



## API SCALE-UP AND TRANSFER TO DRUG PRODUCT DEVELOPMENT: - A BEST PRACTICE GUIDE

### INTRODUCTION

*When a drug candidate is identified many challenges lie ahead. The most costly and complex part of the path to a new pharmaceutical product is still to come. At this point you have a molecule with a shown pharmacological effect that holds potential as a new medicine. However, there remains the need to demonstrate that this molecule is safe, therapeutically effective and that it can be delivered as a convenient drug product. Furthermore, the drug substance itself, as well as drug products based on it, must be manufacturable at industrial scale with acceptable quality.*

For the chemist this means several challenges relating to quantity and quality, as well as safety and technical issues must be considered. The manufacturing scale needs to be increased since a lot of drug is needed for safety studies and clinical trials. It is of course also important to work with the process in order to find a manufacturing method that enables commercial production at a reasonable cost. A process that is scalable from a technical viewpoint as well as economic is needed. From a quality standpoint it is important that a drug substance of reproducible quality can be obtained and that it can be manufactured according to Good Manufacturing Practices (GMP).

During clinical development and also once a product has entered commercial manufacturing, process chemists and pharmaceutical formulation developers have to be in contact all the time to ensure a smooth transition between drug substance and drug product. There are in fact many characteristics of the drug substance that could affect formulation such as particle size, bulk density, polymorphism and other solid state characteristics. Changes in these parameters can affect powder flowability, stability of the drug substance once formulated, solubility profiles of the drug product, and so on.

We will discuss these challenges and how to meet them in more detail below.



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### KNOW THE END DESTINATION

*The development process will take you from making the drug substance at gram scale into commercial manufacturing of hundreds of kilograms.*

To start with, drug substance is needed for safety (toxicology) studies in animals. In the next step the compound will be tested in healthy volunteers (clinical trial phase I). At this stage GMP material is needed and the compound must also be formulated into a product suited for early phase clinical trials. This is usually a simple formulation such as a capsule or powder in a bottle in order to reduce time and keep costs to a minimum.

After completing this phase, the clinical development will move into phase II and then phase III requiring more substance and a more finalised manufacturing method. Eventually a marketing authorisation application is filed. The nature of drug product development changes gradually during the process. In phase I very simple formulations are usually sufficient. However, from phase II onwards, more complex formulations are developed to reach the target product profile. During the course of this development process, the manufacturing method is scaled up in a number of steps. The tech transfer to the commercial manufacturing site is usually performed during phase III so that the manufacturing process used at this stage is ready for commercial scale-up.

In the early stages, relatively small amounts of drug substance is required – typically a few hundred grams for safety studies or a few kilograms for a first in human study. There are still many years until commercial manufacture and there are opportunities to improve the manufacturing process over time. However, this is the time to look forward as some decisions may not be that easy to change or at least the cost of changing may be higher at later stages.

For example, the chosen manufacturing process may impact the purity profile and hence any later changes may impact the validity of the safety studies, analytical methods and carryovers. Characteristics such as stability and solubility should have been considered before selecting the drug candidate. This is also affected by the solid state characteristics of the drug substance, which must be considered from the beginning of the development programme. However, the method of synthesis may affect the solid form and hence these important characteristics. Consequently, it is recommended that route scouting is performed before scale-up in order to start with a manufacturing process that would be suitable for industrial scale manufacture.





## ROUTE SCOUTING

Route scouting is an essential step in identifying a practical, safe and cost-effective process for the synthesis of a compound on a large scale. It is important to find out if the existing route is scalable and to identify if there are alternative more promising routes.

- ▶ Is the process safe to scale up?
- ▶ Are the raw materials available on a larger scale? Are they affordable?
- ▶ Are there any patents on any reagents that may have been ok to use on research scale but that would hinder commercialisation of the process?
- ▶ Are there any solid intermediates, how are they isolated and purified, can this be scaled up?
- ▶ Are there any solvents that should not be used when producing this on scale?
- ▶ Are there environmental aspects to consider?
- ▶ Are there any process safety issues, both deriving from reaction conditions (e.g. exothermicity) or reagents being toxic or unsafe?
- ▶ Are the reagents/intermediates under strict regulations, for example drug precursors or chemical weapons precursors? Which authorisations would you need to handle them on scale?

A literature review commonly takes place during this stage to evaluate whether there are any known alternative routes to the target. There are also a number of software solutions available to assist with this process. Among other things, chemists are looking for ways to reduce the number of synthetic steps in order to save time and money. However, the route chosen may also be dictated by other factors such as starting material availability, that freedom to operate is limited by third party patents, or any other of the factors above.

There may also be regulatory reasons for adding one or more synthetic steps in order to have a suitable number of GMP-steps in the process to meet regulatory expectations. Starting material selection is the dominant regulatory topic nowadays. Correct regulatory starting material (RSM) selection is mandatory from the beginning of a project to avoid starting material redefinition, which will cost time and money and may lead to complete process remodeling.

