LEAN SIX SIGMA

its application to drug discovery

In an increasingly competitive world, the race between pharmas to get high quality candidate drugs to market is on. Contributing to this success is the discovery phase of lead optimisation. The application of Lean and Six Sigma processes have, until now, been theorised to benefit the improvement in the rate at which drugs progress through to development and improve the quality of the clinical candidates[1]. It is the objective of this communication to demonstrate that this is indeed possible.

By Clare Hammond and Charles J O'Donnell

Lean and Six Sigma are process improvement methodologies that have been used throughout industries as varied as the healthcare industry to car manufacturing[2], in order to improve their processes and respond the their customers' needs. Lean investigates the potential to remove non-value adding activities from the process, while Six Sigma attempts to improve the activities that must be done[3]. They are both data driven approaches[4], which respond to the requirements of the 'customer', however, it is only relatively recently that the combination of the two approaches has been considered. Publications have demonstrated the strong performance of Lean Six Sigma (LSS) as an important new direction[5,6]. Businesses are increasingly aware that improving quality with Six Sigma or trying to improve process efficiency with Lean isn't enough – they have to do both to get maximum payback[3].

Based on data generated, it is the objective of all LSS projects to identify and resolve the underlying cause of process blockers, rather than treating the outward symptom of the problem.

The pharmaceutical industry currently faces a difficult time, with competition on the increase. The ultimate aim of getting new or improved drugs to the market as quickly as possible is now beginning to come under the focus of LSS. Initial attempts to reduce the time taken to get a drug to market have focused on the necessarily lengthy development phase. It is only in recent times that the discovery phase has become the target of improvement strategies, with the potential improvements being theorised[1]. In the R&D world, the LSS term 'customer' may mean anything from downstream development departments to the clinical patient. In the first of its kind for AstraZeneca at Alderley Park, a Lean Six Sigma project was embarked upon within the Discovery Drug Metabolism and Pharmacokinetics (DMPK) department (CVGI), with the objective of improving the process of gathering *in vivo* pharmacokinetic (PK) data, the 'customer' being defined as the Lead Optimisation (LO) projects.

The PK process: the past

Based on certain *in vitro* parameters, such as enzyme potency or metabolic stability from hepatocyte assays, a compound was put forward for measurement of *in vivo* PK parameters†. Using these results, usually using rats as the primary species, the LO project would then make decisions on how to progress the specific compound of interest and the chemical series to which it belonged. In the Discovery department at Alderley Park there are multiple such LO projects all vying for *in vivo*

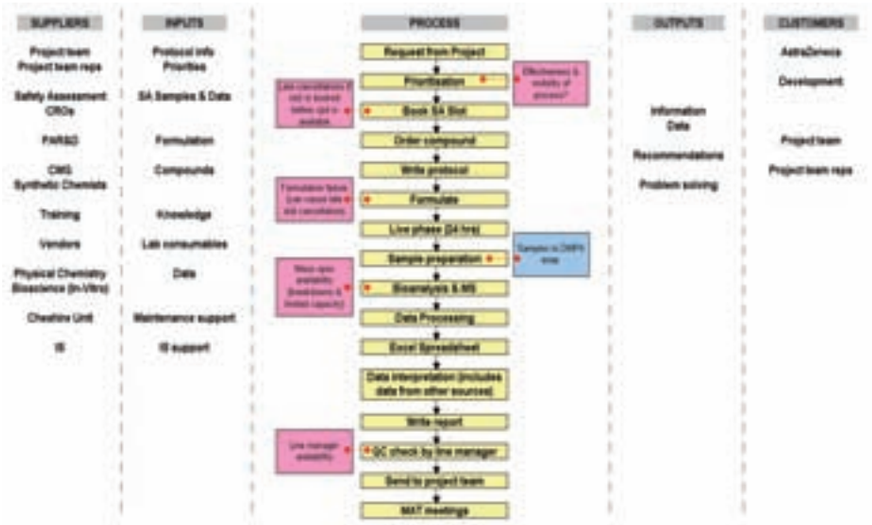

Figure 1: SIPOC Diagram. *Simple flow diagram detailing the people involved in each step of the PK process and what they bring to or receive from the PK process. Areas highlighted in pink boxes are known process blockers or causes of delay.*

PK data and information. In previous years, each LO project would request several dose slots per month, without knowledge of the needs of the remaining LO projects. Deadlines were not realised or adhered to, with demand for dosing often exceeding the capacity of the PK process. Compounding this, was the variability in the time taken for the *in vivo* data to be reported to the LO projects. By November 2005, it became clear the department could not continue in such a manner, and that something must be done to address it. Along came Lean Six Sigma.

