QUALITY BY DESIGN

Technology Transfer Needs a Lingua Franca

Shared means of communication between sending and receiving units

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Bringing new drugs onto the market can take years, so any delay will result in loss of income. Tremendous losses are sustained, if at the end of this long process, the competition then takes off with the innovation. The registration procedure, however, can be speeded up by the efficient transfer of technology between R&D, on the one hand, and production, on the other hand. This transfer lays the foundations for the further production process, the control strategy, the process validation and the continuous improvement initiatives.

However, there are very few companies that actually have policies in place, apply KPIs or even have a standardised approach. Quality by Design has developed a Lean Tech Transfer Framework consisting of a scenario approach combined with templates. The framework acts like a lingua franca and ensures a thorough understanding between both the sending and the receiving units. Adopting a risk-based approach will also increase the chances of success and improve efficiency.

More New Products, Lower Costs

The pharmaceutical industry is undergoing major change. The patents for the blockbusters from the 90s are expiring one by one. The market is now being flooded by generic drugs, and in sharp contrast the income of the original manufacturers is being decimated. Developing new blockbusters and therapies is a lengthy process, despite increased investment in R&D.

FDA legislation is becoming ever more stringent, the current market conditions are not exactly favourable, and healthcare budgets are increasingly coming under pressure. In order to remain competitive, the big pharmaceutical companies have but very few options. They have to get more new products into the pipeline and productivity must increase, whereas their lead times and costs must be cut. The future belongs to those who apply efficient quality and cost control, and can keep a firm grip on their market launch times.

Outsourcing R&D

Manufacturers are moving their production activities to low cost labour countries. Many pharmaceutical organisations view their R&D productivity as their Achilles' heel. The average cost for successfully launching a product onto the market has soared - sometimes by 25% per annum or more – and yet companies see a drop in their net returns. More and more pharmaceutical companies are seeking refuge in outsourcing. They are joining forces with smaller contract research organizations (CRO's) and knowledge centres for at least part of their preclinical and clinical research.
This is probably a wise move, because there is a noticeable link between major medical developments and the size of the company. More than 75% of all breakthroughs stem from small R&D companies, despite large pharmaceutical companies having much larger budgets at their disposal. According to Morgan Stanley, the large pharmaceuticals would be well-advised to outsource their research to external researchers. After all, the latter are 3x more successful than their own in-house research departments.

Technology Transfer in the Limelight

Outsourcing and relocation scenarios always involve a transfer of documented technological expertise and processes between the sending (SU) and the receiving unit (RU). That technology transfer is absolutely crucial as it forms the basis for all the development and production activities involved in bringing a drug out of the lab and onto the market. In addition, this knowledge transfer is also the cornerstone of the further production process, the control strategy, the process validation and the continuous improvement approach.

What happens if there is a failure in the technology transfer process?

If anything goes wrong in technological transfer, the consequences can often be far-reaching. The processes will then be less robust and unreliable, the company will not meet its planned production figures, quality may cause concern, and the validation process may incur delays. In the worst case scenario, the drug registration may be in jeopardy. If this registration fails, the losses can be considerable. Delays through ineffective technology transfer may cost the company millions of euros in lost income every day.

High Complexity

Pharmaceutical companies struggle with technology transfer, both on projects involving external partners as well as with the transfer between departments or sites on their own networks. The level of complexity is usually high. Not working systematically will increase the risk of overlooking crucial factors. The expertise of the SU and the RU will vary greatly, they will have different objectives, and the terminology used may even differ at times. Knowledge and practical know-how are often taken for granted. Researchers by their very nature tend to build in extra room to manoeuvre for the implementation of certain parameters. However, this flexibility may have a flip side. There is the risk of communication becoming increasingly vague, thus rendering the transfer process more difficult.

R&D companies also tend to be less familiar with legislation aspects such as GMP, and with high volume production. They are involved in small scale production. For the transfer, the technology and the processes must be scalable. Otherwise, there is a high risk of inefficiency, quality issues, and increased costs due to compliance problems. In addition, they often just focus on one single product, or just a few at the most. As a result, they do not develop a standard approach or a set routine for the technology transfer.

Problems may even arise during a transfer of production between two sites within one same company. The SU and the RU may even be competitors. Cultural differences and time zones can also encumber the transfer process.

FROM (Sending Unit | SU)	TO (Receiving unit | RU)
University/research/CRO	University/research/CRO
University/research/CRO	Spin-off
University/research/CRO	Manufacturer
Spin-off	Spin-off
Spin-off	Manufacturer
Manufacturer	Manufacturer (intra- or inter-company

Fig. 1 - Most common tech transfers

Systematic Approach and Standard Work Methods Pay Dividends

Numerous pharmaceutical companies have realised the importance of guidelines and measuring points for technology transfer projects. Adopting a systematic approach combined with templates or a scenario will yield measurable advantages. However, there are still hardly any usable models of approach on the market.

