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24 Things I've Learned in 24 Years about Technology Transfer

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"24 things I've learned in 24 Years about technology transfer"

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Abstract
Now into his twenty-fourth year working in the pharmaceutical industry, the author shares twenty-four select things learned and experienced over that time. In this paper the author contextualises these observations, interpretations, lessons, anecdotes and advice to provide general insights into various aspects of technology transfer for a biopharmaceutical drug substance (active pharmaceutical ingredient).

1. Never compromise on quality, and be audit-ready at all times

Audits are always quite intimidating, regardless of how well experienced you are. Be audit ready at all times. Treat every decision as being potentially auditable by the regulatory authorities. The key to audit readiness is practice, practice, practice! Therefore, from the very start of the technology transfer project have a healthy degree of scepticism in all your decisions, as if you were constantly defended a scientific hypothesis or submitting a paper for publication. Be constantly thinking on and practicing the robustness of your scientific justifications. When the time comes around for the audit you should be by now well versed and fluent in your defence, enabling you to present with great confidence to the auditors. Never compromise on quality. To avoid those costly remediation projects be audit ready in everything you do, in every task completed, and every report written. A good scientific argument will always win out in the end, Once the underlying data is dependable and uncompromised (data integrity).

2. Take a right first-time approach and avoid remediation projects

Take a right first-time approach every time and beware those inevitable decisions designed to move the project forward but at the obvious expense of GMP. This will always come back around to haunt you in the end, and by then you will be on your own as most of the project personnel responsible for the questionable decisions have now finished their contracts and have already left the site. Inevitably you will then be involved in expensive and demoralising

remediation projects, with the usual repercussions and recriminations, in order to try and fix that which is broken to any substantial degree of satisfaction.

3. We are all part of the technology transfer project

One way or another, all project personnel who are onsite, employed and contracted as part of a new build, are part of the greater technology transfer endeavour. Technology transfer encompasses many aspects, including:

(a) design, implementation and commissioning and qualification (C&Q) of the process equipment, utilities, facility and warehouse,

(b) design and installation, and qualification of the laboratories;

(c) preparation and implementation of the quality management system (QMS),

(d) preparation of batch and quality control (QC) documentation,

(e) operational and maintenance procedures,

(f) managing the process transfer,

(g) managing analytical method transfer,

(h) personnel training,

(i) supply chain management and material controls,

(j) process validation,

(k) additional process development studies,

(l) comparability studies,

(m) stability studies,

(n) preparation and submission of the manufacturing licensing application to the regulatory authorities, and

(o) inspection readiness.

A visualisation of the many interrelationships amongst key tasks and activities is illustrated in Figure-1, for a typical biopharmaceutical drug substance technology transfer project. There are opportunities in abundance when you are part of a technology transfer project. Seize upon each and every opportunity to learn and to grow professionally.

4. Be accountable, perform well, and offer good value

Every document generated and every task completed with your contributions is a valuable company asset. All project personnel, be they either staff or contractors, must take it upon

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themselves to provide value for the services they provide. Do not be found wanting. Allow yourself to be held accountable for the tasks you perform, individually or collectively. Compete with yourself rather than against others. At the end of the project, for your own professional and personal satisfaction, you need to be able to reconcile your hours and cost against those services you provided, and be able to quantify the value and performance of those.

5. Knowledge sharing

Knowledge is powerful, but only when it is widely shared and liberally distributed. Hoarding knowledge in the interest of power will disenfranchise both the hoarder and the rest of the project team. Carefully manage and counsel those project personnel who tend towards hoarding knowledge, before the inevitable schedule slippages occur and major project milestones are missed. Team work is key.

6. Personnel training

A significant number of contractor personnel are generally required throughout the project phase. For key personnel we must document and demonstrate competence and proficiencies. Carefully customise efficient and effective training curricula for contract personnel. Excessive allocation of extraneous training programs to key contract personnel can quickly absorb much of their limited availability. This can often can lead to the necessity for extended contracts, resulting in higher costs and schedule overruns.