Lean Six sigma

The Lean Six Sigma process is broken down into five interconnected stages: Define, Measure, Analyse, Improve and Control; abbreviated to DMAIC[3,7,8].

Define: *This step sets about defining which aspect of a particular process is to be improved. It included three main deliverables: the project charter, the voice of the customer, and a preliminary process map.*

The project charter

The project charter is a document that clearly focuses attention on a specific aspect of a process requiring improvement. The one-page document clearly defines the objectives, deliverables, benefits, scope, criteria for success and potential risks. The team members, a representative customer, sponsor and facilitator are also named.

Based on preliminary discussions with the LSS project customers (ie the LO project teams), a project charter was written. The LSS project had three key objectives: design a process to deliver rat PK results and information to the LO project teams within 10 working days from original request 80% of the time; to deliver high quality information and direction in the reporting phase; and to minimise the amount of time and resources required to meet the LO project's requirements. The scope was set out to focus on rat PK studies, as this is the primary species used by all LO projects when deciding on the need for further work and the direction it should take. The scope was intentionally set to be very focused on this particular aspect of DMPK.

The deliverables were detailed as: a clear understanding of the requirements of project teams, detailed understanding of the capabilities of the DMPK process with supporting data and information, and a set of recommendations for improving the process accepted as business case.

Five main benefits identified included simplified decision making in LO projects, no hold-ups in projects due to unavailability of PK data, better communication and shared learning amongst LO project teams, DMPK, the Compound Management Group and other external departments, and finally, improved understanding of roles and responsibilities and time freed up to use on other DMPK activities.

Criteria for success were stipulated as: management sponsorship of the Lean Six Sigma process and implementation of improvement opportunities; team members have sufficient time freed up, are committed to the LSS project objectives and feel empowered; required data is of sufficient quality and collected on time; and that the stakeholders and customers are appropriately informed, involved and supportive.

The LSS project team included DMPK team members who routinely conducted PK studies (which included the LSS project team leader), DMPK team leaders, a representative LO project team customer, the LSS project sponsor and the master black belt project facilitator. In total, 10 DMPK (more than half the FTE number employed in the section, emphasising the commitment to success of this project) members were in some way involved in the Lean Six Sigma project.

Voice of the customer

Once the Lean Six Sigma team had been established, they embarked upon a voice of the customer exercise. This took the form of face-to-face discussions with key LO project stakeholders. In this exercise, the customers defined what they wanted to see as a tangible outcome of the project. It was stated that the LO projects would like their data to be reported within 10 working days from request, and that quality information and interpretation of data should be provided in the report, they did not want DMPK to become a service that merely provided numbers. As variability in the time taken to report PK data had been a problem for the LO projects, they required the variability to be reduced, with 80% of all studies to be reported within the 10 working days criterion. They also requested a more consistent approach to the methods used during the conduct of a PK study. Through this exercise, the LSS team ensures they do not correct the wrong things and that the objectives of the charter meet the customers' requirements. The customers are also made aware of the scope and therefore what to expect as a result of the LSS project.

When put to members of DMPK, these figures appeared unreasonable and impossible to achieve without considerable amounts of stress being caused. It was therefore agreed that the turn around time might be negotiated based on the findings of the LSS project. The results of the voice of the customer exercise were used to clarify the objectives, scope and desired outcomes of the LSS project.

Preliminary process map

A simple process map was drawn up in the form of a flowchart (**Figure 1**). This helped define the suppliers, their inputs, the processes key stages, the outputs from these and the customers of them. This SIPOC (Suppliers, Inputs, Process, Outputs and Customers) diagram helped to inform the team who would be appropriate to include in future discussions and whether any further VOC discussions were required. This SIPOC diagram was later developed into a more detailed process map, indicating where decision points, potential blockers and causes of delays may lie.

This approach identified areas of commonality or difference in the conduct of PK studies between LO project teams. It developed unanimous agreement in the process steps within the LSS project team. All LSS team members, including the facilitator, gained a clear understanding of the current PK process and the rationale for change. The process map began to distil the value adding activities that are required but may be improved upon and the non-value adding activities that may be reduced or removed completely.

