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The 5C Framework and Maturity Assessment: A New Approach to Technology Transfer in Biopharmaceutical Contract Manufacturing

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Abstract

A new framework has been developed to provide guidance for cultivating a pragmatic and pro-active culture of technology transfer within the biopharmaceutical contract manufacturing (CM) sector. A review of industry practise was performed, and survey and interview feedback from contract manufacturers and their customers was obtained. The research summarised in this paper describes current experiences of technology transfer in biopharmaceutical contract manufacturing of those working in the industry and investigates the factors currently being experienced that lead to transfer challenges, project delays and difficulties faced by the contract manufacturing organisation (CMO) and customer. The framework and associated maturity assessment model provide an opportunity for both CMO and customer to adopt a culture that encourages shared ownership, managed expectations and more efficient.

Key words: biopharmaceutical; contract manufacturing; framework; technology transfer

1.0 Introduction

Technology transfer (tech transfer) is a frequently debated topic in biopharmaceutical manufacturing and never more so than during the global Covid-19 pandemic of 2020 because of the importance it has in the product lifecycle. The industry has been facing the challenge of intense tech transfers and a shift towards a wider outsourced product portfolio, shorter timelines and increasingly more complex biological products. The role of CMOs is changing and their customers' demands are driving CMOs to adapt their services, facilities and technical capabilities. Recent interviews with Business Development professionals at contract development and manufacturing organisations (CDMOs) highlighted that biotech companies are looking to establish strategic manufacturing partners in the true sense, and not just fee-for-service providers. Multiple products with efficient chemistry, manufacturing and controls (CMC) operations supporting pipeline fast-tracking into, and through clinical development is what is being asked of CDMOs (Interviewee 1, 2020). Customers are presenting with different requirements, whether it be full development, optimisation and

scale-up or process transfer (Interviewee 2, 2020). The demand is so intense that a senior scientist interviewed for this research reported customers wanting to get into the clinic with a new product within 12 months and transfers having gap analysis, small scale work, pilot and GMP production stages overlapping (Interviewee 3, 2020).

The biopharmaceutical (biopharma) sector needs effective support processes and systems in place to fulfil the requirements of the changing tech transfer landscape. Greater demand over the past year due to Covid products, more collaboration and partnerships with global pharma to support accelerated tech transfers are the drivers for change (Interviewee 5, 2020). This paper summarises the changes that are currently occurring, the challenges that are being faced and determines if the industry is matching the technological demands with equally robust tech transfer processes. The research investigates the following questions:

1) Are CMOs and their customers running effective tech transfers and analysing quality of the outputs?

2) Do industry guidance documents adequately support tech transfers to address the issues that are currently being experienced?

3) Has technical advancement been at the expense of properly managed technology transfers?

To answer these questions, the research utilised the following methodologies:

1) Tech transfer guidance documents and published literature were reviewed in context of the research questions,

2) An online survey was issued to gather experiences of those working in the industry from a CMO/CDMO and customer perspective,

3) One-to-one interviews were held with industry professionals with direct experience of biopharma tech transfers.

The scope of the research includes elements of business strategy and processes that, due to a company's competitive advantage, could not be reported publicly. The range of methodologies used supports the gap by gaining insights through feedback from an anonymous survey and by seeking information from industry professionals.

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2.0 Literature Review

There are several references that describe tech transfer, the process and detail the general requirements at each stage.

1. WHO guidelines on transfer of technology in pharmaceutical manufacturing (World Health Organisation, 2011)
2. ISPE Good Practice: Technology Transfer, 3rd Edition (ISPE, 2018)
3. PDA Technical Report 65 Technology Transfer (PDA, 2014)
4. ICH Guideline Q10 on Pharmaceutical Quality System (European Medicines Agency (EMA), 2015)
5. Eudralex Volume 4 Chapter 7 Outsourced Activities (EudraLex Volume 4 Chapter 7, 2009)
6. Contract Manufacturing Arrangement for Drugs: Quality Agreements Guidance for Industry (Food and Drug Administration, 2016)

The WHO defines the transfer of technology as "a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites". It is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and or commercialization to an appropriate, responsible and authorized party (World Health Organisation, 2011). The guidance serves as a framework with general coverage of transfer of development and production (processing, packaging and cleaning, transfer of analytical methods), transfer of analytical methods for quality assurance and quality control, skills assessment and training, organization and management of the transfer, assessment of premises and equipment, documentation, and qualification and validation.

ICH Q10 defines technology transfer as the second stage of the product lifecycle, where "the goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement" (European Medicines Agency (EMA), 2015). Aspects of ICH Q10 apply to technology transfer during 1) the process performance and product quality monitoring system, 2) the corrective

action and preventive action (CAPA) system, 3) the change management system and 4) management review of process performance and product quality.

2.1 What makes a successful Tech Transfer

Technology transfer of bioprocesses is common in the biopharmaceutical industry yet can be complex and presents numerous challenges. The process introduces additional risk to the development and commercialization of biopharmaceuticals, so minimizing risk is fundamental to success. Challener (Challener, 2020) summarises that experience, communication, collaboration, transparency, planning and prioritisation contribute to success and that CMOs/CDMOs and customers can facilitate this by using pragmatic approaches that mitigate risks and ensure collaboration between all parties involved. It is important though, that all parties define what a "successful" transfer is, and ultimately this should be success of the first GMP manufacturing campaign.

Successful tech transfers have been summarised to have the following principles, omitting any would have serious consequences on the outcome (Perry, 2010):

1. Robust information exchange, providing the receiving party with all information that is relevant to the process and associated assays.

2. Careful front-end planning and project management, with the designation of point people for specific portions of the project.

3. Ensuring that analytical assays are transferred ahead of the process

4. Performing small-scale verification at the receiving site.

5. Always perform pre-GMP engineering runs.

6. Put the tech transfer project in context by defining GMP success and failure and don't dismantle the project team until success here has been verified.

2.2 What are the challenges?

One of the first challenges to overcome in transferring a manufacturing process is to fit the process into the receiving facility (Newcombe, 2020) and (Newcombe and Brown, 2020). In the initial stages of the technology transfer, a comprehensive review of process requirements and comparison with facility capabilities should be performed (Chang, 2011).

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Additional challenges are faced when tech transfer is to a facility in a different country than the originating site. There may be additional communication challenges of a different culture, different language, and/or different time zone. Even where English is spoken proficiently by all team members as the common language, different cultural influences can result in different interpretations for a given word or phrase (Chang, 2011); technology transfer can mean different things to different people.

