

# Challenges Encountered in Dermatologic Drug Development

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**Abstract.** Few truly new drugs are developed primarily for the treatment of dermatologic diseases. We discuss challenges and special considerations of dermatology drug development which contribute to this relative absence of novel drugs in dermatology. The issues considered are: a) the economic potential of dermatologic drugs including the potential return on investment (ROI); b) the benefit-to-risk ratio for treatments of skin disease; c) the relative absence of surrogate end points for topically applied drugs; d) drug penetration and vehicles; e) shelf life, stability, emulsifiers, preservatives; f) contact irritancy, contact allergy, contact photoallergy and photocarcinogenicity; g) drugs with more than one active; h) semi-quantitative or soft primary end points; i) inadequate basic knowledge of pathophysiology of skin diseases. Of the many challenges, we conclude it is the low economic potential or ROI available with skin disease treatments which inhibits the creation of novel therapies for dermatologic disease.

**Key words:** economic potential, dermatologic treatments, investment.

## LOS DESAFÍOS QUE SE ENCUENTRAN EN EL DESARROLLO DE FÁRMACOS DERMATOLÓGICOS

**Resumen.** Para el tratamiento de enfermedades cutáneas se desarrollan muy pocos fármacos verdaderamente novedosos. En esta revisión discutimos los desafíos y las consideraciones especiales del desarrollo de fármacos dermatológicos que contribuyen a esta relativa falta de fármacos novedosos en dermatología.

Las cuestiones que se consideran son: a) el potencial económico de los fármacos dermatológicos, incluyendo la rentabilidad potencial de la inversión; b) el cociente beneficio-riesgo para los tratamientos de las enfermedades cutáneas; c) la relativa falta de criterios indirectos de valoración; d) la penetración de los fármacos y los vehículos; e) el periodo de validez, la estabilidad, los emulsionantes y los conservantes; f) la irritación de contacto, la alergia de contacto, la fotoalergia de contacto y la fotocarcinogenia; g) los fármacos con más de un principio activo; h) los criterios de valoración semicuantitativos o cualitativos; e i) el conocimiento básico inadecuado sobre la fisiopatología de las enfermedades cutáneas. De todos los retos, el que más dificulta la creación de terapias novedosas para las enfermedades cutáneas es el bajo potencial económico o la rentabilidad de la inversión disponible con los tratamientos para enfermedades cutáneas.

**Palabras clave:** potencial económico, tratamientos dermatológicos, inversión.

While physicians are experts in prescribing therapy for their patients, most physicians are unaware of the details of how these products are brought to market or what their “regulatory classification” might be. For example, the dermatologist realizes that devices such as lasers and phototherapy machines are not drugs. However, few physicians would be totally aware that by regulatory definition devices while used to treat, diagnose or prevent disease must produce their effect by physical, not chemical means. What is also confusing is that we have a category of “drugs”

known as biologicals. From a regulatory point-of-view these agents are not drugs but rather are biologic agents sometimes referred to as “biological drugs”, a category based on factors such as the method of their production (by living organisms or living systems such as cells and animals) and their molecular complexity. To avoid this confusion, most pharmaceutical companies refer to drugs as “small molecules” and biologicals as “large molecules (suggesting that their effects are similar but their structure is different). It may also not be realized that in many countries most of the products available without prescription or over-the-counter, are also drugs or so called non-prescription drugs. In the United States (US) sunscreens are categorized as drugs while in many countries they are

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categorized in the less strictly regulated cosmetic category. The line between cosmetics, which are regulated in a much less rigorous way, and other over-the-counter products is also not totally clear to most dermatologists. This blurriness is especially notable in the category of agents known by dermatologists as cosmeceuticals or functional cosmetics. The “cosmeceutical designation” is not recognized as a category by US law and consequently the FDA considers these products to be cosmetics. However the regulatory agencies of some countries do recognize the cosmeceutical category but refer to these products as functional cosmetics or quasi-drugs. Supplements also referred to as nutraceuticals, tend to be recognized by physicians as clearly in the non-drug category although for patients the line is far less clear. All of this, in order to emphasize and clarify that this discussion is related to the special challenges of developing dermatologic drugs including biologics.

