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Addressing the Medicinal Chemistry Bottleneck: A Lean Approach to Centralized Purification

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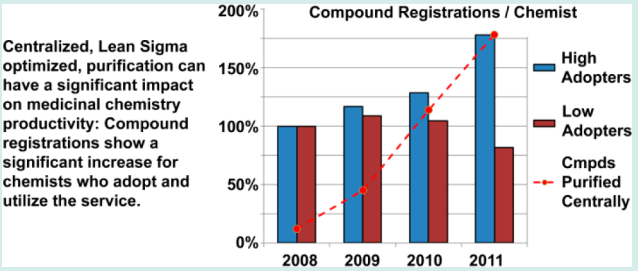
ABSTRACT: The use of standardized lean manufacturing principles to improve drug discovery productivity is often thought to be at odds with fostering innovation. This manuscript describes how selective implementation of a lean optimized process, in this case centralized purification for medicinal chemistry, can improve operational productivity and increase scientist time available for innovation. A description of the centralized purification process is provided along with both operational and impact (productivity) metrics, which indicate lower cost, higher output, and presumably more free time for innovation as a result of the process changes described.



KEYWORDS: *drug discovery, lean sigma, preparative LCMS, productivity, purification*

INTRODUCTION

Pharmaceutical drug discovery is driven by an iterative, multidimensional, structure−activity optimization cycle of design−synthesize−test−redesign that leads to an eventual drug candidate. The Medicinal Chemist is at the center of this process and adds value through core expertise and innovation in molecular design, chemical synthesis, and data interpretation. In the traditional medicinal chemistry model (Figure 1) the medicinal chemist is also responsible for a variety of other activities that, while often innovative, are not part of the core drug discovery value stream and are not well matched to the core medicinal chemistry skill set. One such example is in chromatographic purification and subsequent processing of final compounds for biological testing. Transfer of responsibility for purification and processing to a service group could potentially make chemists increasingly productive in their key areas of innovation, while at the same time enabling other productivity improvements through process optimization in the central purification group. In this manuscript we describe the successful implementation of a centralized, multisite, lean sigma optimized, purification process in drug discovery along with metrics demonstrating its effectiveness.

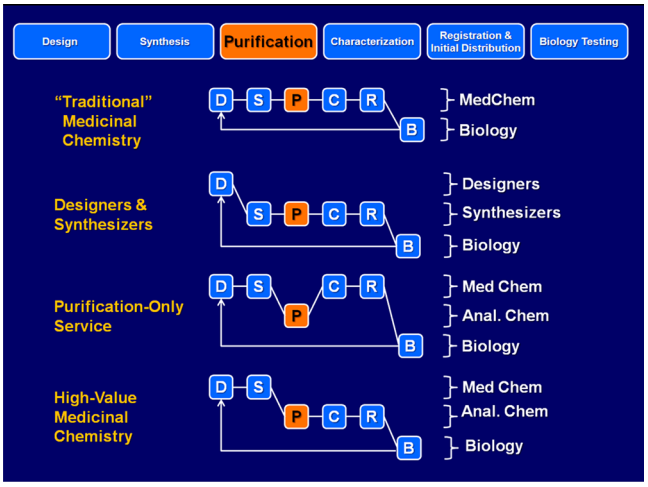


Figure 1. Research models in drug discovery.

Several strategies for improving innovation and effectiveness in drug discovery and development are being explored across the industry. In recent decades, the continuous process improvement methodologies of lean and six-sigma (often combined under the banner of "Lean Sigma") have successfully revolutionized the cost and quality of the manufacturing and service industries.[1] While these successes are nondisputable, observers from other industries, including the pharmaceutical industry, are skeptical that these tools can be applied to a dynamic industry requiring significant innovation. Carleysmith et al.[2] cite challenges faced by GSK in the deployment of lean sigma into their drug development environment and of their concerns relating to deploying lean in innovative environments. Business Week[3] published an article claiming that incorporation of six sigma had suppressed innovation at 3M, a company regarded as one of the most successful innovators of the last few decades. These articles suggest that improved process performance and innovation may be inherently contradictory.

