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Ensuring the greatest return from your poorly soluble molecule

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Abstract

Poor water solubility is a common—and significant—problem facing biopharmaceutical companies today. About 70% of new molecular entities (NMEs) exhibit the problem and enhancements are required to achieve sufficient bioavailability. Potential strategies and a wide variety of technologies are available, but the choices can be overwhelming, especially to those companies feeling pressure from funding deadlines. Seeking new vendors can create further delays with no guarantees. There is no one-size-fits-all process as molecular characteristics require unique approaches. Repeated attempts to find the solution can result in interminable delays tallying four to six years and, in some cases, even the killing of the project. If a solubility solution to generate the bioavailability needed is not found, or if production cannot be scaled up, the entire company could be at stake.

Thermo Fisher Scientific provides trustworthy, scientifically-based guidance that will deliver the best chance of success for your molecule in the shortest viable timeframe. We can assemble a team with a broad skill set that has the extensive experience needed to solve solubility challenges. Within a 2–3-week window, we can evaluate a molecule and recommend a customized strategy. Alternately, the team could quickly determine if a compound is infeasible, allowing the developer to "fail fast", saving time and money. These days, more and more biopharma companies are turning to a CDMO for low-solubility molecule solutions and risk-free strategies to achieve their ultimate goal and a greater overall financial return on their investment.

Introduction

Currently, about 70% of new molecular entities (NMEs) exhibit poor solubility in water and require some form of enhancement in order to achieve sufficient bioavailability, leading to tough questions about how to proceed for biopharmaceutical companies developing such compounds.

The sheer number of potential strategies for improving the solubility of a compound—which include various methods of particle size reduction, solid dispersions, salt formation, lipid formulations, inclusion complexes, nanocrystals, and a wide variety of other technologies—can overwhelm many developers, leaving them unsure how to choose a path forward.

At the same time, companies are under significant pressure to advance development programs in order to move to the next stage of funding as quickly as possible. In their rush to advance their molecules into the clinic, some biopharma companies ignore questions about solubility until later in development when the issue becomes unavoidable. Many other companies are willing to roll the dice and pick a solubility-enhancement technology based on a low initial cost or because they think that the process would be simple to scale up or a trusted consultant advises that the technology works for most molecules.

Of course, one of the reasons so many options exist is because there is no such thing as a one-size-fits-all strategy for low solubility compounds; an enhancement approach that works for one molecule will not necessarily work for another with different physical and chemical properties.

Many developers are unaware that it can take just a few weeks to fundamentally evaluate a molecule's physical and chemical properties, determine the ideal approach for that molecule and recommend a customized solubility solution. As a consequence, companies often choose a technology without undertaking a rigorous assessment.

In some cases, that gamble may pay off, and they may luck into a formulation that provides the required exposure on the first attempt. In too many cases, however, biopharma companies find themselves going down a dead-end path that eats up tens of millions of dollars and years of time, while their competitors go straight to Proof of Concept with the first formulation strategy they try. Unfortunately, it is not uncommon for companies to formulate and reformulate compounds dozens of times over as many as four to six years without success, unnecessarily delaying or even killing the project.

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If a formulation fails in Phase I due to insufficient bioavailability, experience has shown that redoing all of the necessary formulation and process development activities, including stability testing and validation of analytical methods, can easily require up to 12 months of time at a cost of $500,000 to $600,000.

Switching to a new approach is also not desirable, as it can require finding a new solubility vendor, a process that is likely to take an additional three to six months of dedicated effort to perform due diligence and negotiate a new master service agreement. Add in the cost of repeating a Phase I trial, which according to a 2014 US Department of Health and Human Services report averages $4 million, and each subsequent attempt adds $5 million to R&D costs. In the meantime, the company is failing to collect milestone payments, and according to a 2012 Journal of Applied Clinical Trials article by Ken Getz of the Tufts Center for the Study of Drug Development, each day of delay in getting to market costs an average of $1.3 million in lost prescription sales.

Without a deep understanding of the science behind solubility enhancement, there is no guarantee that a second attempt will work any better than the first. When developers lack that understanding, they also lack the ability to discriminate the potential benefit of one technology over another, so they may wind up trying all of them. And when all of their attempts fail, it can be very difficult to draw a definitive conclusion as to whether or not the molecule can be developed.