Technology transfer is embedded as part of a pharmaceutical quality system (European Medicines Agency (EMA), 2015) and audit findings and regulatory inspections are not always associated directly with deficiencies in tech transfer. However, there are examples where customers have questioned the change control process for when a process transfers out of one site to a sister site. Process documentation and comparability strategy may be reviewed from a quality perspective, and process history documents and risk assessments can be requested during a tech transfer audit (Interviewee 10, 2020).

A survey of problems experienced by executives at 10 global companies was carried out in 2011 by Uydess and Schmidt (Uydess and Schmidt, 2011) and despite the frequency of transfer, the results showed the following problems:

1. Corporate decision makers make tech transfer plans primarily on basis of financial and marketing considerations, failing to take into account the effect on the organisation.

2. Senior management significantly underestimate the need for resources and scheduling that supports tech transfer.

3. Little oversight is provided once high-level decisions are made, leaving the work to those without much control.

4. Lack of early and effective coordination between receiving and sending sites is further complicated by lack of clearly defined roles and responsibilities, lack of communication and poor visibility of timelines, progress and results.

5. The transfer runs into problems because a thorough and detailed assessment has not been conducted on comparability of equipment, manufacturing environment and supply chains.

6. Participating organisations fail to clearly identify, define and agree upon which standards and procedures to follow.

7. The organisation fails to take into account impact that the tech transfer has on functions such as quality, regulatory, laboratory and supply chain.

8. Poor process understanding coupled with incomplete documentation of all the required parameters.

The consequences of these common factors in the planning and implementation of tech transfers include budget and schedule overruns, disruption to both sending and receiving organisations, compliance problems, excessive rejects and rework, slower time to market and supply unreliability.

3.0 Effectiveness of current Technology Transfers – Industry Survey

A survey was developed to determine the challenges being faced by those working in the industry and establish if sentiment was widespread amongst those working at CMOs and their customers. The survey was created electronically through an online survey management client and limited to ten questions. A total of 61 participants responded; 39 responded that they were currently working for a CMO that performs technology transfer and 22 were employed by a company that transfers technology out to a CMO. Figure 1 shows the overall distribution of participants based on job roles with representation from a wide range of experience.

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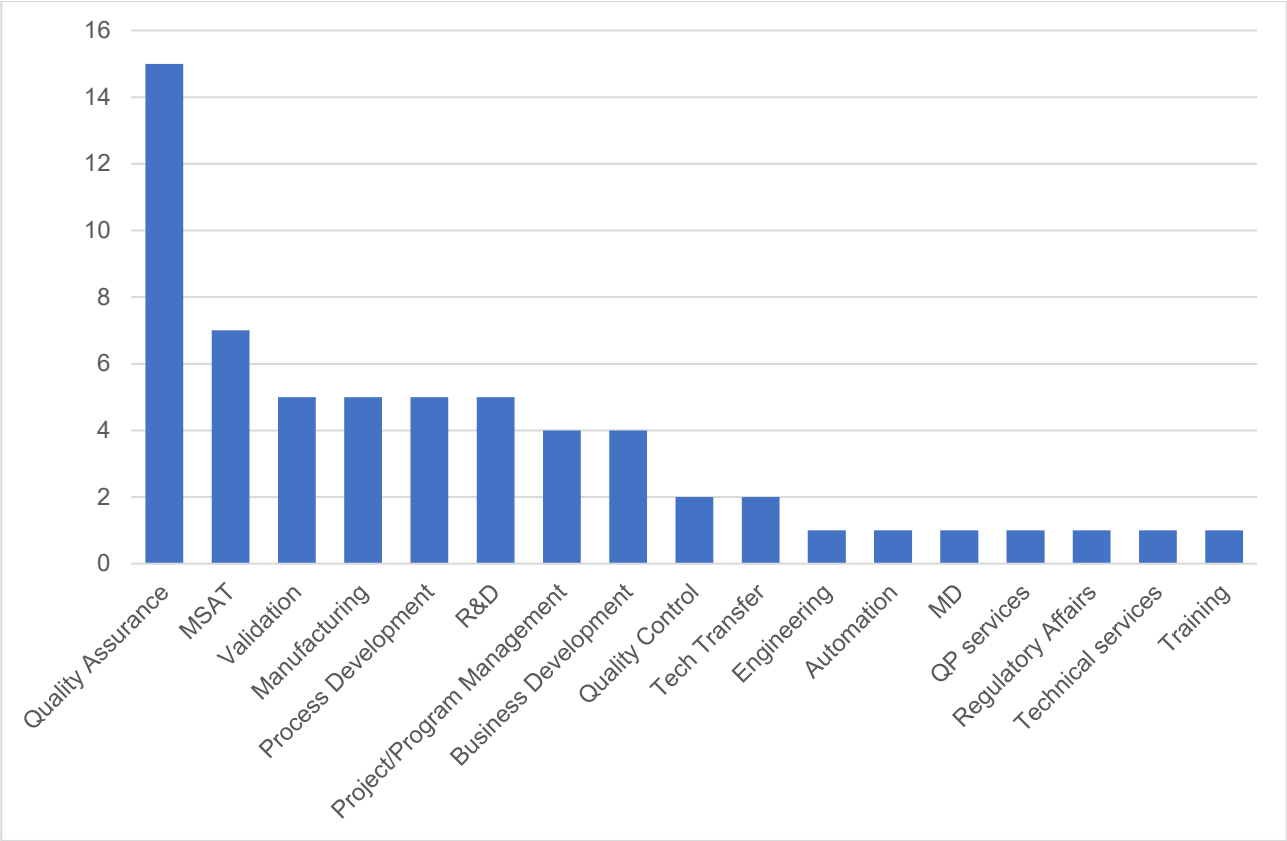

Figure 1: Distribution of survey participants based on job role.

Employees at CMO and their customers were asked what factors were most important to them during technology transfer of a new biopharmaceutical product/process. Table 1 below shows that both groups of respondents shared the same top three responses.

Table 1: Top five factors considered most important by employees at CMOs and their customers.

Factor	CMO Rank	Customer's Rank
Effective communication	1st	2nd
Good project management	2nd	3rd
Expertise of CMO	3rd	1st
Well characterised process	4th	5th
Good knowledge Management	5th	-
Capacity of the CMO facility	-	4th

When asked what factors they had actually experienced during transfer of a new biopharmaceutical product/process, the participants reported the following (Figure 2 and

Table 2). Analysis of the data shows that those working for a CMO have the same top five factors as their customers, see Table 2 below.