7. Staff retention

No one is irreplaceable, but equally no one is readily expendable either, and there are many challenges currently being faced by pharmaceutical organisations globally in the recruitment and retention of talent. Projects are tough environments to be successful and thrive within, with many highly capable people struggling, and reporting stress, feelings of anxiety, fatigue and/or sleep loss. Many personnel will need coaching, mentoring and guidance for them to adapt and achieve. For the benefit of staff retention, a number of initiatives and forums will be required to keep people on board. A culture of well-being and human values in action, and the conflicts associated with modern day business practices and schedules should be

reconciled and harmonised as much as possible. Training of people managers in soft-skills is key, and more imaginative and effective staff performance appraisal are required.

8. Work to the project schedule

The quality of the schedule output is wholly dependent on the quality of the inputs when generating the program. Therefore, knowledgeable and experienced personnel are required to participate into the scheduling program. Once the schedule is baselined, formal progress reporting begins. Consolidate the various project trackers for more efficient and centralised control, and align with the appropriate levels within the schedule hierarchy.

Constant messages, emails and automated reminders relating to timing of deliverables can substantially distract key personnel from getting the actual work done, as much of their limited time is being diverted by incessant demands for tedious progress reporting. This is micro-managing, and this is detrimental to morale. The irony is that little progress is being made due to the excessive amount of time spent reporting on progress (that is not getting done in the first place!). Project managers need to carefully balance this, especially where there is only a very limited number of key personnel per deliverable and/or per project discipline. Do not exhaust or burden your limited supply of subject matter experts with excessive reporting demands.

9. Too many meetings

Meetings can take many forms and are a necessary evil, but excessive meetings are a drain on project finances and schedule. Very soon into a project everyone's calendar fills up, where 100% of our key personnel's time can be taken up with meetings. The irony is constant back-to-back meetings to progress tasks and activities consume the meagre available time left to get those done in the first place. Using a meeting forum to micro-manage key deliverables, rather than trusting key personnel to deliver on their own, is poor use of the limited time and resources available. Make sure your meetings are productive. Come well prepared with your meeting agenda. Summarise the main outputs, and agree any follow-ups. Be careful not to allocate too much work to the too few project personnel whom you mostly rely upon.

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10. Ongoing training in product, process, quality and regulatory

Many people know what to do but not why it is being done. It would be beneficial, therefore, if each and every contributor on the project had an appropriate understand of the 'why'. A suggestion is to have on-going training and communication in basic and more advanced understanding of your (a) product and (b) process, and also your (c) quality management system (QMS) and (d) global regulatory affairs. The more your project contributors understand these four concepts the better it will be for the design, quality, and validation outputs and deliverables. This will also lead to better traceable decision making, particularly when using quality risk management, as the impact on product quality and patient safety will be better understood by all.

11. Practical quality risk management

Embrace all features of quality risk management, and remember that there are more risk assessment tools available to us than just failure mode and effect analysis (FMEA). The truth be told, many subject-matter experts avoid volunteering, and being volunteered for, risk management because of the tedious nature of the classic FMEA spreadsheet approach. Other tools can be more creative, especially for the risk assessment element. This includes fault tree analysis (FTA), cause and effect diagrams (Ishikawa diagrams), hazard and operability (HAZOP) analysis, hazard analysis critical control point (HACCP), and event tree analysis (ETA). The risk review portion of quality risk management program can also be frequently overlooked. Risk review is critical to monitoring that you are identifying the appropriate risks and hazards associated with your systems, and that you are indeed taking the right decisions with respect to subsequent mitigation strategies.

12. Critical quality attributes and process parameters

Have a working list of critical quality attributes (CQAs) available at the earliest opportunity. Although the quality target product profile (QTPP) may not yet be formally established and available, ensure the working list of CQAs are traceable to evolving and documented development studies. Similarly, based on the working list of CQAs, identify associated critical process parameters (CPPs), define the in-process controls (IPCs), and establish the overall testing strategy.

