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The development and registration of topical pharmaceuticals

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ABSTRACT

From our own experience we have seen that over the past 60 years topical delivery of drugs with its advantages and disadvantages has become much more widely understood and much more is now known about the disposition of drugs in the skin. Today, pharmaceutical scientists produce dermatological vehicles which are tailored to patients' needs and better appreciate how the formulation may affect rates of drug delivery, and ultimately, efficacy and safety. The guidelines for developing a New Chemical Entity (NCE) to be administered by the topical route are rather straightforward. What appears to be less well understood are the pathways for development, and the regulatory routes for topical formulations of a known established Active Pharmaceutical Ingredient (API) either in a new formulation, at a different concentration, or with APIs where topical administration is an alternative route of administration. This article provides guidance, on the regulatory routes which can help achieve marketing approval in Europe for topical formulations, with particular emphasis on clinical development. Some comments on NCE's will be given, and further detail is provided in cases where the topical route is a new method of administration for delivering a known API.

1. Introduction

When considering the development of a new topical formulation there are a number of problems to be addressed:

- What is the optimum formulation?
- Are the Active Pharmaceutical Ingredient (API) and excipients stable in the formulation?
- What is the optimum concentration of the API?
- Does the API need to be absorbed to be active systemically, or is its activity solely a local effect? If so at what level in the skin does this effect take place?
- Is the API absorbed and what happens after absorption in terms of pharmacokinetics and in situ toxicokinetics?
- Are the API and excipients likely to be locally toxic? Will they be irritant or cause sensitisation and allergic reactions? As it is applied to skin which may well be exposed to sunlight, is there any potential for phototoxicity or photosensitisation.
- Have packaging and container closures been given adequate consideration?
- What effect does the API have, what are we treating, what are we able to measure in terms of efficacy and safety?
- Do the measurements used provide reliable, accurate, and reproducible results? Any such measurements need to take into account the condition being treated and also any other underlying pathology which could be relevant or have an effect on the pharmacokinetics or pharmacodynamics.

The skin (which is made up of epidermis and the dermis) is the largest organ in the body and the most visible (Kanitakis, 2002). It is affected by a broad spectrum of pathologies and it is surprisingly difficult to find ordinal, accurate and reproducible measurements of skin health or appearance (Fig. 1). Validated rating scales for some of these are in use such as the Psoriasis Area and Severity Index (PASI), global improvement scales, or Visual Analogue Scales (VAS). All are subjective scales, with potential for considerable variation between observers and although providing us with numerical 'scores' the steps between each of these 'scores' will not be an ordinal fixed scale and the appropriate statistical evaluations have to be used. There are limited exceptions to this such as the erythema meter and the chromameter. These can be standardised and, with careful application so as not to apply too much pressure to have a blanching effect, can provide an accurate assessment of colour change in skin (Diffey et al., 1984). They can also provide a measure of therapeutic efficacy, as erythema is a common accompaniment of skin disease (Cox and Coulson, 2010). There are other techniques which may be of particular value during the early stages of clinical development; for example spot counts in the treatment of acne.

