Reducing Risk at ***Every Stage of Drug Formulation***

COREALIS Pharma

> **We cannot solve our problems with the same thinking we used when we created them.**
>
> —Albert Einstein

A **recent pharmaceutical study** is often quoted at Corealis, and not because it is specific to creating oral solid dosage (OSD) products, capsules, and tablets. It is not about a promising new drug delivery route, an advancement in excipients, or a leap forward in providing personalized medicine. This study looked instead at our industry as a whole and sought to answer one simple question …

Why do 90% of clinical trials fail?

Considering the substantial investment of time and resources involved, the number of companies forced to close due to a single catastrophic drug development failure, and the potential reputational harm to a business or an individual, one would expect the pharmaceutical industry to pay a significant amount of attention to these findings.

However, if you've been in our industry for quite some time, you know that very little has changed.

Our team created a comprehensive guide on mitigating risks at every stage of **drug formulation**. Achieving this is possible, but only by identifying the root causes of the most common failures and shifting the mindset that consistently leads to them.

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Why Do **90% of Clinical Trials** Still Fail?

Fortunately, the **answers to this question** are actually very simple and easily quantifiable:

- **40-50% fail due to a lack of clinical efficacy**
- **30% fail due to unmanageable toxicity**
- **10-15% fail due to poor drug-like properties**
- **10% fail due to poor strategic planning or a lack of commercial viability**

Many inherently flawed drug products are proceeding through clinical trials leading to failed projects or costly delays. Most of the common causes for failure could be identified and mitigated in the formulation phase — where mistakes can be corrected quickly and inexpensively.

High failure rates are detrimental for individual biotech companies and the industry as a whole. Investors are, thus, justified in being cautious when funding. Sadly, this results in underserved patients waiting longer for potentially life-changing treatment.

Next, let's explore the key role that pre-formulation plays in building successful drug candidates and identify the factors that often lead to unsuccessful drug development projects.

Selecting the Most Appropriate **Active Pharmaceutical Ingredient (API)**

In addition to targeted efficacious action, high bioavailability, and low adverse effect, the drug substance must also be amenable to the development of a feasible commercial dosage form with long shelf life, reproducible manufacturing processes, and optimum patient compliance.

The druggability of the drug substance highlights the key characteristics to address during formulation development. A Corealis Druggability Assessment evaluates the following strategic physicochemical properties:

/ Size, Shape, and Distribution

Particle size, shape, and distribution are all incredibly important when selecting a drug substance, as they can significantly affect the drug's performance, manufacturability, and therapeutic efficacy.

/ PARTICLE SIZE

Smaller particles tend to be absorbed more easily into the gastrointestinal (GI) tract. Smaller particles also dissolve faster, which can translate into faster absorption, and therefore, action.

/ PARTICLE SHAPE

Particle shape affects how your drug powder will flow during manufacturing. Spherical particles typically flow better than irregular or rougher shapes, like diamonds or rods. But that's not all. The particle's shape can impact how well your drug might adhere to mucus membranes or how it will dissolve. Shape will also affect how your particles might pack together, which may be important when it comes to determining the final tablet size or capsule fill volume.

/ PARTICLE SIZE DISTRIBUTION

A narrow particle size distribution is associated with:

- **More consistent drug behavior across different batches**
- **Lower rates of particle agglomeration (individual particles coming together to form larger clusters), which can affect stability and performance over time**
- **More predictable and reproducible manufacturing processes**
- **Dose uniformity — both across batches and individual units**

If you have a particle that is larger, rod-shaped, and somewhat inconsistent, it may still be druggable. And if you don't already have in-house specialists familiar with how to mitigate these properties, you might want to partner with a highly skilled CDMO early on in the process. From a drug substance perspective, micronization, crystal engineering, or other advanced techniques can be utilized. Formulation processes such as spray drying, geometric dilutions, or wet granulation can also mitigate sub-optimal drug substance properties.

Other properties to consider include:

/ Permeability

High permeability generally leads to better oral bioavailability, as the drug can more easily pass through the intestinal wall and enter the bloodstream. However, much like a drug substance with a difficult size, distribution, or shape, low permeability wouldn't necessarily disqualify an API from consideration.

