gas chromatography oven. A univariate study of reaction temperatures demonstrated that acceptable product purity of ≥99.8% could be achieved between 150–185 °C. Hydrolysis of the DS **1** to aniline impurity **15** was also monitored in these flow reactor robustness experiments, and it was found that at 170 °C the impurities **5** and **15** would be controlled to acceptable levels for reaction times of less than 5 h. To afford the targeted crystal form in batch mode, the workup strategy from Part I was modified to include concentration of the DS **1** product solution, followed by the introduction of cyclohexane to induce a layer separation in the THF/water system. THF and DMSO were then added to the organic solution, and the solution was concentrated to afford **1** in the THF/DMSO solvent identified in Part I.[18] This workup strategy contributed to removal of the reaction byproduct acetaldehyde to <50 ppm in the DS. A

seeded, cooling crystallization with the antisolvent ethanol afforded the desired crystal form. The robustness of this workup procedure was assessed by imposing univariate process disturbances and assessing the multi-component product mixture for composition by quantitative NMR. The robustness of the DS crystallization in delivery of the target crystal form was also evaluated through a series of experiments that tested the seed point, cooling rate, and perturbations to the solution composition including high and low levels of water, DMSO, cyclohexane and the DS **1**.

PAT Strategy and Batch Record Development

In addition to kinetic and thermodynamic process understanding that had been gained through development, the control of product quality was to be ensured based on an analytical strategy and a batch record strategy that verified the process to be operating in the intended state of control. Performance in Steps 1 and 2 was evaluated based on offline UHPLC, LC-MS, and ICP-MS analysis of the product of each step. The analytical strategy for the continuous steps of the process was reliant on a combination of online process analytical technology (PAT) measurements and offline measurements. Online HPLC was installed after the first stage of the Step 3 reactor to monitor conversion of aniline **5** to amide **7** every 30 min. Using the reaction kinetic model and the measured rejection efficiency of the aniline **5**, an acceptable operating range for the process was established as a function of magnitude and duration of a disturbance in the Step 3 reaction purity. The established operating range then informed decisions based on the Step 3 online HPLC results that would instruct the operator to: (i) continue processing, (ii) adjust the feed rates of **5** and **6**, or (iii) divert the reactor outflow prior to the crystallization. These protocols for process manipulations in response to analytical testing were included in the batch record, along with acceptable ranges for mass flow rates, temperatures, pressures, and liquid fill levels that were monitored on an hourly basis. Following the in-process crystallization of the amide **7**, the re-dissolved solution of **7** was analyzed offline every 8 h by LC-MS to confirm that potential GTIs **5** and **15** were both below their respective in-process limits. Because of the risk of formation of **15** from hydrolysis under the thermal

deprotection conditions, the Step 4 reaction effluent was also monitored offline every 8 h by LC-MS to confirm that both aniline impurities were below their in-process limits prior to the DS crystallization.

To accommodate for process dynamics, the batch record for the continuous process was divided by unit operation into separate procedures for sequential and repeating operations. Sequential operations included procedures for startup, shutdown, filtration and dissolution, and process pauses and restarts. Once sequential operations were completed, operators transitioned to a "state-of-control" section of the batch record, where they were instructed to repeat a set of operations at a pre-defined frequency. Tolerances on operating conditions in the batch record were specified within less than the acceptable ranges for the process, such that minor departures from the target range could be corrected without the need for material diversion. Departures from the target operating range with the potential to impact product quality or process safety were explicitly referenced in the batch record. These types of occurrences would have directed operators to a process pause procedure that identified any requirements for material diversion. A limitation of this batch record strategy was that the paper batch record had to be subdivided so that operators could perform multiple tasks at or near the same time on different unit operations. Implementation of an electronic batch record that would alert operators of when tasks were due to be performed would have greatly simplified the activity of batch record maintenance.

CM Equipment Transfer

The equipment build for the continuous process leveraged both existing equipment at STA and newly-fabricated equipment sourced through D&M Continuous Solutions, LLC (Indianapolis, IN). The design and testing of the equipment from D&M was performed with close involvement of the Lilly team. This saved considerable time and provided the team with confidence that the equipment would operate as intended when transferred externally. Automated sequences were configured and tested at Lilly before electronic transfer of the software to STA and installation on local programmable logic controllers (PLCs). Along with the equipment transfer, D&M and Lilly personnel traveled to the Jinshan, China, site to assist the STA team with equipment installation and basic training. STA purchased the Lilly-

designed equipment from D&M and was responsible for equipment qualification. Lilly provided on-site support at STA for equipment installation, 10 days of solvent trials, and throughout the duration of the CM portion of the hybrid cGMP campaign.