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In the end, if the company's empirical search for a solubility solution fails to generate the necessary bioavailability, or if it produces a formulation that can't be scaled up, or if the company has spent years on a compound that was never amenable to development, the entire company could be at stake. Fortunately, it is possible to get reliable, scientifically based guidance to select the approach with the best chance of success in a very short amount of time.

For example, in one case, a company that was developing a poorly soluble molecule for a pain indication had tried almost 50 different formulations, using five different drug delivery technologies including micronization, wet granulation and nanocrystals, while failing repeatedly to meet exposure targets in preclinical and Phase I studies. Following numerous failures, the company's business partner decided not to advance the molecule any further and returned the rights to the developer.

Once the developer decided to consult an experienced solubility enhancement team at a large contract development and manufacturing organization (CDMO), it took only a few weeks for the team to evaluate the molecule and recommend a spray-dried formulation that succeeded immediately in pre-clinical studies. The new formulation demonstrated substantially higher bioavailability in a dog model, then achieved an 8½-fold improvement in Cmax and a 5-fold increase in bioavailability when it advanced to a Phase I PK study.

For another company that had also tried more than 50 formulations of its poorly soluble compound over the course of several years without achieving any significant increase in bioavailability, a scientific evaluation of the molecule and potential delivery technologies determined definitively that further development was neither financially nor technically feasible at that time, allowing the company to end that program in favor of more promising candidates

It generally takes just two to three weeks for a team with extensive experience in solubility solutions using a proprietary formulation design platform to evaluate a molecule, recommend a customized formulation strategy that is likely to provide sufficient bioavailability, and prepare additional formulation scenarios as a fallback. Or, the team may quickly determine conclusively that formulation of the compound is infeasible, allowing the developer to take a "fail fast" approach and end the program without wasting significant amounts of time and money.

Understanding the compound's properties is critical. While all BCS Class II molecules exhibit low solubility and high permeability, the specific molecular characteristics require unique approaches. For example, some low soluble compounds will dissolve fully in gastric fluids if the dissolution rate can be increased, so micronization may lead to success in those cases. Different compounds, on the other hand, will never dissolve no matter how small the particles. One low-solubility molecule may be suited to the creation of an amorphous dispersions by spray drying, while another may not dissolve in the necessary solvents.

Once the analyses have been completed, the development team has access to a wide variety of mathematical and computer modeling tools, ranging from high level quantum mechanical modeling of compounds and excipients to molecular dynamics simulations and quantitative structure activity relationships (QSAR)-based models that are applied to the development program as appropriate. In conjunction with the experimental data, the modeling tools provide deep insight and a mechanistic understanding of the compound's structure and behavior.

In determining what formulation has the best chance of success, the team looks beyond the immediate needs of pre-clinical and early phase trials necessary to achieve proof of concept and keeps in mind the requirements of later phase clinical trials and potential commercialization. After all, a delivery technology that produces sufficient bioavailability to get through an ascending dose study, but which cannot be scaled up might be considered a success by a solubility vendor, but would likely be considered a failure by a biopharma company looking either to take the drug to market or to sell it to a larger company for commercialization.

Global CDMOs have the ability to gather a team and leverage an extremely broad skill base and a breadth of experience that would be unusual to find in a single consultant or small vendor. And these days, more and more biopharma companies are recognizing the benefits of working with a CDMO to minimize risk and help them get their low-solubility molecule all the way to their ultimate goal.

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A CDMO that provides commercial manufacturing services for hundreds of small molecule products in a wide variety of dosage forms has a solid basis to understand the nuances of formulation interactions, such as how a spray-dried intermediate may impact solid-dose manufacturing or how a lipid formulation may affect the filling process into a softgel capsule, or how a formulation with a micronized API will blend with excipients.

A global CDMO also has the expertise to consider a multitude of factors beyond bioavailability that may play a role in formulation selection and the ultimate success of the product. Only a large CDMO that has helped clients earn numerous approvals is likely to have experienced personnel in every area of drug development, approval, and life cycle management, and is able to anticipate issues that can affect preclinical, clinical development, scale up, regulatory submissions, and lifecycle management.

Given the availability of this type of expertise and a proven method of predicting successful solubility enhancement strategies for individual molecules, there is simply no reason to take a risky trial-and-error approach to a development program. Today, biopharma companies can opt for a simple, time-saving method of choosing the best path for a poorly soluble molecule by asking a reliable CDMO to draw them a map. And by doing so they can achieve a greater overall financial return on their investment, whatever their commercial strategy may be.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 55 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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