Toward that end this discussion will deal with special considerations in the following general categories:

1. The economic potential of dermatologic drugs including the potential return on investment (ROI).
2. The benefit- to- risk ratio for treatments of skin disease.
3. The relative absence of surrogate end points for topically applied drugs.
4. Drug penetration and vehicles.
5. Shelf life, stability, emulsifiers, preservatives.
6. Contact irritancy, contact allergy, contact photoallergy and photocarcinogenicity.
7. Drugs with more than one active.
8. Semi-quantitative or soft primary end points.
9. Inadequate basic knowledge of pathophysiology of skin diseases.

## The Economic Potential of Dermatologic Drugs

Because the market for dermatologic drugs (especially topicals) is relatively small, few companies undertake the development of truly new drugs (specifically new chemical entities) aimed solely or even partly at the treatment of skin disease. This has been especially true for the past two to three decades during which the primary strategy of the large pharmaceutical companies, so called big Pharma, has been the identification and development of new drugs which have potential sales of US\$ 1 billion or more. Commonly referred to as “blockbusters”, these drugs have provided the economic base of the industry and justified the high cost and long time (> 800 million US\$ and 15 years) needed to develop new drugs<sup>1</sup>. Drugs for cancers, heart disease and other “serious” or life-threatening diseases have generally produced the greatest revenues. For example, the

top two selling drugs in the United States for 2007 were both from the cardiovascular category; Lipitor® (Atorvastatin) global sales were US\$13.7 billion and Plavix® (Clopidogrel) global sales were US\$ 8.1 billion<sup>2</sup>, interestingly some of these blockbuster drugs for cancers and other life threatening diseases were originally approved as orphan drugs because their market potential was considered to be so small. Yet, Rituxan® (Rituximab) for Non-Hodgkin’s Lymphoma and Epogen (Epoetin Alfa) for the anemia of renal failure went on to achieve sales in 2004 of \$ 1.6 billion and \$2.6 billion/year respectively<sup>3</sup>. Another category of agents which have produced blockbuster revenues are some of the biologics with their unique mechanisms of action. Since 2007, Enbrel® (Etanercept) sales were US\$15.5 billion and Remicade® (Infliximab) sales were US\$ 5.3 billion globally<sup>3</sup>. Presumably, a significant portion of these sales were for the dermatologic condition psoriasis and as such the biologics may represent a category of drugs in which the ROI for dermatologics is attractive enough to stimulate development of agents for purely dermatologic uses.

However, biologics are an exception as most drugs for dermatologic diseases produce fairly low revenues even when the number of potential patients is large. For example the only two topical drugs that surpassed the US\$ 200 million mark in 2007 were Aldara® (Imiquimod) and BenzaClin® (Clindamycin 1%, Benzoyl peroxide 5%)<sup>4</sup>. These drugs are indicated for the treatment of Actinic Keratoses, basal cell carcinoma, or genital warts and acne vulgaris, respectively<sup>5,6</sup>. Accutane, an oral drug for severe acne, achieved one of the highest annual sales totals in the dermatology product category with peak US sales of \$580 million in 2000<sup>7,8</sup>. Some categories of drugs such as oral antifungals and topical antibacterials which are used by dermatologists as well as many other physicians are also able to attain sales in the US\$ 500 million range. However the products that are exclusive to dermatology rarely command annual sales of over US\$ 100 million. In fact, the large majority of these products have annual sales below the US\$ 50 million mark<sup>9</sup>.