The use of standard templates and deliverables will considerably simplify and accelerate the task in hand for all the parties involved. Checklists ensure that all the relevant steps stay at the forefront of your mind. They assist the RU in asking the right type of questions. All the necessary information and documentation will also be easier to locate. If members of staff use the methods repeatedly, these will become second nature. If staff are then required to work in another department or another plant, they will have retained this knowledge and will be able to apply the routine they have acquired. By adopting a structured approach, it will become easier to estimate technology transfer projects. The management will then be able to perfectly check the progress of the transfer projects.

Transfer Process in 4 Phases

Quality by Design has developed a framework for technology transfers based on best practices and templates. The Lean Tech Transfer Framework splits the transfer process into four phases. For every single phase, Quality by Design is at hand to offer advice and consultancy, as well as support with the implementation:

- Phase 1: duties and responsibilities
- Phase 2: data exchange
- Phase 3: testing and process validation
- Phase 4: registration dossier and lessons learnt

Phase 1: Duties and Responsibilities

Phase 1 is taken up with the project preparation. This is focused on two aspects. The legal aspects involve the agreements between the SU and RU for the licence rights governing the use of the technology, and the secrecy rules. The second major aspect is purely organisational. The SU and the RU set up a project team, they appoint a team leader, they set out the duties and responsibilities, and they determine the project timescale. They establish how to exchange their data – e.g. by uploading to an FTP server, by e-mail or by any other method - how to structure the data, and who will be granted access. The project methodology will also be discussed. The parties involved will draw up a project charter to lay down their agreements. The Lean Tech Transfer Framework will not provide any support for the legal aspects, but will provide support for everything concerning the organisational aspects.

Phase 2: Data Exchange

In phase 2, the SU and the RU determine which information they will exchange relating to, for example, the specifications, IPC testing, raw materials and the production process. This is by no means a simple exercise. How do you determine what is and what is not relevant? How to deal with intellectual property? How does one handle potentially sensitive information, such as the change history? Is the SU prepared to share that? The mere fact of making assumptions can lead to major misunderstandings. A general checklist covering all of the available information will clearly set out the expectations of both of the parties from the outset.
The correct and complete transfer of information represents a key factor in the validation process and legal compliance. Both parties would therefore be wise to agree beforehand who will take responsibility for any missing information. The SU will transfer all the relevant data to the RU. For a well-prepared SU, this part is simple ... in theory. In practice, however, this phase can often be quite time-consuming. Quality by Design will help you to determine which information is relevant. And very importantly, the templates of the Lean Tech Transfer Framework establish exactly where all the information is located.

Phase 3: Testing and Process Validation

The third phase is also the most time-consuming. The onus of the work to be performed is now on the RU. The latter analyses the process outlined by the SU, then brings it in line with their own standard operating procedures (SOP) and equipment, and validates it. The SU organises the knowledge transfer, and in its capacity as a subject matter expert will answer any ad hoc questions posed by the RU. This process also involves the practical know-how from the lab which is not quite so relevant for the registration dossier.

What is important is the order of the validation activities. You first transfer and validate the methods, followed by the process.
If the process requires additional equipment or extra ompetencies, then the RU must acquire those or have them transferred from the SU.

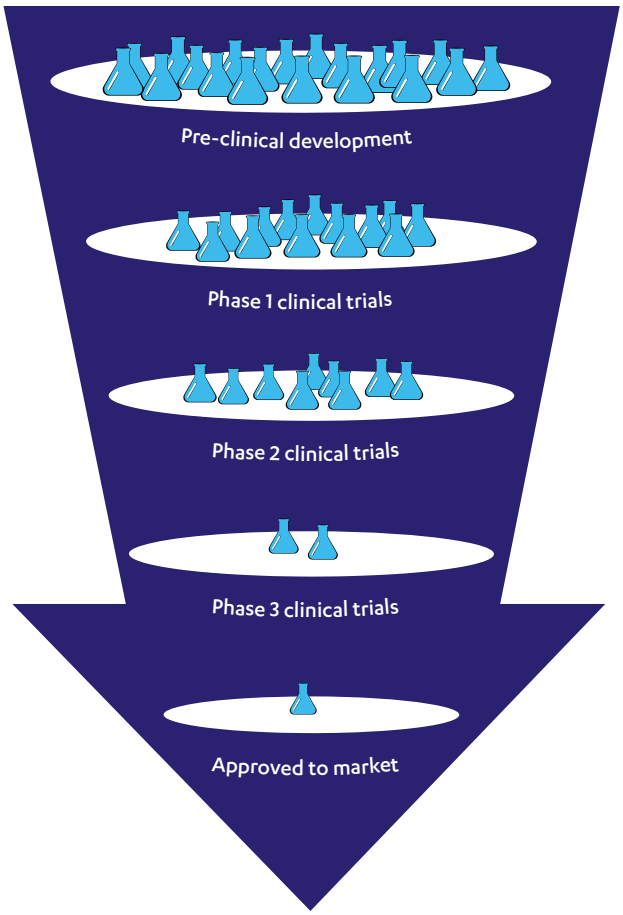

Fig. 2 -Approved to the market

Meeting the phase 1 lead times now becomes the main challenge. Careless work in the phases 1 and 2 will compound the number of potential major issues in phase 3. During this stage, time-consuming stumbling blocks can cost dearly. If these are resolved sooner rather than later, that will reduce the amount of re-work equired and any expenditure. Unresolved problems will result in delays, and difficulties with the delivery of raw materials, excipients and components. New equipment must also be delivered on time and must meet the required specifications.

