From Innovation to Medication – Planning for Patients' Access to Life-saving Medication Right from the Beginning of Drug Development

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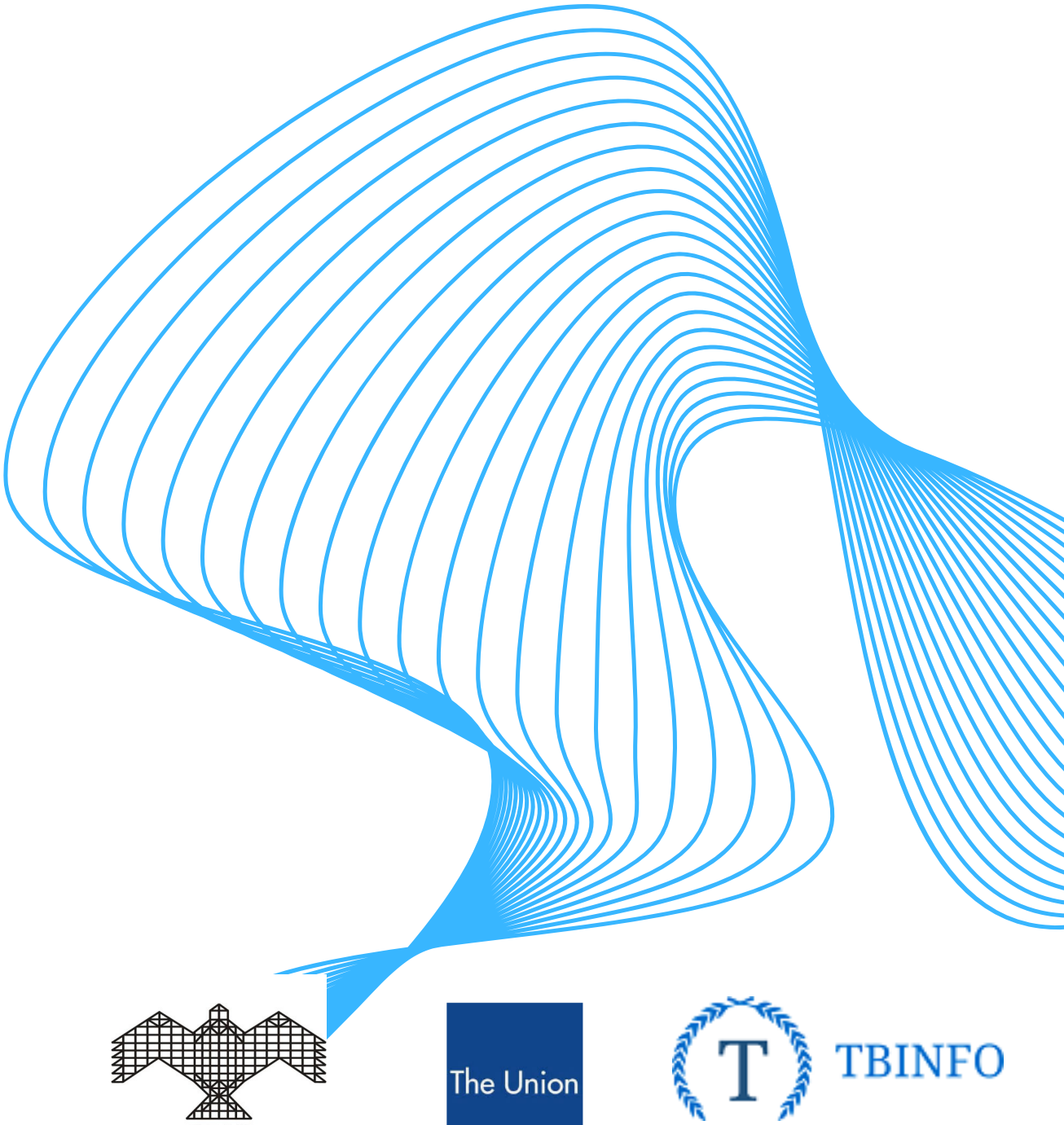

Abstract:
In the field of drug development, successful translation from bench to bedside is crucial for bringing new and innovative treatments to patients in need. However, many promising drug and vaccine candidates face pitfalls and show-stoppers that prevent them from reaching clinical application. By addressing potential issues early in the planning process and utilizing a Target Product Profile (TPP) as a roadmap, developers can navigate the regulatory landscape more effectively and increase the chances of success. This reverse planning technique, starting with the end goal in mind, can help to identify and mitigate risks throughout the development process, ultimately improving the accessibility of life-saving medications for patients worldwide.

Introduction: Tuberculosis (TB) continues to be a major global health challenge. The development of multi-drug resistance contributes to the need for new and improved treatment options. Thus, current research activities which result in innovative treatment regimens and the repurposing of marketed antimicrobials and other drugs for TB are urgently needed [1,2]. Unfortunately, promising drug and vaccine candidates often face unforeseen pitfalls when translating them from bench to bedside. Many urgently needed and potentially life-saving medications never make it to clinical application.