For this reason, few truly unique drugs or biologics are developed with the primary aim of treating dermatologic diseases. Most often the dermatologic indication is developed after a drug is marketed for another indication and is found secondarily to be effective for a skin condition. In some instances agents are found to be too toxic to make it to market by the oral or systemic route for treatment. In such circumstances, dermal penetration may be evaluated to assess safety and efficacy. If both measures are successful, the potential drug is, by default, pursued as a topical therapy. The basic question that has rarely been addressed is “what accounts for this situation of dermatologic drugs producing such relatively low revenues?”. In some cases the small number of people having a certain dermatologic dis-

ease such as xeroderma pigmentosum, might be the explanation. However many skin diseases are in fact among the most common of all diseases. For example, acne occurs in almost all adolescents in various severity levels and seborrheic dermatitis (including dandruff) is also extraordinarily common. Although not formally investigated, it would appear that the perceived unimportance of the common skin conditions somehow results in the drugs' inability to command reimbursement that yields an ROI that encourages investment in unique drugs for dermatologic conditions. Whatever the cause or causes, the end result is that the potential revenue from dermatological drug sales is not sufficient to stimulate or economically justify the large cost of developing new and novel drugs.

### The Benefit-to-Risk Ratio of Dermatologic Drugs

The benefit-to-risk ratio is a concept which is a normal but informal calculus in the physician's thinking and evaluation of therapeutic and preventive interventions. It is however a highly formalized element of the drug regulatory and approval process. The phrase is obviously an attempt to apply or suggest a mathematical precision to a highly subjective process in which various values of regulators, lawyers, physicians, scientists, lawmakers, businessmen and public interest groups are synthesized into binding judgments as to whether and how a drug will be allowed to be made available for sale for the treatment or prevention of disease. For example, people with terminal cancer most often have a different view of the ratio than advisory committees. The AIDS community was notably successful at changing the regulatory calculus in the late 1980s and early 1990s. The AIDS community's activism even led to new regulations which allowed FDA approval ahead of formal phase 3 studies. As suggested above the benefit-to-risk ratio is a considerable hurdle to the approval of drugs for non-life threatening conditions such as dermatologic disease. Most people cannot conceive of a skin disease other than the common afflictions such as acne, dandruff, childhood rashes and poison ivy. And, unfortunately, many physicians other than dermatologists tend to be dismissive of skin disease. Because skin disease does not kill or obviously cripple, it is easily underrated in the conference rooms where decisions about the benefit-to-risk ratio and regulatory approval are made. Hence, not viewing that treating skin diseases and skin symptoms offers a great quality of life benefit, the regulatory tolerance for toxicities and side effects is much lower than it is for diseases which kill, cripple or cause more clearly dramatic and identifiable morbidity.

Compounding this situation at the moment is the higher level of pre-approval safety concern as a result of the

recent withdrawals of Vioxx® and other drugs from the US market. This will tip the balance of the risk-benefit ratio even further against products for non-life threatening conditions.

### Relative Absence of Surrogate End Points for Topically Applied Drugs

This issue affects the development of topically applied drugs, both new and generic. In order to appreciate or understand the specific challenges for generic topical drugs one must be aware of the fairly easy regulatory pathway deliberately created to make generic drugs readily available with the minimum of development costs. To obtain regulatory approval, systemic generic drugs do not have to undergo costly clinical trials proving that the generic drug is effective at treating the intended disease. Rather, oral generic drugs are approved based on demonstrating that blood levels of the oral generic are more or less ( $\pm 20\%$ ) the same as the blood levels of the pioneer or original drug. Thus blood levels, not clinical efficacy, are measured. This creates a disparity between oral and topical drug development costs as it is far less costly to conduct a blood level equivalency test than it is to conduct a clinical trial that assesses product efficacy. This does not mean that the regulatory standards are different for topical drugs, but rather that the methods of demonstrating bioequivalence is more complicated and thus more costly for topical drugs. For example, the cost per subject of studies that evaluate the topical treatment and improvement of disease are in the range of US\$ 6,000 to \$ 12,000 when multiplied by the high number (1000+) of subjects required to attain success of a specific clinical endpoint, such studies may cost millions of dollars (Angulo D. Senior Director of Clinical Operations, Stiefel, a GSK Company. Research Triangle Park, NC, Personal Communication, 28 May 2009). By contrast, studies to prove equivalent blood levels cost only a few hundred dollars per subject. By their nature, most topical treatments are not intended to act systemically; thus, blood levels are not even desired and are therefore not a useful substitute or surrogate end point. Topical generics have the special problem of having to be proven to be bioequivalent by costly clinical trials showing efficacy in subjects with the indicated condition, e.g. acne or impetigo, as were needed for the pioneer or original drug. The vasoconstrictor assay end point is a major exception to the general lack of surrogate endpoints in topical drug development<sup>10</sup>. With the recent exception of topical generic steroids for treatment on the scalp, vasoconstriction of normal skin in response to application of a corticosteroid has proven to be an acceptable surrogate for approval of topical anti-inflammatory corticosteroid generics. Many attempts to find other surrogate end-points for topical

