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Ozgene: to advance humanity – inspire curiosity

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Once we understood that things are truly just processes,
we became empowered to say, 'Let's give it a go. Let's build the process.'

- Frank Koentgen -

How far we've come

Dr Frank Koentgen, Ozgene CEO, was sitting in the Monday staff meeting, listening to each team discussing their weekly output. Projects had been steadily flowing through each process and team with predictable inputs and outputs. Any issues impacting processes were raised and discussed. The lead time average was holding steady at 29 weeks. Frank was not satisfied, he knew they could do better, but then reminded himself about how far they had come. He could remember only too well how it was in the 'bad old days' before he stumbled upon the book *The Toyota Way* by Jeffrey K. Liker at a bookstore looking for some travel reading. Back then people were working hard, doing their best, but the project timelines did not reflect that. There were numerous delays and queues, failed processes and repeated work. Customers were used to 18-24-month lead times – that was 78-104 weeks! In those days there was no point in measuring project timelines in weeks. Frank's thoughts drifted back to those early days of starting Lean: 'How did we do it? Where did we start?'

Ozgene background

Founded in 1999 in Perth, Western Australia, Ozgene is a small biotechnology company providing contract research services to academic researchers and biotechnology/pharmaceutical companies worldwide. Specifically, Ozgene generates and breeds genetically modified mouse models for medical research. Asked to describe their services, Frank says, 'Imagine a large family and within that family you have a couple of people that have an illness or a disease. They

go to the hospital. The hospital does a DNA analysis and you find that the patients have a genetic difference when compared to healthy people. You then come to us (Ozgene) and we make a mouse with the same genetic change. If the mouse develops similar symptoms, then you have found one of the genetic causes for the disease, and you also then have an animal model that you can use to either find a treatment or a cure for that disease.'

Mouse models are used by research teams around the world to study different cancers, cardiovascular diseases, infectious diseases, neurodegenerative disorders, and so on. They can also be used to discover and study the function of specific genes.

Ozgene's mouse models are custom designed, and each mouse model generation project starts when a customer places an order. Even though the projects are customized on a genetic level, all of them go through the same process and milestones with specialized teams working on the project at different stages.

Ozgene's vision is 'to advance humanity - inspire curiosity'. For the team at Ozgene, the services they provide to aid medical research represent a way to advance humanity. Ozgene has become a company dedicated to this goal, and they do it by inspiring curiosity within themselves and their customers.

Ozgene's process to generate a mouse model

Project Design - All living organisms have a unique set of genes that dictate their traits and characteristics codified by DNA. A genetic modification means locating, targeting, and modifying DNA using what are called *gene targeting vectors.* Vectors are microscopic pieces of DNA that can replicate independently of a host organism's genome. Vectors are designed with specific sequences that allow it to recognize and bind to a target gene in the host organism's DNA. Once the vector has bound to the target gene, it can insert or delete DNA at that location, resulting in changes to the organism's genetic makeup.

Ozgene's Project Design Team collects customer requirements and designs the targeting vector to match their specification. In addition, they create *assays,* specific protocols designed to detect or measure the presence or activity of a specific gene. They also order the project specific materials be used in the construction of the targeting vector.

Vector Construction – After vectors are designed and the needed genetic materials are acquired the vectors are constructed or assembled by the Vector Construction (VC) Team using Ozgene's patented Sequential Cloning System, which requires the assembly to be done in a sequential order (A+B, AB+C, ABC+D and so on). There is a rigorous Quality Control (QC) process where each fragment, assembly step, and the final vector are sequenced to ensure the correct DNA construction before proceeding to the next step.

Tissue Culture and Genotyping – Next, using a pulse of electricity, the Tissue Culture Team implants the assembled vector into mouse Embryonic Stem (ES) cells. After successful delivery of the vector (the process is called electroporation) the Tissue Culture Team then isolate the resulting ES cell colonies and prepare DNA from the individual ES clones. The Genotyping Team then screens the ES cell clones using assays designed by the Project Design team to find the ones that are targeted. Targeted ES cells are moved on to microinjection. If the assay screen shows there are no targeted ES cells, the project moves back to Tissue Culture for another electroporation.

Microinjection Embryos – The Microinjection Team injects the targeted ES cells into mouse embryos to generate mice that carry the desired genetic modification. This process typically generates chimeric mice containing two different sets of DNA, one from the embryo and one from the injected ES cells, however, Ozgene's proprietary goGermline™ technology ensures that only the ES cell DNA (not embryo DNA) can be passed to the next generation. They are therefore called goGermline™ males (not chimeras).