A skilled drug formulator may suggest absorption-enhancing strategies, including the use of **alternate excipients**.

Excipients are often described as inactive substances in a drug product relative to their in-vivo activity, but they can play significant roles in the manufacturing process, product stability, and patient compliance, as well as more advanced functions such as enhancing permeability.

/ Solubility and Drug Dissolution

Poor solubility can lead to limited absorption. The dependence of the dissolution rate as a function of pH will affect where, in the GI tract, the drug will be absorbed. A skilled formulator can achieve exceptional results by carefully leveraging excipients and their roles in stabilizing and enhancing formulations.

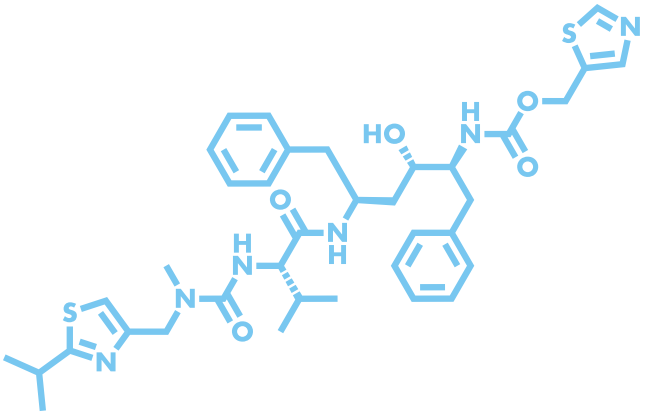
/ ALTERING THE DRUG SUBSTANCE ABSORPTION PROFILE

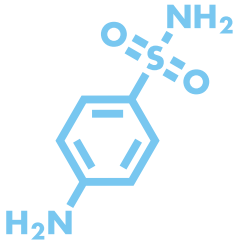
Amorphous solid dispersion, prepared through a spray drying or a hot melt extrusion process, may be used to improve solubility. However, some solubility enhancements could also impact the long-term stability of your product, which can be mitigated with specific packaging strategies to protect it from exposure to light, humidity, or oxygen.

/ Polymorphism

Polymorphism refers to the ability of a substance to exist in more than one crystalline form.

Some polymorphs may dissolve more readily or have different melting points or flowability. Additionally, some polymorphs may eventually revert to a more stable form, which can affect the performance of the drug product.





/ RITONAVIR DRUG DEVELOPMENT JOURNEY

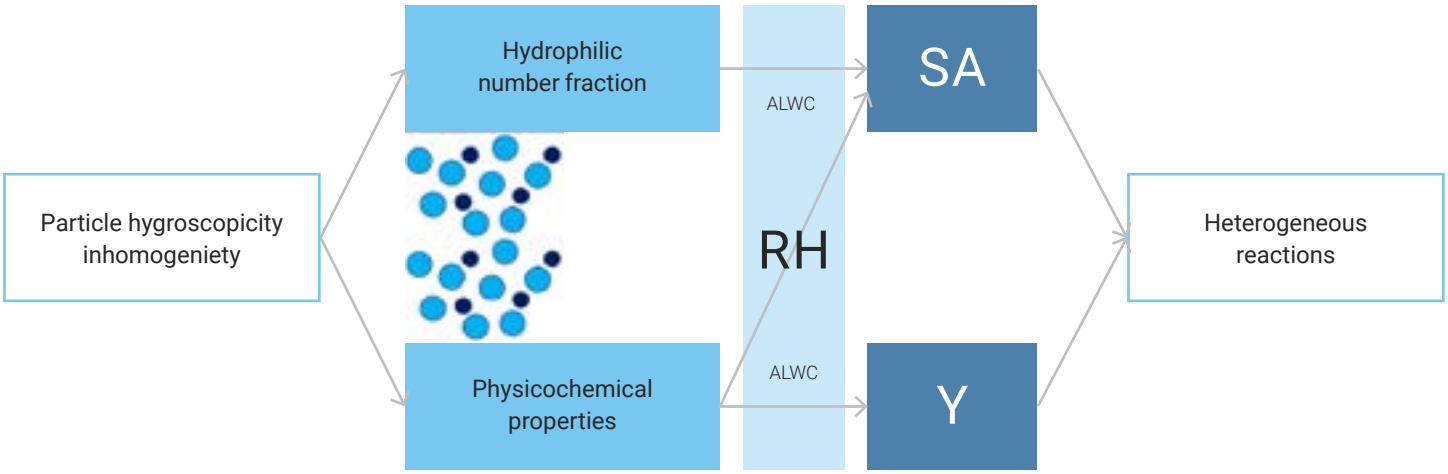
One notable example of how a polymorphic API complicated a drug development journey is Ritonavir (Norvir) — an antiretroviral drug used to treat HIV/AIDS. The API has at least two polymorphic forms. It was initially developed and marketed in one form, but during manufacturing, the API converted to a more stable (but less soluble) form, which adversely impacted bioavailability. The unanticipated polymorphism required the drug product to be reformulated.

