The Value of Lean Sigma: Improving GC Processes in Pharmaceutical R&D

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In an increasingly competitive market, today's science and technology strategies must deliver a superior product to the market in less time and for less cost. Efficient product and process delivery are optimised by encouraging real time analysis; putting the technique into the hands of the customer is essential to this.

Gas Chromatography-Flame Ionisation Detection (GC-FID) and Gas Chromatography-Mass Spectrometry (GC-MS) are techniques fundamental to the pharmaceutical R&D industry. These techniques measure the quality of raw materials and intermediates used in the manufacture of active pharmaceutical ingredient (API) and deliver knowledge into the synthetic organic process for effective learning. Raw materials, intermediates and impurities seen in the manufacturing process typically cover a wide range of polarities and are often highly structurally related, (e.g positional isomers). The supporting analytical methods must therefore be highly efficient and selective.
As a consequence, compound specific methods are typically developed.

Internal data show compound specific methods are struggling to support increased project demand. This article discusses the combination of new lean methodologies with advances in column technologies in order to improve efficiency of the GC process from method development to commercial technology transfer. These improvements have successfully responded to increased project demands in our organisation without requirement for large-scale financial investment.

Introduction

During development each pharmaceutical candidate is assigned its own cross-functional team including synthetic organic and analytical chemists. The level of GC support to a project is dependant on the properties of the process and the impurities generated. As a result an analyst's use of GC can vary from providing daily support to not using the technique for several months.

Historically the primary focus of GC method development has been for a sub- 30 minute method that is selective for the compound of interest and its related impurities. This approach has lead to a broad-spectrum of column chemistries and dimensions being used (our lab has over 185 different columns).

Increased data requirements and associated analytical support means instrument availability has reduced, and without financial investment or a change to the methodology, the current instruments will be unable to meet the project demands. In addition, a desire for increased product and process understanding from both analysts and synthetic chemists has resulted in an increase in the amount of data requested, and without increasing human resource the current way of working cannot fulfil project requirements. As a consequence, instruments are continually re-configured to meet project demands, resulting in high base level of training requirements. To successfully deliver projects, the GC process needs to reduce the turn around time for results and improve user familiarity.

Application of Lean Sigma

To improve the GC process we have adapted the principles of Lean Sigma, a well-established methodology within the service and manufacturing industries.[1,2] Lean Sigma principles are applied to improve speed, quality and reduce cost by removing time spent on wasteful activities and to reduce defects by reducing process variation. The key principles of a Lean Sigma process are:

- Goal: Remove waste from the process
- Benefits: Improved capacity, reduced lead times, increased quality and increased customer focus
- Outcome: Increased productivity and efficiency of processes

We focused on reducing waste by removing the non-value adding activities. We used the Define; Measure; Analyse; Improve; Control (DMAIC) roadmap as detailed in *Table 1*. Each of these areas are discussed below.

Table 1. The DMAIC approach uses five phases designed to reduce waste of an existing process

Define ↓	The business opportunity, voice of the customer and visualise a primary process map
Measure ↓	Time spent on value-added, business value and wasteful activities
Analyse ↓	The root causes of wasteful activities
Improve ↓	Develop and implement improvement solutions
Control ↓	Continually monitor improvement solutions to sustain long-term impact