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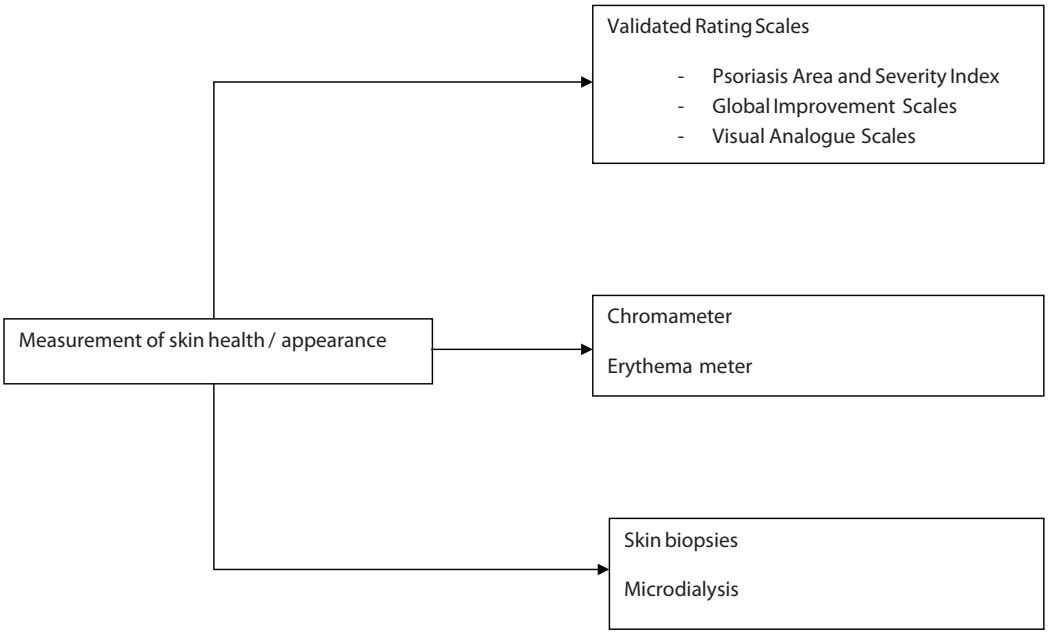

Fig. 1. Ordinal, accurate and reproducible measurements of skin health/appearance currently used.

Skin biopsies may provide useful information on the pharmacodynamics of the drug at the site of action (Phillips and Sachs, 2005). Micro-dialysis can give information on the pharmacokinetics in skin (Tettey-Amalo et al., 2009) and can also be useful in determination of the optimum therapeutic concentration, or for 'proof of concept' studies (Brunner et al., 2005).

2. The role of the formulation

Any change in the concentration of the API, or changes in the excipients may alter the stability, or the pharmacokinetics of the preparation and it is therefore important to define this at an early stage to prevent delays and repetition of work during the development process. Traditionally, the choice of formulation was dictated by considerations such as stability and compatibility of the API in the vehicle as well as patient acceptability. However a number of recent studies have shown that the choice of excipient(s) clearly influences the fate of the active in skin (Hadgraft et al., 2003; Santos et al., 2010; Watkinson et al., 2011). A range of vehicles may be employed for topical delivery and these include powders, semisolids (creams, ointments, gels), sprays, foams and patches. In some instances, patient preference will dictate the choice of formulation. For example the occlusive properties of ointments means that they produce less trans-epidermal water loss and should theoretically be more effective in enhancing delivery of the active to the skin (Curdy et al., 2004). However patients find ointments very greasy to use and creams are far more popular with patients in the management of skin conditions such as psoriasis and eczema (Richards et al., 1999; Aeling, 2000).

As well as delivering a therapeutic agent to the skin the vehicle should not compromise irreversibly the barrier function of the skin. For example, creams are oil and water mixtures and require emulsifiers, stabilisers and preservatives in order for them to remain stable; the compounds that do this are also often irritant to skin and potential sensitisers, which can defeat the objective in the treatment of skin diseases such as eczema (Cork et al., 2003). One example is DMSO (Dimethyl sulfoxide) which is an additive used as a penetration enhancer for other active drugs; as such it may also enhance their toxic effects and in addition may also produce local toxic effects on skin such as itching, burning, erythema and urticaria (Martindale, 2011).