/ SULFANILAMIDE AND THE "ELIXIR DISASTER OF 1937"

Sulfanilamide — a common antibiotic — can take many polymorphic forms, each with varying dissolution rates. While some forms dissolve too slowly, others are absorbed too quickly and can cause unpleasant side effects. The unfortunate outcome in this case wasn't directly related to the polymorphism of sulfanilamide, but it influenced how its polymorphic nature was carefully controlled in later formulations. It's also a textbook example of formulation gone terribly wrong: It was originally dissolved in a toxic solvent (diethylene glycol) and distributed in the US, killing over 100 people.

/ Thermal properties

Thermal properties of the API may influence the design of the manufacturing processes, formulation strategies, and storage conditions. For example, drugs with a low melting point will need to be processed at cooler temperatures to avoid degradation or other undesirable outcomes.



/ Hygroscopicity

Hygroscopicity refers to the drug substance's ability to absorb moisture from the environment. When exposed to humidity, an extremely hygroscopic API may undergo changes to its physical and chemical properties. While a skilled CDMO may be able to find solutions to address hygroscopicity, ultimately, successful commercial manufacturing in large facilities may still be achievable with extensive and costly strict humidity controls.

/ THE CASE OF THE MORPHING API

We were once sent a drug substance to evaluate, and as soon as we opened the jar, the API took on 15% of its weight in water within 24 hours. As it turns out, the API in question was an HCl salt. Our readers with a background in chemistry can predict what happened next. When added to water, HCl salts form hydrochloric acid.

/ The Ideal Drug Substance

Sometimes, a biotech company will, through sheer beginner's luck, stumble upon a "perfect" API.

Here's what that substance looks like:

- **Its size, shape, and distribution make drug formulation and manufacturing very easy**
- **It is soluble and dissolves at the perfect rate for the human body — not too fast, and not too slow**
- **It is permeable and stable**
- **It is not polymorphic, or its most stable form also happens to be druggable**
- **Its melting point won't adversely affect manufacturing or shelf life**
- **It is not excessively hygroscopic**

When all of these stars align, you're likely to enjoy an easy drug development process. And that's a good thing! But it is important not to learn the wrong lesson from a lucky break.