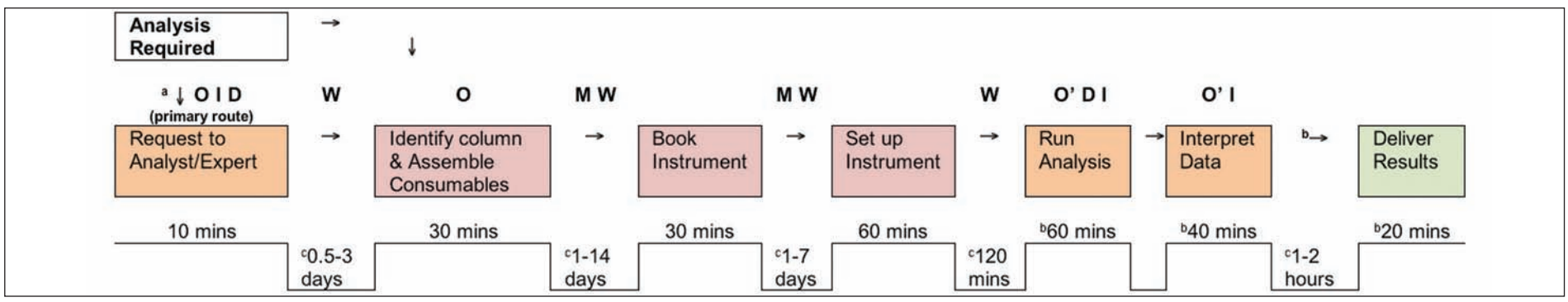

*Figure 1. Value Stream Map of preliminary GC Process. Areas highlighted in red are identified as wasteful activities; areas highlighted in orange are identified as business value activities; areas highlighted in green are identified as value adding activities. [a]Required only when second person is performing analysis. [b]Based on 6 samples with 10 minute total run time. [c]Indicates wait times (delays). The seven categories of waste are highlighted by the letters **T I M W O O' D**, definitions are detailed in Table 2*

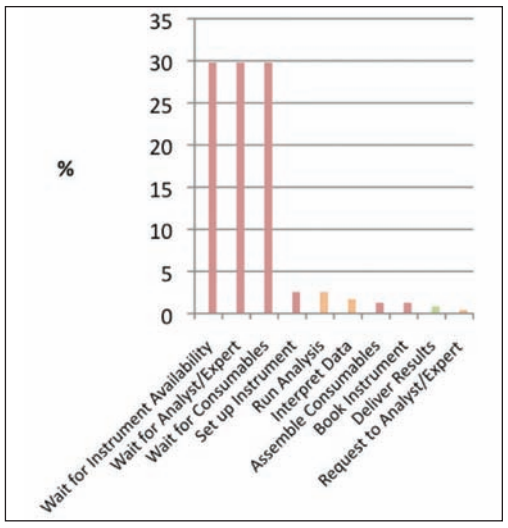

Figure 2. A Pareto chart of the preliminary GC process. Areas highlighted in red are identified as wasteful activities; areas highlighted in orange are identified as business value activities; areas highlighted in green are identified as value adding activities.

Define

Gas Chromatography is a powerful technique that is being underutilised in our department. The reasons for this are (i) the instrument availability is low, (ii) the process isn't standardised and (iii) results turnaround time is slow. As this occurs every time a user wants to perform an analysis, staff avoid using the technique.

The business opportunity identified was to deliver data quicker and exploit the use of GC. Based on a questionnaire, a value stream map of the current GC analytical process was produced (details in *Figure 1*). This investigation reviewed the existing process and addressed the root causes of why staff were underutilising the technique.

Measure

Data gathered indicated that project demand for GC analysis was far in excess of the instrument capacity available. Low instrument availability lead to long result turn around times through high waiting times, which in turn introduced additional wasteful activities that also contributed to increased result turn around time:

- Customers typically requested additional analysis to avoid extra waiting times (over-processing)
- Analysis was often left in an unfinished state because projects had moved on before results were available or additional analysis requested was no longer needed (inventory and over-production)
- Local instruments were not available, staff had to move between buildings to perform analysis (motion)
- Extra columns were ordered to anticipate future demands (over-processing)
- High base level training resulted with people being re-trained to perform the analysis (defects)

Activities that contribute to waste can be split into seven categories; transport, inventory, motion, waiting, over-processing, over-production and defects (TIMWOOD), details in *Table 2*. The wasteful activities identified above were applied to the value stream map to identify where they affected the process (as shown in *Figure 1*).

