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TECHNOLOGY TRANSFER INTRODUCTION AND OBJECTIVES

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Purpose of the Book

The successful technology transfer from research and development (R&D), the transferring site, to the commercial Production site, the receiving site, is a critical process in the development and launch of a new medicinal product. It can be extremely costly for a company if things go wrong during the transfer process, resulting in delays to launching a new product on the market and lost sales. Also, it can take increased resource, time and cost to make corrective actions following an unsuccessful transfer. Progressive pharmaceutical companies are therefore placing more attention to streamlining and optimising their technology transfer process to ensure the rapid and successful introduction of a new medicinal product to market.

The purpose of this book is to give an overview of the technology transfer process for pharmaceutical Drug Substance (sometimes referred to as the active pharmaceutical ingredient [API]), the pharmaceutical Drug Product and the corresponding analytical tests and methods. Also, to suggest key factors considered to be important by the authors in achieving successful technology transfers and getting it right first time and every time. It is intended to be a practical guide to those working in the pharmaceutical industry or related industries, (for example, biopharmaceuticals), or anyone wanting an insight into this subject area.

Technology Transfer and the Drug Discovery and Development Process

Technology transfer is both integral and critical to the drug discovery and development process for new medicinal products.

For a typical research-based pharmaceutical company, drug discovery and development can be broken down into distinct stages. Figure 1.1 illustrates the latter stage of the 'research' or 'drug discovery' phase and the 'development' stages leading to new product launch.

The culmination of the research programme is the nomination of one or more candidate drugs (CDs) for development selected from several lead compounds. The acceptance criteria for nomination will be based on the CD meeting target pharmacological, toxicological and to some extent, pharmaceutical properties, identified in a pre-nomination target profile by the company. Evaluation of the lead compounds is achieved by testing them in preclinical *in vitro* and *in vivo* (animal) studies. From both a Drug Substance and Drug Product development perspective, to aid rapid development, it is important to select a CD with preferred pharmaceutical and drug synthesis properties at this stage. Preformulation and biopharmaceutics studies are undertaken to establish the physicochemical properties and biopharmaceutical properties of the lead compounds to aid CD selection and to identify potential issues for future development. Typical examples are given in Table 1.1.

Table 1.1 Typical Examples of Preferred Drug Synthesis, Pharmaceutical and Biopharmaceutical Properties for Candidate Drugs

Drug Synthesis Properties	Drug Substance Properties	Biopharmaceutical or Drug Delivery Properties
Least number of synthetic steps	Good aqueous solubility over a wide pH range	Good permeability coefficient (determined from *in vitro* assays)
High yields and purity	Crystalline	Complete absorption in the GI tract *in vivo* in several animal species
Least complex structure (none/few chiral centres)	Stable polymorphic form or non-polymorphic	Gastrointestinal (GI) tract stability
Use non-hazardous materials and steps e.g., non-explosive, non-toxic reagents	Non-hygroscopic	Ability to form suitable salts
Low cost of goods	Good solid state stability	Metabolic stability in intestinal fluids
Commercially available starting materials	Acceptable stability in intended formulation vehicles	Compatible with key formulation excipients
Simple isolation and purification methods available	Acceptable organoleptic properties, e.g., odour, colour	Good dissolution properties
No predicted scale-up problems	White or not highly coloured	Good processing properties, e.g., powder flow, particle size reduction