/ Why Druggability Assessments Are Non-Negotiable

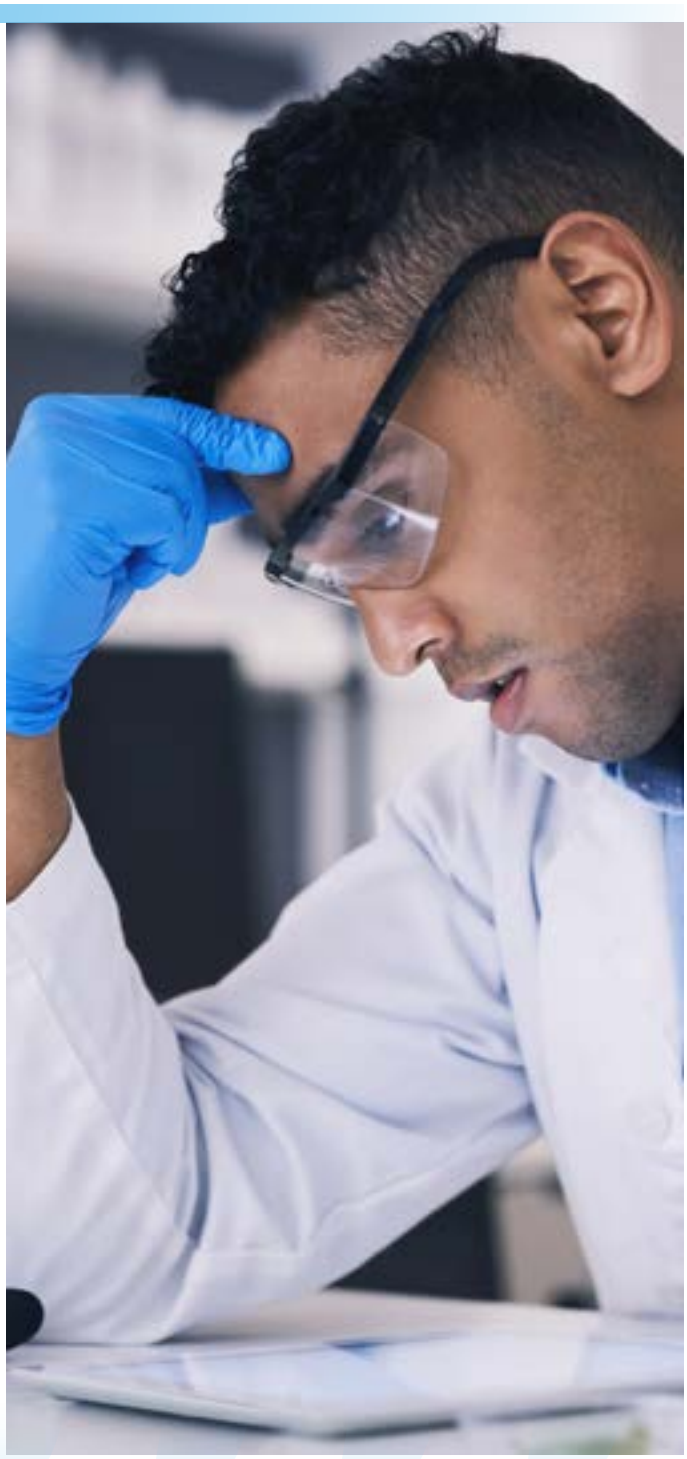
We don't live in a perfect world, and many — but not all — of the APIs that are formulated today aren't ideal candidates. However, many of the problematic properties we listed earlier can be addressed with proper formulation.

/ THE TRADE-OFF BETWEEN INNOVATIVE FORMULATION AND COST

A thorough assessment can help you avoid many common **pitfalls of drug development**. However, many biotech companies will choose to proceed with a drug development project without a thorough understanding of the basic physicochemical properties of the API

In any case, a thorough assessment can help you avoid many common **pitfalls of drug development**, like the delays caused by Ritonovir's polymorphism. However, believe it or not, many biotech companies will choose to proceed with a drug development project without a thorough understanding of their API's basic physicochemical properties.

Unfortunately, these biotechs are investing a significant amount of time and money into a product that is doomed to fail.



/ ACIDIC CASE IN POINT

We were once sent a drug substance to evaluate, but the API took on 15% of its weight in water within 24 hours. The API was an HCl salt. Our readers with a background in chemistry can predict what happened next. When added to water, HCl salts formed hydrochloric acid.

We told them that without significant alterations to their drug substance, it would likely be impossible to proceed. They insisted on moving forward anyway. Unfortunately, due to the technical challenges posed by the hygroscopicity and corrosiveness of the drug substance, drug product development was eventually halted.

Investors lost confidence in the company's management, and it closed soon after due to financial constraints.

Stories like these are part of the reason we decided to offer **druggability assessments for OSD projects** at no cost and with no strings attached. There will always be an element of risk involved with drug development. However, a thorough assessment can catch small problems before they cause significant harm.

/ ENHANCING DRUG DISCOVERY PLATFORMS

One biotech company we worked with had raised millions to establish their proprietary drug discovery platform. However, unlike the other biotech, they decided to conduct simultaneous druggability assessments on multiple drug substances. They discovered that some of their candidates were poorly soluble, unstable, hygroscopic, or polymorphic — or a combination of these. They selected the one candidate that proved to be the least challenging, and therefore, they were able to minimize costly setbacks.