Analyse

Data collated in the measure stage were displayed in a Pareto chart details are in *Figure 2*. The Pareto chart identified less than 5% of activities were associated with the actual analysis. Approximately 90% of the total process time was due to unavailability of instruments, analyst/expert and consumables.

The broad-spectrum of columns in use was identified as one of the root causes of unavailability of instruments and consumables. Additionally the broad-spectrum of columns used meant there was no direct alignment with GC-MS platforms. Standardisation of column choice was identified as the main proposal to reduce the waste in the process.

Choice of Traditional Columns

To understand why so many columns were in use we reviewed the columns available to project analysts when developing a new method. These were;

- Standard low polarity stationary phases (1, 5 and 17, shown in *Figure 3*). These are robust and have high maximum operating temperatures (~300°C); however they give poor peak shape for polar compounds.

This is a good choice for low to mid-range polarity and semi-volatile compounds that are thermally stable

- Polar stationary phases (1701, 624 and WAX, shown in *Figure 3*) introduce selectivity and improve peak shape for polar compounds; however they have a low maximum operating temperature (~240 °C) and are less robust.

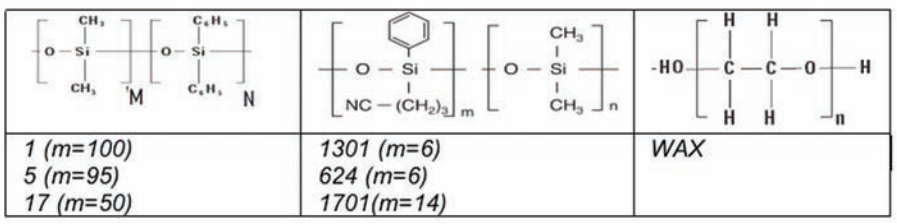

Figure 3. Column Chemistry

This is a good choice for high polarity compounds and complex volatile samples

- High capacity columns are suitable for strong solution concentrations; however they are unsuited to MS due to column bleed.

This is a good choice for routine analysis when strong sample concentrations are needed to obtain sufficient sensitivity when looking for impurities

- Low capacity columns are suitable for MS; but are easily overloaded.
- Wide bore columns are typically chosen for thermally sensitive compounds; however they are unsuited to MS due to flow incompatibility.

A review of these column limitations against our project portfolio showed why methods have been developed on a broad-spectrum of columns. For a standardised approach to be successful either more instruments have to be configured for project specific analysis or columns need to be suitable for a wider range of applications.

The next step of our evaluation was to assess new technology columns. These columns possess the same stationary phases as traditional columns but claim to have superior inertness, high sensitivity with low bleed and can be operated at high temperatures.

Improve

Evaluation of New Technology Columns

The initial assessment was carried out on InertCap columns (Hichrom, Theale, UK). Stationary phases chosen for evaluation were 1 and 17 with column dimensions; 10 m, 0.1mm i.d, 0.1µm film thickness. Polar analytes (including alcohols and primary amines) were tested for inertness, sensitivity and speed of analysis. The evaluation columns demonstrated improved peak shape for polar functional groups when compared to traditional columns. Good separation was achieved with sub-10 minute methods. However the column capacity was not sufficient to analyse typical sample concentrations.

The assessment was continued on the InertCap and RXI columns (Thames Restek, Saunderton, UK). Stationary phases chosen for evaluation were 5 and 17 with column dimensions; 20 m, 0.18mm i.d, 0.36µm film thickness. Project analysis (performed on existing methods) was repeated on the evaluation columns. These columns demonstrated improved peak shape for polar compounds (even when compared to polar (1701 and 624) traditional stationary phases), the sharper peaks contributed to improved resolution of the analytes. Multiple injections were run over evenings and weekends, low bleed was observed and chromatograms were reproduced throughout the evaluation to demonstrate robustness.

