A Guiding Hand: Managing Risk on the Way to the Clinic

Imagine you work for a biotech startup, targeting new molecular pathways to develop innovative treatments. After years of experiments, you have finally identified a set of specific and efficacious novel compounds. The morning after a spontaneous party in the lab, you feed the first compound to your mouse model. The result: Nothing. What now?

Ciriaco Maraschiello, Global Head, Drug Development at Evotec

Ciriaco Maraschiello, Global Head, Drug Development at Evotec, has heard this story many times before. *"Identifying an active pharmaceutical ingredient requires significant effort. However, the road ahead of drug development is just as challenging: The rate of drug candidates eventually reaching clinical phase III is only 5%. Our goal is to increase that number in a time and cost efficient way—in close collaboration with start-ups, biotechs, and pharma companies."*

Where's the drug?

"First, we check if the drug can be detected in the target organ," Maraschiello says, *"and determine its systemic exposure. For example, if it's not found in the brain, it might have failed to cross the blood brain barrier. Then we should be able to detect it in the blood."*

If the drug still cannot be found, the Evotec experts take yet another step back. Has the drug been inactivated by liver enzymes? Or has it just passed through the gastrointestinal tract without any effect?

"We analyze each molecule in great detail to understand what is going on," Maraschiello explains. *"As part of our preformulation studies, we measure all relevant physicochemical and biopharmaceutical properties. For example, we determine efficient solvating agents, and investigate drug solubility in biofluids mimicking physiological conditions over a broad pH range to understand the intrinsic capacity of the drug to permeate the physiological barriers, and to reach its target."*

If oral administration is preferred to other routes (which is often the case), the next step is to determine absolute oral bioavailability, defined as the percentage of the orally administered drug that reaches the bloodstream, compared to an intravenous injection as reference.

"We recommend to target bioavailability of at least 20-30%. Otherwise, too much of the drug is wasted and manufacturing costs can skyrocket", Maraschiello explains. *"Next, we determine how much of the drug you need to feed the animal to achieve an effect —that is, to reach the efficacious dose within the target organ."*

Is it safe?

At early stages of development, Evotec advises determining formulation and bioavailability for several compounds in parallel and then ranking the promising candidates based on their safety profiles.

"In our preliminary toxicity evaluation, we identify a safe dose that can be extrapolated to human physiology. Skipping this step can lead to significant delays, and, of course, extra cost during the regulatory drug development stage", Maraschiello points out.

Toxicity studies, often done with animal models, are crucial to identify compounds safe for use in humans.

In early toxicity studies, compounds are administered at an increasing dose to force the appearance of clinical signs, and, eventually, adverse reactions. Biochemical and organ status, tissue and skin pathology, and behavioral changes are carefully monitored over time.

Again, formulation can turn out to be an important factor, and both type and concentration of additives and excipients must be monitored carefully for potential toxic effects. *"To ensure safe use in humans, we must consider all clinical*

implications right from the start," Maraschiello says.

Can it be misused?

If a drug or its metabolites is able to cross the blood brain barrier, the authorities request an assessment for potential psychoactive properties analyzing the drug's behavioral effect, along with ease of synthesis, availability, and potential negative outcomes resulting from abuse through an exhaustive set of additional animal and clinical studies, to determine the appropriate level of control for manufacturing, distribution, and prescription.

Potential psychoactive properties are a significant risk in the drug development process. Evotec ensures procedures are put into place to mitigate potential abuse.

"Because time and cost associated with abuse liability studies can determine the commercial viability of the entire drug development program, we perform a detailed assessment of pharmacokinetic and pharmacodynamic properties very early on in the process," Maraschiello emphasizes. *"Our data help companies judge whether the benefits of the compound outweigh its risks, and take a strategic decision."*

Evotec's assessments include receptor binding studies and second messenger system analyses to determine mechanism of action and off-target activity of the compound itself, and all its expected metabolites, and a comparison to drugs known to have abuse potential.

Failure? Or just a step along the way?

"Through our years of experience, we are well aware that compounds often fail in clinical phase due to inadequate chemistry," Maraschiello points out.

Hence, Evotec project teams are set up following an integrated, interdisciplinary approach, always including discovery chemists along with formulation experts and pharmacologists, to anticipate issues in advance, suggest chemical modifications, and increase the overall success rate.

The list of possible measures is long and includes influencing solubility through minor structural modifications, protecting functional groups from *in vivo* metabolism, and use of alternative scaffolds. *"We can do quite a few things to increase the quality of the drug candidate once we understand what is going on,"* Maraschiello states.

Finally: clinical phase!

Once all risks have been identified and mitigated, the drug is ready to move to regulatory development. With Evotec's optimized pre-evaluation process, phase I can often be reached in less than one year.

Reproducible and scalable production are essential for successful clinical studies

"*The comprehensive knowledge gained during our preclinical assessment allows us to define a fully characterized formulation and dosage form that is safe for use in humans,"* Maraschiello says.

During phase I, the needs for later clinical phases are already anticipated, including drug production scale-up, long-term stability studies, additional safety tests, and a complete understanding of the drug's fate inside the body.

Why Evotec?

Remarkably, many Evotec research centers are former pharmaceutical sites. *"We strive to build the best environment for our staff, and managed to keep many highly skilled and qualified scientists," Maraschiello says.* Additional team members were hired from leading universities and organizations worldwide.

"With their long years of industry experience, our scientists know the potential pitfalls in drug discovery and development projects, and apply their knowledge to the next generation of drugs in multiple therapeutic areas: Neuroscience, pain, fibrosis, respiratory diseases, metabolic diseases, oncology, inflammation, and infectious diseases." Maraschiello concludes.

Learn more about how Evotec's expert advice and well-established, integrated approaches help biotechs manage time and mitigate risk to accelerate the journey from discovery to clinical development success.

Images from Shutterstock

The original article was published on 10/10/2018 under https://labiotech.eu/sponsored/biotech-risk-management-evotec/