

Almac Voice

The Road to GMP



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Moving from the pre-clinical to clinical phase is a difficult jump to make with consideration of multiple aspects. This stage in the development process is notoriously difficult, and is commonly known as the “valley of death” due to the number of compounds that don’t make it through.



There are a myriad of challenges at this stage, such as animal models and funding. This article will focus specifically on chemistry, manufacturing and control (CMC) challenges, and how risk mitigation at an early stage can prevent later headaches and potentially add value to the data package for the compound.

The industry has long aimed to “fail fast, fail cheap” and by extending the range of CMC activities performed at early stages, multiple parameters can be investigated to highlight no-go milestones.

Almac develops and manufactures active ingredients and finished products from pre-clinical to commercial launch, and guides over 35 projects each year through scale up to GMP for the first time.

API Scale up

One of the main challenges is to produce chemistry that is robust and reliable, whilst balancing development requirements. It is important to complete a significant amount of process development to enable a safe and successful scale up without burning through the budget. Key areas for consideration are:

- Removal of prep HPLC purification
- Increasing efficiency of expensive metal catalysts
- Investigating replacement of metal catalysts with new technologies e.g. biocatalysis or flow chemistry
- Obtaining good chiral purity (if applicable)
- Producing material with sufficient impurity coverage for tox batches
- Ensuring reactions can be safely scaled up

Analytical methods

When producing material, it is imperative that there are suitable analytical methods that demonstrate the material is as stated both in terms of structure and purity. Method validation of some degree is required for GMP manufacture and Almac has undertaken a wide range of approaches to this. Our GMP systems and SOPs are designed to be flexible enough to encompass each scenario.

Analytical methods depend on the nature of the compound, and typically include an assay/purity method (usually HPLC), with a range of spectroscopic tests, undertaken to verify identity. Additionally, an ICPMS method is also performed to verify metal levels in the final product which is particularly important if the scale up uses a metal catalyst.

There is also a need to include some tests for physical characterisation e.g. XRPD and PSD. The analytical specification then requires to be set in line with the regulatory guidelines and the limits of the methods.

Physical form

At a medchem lab, isolation of a compound is typically by preparative HPLC chromatography which is only suitable at small scale. To allow a robust scale-up, a crystallisation process is typically developed.

The crystallisation process has an impact on the final physical form of the compound, so it is prudent to conduct some screening work in conjunction. The screening typically explores different salt and polymorphic forms of the molecule, and compounds with a complex polymorphic landscape may not be suitable for further development, and a related candidate may be selected in preference. Different physical forms also have different properties which can cause issues for the formulation team who consider the solubility and flowability of the powder.

Physical forms also generate intellectual property, so it is useful to assess this at an early stage to ensure that any patents provide appropriate coverage.

Formulation

Manufacture of the active ingredient is only half the battle! It is imperative to formulate this into a dosage form suitable for humans. There are various considerations and there are typically two schools of thought; the first looks at an

exploratory approach, producing a simple API in capsule formulation to enable early clinical studies, with a view to refining this at later stages when budgets allow. The second is to perform a package of formulation development with an aim to produce a formulation as close to the intended commercial dose as possible to minimize any bridging work between multiple formulations. Both of these approaches are routinely seen in practice.

Whilst API in capsule is an attractive formulation due to the relatively low barrier to entry, this is not always possible based on the physical properties of the drug. APIs with poor bioavailability will require the addition of functional excipients to the capsule, and the flow properties of the compound may prevent the use of automated capsule filling machines

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