Measure: *This phase consists of a period of time spent gathering data in order to understand the performance of the current PK process.*

During the first three months of the LSS project, data was gathered in order to understand the current state of the PK process. Information on the speed, quality and costs of the suboptimal process were collected. A simple tool called 'deviation reports' were used extensively to describe the problems encountered that prevented the successful transition from one step of the PK process to the next.

Once a process blocker or delay was encountered, the DMPK scientist experiencing the issue wrote down information describing the problem on a simple form, referred to as a deviation report. Costs in terms of days delay to the LO project and time lost by the scientist trying to resolve the problem were also recorded. The data was used to expose the underlying root causes of problems. These details were used to indicate which blockers would yield the greatest benefits if improved. It also enabled the identification of the non-value adding steps that may be of most benefit to the PK process if reduced in timescale or removed from the process. The PK process had not significantly improved, despite a general trend seen, during the measure and analyse phases (**Figure 2**) of the LSS project. The reduction in the average turnaround

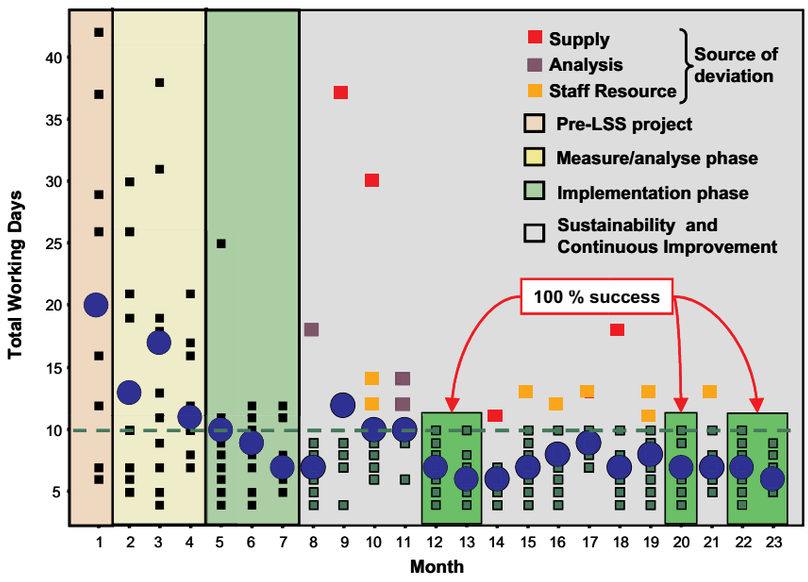

***Figure 2.* PK Turn around times.** *Data gathered at the end of 2005 was used to initiate the project. Similar data gathered during the measure and analyse phases of the lean sigma project demonstrated no initial improvements due to focussed attention or the structural changes within DMPK. It was seen that average turn around times (blue circles) exceeded the desired 10 working days and that they are highly variable (black/green filled squares). The green dashed line represents the target turnaround time. Variability and average turn around times dramatically reduced during the implementation phase. This trend has been maintained and improved upon throughout the continuous improvement phase.*

times may have been as a result of trials in certain improvement solutions, however, the average turnaround times had not reached the desired 10 working days and the variability remained high. It was clear that the full package of solutions were required to be implemented in order to achieve the LSS project's objectives.

PK capacity

Demand for PK studies was examined and information on the number of studies dosed and the number of compounds studied per month was recorded. Calculations into the maximum capacity were made, investigating human resource, plus dosing and analytical capacity. These capacity calculations were conducted in order to ensure demand meets capacity throughout the PK process and that bottlenecks are avoided. Dosing capacity was fixed at 10 dose slots in-house with a further four through a contract house. Analytical capacity was determined to be 14 slots per month, equating to 50% of current capacity of all mass spectrometers running 24 hours per day, 7 days per week (the remaining 50% was assigned for all other non-PK related activities).

Human resource was found to be capable of running 21 studies per month. The limitations would therefore be analytical capacity and dosing slots. It is widely accepted that a process should be run at approximately 60% of capacity in order to absorb times of excess or failures, if and when the need arises. It was calculated that the maximum number of studies the PK process would be able to cope with was 16 studies per month, divided between all species and strains available.