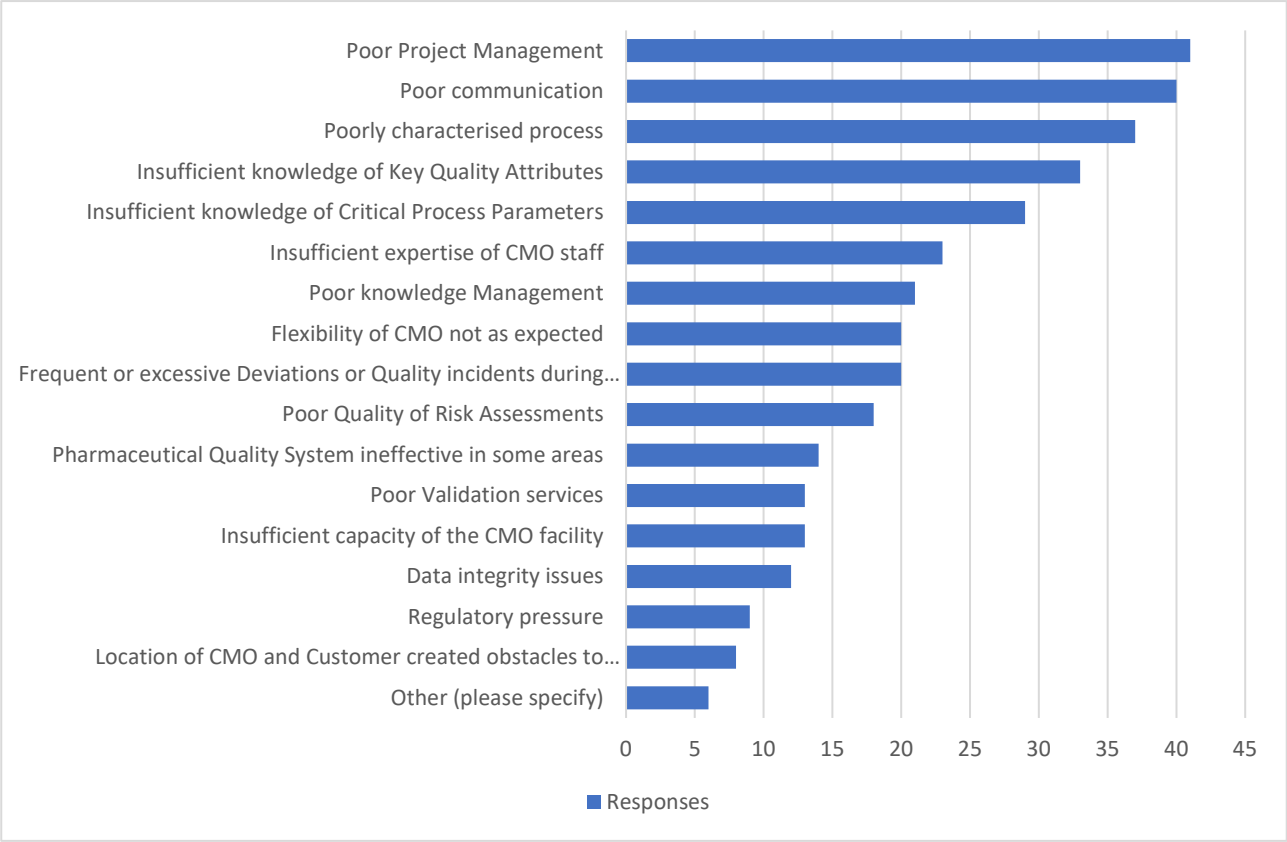

Figure 2: Factors experienced during tech transfer by employees at CMOs and their customers.

Table 2: Top five factors experienced by employees at CMOs and their customers during tech transfer.

Factor	CMO Rank	Customer's Rank
Poorly characterised process	1st	-
Poor project management	2nd	1st
Poor communication	3rd	1st
Insufficient knowledge of CPP	5th	2nd
Insufficient knowledge of KQA	4th	2nd
Insufficient expertise of CMO	-	3rd

The use of assessments prior to a tech transfer was investigated, and the survey responses showed that a range of tools and formats were being used (Figure 3).

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Figure 3: Summary of tools used prior to a technology transfer

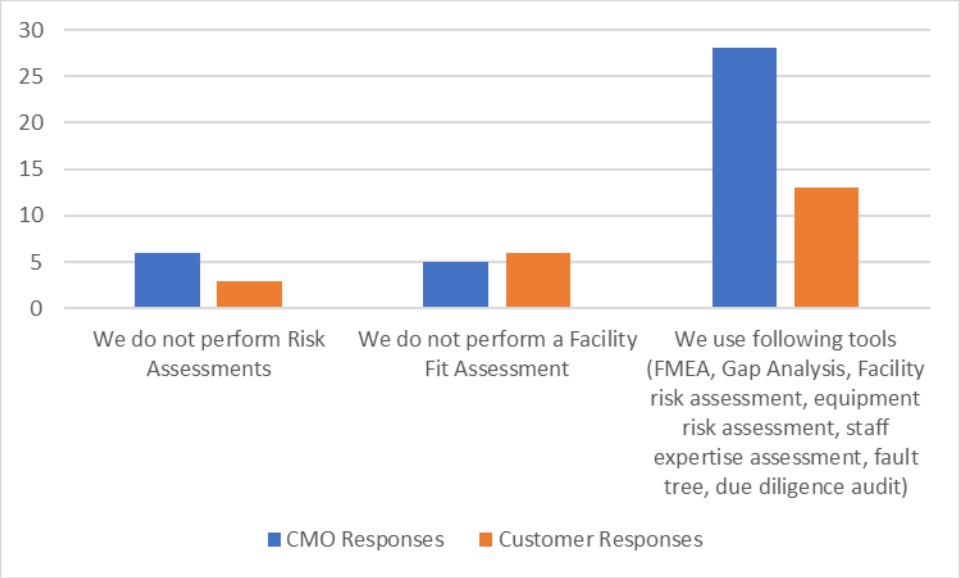

Figure 4 shows that a wide variety of post tech transfer review tools were being used.

Figure 4: Tools used to monitor outcome of the technology transfer.

To determine the success of assessments compared to the overall outcome, participants were asked to select the outcome they experienced. The data shows a broad range of responses and experiences were varied amongst CMO professionals and their customers.

