# From crude samples to highly pure isolated solids in 4 hours

## Delivery of pure, dry, free flowing solids by a customer focused, medicinal chemistry purification service, using a Lean Sigma approach

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**Over the past few years the concept and benefit of Lean Sigma has become increasingly valued within the pharmaceutical industry. The necessity to drive efficiency and streamline processes is critical to the delivery of compounds through the R&D process in the most effective ways. Aiding the reduction of turnaround times and costs for a purification service, whilst retaining the quality of compound delivered highlights the value of customer insight and collaborative working. Approaching an improvement project in this way ensures the implementation of the most effective and appropriate improvement strategies.**

### Introduction

As pharmaceutical companies continually strive to reduce the time and cost of bringing a new drug to market, the efficiency of each phase in the Drug Discovery/Development cycle becomes even more critical. With specific reference to early stage Discovery, numerous compounds are synthesised in design sets, with the intention of improving overall properties to develop these compounds as pharmaceutical agents. Naturally, collaborative working between scientific disciplines is crucial to progressing projects through into Development and the need to maintain efficiency of these individual processes is vital. At AstraZeneca, ensuring efficiency throughout the design, make, test cycle (DMT) has been achieved through streamlining processes within each discipline and aligning their functions to enable parallel testing.[1] Routinely, primary biological assays are now scheduled on a weekly basis to enable advanced planning and focus for the Department. This weekly planning system places an emphasis on Chemistry to deliver compounds by Friday each week to maintain the flow and efficiency required for projects to reach milestones and progress forward.

Obviously, with the increase in demand on Chemistry it becomes vital for each component of the synthetic process to run in the most efficient manner. Consequently, Synthesis has adopted visual planning boards as a tool for tracking Work In Progress, allowing continual project discussion and forward planning. However, it is recognised that the efficiency of compound delivery through the Chemistry Section relies on the success and turnaround times for purification. The inclusion of a purification service within the department has allowed individual dedication to both of these specialist areas. As a result, the demand on a purification service to deliver pure, solid compounds in line with specific customer expectations became challenging. This was heavily influenced by the discrepancy between the turnaround time achievable within a multi sample purification service and the expectation of the synthetic customer. Consequently, the service provided to customers failed to meet expectations, impacting efficiency parameters through lengthy turnaround, delaying the flow of samples. This indicates the need to critically investigate the purification process in relation to turnaround time to help improve efficiency of the DMT cycle.

### Discussion

Addressing the above concerns was possible using a Lean Sigma approach through working with the key fundamental concepts to facilitate the improvement in quality and speed at which processes can deliver.[2] The two most crucial aspects specific to the nature of this project were to outline and understand the purification process, specifically its individual steps and establish the key requirements of immediate customers. Creating a framework for understanding the flow of compounds through a process can be illustrated with a SIPOC diagram (Figure 1), detailing the input required from suppliers, process steps and the output delivered to the customer. [3]

In addition, understanding what the customer believed to be critical to quality in terms of the level of service they receive can easily be captured using Voice Of the Customer (VOC) questionnaires.[4] These assessments were made during face to face 1:1 discussions with the individual customers, in this case the synthetic chemistry community. The main requirements asked for were to ensure delivery of pure, free flowing solids within a guaranteed consistent delivery time. Further clarification highlighted the need to concentrate on routinely providing