Breeding Genetically Modified Mice – The Vivarium Team breeds the goGermline™ males with females to obtain offspring derived from the ES cells. The resulting offspring are screened by the Genotyping Team using the same assays as in the ES cell step to confirm that the mice carry the desired genetic modification. These mice can then be sent to the customer. If no mice with the desired modification are identified in the screen, more breeding or repeated microinjections are required. These repeated processes rarely occur as the goGermline™ technology usually produces the desired mice from first injection and breeding steps.

Shipping – The Shipping team organizes a delivery of 2-4 breeding pairs of genetically modified mice to the customer to enable them to generate a mouse colony in their facility.

(The process flow diagram of a typical Ozgene project is included as Exhibit 1 and the current lead time and average weekly output per stage as Exhibit 2.)

Competing against time

Frank's thoughts wandered back to those early days. The principles in Liker's book had immediately resonated with Frank, especially the ones related to process. (See the list of principles in Exhibit 3).

Ozgene's customers rarely reported that mice didn't meet standards; however, they were often disappointed in the amount of time it took to get the mice. The industry standard for mouse model generation using ES cell targeting was 12 months and Ozgene's projects generally took 18-24 months. A leading competitor was advertising 40-week (9.2-month) timelines, which were considered the best possible at the time.

Upon closer reflection, Vector Construction (VC) immediately stood out as the longest and most variable step. Approximately 80 vectors were generated annually by the VC team. A team of six staff worked on multiple vectors at the same time following Standard Operating Procedures (SOP) to create DNA fragments and to assemble them in a sequential order to create a final DNA construct. There were QC steps associated with each fragment creation, each assembly step, and to fully assess the final vector. The process took an average of 52 weeks per vector with a standard deviation of 26 weeks.

Frank worked with the VC team to map the value stream, a sequence of value-adding processes required to transform raw materials and information into a finished gene targeting vector. The team discovered that if all processes were completed one after another, without any waiting time, and ignoring any people or equipment capacity constraints, VC should take 11 days (if working 24 hours a day). Then why was the average throughput time for VC 52 weeks?

Building the process flow allowed Frank and the team to see what an ideal, Lean process looked like and to identify areas where waste and delays occurred. While this in itself did not reduce lead time, it was the first, crucial step to expose waste, unmask problems and build the improvement mindset within the team. It also highlighted the challenges to parallel process the complex VC flow.

Frank expressed his thoughts, “Many of the VC processes needed to be done in a sequential order, so how do you not keep the process linear? Where can you save time?” He knew that there were hands-on processes and incubation times, that is, you set up a process to run on a piece of equipment and it had a 15-minute incubation time. What did you do in those 15 minutes, just wait? Top chefs did this all in their head to ensure that the different parts of the meal all came out exactly at the same time, ready to be served. How could this be achieved in the laboratory?

While important, it became apparent that scheduling alone would not be enough. Even if each process was done with a minimal waiting time, there were many process failures that caused the projects to loop back to the previous steps. Team members worked on their specific process task and did not have visibility to the delay loops that some projects were caught in.

“Most businesses are 90% waste and 10% value-added work.”

- Jeffrey K. Liker -

Getting to (standard) work

The principle of standard work appeared to be the countermeasure to both scheduling issues and process failures. In order to schedule parallel tasks into a schedule to maximize productivity and capacity, the team first needed to know how long each individual task took. The process and the human aspects were separated – they went about trying to identify the optimal way to perform the process itself regardless of the person doing the work. The first in-house application of Step-by-Step (SBS) was launched. While the old Standard Operating Procedures were stored in a computer folder and accessed periodically for updating or training, the SBS was used on iPads in the laboratory where the work was done. The SBS steps included a simple 'verb: noun' instruction with an image and associated time. (Watch video https://youtu.be/vRY5BOqhEuU or see Exhibit 4 showing the SBS being used in the laboratory).

Frank drove a mindset of focusing on the process, not the person. The team members were only held accountable for executing the processes according to the SBS. If the outcome was not as expected, the team member could not be held responsible for the outcome as long as the SBS was followed. Frank appointed himself as the responsible person for the entire system, and therefore each process outcome. The previous culture of blaming the team members for failures was replaced by a culture of empowering team members to find flaws in the processes that could be improved.