treatments, such as measuring the amount of drug in stratum corneum samples stripped by pressure sensitive tape, have unfortunately not yet proven sufficiently reproducible to allow their use as surrogates in developing topical drugs<sup>11</sup>. For completeness in thinking about surrogate end points for regulatory approval it should be noted that in some situations even new oral agents are approved based on what are essentially surrogate end points. For example, reduction in cholesterol blood levels is sufficient for approval of drugs whose real aim is the treatment of cardiovascular disease. This would be similar to approving a drug for the treatment of psoriasis that had only proved that it reduced the proliferation of epidermal cells. In any event, the absence of widely applicable surrogate end points is a special burden for generic topical dermatologic drugs.

## Drug Penetration and Vehicles

Topically applied dermatologic drugs need to reach the site they are intended to treat which is usually below the stratum corneum. Unlike the gut, the principle function of the stratum corneum is to prevent penetration into the body and this is a special problem for developing dermatologic drugs. Penetration is needed in sufficient amount to affect the local skin condition but not in amounts that may reach the blood and have systemic effects. The carrier or vehicle of an agent may enhance or retard skin penetration and while the vehicle's effect on penetration is an important consideration the dermatologic drug developer must also produce a product that is sufficiently elegant that it will be applied by patients. Although a sense of cosmetic elegance can be obtained from testing on normal skin, the absence of surrogate end points makes it difficult to deeply evaluate the relationships between elegance and penetration at an acceptable cost. In vitro penetration studies using ex vivo skin specimens or tissue engineered skin systems are used to help evaluate the penetrability of potential topical drugs in various vehicles in the initial or screening stages of development. However, ultimately more costly clinical studies of the agent in various vehicles on normal and diseased skin are needed, especially since diseased skin is physiologically different from healthy skin. Also unique to topicals is the rather large therapeutic effect produced by some vehicles alone. Excipients such as petrolatum, glycerin, and dimethicone are known to improve skin barrier function which may contribute to enhanced clinical outcomes for both the active drug and "placebo" groups. This represents an additional challenge to the regulatory requirement of proving significantly greater efficacy of active over placebo. Conversely, the effect of oral placebo agents is usually independent of a known physical effect. Hence, while topically applied agents offer significant advantages, they pose unique de-

velopment challenges which account for not only fewer dermatologic drugs but also for a relatively low level of optimization. For example, because the skin responds to topical placebos, trials require larger numbers of subjects. Therefore, it becomes cost prohibitive to undertake a sufficient number of trials to determine optimal dose and frequency of application.

## Shelf Life, Stability, Emulsifiers, Preservatives

Although the need to have a sufficient shelf life is not unique, certain related features are distinct to the dermatologic topical drugs. For example, for purposes of cosmetic acceptance and in some cases penetration, many vehicles contain both oil(s) and water. In order to allow oil and water to mix, one or several chemical emulsifiers are often necessary. Such emulsions are apt to become unstable over time or with extreme heat which causes the oil and water containing vehicle or mixture to "breakdown" or separate into its separate water and oil components. Another problem is occasioned by having water in the vehicle. The presence of water in the preparation allows for the possibility of bacterial or fungal growth within the vehicle especially as when applied from tubes, jars and other multi-dose containers for which contamination from the outside is possible. To combat these problems, water containing and other vehicles must often have antimicrobial or so called preservative chemicals. Hence, not only is the development of a vehicle complex from the point of view of drug delivery and stability but also because of the many chemicals involved from the point of view of allergy and irritancy. Each of the preservatives and emulsifiers will cause contact allergy in some people. The challenge is to avoid high concentrations that may prove to be irritants; however, too little will result in the product's becoming microbially contaminated presenting the risk of causing skin infections and impaired product integrity<sup>12</sup>. All of these factors are distinct to the creation of topical drugs and pose a set of problems and costs which serve as challenges to the creation of dermatologicals.