A flow chart illustrating the CM unit operations in the hybrid cGMP campaign is provided in Figure 2. Select equipment photographs for Step 3 are provided in Figure 3, and additional photographs and operating procedures can be found in the Supporting Information. The sequencing of unit operations for Steps 3 and 4 was the same as in the non-GMP CM laboratory demonstration campaign.[18] Select changes were made to the process and equipment design for both steps to address findings from the process demonstration. The continuous process was operated to produce 15 kg/day of **7** from the Step 3 reaction and 12.5 kg/day of **1** from the Step 4 reaction.

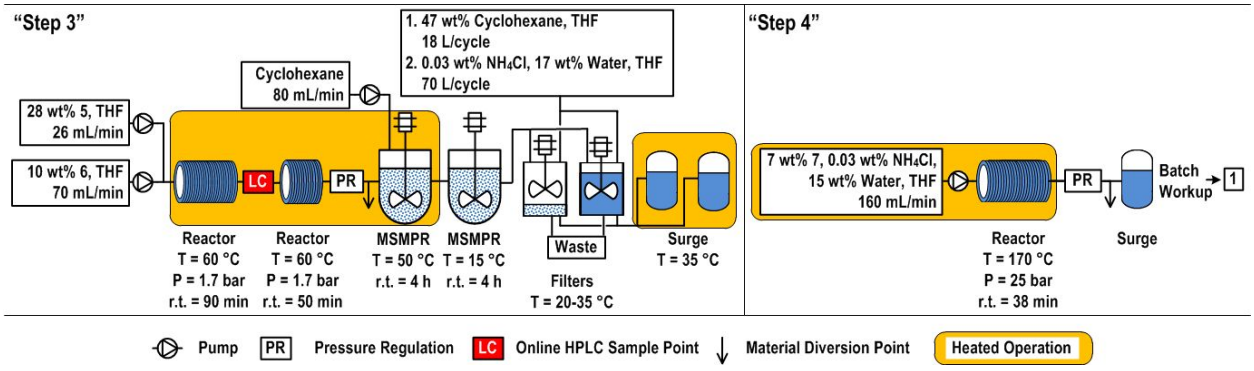


Figure 2. Flow chart illustrating the CM portion of the cGMP production campaign.