More recently, Johnstone et al. highlighted strategies for the creation of a unified climate that encourages and enables both innovation and continuous improvement.[4] Our hypothesis is similar to this approach. We believe that specific research

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workflows are highly amenable to the concepts of continuous improvement and lean sigma. In fact, the existence of such a lean sigma amenable process within the overall responsibilities of a scientist whose primary responsibility is to innovate represents an inherent inefficiency. Rather than expect scientists to shift between modes of innovation and continuous improvement, we believe it is most efficient to create specialty groups within research whose primary focus is to optimize a lean sigma amenable process.

In the traditional medicinal chemistry model each of the iterative drug discovery steps except biology testing is handled by a single medicinal chemist who designs, synthesizes, purifies, characterizes, and registers each new compound (Figure 1). This model dilutes medicinal chemists' opportunity for innovation and fails to take advantage of process optimization opportunities that may exist within the overall process. In recent years drug discovery organizations have attempted to apply new models to separate the most innovative steps from those that are thought to be more amenable to process optimization. For example, there has been recent discussion of a hypothetical "Designers and Synthesizers" model where compound design is separated from the physical execution steps of synthesis, purification, and characterization. This would create opportunities for creative staffing models but does little to enable lean sigma processing, and it would separate the integrally linked design and synthesis activities. Some groups have focused on the purification step and have attempted to expand traditional purification-only services which return the purified sample to the medicinal chemist for characterization and registration before passing the sample on to biology for testing. This model enables lean sigma optimization of the purification step itself but suffers from the disruption of handing the sample back to the originating chemist for further processing, and fails to take advantage of optimization of those further processing steps. We and others[5−7] have adopted a model that we call *High Value Medicinal Chemistry*. In this model, design and synthesis steps are carried out by medicinal chemists, while the subsequent steps of purification, characterization, and registration are carried out by scientists trained in those specialties. Innovation is enabled throughout the process by matching scientific skills with actual tasks while high instrument utilization and process optimization are enabled by centralization of the capital intensive tasks of purification and characterization.

RESULTS AND DISCUSSION

Before embarking on an enterprise-wide deployment of the High Value Medicinal Chemistry model, we sought to validate our hypothesis that the return on investment would be favorable. To do this, we embarked on a pilot study with one chromatography scientist supporting one group of 8−10 medicinal chemists. The goals of the pilot were to demonstrate acceptance of a centralized purification service by medicinal chemists, to gain data to estimate the size of a fully deployed purification service (staff, instrument infrastructure, and lab space), and to gain data to allow estimation of the eventual return on investment either in direct cost savings, productivity improvements, or improved opportunity for medicinal chemistry innovation. We quickly learned that keys to user acceptance included overall success (never losing a compound), cycle time (competitive with purification by medicinal chemists themselves), final purity, yield, and flexibility. By emphasizing these attributes we quickly gained user acceptance. For example, no specific acceptance criteria were established for inbound crude products. Instead, chemists were asked to perform the experiments they would normally perform prior to self-purification (commonly TLC or analytical LCMS) to establish presence of the desired product; the centralized team would attempt purification of any sample that met the client's acceptance criteria (rather than arbitrarily imposed standard criteria). User acceptance was supported by customer surveys which suggested significant time saved for the medicinal chemists using the service, which enabled them to spend more time on more innovative activities. We also observed that the centralized team had higher first attempt success rates than individual medicinal chemists. This resulted in significant reduction in repurification with associated direct cost saving (vide infra). These early suggestions of high user acceptance, increased medicinal chemistry innovation and productivity, and direct cost savings supported the decision to move to enterprise-wide deployment eventually supporting the entire medicinal chemistry community at three geographic locations.