Data gathered during the early stages of the LSS project indicated that the number of studies dosed was far in excess of the maximum capacity of the PK process for much of the time. This was found to be as a result of the LO projects not being aware of the maximum capacity. Times of highest activity coincided with LO projects aiming to achieve particular project milestones, and also coincided with the longest turnaround times recorded. In 2006, the DMPK team struggled to clear backlogs when failures arose due to the demands placed on it. Through the Lean Sigma project it was argued that we should aim to avoid the spikes in demand seen in early 2006. It was agreed that where possible, these milestones

should be staggered throughout the year in order to prevent the PK process being operated at 100% for extensive periods of time.

Matching demand for PK slots with capacity was indeed reported as being a problem. However, matching demand to dose compounds and the ability to do so was not the only example where demand and capacity did not marry. Human resource and the capacity to analyse the samples via mass spectrometry were also reported capacity deviations.

Analyse: *The root causes of the blockers are identified by using the data gathered during the measure phase.*

Using the collated information, the cumulative time lost to both the projects and the scientists were determined. The frequency with which a deviation occurred and the related costs were plotted. Root cause analysis using a '5 why?' exercise allowed the underlying cause of the problem to be determined and therefore the most appropriate solution to be determined, rather than a 'sticky plaster' approach to remove the symptoms.

A '5 why?' exercise uses the information gathered in the deviation reports, and asks the question 'why?' at a particular problem. After asking 'why' five times, the underlying root cause is determined. Solutions are then designed to target the root cause revealed, rather than the problem reported.

The cost of action verses the cost of no action was determined and problem areas that would be of most benefit to resolve were established. Various improvement opportunities were identified. Many opportunities were presented, however, it was not possible to address all of them at once. Improvement opportunities were prioritised and solutions determined to resolve the most costly problems and those that would reveal the greatest benefit to resolve. The criteria for the solutions were that they should not add time or effort to the scientist, and should address the underlying root cause.

Improve: *Changes are identified and implemented during this phase. The changes (or solutions) are designed to collectively improve the process. Changes may include the complete removal of some steps in a process or the introduction of tools to improve those that remain.*

Kaizen events were held in order to determine and develop the most appropriate solutions[8]. Kaizen events are highly structured meetings, in which an agenda and meeting objectives are circulated prior to the meeting. Any activities are required to be completed before the start. Such events were conducted as two-hour meetings. The chairman ensured any discussion was kept relevant to the subject and that the timescale was strictly adhered to. Through these focused discussions, appropriate solutions and tools were developed. Trials were conducted on some of the tools to be implemented and allowed to evolve into a more robust solution as a result. Before the solutions were fully implemented, they were communicated to the CVGI community and agreed with the key customers. Comparison against the project charter ensured the solutions were as appropriate as possible.

Many tools were implemented as a result. Changes included visual planning tools for scheduling ongoing PK studies and mass spectrometer use. Working practices, 'super-users', improved preventative maintenance, QC checks and service contracts, all relating to the mass spectrometers, have been revised and implemented. Improved lines of communication, both inter and intra LO project teams and within DMPK allow enhanced time and resource management. A PK study index has been made available to all LO project team members in order to allow improved transparency and planning of studies. A service level agreement was approved and signed by LSS stakeholders and project sponsors alike. Visual planning tools, mass spectrometer logs and reporting tools have been installed in an attempt to improve efficiency and reduce the time required to complete a PK study.

Training in tools developed was offered to all DMPK members. Visual planning tools have been installed in order to clearly see where a LO project or team is most busy, whether they may need additional resource, and whether there are any problems resulting in the process being slowed or halted, allowing more effective planning and use of all resources available.

Throughout the LSS project, PK turnaround times were recorded. Data collected in the first three months of the LS project (pre-implementation) correlated with the data compiled at the inception of the project (**Figure 2**). These turnaround times were recorded immediately after the implementation of the tools developed to improve the process. As can be seen in **Figure 2**, an immediate and marked improvement was made, with the average turnaround time being reduced to the desired 10 working days and the variability being much reduced on implementation of the various tools.

