3D PHARM CHANGE

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EVALUATION OF DRUG SAFETY DOES NOT START AT CANDIDATE NOMINATION:
CREATE VALUE BY DE-RISKING EARLY

Drug development is a daunting and difficult task where all the puzzle pieces need to click to result in an efficacious and safe treatment for patients. It is a high-risk endeavor involving many different scientific and non-scientific disciplines over a long period of time. The current estimates to develop a drug are about 2.3 Billion dollars, spend from discovery to launch, over a period of 8-13 years.[1]

Late-stage attrition in drug development remains a problem

Even with all the technology and knowledge today, attrition is still high in the different developmental phases of drug development. A fairly recent analysis provided by Dowden and Munroe estimated the rate of drug attrition in the clinic at about 90%.[2] About 35% of the compounds discontinued in Phase 1 or phase 2 are a result of (non)-clinical safety events, and 59% of compounds fail at candidate nomination as a result of non-clinical safety.[3]

Companies have been deploying de-risking strategies to reduce late-stage attrition because the earlier you can kill a potential drug, the less money, resources, and time you have spent on something that is likely to fail and at the same time you free-up these resources to work on approaches that may have a better outcome.

One of the approaches for de-risking safety-based attrition deployed in larger pharma companies has been to involve non-clinical safety experts (e.g. toxicologists and pathologists) at earlier stages of drug discovery.

The idea behind this approach is to evaluate potential safety issues as early as possible so medicinal chemists have opportunities to adapt their design. Thereby designing molecules that have a lower risk for safety events later-on in the program. These de-risking programs lean in essence on 4 pillars: 1. In silico prediction assays for physicochemical profiles that impact safety. 2. High-throughput screening assays for known off-target safety liabilities[2] 3. Potential to include safety biomarkers in pharmacology studies. 4. Bespoke assays for evaluating safety of the drug target or drug modality based on a target safety assessment.

Although it is understandable that smaller companies and/or biotech companies are more limited to set-up routine off-target screening paradigms, understanding of the safety implications of the chosen target is still of high value. Especially because they must rely on only a limited number of targets or approaches.

A target safety assessment will help to make informed decisions

Ok, so what is the big value of a target safety assessment? The main advantage that a target safety assessment will provide you is that you will be able to make informed decisions during the entire process of your drug development.

At the start of your program, it will enable scientists to decide about whether to proceed with a particular drug target, or consider other targets that may carry less safety risks for their clinical indication of interest.

By having an early overview on most likely potential toxicities of the drug or modality, several key attributes or behaviors of the compounds may be screened for during the discovery phase resulting in a better candidate selection with regards to safety attributes.

It will allow you to streamline the drug development strategy, because understanding the safety risks associated with your program will let you plan a proactive mitigation strategy for all these risks. Some risks may result in no-go criteria early in your program, while others are better off managed later in your program. In the end this results in a strategy where available resources can be spent as efficient as possible, while having a clear view on the amount of risk you are taking at each step of your program.

Finally, it will assist in portfolio decisions, interactions with health authorities, grant applications and communication to any potential investors. It may feel counter-intuitive for small companies to generate data that may not be positive for the compound or target. However, Investors will appreciate that you can provide clarity on the specific risks in a program and will be reassured that you have the mitigation strategy in place. It builds trust and prevents unnecessary disappointments because on-target risks were known and communicated. This 'eyes wide-open' relationship with your investors will pay back if the program does run into unpredictable obstacles.

Bioinformatics have a prominent role in target safety assessment

The advantages of a target risk assessment are numerous, but what is needed to conduct a target safety assessment? The answer is…it depends.

In essence a target safety assessment is an expert review on data that is available on the target and drug modality that spans from gene expression, and knockout models up to clinical trial information. The reason for conducting the target safety assessment, by example single target strategy planning versus identification of liabilities of multiple targets for selection, may determine the amount of data necessary on a target. Additionally, depending on the novelty of the target, data available for evaluation can be sparse or overwhelming. In case of sparse data on the target it may be necessary to expand the scope to the pathway in which the target it is present, and one can likely manage to retrieve the most critical information available. If available data is overwhelming, bioinformatic tools are advisable to gather and condense data to something that is manageable and interpretable. In that case there are service providers available that leverage bioinformatical pipelines, machine learning approaches and (manual) curation to collect data on targets. These (semi) automated reports can provide very valuable starting resources but come at an additional financial cost.

Whole package of data on the traget, what now?

Interpretation, validation, and translation to an actual non-clinical strategy that is fitting to the objectives, taken into account the specific patient population and development stage of the project is often required. This part of the target safety assessment can be performed by a toxicologist. The toxicologists will evaluate the body of data and translates this to an actionable strategy outlining major and minor risks and their likelihood of occurring for your development program. As mentioned before, a toxicologist will not only outline the risks, but also put together potential mitigation strategies and indicate the most appropriate phase of development to address these risks. A target safety assessment is a living document that evolves over time including new insights from public literature and conducted experiments. Therefore, it is good practice to review and actualize when moving through the different stages of drug development.

3D-PharmXchange in target risk assessment

We, at 3D-PharmXchange, believe that drug development is an end-to-end multidisciplinary process, which starts at target identification and extends beyond market authorization. Although not always apparent on the classical drug development timeline, involving an expert review by our toxicologists early in your program by

performing a target risk assessment can help you to streamline your drug discovery and development path and plan out by when you want to deploy certain mitigations. It is an additional early cost, but will result in more robust candidate selection, lower chance of attrition in later stages, and an improved communication plan to your investors.

Do you want to know what other value our non-clinical safety experts can create? Stay tuned to our blogs.

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Further Reading

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