Expansion of the small scale pilot study to full enterprise-wide deployment required refinement of the centralized purification process to maintain customer satisfaction, drive efficiency, and ensure competitive purification cycle times, while operating sustainably in a high capacity environment across multiple geographical sites. Building on previous experiences in our lab,[8] lean manufacturing principles were used to drive process optimization. As with library synthesis, proximity to client chemists and biologists was considered to be a key enabler of trust and communication. A federated model was thus adopted where purification laboratories were installed at each major research site with a single central management structure. Since chemists and biologists are commonly colocated this also avoided delays inherent in shipping samples from site to site.

An early process decision was that the handoff from synthesis chemist to the centralized purification team would be one-way (the *High Value Medicinal Chemistry* model). That is, both chromatography and all postpurification processing steps would be handled centrally with no physical material handed back to the originating chemist. This allows the efficiency of the centralized process to impact both purification and postpurification steps and it eliminates a potentially inefficient hand-back from the purification team to the originating synthesis chemist for further processing. Postpurification steps included in the centralized process are fraction combination and dry down, weighing, characterization (by orthogonal LC-MS and NMR), registration into the corporate database (in the name of the synthesis chemist), and initial distribution for biology testing. These are among the most inefficient steps in the distributed model and are highly suitable for lean process optimization in the centralized model. Eliminating the hand back allows the originating chemist to move on to other activities without the potential for the wasteful delays upon sample return. This process change required significant cultural change on the part of the medicinal chemistry group, particularly the enablement of a third party to handle compound registration. Change management was handled by gradual roll out, starting with a small group of chemists and expanding in a staged manner, accompanied by extensive communication to set expectations and quickly address concerns. Customer satisfaction with the new process (supported by favorable word of mouth opinion from participants in the pilot study) drove acceptance and, after

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some initial hesitancy, this change was eventually embraced by the community as one of the primary drivers of innovation, productivity, and cycle time improvement.

An important success factor for the centralized process was to minimize cycle time to ensure timely delivery of purified products. Lean principles teach that processing samples in large batches leads to unnecessarily long cycle times for individual samples and that the most efficient batch size is a batch of one.[9] This conclusion follows from value stream analysis where the emphasis is on the product rather than the operator. Single piece flow is in direct conflict with the design of most common laboratory equipment including HPLC and LC-MS equipment, liquid handlers, and evaporation equipment, all of which are designed for processing large numbers of samples in batches. An example of this would be a purification step by preparative HPLC or LC-MS. After the first sample is complete its resulting fractions are waiting in a fraction collector for further processing. In a batch process those fractions wait for completion of the entire batch (potentially for many hours) before proceeding to the next step as part of the batch. With single piece processing, those fractions are processed immediately while the next sample is being purified. In practice, however, this is challenging because the next step following prep HPLC is often an evaporation step that is typically done using a large centrifugal concentrator designed for processing large batches. This was overcome by introducing a newly commercialized single piece evaporator, the Biotage V-10,[10,11] to the process. The V-10 allows drydown of purification fractions from one sample while the next sample is undergoing chromatographic purification, thus enabling single piece flow while being more amenable to automation than traditional rotary evaporation. Similarly, HPLC and LC-MS sample queue management is typically performed by instrument control software operating in batch mode. We overcame this by internal development of cross platform queue management software called *AutoQueue* to manage a dynamic queue of single samples, rather than a batch of many samples, by loading a "batch of one sample" into the instrument control software at the appropriate time.

Efficient single piece flow was further enabled by using a modular work flow model. In this model, the overall process is divided into a sequence of steps with well-defined inputs and outputs. This allows interoperability of both instruments and staff, and allows for dynamic matching of available resources with available sample-steps. In this model a scientist may complete prepurification analysis using one or more instruments. Another scientist may then review the analysis data for that sample and from that design a purification method which would then be executed on an instrument by yet a third scientist. In this model scientists move among samples and steps to perform the most critical task available at a given time. Similarly, instruments capable of performing given tasks are used interchangeably to maximize utilization and throughput. Both scientists and instruments can be "qualified" to perform specific tasks as long as at least one qualified scientist and one instrument are on hand for each task in the sequence. In practice, after an initial training period, all our scientists are qualified to perform all the steps. Some steps, however, require physical presence in the lab whereas others (virtual method creation, compound registration, etc.) do not. Remote access can thus be used to expand the universe of available scientists for certain tasks, especially during nonroutine hours.