While writing the SBS, staff recognized significant variation between different people performing the same task. They were able to refine the processes as a team and find a common SBS that everyone could follow and consistently reach a specific throughput time. These standardized processes and accurate times were then used to create schedules with 5-minute increments to allow parallel processing, using the incubation time of some processes to perform other processes. (See a typical VC schedule included as Exhibit 5). Each employee followed a set schedule using standard work with defined inputs, processes, outputs, and timing, as guided by the SBS. The waiting time decreased and throughput time improved.

The introduction of standard work and the SBS were necessary stepping stones enabling the substantial lead time improvements that were yet to come. They focused the staff on the process and empowered them to make improvements. Standard work and the SBS also facilitated the building of schedules for parallel processing using predictable process times.

Removing red

Value stream mapping with VC had revealed issues in processes, consumables, practices, work instructions, quality, and handovers from other teams, which were all leading to waste. Frank asked everyone at Ozgene, regardless of the team they worked in or processes they worked on, to write down each problem they came across on a red sticky note and put it on the wall. Frank had no idea what the actual number of red was, so inspired by the Fibonacci number

sequence, he set a target of 377 red stickies to be found. As a reward for reaching the target, Frank promised to treat everyone for a pizza. The pizza was ordered in only a matter of days.

As a result of the exercise, the team learned to identify the broken processes, unacceptable quality, and outdated consumables and practices. Surrounded by their new red wallpaper, each team was now 'removing red' by ticking off their red stickies and fixing their issues one by one. This signified another change in the company culture and overall mindset, where finding errors and flaws was embraced and even celebrated as it was a way to make improvements going forward.

Organizing the workplace

One of the many outcomes of the 'remove red' exercise was the obvious need for workplace organization. With the help of a consultant, the laboratory and vivarium teams reorganized their workplaces using 5S principles by 1) Sorting items to necessary/unnecessary and removing the unnecessary, 2) Straightening, labeling and organizing all items in their optimal positions on a workstation based on the workflow, 3) Shining/cleaning the items, 4) Standardizing the new practices and 5) Sustaining the standards to maintain the achieved improvements. (See examples of Ozgene 5S as Exhibit 6.)

Having an organized workplace eliminated clutter and helped reduce the time wasted on searching for tools, equipment or information. This resulted in lead time gains through streamlined workflows and faster completion of tasks.

Getting it right the first time

While standard work, remove red and 5S had eliminated a lot of the variation and problems in the system, it did not prevent all failures from occurring. Frank had visited a Toyota assembly plant in Japan as part of a Shingo Study Tour where he was introduced to the 'Andon' cord. If workers spotted a problem in a car, they could pull a cord that would stop the assembly line and everyone around them would collaboratively fix whatever was wrong before the line was started again. The Andon cord made problems more visible and encouraged workers and managers to find and fix the root-causes of problems.

Ozgene's projects did not run on assembly lines, but data could be collected and analyzed to identify the most commonly occurring failures. The issues were investigated to find a root cause of each issue, and countermeasures were deployed to fix them. Employees no longer attempted to hide mistakes. The psychological safety was created largely by Frank, who had made it his goal to build trust and confidence in the team through coaching, teaching and mentoring, centered on the core values of being humble and respectful. This mindset was adopted by others in leadership positions and eventually trickled through to the entire team.

Finding issues was now applauded since it ensured that ‘bad work’ did not get passed onto the next team. The Andon principle, if not the physical cord, was adopted at Ozgene. ‘Does anyone have any Andons?’ became the first question of the daily staff meeting. It was acceptable and even encouraged to stop the standard work so that the team could investigate the issue and implement a countermeasure before proceeding. While stopping work appeared counterproductive when attempting to improve lead times, fixing problems at the source and getting quality right the first time contributed to the overall lead time reduction in the long term.

Mapping the value stream

Encouraged by the success with the VC value stream, Frank decided it was time to tackle the flow of the entire mouse model generation project. The flow was mapped on a wall with sticky notes, starting from the end deliverable; a mouse model ready to be shipped to the customer, and working backwards to see what each team needed to ‘pull’ from the previous team and process. By visualizing the entire project as a continuous workflow, the team was able to identify essential, value-adding processes, as well as non-essential, wasteful processes that could be eliminated. The pull principle helped to eliminate bottlenecks, reduce waiting times and improve flow. It ensured that resources and efforts were directed towards delivering value to the internal and external customers in a timely manner, playing an essential part in reducing lead times.

In addition to the company-wide project value stream, each team concentrated on improving their part of their value stream. Typically, this was done during a dedicated week-long 'Jishuken’ event, where the team stopped production activities to exclusively focus on improvement. A Jishuken usually brought together Frank or other Lean leaders, subject matter experts from the team and additional contributors who offered an external perspective. Jishukens were guided, but not led, by Frank and the Lean leaders. Their role was to coach the team and to truly empower the staff members to improve their own value stream. Jishukens were held regularly and acted as a catalyst for significant process and lead time improvements in each area.