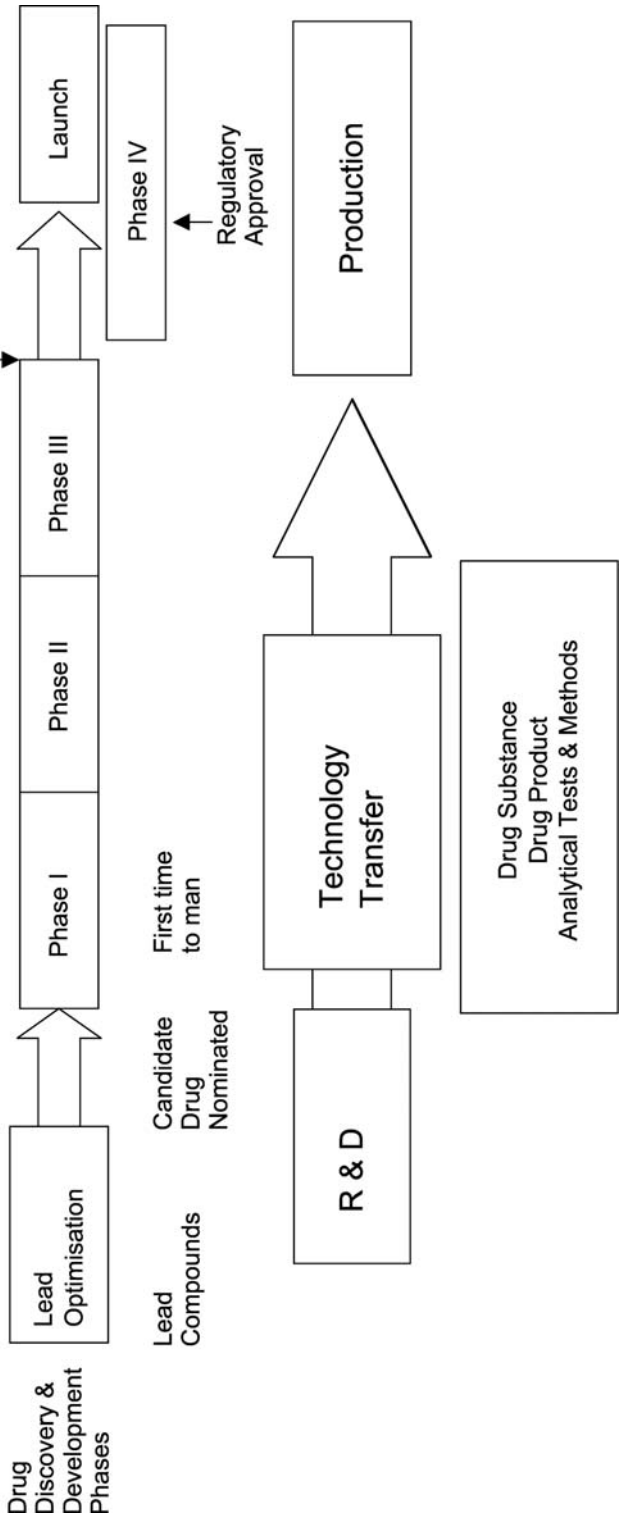

Figure 1.1 The Drug Discovery and Development Process and Technology Transfer

Clearly, the absolute value of certain properties will depend on the intended route of administration and type of dosage form to be developed. If a parenteral dosage form is required, then good aqueous solubility and stability will be extremely important. If the preferred properties are not obtained, then the synthetic chemists and the formulation scientists will have more challenges to address during later development.

At the early stages of development, there is still a lot of uncertainty about the success of the new CD because it will not yet have been assessed in humans. During the 'exploratory development' or 'concept testing' stage, studies are designed to assess how the CD is absorbed and metabolised in healthy human volunteers (First Time in Man studies [FTIM]), before studying its effect on those actually suffering from the disease for which it is intended. Sometimes it is necessary to conduct small-scale studies in patients (also referred to as Phase I clinical studies) in order to make a decision whether to progress the CD to 'full development'.

For Phase I, relatively small amounts of the CD are made available by the process chemists. It may be the first and only batch of Drug Substance available at this time and will more than likely be prepared using a sub-optimal synthetic route at laboratory scale. Phase I safety and clinical studies are often provided for in the form of a simple non-optimised formulation, quite different from the intended commercial formulation, because time for development and availability of drug are limiting factors at this stage. Simple formulations used for Phase I studies may involve an oral solution or suspension of the CD, rather than a more complex dosage form such as a tablet or capsule.

There is a high probability that the project will be terminated during Phase I due to toxicity findings or clinical findings (safety, efficacy and pharmacokinetics/bioavailability). If unwanted or unexpected effects are observed, the programme will most likely be stopped and the project goes back to the research group to try and find another lead compound. Alternatively, if the outcome is positive, the CD may be progressed to 'full development'. As only a few candidate drugs tend to progress beyond preclinical and Phase I, there may not be much value in investing too much effort into developing the intended commercial API manufacturing process or formulation until the project is approved for full development. There can be exceptions to this rule, when a company decides to 'front-load' the development programme on a risk basis so that delays are avoided in commencing full development if the Phase I testing turns out to be successful. Companies may invest time in developing a larger batch of Drug Substance and in optimising the synthetic route, while the formulators will start to develop a Phase II Drug Product, in anticipation of a successful outcome from the concept studies. It is often considered appropriate to accept the risk of manufacturing a batch of Drug Substance that is not needed if there is a negative outcome, than to have to wait several months for material to be made before the programme can continue.