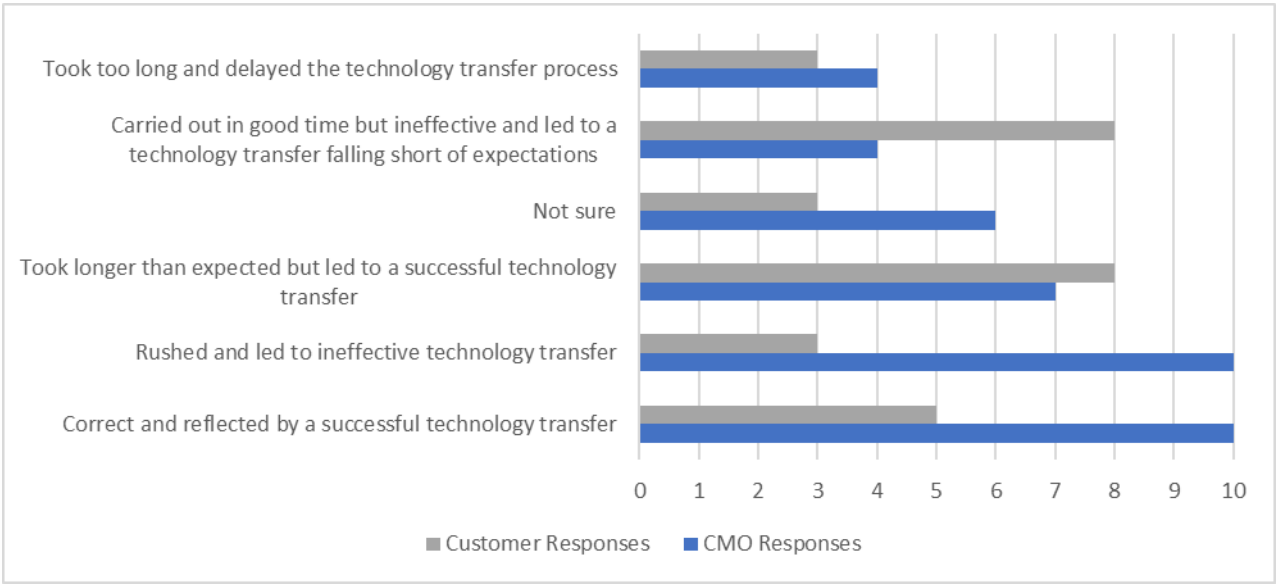

Figure 5: Outcome of the tech transfer assessment process.

The survey concluded by asking participants what aspects of technology transfer they thought could be improved and what could contribute to shortening the transfer cycle.

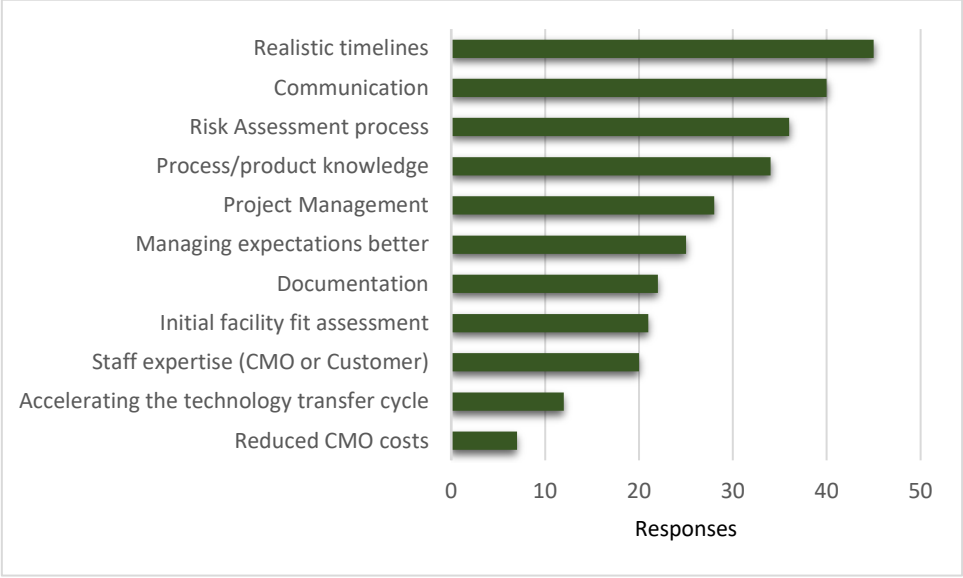

Figure 6: Aspects that could be improved, overall feedback.

Table 3: Top 5 aspects of tech transfer that could be improved from a CMO and customer perspective

Factor	CMO Rank	Customer's Rank
Communication	2nd	1st
Realistic Timelines	1st	2nd

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Process/product knowledge	5th	3rd
Risk Assessment Process	3rd	4th
Project Management	-	5th
Managing expectations better	4th	-

Table 4: Aspects that were thought may possibly contribute to shortening the tech transfer cycle.

Aspect	CMO Rank	Customer's Rank
Cultivating the "one-team" approach between CMO and Customer, sharing staff and knowledge earlier in the product lifecycle	1st	1st
Bigger emphasis on shared ownership between CMO and Customer	2nd	2nd
CMOs providing a development service to Customers and engaging earlier in the product lifecycle	3rd	4th
Educational initiatives in the biopharmaceutical industry focused on technology transfer	4th	5th
Regulators working closer and sooner with CMOs and Customers to reduce regulatory pressure	5th	3rd

The participants agreed that creating a "one-team" approach and bigger emphasis on mutual collaboration with shared ownership were most important, with general agreement that a wider service offering by CMOs, support from regulators and educational initiatives would also benefit.

4.0 Trends in Technology Transfers – Expert Interviews

Following from the literature review and industry survey, interviews were held with various professionals with extensive experience of technology transfers to understand the detail behind the trends they had observed, the changes within the industry and what the current challenges were. Technology transfer policy and procedures are business sensitive and therefore commercial advantage limited the availability of reference material and disclosure of specific processes. The identity of the participants has been concealed and it must be noted that the opinions expressed by the interviewees are solely their own and do not represent that of any of their previous or current employer. What follows is a summary of the discussions.

4.1 Challenges in Tech Transfer and Collaborating with a CMO/CDMO

Choosing the right CMO and engaging in technology transfer requires amongst other things good knowledge management, technical expertise and facility fit. When all these are in place, what makes a customer select one CMO over another?

