



CONCEPT LIFE SCIENCES



Bridging the gap between
R&D and GMP



Companies prioritizing optimized synthetic routes, stable API forms, and verified analytical tools set the stage for phase I clinical manufacturing success.

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Introduction

Developing small molecule drugs is exceptionally challenging. Pharmaceutical companies face high costs, huge attrition rates and considerable risk. One particular difficulty lies in getting a small molecule to the clinic.

Here, we summarize what is needed to move a small molecule candidate from R&D to GMP-compliant phase I clinical manufacturing, focusing on the critical considerations across chemical synthesis, analytics and materials science.

The R&D-GMP gap

A considerable gap often exists between the synthetic routes developed for R&D and those suitable for a GMP campaign. Whereas the latter must meet stringent GMP regulations and be suitably scalable and cost-effective, routes created during R&D typically contain slow, low-yielding, non-scalable and capricious steps.

Some synthetic routes at the development phase may even struggle to produce more than 100 mg of active pharmaceutical ingredient (API), let alone the quantities sufficient for clinical development. R&D chemistry is also often performed by Ph.D.-trained chemists in a laboratory setting, whilst GMP manufacturing must be carried out by skilled operators in a dedicated manufacturing facility often with very different equipment – a robust process is critical for success.

While bridging this gap often necessitates considerable synthetic route optimization, companies do not need to create a perfect route for early clinical phases. Given the high failure rate at each stage of clinical development, companies may opt not to pursue further development beyond essential milestones, particularly in situations where financial and resource constraints are significant (e.g., small pharma and biotech companies, startups and spin-outs) or when seeking to sell their assets to larger pharmaceutical organizations for clinical trial progression.

So, how can companies know that their synthetic route is suitable for GMP manufacturing? And how can they strategically optimize their routes to be suitable for phase I clinical trials while not investing unnecessary time, money and resources?

SELECTing phase-appropriate route development

The SELECT framework provides a rational approach to help answer these questions. Broadly, SELECT helps pharmaceutical companies assess and develop their synthetic routes by considering six critical aspects of route optimization: Safety, Environment, Legal, Economics, Control and Throughput.

Looking at SELECT with phase I in mind

While environment, legal, and throughput considerations are important at phase I, they should not be the focus of route optimization and selection (these considerations become a much bigger concern at later clinical development stages). For phase I, it is sufficient that your route does not infringe on another company's IP, and can produce enough API. In the best case scenario, your route would also have a low environmental footprint, and be amenable to further phase-appropriate optimization, too.

For phase I readiness, safety, economics and control should be the focus of your route optimization and evaluation.

- **Safety:** Safe working practices are critical across all sectors, including the pharmaceutical industry. That's why a synthetic route with an acceptable safety profile is non-negotiable for phase I, no matter how high yielding or easy your route is to execute. Appropriately optimizing a synthetic route for safety could mean any number of things, from ensuring sufficient headspace and venting of the reaction vessel to prevent pressure buildup, to using the appropriate equipment and engineering controls to manage exotherms and prevent runaway reactions with the ability to crash-cool.
- **Economics:** Many companies entering phase I clinical trials are small and rely on seed funding or venture capital investment. They don't have access to the expansive budgets that larger pharma organizations often wield. Having a cost-effective synthetic route for phase I is therefore critical. Ideally, then, a phase I optimized route should utilize starting materials and reagents that are inexpensive, commercially available long-term, and supported by robust and reliable supply chains. Your route should also minimize the number of reaction steps, reduce the amount of metal catalysts, and proceed in a reasonable timeframe by avoiding convoluted and laborious purifications (such

as column chromatography). The latter is particularly important, as it means companies can minimize the time spent in manufacturing facilities, which is costly.

- **Control:** For GMP manufacturing, having a safe and efficient synthetic route is not enough. Manufacturers must also ensure their reaction profile and the reaction product are the same every time. That means carefully controlling critical process parameters (CPPs) to reliably deliver a stable product that meets critical quality attributes (CQAs). For example, manufacturers must ensure that purity, color, water content, residual metal levels, solid form, and many other attributes are as planned and within acceptable ranges.