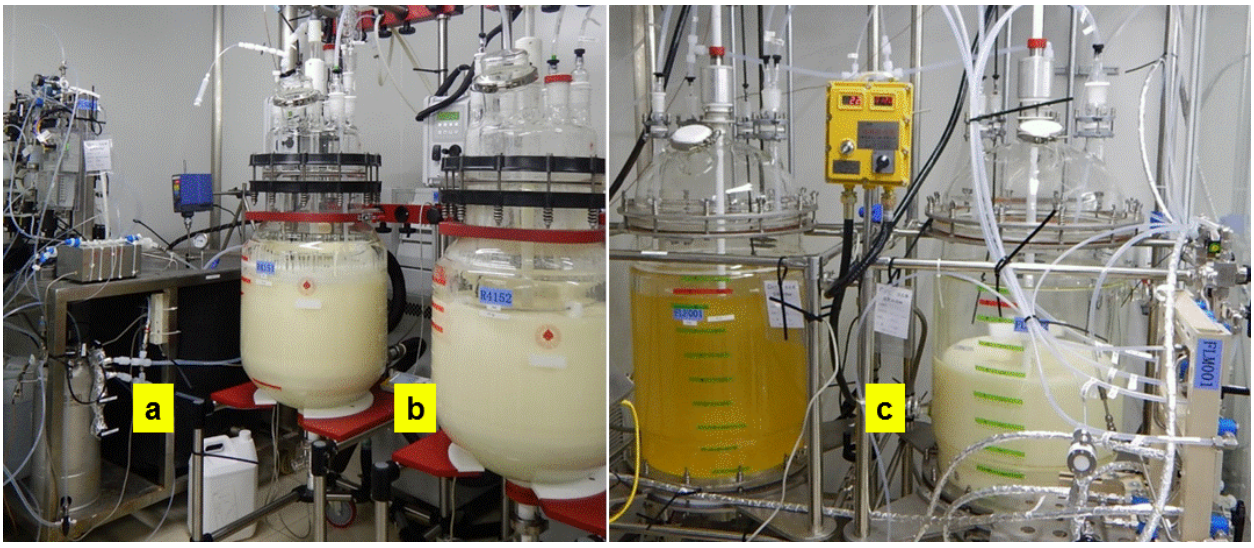


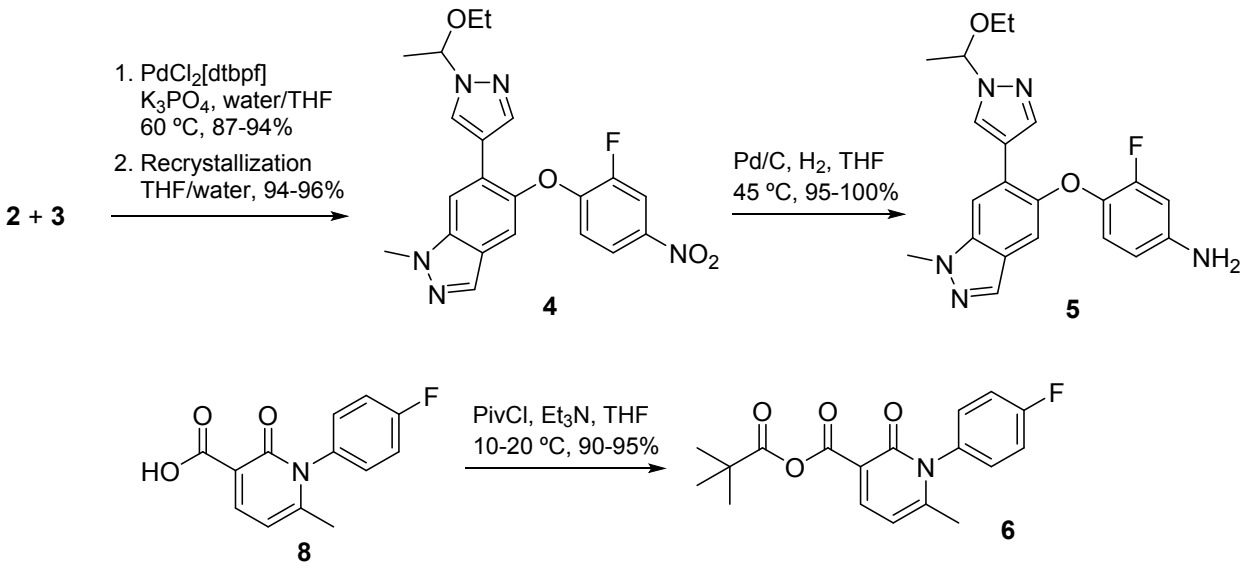
Figure 3. CM unit operations for cGMP campaign Step 3. (a) two-stage PFR (submerged in heated bath) with online HPLC; (b) MSMPR crystallizers; (c) filters.

Feed solutions containing aniline **5** and anhydride **6** in THF were dynamically mixed using a series of magnetically-driven stir bars in a tube[27] and charged to the series of PFRs, which were submerged in a heated water bath operating at 60 °C and 1.7 bar. To improve control for stoichiometry at Step 3, Coriolis mass flow controllers (Micro Motion) were installed and configured with the peristaltic pumps (Masterflex L/S) and a PLC to enable feedback control of the feed rates of aniline **5**, anhydride **6**, and the antisolvent cyclohexane. The installation of feedback controllers offered a significant improvement in flow rate regulation compared to previous Lilly processes employing similar peristaltic pumps which, without a controller, required routine calibration to prevent drift over time. Product solution exiting the PFRs was transferred through a heated transfer line at 50 °C into the first of two 50 L MSMPR crystallizers, which operated at 50 °C and 15 °C, respectively. Cyclohexane was added to the first MSMPR crystallizer. Slurry was intermittently transferred from the first to the second MSMPR crystallizer and then was intermittently transferred to one of two parallel agitated 100 L jacketed filters. The frequency and volume of transfers was such that both MSMPR crystallizers operated with a mean residence time of 4 h. Accumulated slurry on either filter was continually stirred and cooled to below 20 °C. Sustained cooling ensured impurity control consistent with that demonstrated in the laboratory two-stage MSMPR crystallizer system and resulted in greater yield of **7** compared to the earlier non-GMP CM process demonstration. After 8 h of accumulation, the slurry was filtered, washed with a 50:50 mixture of THF/cyclohexane, and then dissolved *in situ* in a solution of 85:15 v/v THF/water with 5.0 mol% NH_4Cl. Unlike the previous non-cGMP process demonstration, all filtration operations in the cGMP campaign were performed manually, and vacuum (rather than pressure) was used to deliquor the wet cake. The dissolved solution was heated to 35 °C to maintain solubility of the intermediate **7** and transferred to one of two jacketed surge vessels.

