Cleaning Process Optimisation - Leveraging Global SME Knowledge to Enable and Empower Site-Lead Teams to Achieve Your Efficiency Goals

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Abstract

The current global economic environment is applying pressure to API, pharmaceutical and biotech facilities in a variety of ways; ever-increasing awareness of the environmental impact, pressure on supply chains, efficiency, costs and margins. Manufacturing facility management teams are taking a hard look at the manufacturing capacity and inefficiencies within their site. Local management must deliver this with little investment and often without acknowledgement of the return they achieve. Hyde Engineering + Consulting Europe has undertaken several projects where client sites were under severe pressure to achieve challenging goals from global management. The projects have involved limited investment in staff-hours, and capital expenditure might only be obtained after a significant return had already been achieved and a strong business case had been advanced based on demonstrated achievement of efficiency gains and cost savings. Hyde has developed a methodology for both site assessment and opportunity realisation that brings to bear our decades of global knowledge and experience, channelled through local SME's, and consistently delivers client requirements. This paper will discuss two such examples (1) a 67 % reduction in cleaning turnaround times, and (2) a > 20 % reduction in water consumption. Both were targeted specifically to allow for a significantly increased number of batches produced per year without significant capital investment.

Keywords: *pharmaceutical, biopharmaceutical, API, cleaning, efficiency, cost-saving, capacity increase, manufacturing, validation, environment, water usage, solvent, de-bottlenecking, resources, waste reduction, turn-around time*

1. Introduction

The current global economic environment is applying pressure to API, pharmaceutical and biotech facilities in a variety of ways, including increased pressure on supply chains, efficiency, costs and margins, along with an ever-increasing awareness of the environmental impact of our activities. Local manufacturing facility management teams are required to take a hard look at their manufacturing capacity and inefficiencies on their sites. This is particularly true for legacy sites and products, API manufacturing, CMO operations and more traditional pharmaceutical manufacturing facilities. Global leaderships are mandating challenging targets for improvement. Local management has to achieve this with less and less investment and often without an acknowledgement of the great return they will achieve with appropriate investment and the diligent work of staff.

Hyde Engineering + Consulting (Hyde) has developed a methodology for site assessment and opportunity realisation that brings to bear our decades of global knowledge and experience. This experience is channelled through local SMEs and consistently delivers client's improvement requirements.

Recently, Hyde Europe has undertaken several projects where client sites were under severe pressure to achieve challenging goals. The projects were conducted in circumstances whereby the client's initial investment was a limited allowance of resource-hours, and capital expenditure might only be obtained after a significant return had already been achieved and a strong business case had been made. This is not an unusual situation. Hyde often works in scenarios where a first round of improvements must be achieved and demonstrated on target, in order to build confidence and enable the release of capital funding to realise more complicated efficiency gains or cost savings.

This paper will discuss two such examples where clients achieved notable improvements: in one case, a 60 % reduction in cleaning turnaround times, and in the other a 20 % reduction in water consumption. Both projects were specifically targetted to allow for a significantly increased number of batches to be produced per year.

2. Assessment Methodology Basics

Over many years and dozens of assessments, Hyde has developed a standardised protocol for dissecting and diagnosing cleaning processes and cleaning validation programmes. The assessment has an equipment element, a process element, and a documentation element (encompassing all 4 levels of standard documentation from Masterplans to Forms) which allows Hyde SMEs to find areas of inefficiency or bottlenecks, and unearth opportunities for efficiency and improvement.

There is a structured documentation request and pre-review process. The relevant SMEs use this to inform a structured on-site equipment walkdown, facilitated discussions, and deep-dive on individual topics with relevant site specialists. Hyde SMEs then examine the data gathered, review the client responses, activities and data, and apply a standard risk ranking to gaps and impact rating to opportunities identification. Actions required to realise the opportunities are rationalised by the Hyde team and they are combined with the impact rating and any client needs/restrictions, to determine an overall benefit ranking and implementation strategy.

The Hyde SMEs summarise the risks and gaps identified and present these in a report. In addition, opportunities are identified and discussed. An implementation strategy is detailed which aims to combine gap closure with opportunity realisation. The assessment report is presented to the client site for discussion and clarification, at which point it may be updated to reflect any other site priorities or needs.