Pitfalls and show-stoppers

There are various reasons why promising drug and vaccine candidates fail on their way from bench to patients and people in need. When asking regulators from National Regulatory Authorities (NRAs) about the most often seen reasons for development failures, it turns out that very often candidates do not fail early but rather late in the translational development process. The main causes are as follows: in some cases, they are clinical development-related (e.g. fatal flaws in the design or inappropriate key efficacy endpoints in the pivotal phase III trial). In other cases, they are manufacturing process-related. But even though the show-stopper may come into effect late in the development process, the mistake that finally caused the failure might have been done already at the bench level. One well-known example of this is the use of fetal calf serum (FCS) when building up the master cell bank for a vaccine candidate. In principle there is nothing wrong with that, but, unfortunately, scientists doing lab research are often not aware that later in the development when permission for clinical trials in humans is applied for, the Regulatory Authority will request from the applicants that they have a certificate at hand that confirms that the FCS was sourced from a country that was TSE/BSE free [3]. Likewise critical is, if a biological (i.e. a vaccine or monoclonal antibody) needs a change in its composition or production process.

This may happen if a replacement for the contract manufacturer or a supplier of an important ingredient, e.g. the adjuvant or a stabilizer, becomes necessary during the development process. Due to the fact that with biologicals the process as such is seen as the product, this change will severely jeopardize the marketability and hence the accessibility of the medication for patients and people in need.

In other cases, the reasons for failure may be purely related to the marketed product. A drug may simply be too big to swallow or it may contain ingredients that are not acceptable for patients or societies. This would be the case e.g. in Muslim countries if a medicinal product contained porcine ingredients.

Reverse planning – starting with the goal in mind

To avoid these pitfalls and potential show-stoppers, it is advisable to address them early in the planning process, i.e. already when setting up the translational project development plan. Specifically, the plan should follow a label-oriented regulatory strategy that starts with the final product that will be suitable and available for patients in need. In this respect, defining the Target Product Profile (TPP) as a first step in the translational planning process is a straightforward starting point. Originally, the TPP was issued by the FDA as a guidance document for industry and review staff. [4]

The Target Product Profile

The TPP outlines the desired ‚profile' or characteristics of a target product that is aimed at a particular disease or disease [5]. TPPs state the intended use of a product, target populations and other desired attributes including safety and efficacy-related characteristics. In principle, the compilation of a TPP by the applicant is voluntary. However, I'd like to encourage any drug-developing party to design a TPP early in the planning process of the project. The reasons are as follows:

The benefit of a TPP

First and foremost, the TPP provides a valuable format for discussions between a sponsor and Regulatory Authorities (FDA/ EMA/ NRAs) that can be used throughout the entire drug development process as well as for post-marketing programs to pursue new indications. Second, a TPP embodies the notion of beginning the project planning with the goal in mind. Furthermore, it documents the specific studies that are planned to support the intended label. Ideally, the final version of the TPP will be identical to the annotated draft labelling submitted with a new Marketing Authorization Application.

In a nutshell, it can be stated that a TPP assists in a constructive dialogue with the Regulatory Authorities. The applicant learns the Regulatory position already during the early stages of development. The risk of unforeseen regulatory issues at the late stages of the product's life cycle is substantially reduced.

TPP - the starting point for the project planning process

Once the TPP has been designed and discussed with the Regulatory Authorities, it is advisable to use it as the starting point when the translational project plan gets designed. Subsequently, the design of the pivotal phase III trial will be drafted, with the intention that you, as the applicant will get market authorisation if the key efficacy endpoint is met and the investigational medicinal product (IMP) is found to be efficacious and safe. As the next step, the design of the phase II trial will be drafted that allow a transition into phase III, if successfully completed. Then the design of the phase I trial will be designed and subsequently the pre-clinical studies and experiments will pave the way to the phase I (first-in-human) trial.

The advantage of the reverse planning technique

Starting with the goal in mind and planning the developing process from patients' access to the marketed medication back to the bench of the laboratory will substantially reduce the risk that "unknown unknowns" will show up and become show-stoppers late in the development and life cycle of a drug. Therefore, the reverse-planning tool will increase the chances for drug candidates to successfully pass the translational R&D process and become accessible to patients and people in need.

Conclusion:

Successful translation of promising drug and vaccine candidates from bench to bedside is essential for bringing innovative treatments to patients in need. By addressing potential pitfalls and show-stoppers early in the planning process and utilizing a Target Product Profile (TPP) as a roadmap, developers can navigate the regulatory landscape more effectively and increase the chances of success. The reverse planning technique, starting with the end goal in mind, can help identify and mitigate risks throughout the development process, ultimately improving the accessibility of life-saving medications for patients worldwide. By implementing the TPP as the starting point for project planning, developers can engage in constructive dialogues with Regulatory Authorities and reduce the risk of unforeseen regulatory issues late in the product's life cycle. This approach enhances the likelihood of successful market authorization and ensures that new treatments reach those who need them most.

References:

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