The consequences of out-of-specification products can be disastrous. For example, the discovery of a novel contaminant can halt manufacturing and may mean missed clinical trials, incurring substantial costs and timeline delays. Smaller companies simply cannot afford to fail at manufacture, owing to the direct costs involved, the risk to future funding and the significant setback in the race to market.

To effectively control a reaction, companies need a deep understanding of it, including what reaction conditions can be tolerated, the reaction's impurity profile and how to effectively clean up any impurities.

Your key to control

A significant part of understanding — and therefore controlling — your reaction comes from obtaining appropriate analytical data. Indeed, regulations require that companies establish and verify a suite of suitable analytical methods, in-line with pharmacopeial expectations and ICH guidelines. These analytical methods enable manufacturers to appropriately measure purity and other attributes of raw materials, process solvents, and APIs for release. Ultimately, they are critical to ensuring materials meet specifications and to prevent poor-quality, unstable APIs entering the clinic, which could result in patient harm.

N-Nitrosamine contamination

Many potentially toxic, carcinogenic and mutagenic compounds can find their way into the API manufacturing process which is managed by ICH M7 guidelines. One of the most pertinent contaminant classes is *N*-nitrosamines, which are a probable human carcinogen. In 2018, the European Medicines Agency (EMA) became aware of nitrosamines in some human medicinal products. As a result, a threestep process is now being followed involving (i) the assessment of drug products for the potential presence of *N*-nitrosamines, (ii) analytical testing where potential risks were identified, and (iii) remediation where an *N*-nitrosamine was determined to be present in a product above an acceptable level.

Therefore, the presence of small *N*-nitrosamines and larger, more complex, *N*-nitrosamine drug substance-related impurities (NDSRIs) must be well understood and their liabilities determined. Drug manufacturers must demonstrate no quantifiable levels of nitrosamine impurities in their API, raw materials, intermediates and process impurities; demanding rigorous analytical testing, and highlighting the crucial importance of appropriate analytical methods to support clinical manufacturing.

On solid form

Of the many potential CQAs that manufacturers need to analyze and control, an API's solid form is perhaps one of the most overlooked in the early development stages. This is surprising given the potential risks. Indeed, getting the wrong solid form at the end of manufacturing can leave companies with few or no remedial options.

APIs can exist in many different solid forms and crucially, each form can display varying physical, chemical, and

mechanical properties, which can affect bioavailability, manufacturability and stability. Identifying a salt of your API that has the optimal physiochemical properties is a great place to start. Polymorphism, the ability of a solid to exist in two or more crystalline forms should then be investigated. Ideally, manufacturers should identify – and then consistently produce – a polymorph stable over the intended shelf life of their API or API complex, even if that requires an additional post-manufacturing step. Stability is so important here, as however optimal an API's other attributes, an unstable polymorph can degrade over time, leading to a less efficacious and potentially dangerous medicine.

To identify the optimal solid form for clinical manufacturing, companies should incorporate screening into their pre-GMP workflow. Several tools

and solutions are available to help companies find a solid form that is efficacious and stable. Again, a suite of robust and reproducible structural characterization techniques, such as X-ray powder diffraction (XRPD), are critical for enabling insight into your API's solid form before a GMP campaign.

A confident path to the clinic

Getting a small molecule to phase I clinical trials is a monumental task – and the stakes are high. But success is by no means out of reach. Companies that phase-appropriately optimize their synthetic route, prioritize a stable API solid form, and deploy a suite of verified analytical tools will be well on their way to phase I clinical manufacturing success.

About Concept Life Sciences



CONCEPT LIFE SCIENCES

We are a multi-disciplined Contract Research Organisation based in the UK, providing market-leading scientific services globally. Over the past 25 years, Concept Life Sciences and its heritage companies have played a pivotal role in guiding numerous clients along their path to clinical success and many of these clients have evolved into enduring scientific collaborators.

Within a decade, the collaborative efforts of experts from our heritage businesses – Peakdale Molecular, CXR Biosciences, and Aquila Biomedical – have propelled us beyond the cumulative impact of our individual components, fostering substantial growth and advancement.

On an individual level though, each one of us is a scientist. This means that what drives us is simply wanting to make a difference and is why throughout that changing past and subsequent growth, 2 things have remained constant:

- 1. Our desire to progress and make the world a better place, and;**
- 2. Our conviction that truly integrated and connected science is the best way to achieve it.**