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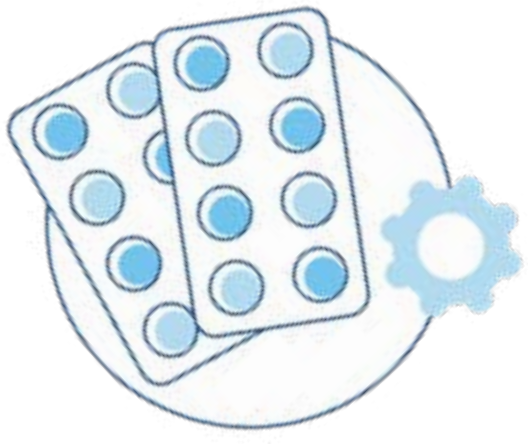
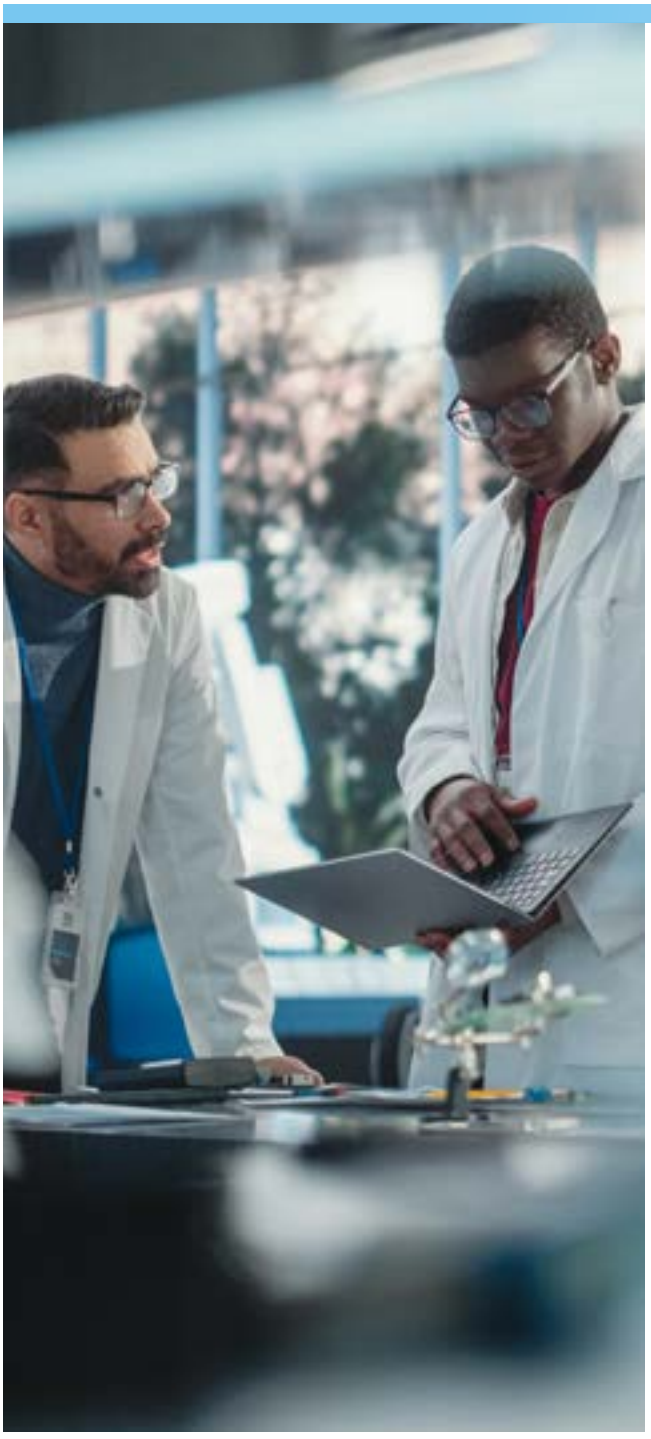


Defining a **Formulation Development Plan** Based on Your Druggability Assessment



If your druggability assessment has been thorough, you should come away with a much clearer idea of the time and costs that your project will require, clearly easily anticipate next steps, and therefore attract **additional funding more easily**.