Usually, stable intermediates during the synthesis, such as a salt forming step, are required for each GMP step, allowing for purification of the intermediate by crystallisation. However, the salt formation is also extremely important for subsequent processing. As most pharmaceutical products are solid, the solid-state characteristics of the drug substance are often important. Crystal form, particle size and hygroscopicity will impact processability as well as bioavailability and hence therapeutic effect. It is strongly recommended that the formulation scientists are consulted before any decisions affecting the solid-state characteristics are made. In many cases, micronisation of the drug substance is used in order to achieve sufficient homogeneity or dissolution rate of the final product. Even though drug substance synthesis and formulation development of drug products are separate disciplines they are interdependent and close collaboration between teams is a prerequisite for success.

When a suitable route is discovered patent aspects should be considered. Most importantly – do we have freedom to operate? But also – do we have opportunities to file for process patents?



### SCALE UP FOR TOXICOLOGY AND CLINICAL STUDIES

When moving through the clinical phases, larger amounts of drug substance are needed and it has to be manufactured according to GMP. For this reason, the synthesis method needs to be scaled up and adapted in order to meet plant manufacturing and GMP requirements. Although batch sizes vary between projects, typically a batch of about one kilogram of Good Laboratory Practice (GLP) material is manufactured for pre-clinical animal studies. This is more than usually needed for safety studies at this stage but material is also needed for other development work. As development progresses, batch sizes need to increase depending on dose, size of clinical studies, stability and the expected market for the new product.

The drug substance intended for safety and clinical studies must of course adhere strictly to specifications. For this reason, analytical methods must be developed and specifications must be set. These methods will be refined and validated during the development process and finally transferred to the commercial manufacturing site.

### TRANSFER TO DRUG PRODUCT DEVELOPMENT

The formulation scientist responsible for developing a drug product is dependent on the work of the process chemist who is responsible for developing the manufacturing method for the drug substance. The design of a drug product must always be adapted to the characteristics of the drug substance. Hence, it is vital that sufficient quantities of drug substance of reproducible quality are made available for formulation development at a reasonable time before the planned clinical study.

During the course of the project formulation scientists will remain dependent on the process chemists. Scale-up and manufacture of clinical trial material for the different clinical phases will need increasing amounts of drug substance. Moreover, changes in the manufacturing process for the drug substance may impact particle size and other solid-state properties that are of vital importance for the formulator.

It is advantageous to use GMP material, rather than GLP material, for formulation development as purity profile and solid state characteristics may vary at this stage. However, as the GLP material is usually available earlier than the GMP material, formulation development of the phase I drug product is often started using GLP material. There are of course some risks associated with this. However, for the simple formulations that are usually favored in phase I studies these risks are relatively small; a solution would not be affected by solid-state properties except solubility of drug substance, and drug in bottle or drug capsule formulations require less development work than formulations suitable for large scale manufacture.

In addition to formulation development, development of analytical methods is an indispensable part of drug product development. The analytical methods must be adapted to the excipients used in the drug product and consequently it is not sufficient to use the same analytical methods that were developed for the drug substance. In addition, methods for new characteristics such as dissolution rate may need to be developed. Nevertheless, the experience gained from developing analytical methods for the drug substance will provide a good foundation for the new methods needed.

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### COMMUNICATION

The work described above involves a number of experts including medicinal chemists, process chemists, engineering, analytical chemists and formulation scientists. In order to adhere to strict timelines and meet go-to-market goals, cross-functional, effective collaboration is needed. The timely commencement of clinical studies is almost always extremely important. In order to achieve this, the clinical trial material must be manufactured on time, which cannot be done unless the GMP drug substance is supplied in a timely manner, which depends on route scouting and scale-up activities and so on.

It is vital that an efficient and smooth collaboration is established between the different specialists. Professional project management plays a key role in achieving this.

### PROJECT MANAGEMENT

#### MEDICINAL CHEMISTS

How to manufacture a molecule with a pharmacological effect.

#### PROCESS CHEMISTS

How to manufacture the drug substance at large scale at a reasonable price.

#### FORMULATION SCIENTISTS

How to incorporate the drug substance in a suitable formulation.

#### ANALYTICAL CHEMISTS

How to measure drug concentration, purity and degradation products.





## COMMON QUESTIONS ANSWERED...

### *How much material is needed for safety studies?*

This will depend on the intended dose. In many cases a few hundred grams may be sufficient. However, in most cases it is recommended to prepare a batch of at least 1 kg. This batch may also serve as a feasibility batch for later GMP manufacture and provide a pool of material to run multiple toxicology studies. Material that is not used for safety could be used for initial formulation development, although there is a risk in using non GMP substance for formulation development as solid-state characteristics could vary between batches at this early stage.

### *How far in advance do you need to plan material for safety studies?*

As it is important that safety studies are performed on material that has a similar impurity profile as material from an up-scaled process we recommend that at least 3–6 months are allowed for route scouting and subsequent manufacture of material for safety studies. However, for complex syntheses as much as 12 months may be needed in some cases.

### *How much material is needed for clinical studies?*

This will depend on factors such as the dose, the size of the study and the amount of formulation development and testing that is needed before the clinical trial material is manufactured. In general about 1–5 kg will be needed for the development and manufacture of material for phase I first in human clinical studies.