Tracking the progress

The ‘remove red’ stickies had been a visual way to keep track of improvements, but data on processes was not systematically collected or reviewed, and the project database system did not have a timeline to show which stage the project was on in the value stream, when it had arrived at that stage, and when it was expected to move onto the next stage. Frank implemented simple visual indicators on the staff room wall to be updated and reviewed on a weekly basis.

'You can't manage what you don't measure.'

- Peter Drucker -

'Run charts' were implemented to record completed and failed milestones. They were printed and posted on the wall with a target line. A green dot was entered each week to show the number of successful completions, and a red dot was entered to show the number of failures.

A kanban board - or in this case a whole wall - was utilized to track the individual projects. Each project name was written on a sticky note. The project sticky would then travel on the wall from milestone to milestone. Calculations were inserted in the corners to show the length of time the project had spent in each area. While this made the tracking visual for individual projects, it was difficult to see an overall picture of the timelines and successes and failures of each project.

The visual measurements on the wall had several limitations and it soon became evident that a technical solution was required for comprehensive tracking. To achieve this, a new software application was custom-built to enter all project steps with rules determining where the project would go next based on the outcome. For example, if a DNA fragment passed QC, the flow would continue to the next step, but if it did not pass QC, the flow would go back to the fragment generation step to create a new one. This application was named the 'Corporate Notification System', or CNS for short. Frank termed the CNS Ozgene's 'Central Nervous System'.

The CNS also measured a crucial aspect of each process and project - time. Each task within the project flow was scheduled as soon as the previous one was finished and placed on the to-do list for the relevant team. The CNS measured the start and finish time of each task and used it to build a timeline for each individual project. (See a typical CNS project flow on Exhibit 7 and a sample of a CNS to-do list for VC on Exhibit 8.)

Digital tracking elevated the process improvements and timeline reduction to a whole new level. The CNS now allowed the tracking of successes/failures and timelines both on the process and project level. It could be used by individual teams to track and improve processes, and the project timelines could be regularly reviewed in staff meetings. Digital dashboards were built to analyze and display the data originating from the CNS and customers were also given access to a CNS generated project timeline through their 'myOzgene' portal, which also sent email notifications on completed and failed processes.

Frank acknowledged that while all the previous developments, such as cultural changes, value stream mapping, and process improvements, had led to improvements in lead time, the introduction of the CNS had the most substantial impact. The CNS enabled both the Ozgene team and customers to monitor lead times in real time, making delays and issues visible to all. This newfound visibility played a crucial role in driving further continuous improvement efforts.

Leveling the workflow

With the increased visibility into milestone and project data, variation in the workload became evident. For example, Project Design would sometimes batch up several new projects into one week while doing other research tasks on another week. This practice created inventory and overburdened the VC team who had to start working on several new vectors one week and none on others.

Since Ozgene received two new customer project orders each week on average, a target was set for two projects to be completed in each area each week. This meant that the next team would then receive an input of two projects each week, leveling out the inputs and outputs along the entire project pipeline. Smoothing out the production schedule and balancing the workload helped minimize fluctuations and variability in the production process. The balanced approach reduced delays and idle time, resulting in improved overall lead times.

'The slower but consistent tortoise causes less waste and is more desirable than the speedy hare that races ahead and then stops occasionally to doze.'

- Taiichi Ohno -

Conclusion

Frank was startled from his thoughts as the staff meeting finished and people were chatting and getting out of their chairs. He had reminisced his way through the steps that were taken all those years ago to reduce the project timelines from 18-24 months to a mere 20 weeks! The process took several years but the results were worth it. The first 20-week project had been completed as a result of a lot of effort and monitoring, while the second one came almost as a surprise, simply going through the pipeline without a hitch! The customers were incredulous at first, not believing that ES cell targeting could be achieved in such a short period of time, some thinking that corners had been cut in the scientific processes. Once they were satisfied that the service was still following the established scientific standards, Ozgene gained loyal customers who valued the improved lead times as a way to achieve their scientific goals faster.