2.1. Development of a New Chemical Entity (NCE)

The development of a NCE requires the standard preclinical pharmaceutical and toxicological development before administration to humans in Phases I, II and III clinical trials. Regulatory requirements in Europe come under Directive, 2001/83/EC and amendments (Directive, 2001/83/EC; Directive, 2004/27/EC). In all cases applications for New Chemical Entities will come under Article 8(3), under the section "Requirements for a Marketing Authorisation" requiring a full Common Technical Document (CTD: Eudralex Volume 2B Notice to Applicants Presentation and Format of the Dossier) which will include a full data set of non-clinical (Module 4) and clinical data (Module 5). The European Medicines Agency (EMA) provides access to a series of Guidelines and Points for Consideration regarding recommended requirements on what is needed by a regulatory authority which will aid in generating data during research and development of topical APIs. There are well established preclinical methods such as the Draize test; the EMA also offers guidance on preclinical requirements on its website. At this stage previous research should also have established the type of formulation and the concentration needed to achieve efficacy, although Phase I studies using a limited variety of vehicles and concentrations of the API can additionally generate useful data. It is important to recognise that should the formulation or concentration used in preclinical studies differ from those to be investigated in the Phase I, II and III trials it may be necessary to repeat much of the early work creating additional costs and delays.

There are various validated methods for measuring local toxicity in volunteers in Phase I. It is good practice to seek scientific advice on the number of subjects and study duration from one of the National Competent Authorities in an EU Member State or the European Medicines Agency (EMA) through its Scientific Advice Working Party (SAWP). Potential developers should consider carefully the therapeutic area for development for an NCE since certain areas come under the exclusive responsibility of the EMA such as NCEs in oncology (refer to the EMA website). There are no specific guidelines, which define the number of subjects and the specific

protocol to use that encompasses the duration of the exposure and timing for sensitisation testing. This is generally determined on a case by case basis with the developer submitting trial designs to the regulatory authority for critical review at the time of scientific advice. Methods used should be shown to be validated and reproducible.

Irritancy and sensitisation potential can be, for example, measured by repeat insult under occlusion over a 2–4 week period (Shelanski and Shelanski, 1957), and sensitisation potential by means of re-challenge after an interval in a different test area. Up to 6 variants can be assessed using this technique, which permits the comparison of a range of formulations or concentrations of the active versus the vehicle and/or a reference where possible. *Phototoxicity* is a possibility when the API or excipients absorb light in the 240–700 nm range.

This can be determined using a similar protocol, and often requires a smaller number of subjects and includes the addition of the application of UV light after assessment of *Minimal Erythema Dosage* (MED) in each subject. *Photosensitisation* potential can also be studied using the method of repeat insult under occlusion with the addition of UV light and re-challenge in a new area of skin following an interval (Kaidbey and Kligman, 1978, 1980).

Knowledge of the local and systemic pharmacokinetics of the drug when applied to the skin is often a regulatory requirement. There are various ways of measuring transdermal penetration, both in vitro and in vivo (Fig. 2). The in vitro Franz cell method (Franz, 1975) using either cadaver skin, or skin supplied following cosmetic surgery is a well established technique and the flux across skin often provides a good estimate of what is likely to happen in vivo. Measurement of drug by skin stripping techniques where adhesive tapes are applied with a standard pressure after application of the formulation in vivo, may also provide useful information (Pershing et al., 2002). However, it is important to note that this technique does not distinguish between drug, which has crystallised in skin and drug which is in fact, actually in solution in skin. Where the drug has crystallised out into its solid form, it is no longer immediately available to exert a therapeutic action in dermal tissue although it may still add to bioavailability by slow dissolution over time. This approach therefore has its limitations when attempting to determine useful therapeutic levels in skin. Regulatory authorities have yet to comment on this deficiency in the tape stripping approach. Microdialysis, which does measure drug in solution in skin, can supply in vivo data in terms of absorption and, should there be sufficient absorption, pharmacokinetic studies may also be performed. The usefulness of data produced in this manner will be evaluated on a case by case basis by the relevant regulatory authority. The sponsor developing a topical formulation using these techniques should seek scientific advice from the concerned regulatory authority before conducting such trials. It should also be noted that some National Competent Authorities may have their own National Guidelines. For example AFSSAPS (the National French Authority) may have specific guidelines regarding topical formulations which may be necessary for topical formulations for NCEs which do not come under the therapeutic exclusivity of the EMA.