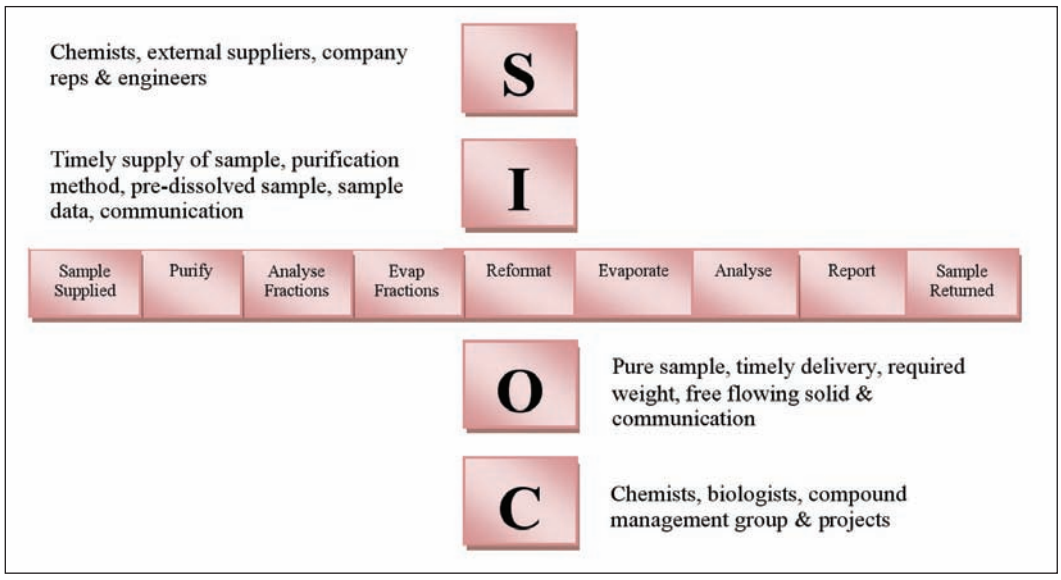


*Figure 1. SIPOC diagram illustrating flow of compounds*

| Day | 1 | | | | Overnight | 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Process | Sample Supplied | Purify | Analyse Fractions | Rack Fractions | Evaporate | Reformat | Evaporate | Weigh & Analyse | Report | Sample returned |
| Time (mins) | 0 | 30 | 15 | 5 | 900[a] | 5 | 300[b] | 10 | 10 | 5 |

- 2 Key Principles
  - Value Adding (VA) – 55 minutes
    - Beneficial steps of the process, providing value to the customer
  - Non Value Adding (NVA) – 1225 minutes
    - Process steps that provide no additional value to the customer
    - Total process time of 1280 minutes (21hours)

Process Cycle Efficiency (PCE) : 100xVA(min)/ Total Process Time(min) 100x55/1280 = 4.3%

*Table 1. Initial analysis of process steps for purification process*

[a] *Samples batched together for parallel evaporation, 12 – 15 hours overnight in a centrifugal evaporator*
[b] *Samples reformatted, dried down into vials via parallel evaporation, up to 5 hours in a centrifugal evaporator*

a daily consistent turnaround time that would easily align with weekly planning activities within the DMT cycle.

Managing these demands effectively, required critical analysis of each process step to understand its necessity, identify the time taken to complete and the value it provided from the perception of the customer. The outcome of this data analysis is represented in Table 1.

The high degree of inefficiency demonstrated by the PCE calculated in Table 1 strongly highlighted the need for improvement, prompting discussions to investigate the most effective way to reduce time taken to complete NVA (non-value adding) steps. It became necessary to identify causes and barriers influencing working practices, helping to understand why day to day procedures were conducted in a particular way. Continually questioning the nature and influence of these factors enabled detailed root cause analysis (RCA), establishing the underlying core reasons for the occurrence of individual problems. This concept of RCA was demonstrated when evaluating the concerns over solvent evaporation, accounting for 97% of the wasted time, totaling 1225 minutes.

Compounds were routinely purified on an individual basis and then batched together for parallel evaporation. Following on from this, samples were reformatted into registration vials using organic solvent. Historically, these processes were used to overcome the continual lengthy removal of water from the numerous aqueous fractions produced during purification. Fundamentally, these aqueous fractions only occurred with the use of preparative HPLC, which due to its benefit was the preferred choice of technique within a purification service environment. Identifying this as the root cause of problematic evaporation provided opportunity to suggest and assess alternative methods of working. In particular, attention was focused on looking for appropriate alterations that provided large impact on time but that required the minimal amount of effort in terms of implementation. Specifically, emphasis on effort considered both the cost whilst attempting to avoid the introduction of an additional process step. Prior to the commencement of this project, a rapid solvent evaporator using vortex & vacuum technology was purchased for its ability to effectively evaporate reformatted individual samples using organic solvent straight into registration vials. During the initial stages of this project this system was gradually introduced, removing the second batch evaporation step in the original process, providing some initial steer for further improvements.

Numerous ideas and suggestions were discussed focusing on alternative purification techniques and different methods of evaporation. Both of these avenues were explored extensively, providing five major suggestions for improvements, each varying in their approach. Alternative purification techniques such as normal phase flash silica or SFC were considered as they would avoid the utilisation of water, whilst the removal of water from fractions post purification using Fraction Trapping techniques was also proposed. Alternatively, final discussions focused on answering two evaporation queries, could we routinely adopt a single rather than batch sample evaporation process and/or a method of evaporation from aqueous fraction straight into registration vials avoiding the time taken to reformat. The common use and availability of rotary evaporators provided the obvious answer for single sample processing, whilst for the second option the automated use of the vortex and vacuum technology was proposed.

Each of these proposals were ranked regarding the impact they provided on reducing turnaround time against the physical and financial effort required for effective implementation, summarised in Figure 2.

Evaluating potential improvements in this way simplified the most appropriate cause of action, with an ideal solution appearing in the top left corner of this diagram. Utilising the availability of spare rotary evaporators in-house was the most cost effective way to routinely achieve single sample evaporation.