Glossary

Assay	Protocols designed to detect or measure the presence or activity of a specific gene
CNS	Corporate Notification System
Embryo	A multicellular organism in the early stages of development, before it has become a fetus. In mice and many other animals, the embryo forms from the fertilization of an egg cell by a sperm cell, resulting in the formation of a zygote.
Embryonic Stem cells	Embryonic stem cells (ESCs) are a type of stem cell that are derived from the inner cell mass of a developing embryo. ESCs have two unique properties: they can divide and replicate indefinitely (unlimited self-renewal) and they have the potential to differentiate into any cell type in the body (pluripotency). These properties make them a valuable tool in scientific research, particularly in the fields of developmental biology, regenerative medicine, and genetic research.
ES cells	See “Embryonic Stem cells”
Genotyping	DNA analysis to investigate the genetic constitution of an organism
Gene targeting vector	DNA construct used to modify the genome of a mouse. It's designed to integrate into the mouse's DNA and replace or modify a specific gene.
goGermline™	Ozgene’s proprietary mouse model generation technology https://www.ozgene.com/gogermline-knockout-and-knock-in-mice/
QC	Quality Control
SBS	Step-by-Step; Ozgene’s in-house application that captures the ‘verb: noun’ instruction for every process step with visual images to guide the work
VC	Vector Construction; constructing the gene targeting vector using DNA fragments.
Vector	See “Gene Targeting Vector”
Vivarium team	The team that breeds the goGermline mouse after vectors have been implanted into embryos

Exhibits

Exhibit 1: Process flow diagram of a typical Ozgene project

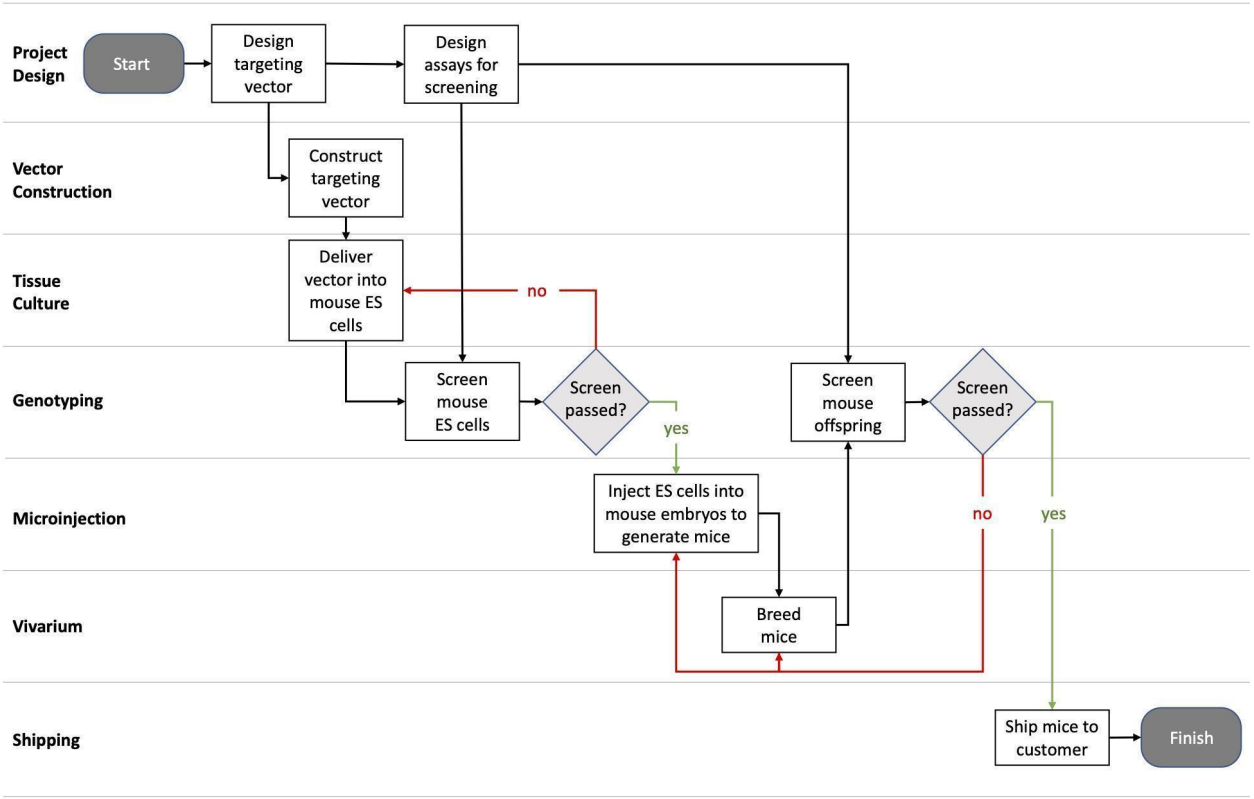


Exhibit 2: Ozgene's Throughput Time and Output per Milestone

Step	Milestone	Fastest time (weeks)	Average time (weeks)	Average output (weekly)
1	Project Design	1	2	1.27
2	Vector Construction	3	8	1.29
3	Embryonic Stem (ES) Cells	3	3	1.31
4	Microinjection into Embryos	4	5	1.27
5	Genetically Modified Mice	9	11	1.38
	TOTAL	20	29	