Implementing Solutions

The evaluation lead to the development of two methods (method parameters are listed in *Table 3*)

- Method A was an 8 minute method that had resolution for most applications during the evaluation. The initial temperature of 80°C improved peak shape for polar compounds and reduced total run time by 30% (compared to the traditional starting temperature of 50°C).
- Method B was a 12 minute method that improved resolution of complex volatile (<80°C multiple component) samples.

Table 2. Lean waste categories

Waste Category	Description
Transport (T)	Unnecessary movement between processes
Inventory (I)	Production of 'non-value' added goods
Motion (M)	Unnecessary movement of people or parts
Waiting (W)	For a process to be completed
Over-production (O)	Extra ordered 'just in case'
Over-processing (O')	Process more than required by customer
Defects (D)	Not right 1st time, repetition of a process

The R&D portfolio in our organisation is broad and therefore four columns were initially selected for the standardised method suite (column details are listed in *Table 3*)

- Column 1 was chosen as the primary column. The parameters demonstrated good selectivity and peak shape across projects and the capacity was adequate across typical sample concentrations (project examples are shown in *Figure 4*)
- Column 2 improved resolution of complex volatile samples and improved peak shape for highly polar compounds (small acids).
- Column 3 (50%-Phenyl) was chosen to complement selectivity; however with the high success rate of columns 1 and 2 there are no applications to date.
- Column 4 was chosen for thermally sensitive compounds. However increasing initial oven temperature and reducing the temperature gradient column 1 produced good chromatography whilst maintaining selectivity for compounds (an example is shown in *Figure 5*)

Table 3. Column and method details to support the suite of standardised methods

	Chemistry	Dimensions
1	RXI-5Sil MS (or equivalent)	20 m, 0.18 mm i.d, 0.36 µm film thickness
2	RXI-5Sil MS (or equivalent)	20 m, 0.18 mm i.d, 0.72 µm film thickness
3	RXI-17Sil MS (or equivalent)	20 m, 0.18 mm i.d, 0.36 µm film thickness
4	RXI-5Sil MS (or equivalent)	15 m, 0.25 mm i.d, 0.1 µm film thickness

	Method A	Method B
Injector:	Volume: 1 µL Temperature: 250°C Split: 150:1	
Carrier Gas:	He at 1.0 mL/min, Constant Flow	
Oven Parameters:	Initial Temperature: 80°C Initial Hold: 1 min Ramp: 45°C/min Final Temperature: 300°C Final Hold: 3 min	Initial Temperature: 40°C Initial Hold: 5 min Ramp: 45°C/min Final Temperature: 300°C Final Hold: 3 min
Detector:	320°C H_2:Air:N_2 30:300:30 mL/min	

To date column 1 combined with method A is predominantly used for new project analysis (>90%). Column 2 has been used for highly polar analytes that overloaded on column 1 and for improved resolution of complex volatile samples. These two columns have been set up as open access on 30% of our GC instruments (the value stream map of this process is illustrated in Figure 6) and column 1 has been set up as open access on a GC-MS. The resulting standard set up of instruments and reduced results turn around time has lead to improvements of GC support to projects through:

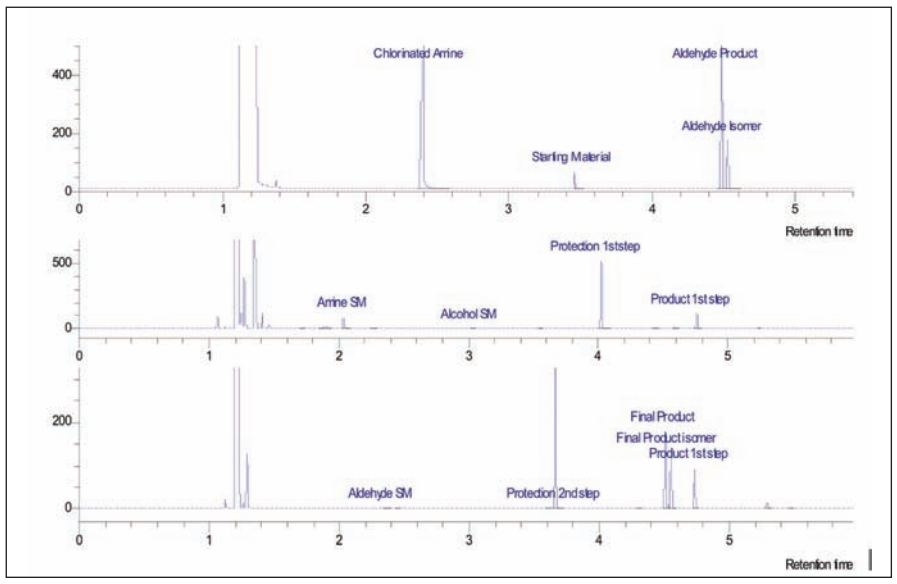

Figure 4. Project examples using Column 1 Method A. Chromatograms 1 and 3: High efficiency is demonstrated by resolution of positional isomers. Chromatograms 2 and 3: High inertness is demonstrated by good peak shape for reactive analytes (analytes with protection group chemistry)

- Completed analysis; results are generated in sufficient time to support project decisions
- Increased instrument capacity and availability; multiple projects are using thesame instruments
- Increased availability of a local instrument; an open access system is available in every area of the analytical and synthetic chemistry departments
- Increased colleague engagement; over % of synthetic chemists have been trained to use GC
- Increased analytical support to projects; data has shown the standard set up instruments are performing over 4 times the analysis compared with traditionally set up instruments
- Increased process understanding; feedback shows in-process analysis is routinely performed
- Enhanced learning: Experts can focus their time on problematic analysis
- Enhanced learning: The methods provide direct alignment between GC-FID and GC- MS instruments

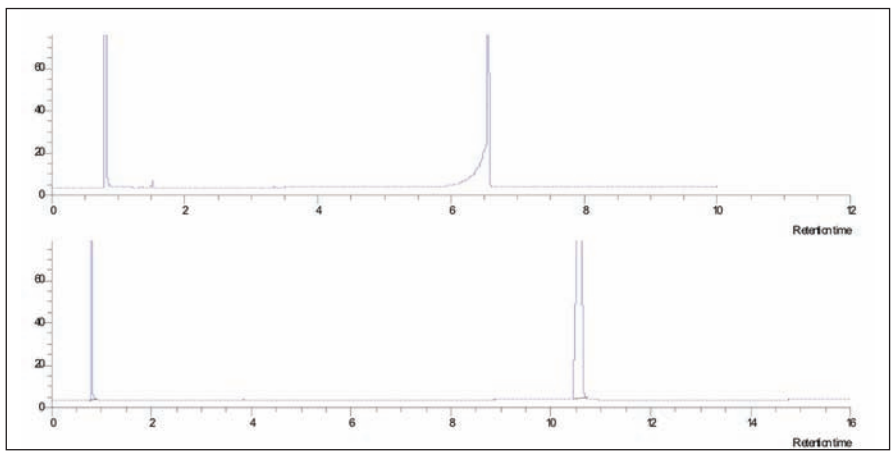

Figure 5. Project examples using Column 1 modified oven parameters to improve peak shape for a thermally sensitive compound. Chromatograms 1 Method A, chromatogram 2; initial oven temperature of 180°C, temperature ramp 5°C/min until 240°C. Positional isomer is seen at RT=11.0 minutes.

Additional benefit will be a reduction in batch failure due to method error. Increased data volume produced by multiple users on multiple instruments, means method variance can be monitored and addressed.