Here's what you'll need to determine before formulation development:

/1 Select Appropriate Excipients and Drug Delivery Technologies

Drug delivery technologies can control the release profile of a drug, such that the API interacts with the body exactly when and where it is most efficacious. Excipients can enhance the stability and bioavailability of the API, and they can improve taste and mouth feel, which can be important factors impacting patient compliance.

We always keep the patient experience top of mind. A product that is difficult to swallow, feels sandy, or forms an unpleasant gel will raise red flags with our team, and we address these issues early in the formulation process to mitigate their impact.

/2 Determine the Best Manufacturing Processes With Eventual Scale-Up in Mind

Your manufacturing process will ultimately need to be efficient and cost-effective while producing consistent results. Many things — like filling a capsule by weight instead of volume — are only possible on a small scale. It is not advisable to allocate extensive resources to designing formulations that will be used in the next phase that are overly time-consuming or costly to reliably reproduce, or scale up.

/3 Understand the Risks Associated With Skipping or Disregarding Your API Analysis

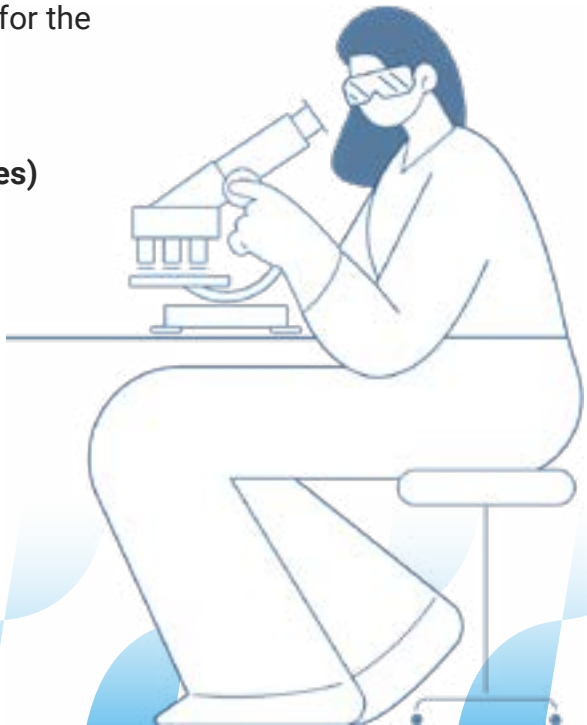
If your assessment was incomplete or you decide to disregard the data, your drug product may not be stable or sufficiently bioavailable. These failures often reveal themselves in phase I single ascending dose (SAD) or multiple ascending dose (MAD) studies, which may necessitate restarting the formulation development process from the beginning.

Selecting Your Drug Product Formulation for Phase I **Clinical Studies Based on Good Data**

There are several ways to proceed at this stage. If you've gathered sufficient data, you will be able to make more confident decisions based on your tolerance for risk.

At this point, your primary goal will be testing your prototype(s) for the following properties:

- **Appearance**
- **Friability (how a substance will break down into smaller pieces)**
- **Hardness**
- **Flowability**
- **Dissolution profiles**
- **Blend and content uniformity**
- **Stability**
- **Pharmacokinetic (PK) profile in animals**



/ 8 Steps to Producing High-Quality Early-Phase Clinical Trial Materials

After identifying a promising prototype (or several prototypes), it will be necessary to follow many, though not always all, of these eight steps.

1. **Manufacturing additional optimized prototype formulations**
2. **Evaluating manufacturing reproducibility**
3. **Evaluating dissolution profiles in conditions that resemble a human GI tract (biorelevant dissolution)**
4. **Performing stability studies in different environmental conditions on the most promising prototypes**
5. **Conducting further stability tests in animal models to select the formulation with the optimum absorption profile**
6. **Selecting the most suitable prototype for the manufacture of clinical trial supplies**
7. **Scaling up your manufacturing processes**
8. **Packaging, labeling, analytical method validation, release testing, and further stability testing of your clinical trial materials (CTM)**

If you have an ideal API, you might be able to streamline some of these steps. If your API has presented formulation challenges, you will probably want to diminish your risk.