The modular work flow model enables dynamic sample reprioritization based on sample due date. The end point of the drug discovery cycle is publication of biology testing data to drive the next iterative cycle (design−synthesize−purify−test biology), and short timelines between synthesis and biology testing can be one of the major factors in ensuring competitive drug discovery success.[12] Since many biology programs still operate in batch mode and perform testing only on a certain day of each week, a static "first in−first out" model for purification would potentially delay the cycle. For example, it could lead to one sample being unnecessarily delivered several days prior to the testing date, only to wait while a second sample narrowly misses its own testing deadline because the team was purifying the first sample. To maximize the opportunity for on time biology testing, a dynamic due date model is used whereby the due date for any given compound corresponds to the submission deadline for the next available biology testing day relevant to that compound. Each sample is coded and tracked according to its individual due day; modular operations are prioritized to maximize the number of samples delivered in time for the next available testing cycle. A laboratory dashboard displays the number of samples currently at each step of the process along with a color code indicating sample due date. This allows rapid identification of both ongoing and unexpected bottlenecks to define areas for intervention.

Samples are received at a relatively steady rate throughout the work week (Monday through Friday), but their due dates may be distributed unevenly based on the mix of programs and testing days in the overall portfolio. This, in turn, leads to work bottlenecks immediately prior to the most common due days and low work load prior to the less common due days. In addition, since samples are processed individually and not in batches, most lab instruments remain idle when staff are not available to operate them. To increase instrument utilization and address the sample flow inconsistency to ensure the maximum number of samples delivered for on time biology testing, a dynamic staffing model was adopted. According to this model the lab is operated with fewer staff on slow days of the week and with more staff and for more operating hours (by staggering individual staff hours) on the most critical days just before the most common due days. Since the testing schedule is relatively stable from week to week, the staffing model remains relatively stable for long periods, but undergoes periodic review and adjustment. An example of the impact of dynamic staffing is shown in Figure 2. One of our major research sites is currently dominated by programs with a submission deadline on one particular day of the week. Figure 2 shows the percent of samples from that site delivered on time for testing on that day (vertical axis) based on the day of the week received for purification (horizontal axis, shown as days prior to due day). In the "before" curve, representing a three month period immediately before the staffing change, the purification lab ran at full staff for 8 h per day and five days per week and, for example, only about 15% of samples received on the morning of "Day minus 3" were completed on time. In the "after" curve, representing a three month period immediately after the staffing change, the lab operated with partial staff and short overall operating hours on some days, and with full staff and extended operating hours (using staggered shifts) on days closer to the due day. In this case, nearly 80% of samples received on the morning of "Day minus 3" were completed on time. Thus, by adjusting the staffing model to meet portfolio

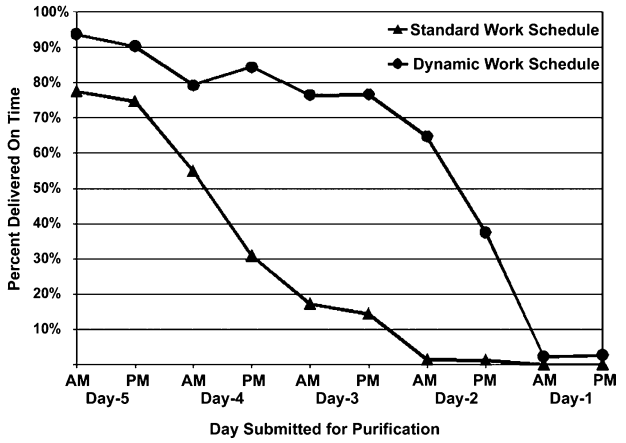

Figure 2. Impact of flexible staffing model on on time delivery: Percent success for meeting assay deadline based on compound submission day and time (days prior to due date).

needs, samples received close to the due day have a significantly higher probability of being delivered for on time testing than with a traditional staffing model. Further process improvements have since led to on time delivery of the majority of compounds received even on Day-1. This rapid delivery drives drug discovery by providing timely biological data to inform the next design cycle, which is a key component of an overall drug discovery optimization strategy.