Hyde is then available as the client requires to deliver the targets of the report. This can vary from a single off-site Hyde SME (who was part of the initial assessment team) to guide, inform, enable, and consult with the client site as they realise the deliverables, or an on-site team that can lead and implement the project where client resources are constrained.

3. Case Study 1: Cleaning Process Streamlining, Changeover Time Reduction and Failure Elimination

Client A (*A*) approached Hyde with a not unusual request – 'Can you help us reduce the burden of cleaning process during product changeover?' Further discussions revealed that *A* was operating:

- a legacy site
- at least 20 years old (up to 40 years old in parts)
- conducting solvent-based processing of APIs
- a steadily increasing product demand profile
- extended campaign manufacturing
- with minimal budget for improvements

A had a strategic site initiative tasked with optimising the manufacturing time in the plant in line with the overall goal 'To be Best in Class at API Manufacturing' within the parent organisation.

More specifically, *A* required that their cleaning processes be improved (to enable more straight-forward validation of changeovers and deviation reduction) and streamlined (to reduce cleaning time and increase production capacity). When Hyde engaged with *A,* their current cleaning processes and product changeover were scheduled to take 40 shifts, with cleaning occupying 32 of those shifts. Every 5 shifts lost to cleaning and changeover reduced production capacity with a lost revenue opportunity of 1.5 batches. The actuality of *A*'s changeover at that time resulted in cleaning consuming up to 98 shifts per changeover.

Furthermore, cleaning failures at the sampling stage were routine, occuring on a majority of equipment. These failures were often not remedied by repeat cleaning and it would not be uncommon for costly unique approaches to be adopted after repeated failures. Eliminating these failures was a key metric by which the success of the project would be measured.

3.1. Project Initiation

An internal analysis had identified several challenges, one of which was that the site did not necessarily have the SME knowledge to find the right opportunities and chart the correct course to realise the improvements. It was at this stage that *A* engaged Hyde's local SME team, who conducted a site assessment as outlined in Section 2, modified appropriately to suit the needs of *A.* The assessment report identified several key areas of opportunity to help *A* reduce the changeover burden, including but not limited to:

- Visual Inspection process improvements
- Swabbing process improvements
- Cleaning Process Flow Optimisation
- Spray-ball Testing and Remediation

- Mobile CIP skid support for Problem Areas
- Cleaning Batch Record Re-Design
- Changeover Process Management Improvement
- QC Testing Stream-lining
- Cleaning Limit Review

In collaboration with the Site Project Team and taking account of management preferences, budget and cost-benefit analysis, Hyde engaged with *A* on the delivery of several items, the identification of key suppliers or expertise to enable other items to be realised, and placed several items in a parking lot for potential future action. At this time *A* was limited to an immediate action period of only 14 weeks to realise any optimisations (prior to the next changeover).

3.2. Actioned Opportunities

During the assessment Hyde identified that several of the most impactful opportunities were offline and procedural changes that could be worked on and implemented before physical activities would occur, namely:

- Visual inspection process improvements
- Swabbing process improvements
- Cleaning Process Flow Optimisation

The nature of site operations would not require automation changes or significant modification to individual operation tasks, only some additional training and a re-ordering and reduction of already executed tasks. Thus, it was agreed that Hyde would provide detailed guidance and SME support on these opportunities.

A would internally action other items at a later date, now that the pathway had been structured for them. Hyde provided additional SME guidance with these items as the client teams developed and realised these improvements.

From an Engineering perspective, Hyde supported a spray-ball functionality review and engagement with a separate Specialist Vendor for remediation of any potential issues discovered.

The largest opportunity for improvement Hyde identified was in the Cleaning Process Flow. *Figure 1* shows a segment of the overall process flow. It was operationally heavy, with repeated tasks, or tasks in a sub-optimal order, sometimes creating problems rather than solving them. Many years of adjustment had resulted in an unwieldy and difficult to execute process, with frequent failures. In Hyde's experience, this is not uncommon, particularly for campaign manufacture where validation and improvement opportunities are irregular, and where there isn't a dedicated cleaning specialist(s) and campaigns can be up to 50 batches. In and of itself, this leads to cleaning difficulties to which a Global SME can offer solutions that are not obvious without the weighty and hard-won experience of multitudes of other manufacturing operations and cleaning processes.