Exhibit 3: The 14 Principles in The Toyota Way by Jeffrey K. Liker

Philosophy	Principle 1: Base your management decisions on a long-term philosophy, even at the expense of short-term financial goals.
Process	Principle 2: Create continuous process flow to bring problems to the surface.
	Principle 3: Use "pull" systems to avoid overproduction.
	Principle 4: Level out the workload (Heijunka).
	Principle 5: Build a culture of stopping to fix problems, to get quality right the first time.
	Principle 6: Standardized tasks are the foundation for continuous improvement and employee empowerment.
	Principle 7: Use visual control so no problems are hidden.
	Principle 8: Use only reliable, thoroughly tested technology that serves your people and processes.
People and Partners	Principle 9: Grow leaders who thoroughly understand the work, live the philosophy, and teach it to others.
	Principle 10: Develop exceptional people and teams who follow your company's philosophy.
	Principle 11: Respect your extended network of partners and suppliers by challenging them and helping them improve.
Problem solving	Principle 12: Go and see for yourself to thoroughly understand the situation (Genchi Genbutsu).
	Principle 13: Make decisions slowly by consensus, thoroughly considering all options and then implement the decisions rapidly.
	Principle 14: Become a learning organisation through relentless reflection (Hansei) and continuous improvement (Kaizen).

Exhibit 4: Step-by-Step (SBS) application used in the Ozgene laboratory

Exhibit 5: An example of a Vector Construction daily schedule using 5-minute increments

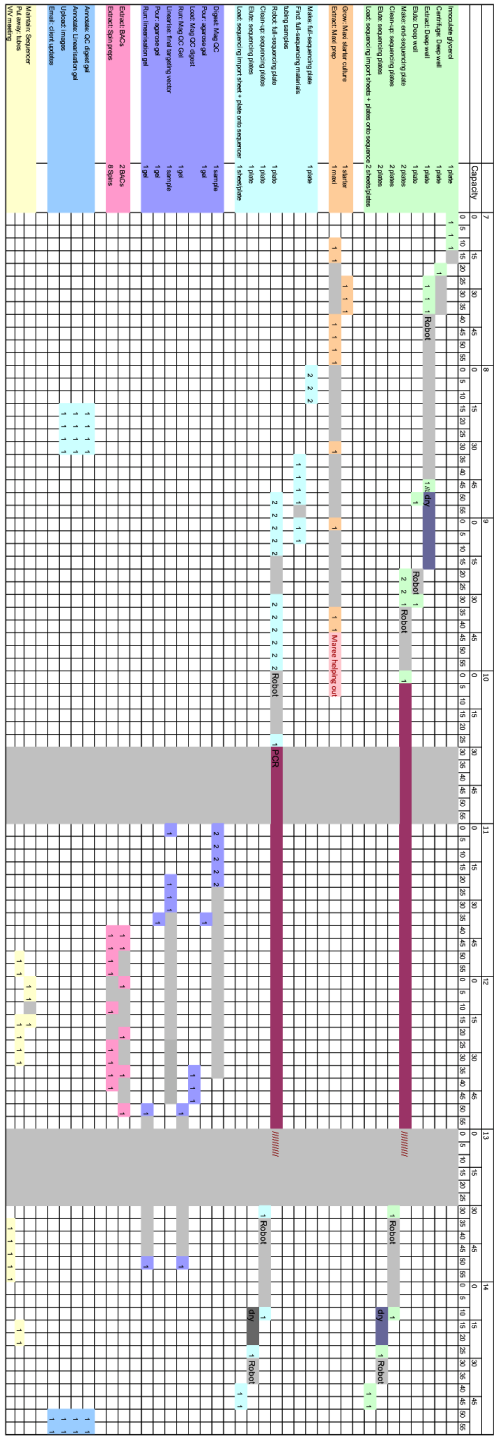
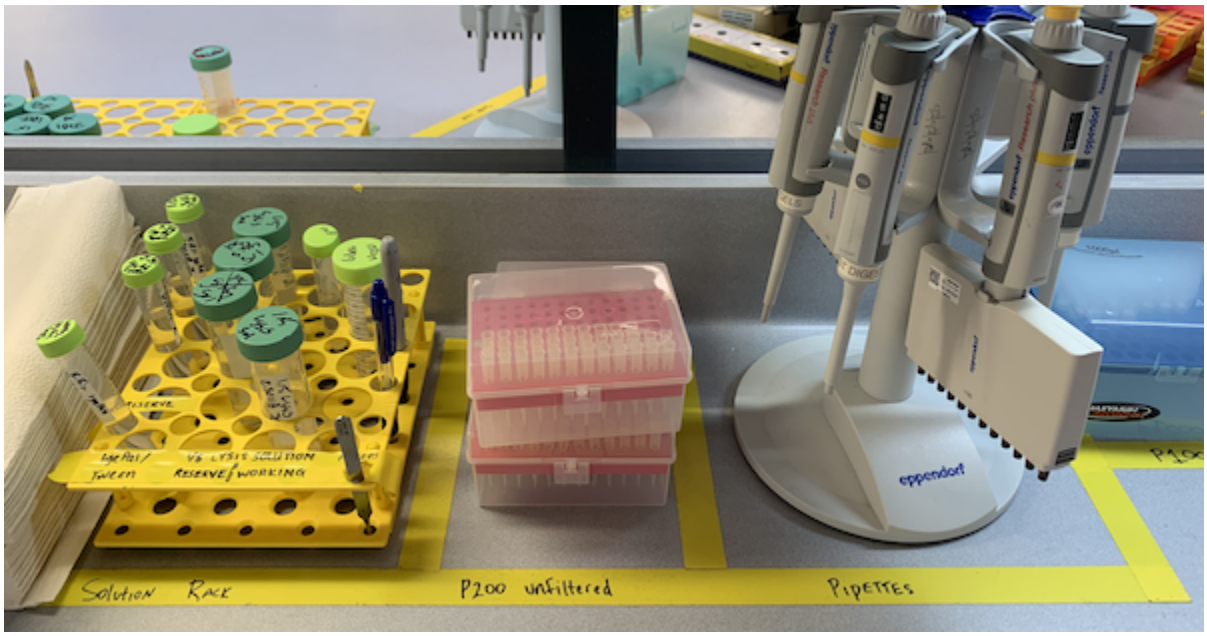