The primary dashboard for medicinal chemists is their individual electronic laboratory notebooks (ELN, in our case this is the *E-Notebook* from PerkinElmer Informatics[13]), while the primary dashboard for the purification team is an internally developed custom software tool known as *SATT Lab*. A straightforward submission process including tight integration between ELN and *SATT Lab* was viewed as a requirement for customer satisfaction. This was accomplished by creation of a custom ELN menu selection ("Submit for Purification") on the Reaction tab of the ELN experiment. This causes key sample information (including reaction scheme, targeted product, reaction scale, and chemist name) to be collected from the ELN and deposited as a pending process in *SATT Lab*. The chemist then physically delivers the sample to one of several submission stations, each of which displays the list of pending samples. The chemist selects his or her sample from the list, reviews the data and enters any customization requests, then formally submits the sample by clicking a "Submit" button. Upon formal submission a tracking bar code is printed which the chemist applies to the submission vial prior to placing the vial into the submission bin. As samples progress through the purification lab a number of LCMS analyses are performed, including initial analysis and final quality control (vide infra). As these data are generated the resulting chromatogram results files are sent by *SATT Lab* to the ELN inbox of the submitting chemist. This serves as both an in-process communication tool and as an experimental archive.

After the purification process is completed and a compound is registered, a summary of the purification and analysis work that was done is collated and formatted as a PDF report. The report is generated from a template that includes embedded variables that reference key process information from SATT Lab. For example, the analytical LC-MS, preparative LC-MS, and NMR conditions are uploaded to a database by operators as they queue instruments. The purity, yield, and registration ID of the purified compounds are similarly uploaded from the corporate registration system. When all work on a compound is finished, an operator will preview the text that is assembled with the variables replaced by actual data, make minor adjustments to the template as needed, and submit the text for report creation. The report is automatically emailed to the chemist who submitted the compound and is simultaneously uploaded to the electronic notebook to be included in the chemist's final experiment record.

The original goals for this project were to improve medicinal chemistry productivity while reducing direct and indirect costs of compound purification. Improvements to productivity should in turn create free time for medicinal chemists to invest in other activities, including synthesis of more compounds or performing more experiments (which can be easily measured) as well as intellectual pursuits such as expanded SAR, compound design, alternate chemotype design, etc. (which are less easily measured). We used three key metrics to measure medicinal chemistry productivity: chemist surveys, ELN experiment growth, and new compound registration growth. Chemist surveys consistently suggest about a 20% productivity improvement for medicinal chemists using the central purification service, accompanied by increased opportunity for innovation. To assess ELN and compound registration metrics, we performed a retrospective analysis at the geographic site where the service has been in operation the longest. To perform the analysis we divided medicinal chemists into two groups: "high adopters" (chemists with at least 50% of their individual final compounds purified by the central service in the most recent year) and "low adopters" (less than 50% of final compounds purified by the central service in the most recent year); the two groups are approximately equal in size (number of chemists). We then analyzed the total number of ELN experiments and new compound registrations for the two groups of chemists going back to 2008 (prior to introduction of the service). Since the two groups had slightly different starting numbers in 2008, we normalized the 2008 values to 100% for each of the two groups. We then measured and plotted the number of ELN experiments and compound registrations for the two groups relative to their 2008 baseline (100%). The results are shown in Figures 3 and 4, with the relative number of compounds purified centrally overlaid for reference. As seen in the Figures, ELN experiments grew over a four year period by approximately 40% and new compound registrations grew by 75% for the high a adopter group, while both measures