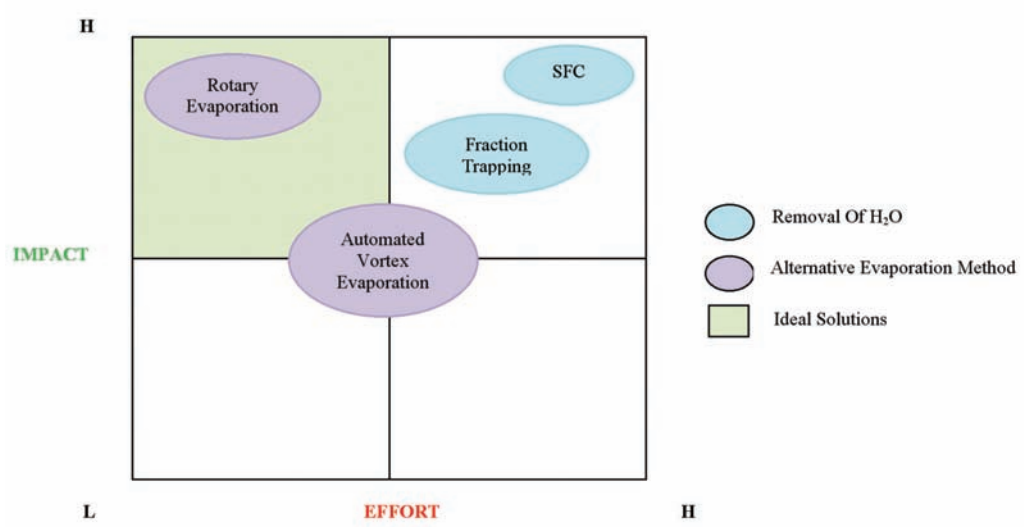


*Figure 2. Impact vs Effort of proposals on reducing turnaround time*

| Day | | | | | 1 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Process | Sample Supplied | Purify | Analyse Fractions | Transfer | Evaporate (Rotary) | Transfer | Evaporate (Vortex) | Oven Dry | Weigh & Analyse | Report | Sample returned |
| Time (mins) | 0 | 20 | 20 | 5 | 45 | 5 | 20 | 60 | 10 | 5 | 5 |

- Total process time of 195 minutes (3.25 hours)
- Process Cycle Efficiency (PCE) : 100x VA(min)/ Total Process Time(min) 100x100/195 = **51.3%**
- 44.4% Improvement in Efficiency!
- Reduction in individual sample turnaround time from **21** hours to **3.25** hours

*Table 2. Analysis of process steps in purification process following Lean Sigma optimisation*

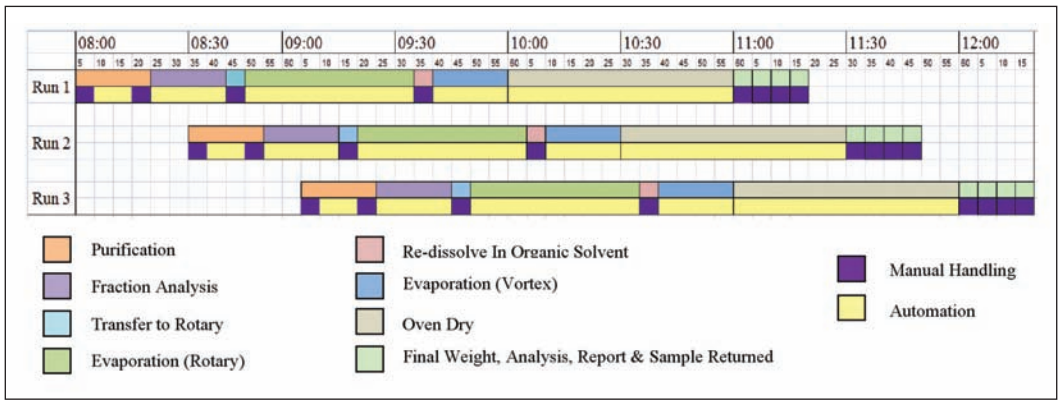


*Figure 3. Improved process work flow*

It was also possible to utilize existing instrumentation, for standard flash silica normal phase chromatography. However, it was difficult to establish an effective TLC system for all compounds as some were more suited to/easier to purify using HPLC. In addition, the ambiguity of the chromatography and lack of LCMS correlation can cause this technique to be more time consuming. Inevitably, these factors prevent the suitability and routine use of flash silica rather than preparative HPLC within a service environment. Consequently, the necessity to investigate alternative solutions that could be easily incorporated with the use of prep HPLC became apparent. This focused discussion towards different methods of completing the evaporation process and again provided support for the use of the rotary evaporators.

The second option to improve evaporation would have involved the automated use of a vortex & vacuum instrument which, as this had already been purchased required no additional cost. Unfortunately, through equipment trials this process was found to be extremely time consuming, directly impacting the overall value that could potentially be gained. It became apparent that the most effective improvement would be to routinely evaporate each sample independently. To ensure continuity throughout the system, samples would be processed by using a rotary evaporator for the aqueous fractions, re-dissolving the compound in a small amount of organic solvent, reformatting and evaporating into a registration vial using vortex & vacuum technology.