Exhibit 6: Examples of 5S in the Ozgene laboratory



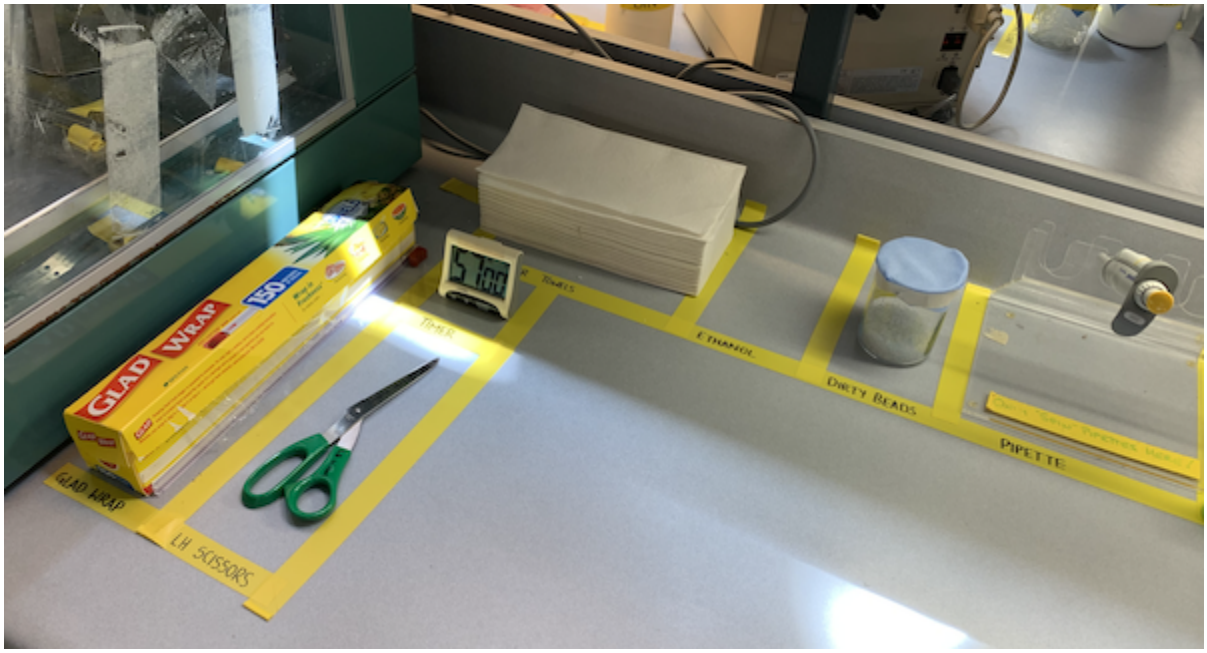


Exhibit 7: A typical project flow in the Corporate Notification System (CNS)