## Contact irritancy, contact allergy, contact photoallergy and photocarcinogenicity

Testing both in animals and humans is required by regulation to ensure sufficiently low levels of contact allergy and irritancy in all new topically applied drugs (both new chemical entities and new excipients). Especially with agents which absorb ultraviolet (UV) light, testing for photoallergy will also be needed. By contrast, contact

allergy and irritancy and photocontact testing is generally not required for orally administered drugs. In addition, at least in the US, all new topical drugs and new excipients that are expected to be used for significant periods of time must be evaluated for their potential to cause cancer when on the skin and exposed to sunlight. This includes active pharmaceutical ingredients (APIs) and vehicles which do not absorb light. In particular, topical vehicles are believed to have the potential to alter the way UV and other portions of the light spectrum interact with or penetrate the skin even in the absence of absorption. Although testing in bacteria may help detect potential problems early and at relatively low expense, those passing these screens need to be studied in animals, usually rats. These studies are such that from conception/initiation to completion/analysis they actually take between 3 to 4 years. The cost is in the US\$2 to 3 million range. Again, this is a cost and effort unique to the development of topical dermatologic drugs. Hence topical dermatologic drug development incurs the special costs of testing for contact allergy and irritancy and of photcontact allergy and carcinogenicity and photocarcinogenicity.

## Drugs with More than One Active

For products with more than one active agent, regulatory agencies require that each agent (or active) provide a unique contribution to the product's efficacy. That is the combined efficacy must be greater than any one or combination of the other agents alone. This requirement is not unique or restricted to dermatologic drugs, but is a general requirement for combination drug products. However, because topicals can act locally, certain combinations are far more likely to be desirable in topical dermatologies than in oral agents. For example, the combination of an anti-inflammatory corticosteroid with an anti-infective is very appealing as a topical but is a combination which would be much less likely to appeal if the steroid was to be given systemically. The burden of development for such combinations is considerable. For example, to study the combination of betamethasone dipropionate and calcipotriene (Taclonex<sup>®</sup>) four arms, betamethasone dipropionate alone, calcipotriene alone, vehicle, and combination of Betamethasone and Calcipotriene (Taclonex<sup>®</sup>) must be studied. The studies usually need to be quite large resulting in significant development costs. Adding another level of complexity is the fact that when added to one another in a single topical vehicle, the active agents are delivered at reduced concentrations to the stratum corneum. This is a very common strategy in dermatologic treatment regimens which is evidenced by the number of topical combination products, such as Duac<sup>®</sup> (Clindamycin Phosphate/Benzoyl Peroxide), Tri-luma<sup>®</sup> (Fluocinolone acetonide/Hydroquinone/Tretinoin), Lotrisone<sup>®</sup> (Clotrimazole/Bet-

amethasone Dipropionate), Acanya<sup>®</sup> (Clindamycin Phosphate/Benzoyl Peroxide), EpiDuo<sup>®</sup> (Adapalene/Benzoyl Peroxide), and Ziana<sup>®</sup> (Clindamycin/Tretinoin)