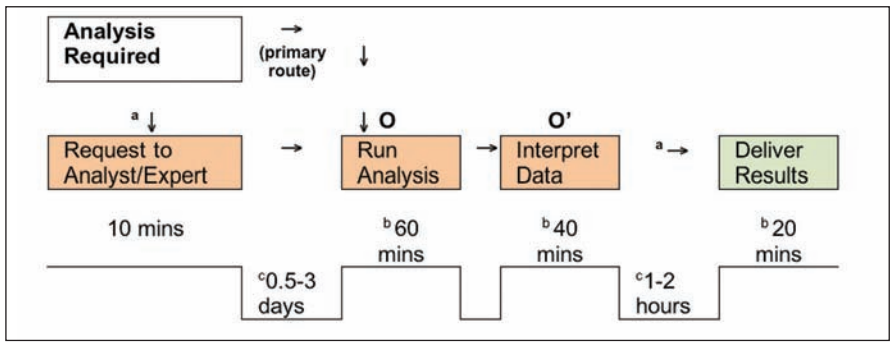

Figure 6. Value Stream Map of standardised GC Process. Areas highlighted in orange are identified as business value activities; areas highlighted in green are identified as value adding activities. [a]Required only when second person is performing analysis. [b]Based on 6 samples with 10 minute total run time. [c]Indicates wait times (delays). The seven categories of waste are highlighted by the letters T I M W O O' D, definitions are detailed in Table 2.

Control

To support continuous improvement GC usage and instrument availability is now routinely monitored and feedback is provided by the user to ensure the defined and standardised suite of methods are being used. An initial roll out of training was delivered to our department and GC training is incorporated to the induction package for all new starters.

The Pareto chart of the standardised process (details in *Figure 7*) illustrates more than 90% of activities are now associated with the actual analysis. Following the reduction of wasteful activities, the process is now suitable to focus efforts on reducing the number of defects by reducing method variation.

Evaluation on the RXI-624 Sil MS; 20m, 0.18mm i.d, 1.0µm film thickness column is in progress to compliment the existing standardised suite of methods by further improving sensitivity and selectivity for highly polar analytes.

Conclusion

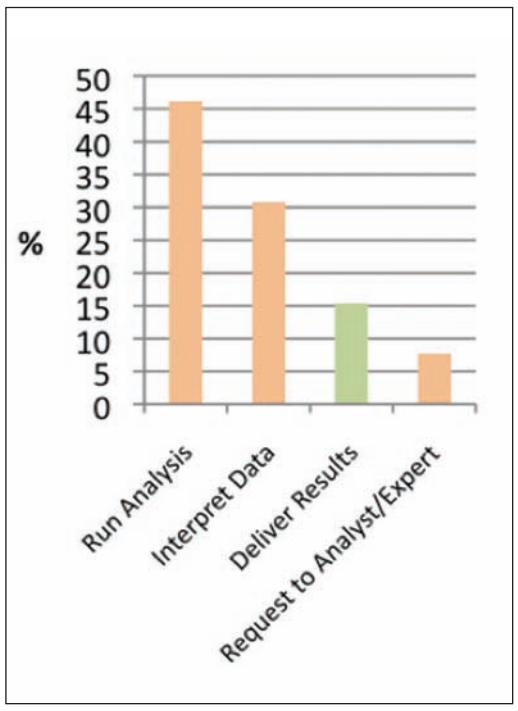

Figure 7. A Pareto chart of standardised GC Process. Areas in orange are identified as business value activities; areas highlighted in green are identified as value adding activities.

The standardised approach has reduced results turn around time from typically 1 week to <0.5 day. The instrument capacity has increased through better instrument availability because multiple projects are using the same instrument. This has lead to increased GC support to projects for both analytical and synthetic chemistry without the requirement for extra human resource or large-scale financial investment. An additional benefit is a reduction in costs due to less columns being ordered.

References

1. C.K Swank (2003) 'The lean service machine'. Harv. Bus. Rev. October

2. M Holweg, The genealogy of lean production. Journal of Operations Management 25 (2): 420-437