To successfully align our improvement plans with the requirements of the customer, it was necessary to ensure that the service also strived to deliver free flowing solids. The use of a one hour high vacuum oven drying step as a potential solution was suggested. The inclusion of this additional step was supported through the impact on overall quality delivered to the customer. This indicated the value of customer relations and by collaborative working the service was able to implement the most effective and beneficial solutions.

By altering the methods for solvent evaporation, the purification process has become more streamlined, positively impacting the PCE as represented in Table 2.

The outcome of these improvements dramatically reduced the turnaround time to within 4 hours per sample and by adopting a workflow system, numerous samples could be processed individually throughout the working day. An example of this process work flow is shown in Figure 3.

By using this workflow on a daily basis, it has become possible for one purification analyst to complete the purification and processing of up to 8 sample injections per day. A visual submission process was created to aid the execution of this daily workflow, allowing for 8 submission slots ranging from 8 am to 11.30 am. Each of these slots is staggered so that a new purification is begun every 30 minutes and all samples are submitted with an LC/MS and additional compound information. To ensure continual flow throughout the day each compound is purified using a single 5 ml injection over an independently focused 17 minute gradient. The analysis of fractions generated is achieved using LC/MS, taking 5 minutes to complete each fraction. This workflow was generated with approximate average values for each process step and is not absolute. Some samples may only yield one or two fractions as opposed to the four

that have been included here, again reducing the analysis, evaporation and overall process time for completion of the related sample.

The management of the revised process workflow has been achieved through standardization of the two preparative HPLC instruments used. To ensure each purification is achieved through a single injection, both systems have a 20 ml sample loop, allowing flexibility to inject >5 ml volume if required. Each of these systems utilises a 5 µm 50 x 150 mm column sufficient for all purifications up to approximately 1 g of crude material. Typically, most samples purified range between 100 – 500 mg and could easily be accommodated. These columns were chosen for their robustness, efficiency and ability to sustain both acidic and basic separations. To ensure that each individual sample could be purified accordingly and without delay, each instrument was provisionally dedicated to either acidic or basic modifier. However, the ability to switch modifiers through these columns allowed the flexibility of using both systems simultaneously with the same modifier. This allowed the service to accommodate larger workloads when required. The availability and standardisation of these HPLC systems provided a contingency plan to support the service with back up in the event of failure of one of the instruments. In addition, this also helped to maintain continuity for the individuals providing cover in times of absence.

### Conclusions

This revised process workflow has been functional within the department for over 18 months and has proved to continually support customer requirements, with an average of 80 final compounds per month generated from synthetic chemistry. As the capacity available in the service allows for 160/month, this can comfortably accommodate increases in demand whilst maintaining the efficiency and turnaround time in line with the customer expectations. This improvement project has been modeled on a prep HPLC purification platform but the flexibility in capacity allows for further adaptations. As part of Continuous Improvement, the service has progressed to the incorporation of normal phase chromatography in line with changing customer demands. To accommodate both 12 g and 40 g silica columns, the process workflow is maintained utilising 1 & 2 purification slots (30 minutes) per run respectively. The timeframe to complete these purifications can vary between samples but this time can be redeemed through the evaporation of purely organic solvent.

Offering this technique as part of the service has proved successful and encourages the use for key intermediate purifications alongside final compounds if spare capacity is available. It is envisaged that this revised process will continually improve through innovative thinking and customer feedback, critically assessing the ability to meet alternative or additional requirements.

Through adaptation of the working practices and customer collaboration a valuable reduction in turnaround time from 21 hours to 4 hours has been achieved. In addition, the alternative evaporation techniques have reduced the overall energy costs to 25% of the pre-improvement cost per individual sample. Consequently, the successful outcome of this project demonstrates the benefit of observing processes from a Lean Sigma perspective to implement the most appropriate, efficient and effective improvement strategies.

### References

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*3.http://www.isixsigma.com/index.php?option=com_k2&view=item&id=1013:sipoc-diagram&Itemid=219*
*4. http://www.valuestreamguru.com/?p=123*

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## ASTM Approves Column Set

Labs testing ethanol-containing finished gasolines now have a better alternative to TCEP columns. At its recent meeting, the **ASTM** D02 Committee announced a revision to method D3606 which now includes the D3606 column set from Restek. This column set separates benzene from ethanol completely and much more reliably than TCEP columns, resulting in more accurate quantification and tighter process control. Since a third column is not required, use of this column set simplifies installation and analysis. Additionally, all D3606 column sets are tested for method applicability and have higher thermal stability than TCEP columns, resulting in longer column lifetimes.

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