At Step 4, feed solution containing the intermediate **7** was pumped and warmed to greater than 100 °C in a series of three heat exchangers. This solution then continuously flowed into a 7.2 L Hastelloy C276 PFR. This PFR was maintained at 25 bar and was heated to 170 °C within a 1 m^3 electric oven. Prior to use, the PFR was tested with pressurized nitrogen to confirm that it was sealed with no leaks, and pressure relief valves were installed that would divert material to waste in the event of over-pressurization to 100 bar (significantly less than the rated pressure of the PFR and connections). The reactor temperature and pressure were continuously recorded using a PLC and monitored as part of the hourly process inspection. Reaction solution was passed through the reactor for a residence time of 38 min, cooled in flow through a series of heat exchangers, and then collected in drums that were supplied as feed to the DS batch workup and crystallization.

cGMP CAMPAIGN

The synthetic route used in the cGMP campaign for Steps 1 and 2 and the preparation of anhydride **6** is summarized in Scheme 3. Scale-up for the Suzuki cross-coupling reaction proceeded without event, but use of sodium diethyldithiocarbamate for metal treatment proved challenging. The workup sequence included washing the organic layer with carbamate solution followed by layer separation, polish filtration to remove precipitated metal complex, partial concentration by solvent distillation, and antisolvent and cooling crystallization. It was found that two of the three isolated batches of indazole **4** contained high residual sulfur levels, which proved detrimental to the subsequent hydrogenolysis during use testing. Similar sulfur contamination had only been observed during development if the concentration step was taken too far and the product nucleated and crystallized in an uncontrolled manner. Recrystallization of **4** was then conducted, which removed sulfur contamination to acceptable levels. Overall, the Suzuki coupling afforded 181 kg of indazole **4** in 87% yield.



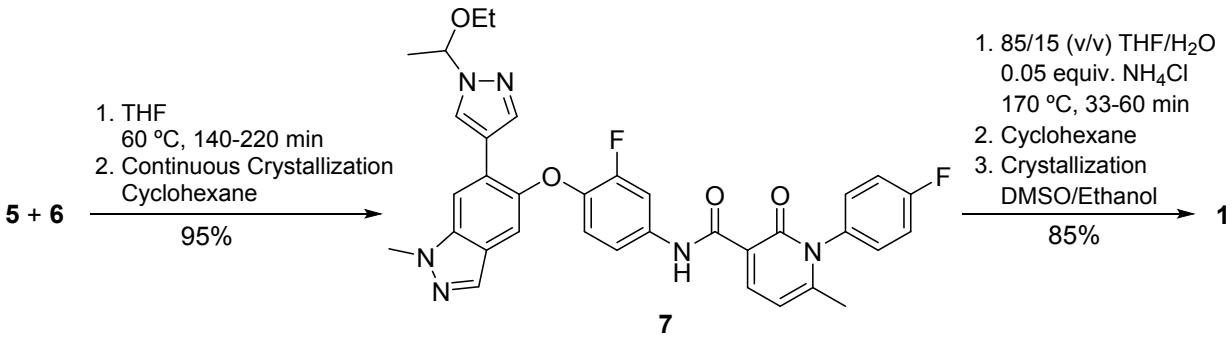
Scheme 3. Batch portion of synthetic sequence used in cGMP manufacturing campaign for Steps 1 and 2 and preparation of the anhydride.