The purpose is to illustrate the complexity of the CNS flows, not to examine the individual steps.

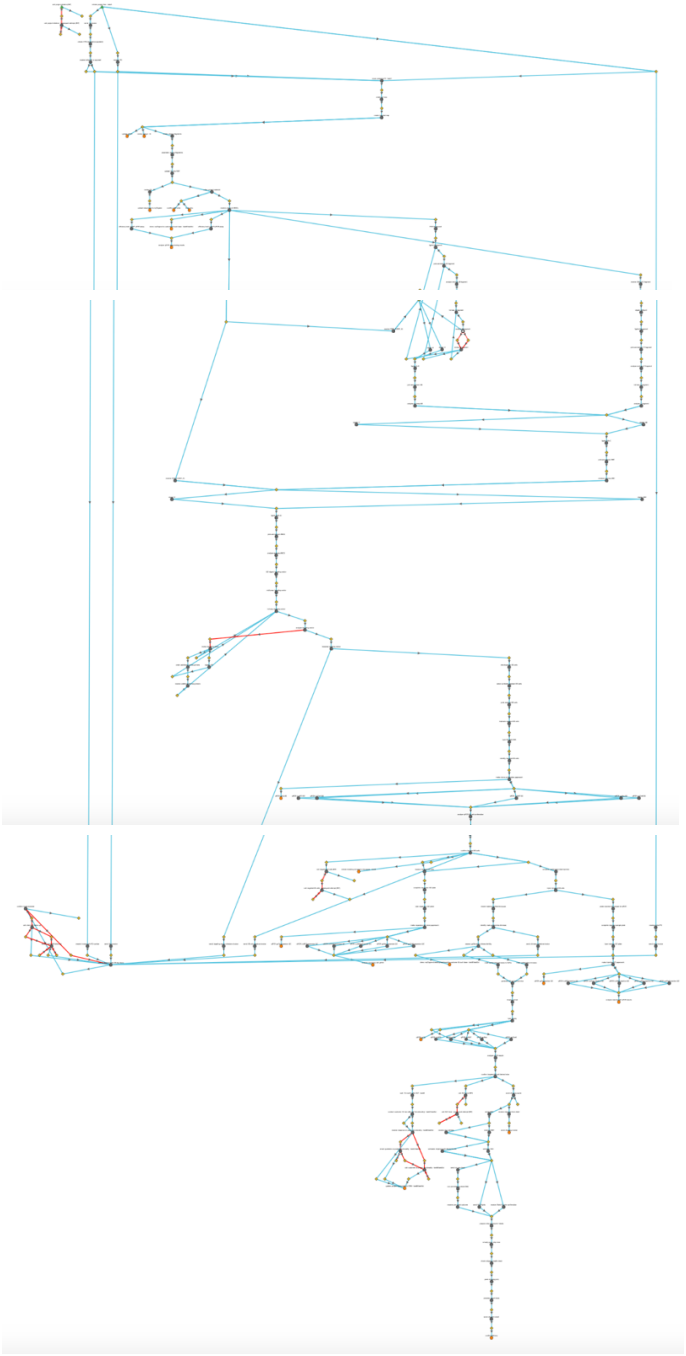


Exhibit 8: A sample of a CNS to do list for VC

Area	Object	Object Group	Procedure
VC	2476_Wick	SP	analyse: end-seq ABCD
VC	2507_Ajak	DEFAULT	pick and extract: A fragment
VC	2507_Ajak	DEFAULT	pick and extract: B fragment
VC	2471_Magma	SP	analyse: end-seq E fragment
VC	2492_Spiny_B*	SP	linearise: TVBAC
VC	2495_Rook	SP	ligate: AB+C
VC	2510_Dunn*	DEFAULT	full-seq: C fragment
VC	2454_Power	DEFAULT	full-seq: clone mutDiagPCR
VC	2481_Dazzle	SP	receive: GWsynB fragment