Clinical and Regulatory strategies to avoid Pitfalls in Clinical Trials

Summary of session 2

As a drug developer, engaging with regulators facilitates your journey from compelling preclinical data to clinical development and beyond. There is a broad variety of regulatory guidance available covering different therapeutic areas, clinical trial design and strategies to accelerate development pathways. If no applicable guidance is currently available, the chance of succeeding with your development programme is in the hands, or perhaps the brains of regulatory experts. In this second session, Steffen Thirstrup, Advisory Board Director at NDA addresses why, when, and how to interact with the regulatory agencies to optimize the success of clinical development of a new medicinal product.

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First and foremost, a 'Regulatory Agency Interaction Plan' is recommended. This plan can anticipate potential issues which need to be discussed with regulators such as:

- determine the robustness of the current development program
- anticipate and address potential issues during development
- determine feasibility for Accelerated Approval Procedures
- address important requirements, e.g., PIP, ODD, SME

Early engagement with regulators is imperative in order to make better and more timely decisions, which can avoid costly changes later on.

Unmet medical need

Any underlying requirements for expedited pathways always focuses on unmet medical need. This unmet need must be substantiated by the regulators. Here, robust epidemiological data regarding the medical condition is needed. Frequency, symptoms, subsets within the disease population that may have a specific unmet need and long-term morbidity and mortality. What is the

current standard of care for this condition? This may include non-drug treatments (e.g., surgery) or off-label use of licensed drugs, both will have to be considered. This information needs to be mapped out and explained to the regulator.

The development programme may entail a completely new chemical entity or biopharmaceutical with a new mode of action, and a new target. However, novelty is rarely enough to meet regulator's expectations regarding fulfilling an unmet medical need. When applying for expedited pathways it becomes a major challenge to demonstrate that this might develop into something tangible for patients. It must be evident to the regulators that this new product is clinically relevant and could improve the outcome for the patients compared to existing therapies.

Accelerated pathways / PRIME

In Europe, the most important accelerated pathways are:

Accelerated assessment enabling marketing authorization approval within 150 days instead of the standard 210 days. A prerequisite is that your marketing authorisation application (MAA) is very comprehensive with only minor outstanding issues for the Medicinal Products for Human Use (CHMP) to question.

Conditional marketing authorization offering a temporary, one-year approval in situations where the benefit of immediate drug availability outweighs the risk of less comprehensive data than normal. The conditional approval will have to be renewed annually and is linked to an obligation to submit further, more comprehensive, confirmatory results within an agreed timeframe.

Authorization under exceptional circumstances can be used when there is a shortage of data which cannot be obtained, i.e., in rare disease studies involving exceptionally small patient populations. This pathway allows for ongoing post authorisation safety monitoring.

The PRIority MEdicine (PRIME) pathway enables early, proactive, continuous, and strengthened regulatory dialogue between the applicant and the EU regulators, ensuring robust data packages designed to address MAA requirements. PRIME has two entry points. If you are a small or medium sized enterprise, or if you came directly out of academia, you could enter at the stage of proof of principle, demonstrating to some extent that the compound targets an unmet medical need. Any other sponsor must wait until proof of concept.

One of the key benefits is the early appointment of a rapporteur from EMA's Committee for CHMP or the Committee for Advanced Therapies (CAT), to provide support to build knowledge ahead of an MAA. Around 25% of the applications submitted are considered eligible for PRIME, therefore careful consideration is recommended before embarking on this challenging path.

Orphan Drug Designation

The purpose of the orphan drug designation (ODD) is to create financial incentives for companies to develop new drugs and biologics for rare diseases. The incentives in the EU are:

- No fees for OD application and fee waiver for MAA
- Free regulatory/scientific advice (normally ~ €60,000) for ODs called 'protocol assistance'.
- First marketing authorisation has 10 years exclusivity in the market.

The entry criteria that needs to be met is that the medicine must be intended for the treatment, prevention, or diagnosis of a disease that is life-threatening or chronically debilitating. The prevalence of the condition for which the product is intended is < 5 in 10,000 people

in the EU or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development. There currently isn't a satisfactory method of diagnosis, prevention or treatment of the condition, or, if such a method does exist, the new product must be of significant benefit to those affected by the condition.