Hydrogenolysis of **4** to aniline **5** was accomplished in six equal sized batches, affording a total of 161 kg of **5** in 98% assay yield and >99.7% purity. These batches were combined in pairs and concentrated to the desired ~30 wt% strength to afford three batches, each traceable to the three different feed lots of the starting material **2**. The three batches were stored in drums until use in the continuous process. UHPLC analysis of the three concentrated feedstocks showed the aniline **5** purity to be >99.7% and that all named impurities were controlled through Step 2 to below the 0.05% UHPLC LOQ.

Production of the anhydride **6** was completed in two batches, affording 156 kg in 92% averaged yield. As a change from the CM demonstration, anhydride **6** was crystallized and re-dissolved prior use in the Step 3 process. The revised isolation procedure successfully alleviated the risk of fouling at Step 3—caused in development by precipitation of residual TEA·HCl—and offered advantages including improved stability of the anhydride and control of residual pivaloyl chloride. After the anhydride was formed, TEA·HCl was removed by filtration and the THF solution was partially concentrated under vacuum. Heptane was then added to drive the anhydride **6** out of

solution. The solid anhydride was filtered and stored as a solid. Prior to use in the continuous flow sequence, the solid was re-dissolved in THF and polish filtered to remove low levels of additional TEA·HCl.

A summary of processing Steps 3 and 4 is provided in Scheme 4, and a summary of feed flowrates maintained throughout Step 3 processing is provided in Figure 4. Online HPLC results for the Step 3 reaction are provided in Figure 5. Owing in part to improvements made to the Step 3 reaction robustness that included adjusting the feed stoichiometry, extending the PFR residence time, and installing feedback mass flow control, the aniline intermediate **5** was controlled to <0.05 HPLC area% throughout processing. The purity of the intermediate **7** was generally maintained at ≥99.0 HPLC area%, with the remaining species detected by HPLC being the anhydride **6** and the acid **8**. The process operated uninterrupted and without the need for material diversion, aside from material diversions at process startup and shutdown. These diversions were specified in the batch record based upon a fixed number of reactor turnovers and collectively amounted to loss of less than 1% of intermediate **7**. Consistent with established acceptable ranges for product quality, the STA team elected to slow the overall process flowrate on the final day of operation for convenience so that process shutdown procedures could be performed during daytime hours. The continuous crystallization of **7** also operated without interruption for 17 days. Subsurface solids coating persisted throughout the campaign in both MSMPR crystallizers but did not impair operation.



Scheme 4. Synthetic sequence used in cGMP manufacturing campaign for Steps 3 and 4.

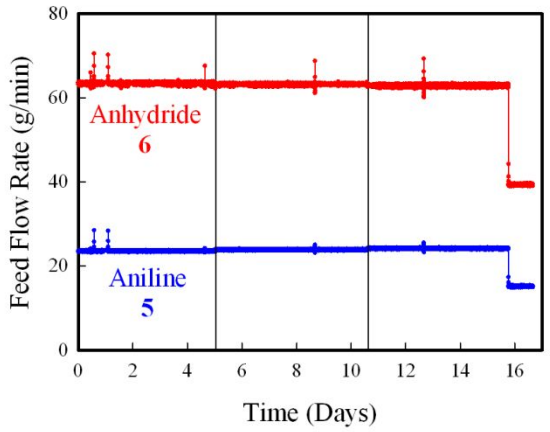


Figure 4. Flow rates of aniline **5** and anhydride **6** for the cGMP campaign (as measured by Coriolis mass flow meter). Flow rates were intentionally reduced during the evening of day 15 to allow shutdown to occur during daytime hours. Vertical line denotes change in intermediate **5** feed solution potency, leading to flow rate correction.

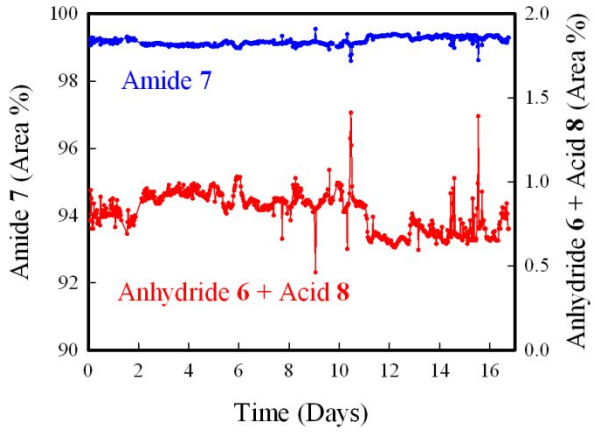


Figure 5. Online HPLC measurement of Step 3 reaction purity for cGMP campaign. Aniline **5** was not detected during the campaign (LOQ = 0.05 area%).