Pro tip:

When in doubt about how and when you might save time and money without incurring too much risk, ask a skilled CDMO!

We understand that being first to market is important, and time is money. We will at times advise clients with inherently low-risk drug development projects that they might want to eliminate a few steps, depending on their risk tolerance.

Here are a few examples of high-risk vs. low-risk scenarios at this stage.

/ SCENARIO 1

Highest Risk/Fastest Development

If your API makes formulation exceptionally easy, your next steps may look something like this:

- **Select only 1 prototype for further testing**
- **Skip initial stability studies**
- **Spend a minimal amount of time on additional testing — enough to file your investigational new drug (IND) application and clinical trial application (CTA)**
- **Reserve most of your time and resources for executing step 8**

/ SCENARIO 2

Moderately Aggressive Risk/Moderately Aggressive Speed

If your API might involve a bit of complexity, and you're comfortable absorbing some risk in order to save time, here are our recommendations:

- **Select 2-3 prototypes for further testing**
- **Perform step 2 on all prototypes**
- **Perform step 3 on all prototypes**
- **Skip steps 4-5, but pay close attention to step 6**
- **Skip step 7 and move directly to step 8**

/ SCENARIO 3

The Most Common Drug Formulation Plan

Most biotech companies these days will still choose to rush through evaluating their API and then spend more time on this step. However, reversing the two would often get them to the finish line faster.

Here's what most companies do at this stage in drug development:

- Select 3-6 prototypes
- Perform step 2 on all prototypes
- Perform step 3 on all prototypes for a minimum of one month
- Steps 4-5 are optional, depending on your prototypes and what you're trying to treat
- Perform step 6
- Perform step 7 for your selected prototype
- Perform step 8

/ SCENARIO 4

Lowest Risk/Longest Timeline

When your formulation is extremely challenging or a setback at later stages would prove catastrophic to your company, this plan may be the best choice:

- Prepare around 6 prototypes
- Perform step 2 on all prototypes
- Perform step 3 on all prototypes for 2-3 months
- Steps 4-5 are optional, depending on your prototypes and what you're trying to treat
- Perform step 6
- Perform step 7 for your selected prototype
- Perform step 8

/ What Risks Should You Keep in Mind?

Any cut corners here will likely show up in your clinical trials. For example, your materials might not be sufficiently stable, or participants might not receive a consistent product, which will skew your data. Your CTM may also not have a suitable PK profile in humans — for example, blood concentration may saturate after a certain dose or may not be absorbed into the GI tract.

Ultimately, only you can decide how much risk you're ready to take. If you're aggressive, you might have a higher risk of failure. If you're lucky, it will work, and you'll have saved your company a great deal of time and money. If not, you could lose a great deal of time and money and disappoint your investors.

/ THE TRADE-OFF BETWEEN INNOVATIVE FORMULATION AND COST

Innovative formulations can add complexity to commercial manufacturing and must also be considered in terms of short-term and long-term costs. Using excipients or manufacturing processes that regulators aren't familiar with may lead to costly delays in the review process. After the initial costs of upgrading the manufacturing site and new skills training, long-term operating costs and reliable supply chain management also figure in the evaluation.

Innovative formulations can address the druggability weak points of the drug substance and may also bring efficiency in the drug product's long-term supply.

Selecting Your Drug Product Formulation for **Phase II and III Clinical Studies**

Your phase I clinical studies may have revealed that your drug product requires some additional optimization. That's common!

However, any major changes (e.g. adjustments that will alter your product's PK profile or bioavailability) may add significant time and costs to your project.

/ Bridging Studies and Other Potential Challenges

You may need to conduct a bridging study to demonstrate that the release pattern within the human body is the same in both drug products — the one you used in phase I trials and the one you intend to use in phases II-III. If you can establish equivalence, you can use your previous data. If you can't, you'll need to repeat earlier clinical studies.