Figure 1: Snapshot of a small section of the original detailed Cleaning Process Flow, each blue box identifying a cleaning operation/task, each line a different major piece of equipment. The red box below highlights the small segment of the overall cleaning process (dotted blue box) represented in the top image. The image has been deliberately blurred.

Hyde SMEs performed a step-by-step breakdown of the cleaning process flow. We examined each piece of equipment, cleaning agent, time, and sequence. We looked at the history of failures and deviations, and difficulties associated with each step. We examined the time-consuming preparation and return to service phases. All of these elements, and more, were then drawn together to make recommendations for a new cleaning process flow, which primarily served to eliminate and/or correct the following items:

- Double or re-cleaning
- Moving soils from one system to the next
- Linear cleaning processes (parallel processing)
- Over-cleaning
- Under-cleaning
- Re-use and under-use of solvent batches
- Misaligned process steps
- Sampling sequences and locations

These optimisations were then summarised into a new overall cleaning process flow and new individual equipment cleaning processes. *Figure 2* illustrates how the revised cleaning process was presented and how each equipment cleaning step was now a self-contained unit but also easily linked to and understood in the context of the overall cleaning process flow.

Coupled with the process flow optimisation, Hyde SMEs worked with *A* to review the Visual Inspection processes: when they were executed, who performed them, what training was conducted, how the inspection was carried out, classification of observations, and remediation actions. Hyde worked with the Operations and HSE teams to remove/reduce vessel entry and establish remote inspection protocols, which,

coupled with the correct assessment criteria and procedures reduced not only resource requirements but also substantially reduced the Health and Safety risk for operators.

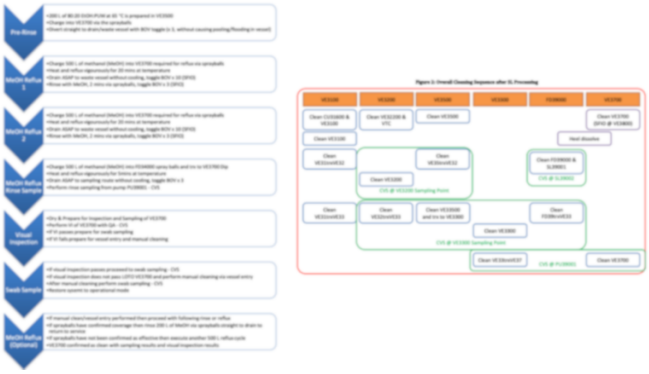

Figure 2: The revised cleaning process flows. On the left, sequence for an individual piece of equipment, containing details and parameters for each step. On the right the overall equipment cleaning sequences and sampling strategies. The image has been deliberately blurred.

In concert with the Visual Inspection process improvements, a revised procedure for Swab Sampling was also implemented, concurrently eliminating vessel entry. The development of remote swabbing practices, training and limits again improved not only the time and resource requirements but also significantly reduced the HSE risks and Engineering department requirements to support system Lock-Out-Tag-Out and dismantling.

3.3. Outcomes and Achieved Savings

In this brief discussion of some of the items actioned with *A*, it must be recognised that the site team for *A* were a very engaged and highly motivated group that took on all projects and suggestions with enthusiasm and dedication. Their hard work is a significant factor in the successes of this project. Some of these successes are as follows:

- Cleaning time reduced to 32 shifts from 98, a 67 % reduction, and less than the stated goal of 40 shifts
- Revenue differential for the site is up to 19 batches
- Cleaning time per piece of equipment is now measured in hours, not days
- Cleaning failures reduced from 7 pieces of equipment to 2 pieces of equipment, 1 of which was determined to be a design failure
- No repeat cleaning failures - where 3 items of equipment had experienced multiple repeat failures previously
- Vessel entry requirements reduced or eliminated
- Sampling is occuring at the correct locations at the correct time
- Procedures streamlined and simplified
- Solvent usage for cleaning decreased
- Daily cleaning management processes improved
- QA and QC engagement in 'normal cleaning' reduced, enabling them to focus on other tasks
- Deviation workload significantly decreased

Overall this was a highly successful project, with the client achieving and indeed exceeding all of their stated goals. Furthermore, should additional pressures be exerted in coming years, Hyde has identified and discussed several additional opportunities for improvement and implementation strategies.