The manual filtration, washing, and dilution operation was the most labor intensive and time consuming aspect of the continuous process, occupying approximately 5 h of a single operator's time per 8 h cycle. The process was slowed by the use of vacuum in lieu of

pressure filtration, resulting in an average filtration time of greater than 1 h. Shortly after process start-up, the filtration operation was paused when it was discovered that the THF/water solution of **7** became turbid upon heating to 35 °C, as shown in Figure 6. Closer observation revealed that this turbidity was caused by a slight phase separation of the THF/water mixture. It was hypothesized that this phase separation could have been a result of residual cyclohexane retained in the wet cake after vacuum filtration. No impact to quality was observed, and processing continued as intended. The temperature-dependent phase separation was observed consistently throughout the campaign.

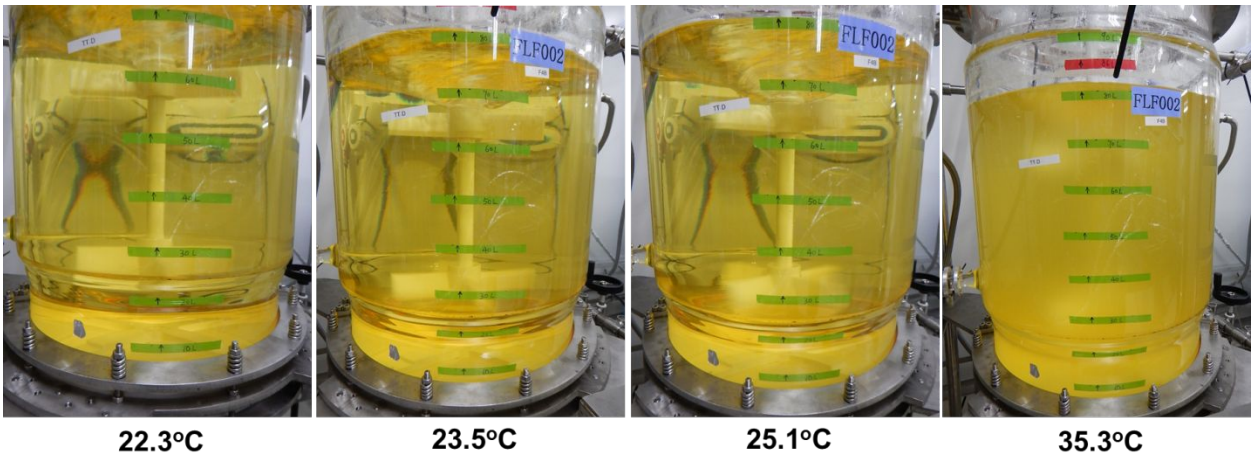


Figure 6. Evolution of dissolved compound 7 solution turbidity with increasing temperature.

All solutions of the product **7** were sampled during the transfer to Step 4 and analyzed offline by LC/MS. These analyses showed the aniline **5** to have been controlled exceptionally well throughout the Step 3 process with a concentration not exceeding 10 ppm with respect to the amide product **7**. The overall purity of the intermediate **7** was consistently found to be greater than 99.9 area% by HPLC, with the primary byproduct being the DS **1** (the deprotected analog of **7**). Defluorinated impurity **19** was occasionally detected at 0.05 area%. The flow rate for the thermal deprotection reaction was adjusted infrequently throughout the campaign within proven acceptable ranges to accommodate the supply of **7** solution from Step 3. As expected, reducing the flowrate to the Step 4 PFR resulted in observation of higher levels of **15** (formed via amide hydrolysis of **1**). Importantly, analysis of 50 L product drums by LC/MS confirmed that

potential GTIs **5** and **15** were consistently controlled to less than 80 ppm in the reactor effluent (Figure 7). Based on solution assay, the collective yield for the continuous process was 94%. Approximately 14.2 kg/day of the intermediate **7** was afforded from Step 3 (95% yield) and 12.5 kg/day of the product **1** was afforded from Step 4 (>99% yield).

