

Drug development requires a careful balancing of priorities. But API decisions based on tight timelines and strained budgets often result in expensive delays in the process—or might even lead to failure of the process.

To succeed in a reasonable amount of time and at a reasonable cost, your API must be well-characterized in terms of structural identity, counter-ions and co-crystals, impurities, stability, chirality and enantiomers, appearance, and solubility. These properties will continue to be referenced throughout API scale-up, process chemistry and GMP manufacturing. To help avoid downstream issues, you need to keep a careful watch on these four steps in particular:

FOUR WAYS TO ACCELERATE DOWNSTREAM DEVELOPMENT

FASTER DRUG DEVELOPMENT STARTS WITH SLOWING DOWN

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1

Purity

API purity is a good thing, right? Not necessarily. While it may be easy and affordable to achieve high purity in the lab, it can be difficult at scale.

For small-molecule drugs, milligram or gram quantities of research-grade material are usually suitable for early-stage in vivo efficacy and ADME testing, as well as small PK and dose range-finding studies. However, when you're ready for Phase III—or market—you could run into problems:

- **Scaling issues**—if your catalyst is extremely expensive or unavailable in large quantities
- **Repeating toxicity studies**—if a catalyst change yields lower purity
- **Reformulation**—if lower-purity API behaves differently

Think about...

Using a common, easily sourced catalyst at the start and testing a lower-purity sample in toxicity studies. You can always aim for higher purity later in the process, but you can't reduce it without reworking previous steps.

2

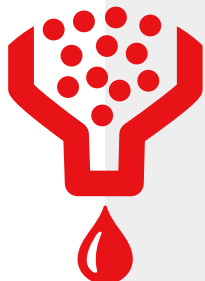
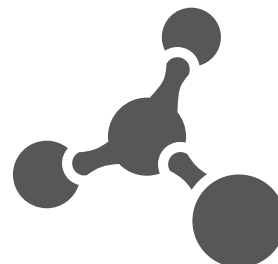
Formulation

Formulating the API is a critical step that can easily be derailed. Select the wrong crystalline structure and you could have tablets that won't hold their shape, or crystals that won't dissolve in the stomach. These problems can manifest in many different ways:

- **Polymorphic issues**—if dissolving your API for safety and efficacy studies masks crystalline issues
- **Fit-for-purpose thinking**—if you are overlooking future needs that will be revealed downstream
- **Amorphous shapes**—if your complex molecule is more difficult to crystallize due to its weight

Think about...

Screening for possible polymorphs of your API and appropriate counter-ions early in the process.



3

Solubility

Approximately 75% of drug candidates have bioavailability issues, so it makes sense to invest in evaluating your molecule's physiochemical characteristics early. You might have to revisit some steps due to several issues:

- **Proof of mechanism failure**—if low bioavailability is an issue
- **Reformulation**—if you have to change the molecule's delivery to increase uptake
- **Repeat of Phase I**—if you need to prove safety and efficacy of a new formulation
- **More expensive processes**—if you need to move to spray drying to increase solubility



Think about...

Investigating solubility early, because most modern, complex APIs have bioavailability issues that might steer you toward killing a promising molecule for the wrong reason.

4

Scalability

Scaling up for Phase III reveals how completely your drug development program has been thought through because there are so many opportunities for things to go wrong. Careful planning, however, can help you avoid common issues:



- **Raw material shortages**—if your API is only easy to find at lab-scale quantities
- **API bottlenecks**—if your therapy requires complex chemical synthesis
- **Marketability issues**—if your API or catalyst is expensive at scale, your therapy may be economically unviable

Think about...

Balancing fit-for-purpose characteristics such as safety and efficacy with fit-for-future concerns such as a secure supply or raw ingredients at a price that makes sense for marketability.

Cash-strapped pharmaceutical companies often make development decisions aimed at helping them get to the next round of funding as quickly as possible.

Ironically, your timeline may be the biggest casualty of deferring API decisions to prioritize an expedited schedule. Skipping steps can delay development longer than it would take for a complete investigation of your API at the onset of the project. When both timing and budget are critical to downstream success, rely on a trusted partner who can help guide and solidify your development plan.

To learn more about how Patheon pharma services can help solidify your API development plan, please [download our fact sheet](#).