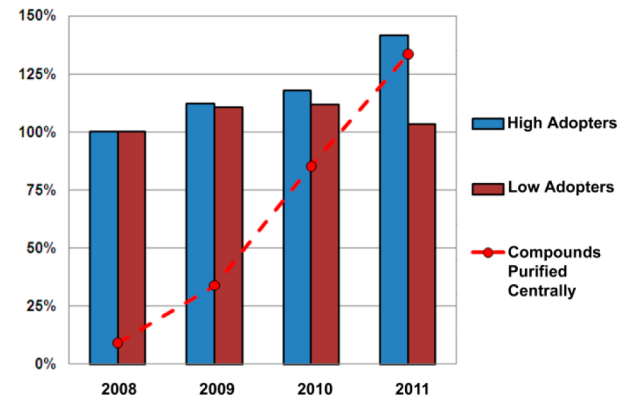

Figure 3. Growth in ELN experiments per chemist for high and low adopters of centralized purification.

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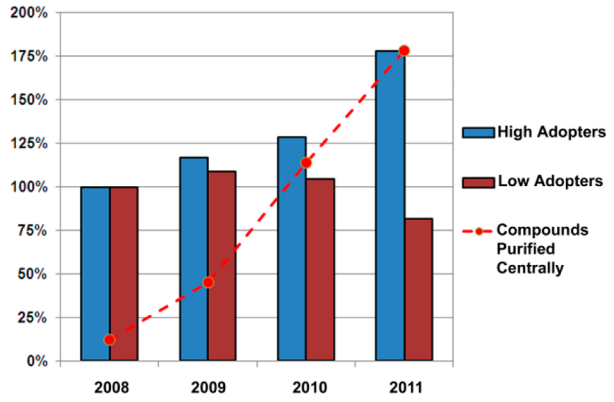

Figure 4. Growth in new compound registrations for high and low adopters of centralized purification.

remained essentially unchanged for the low adopter group. While it is difficult to conclusively link cause and effect, the productivity growth corresponds with the simultaneous growth of centralized purification output and is suggestive that utilization of the central service can have a significant (20−75%) impact on measurable chemist output. When multiplied by the large size of the typical large pharmaceutical medicinal chemistry group (often hundreds of medicinal chemists) this productivity improvement translates into the equivalent output of dozens of medicinal chemists, or thousands of hours of time freed for core medicinal chemistry innovation, including novel chemotype design, expanded SAR studies, expanded off-target and liability studies, etc. It should be pointed out that, while some of the low adopters are by choice, the centralized service model is not appropriate for all chemists in all programs for a variety of technical reasons (for example requirement for chiral separation which is currently outside the scope of the project, products that readily crystallize and thus do not require chromatography, etc.). Our current metrics suggest that about 70% of all final medicinal chemistry compounds are amenable to purification by the centralized service at full utilization.

The direct cost of compound purification is impacted by equipment utilization and purification success rates. Purification instruments in the centralized lab have, on average, about three times higher utilization (operating hours/week) than "open access" instruments set up for use by medicinal chemists. The centralized purification model can thus purify the same number of compounds with fewer instruments, resulting in up to two-thirds lower cost of capital (including capital investment, maintenance cost, and laboratory footprint) than the traditional open access model. Purification success rates also have a significant impact on direct purification cost. The centralized service successfully purifies compounds with an average of less than 1.2 preparative HPLC injections per compound. In contrast, the average number of preparative HPLC injections made by medicinal chemists to purify a single compound is two injections per compound (based on questionnaires and data mining from electronic lab notebooks). This is not driven by scale of the injection but rather by either fear of loss (dividing the sample into two parts before attempting purification) or by failure to achieve desired purity on the first injection, thus requiring a second purification. With an average of about one liter of chromatography mobile phase solvent required for each preparative HPLC injection, this improvement alone represents as much as 20 000 fewer liters of solvent used per year when supporting all of medicinal chemistry at our major research sites.