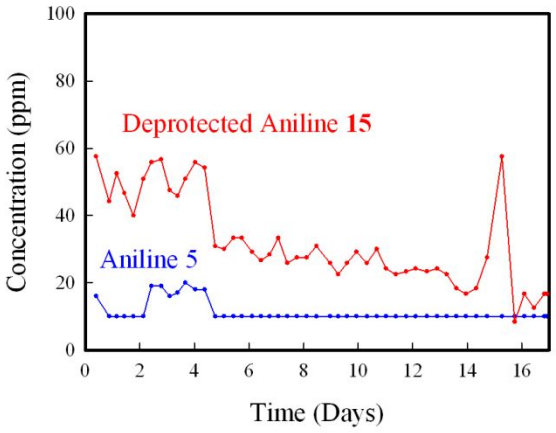


Figure 7. LC/MS analysis of Step 4 reaction effluent product drums showing impurities **5** and **15**, relative to **1** (LOQ = 10 ppm).

Product solution from the Step 4 flow process was purified in batch mode following the revised workup and crystallization procedure, which afforded the targeted crystal form in 85% yield. Batch workup was completed in four approximately equal portions. Two of these batches were completed before the conclusion of continuous operation of Steps 3 and 4, an illustration of process intensification afforded by continuous operation. In total the process afforded 183 kg DS, with the Step 3 and 4 hybrid process requiring 25 days to complete. Product purity was measured at ≥99.95% by HPLC, and impurities **5** and **15** were controlled to less than 10 ppm in the DS. All other targets for registration stability were satisfied for all DS batches, including residual solvent levels, metals, and crystal form (Table 4). The overall process yield (Steps 1–4) was 69%. After the cGMP campaign, a residence time distribution model of the CM process train was constructed to simulate material flow into and out of the reactors, MSMPR crystallizers, filters, and surge vessels. The model was used to follow the progression of feed lots of the aniline **5** and anhydride **6** throughout the CM process and to calculate the source material composition of the four product batches.

Table 4. Summary of non-cGMP CM demonstration campaign at Lilly[18] and CM cGMP campaign at STA. DS for the cGMP campaign was isolated in batch mode.

	CM Demonstration	*CM cGMP*
Continuous operation time per step	~100 h	17 days[c]
CM throughput	5–10 kg DS/day	12.5 kg DS/day
DS isolated (overall yield)	20 kg (61%)[a]	183 kg (69%)
Aniline **5** in DS	< 10 ppm	< 10 ppm
Deprotected Aniline **15** in DS	65–77 ppm[b]	< 10 ppm
Total impurities in DS	≤ 0.1%	≤ 0.05%
Crystal form	Compliant	Compliant
Residual metals	Compliant	Compliant
Residual solvents	Compliant	Compliant

[a]-Some material was reserved for development activities.

[b]-Attributed to variable control of Step 3 reaction stoichiometry, and decision not to isolate anhydride **6** leading to fouling event in the non-GMP laboratory demonstration.

[c]-Steps 3 and 4 were offset by one day.

KEY LEARNINGS

Perspective from STA

Collaborations in technology transfer from Lilly to STA have significantly sped up the CM capability build at STA. With the onsite training and direct equipment transfer, STA has rapidly accumulated experience in continuous process development and manufacturing.

Currently STA develops CM processes and technologies independently and has scaled up a number of unit operations in its Jinshan plant in China. It is critical that process knowledge and operational details are well communicated to achieve successful manufacturing at STA or other CMOs. STA has been involved in continuous process development for early phase projects, which has led to more experience in managing continuous cGMP manufacturing campaigns. Such opportunities also exist for other CMOs.

STA is still developing in its use of automation technology, and consequently many dedicated chemists, engineers, and operators were required in order to meet the staffing requirements during the continuous cGMP campaign. Manually intensive responsibilities included batch record maintenance, the filtration and dissolution unit operation, feed/product solution can changes, and analytical support. Division of the batch record into several parts (managed in parallel) implied that multiple operators were needed to monitor the process at a given time while the process operated in a state-of-control. For future campaigns, it is of primary importance to develop additional automated equipment as well as PAT to minimize manpower requirements and improve the feasibility for multi-step operations in CM.