13. Primary gap assessments

As early as practically possible, complete the necessary comparisons between the sending unit and the receiving unit. Identify the gaps between the facility arrangements, equipment systems, consumable and disposable components, the raw materials, and the process itself. Map out the gaps and implement suitable mitigation strategies. Test out the mitigation strategies before and during the engineering runs, and have everything closed out in time for subsequent process performance qualification (PPQ) runs.

14. Process risk assessments and control strategy

Based on the proposed manufacturing set-up, conduct a robust process risk assessment, and establish a suitable process control and microbial control strategy. These take up a lot of time and energy, and need to be planned and resourced meticulously. Ultimately, we should end up with all the necessary setpoints, and normal and proven acceptable ranges for critical and key process parameters, as they relate to critical quality attributes.

15. Supply chain for services and materials

Globally, supply chains are over-stretched for just about every industry, and particularly in this unprecedented era of the Covid-19 pandemic. Baseline the bill-of-materials (BOM) at the earliest opportunity. Be careful in your decisions to go with either sole-source or multi-source suppliers. Have a dedicated team in place to expedite, with appropriate quality oversight, orders or to source alternative vendors and suppliers.

Do not underestimate how long it can take to get a new supplier or vendor approved and added to the bid list for both services and materials (can take up to a year and longer). This is especially true if you intend designing and ordering bespoke single-use disposable components (plastic/polymeric containers, connectors, assemblies and manifolds) as this list can run into hundreds of items, and a multitude of supplies and vendors can quickly become hard to manage due to the numbers involved.

Allow sufficient time to prepare the material specifications, design bespoke single-use components, conduct audits and qualify suppliers, place purchase orders and agree lead

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times. Allow sufficient time for preparing the warehouse for receipt, quarantining and subsequent QC release of goods. For each batch prepare an adequate timetable for dispensing the raw materials, and for assembly of the consumables and disposable components into a kit for subsequent transfer into the production environment.

When it comes to single use consumables, order in sufficient quantities for engineering batches. In the earlier engineering batches confirm all single-use consumables, and their manifold and assemblies, can all be configured and fitted correctly in place. Get any modifications incorporated into the controlled specifications as soon as possible, and ensure GMP orders for the updated designs are placed in plenty of time for PPQ runs and subsequent GMP manufacturing.

16. The warehouse is not ready, or is not big enough!

The warehouse is not big enough and will not be ready on time, and whatever you think you need in terms of space and spare capacity it will not be enough! Single-use consumables can often be delivered in large boxes with lots of packaging that takes up an inordinate amount of space. As a contract manufacturing organisation (CMO), you can also expect free-issue of equipment from clients that will be dedicated to their process and their processes only. Additional space and strict controls will be necessary to store client dedicated equipment, otherwise clutter may quickly result if not properly managed.

For a new build, allow for receipt of deliveries earlier than expected, because long lead items might arrive sooner than expected due to suppliers juggling other customers' orders and cancelations. Too early receipt of GMP ordered materials when your warehouse is not finished or qualified can invalidate the chain of custody of your GMP materials. The worst-case scenario is that you may have to discard the delivery and reorder the goods, and this can have major implications on cost and schedule. A suggestion is to hire warehouse space from a third-party to be ready for early deliveries or delays to your new warehouse build. Make sure you qualify the third-party warehouse provider in advance, and have qualified controls in place for transportation of goods to your facility.

17. Computer system validation

Develop efficient and risk-based practices for validating and maintaining your computerised systems for capable operational and capable performance within the GxP environment. This is because the majority of software can involve bespoke and/or involves relatively complex configuration requiring many hours of design, implementation and testing. Most GxP manufacturing systems and business applications require significant validation investment. Computer system validation and data integrity assessments therefore need to be carefully planned and managed, otherwise a disproportionate amount of resources and energy get diverted constantly to remediate deficiencies. Even after many years of GAMP guidance (good automated manufacturing practice), computer system validation still presents ongoing challenges for the industry. Companies need to cease imposing upon themselves excessively elaborate validation practices. Onerous validation practices can actually detract from the primary intent of providing evidence that a computerised system is fit for intended, and instead only result in masses of paperwork that do not necessarily add value or understanding.