Drug discovery productivity has been flat at best for many years[14] in spite of introduction of many new technologies. In the current work, we demonstrated that selective introduction of centralized services can enable lean process optimization with significant impact on overall medicinal chemistry productivity while improving opportunity for innovation. Given the large size of most medicinal chemistry groups, even small productivity improvements can translate into the equivalent of many FTEs. For example, a 20% productivity increase (at the low end of our current estimates for the impact of optimized centralized purification) would be the equivalent of 20 new FTEs in a group of 100 medicinal chemists. The productivity improvement is accompanied by a decrease in both operating and capital cost, thus further improving the overall return on investment. The *High Value Medicinal Chemistry* model increases time available for the key innovation steps in drug discovery such as molecule design, synthesis route design, and synthesis execution, thus demonstrating that optimized lean sigma processes can be enablers of creative innovation when thoughtfully applied.

EXPERIMENTAL PROCEDURES

The process described in this manuscript is operated at multiple geographic locations, each focused on different disease and target types, with different infrastructure, and with total throughput of tens of thousands of samples per year. As a consequence, it is not possible to fully describe each possible combination of instrumentation and chromatography methods used as part of the process. Instead we describe the process steps that are in common among all samples and illustrate with a complete description of processing of a representative sample.

Sample scale (reaction scale of limiting reagent) is generally from 20 to 100 micromoles (about 10−50 mg of target, though initial sample weight is often greater due to presence of impurities), and samples are received in solution (up to 2 mL volume in an HPLC compatible solvent such as DMSO, DMF, or the like). Sample vials are bar coded immediately upon chemist submission. Upon receipt, a small aliquot is removed and diluted for initial analysis screening, which consists of several (typically two to four) orthogonal LC-MS analyses of the sample to confirm presence of the target and assess separation using the various mobile phase/column combinations. A mobile phase/column combination is then chosen for purification based on review of the results of the initial analyses. A gradient method for purification is created based on target retention characteristics, but no attempt is made to use a direct scale up of the initial analysis method (gradient prediction algorithms vary based on site specific instrument availability, but generally lead to a focused gradient chosen to optimize retention factor of the target [15]). The bulk sample is then injected onto a preparative LC-MS system and is eluted using the chosen gradient; peaks are detected using both UV detection at a target appropriate wavelength and mass detection using the extracted ion chromatogram of the target molecular ion (or appropriate adduct). Fractions are collected into collection tubes in a smart fraction collector using either the UV signal, the MS signal, or a combination of the two ("and/or" logic), based on sample characteristics identified during the initial analysis, to trigger fraction collection; the waste stream (areas where no peak is detected) is directed into a sample specific 500 mL bottle in a separate waste stream collector from

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which the sample can be recovered in case of catastrophic failure of the smart fraction collector. Following purification, fractions containing the desired target (based on inspection of the preparative chromatogram and mass spectra or, in rare cases, by reanalysis of specific fractions) are combined and concentrated using the V-10 evaporator. The sample is then redissolved in a volatile solvent, a small aliquot is removed for a tentative purity assessment by LC-MS, and the sample is reconcentrated to dryness. If the sample passes the tentative purity assessment (generally >95% pure), then it is passed to the subsequent steps; if purity is not acceptable the sample is repurified by preparative LC-MS using an orthogonal method. Samples proceeding are then weighed and redissolved in a volatile solvent; aliquots are distributed volumetrically for initial biology testing, two aliquots are taken for final quality control assessment, and the remainder is transferred to a standard vial for storage in the corporate compound collection. One quality control vial is diluted if necessary and subjected to two orthogonal LC-MS analyses with high (>110) peak capacity[16] to determine final purity, while the second is dried and the residue is used to acquire a ^{1}H NMR spectrum. The remaining vials are dried using a Genevac centrifugal evaporator[17] and are then distributed to the central compound management facility for further routing to biology laboratories or storage. The above process is illustrated with the following example.

A crude reaction mixture resulting from benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) mediated amide bond formation, run at a scale of 48 μmoles in 1 mL of DMF, was submitted directly (without workup) by the synthesis chemist to the purification team for purification. The target formula weight was 455.5 thus the theoretical yield was 21.8 mg. From this point onward all operations were carried out by members of the central purification team.