Full development involves the completion of longer-term safety and clinical studies (Phase II and Phase III) in larger groups of patients (hundreds to thousands) suffering from the disease. During full development, the synthetic route for the Drug Substance is optimised and the manufacturing process scaled up and fixed. Larger scale batches of Drug Substance will be required to support larger safety and clinical studies and also to support the pharmaceutical development work to optimise the formulation and Drug Product manufacturing process. During full development, the pharmaceutical scientists develop the intended commercial formulation guided by the product design criteria. Product and process optimisation of the Drug Product are progressed and the manufacturing process is scaled up to meet the increasing demands of the later phase clinical trials. If sufficient Drug Substance is available and the Phase III supplies are very large, it may be preferable to scale-up the manufacturing process to production scale and transfer the process to the commercial Production site to make the Phase III supplies from there (see Technology Transfer Strategy Considerations in Chapter 3). One potential downside of transferring early to production is that all the development work has to be completed earlier in the development programme to fix the formulation and manufacturing process and this puts the pharmaceutical development on the critical path. It is possible to make further changes after transferring the process to production, but these are more difficult and involve documented change control. Starting the technology transfer prior to the start of Phase III is also a risky approach because statistics show that there is still a relatively high attrition rate during Phase II due to both efficacy and clinical safety failures.

However, one positive benefit of this approach is that it is usually easier for the company to demonstrate that Drug Product used in the pivotal Phase III clinical trials is equivalent to the intended commercial product, assuming that any changes during Phase III are minimal. This should pave the way for a more straightforward Pre-Approval Inspection (PAI) when it comes to regulatory review of the Product Licence Application (referred to as the Marketing Authorisation Application (MAA) in Europe and the New Drug Application (NDA) in the USA and Japan). Most regulatory authorities, including the US Food and Drug Administration (FDA), the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the European Agency for the Evaluation of Medicinal Products (EMEA), require three phases of clinical trials and sufficient data to show that the new Drug Product can be licensed as safe, effective and of acceptable quality.

If clinical batches of Drug Product are being manufactured under replicated conditions during the latter stages of development, e.g., Phase III, even if still at the R&D site, the regulatory authorities will expect that some process validation will have been undertaken. Once the commercial manufacturing process has been transferred from R&D to Production, the process must be validated to meet regulatory requirements if an MAA or NDA is progressed. More detail of the requirements for product and process design, optimisation, scale-up and process validation for the Drug Product are given in Chapter 6 of this book.

Once the Phase III clinical trials are completed successfully and the Drug Substance, Drug Product and analytical methods have been transferred to the intended Production sites, a regulatory submission can be made. Pending approval of the submission and a successful Pre-Approval Inspection (required if the product is intended for the United States), the new product can be launched on the market.

For the purpose of this book, technology transfer (TT) is defined as "*the transfer of the manufacturing process for a new pharmaceutical Drug Substance (DS) and Drug Product (DP), respectively, from the transferring site (in this case R&D) to the receiving site or designated commercial Manufacturing site. This includes all the associated knowledge, information and skills to be able to manufacture the DS and DP at the receiving site.*" Information will include that related to the Drug Substance, the formulation, the pack or device used, the manufacturing process and the associated critical quality parameters. TT also involves the development and successful transfer of the analytical and microbiological test methods and specifications for the DS and DP that will become the final Quality Control (QC) procedures used at the commercial Production site.

Why is Technology Transfer Important?

There is a clear need for pharmaceutical companies to speed up delivery of new Drug Products to the market to maintain competitive effectiveness. New drug discoveries must be rapidly brought to market to generate cash flow to re-invest back into the business and support the drug pipeline. It is estimated that 70% of new products on the market fail to recoup the costs of R&D. The number of new medicines launched in recent years has slowed down because it has become more difficult to meet all the requirements of safety, clinical and regulatory in areas of unmet medical need. Statistics from the pharmaceutical industry success rates show that there is a high risk of failure in drug discovery and development, with only one in five to one in ten new Candidate Drugs nominated from research to development actually achieving registration and reaching the market (Tucker, 1984; Resch and Lee-Houghton, 2003). The rate at which pharmaceutical companies are clearing the final hurdle of clinical trials has declined since the mid-1990s when 56 New Chemical Entities (NCEs, i.e., small synthetic molecules) were approved in 1996, down to only 29 worldwide approvals of new molecular entities in 2002. On average, an NCE takes 10–12 years of research and development from drug discovery to product launch. This is at a currently estimated cost of $1–1.5 billion before it comes to market, which has to cover the costs of research, development, manufacturing, distribution, marketing and launch and also the cost of failures (NCEs that did not make the market).