18. Software applications

Carefully consider what software applications are wholly necessary for the business, and decide who needs what access and level of training. Learning and keeping up to date with more and more software applications in our place of work can distract our key personnel from their primary responsibilities and core tasks, especially with constant upgrades associated with proprietary software. Perhaps the approaching era of artificial intelligence (AI) might just consider this challenge in the future.

19. Cleaning validation

Cleaning validation can never start too soon. Nowadays, many multi-product contract manufacturing organisations (CMO) tend towards the use of single-use components, thereby reducing/eliminating product cross-contamination concerns. It is recommended to formally document and confirm what components are within scope and what are outside the scope of cleaning validation. You may potentially only have one or two systems that are multi-use with multi-product process flow-paths. It does not matter, however, if only one or all equipment

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systems fall within the scope of cleaning validation, a full cleaning validation program needs to be developed and maintained. This includes cleaning development trials, sampling method development (swabs and rise samples), sample recovery studies, procedures and protocols for cleaning validation studies, cleaning validation master plan, project specific cleaning validation plans, carryover calculations, and rational for setting cleaning and microbial limits.

20. Leveraging the engineering runs for process validation studies

Rather than leaving process validation supporting studies to the PPQ phase, try instead to get them started during engineering trials, at least in the later batches of the engineering batch campaign. Agreement would be required by QA, based on an output from quality risk management, and could include mixing and hold-time studies for example. For this It would be best to utilise QC released materials and consumables. Although the environment might still be undergoing qualification in parallel with engineering batches, the use of closed equipment systems and application of quality risk management may mitigate risks and allow us to proceed with process validation studies upon receiving QA approval. Consider executing cleaning validation after each engineering batches also, rather than waiting for the PPQ phase. Liaise with the production director to determine worst-case operational hold-time values (for holding buffers and media, in-process materials, and also for dirty and clean hold-time studies) and, if possible, try an validate beyond those maximum predicted timepoints beginning with the engineering runs.

21. Reprocessing

Reprocessing studies can always be challenging. Know in advance the extent of allowable reprocessing steps and confirm these first at small scale. Decide what commercial scale reprocessing steps are feasible and schedule such additional runs during or after the engineering and PPQ runs. Design and schedule suitable stability and comparability studies for any reprocessed batches. It is probably a good idea to discuss this with the regulatory authorities in advance, if practical.

22. Change control and CAPA

As early as possible in the project, put in place approved processes, procedures and hierarchies for change control and corrective and preventive actions (CAPA) programs. Changes to approved documents occur very early in the design phase, and practical and traceable controls are necessary to manage evolving designs, specifications and procedures. Consider also putting in place, as soon as possible, robust procedures for deviation handling and root cause analysis.

23. Sampling Plan

The quality control (QC) department will invariably require the sampling plan much sooner than you anticipate, for both routine manufacturing and for the non-routine engineering, PPQ batches and process validation studies. This is especially true when the QC team are involved with configuring a laboratory information management system (LIMS) application in accordance with a parallel project schedule.

24. E&L Assessment and GMO licence

It is never too early to commence extractable and leachable (E&L) assessments. Start once all single-use polymeric consumables have been selected and the purchase orders placed with the vendors and suppliers. Depending on the extent of the vendor documentation and the risk categories, the sooner we know in advance the better what, if any, specific extraction studies will be required and under what exaggerated process conditions they are to be conducted under. The assessment data will then require review by a trained toxicologist, who will then make any recommendations regarding the requirements for specific leachable studies. Similarly, it is never too early to apply for your genetically modified organisms (GMOs) licence. Robustly prepare, as soon as practically possible, the facility and the QMS for the audit inspection by local the health and safety authorities. Any delay in the GMO licence being issued will delay the start of the engineering batches, and put on hold any small-scale studies where it is required to culture cells