### *How far in advance do you need to plan material for clinical phase I studies?*

In general work to develop and manufacture clinical trial material should be initiated no less than 12 months before the intended study start date. In urgent cases there may be possibilities to shorten this time somewhat but in general it is better to have some margin.

### *What is a suitable synthesis method for different phases?*

- The requirement on the method increases as the project progresses. Purity and yield are of course important but a number of other factors must also be considered. The availability and cost of raw material are important and patent limitations regarding intermediates and process steps should be taken into account. The manufacturing method must be scalable. Some processes are readily performed at small scale but are more difficult at large scale, e.g. chromatographic purification is usually avoided for small molecules for cost reasons. Safety concerns are also important when determining scalability. A risk analysis should be performed regarding the scale-up of the manufacturing process. When selecting a process for industrial use the isolation/purification of the compound is important and usually precipitation of solid intermediates and final products are preferred.

- In order to ensure reproducibility and for process optimisation Design of Experiments (DoE) and the concept of Quality by Design (QbD) is very useful.

- Since drug substance is produced for safety and clinical studies it is important that it adheres to specifications and that manufacturing and development is carefully documented.

- Starting material selection must be taken into account as early as possible to avoid redefinition in a later step.





**What are the requirements on the drug substance for safety (toxicology) studies and clinical trials?**

The purity of the final product must conform to ICH guidelines and be reproducible. During safety studies, it is preferred that material is not overly pure. The ideal situation here is that the same impurities are present as those in the final large scale material but in somewhat higher (or at least not lower) quantities. Identification of impurities may be needed and in particular Potential Genotoxic Impurities (PGIs) should be avoided or kept at very low concentrations. As the solid-state characteristics of the drug substance can be extremely important for subsequent processing this has to be reproducible. In general, every different type of formulation has its unique requirements for the solid-state characteristics of the drug substance.

**What are the most important regulatory requirements for a drug substance to be used in a clinical study?**

The drug substance must respect all ICH requirements for clinical phases and must comply with regional regulations of the country where the clinical trial is to be conducted. For example, the requirements may differ in the US and the EU. Moreover, for phase I the starting material selection usually has broader limits. When moving up to phase II and III the starting material must be selected based on stricter ICH and regional authority regulations. Specifications must be in line with guidelines during all the development stages, so the most suitable set of tests must be selected early on in the process. Very high purity is not always required in the very early stages, provided that the manufacturer can show control over the identity of impurities which are found in the drug substance. Stricter control of impurities at much lower limits is required as the project moves into the later phases. This is also true for other tests, such as assays, residual solvents content, content of inorganic impurities and residual catalysts and so on. Generally speaking, in early phases you have to show control and understanding of the process/product, while moving up you have to show that your understanding makes you able to obtain a higher quality/purity/reproducibility for the product/process.

**What are the most important regulatory requirements for a drug substance in a product to be registered for market?**

When moving through the clinical phases to commercial manufacturing, starting material selection becomes most important. Specifications and analyses must be fully compliant with ICH and regional requirements, and you must demonstrate full control of the process. Validation is required for analytical methods starting from phase II and processes starting from phase III. Impurity control and Potential Genotoxic Impurity (PGI) carryover control is mandatory, and you must show that toxic material/solvents/reagents/etc are avoided.



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### WHAT RECIPHARM CAN OFFER IN THIS AREA

In short, Recipharm has extensive experience in the development and manufacture of both drug substances and drug products. This means we offer a seamless service from the pre-clinical stage right through to registration and commercial manufacturing. We understand the whole process, which means we have the expertise to guide you down the best route, saving time, cost and reducing complexity.

- ▶ Our development facilities have excellent track records in medicinal chemistry and can carry out exploratory work, optimisation and up-scaling of early syntheses.
- ▶ Recipharm has extensive knowledge of process development and many years of hands-on experience of small to medium-scale manufacturing of drug substances. Our development chemists know what it takes to go from a milligram synthesis to a kilogram process.
- ▶ For smaller research focused companies, we offer the industrial, large scale perspective necessary to achieve commercial success.
- ▶ We perform route scouting and process development and can verify a process at 20 L scale to manufacture material suitable for toxicology studies in our development facilities. We can also offer further scale-up services and GMP manufacturing.
- ▶ Recipharm's multi-purpose plant can manufacture several drug substances at a time, including generic APIs. The facility is equipped to handle high pressure reactions as well as high temperature (up to 150 degrees Celsius) and low temperature (down to -80 degrees Celsius) reactions. We also offer reactors ranging from 20L to 6000L, supporting early development and commercial needs.
- ▶ Recipharm's drug substance manufacturing capabilities range from batch sizes of a few hundred grams (for low dose APIs) to hundreds of kilograms. Our Italian site is equipped with four manufacturing plants covering all scales and complies with GMP standards from all over the world, including EU, US and Japan.

### ABOUT RECIPHARM

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and are continuing to grow and expand our offering for our customers.

Employing around 6,000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 20 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite our growing global footprint, we conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do. That's the Recipharm way.

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