If the process grinds to a halt due to bottle-necks, the project team will usually have two options: to opt either for the fast solution that will get the project back on track, or for the longterm solution. Any variations to the suggested approach must be assessed and validated. A type II variation will have quite a different impact on the further process and planning of the project compared to a type IA or IB variation[1]. That is why it is so important to involve your legal experts in the technology transfer in phase 3. If a tight budget or deadlines do not leave any room for modifications, then explore the long-term options and check whether the business case stacks up.

[1] Type IA, IB and type II variations according to the European variations guidance (Commission regulation No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products). Variations of type IA and IB are considered minor variations, type II variations are considered major.

Phase 3 can only start when all the necessary information has been exchanged in phase 2. Does that only apply to certain headings on the checklist? Then the phase 3 activities can already start with that, albeit with a major proviso, as missing information can upset the entire validation process of the technology transfer. Phase 3 will be completed as soon as all the stumbling blocks have been eliminated, and when all the processes and production nstallations meet the GMP instructions and the SOPs, and when the final validation report has been completed.

Phase 4: Registration Dossier and Lessons Learnt

In the course of the last phase, all the necessary information is assembled into the correct format ready for the registration dossier. Phase 4 often runs partly in parallel with phase 3. It will be completed as soon as phase 3 has come to an end. It is at this stage that the SU and the RU will sit down to jointly write a technology transfer report. In this report they will describe any deviations from the original scope and any lessons learnt. The report will assist with the continuous improvement process.

The systematic approach for the technology transfer will safeguard any lessons learnt for future projects. Have we possibly lost sight of the lessons learnt from previous transfers? How did we tackle the critical situations? Which tips & tricks could be valuable for future projects? Could the checklist still be improved? It is mportant to obtain feedback from all the various parties, i.e. from the SU and the RU, but also from third parties, such as suppliers.

Thorough Preparation Simplifies the Set-up

Thorough preparation simplifies the set-up of a technology transfer project and increases the chances of success. If you are equipped with a good quality control system, validated methods and clear documented production processes, then you will already have made a head start.

If you are setting up a technology transfer project, then a risk-based approach will pay dividends. The life sciences industry is competitive and highly regulated. Pharmaceutical companies aim to use their resources as efficiently as possible whilst imultaneously minimising the risk to patients. A risk-based approach will be a great asset. It will teach you what can go wrong, and what the chances are of anything going wrong, what the consequences will be, and how to contain the risk without triggering any others. Setting priorities thus becomes so much easier. The same applies to technology transfer projects. The staff involved often find it difficult to distinguish between what is important and what is not so important. If you draw up your risk analysis first, then your priorities will be clear from the start.

The SU would be well-advised to start its preparations well before the launch of the tech transfer project. If there is any documentation that is not yet ready at the start, this will cause major delays. The Quality by Design experts can also lend support with this preparatory work.

Conclusion: Risk-based Approach and Scenario Bear Fruit

An effective technology transfer project will accelerate the introduction of a new drug onto the market, and will therefore quickly generate money. The success factors are the risk-based approach, a funded project plan with clearly defined duties and responsibilities, a structured approach supported by strong leadership, good communication between the sending and the receiving unit, efficient documentation of the process, and sufficient focus on knowledge transfer.

Scenarios and templates will simplify the process of implementing those objectives. They provide a lingua franca: a shared means of communication between the parties concerned. Its performance will increase with every new project, because any lessons learnt are shared. The lingua franca has yet another advantage; it immediately inspires confidence in that you are working with a professional and efficient partner.

Quality by Design Bridges the Knowledge Gap

A technology transfer process involves a lengthy list of action points and checks. By focusing on the right 20%, you already have 80% of your project on track. That is the pragmatic principle applied by Quality by Design.
The Quality by Design validation experts and QA specialists bridge the knowledge gap between the sending and the receiving units. They are familiar with the processes on both sides, with the complex regulations and with the quality challenges facing the pharmaceutical industry. Quality by Design will guide you with the implementation of an approach for technology transfer based on scenarios and templates. The Lean Tech Transfer Framework offers strong support with ensuring legal compliance. It will help you to set the right priorities and to avoid any pitfalls, and to allow the transfer process to proceed much more efficiently and speedily.

About Quality by Design

Quality by Design delivers consultancy services to companies in the pharmaceutical, bio technical and cosmetics industry. With its years of experience, QbD helps these companies set up and improve quality assurance, and with an optimal validation of products and processes. To do so, QbD employs forty specialists in the field of validation, technology transmission and quality control.

The renowned company operates mainly in the Netherlands and in Belgium, and works for small and innovative companies as well as influential and worldwide organizations. QbD's clients include Alcon, DSM, Genzyme, Heel Belgium, Janssen Pharmaceutica, Labo Wolfs, MSD, Multipharma, Pfizer, Pronails, UZA and Wase Werkplaats. For more information, please visit www.qbd.eu.

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