Partnering with a CMO is the reason why companies outsource, because to do it in-house is slower, more difficult and more expensive when the biotech companies do it themselves. Biotechs know this and they outsource their risk and exposure, so they will push to justify their outsourced decision and return as they are answerable to their financial backers (Interviewee 1, 2020). CMOs also have different levels of previous tech transfer experience, dedicated project management support, communication skills (bilingual, where necessary), inspection history and previous regulatory approvals (Interviewee 5, 2020). A strong quality function, and personnel and cultural fit (operational and management) are also important (Interviewee 1, 2020) especially in this era of globalisation.

The challenge is that there are different pressures at each stage of a product lifecycle, which may include change of ownership of the product or the company and the focus is often on short term goals for a specific product with regards to clinical development, so this whilst it sounds good, may not be possible to achieve (Interviewee 4, 2020).

Lean organisations and professionals are always challenging themselves to be more productive with their time application and ability to prioritise & plan accordingly. Often, it's

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not on a Biotech's radar to engage a CDMO when in R&D/pre-CMC phases. Also, some CDMOs only want to engage when the project is CMC/facility ready or near ready, and the associated funding is secured. Hence prioritisation is a factor, as is available budget. But there is frequently an element of naivety in early stage of looking to run before you can walk, underappreciating some of the constraints, limitations, of scale-up and manufacturing under GMP (and regulatory pathway). Education (training), knowledge sharing and awareness are factors to avoid the common pitfalls (Interviewee 1, 2020).

4.2 The Earlier the Better

Witcher is the ultimate "the earlier the better" proponent when it comes to working with external partners. "You might call it science transfer," he said. The biotech with few internal resources should partner with a CDMO as early as possible (Garguilo, 2020d).

Selecting potential CMOs in early stage (e.g., during phase 3 clinical manufacturing) ensures the process can be adapted to fit better at the CMO, resulting in lower costs, higher quality and operationally faster processes. Experts agreed that it's always a good idea to get both teams together when developing in the R&D phase and introduce controls and practices that make the transfer easier, e.g., evidence of successful testing, analytical method development and validation.

Of readiness to transfer, the interviewees agreed that all too often a product is developed in R&D by people who have no experience beyond test tube scale manufacturing and don't appreciate that changes to processes may have to be accompanied by comparability exercises. All too often a poorly developed product is presented to a CMO (or in house manufacturing unit) and has to be sent back because the product is not capable of being manufactured using the R&D method within a GMP environment (Interviewee 6, 2020).

Smaller companies with limited funding often wait as long as possible for clinical data before partnering with a CDMO, larger companies often try to manage large scale manufacturing based on internal capacity and other manufacturing options. Global pharma also consider adding a CMO as a second site of manufacture. Most companies are aware that tech transfer is likely to take at least 6 months and try to initiate discussions at least a year before the

first engineering batch. Engaging earlier in the product lifecycle may not add much benefit as there may be limited process information available (Interviewee 5, 2020).

Bringing in the vendors / suppliers to share in the objective from the early stages, offering their knowledge & expertise supporting the process design come together, is a big plus point. At the same time, you support to mitigate your supply chain. Effective (not excessive) risk mitigation planning, using solid yet simple tools, helps to focus the effort, eliminate the blind spots & ignore non-value adding waste. A successful tech transfer process is well structured, managed, tracked and continually assessed for very good reasons, because without doubt this is the highest risk and unfortunately often most overlooked phase of the CMC project (Interviewee 1, 2020).

4.3 Managing Expectations

"How can we say we are ineffective at tech transfer, but at the same time have established a thriving industry of virtual biopharma and start-ups reliant on outsourcing most all development and manufacturing to external partners? We must be doing something right" (Garguilo, 2020c).

The fact that biopharmaceutical products are making their way to market is testament to the dedication of CDMO and Sponsors to manufacture safe, potent products on time when faced with numerous tech transfer challenges. Nevertheless, if expectations are clear and agreed earlier, then the process could run smoother (Interviewee 4, 2020).

Expectations can be unrealistic especially if the client has no experience of working with CMOs. They are often not aware of the intense work which goes on behind the scenes (Interviewee 2, 2020). Project management experience is a critical factor in CDMO selection and key to achieving the outcomes expected by the client. One industry expert said that he had seen a deterioration of the management skills necessary to complete such projects. Problems seem to be occurring because projects get badly over managed with full time project managers building overly detailed schedules (Gantt charts, etc.) that are out of date almost immediately and too many regularly scheduled meetings that do not address problems in a timely fashion. Successful projects are usually run by project managers that

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focus much more on doing by making things happen as fast as possible rather than planning (Interviewee 8, 2020).

Customers generally understand the timelines required for a typical tech transfer as project deliverables and costs are provided as part of a project proposal and typically expectations are aligned. Often additional batches are requested at short notice and whilst everything is done to accommodate, this is often not possible due to scheduling and capacity constraints and some clients may expect too much. Technical issues associated with timely closure of manufacturing deviations may be an issue if a CMO has limited technical or QA experience (Interviewee 5, 2020).

CMOs understand their own processes and facility limitations, but the more complex the product, more work may be required to de-risk the manufacturing. For other transfers, the customer is the expert, and sometimes they either forget this, are not willing to share data or haven't got the data to support the process (Interviewee 3, 2020). When transferring a legacy process, there is sometimes too much reliance on a carbon copy. One should explore new possibilities and technology upgrade, even if it may increase validation activities.

Most CDMOs do not have significant flexibility in accessing manufacturing resources. Even very large CDMOs have trouble accessing the necessary resources as the manufacturing requirements increase as the product progresses through the clinical pathway to launch. Those that can afford it, are building assets, but these assets use the same inflexible facility design concepts (Interviewee 8, 2020). There is a current shortage of Qualified Persons (QPs) with biologicals experience in the UK (Interviewee 11, 2020), and it is unclear if Quality staff, on both sides of the transfer process really have the necessary skills and knowledge to directly support tech transfers (Interviewee 4, 2020).

Having an experienced gate keeper is key to business success says one industry expert (Interviewee 7, 2020). At the start of the process few team members have the same understanding and skill, but towards the end of the process they do. That journey needs someone to guide the team who has knowledge of the technology (Interviewee 7, 2020).

Post-tech transfer reviews are indeed common, but all too often they are only "end of project tick box exercises", and they aren't well contributed to by either CMO or the sending unit. There is almost total disregard for lessons learned in the following project as there is usually no mechanism for sharing information and as such, the lessons-learnt file gathers dust in the previous project files. There is a great lack of implementing /following-on lessons-learnt reviews. Poor communication and poor project management are usually the result of a failure at the start of the project to understand, align and agree technical and business goals alongside realistic expectations (CMOs promise the world to get the work – even though they know they can't achieve and thus make unrealistic promises to clients, and clients aften "mis-inform CMOs of the true state of product development at the start of the project) (Interviewee 6, 2020).