Drug development times have increased in recent years because all phases of development are taking longer. The initial concept testing stage can be completed in

less than two years if more work to assess the risks is conducted during drug discovery leading to a better quality CD. The need to do larger patient studies and the increased patient enrolment times have resulted in increased clinical study duration. Typical times to complete Phase II and III trials can add a further 4–6 years depending on the size and complexity of the Phase III clinical programme. It will take longer, for example, to study a treatment for a chronic disease to gather sufficient efficacy and safety data to support registration.

Achieving a faster time to market by streamlining the development process and, for example, introducing more efficient safety and clinical programmes with some risk taking, tends to put synthetic drug development and product development, including the respective technology transfer, on the critical path. In addition to condensing the timescales, there is increasing pressure to define the final synthetic route of the drug, to define the final formulation, packaging and manufacturing process and to get it right first time; thus avoiding changes at later stages of development that could cause unnecessary delays to registration and launch.

The financial cost of getting the technology transfer wrong can be significant; a product that is six months late to market could miss out on one-third of the potential profit over the product's lifetime (McKinsey & Co, 1991). This could be due to competitor companies being first to market, capturing the market share and dictating the price, as well as the loss of effective patent life.

The cost of a retrospective fix after product launch due to poor product or process development can also be expensive and embarrassing. A product recall could easily wipe out the profits from an early launch. Significant post registration changes require regulatory approval and come with time delays. The longer-term consequences can be that a company's credibility with the regulatory authorities and its customers are affected and this could ultimately impact on the value of the company (share price) and more difficult regulatory inspections.

In conclusion, the transfer of technology for Drug Substance and Drug Product between R&D and the respective Production sites is critical to successful and timely development. The aim is to get to market quickly with the development of a drug and product of the appropriate quality and to do it "right first time, every time".

Scope of the Book

For the purposes of this book, technology transfer covers the activities associated with Drug Substance, Drug Product and analytical tests and methods, required following candidate drug selection to completion of technology transfer from R&D to the first receiving site. Transfer of established Drug Substance or commercial products from

one commercial site/facility to an alternative/additional commercial site/facility is not included here. This aspect of product transfer has already been covered in an excellent short guide written by Green and Warren, 2002.

The book is written with traditional New Chemical Entities (NCEs) and conventional type dosage forms in mind, such as tablets or capsules. There is a growing trend in the number of biological type pharmaceutical products in development and reaching the market. One fifth of the total new drug approvals by the US FDA in 2002, and one third in 2003, were biological in nature. It is widely predicted that biotechnology will be the major source of new products in the future. Biologicals include peptides, proteins, nucleotides and viruses, for example, where the active pharmaceutical ingredient is produced by fermenting microorganisms such as bacteria or yeast systems, or culturing mammalian cells. These are purified to isolate the active pharmaceutical ingredient and then formulated and administered, usually by the parenteral route, although alternative routes such as intranasal and inhalation may be considered.

In recognition of this trend for biological products, there is a separate Annex (2) in the EC Guide to GMP dealing with the *Manufacture of Biological Medicinal Products for Human Use*. The guide defines biological medicinal products by reference to their method of manufacture:

- Microbial cultures, excluding those resulting from recombinant-DNA techniques
- Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques
- Extraction from biological tissues
- Propagation of live agents in embryos or animals

The guide recognises that the manufacturing processes needed are specialised to maximise the yield and to minimise chemical or physical degradation of these more sensitive biological materials. Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials that display inherent variability, so that the range and nature of byproducts is variable. There is a higher risk of cross-contamination between biological medicinal products, especially if live organisms are employed in the manufacturing process. Additional precautions may be required to contain the process, including the use of dedicated facilities and equipment, and the use of a continuous process rather than batch process. Specialised analytical methods are required to undertake chemical, physical and biological characterisation of the active and Drug Product and to conduct stability and QC testing. These techniques tend to have a

greater variability than physicochemical determinations. In conclusion, quite clearly the development of biologicals present some specific technical challenges, but it is believed that the principles of good technology transfer described in this book can still be applied usefully to achieve the successful technology transfer of biologicals as well as conventional type Drug Substances and products.

In Chapter 2, business, economic, cultural and regulatory considerations are discussed with respect to how they impact on technology transfer. New Drug Substances and Drug Products need to be transferred across international boundaries. Difficulties such as language barriers and international cultural differences have to be overcome. Requirements surrounding technology transfer tend to differ based on local policies and practices. Understanding regulatory variations between the different countries involved to ensure compliance is critical. The regulatory authorities are getting tougher on what is required to validate the transfer of processes. All the above-mentioned factors are extremely important to understand because of the implications for successful technology transfer.