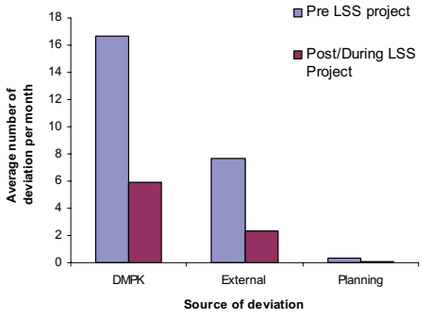

***Figure 3:* Deviation reports.** *Showing the frequency with which a particular problem occurred. An example of a DMPK related deviations would be a sample analysis failure, an external deviation could be lack of compound availability and a planning deviation might be a problem concerning communication between DMPK and another department resulting in a scheduling problem Deviation reports collected during the continuous improvement phase indicate DMPK related issues and those external to DMPK have dramatically reduced and remain low. Planning issues have been eliminated.*

The PK process: current times

Control: *During this final phase, the improvements are monitored and controlled in order to sustain the long-term impact of the changes.*

The outcomes of the Lean Sigma project had an immediate impact on the turnaround times. However, the purpose of utilising a LSS approach was to ensure that these improvements were sustainable. Data on turnaround times continues to be collated in the continuous improvement phase the DMPK team is now in. Data collated in the first few months of the LSS project (prior to the implementation of solutions) revealed variability in the turnaround times was large, with the mean turnaround time being above the desired 10 working days. This data closely agreed with the pre-LSS project figures used to instigate the Lean Sigma project (**Figure 2**). Immediately after implementation of the various tools, the average turnaround time fell to the required 10 working days and variability was markedly reduced (**Figure 2**). Data shows that the results have indeed been sustained during the 18 months post implementation.

During 2007 only one month fell below the target of 80% of studies being reported within 10 working days. This was as a result of large-scale mass spectrometer failures. All other months have achieved 90% or more of all rat PK studies being reported within 10 working days, with most months achieving an average turnaround time of seven working days. This result is an improvement on the objectives originally set out in the project charter, clearly demonstrating the sustainability of the solutions implemented. Additionally this should be seen in the context that the team originally viewed the objectives as unrealistic.

On occasion, a potential deviation may be predicted and therefore planned for. For example, PK studies conducted through a contract house were routinely turned around within 12 working days, due to transit times. The LO projects were made aware and exemptions to the 10 working day rule were agreed. The anticipation or prediction of such one-off deviations may be planned for, lessening the impact should the deviation occur.

Deviation reports continue to be filed to ensure the department does not return to 'the bad old ways' and that any new problems that occur may be highlighted and dealt with early. The total numbers of deviations have reduced since the implementation of various solutions (**Figure 3**). Through monitoring this information, the DMPK department is able to maintain the improvements made and to further improve the PK process. Learning was applied to PK species other than rat, with improvement in mouse and dog PK studies being evident. Deviation reports now describe issues outside of the control of the DMPK department (eg routine building maintenance) and do not arise very often. Indeed, it had been shown to be possible to turnaround all PK studies within the desired 10 working days during five months of 2007.

In an attempt to match demand and capacity, PK slots are no longer for the sole use by a particular LO project. Each slot is assigned to a project (*vice versa* during pre-implementation) for them to use as they wish. Any unneeded capacity is then offered to the remaining LO projects. **Figure 4** shows that the implementation of this approach has not resulted in a compromise in the number of compounds able to be dosed. Improved protocols has resulted in more compounds being dosed in 2007 (cf 2006), evidence that limiting dosing capacity has not negatively impacted the LO

projects. In later months, demand has fallen, with initial PK data being used to make more informed decisions about future dosing strategies.

Access to a study index enables the LO projects to more effectively plan their workload and resources. Through the improved planning process, LO projects continue to achieve milestones in a timely manner without sacrifice. The staggering of milestones throughout the year ensured the large spike seen in 2006 was not reproduced. Dosing capacity was rarely exceeded during 2007.

An additional problem area highlighted through deviation reports was the failure rate of the mass spectrometers. Through analysis of the data available, it was found that mass spectrometer or auto sampler failures resulted in ~30% of the time lost to both the scientist and the LO project teams. It was realised, although it may take a large amount of effort to resolve, mass spectrometers must be made to work more reliably, with initial targets set at 90% of all studies to work at the first attempt, as opposed to the 50% determined. This required a large amount of work and changes, including improved Mass Spectrometer user training and the use of simple templates to avoid human errors.