4. Case Study 2: Takt Time Improvement Enabling by Mitigating Utility Constraints

When Client B (*B*) approached Hyde Europe, they already had previous experience working with Hyde several years prior, when *B* was working with other CMO sites to develop a harmonised approach to their cleaning practices and strategies. Now, however, *B* had a very different issue. They needed to increase their batch takt rate from 3.5/week to 4.5/week. But there were two significant issues: as far as they were aware their cleaning and product-related processes were optimised, and their utilities systems were not capable of supporting the increased load. Furthermore, this improvement had to be achieved while maintaining production schedules for their clients over the coming two years, and without capital investment. Aside from the cost issues, the site was also geographically restricted – there was no additional room on-site for additional utilities or facilities. The site had also originally been an API facility which had been modified over many years in order to produce biologics products.

Particularly constraining for this site were three particular utilities: RO water, WFI and wastewater processing capacity. To realise the increased takt rate, a WFI system already nearly at capacity operation would have to produce at least 25 % more WFI. Additionally, the RO system would have to produce at least 30 % more to support the RO needs and the increased load from the WFI system, pushing it beyond its production capacity. But, perhaps most importantly, even if these volumes could be realised, there was no spare wastewater treatment capacity at the site. An increased rate of batch production could only be realised by reducing the water demands of the site's thirstiest activity – cleaning.

4.1. Project Initiation

Hyde began this project by completing the site assessment as outlined in Section 2. This was an invaluable process not just for the Hyde SMEs, but also for *B*. Hyde was able to identify several areas within the site strategies and documentation that were limiting continuous improvement and placing extraordinary burden upon change implementation. Specifically related to the water consumption issue, Hyde was able to identify 10 areas whereby significant reductions could be achieved. Through analysis of the

workload, cost and benefit, Hyde divided these changes into 4 distinct phases. Phase 1 described the 'easiest to implement' and most impactful changes with the lowest cost of implementation. Phase 4 would be the 'most difficult to implement' segment and would require the most amount of work for the lowest level of return. A brief description of each Phase is outlined below (primary outcomes in brackets):

- Phase 1: cycle parameter modifications, water phases only (potential for up to 300,000 L of water saved per batch)
- Phase 2: low-level engineering changes to drain valves, upgrade a media line (additional water savings, cleaning time savings)
- Phase 3: new cleaning cycle pathways, automation development, minor engineering modifications (cleaning process de-bottlenecking, resource constraints alleviated, water savings)
- Phase 4: deep dive into cycle development and process parameters (water savings, cleaning time savings)

In addition to these items directly targeted, and the cleaning programme documentation updates suggested, Hyde was further able to identify and suggest remedies for manual cleaning operations, hose cleaning operations, and temperature control difficulties within CIP cycles. A visual representation of the 4 phase cycle modifications and programme changes is shown in Figure 3.

Figure 3: The recommended action items for B. *Two parallel workstreams of cycle/equipment modifications and programme improvements were recommended. The actions were complementary and enabling, progressing in the difficulty of implementation and diminishing return. The image has been blurred deliberately.*

The phases in the workstreams were designed to complement each other, enabling change, and reducing the burden of implementation in a stepwise manner.

4.2. Actioned Opportunities

Due to the magnitude of savings identified with the Phase 1 recommendations, *B* decided that a focussed implementation of this would be the best fit solution for the site at that time. Other actions may follow in future to ensure that systems were not continually operating at their maximum capacity, and the site would internally take on some of the programme strategy recommendations in consultation with partner sites and QA.

As a CMO site, additional complicating factors had to be considered – such as the agreed technical arrangements with *B*'s clients regarding process modifications and the impact on process validation statuses. For an integral site without external clients these issues would be significantly diminished or eliminated dependant on the type of change to the cleaning cycle parameters and the method of implementation.

Phase 1 mostly consisted of modifying the quantity of water being used in the rinse phases for cleaning cycles, buffer tank cleaning cycles and the cleaning of agitators. A strategy for determining the changes, documenting and justifying them was developed in conjunction with site QA, Engineering and the Hyde SMEs.