A small aliquot (25 μL) of the inbound sample was removed and diluted with 325 μL of methanol for initial analysis. The diluted sample was injected onto an analytical LC-MS system consisting of Shimadzu LC-10 series pumps, variable wavelength UV detector (SPD-10Avp), and autosampler (SIL-10Avp), and under control of Shimadzu ProminenceVP v 7.32.0.190 software, with a Waters model ZQ mass detector running MassLynx version 4.1 data acquisition software. Sequential injections were made onto a Waters X-Bridge C18 column (4.6 × 50 mm, 5 μm particles) using two different mobile phase combinations (acetonitrile/water +10 mM ammonium acetate, and acetonitrile/water +0.05% trifluoroacetic acid); both were run in linear gradient elution mode from 5% to 95% organic over 4 min at a flow rate of 4 mL/min. Samples were detected by UV absorbance at 220 nm and by mass spectrometry including the extracted ion chromatogram for the target $(M + H)^+$ ion (456). The two resulting chromatograms gave qualitatively similar results with the target peak representing about 40−50% of the total retained UV absorbance. The acetonitrile/ammonium acetate combination gave better peak shape and nearest neighbor resolution than the TFA combination.

The bulk sample (1.0 mL) was then purified by preparative LC-MS using two Shimadzu LC-8A pumps, variable wavelength UV detector (SPD-10Avp) with preparative flow cell, SIL-10Avp autosampler, and FRC-10A fraction collectors under the control of the BMS proprietary version of Shimadzu DiscoveryVP software,[18] combined with a Waters model ZQ mass detector running MassLynx 4.0 sp 4 software; the MassLynx software was sending a real time analog signal representing the extracted ion chromatogram to the FRC-10A for fraction trigger using the mass signal. The sample was run on a Waters X-Bridge C-18 column (19 × 250 mm, 5-μm particles) using linear gradient elution from 15% to 95% acetonitrile/water +10 mM ammonium acetate over 25 min at 20 mL/min. Fractions were triggered in this case using the analog extracted ion signal from the mass spectrometer; fractions containing the target were combined and concentrated using the Biotage V10 evaporator. The concentrate was then transferred to a suitable container and concentrated to dryness using a Genevac HT-24 centrifugal evaporator, resulting in 3.0 mg (6.6 μmol) of purified product (14% overall yield including both synthesis and purification).

The product was then dissolved in 3.3 mL of DMF and aliquots were volumetrically removed for final QC (LC-MS analysis), NMR, and initial biology testing (4 vials). The NMR and biology samples, along with the residue in the original vial, were dried using the Genevac HT-24. The NMR sample was dissolved in DMSO-d_6; a 1H NMR spectrum was acquired and was consistent with the assigned structure. The LC-MS sample was diluted with methanol and analyzed twice by two orthogonal uHPLC-MS methods using a Waters Acquity uHPLC-MS system fitted with a Waters UPLC BEH C18 column, 2.1 × 50 mm (1.7-μm particles) operated at 50 °C. Linear gradients were used from 5% to 95% acetonitrile over 3 min with a 0.75 min hold at 95% acetonitrile. The aqueous phases were 10 mM ammonium acetate and 0.05% aqueous trifluoroacetic acid for the two runs, respectively. Purity by both methods was estimated to be 100% based on the UV chromatogram at 220 nm; target molecular weight was confirmed by presence of the molecular ion $(M + H^+)$ ion at 456. After assignment of a corporate registration number, the biology samples were transferred to the central compound distribution group for further delivery to biology laboratories.

In this example, the sample was received for purification on a Monday afternoon and the due time for biology testing was the following Monday at 8:00 a.m. Because of this sample prioritization, work did not begin on the sample until Wednesday, and the purified sample was registered into the corporate database on Thursday, well in time for the next biology testing cycle.

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Notes

The authors declare no competing financial interest.

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