Paediatric investigation plan

With the patient population of children being more vulnerable, the paediatric drug obligations are rigorously regulated. Paediatric development is mandatory in the EU for all new drugs under development (unless granted a waiver). The paediatric investigation plan (PIP) describes the planning and conducting of separate efficacy and safety studies required by the regulatory authorities and is the basic document for development and authorization of a medical product for children. This document is submitted at an early phase of a new compound development (after Phase I, upon adult pharmacokinetic studies being available).

The official time taken by the agency to review the paediatric plan is two times 60 days with a clock stop in between for the applicant to address questions. All in all, the PIP review process takes around six months. Having an agreed PIP is a prerequisite for getting the MAA validated by the European agency, without passing this checkpoint the company cannot submit their MAA.

Every product needs to have a paediatric investigation plan but if the condition does not exist in children or if the product developed is not suitable for the paediatric population, a waiver can be issued. Complete waivers are rarely issued unless the condition does not exist in children at all (e.g., dementia), in some circumstances a partial waver can be issued, covering a subset of the paediatric population. Nevertheless, no matter which product is being developed, early engagement with the European regulators regarding the PIP is a must.

In the US, FDA strongly encourages the sponsor to submit the Paediatric Study Plan (PSP) much later in the process, prior to initiation of the Phase III studies. This can be a major hurdle for a US company moving into Europe. As these companies are used to engaging with regulators in late phase II or early phase III, this will be too late for the European regulators and could have serious implications on the development progress.

Scientific advice

Under certain circumstances, there will be no scientific guidelines available (existing guidance is limited, outdated or in one way or another not suitable) and therefore, there may be a need to consult the regulatory authorities directly by seeking scientific advice. Depending on the programme, the development strategy most often benefits from scientific advice on how to plan the clinical study. It is, however, important to remember that it is still the responsibility of the drug developer or the product development company to do appropriate product development and to conduct the right trials.

Some companies seek scientific advice very late in the development process, where t it is already a *fait accompli*, finalised. Under these circumstances, the scientific advisor will not assess the data in depth, but possibly give some feedback on whether the approach is sufficient or not.

Done in a timely manner, seeking scientific advice with the national agencies in a decentralised route can be a sensible approach. The different agencies have different national interest and have professionals that all contribute to the European pool of experts. Therefore, it is always a good idea to consult one to three of the different national agencies, depending on

their particular interest, before going for centralised approval. This is, however, a unidirectional process, multiple member states can be visited on a one-to-one basis before going to EMA/CHMP for scientific advice, but it cannot be done the other way around. By starting out with centralised scientific advice the individual member states will refrain from giving advice on the same issue.

Scientific advice is not delivered off-the-shelf, it is a very time-consuming process. The timelines for applying, assessment and expected response normally takes 70 days, 40 days if there are no issues that require clarification. This is the main reason to plan for interactions with regulatory agencies early on, to decide whether scientific advice is necessary and if so, when to do it.

Investing in Scientific Advise and being compliant to the advice given increases the path to success significantly according to a Nature study from 2015 [1]. The overall success rate for a MAA was approximately 84 percent if the development plans match regulatory expectations. If the initial plans at the time of scientific advice deviated from regulator's expectations but were rectified the overall likelihood of success is unchanged. However, continuing the development program as planned and contradicting the scientific advice reduces the chances of a successful MAA review to 41 precent. Preparing for scientific advice is a time-consuming and expensive process that when used will optimally increase your chances of approval.

How to meet the regulator's expectations according to Steffen:

Know your product: The manufacturing, non-clinical and clinical strategies, the science, and the literature as well as the regulatory precedents.

Prepare for the meeting: Set the strategy, define the goal, decide on the content and data to present, prepare for questions, rehearse.

Presentation requisites: No information overload, keep the presentation short and the text on the slides to an absolute minimum. Too much information most often leads to less clarity and more questions.

References:

[1] Regulatory watch: Impact of scientific advice from the European Medicines Agency. Hofer et al. *Nature Reviews Drug Discovery 2015*; 14: 302–3.

About the presenter

Steffen Thirstrup has been with NDA since 2013 and excels at advising companies on their development strategies to meet expectations of regulatory agencies around the world. He applies his skills to a broad range of therapeutic areas and has successfully helped numerous clients interact with regulatory agencies throughout the stages of development and during regulatory review.