Abstracts

Symposium

„Development and Regulatory Aspects of Topical Dermatics Today“

BfArM

Session 5
Clinical development

Symposium of GD in cooperation with BfArM

Bonn, 27. January 2010

Session 5: Clinical development

Optimizing your development plan through scientific advice processes

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Constantly evolving needs and demands related to the safety and efficacy of new medicines contribute to the increasing volume and complexity of drug development programs and a successful development program has to meet numerous criteria and targets in order to deliver a valuable medicinal product.

To meet regulatory needs is one of several key success criteria and has big impact on timelines and costs of a development program. Therefore, regulatory needs should be understood and implemented in the development program from the beginning.

Scientific advice from a regulatory authority in relation to the development of a new medicinal product can contribute to the understanding of scientific and regulatory expectations a medicinal product has to meet prior to receiving a marketing authorization. Scientific advice may be requested at any time during development of the medicinal product and may cover questions related to pharmaceutical quality (including biological and biotechnological aspects), design and conduct of preclinical investigations and clinical trials, including biostatistics.

Scientific advice meetings are an important element of the process to enable a dialogue to take place with a national and/or international competent authority or advisory committee and they should be considered an essential part of the development strategy. Whilst such a dialogue may help the future applicant to understand regulatory requirements, it does also contribute to the competent authority's understanding of the science and technology of the new medicinal product which they may have to review during the marketing authorization process.

Selection of the most appropriate competent authority or advisory committee and careful preparation of a scientific advice meeting, both from a scientific, documentational and organizational perspective, is of great importance. Whilst competent authorities are usually happy and interested to give scientific advice, they expect the applicant to seriously consider and implement advice given. Minutes from an authority's scientific advice received during development of a new medicinal product need to be submitted with the marketing authorization application and will contribute to the authorities review and approval.

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Human Safety Phase I Studies

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The safety battery for topically applied products typically includes evaluation of the final to-be-marketed formulation for cutaneous toxicity, most notably dermal irritation, potential for inducing contact sensitization, phototoxic potential and photoallergic contact sensitization. Even though these phase 1 safety studies are an integral part of almost every topical development program and help lay the groundwork for responsible and safe clinical development in later phases, there are no current FDA or EMEA guidelines available specific to these studies. Unfortunately, in the absence of guidelines setting down the requirements and designs for these studies, sponsors are often at a loss for rational designs and how to manage agency expectations. This presentation is intended to give an overview of the basic study designs for irritation, sensitization, phototoxicity and photosensitization as standard dermal safety tests in humans.

Studies for dermal irritation and phototoxic potential are normally conducted early in the clinical program. However, it must be kept in mind that the safety studies for the licensing application should be conducted with the to-be-marketed formulation, and that this may not be available at the earliest stages of clinical development. It may be necessary to provide human safety date before proceeding with Phase IIa studies with concept formulations, particularly in the case of NCEs. For this purpose, abbreviated designs with shorter treatment duration and fewer subjects are generally acceptable. Testing of sensitization and photosensitization is often delayed and conducted in parallel with Phase IIb or III.

The exaggerated conditions (such as occlusion) used in Phase 1 cutaneous safety testing serve to ensure that potential safety problems are not missed and can be appropriately addressed in later phase clinical trials. In order lo have confidence that tolerability issues will indeed be recognized, it is important to optimize the design used for these safety studies. After all, early recognition of safety problems may save considerable development time and costs.

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Phase II Clinical Development: Strategy for a robust Phase II program

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Phase II clinical trials are conducted to investigate a drug's therapeutic efficacy and relative safety in patients. Typically these trials are well-controlled, closely monitored, and conducted in a group of patients who are selected by relatively narrow criteria. Most trials in this phase can be classified as therapeutic exploratory. At the minimum, phase II trials should generate enough data to strongly suggest, if not prove, efficacy and identify the most common side effects.

Two of the most important goals of a successful Phase II program are Proof-of-Concept and dose optimization. These goals are not necessarily distinct as an important objective of many early studies in Phase II is often an early estimate of dose response which is then confirmed in later trials. Other important objectives of Phase II trials are evaluation of study endpoints, therapeutic regimens and target populations (e.g. mild vs. severe disease). Exploratory analyses and multiple endpoints may be used to best advantage in this phase of testing.

It is common to divide Phase II trials into IIa and IIb. These trials are different is scope, size and often rigor of design. Surrogate markers for efficacy, e.g. objective measures of skin function obtained using biophysical measurement methods, may be built into designs of Phase IIa trials with fewer patients and only one or two sites. However, in later Phase II studies it is important to choose and validate, if necessary, clinical scores and patient reported outcomes (PROs) which will be used for pivotal studies. In particular, Phase IIb can be defined as a learning phase which lays the groundwork for confirmation in Phase III.

There are many advantages of a robust Phase II program: The indication and inclusion/exclusion criteria for Phase III can be justified by Phase II outcomes. Outcome measures for pivotal studies can be optimized. Safety parameters for Phase III may be better defined, possibly with reduced need for post-marketing risk management and labeling restrictions. Further, there is a lower risk of the necessity of formulation changes in Phase III which may lead to repeated or bridging studies from earlier phases.

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Phase III Clinical Trials for Topical Dermatological Products

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Following successful proof of concept and dose finding phase II trials at least one pivotal study with sufficiently large numbers of patients is required to confirm the safety and efficacy of a new investigational drug.

These phase III trials are usually the most time consuming and expensive studies in the whole drug development process.

While guidance documents exist for some indications, e.g. psoriasis most of the time it is not obvious what regulatory agency will require in order to grant marketing authorization. It is therefore highly advisable to seek scientific advice from regulatory bodies before initiating phase III trials.

According to the size and complexity phase III trials require not only regulatory and dermatological expertise but a competent and experienced interdisciplinary team of data managers, statisticians, field monitors, trial physicians, study nurses, administrative staff all coordinated and directed by an efficient project management.

In this presentation key aspects of phase III studies will be described and illustrated by practical examples.

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Phase IV Trials and Non-interventional Studies

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After the authorisation of a new drug further studies are initiated to further investigate its effectiveness and safety. They are summarized under the term Post-authorisation Study (PAS), which is any study conducted within the conditions of the approved Summary of Product Characteristics or under normal conditions of use. This covers both interventional clinical trials (Phase IV) and Non-interventional Studies (NIS). An overview is provided about the various designs and (German) regulations of PAS. Besides the efficacy, the safety of a registered drug is a major focus of a PAS as it is possible to document and to evaluate larger patient populations than in the preceding Phase I to III trials. In addition, subgroup populations, daily usage or the optimization of the therapy may be investigated in a PAS. However, according to the design chosen the informative value can be limited compared to clinical trials of the former phases, in particular if it is not a controlled study. The potentials and limitations of a PAS will be presented from a practical and methodological point of view. In summary, the different variations of a PAS are valuable tools in clinical research provided the PAS is well-designed, well-conducted and well-interpreted.