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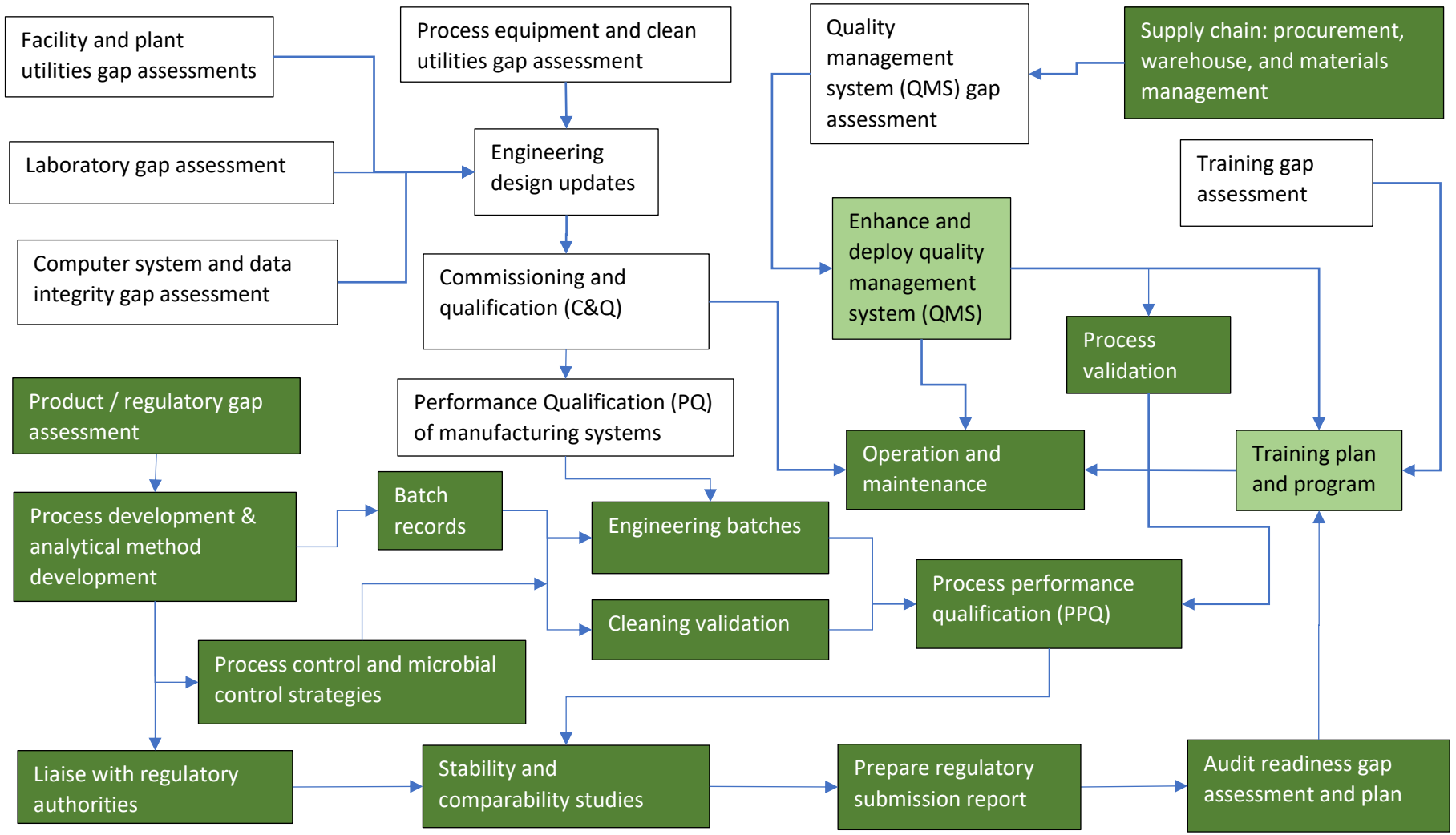

Figure-1: Visualisation of the many interrelationships amongst key tasks and activities for a typical biopharmaceutical drug substance technology transfer project. Text boxes with dark-green shading represents end-user responsibilities, unshaded text boxes represent contractor/service-provider responsibilities, and light green text boxes are potential shared activities.