We touched on this earlier, but it's worth repeating: Phase II and III clinical studies are critical stages where early investments in comprehensively characterizing the API—including its physical and chemical properties—and in selecting an appropriate prototype yield significant returns. However, these phases are also where costs and timelines frequently escalate, particularly for inexperienced biotech firms. The need to repeat preliminary work is costly, underscoring that bypassing early developmental steps can be counterproductive. Rigorous groundwork in the initial stages is, therefore, crucial to avoid delays and ensure the success of later clinical phases.

Aside from risking the commercial viability of your drug product, there is more on the table.

/ Your Reputation for Presenting Reliable Data Matters

When regulators eventually review your data, they are hoping that it is clean and detailed and that you've proven that your drug product is safe and effective at every step in the process. A well-organized package with detailed supportive data based on solid science can reduce the workload and time in the review process.

Changing Our Thinking To **Change Our Results**

Now that you know what often goes wrong with drug development and why, we'd like to present you with a typical story of drug development gone wrong.

It's probably one you've heard yourself, and at one time, may even have believed.

The Hard Luck Tale of Company X

Company X was a promising one — full of medicinal chemists who understood how to make compounds, researchers, and medical experts who understood the conditions they were trying to treat and the problems with the drugs already on the market. The number of PhDs they had on their roster would make a startup in any other industry envious.

Company X identified an incredible opportunity, and it had all the makings of a marketplace sensation! They found a promising API that could potentially treat a common condition — one where existing treatments were unsatisfactory. They were so excited about their API that they moved full steam ahead.

In their haste to make a prototype, they rushed through evaluating their API's properties. Afterward, they struggled to make good decisions regarding how they'd identify the best drug products for their phase I study. In fact, they got bogged down there, which added time and costs.

Unfortunately, when they finally moved to phases II and III, they realized they had to make major changes in order to move forward. Unanticipated time and costs really started to add up at this point. So they brought their projects to more investors, who knew the kind of **data they needed to see**. When they couldn't find it, they passed.

Company X eventually released a statement saying that they were forced to close their doors due to — what else?

Bad luck.

Of course, the good folks at Company X took solace in the knowledge that the pharmaceutical industry is full of stories like these. They put it down to just an unfortunate but unavoidable part of the business. After all, 90% of drug trials fail. That's just a fact.

There are numerous ways that a company's trajectory can deviate from success, and even within this comprehensive guide, it is impossible to list all of them. However, by having read the material presented, we believe that you will hear this story with a deeper understanding of the challenges and complexities involved.

How To Avoid **Becoming Part of the 90%**

1. **Getting a thorough understanding of your API can potentially save you millions of dollars down the road. It can also help you preserve your professional reputation and protect your company. Since most biotech companies do not follow this, you will gain a competitive advantage.**

2. **It's very difficult to know what you don't know when it comes to formulating a new drug. So even with the best intentions, eliminating skill gaps in-house is almost impossible when you don't know where they are. Don't be afraid to call on the experts!**

3. **If your team doesn't understand everything that can possibly (and frequently) go wrong with a certain type of API or drug formulation strategy, it's best to consult a skilled CDMO early on in the process.**

4. **CDMOs are not all the same. Sometimes, the "cheapest" one will end up costing you far more in the long run, while the "more expensive" one can advise you on ways to save a significant amount of time and money and help you attract additional investment.**

5. **Too many biotech companies interpret regulatory approvals as endorsements. Regulators aren't going to tell you how things should be done, nor is it their job to prevent you from making a costly mistake. For example, if your drug substance is approved for phase II trials, it only means that regulators have verified that your clinical trial materials are safe at the stated dose. It doesn't mean they believe your product will be effective. And it certainly doesn't mean that your product will be commercially viable.**

Final Thoughts

Within any industry that must constantly push the boundaries of science, you will likely find individuals and organizations that will inflate their capabilities.

Add the possibility of making billions and the pervasive attitude that luck is the biggest driver of success, and it's no wonder that little has changed in the many years we've been in business.

But for us, what gets us out of bed every morning isn't sensational headlines about fortunes made or fortunes lost. What gets us out of bed in the morning is a genuine love for the work and for our steady contributions to the field.

Our values are something we live and breathe. And that means if a project isn't a good fit for our skills, we will be upfront about it. At Corealis, we play the long game. And we'd always rather lose a project than a relationship. If we can be of help in your next drug development journey, we'd welcome your call.

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