The process for technology transfer can be improved by putting some clear objectives and targets working off a benchmark. If there's a sister site within the company which is performing better than perhaps that could become a very good start. The key to establishing if a tech transfer performed better or at least as expected is by gaining good quality data. Knowledge management becomes very useful in collecting data.

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5.0 The 5C Framework

"Technology transfer is an intelligent way of thinking. It is not a formula or a standardised process, otherwise we only get black Ford Model Ts but the use of standardised processes form the backbone" (Interviewee 7, 2020).

The research undertaken shows that the industry is challenged with less than ideal communication, project management (expectations and collaboration), process characterisation, knowledge management and risk assessment during technology transfer, some of which have already been discussed with Louis Garguilo, Chief Editor of Outsourced Pharma (Garguilo, 2020b) and (Garguilo, 2020c). Although guidelines are detailed documents, feedback from industry professionals suggests that the ISPE and PDA guidelines over complicate the process (Interviewee 4, 2020) and (Interviewee 6, 2020).

Early engagement, open communication, good knowledge management, a willingness to share knowledge and early planning or understanding of a product's manufacturing requirements and regulatory constraints are clearly good goals, and well known throughout the industry, yet these factors have not been perfected.

Taking all the findings of the research in to consideration has resulted in the development of a new framework for biopharmaceutical technology transfer that highlights the biggest issues as five categories. The *5C Framework* aims to instil a pro-active, pragmatic culture of tech transfer driven by specific triggers in organisations.

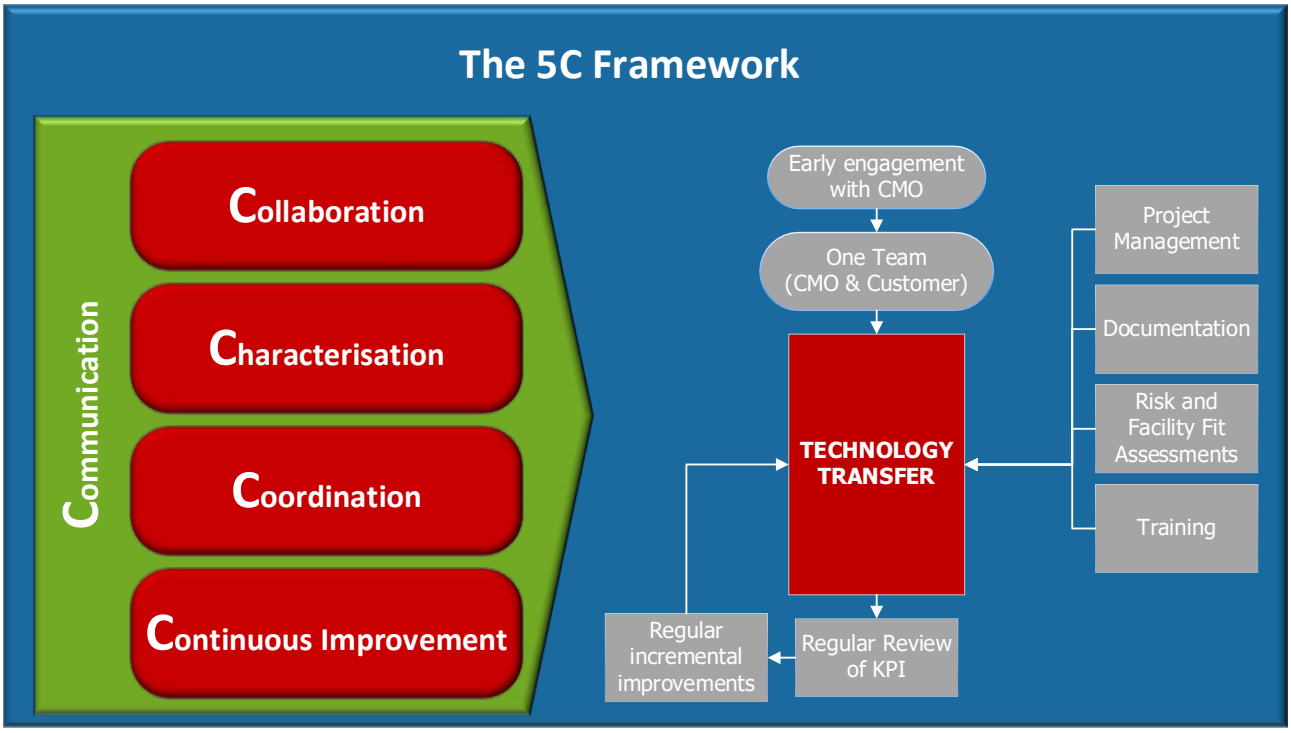

Figure 7: The 5C Framework for Technology Transfer (image source Layth Ujam, Nov 2020)

The 5C Framework supports a tech transfer process that has it's foundations based on early engagement with a CMO and initiating the project as a team. The technology transfer process, as a whole, supported by project management, documentation, risk and facility fit assessments and training. Regular review of key performance indicators (KPIs) allow regular incremental improvements to the process to be made. The 5Cs feed into the technology transfer process and are enables for success.

5.1 Communication as an intrinsic tool

An enabler for the entire Framework and tool for effective tech transfer, *Communication* runs through each of the other four categories. Modern methods of communication allow people to instantly meet and talk through live video conferencing, email and instant messaging, remote working is a reality and tech transfer teams can be far apart yet continue to converse and work together. However, occasional face-to-face meetings are still invaluable in establishing relationships and developing an innate understanding of each team member's communication style. With these tools and technology at our disposal, there is no excuse for "poor communication".

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5.2 Collaboration

Too often, people blame poor communication for problems during tech transfer (Interviewee 9, 2020) and (Garguilo, 2020b). Yet communication itself may not be the root cause. If *Collaboration* is ineffective, expectations aren't managed and as a result, the appearance is that project management is not good and communication is poor (or it gets the blame). The integration and combined effort of both teams ultimately determines the success, or failure, of a project. A successful relationship is genuinely mutual and Customers would not want a subservient CMO partner. The aim is knowledge sharing to get to the clinic faster, safer and within budget. This is why expectations management (both ways) in the bidding and outsourced selection phases is essential to managing the true success of the relationship longer term.

