

EVALUATING ORAL DRUGS FOR TOPICAL APPLICATION

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ABSTRACT

Dermatology provides an unmet need for drug development. There are two reasons to develop drugs for topical use. The first is to treat skin diseases and disorders such as psoriasis, acne, actinic keratosis, cancer, eczema, etc. These conditions represent some of the most common and chronic disease states in man. The second reason is to deliver systematically active drugs through the skin to enhance drug activity by, 1. avoiding first pass metabolism, 2. reducing toxicity and 3. improving compliance. There are many drugs that have failed in development as oral formulations for which there are extensive pharmacology, pharmacokinetics, toxicology, and even clinical data which could support topical use. Companies could reassess the use of "old" drugs for topical application and open up new therapeutic approaches. In order to reassess a company's portfolio, a company needs to search their libraries to identify potential topical therapeutics. Once this is done, an assessment can be made of the usefulness of already accumulated toxicology and/or clinical data. Pharmacokinetic approaches should be considered in order to accelerate the drug approval process. Most important to this process, is utilizing the FDA as a partner to assess the steps needed to satisfy regulatory requirements that establish the drug's safety and efficacy. This poster will outline and illustrate the important and necessary steps to evaluate topical use of drugs developed for oral use.

Key Words: Drug Development; Topical Drugs

INTRODUCTION

1. Dermatology provides an unmet need for drug development.
2. There are two reasons to develop drugs for topical use.

- The first is to treat skin diseases and disorders such as psoriasis, acne, actinic keratosis, cancer, eczema, etc. These conditions represent some of the most common and chronic disease states in man.
- The second reason is to deliver systematically active drugs through the skin to enhance drug activity by, 1. avoiding first pass metabolism, 2. reducing toxicity and 3. improving compliance.

CONCLUSIONS

Many drugs which have been evaluated for oral use may also have applications as topical therapies. As part of the "discovery" phase of drug development, companies interested in topical drug therapy should examine their libraries to identify drugs which already have toxicology and clinical data.

DRUG DEVELOPMENT

Drug development occurs during three basic phases.

Phase 1:

During this phase, the following is established, usually in normal volunteers:

1. Initial safety measures
2. Pharmacodynamics
3. Pharmacokinetics
4. Tolerance as measured by dose ranging studies

Phase 2:

During this phase, the following is established in patients with the disease under investigation:

1. Continued safety measures
2. Initial efficacy studies
3. Dose response
4. Drug interaction studies, if indicated

Phase 3:

During this phase, the following is established in patients with the disease under investigation:

1. Continued safety measures
2. Large scale efficacy studies
3. Drug interaction studies, if indicated

DEVELOPING DRUGS FOR TOPICAL USE

Portfolio of Data

Most drugs are developed based on a known mechanism of action which is theoretically sound. In order to reach the clinic, a large number of animal pharmacology studies are usually performed to support efficacy; key toxicology studies are performed to support drug safety; and sufficient effort is put into chemistry, manufacturing and controls to support both animal and human studies. Unfortunately, once a drug reaches the clinic it may prove to be less efficacious than expected, less bioavailable than expected or perhaps the drug is beset with safety issues. Nevertheless, for these drugs, there is extensive background information which could be used to support topical use. These data include extensive pharmacology, pharmacokinetics, toxicology, and even clinical data which could support topical use.

Strategic Approach

If a company chooses to enter the "topical" market, whether it be for topical delivery of a drug for systemic use, or localized treatment of a topical condition, there may be a portfolio of products already in their "libraries" primed for development. Companies could then reassess the use of "old" drugs for topical application and open up new therapeutic approaches.

One of the first orders of business is to identify mechanisms of action of interest. For example, the company could search all of its 5 alpha reductase inhibitors if it chooses to enter the hair growth market. Ideally, the drug may already be marketed as an oral compound for a systemic indication, so that a lot of the nonclinical development, especially toxicology of the topical product, can be "piggybacked" with the oral drug.

No matter what approach is taken, an assessment is made of the usefulness of already accumulated toxicology and/or clinical data. Pharmacokinetic approaches should be considered in order to accelerate the drug approval process. For topically applied drugs for local use, it would be ideal if there is little or no systemic absorption. This can be confirmed by comparing bioavailability of the orally delivered compound with the one delivered topically.

FDA Is Your Partner

A very important step to this process, is utilizing the FDA as a partner to assess the steps needed to satisfy regulatory requirements to establish the drug's safe efficacy. It is suggested to meet with the FDA early in the development process at a pre-IND meeting and schedule appropriate meetings thereafter at the appropriate milestones.

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LIDOCAINE AND LIDODERM