In the specific case of steroids, the skin blanching pharmacodynamic response is a useful technique which provides information on potency and also possibly on dose response which can improve our understanding of the likely range of concentration of the active required for clinical use (Smith et al., 1993). The EMA Guidelines using blanching for measuring Therapeutic Equivalence, Clinical Investigation of Corticosteroids Intended for Use on the Skin 3CC26a may be found at http://www.ema.europa.eu/pdfs/human/ewp/3cc26aen.pdf.

Many of the above studies are performed in healthy volunteers under the considerations of Phase I trials. Phase II/IIa studies which determine 'proof of concept' or validate that the formulation and concentration of the API are safe and effective in the relevant clinical condition in patients will require considerations relevant to the target condition. Of primary importance will be trial design, reference product and/or standard of care, validated parameters, duration of treatment and definition of inclusion/exclusion criteria of the target patient population. There may be a need to conduct Phase IIb studies in order to establish the optimal dose and dose range of the topical formulation and API studied. This should integrate the safety considerations of dose ranging Phase Ib studies.

Larger Phase IIIa clinical efficacy and safety studies are generally performed once the formulation composition and the optimum concentration of the API is established. These studies are generally designed to confirm the Phase II proof of concept studies and to increase the number of patients exposed to the formulation for safety considerations. This is essential for the evaluation of the benefit/risk balance, which the medical assessor (medical reviewer FDA) will need to make in order to determine the eligibility of the product for licensing. Of importance are the use of validated methods of measurement of efficacy in the target condition, clear definition of standard of care and/or reference product as well as a clear definition of the inclusion/exclusion criteria of the target patient population. Safety recordings should follow standard Medical Dictionary for Regulatory Activities (MEDDRA) classifications which, are accepted by FDA and EU EMA/National Competent Authorities. Particular attention will be made by the regulator to local and locoregional effects which may be associated with the API and substances found in the formulation. Certain excipients for example are known to induce skin reactions which the regulator will take note of in the risk assessment.

The number of patients to be included in the trial should reflect adequate statistical considerations, which are dependent on the primary objective and end point of the study. These need to be clearly described in a Statistical Analysis Plan (SAP) which should be annexed to the study protocol and finalised and formally endorsed before patient recruitment into the study starts. Adequate numbers of patients and controls should be clearly defined in the SAP. Specific designs should be clearly defined to described how sufficient number of patients for safety considerations will be generated (2:1 or 3:1 ratio trial designs where the large number reflects the number of patients exposed to the product vs the control group). Safety measurements will depend on the dose of the API, the excipients used as well substances which enhance the penetrance of the API in the skin.

In the case of long established topical therapies such as the steroids, side effects both locally on skin atrophy and rebound effects on cessation of treatment, plus central effects on the HPA axis, are well known. Particular attention must be given to the potential systemic adverse effects of newer molecules as the skin. Consideration regarding the delivery system for a drug is particularly important because of the avoidance of the first pass effect in the liver which may lead to potentially highly effective systemic levels from remarkably small amounts of a topically applied active. A good example of this can be seen with oestradiol which, from a 22 cm^2 area of skin, under occlusion from an adhesive patch delivering 50 μg per day, achieves similar efficacy to the oral dosage form of 2 mg per day (British National Forumulary, 2011). In addition, occlusion and regional variation in skin permeability will affect transdermal penetration and absorption rates and this may have implications for both efficacy and safety, an example being the adverse effects of steroids when applied to the face. Similarly steroids when applied topically for their topical effects are well known to have the potential to deliver sufficient drug to affect the HPA axis, either by suppression or an iatrogenic form of Cushings Syndrome.