Expectations of effective collaboration include:

1) Early engagement between CMO and Customer.
2) Share the company's mission.
3) Communicate your expectation for collaboration.
4) Define and communicate your team's goals.
5) Highlight individuals' strengths.
6) Promote a community working environment.
7) Foster honest and open communication.
8) Encourage creativity.
9) Share knowledge, insight, and resources.
10) Lead by example.
11) Visit the sending/receiving site and see for yourself.
12) Invest in collaboration tools.
13) Celebrate and reward successful teamwork.

5.3 Characterisation

The *Characterisation* factor relates to product and process knowledge leading up to a well-developed process based on scientific principles, with an organisation demonstrating maturity from the following examples:

1) Consistent and controlled procedures.
2) Knowledge of CCP, CQA and other important parameters.
3) Use of prior knowledge from similar products.

4) An assessment of transfer readiness.
5) Assurance of equipment understanding and capability.
6) Assurance of analytical method robustness.
7) Request information from the Customer related to raw materials, equipment and facility.

5.4 Coordination

This factor relates to effective transfer management, planning and assessing the product and business risks:

1. Clearly defined CMO tech transfer process.
2. Risk assessment and risk mitigation procedures.
3. Assign a single project manager for the entire lifecycle of the project, this best serves the client's needs and leads to project success. Project management teams should comprise of professionals with a strong background in technology transfer. A tech transfer process will face problems if a project manager leaves during the transfer. This happens quite often during mergers and acquisitions or if a tech transfer project continues for many years (Interviewee 4, 2020).
4. CMOs should continuously improve their project management operations through ongoing training and development, both with formal education and training, and with company internal development programs.

5.5 Continuous Improvement

Tools for continuous improvement are numerous (George *et al.*, 2005) and are often applied to manufacturing processes, where their benefit could also be realised during tech transfers. Continuous improvement in tech transfers would be to:

1) Improve the tech transfer as you would a manufacturing process.
2) Working with metrics in a way that measures and monitors effectiveness.
3) Scientific support for identifying the root cause of failures or problems.
4) Work to create behavioral changes to address lessons learned.
5) Use satisfaction surveys.
6) Roll out effectiveness checks for aspects of tech transfer and change management.
7) Visualize successes and share with the organization.

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For an organisation to implement effective tech transfer processes with the 5C Framework, each factor is required to be an active part of the process. When one of the 5C Framework factors is missing the outcome of a tech transfer is not achieved as the end result is a multiplier of each factor (based upon the engagement equation by Rice, Marlow and Masarech, 2012). Figure 8 shows an ideal process and one where the consequences of any of the 5C factors being missing or is under developed adversely influences the outcome of the tech transfer process.

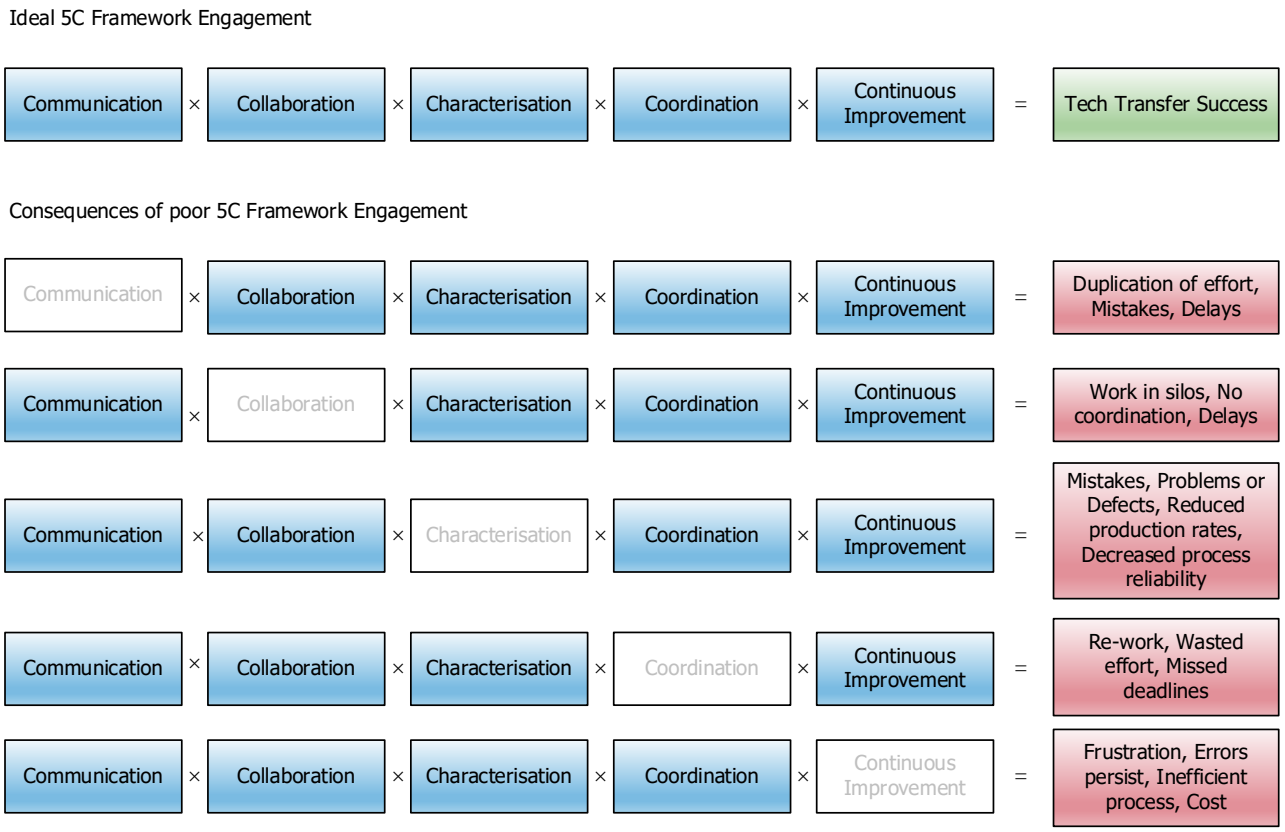

Figure 8: An engagement equation as it applies to the 5C Framework showing an ideal process and the consequences if any of the factors is missing or is under developed.

5.6 5C Framework Maturity Assessment Model

The Maturity Assessment Model uses five levels of maturity to determine effectiveness of each of the five Framework factors. Each maturity level has a definition clarifying what it means to be at that level, see Table 8 below. The output of the assessment is documented on a table as shown in Table 9.