In Chapter 3, the organisation of technology transfer is discussed in more detail. Pharmaceutical companies vary in the way they divide responsibilities for technology transfer between R&D and Production and the point of handover of responsibility. There does not appear to be any significant advantage to any particular organisational approach as long as the responsibilities and accountabilities are clearly defined and agreed within the company. This is best achieved by documenting in a technology transfer policy that is approved by senior management from both the R&D and Production organisations, and is complied with by the staff. The policy may be supplemented by additional guidelines outlining the detailed requirements, responsibilities and how the transfer of documentation, technology and processes is to be managed within the company. The importance of establishing a technology transfer strategy prior to starting is emphasised in Chapter 3. The strategy will vary depending on the situation. Some typical scenarios that would need to be taken into account when developing the strategy might include the following:

- **The company's existing experience with the technology**: The need to build new facilities, acquire new equipment, introduce a new process or to transfer novel analytical methods etc., will require careful consideration, decision-making, investment, time and additional training.

- **The selection and location of the receiving sites for Drug Substance and Drug Product**: Global pharmaceutical companies tend to have receiving sites for Drug Substance on a different site or location to the receiving site for the Drug Product. Different Production sites might be selected depending on the product type or intended countries where the product will be marketed.

- **Use of Contract Research Organisations (CRO)**: Sometimes a third party is required to supply intermediates for the Drug Substance or to supply packaging components or drug delivery devices for the Drug Product. The sourcing strategy needs to define the CRO and the timings for transfer and the principles and processes to be used for establishing the technology transfers from the CRO.

- **Timetable for the transfer of the Drug Substance, Drug Product and QC methods**: It may be required to scale-up and to transfer early to meet the demands of the clinical programme from the Production site, dictated by a lack of availability of large-scale equipment at the R&D site.

The strategy document should address technical issues, manufacturability aspects, sourcing decisions for both Drug Substance and Drug Product, cost implications, decision points and responsibilities. Once the timelines are agreed, then the importance of good planning cannot be over-estimated.

In Chapter 4, the importance of training is emphasised. The technology transfer process involves a multidisciplinary team of professionals working together to achieve a common goal. R&D and Production must not work in isolation, but must adopt a team-orientated approach and establish and maintain good communications. This may not be too much of a problem if R&D and the receiving site departments are located on the same site, the technology is standard and a technology transfer process is well established. It is a much greater challenge if R&D is located geographically in a different part of the world from the receiving site and the respective staff do not speak the same language. Also, if the receiving site has to be built or modified to accommodate a new type of technology for the company, there will be a strong need to train the production staff in how to handle the new technology.

In most pharmaceutical companies there are specialist groups who deal with the development of Drug Substance (process chemists, engineers and analysts) and Drug Product (pharmaceutical scientists, process engineers and analysts). Although there are similarities with the technology transfer process, there are some specific considerations for the development and technology transfer of Drug Substance and Drug Product, respectively. For this reason separate chapters have been devoted to DS (Chapter 5) and DP (Chapter 6) in this book written by experts in their respective fields. Chapter 7 covers the key requirements for developing analytical test methods and specifications, including the difficulties in analytical method transfer from R&D to the respective QC laboratories responsible for the testing of DS and DP. Critical success factors for effective transfer are discussed.

A variety of case studies are presented throughout the book to illustrate real experiences encountered during various aspects of technology transfer. The contributors highlight the potential pitfalls and learning points from the different scenarios.

The ultimate goal for successful technology transfer is to have documented evidence that the manufacturing processes for DS and DP, respectively, are robust and effective in producing the Drug Substance and the Drug Product complying with the registered specifications and Good Manufacturing Practice (GMP) requirements. At the highest level, evidence of success can be measured in several ways. For example, by the successful completion and reporting of three validation runs or process qualification (PQ) batches performed at production scale at the commercial production site. Alternatively, it could be having a successful pre-approval inspection (PAI) by the FDA. Sometimes success is considered only after several production scale batches have been made and successfully tested and QC released. At a more detailed level, successful technology transfer can be measured by means of performance indicators. For example, in terms of "manufacturability" and "robustness" of the process, measurements of batch yields and cycle times are important. Although, Drug Substance and Drug Product are considered separately in chapters of this book all aspects must be collated in the final Development Report. Although there are no regulations for technology transfer operations, the results of any transfer will be evaluated by FDA during the Pre-Approval Inspection if intended for the US market. Success factors for passing Pre-Approval Inspections and the importance of the Development Report are discussed in Chapter 8 of this book.

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