Matching demand with capacity was required with respect to analysts requesting Mass Spectrometer time. Planning tools have been implemented, making it easier to schedule analytical time or times of preventative maintenance and servicing. Users may also use this tool to document any issues encountered and relate this information to the remaining DMPK team.

Implementation of various solutions has resulted in the reduction of many problems, particularly those under the control of the DMPK department, as shown in **Figure 3**. Improved communication has resulted in the reduction of problems not directly under the control of DMPK but under their influence. Although many of the solutions are very simple, the cumulative effect of all of them has resulted in a significant improvement in the turnaround of all PK studies conducted.

The original target of 80% of all rat PK studies to be turned around within 10 working days appeared to be an unobtainable target at the onset of the LSS project, however, the DMPK team are now able to turnaround 90% of rat PK studies within seven working days. Past experience has shown that initiatives that have attempted to address similar problems often result in short-term improvements that are hard to sustain. However, the solutions implemented here have been demonstrated to be give sustainable results with the immediate effects being the norm over a year later, as shown in **Figure 2**.

Working within the constraints of the PK process capacity has enabled the turnaround times to be rapidly reduced and maintained. Backlogs are less likely to occur and are more easily cleared if they do. A large amount of work based on a considerable body of data has resulted in the initial objectives of the project being met. Tools and learning that were originally developed to address issues within the generation of rat PK have been

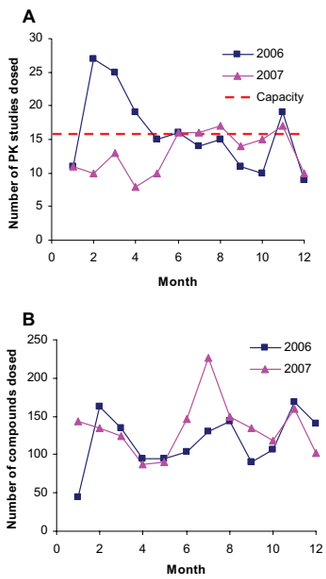

Figure 4. **Throughput.** *(A) shows the number of rat PK studies conducted per month. Greater fluctuation is seen in the 2006 data. Data shows that the number of studies dosed during 2006 at times greatly exceeded the maximum capacity of the PK process. Similar figures show that in 2007, the process successfully remained within capacity range. (B) shows the number of compounds dosed for the same period. Improved study design has resulted in a larger number of compounds being dosed through 2007 (1,618) as compared with 2006 (1,410).*

applied to other species, with these species also showing improved turnround times. Consistency in the methods used has enabled flexibility within the DMPK team, enabling improved support of many LO projects by a relatively small team. The number of deviation reports to be filed has reduced since the implementation of the tools developed, with a larger proportion detailing factors outside of the department's control.

The future: life after LSS

Life in the post-LSS era bears testament to the activities and achievements of the LSS team. The PK process is now a much more refined model, satisfying the LO project's (ie the customer's) needs. It has also created a much calmer and less stressful environment. It has provided the opportunity to improve other aspects of DMPK life. Learning has been applied to *in vitro* assays, such as metabolic stability in hepatocytes, and CYP inhibition. It also allows the DMPK scientist more time to embark on other value adding past-times such as assay improvement and innovative assay development.

Original fears relating to the PK process becoming a production line, with the scientist acting as an 'automaton' have not been realised. Stress has been much reduced, resulting in a markedly improved working atmosphere. While in the past, a DMPK scientist may have spent a large amount of their working week trying to resolve problems encountered, this time has now been released enabling them to work as scientists. There are currently in excess of 10 new technologies being investigated and validated with a view to their introduction to the DMPK toolbox of *in vitro* assays. We are experiencing the benefits of a more innovative culture. Not only are we able to keep pace with science and technology, we are now moving into a position where our improved innovative prowess has resulted in the potential to set it.

Summary

The application of a Lean Six Sigma approach to the rat PK process has greatly improved the turnaround times and support offered to LO projects with 90% of rat PK studies reported within seven working days. Learning has also been applied to non-rat species without the need to conduct a full Lean Six Sigma project. Improved decision making within the LO project now provides the possibility to generate candidate drugs of higher quality and more quickly. Innovation is also on the increase, allowing the DMPK scientist opportunity to work in more scientifically stimulating environment.

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† Any procedures involving animals were given ethical approval by the UK Home Office under the Scientific Procedures (1986) Act. DDW

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