## Semi Quantitative or Soft Primary End Points

Many of the most medically important end points used in studying the efficacy of agents for dermatologic disease, such as the amount or intensity of symptoms such as pruritus or signs such as redness or scaling, are difficult if not impossible to measure by objective means. That is their measurement requires subjective assessment which may contribute to greater variability. This also increases the number of subjects required in the trial due to the need to accommodate wider statistical variability. Even measures such as the extent or percentage of the body involved (e.g. psoriasis) are not made mechanically or with totally reproducible methodologies. Counting of lesions, such as inflammatory papules in acne studies, is clearly subject to many variables such as when a lesion is visibly clear or minimally present. Such imprecision of end point detection and measurement forces studies of treatments for these conditions to utilize a larger number of subjects, requires a documented training of the various investigators and generally results in higher cost than would be encountered in developing other agents with objective end points (e.g. serum cholesterol levels). Also contributing to this general problem, at least with regard to the development of topicals, is the imprecise nature of the amount of an agent that is applied to a given surface area on each occasion and other variables such as absorption through diseased skin in various stages and at differing body sites. While the degree to which such factors affect dermatologic drug development has not been fully elucidated, they are clearly special challenges not encountered in developing drugs for many other organs.

## Inadequate Basic Knowledge of Pathophysiology of Skin Diseases

While knowledge of the pathophysiologic basis of disease may be an important element in the development of medical treatments for diseases of most organs it is no more or less significant for the development of drugs for skin disease. However, it is clearly true that the amount of funding and the number of investigators working on developing the fundamental pathophysiologic knowledge needed to identify targets and strategies for new drug development is lower in the skin disease area than many other areas. The disparate numbers of investigators is most pronounced when comparing skin disease with heart disease, cancer

and neurologic disease. However, this difference does not reflect inherent difficulty in studying skin disease as much as it probably reflects a societal (governmental) judgment as to where such investments will best “pay off” and, in the case of private enterprise, the ROI. As discussed earlier, this reflects a social judgment as to the value of treating skin diseases versus the value of treating other diseases.

## Summary

As discussed above there are a significant number of unique or unusual challenges associated with the development of drugs for the treatment of dermatologic or skin disease. While perhaps the numeric majority of these challenges are related to the development of topical treatments some of them, such as the soft end points, benefit-to-risk ratio and the ROI, apply equally to topicals and systemics and are more related to the therapeutic area than the modality of treatment. Since, perhaps with the exception of the benefit-to-risk ratio problem, all of these challenges can be overcome it might be legitimately pointed out that they can mostly be thought of as only adding cost to the process of developing drugs for skin disease. With that in mind we might conclude that the major challenge or special problem for development of drugs for dermatologic diseases is the low economic potential or ROI available with skin disease treatments. This does create an opportunity to challenge academia, governments and the private sector to look for ways to reduce the cost of these challenges specific to these development programs so that we

can continue to assure the creation of novel therapies for skin diseases.

## Conflicts of interest

Dr. Eaglstein, Cash and Corcoran have professional relationship with Stiefel, a GSK Company.

## References

1. DiMasi JA, Hansen RW, Grabowski HG. The Price of Innovation: New Estimates of Drug Development Costs. *J Health Economics*. 2003;22:151-85.
2. *Med Ad News*. 2008.
3. *The Wall Street Journal*. November; 2005.
4. IMS Health Data; 2008.
5. Aldara® (imiquimod) Cream, 5% [prescribing information], Graceway Pharmaceuticals, LLC. Bristol, TN. Revised-April 2009.
6. BenzaClin® (clindamycin 1%, benzoyl peroxide 5%) Topical Gel [prescribing information]. Dermik Laboratories, a business of Sanofi-Aventis U.S. LLC. Bridgewater, NJ © 2009.
7. Accutane (isotretinoin) capsules [prescribing information]. Roche Laboratories, Inc., Nutley, NJ. Revised November 2008.
8. MIDAS, IMS Health, 2008.
9. IMS Health Data; 2008
10. Mackenzie AW. Method for comparing percutaneous absorption of steroids. *Arch Dermatol*. 1964;86:608-10.
11. Navidi W, Hutchinson A, N'Dri-Stempfer B, Bunge A. Determining bioequivalence of topical dermatological drug products by tape-stripping. *J Pharmacokinet Pharmacodyn*. 2008;35:337-48.
12. Hughes-Formella B, Bucks D. Topical drug development: Formulation through Preclinic. *World Pharma Network*; 2007.