Perspective from Lilly

CM technology has matured and now presents an opportunity for CMOs. Capabilities in DS CM may allow for differentiation among CMOs for processes that involve unstable intermediates, operation under hazardous reaction conditions, containment in fume hoods for cytotoxic compounds, and/or risk mitigation through process control. It is important that pharmaceutical companies investing in CM continue to provide CMOs with opportunities to develop CM capabilities and expertise, so that a greater number of individuals can be trained in the operation of continuous facilities. The nature of continuous processing is such that teams are best composed from individuals of diverse backgrounds (e.g. process and analytical chemists, chemical engineers, automation engineers, and technicians). Training and personnel retention at the CMO are potential barriers to externalization of flow technology and present a risk to building long-term partnerships between pharmaceutical organizations and CMOs. The core pharmaceutical companies invested in CM can lessen

this risk by standardizing the continuous equipment sets that are used in manufacturing. CMOs can absolve some of this risk by appointing a team that repeatedly engages in CM projects, so that learnings are more efficiently transferred from one project to the next.

Even with increased training, technology transfer and cGMP operation of continuous processes at CMOs will be challenging in the near future. Both process knowledge and equipment operational knowledge must be communicated effectively in order to achieve technical success. Development organizations may stress the technical aspects of the operation and risk overlooking other factors that are equally critical to success. Efficient implementation of CM currently requires around-the-clock activity from plant engineers and operators in monitoring online measurements, sampling, and replacing feed and product solutions. Close attention must be paid to how continuous projects are staffed, and PAT and automation should be utilized whenever advantageous. In this process, repeated tasks such as filtration operations, feed can recharges, routine monitoring of process conditions, and decisions to divert or forward process material based on online HPLC results all presented opportunities for automation. If engaged, this level of automation would have significantly lessened operational resources, lessened risk for inadvertent operational errors, and increased the likelihood of identifying process failures before they became a risk to quality or safety.

At present, both the development and operation of CM processes generally require more resources and more strategic planning than their batch analogs. In addition to the aforementioned staffing demands, the general unfamiliarity of manufacturing organizations with the continuous processing equipment (compared to the knowledge of batch vessels) adds complexity to the campaign preparation and operation. Furthermore, the simultaneous operation of multiple synthetic steps and unit operations requires that the development organization be prepared with a more holistic understanding of the process control strategy, and likewise that the manufacturing organization be prepared to identify and correct for disturbances in less time than would usually be afforded in batch processing. This implies that the analytical organization at the CMO needs to also accommodate around-the-clock activity, and that more opportunities for PAT and/or parametric control be leveraged to lessen the burden on analytical support.

This CM process achieved significant technical success and milestones for Lilly and STA. This campaign joins the work previously reported by Lilly[1] as one of the few multi-step continuous cGMP processes in the literature and is among the first of its kind to be performed at a CMO. This process ran longer and afforded more DS than the previous Lilly process. Experience gained in the non-GMP process demonstration was critical to the identification of equipment, process design, and process control elements that were taken forward to the cGMP campaign. The Lilly team is grateful to the persistence shown by the STA team over the course of process installation, qualification, and operation, and for the transparency granted by STA to Lilly team members throughout the campaign.

CONCLUSIONS

This report has documented the externalization of a hybrid batch/CM process to afford 183 kg of in-specification merestinib DS under cGMP manufacturing. A control strategy for the cGMP process was developed, based first on learnings and data collected from a 20 kg CM demonstration campaign and then on additional development research performed in both batch and continuous modes. While the control strategy examined all quality attributes, this report has focused especially on the control of process impurities through collective efforts in reaction analysis and modeling, crystallization rejection studies, and engineering of the CM unit operations. PAT, offline analytical, and batch record strategies were developed and implemented in support of the control strategy during continuous operation. Technology transfer of the hybrid process and control strategy from the development organization to the CMO occurred over six months. This timeline was accelerated by knowledge transfer on CM that had occurred during collaboration between the two organizations several years prior to engagement on this campaign. Perspectives offered by both organizations have highlighted the importance of staffing decisions, PAT, and automation in making multi-step DS CM sustainable in the future. Overall, the success of this campaign can be attributed to the robustness of the control strategy and to collaborative efforts shared between both organizations.

ASSOCIATED CONTENT

Supporting Information. Additional experimental procedures and equipment descriptions can be found in the Supporting Information for this article.

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