Duration of treatment for the condition will determine the minimum trial period the requirements of which may vary between the

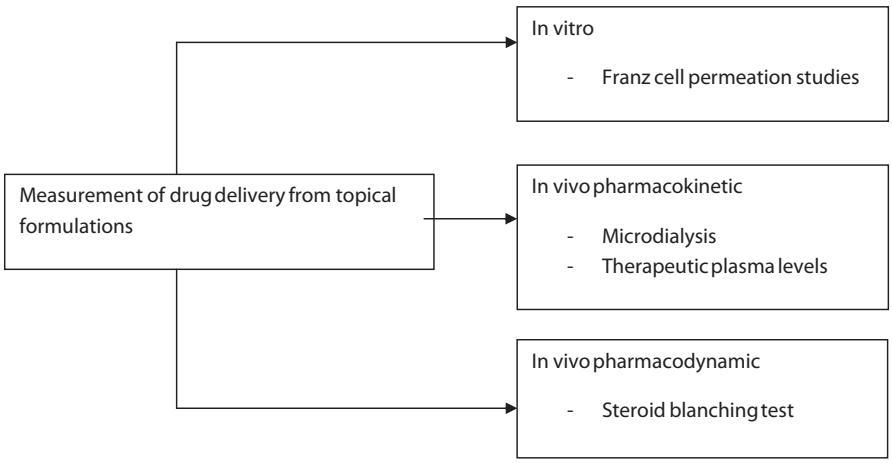

Fig. 2. Assessment of drug delivery from topical formulations.

EU Regulatory Authorities and the FDA. For example if the therapy is for chronic use then the EU will generally require a trial duration of a minimum of 6 months whereas often the FDA may be satisfied with 3 months.

The inclusion of a placebo group can be a difficult decision. Most dermatological diseases are chronic and the inclusion of a placebo group is particularly feasible in short duration studies where it is possible to offer all subjects current best therapy on completion of a trial period. These data are also beneficial from a statistical and regulatory viewpoint. If the vehicle cannot be used the EU guidelines in general encourage the use of a reference product which is licensed in the EU ICH Topic E 10 Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 http://www.ema.europa.eu/pdfs/human/ich/036496en.pdf).

It is not possible to provide exact advice on the number and finite size of the studies required, and the authors recommend that once the overall development plan is designed in detail it is then discussed with the regulatory authorities in a scientific advice session. National authorities offer scientific advice for a fee in many instances. The EMA has, as mentioned before, the Scientific Advice Working Party which gives advice on a wide range of topics. Fees for this service are reduced for small to medium sized enterprises who register with the EMA. In the case of NCEs or new topical formulations for products where one does not exist, good proof of concept studies Phase IIa and Phase IIb where necessary enhance the understanding of the usefulness of the applicants' product. Generally speaking, at least two well designed studies of adequate size and power will be required in Phase III for benefit risk assessment. In some instances a single pivotal Phase III study may be sufficient providing the sponsor considers the recommendations of the EMA for example in relation to meta-analyses and one pivotal study (CPMP/EWP/2330/99 http://www.ema.europa.eu/pdfs/human/ich/036496en.pdf). This is considered in the event where patient recruitment will be difficult (for example, Orphan Medicines) or where effectiveness will be evident and the power calculation will reflect this. The other consideration is a company's capacity to finance two studies. Often small to medium sized companies do not have the money for this and request the possibility of doing one pivotal phase III study.

2.2. Developing a topical formulation for a well-established API

A well-established product is often described as having been on the market for more than 10 years and whose patent has expired. Topical formulations may present an attractive alternative mode of delivery of the API which may not have been considered or developed during the patent exclusivity period for the original indication. A topical may also be associated with a target condition not considered under the original marketing authorisation and its variations. Often, the data requirements for these new formulations may be less extensive than for NCEs. These are often called hybrid applications where data already used in previous applications can be referred to via a derogation. This often involves pre-clinical toxicology and safety in man considerations. Consultation with a regulatory authority is recommended prior to launching a development programme in these instances.

For a well-established API which has never been delivered dermally in an indication that has already been licensed for other formulations with API, proof of efficacy and safety data associated with the topical formulation may be required. A limited number of clinical trials (a single pivotal or two pivotal trials) may be needed to establish the benefit risk balance.

In the case of the development of a new topical formulation of a well-established API in a new indication, it is possible that Phase II and Phase III data will be needed to establish proof of concept and benefit risk balance for a marketing authorisation application. If for example the indication is in an Orphan Condition then limited data considerations in the form of small trials will be consideration.