Table 8: 5C Framework Maturity Levels

Maturity Level	Definition
Initial	No standards are in place and inconsistency exists across the organization. Processes are unpredictable, poorly controlled and reactive.
Managed	A process is in place and activities are managed, but the responses are reactive.
Defined	A process is defined as a standard across the organization and is tailored for individual projects. Responses are pro-active and data is used to understand why situations occur.
Quantitatively Managed	The process is measured and any deviation from the standard is controlled. Data is used for trending and improvement.
Optimizing	The process is continuously improved. Organisation adopts data-driven strategy. Data is used to create performance culture.

Table 9: Table for the 5C Framework Maturity Assessment Model (based on *IBM IT Maturity Model*, 2020).

Maturity Level / Factor	Initial	Managed	Defined	Quantitively Managed	Optimizing
Communication					
Collaboration					
Characterization					
Coordination					
Continuous Improvement					

Overlaid onto the table are indications of both the *As-Is* and *To-Be* states for the particular organization (see the example in Table 10). Where As-Is defines where the organisation assesses the maturity for that Framework factor is, and where To-Be is the level the organisation is aiming for. The transition from As-Is to the To-Be state can cross any number of levels since progress does not have to be in single steps.

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Table 10: Example 5C Framework Maturity Assessment Model

Maturity Level / Factor	Initial	Managed	Defined	Quantitively Managed	Optimizing
Communication					
Collaboration		As-Is →	To-Be		
Characterisation		As-Is →		To-Be	
Coordination					
Continuous Improvement					

The criterion for each level of the maturity model must be specific and it must be clear how each of the criteria for that level is met. Each criterion can be a statement of fact or can contain a measurement that must be achieved. Table 11 below gives example KPI criterion for three maturity levels using collaboration and characterisation as examples of the 5C Framework factors. It is the responsibility of the organisation to determine the KPIs that define the criteria for each maturity level.

Table 11: Example criterion for Maturity Assessment Levels for Collaboration and Characterisation

Factor	Managed Criterion	Defined Criterion	Quantitively Managed Criterion
	A process is in place and activities are managed, but the responses are reactive.	A process is defined as a standard across the organization and is tailored for individual projects. Responses are pro-active and data is used to understand why situations occur.	The process is measured and any deviation from the standard is controlled. Data is used for trending and improvement.
Collaboration	Documents are issued for review but the required turnaround time is not specified.	The time taken to review manufacturing documents is no more than three working days.	A regular review of adherence to schedule is in place.
Characterisation	Customers are asked if they have process buffer stability data at the start of the tech transfer process.	A standard checklist exists for obtaining process buffer stability data. Out of specification data is used to investigate the reasons behind the finding.	A scheduled review of stability data is in place and regularly reported.

The As-Is state should be defined by cross functional collaboration across a number of involved parties. A face-to-face workshop is an ideal forum, where attendees discuss and

respond to comments and questions, and where they can decide on a level that they all agree with.

When defining the To-Be state, the objective isn't to achieve the highest level in all areas. That objective entails a huge amount of expense because it might require changing significant parts of the current process and utilise resources that may not be available. It may also be inappropriate, especially when the needs of the organization can be met with a lower level of maturity. Each level indicates the gap that must be closed for each factor, based on the maturity aspirations.

Application of the maturity model should be regularly reviewed to avoid complacency within the organisation. Reapplying the maturity model provides a coarse indication that things are heading in the right direction towards the To-be state.

6.0 Conclusion

1) Technology transfer processes are well defined and supported by guidance documents, yet biopharmaceutical transfers continue to be hampered by factors that are not necessarily associated with the science. The success of transfers heavily relies upon sharing of explicit knowledge and it is this element that professionals working in the industry report to cause most challenges. The need for improved transfer of information is evident given the findings presented in this research and is shared by CMOs and Customers that partner them.

   Industry associations, CMOs and biopharma companies recognise technology transfer as a critical activity in the product lifecycle. Guidance documents and articles related to the subject all provide a representation of what an ideal tech transfer should be, yet the same problems highlighted nearly a decade ago are still being reported. Tech transfer clearly relies on explicit knowledge, and guidance documents provide extensive lists of activities and knowledge that should be transferred but little means of how to do this or how to measure effectiveness of a transfer. Industry professionals and those partnering with CMOs share the same common issues of project management, management of expectations, collaboration and communication. The PDA has recognised this and are

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initiating change to their guidance document, Technical Report 65 Technology Transfer (Haas, 2019).

2) Technological advances have surpassed those of collaboration and coordination yet these are factors that are relied upon for a successful tech transfer outcome. As more biotech companies outsource and partner CMOs, the need to collaborate effectively becomes more important, and effective means of doing this will be required to sustain the intensification of biological, and soon to be gene and cell therapy products.

   Of the 5C Framework categories, collaboration is the one that is least supported by tools. Collaboration requires the right mindset and perhaps the industry has progressed communication, characterisation, coordination and continuous improvement at the expense of collaboration. People fit and cultural alignment will determine the success or failure of the project.

   The search for a Covid vaccine is a prime example of how the industry is collaborating effectively. Many tech transfer projects have been fast tracked due to Covid through accelerated regulatory procedures, such as emergency use authorisation (O'Sullivan, Rutten and Schatz, 2020) and (Garguilo, 2020a). There is a general view that accelerated tech transfers of 3-4 months may now become an industry expectation moving forward and accelerated programs will become the 'new normal'. However, such accelerated programs are largely dependent on lead times for equipment and raw materials and may require materials to be shipped from customer sites. In addition, the timelines may not permit full analytical testing at the CMO site, requiring some release testing at the client site or third party facilities also (Interviewee 5, 2020). Accelerated tech transfers may be considered to provide pandemic treatments with a global unmet medical need, but also present higher risks of delays and possible batch failure (Interviewee 5, 2020).

3) A change of mindset is required within the industry to truly adopt the one-team approach; sharing ownership, openly sharing information and regarding the CMO as an extension of the customer's team rather than a pay-as-you-go service provider. This change in culture can be brought about by focussing on collaboration, good project

management and continually assessing effectiveness of tech transfer processes. The industry has shown to be capable of collaborating, but it has taken a global pandemic to realise this.

The 5C Framework and associated maturity assessment model provide a pragmatic approach focussed on the factors that heavily influence the outcome of tech transfers. It is hoped that this tool can bring about measurable changes within an organisation's approach to an effective tech transfer programme.

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