The approach leveraged the recorded process system data. We mined, analysed and documented current water usage and outcomes within a cleaning cycle, with simple statistical analysis of multiple randomised cycles across different products. We used this data to identify and justify opportunities for water usage reduction. The team decided to use an approach of a minimally sized data set to achieve reliable data with validation, instead of a more extensive data set with a verification. This was mainly driven by client requirements, rather than ease or outcome. We also decided to target only the rinsing phases of the cycles, as the impact on the validation status would be significantly less, and the outcomes far more predictable.

Client *B* had a dedicated resource extracting data files and sharing them in a controlled manner with Hyde. The Hyde SME established a team of remote engineers and delivered training and oversight of the data extraction process. Hyde then confirmed blinded-cross-team consistency of analysis for all team members. The team of engineers completed the data compilation process independently from the lead SME, managed by a local manager. This ensured the integrity of the data set.

The lead SME then performed worst-case analysis of the data sets to establish the maximum change possible without reaching an inflection point whereby further change might affect the performance of the cleaning cycles. An additional safety factor in the analysis was then included to ensure that *B* would not risk any cleaning failures. This was a key requirement – no cleaning failures would be permitted, or the changes would be scrapped.

On completion of the analysis, the lead SME then had two other SMEs review and confirm the conclusions reached about savings that could be made. A sample of the recommended savings is shown in Table 1. For simplicity in validation, Hyde recommended changes to the initial and intermediate RO rinses, and the pre-final WFI rinses. The data presented below

is a % reduction based on the initial volume used for all rinsing phases.

Table 1: Reduction in RO and WFI volumes for rinse phases within CIP cycles recommended by Hyde. Data presented is % reduction in volume based on initial total usage across all rinsing phases within a cycle.

System Type	RO Rinse Volume Reduction	WFI Rinse Volume Reduction
Fermenters	37.5 %	62.5 %
Buffer vessels	25 %	43 %
Purification vessels	25 %	62.5 %
Media vessels	37.5 %	57 %
Agitator Submersion	Eliminate	Eliminate

Although the analysis and modifications were focussed on only the rinse phases of the cycles, it is easy to see that the possible reductions determined were significant. Overall, they would more than realise the goal of saving 300,000 L of water per batch.

4.3. Outcomes and Achieved Savings

Overall, Client *B*, with minimal investment, was able to determine several paths of improvement and detailed methodologies and evidence for significant savings in water consumption and wastewater generation. This achieved their goal of enabling an increased takt rate from 3.5/week to 4.5/week. Furthermore, pinch points within the process were examined, and ways to de-bottleneck these points were elaborated on.

B was able to develop the roadmap required to their increased production capacity, without requiring capital investment in facilities or increased labour costs.

At the time of writing this paper, the validation of the Phase 1 changes discussed is still ongoing, with completion expected in the near future. So far, *B*, after taking a conservative approach to implementation for site specific reasons, has achieved median savings of at least 20 % of water volumes across a full CIP cycle. Additional detailed reporting is anticipated in the future.

Consequently, operating costs per batch have also been reduced. This has helped achieve another vital goal for the site – maintaining cost competitiveness in a complex and competitive CMO market both within their global company network of sites and with other CMO companies.

Correct employment of SMEs, and leveraging knowledge was key to allowing the local facility team to achieve success.

5. Summary and Conclusions

With the global pharmaceutical market growing ever more competitive, it is essential that legacy sites maintain competitiveness with newer sites and newer technologies. However, it frequently occurs that legacy sites do not have the key SME staff that can drill down into their particular situation and extract the most relevant opportunities for improvement. This is where employing global SMEs and specialist companies, such as Hyde Engineering + Consulting, becomes essential.

With our decades of experience, highly knowledgeable SMEs, multi-disciplinary and multi-platform engagements, and our continuous development - a result of being at the leading edge of technological and process advancement, Hyde is excellently placed to enable your site to achieve its efficiency goals. We have learned that there are several items that are key to success in these circumstances:

- An open discussion with no information withheld
- An engaged and motivated workforce
- A willingness to listen to and absorb hard-won experience
- A realistic set of goals
- Vision to see the rewards and invest appropriately

The two projects discussed in this paper had all of these attributes within the project team and site leadership. Together, Hyde and our clients made a significant difference to their bottom line:

- Client *A*
  - Reduced cleaning time by 67%
  - Eliminated nearly all cleaning failures
  - Streamlined work practices
  - Improved safety and process relating to cleaning
  - Enable manufacture of 19+ additional batches
  - Determined further improvement projects should they be required
- Client *B*
  - Reduced overall water consumption for cleaning by at least 20%
  - Prevented the need for capital investment in RO or WFI generation capacity
  - Prevented the need for capital investment in a new wastewater treatment plant
  - Enabled takt increase from 3.5 to 4.5 batches/week
  - Determined further improvement projects for equipment and cleaning validation strategies that will realise further savings into the future

All of this is achievable through correct engagement with, trust in, and leveraging of knowledge from appropriate and true global SMEs.

What can your organisation achieve?

About Hyde Engineering + Consulting

Hyde Engineering + Consulting is a global design and consulting organisation providing process system design, commissioning and validation, FDA compliance, and state-of-the-art cleaning technologies to pharmaceutical, bioprocess and other regulated process industries.

Global capabilities and offices throughout the United States, Europe and Asia gives Hyde clients the convenience of a single worldwide partner. Our staff of over 200 professionals are dedicated to understanding client needs and exceeding their expectations.

Regardless of the size of the facility or complexity of the project, Hyde delivers peace of mind through global expertise.

About the Authors

Kenneth Pierce, Ph.D., is an Engineer III, Cleaning Science and Validation specialist at Hyde, Europe. Kenneth holds a B.Sc. in Chemistry and Experimental Physics, and a Ph.D. in Bioanalytical Neurochemistry from Maynooth University. He has completed an Institute of Project Management Professional Dip.,Technical University Dublin.

Kenneth joined Hyde in 2013. In his 7+ years with Hyde he has been involved in many aspects of Hyde's core business strands – leading cleaning science studies Hyde's Lab, Cleaning Validation Engineer site secondment, the Technical Sevices Cleaning Validation Specialist on a green-field biotech facility, and several SME roles on site assessment projects and remediation efforts. As Technical Lead on both projects presented in this paper, Kenneth has delivered real and meaningful value to clients while limiting expenditure.

John Byrne is Associate Director of Technical Services Europe for Hyde. He holds a B.Sc. in Physics and Instrumentation from GMIT. John has more than 18 years of experience, working in manufacturing, primarily as cleaning validation SME. He has worked with MSD, Pfizer, Sanofi and Bristol-Myers Squibb in lead and managerial roles.

John joined Hyde in May 2017 as Associate Director of Technical Services Europe. In this role he manages projects and teams for clients in Europe in PQ execution, cleaning optimization and cleaning validation implementation. He manages and co-ordinates activities in Europe for the Hyde Cleaning Science Lab based in Colorado, USA. Since joining Hyde, John has grown the Cleaning SME team, allowing Hyde to keep up with the ever-increasing demand for services within Europe.

Fearghal Downey, Ph.D., is Vice President, Engineering & Project Delivery at Hyde, Europe. Fearghal holds a B. Chem. Eng. from University College, Dublin and a Ph.D. in Chem. Eng. from Cornell University. Fearghal is a Chartered Engineer and a Fellow of the Institute of Chemical Engineers.

For 27 years Fearghal has been responsible for both technical and managerial project delivery. His career started in MSD, Tech. Ops., specializing in new product and process introductions. He has delivered large scale projects from design through to qualification. Fearghal's core expertise includes high containment systems and transfer systems (powder & fluid), CIP systems and Sterile processing. Fearghal joined Hyde in September 2012 as Technical Director Europe, also providing specialist knowledge to the global organisation.

Keith Bader is the Vice President, Cleaning Science & Technical Services at Hyde. He holds a B.Sc. in Chem. Eng. from the University of Colorado, Boulder. Prior to joining Hyde 1999, Keith was a Research Engineer in Advanced Materials at TDA Research in Wheatridge, Colorado.

As VP of Cleaning Science & Tech Services he provides high level consultation to Hyde's clients on topic ranging from strategic quality and validation documentation architecture to detail oriented support, such as design of experiments, supporting study design, implementation of online instrumentation and PAT for CIP systems, and the development bench Cleaning Process Optimization systems, and the translation of the development data to full scale manufacturing systems. Leveraging this expertise, Keith founded Hyde's industry leading Analytical Lab in 2012.

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