Alternative topical formulations to well-established topical APIs may present therapeutic advantages and a major contribution to patient care may need a pivotal Phase III data to establish therapeutic equivalence or superiority. In the case where a generic topical formulation is being produced of a well-established topical API a therapeutic equivalence trial with the comparison to the original formulation will be needed in most onstances. These well-established APIs come under Title III Marketing Authorization Article 10(3) of EU Directive 2001/83 (Directive, 2001/83/EC) which states:

> "3. In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-á-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided."

The EMA website provides a Guidance document regarding generic topical API formulations; see Note for Guidance on Local Acting and Locally Applied Agents (CPMP/EWP/239/95, 1995). If what is sought is a generic substitution then a therapeutic equivalence study may be needed to establish essential

similarity to the original topical product. The type of skin condition and the validated parameters for measuring therapeutic effect(s) can then be chosen and the statistical modelling built on these assumptions.

2.2.1. Guidance regarding legal basis for marketing authorisation application submission

Regulatory advice should be sought regarding the legal basis for the submission of a marketing authorisation application from a National Competent Authority such as the Medicines Healthcare Regulatory Authority, or other European National Authority, EMA or the FDA. The following cases below are examples of potential scenarios and the legal basis for submission.

Submission under Section 8(3) Title III Marketing Authorizations of EU Directive 2001/83.

This section of the legislation is generally used when developing a New Chemical Entity or a new topical formulation for an existent API where no topical formulation exists. Both situations will require different submission packages.

In the case of a New Chemical Entity the applicant will need a complete submission package covering the pharmaceutical manufacturing of the API and its packaging, a toxicology section (non-clinical studies) and clinical studies for safety and efficacy.

In the case of an established API where a topical formulation has never been authorised the applicant can consider a hybrid application. In this case the applicant can refer to data used in previous applications for market authorisation and supplement the submission document with new data generated specifically concerning the topical formulation. Considerations regarding the manufacturing of API, toxicology data and clinical safety data can be cross-referenced. New data specific to the manufacture of the topical formulation as well as toxicology data and efficacy and safety data specific to the topical formulation will in most instances need to be generated to supplement the submission. This later case is often called a hybrid submission.

Hybrid submissions are associated with applications for APIs, which have already obtained a market authorisation or are well-established. Companies, considering developing a topical formulation for an API which is already licensed should consider discussing development and data requirements with a National Competent Authority in the Europe (a Member State or EMA) and the FDA for the USA. The legal basis for submission can be in Europe as discussed above an Article 8(3) when a new topical formulation for an existent API or Article 10(3) for a generic formulation of an established licensed topical API. In this later case data requirements will be more limited and generally a therapeutic equivalence study will be needed.

Guidance on this type of trial can be obtained on the EMA website Guideline on the choice of the Non-inferiority Margin EMEA/CPMP/EWP/2158/99 and Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) CPMP/EWP/280/96.

3. Conclusions

In this article the potential routes to registration of topical formulations have been reviewed, with emphasis on known molecules or APIs. The various abridged routes available for development of topical formulations are discussed. Those interested in developing topicals either as generic substitution or as a new formulation of an off-patent molecule should give careful consideration to the legal basis for submission in the different world regions (such as EU, US and Japan). This will determine the type of data that needs to be supplied which will vary accordingly. In the EU, the legal basis and data requirements for registration are defined by EU Directive 2001/83. Extensive Guidance which type of trial design and parameters are considered adequate is provided by the EMA website. In some instances national authorities, for example, French Drug Agency AFSSAPS, German Drug Agency BfArM may in addition have national requirements which should be consulted. Developers are encouraged to seek scientific advice with the concerned National Regulatory Authority or with the EMA.

Consideration of the science and these issues at an early stage of development planning should be approached with great care so that investment and resource is adequately targeted to ensure success in obtaining a registration.

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