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Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products

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Abstract

Dermatologic diseases can present in varying forms and severity, ranging from the individual lesion and up to almost total skin involvement. Pharmacokinetic assessment of topical drug products has previously been plagued by bioanalytical assay limitations and the lack of a standardized study design. Since the mid-1990's the US Food and Drug Administration has developed and implemented a pharmacokinetic maximal usage trial (MUsT) design to help address these issues. The MUsT design takes into account the following elements: the enrollment of patients rather than normal volunteers, the frequency of dosing, duration of dosing, use of highest proposed strength, total involved surface area to be treated at one time, amount applied per square centimeter, application method and site preparation, product formulation, and use of a sensitive bioanalytical method that has been properly validated. This paper provides a perspective of pre-MUsT study designs and a discussion of the individual elements that make up a MUsT.

Keywords

Dermatology; Topical Drug Delivery; Absorption; Clinical Pharmacology; Maximal Use

Introduction

Dermatologic diseases are complex and present in varying forms and severity. Since these diseases are present in and manifested on the skin, they are usually treated by applying the drug topically to the target site. With the topical treatment, the general assumption, historically, was that the systemic absorption was generally low when compared to systemic administration. However, due to the compromised barrier properties of diseased skin, the topically applied drug can reach the systemic circulation and lead to systemic adverse effects. The classic example of this is hypothalamic-pituitary-adrenal axis suppression due to the use of potent topical corticosteroids.¹⁻³

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Since the mid-1970s, as part of the evaluation of any drug product, sponsors have been required to investigate the in vivo bioavailability of their products.^{4,5} For topically applied products, this has not always been possible due to limitations in analytical methods and an uncertainty in appropriate subject selection and trial design. In response to the regulatory need and the need to address questions from the pharmaceutical industry regarding appropriate trial design, the US Food and Drug Administration in the late 1990s internally developed and implemented a pharmacokinetic (PK) maximal usage trial (MUsT) design to address these issues. This trial design is also referred to as a maximal use PK trial. This paper provides a perspective of pre-MUsT study designs and presents a discussion of the individual elements that make up a MUsT.

Background

Dermatologic diseases are very common, with current estimates being that, at any time, 1 of 3 Americans has an active skin disease.⁶ Based on the 2004 estimates, for example, the prevalence of acne is reported as 50.2 million people, and the prevalence of contact dermatitis (allergic and irritant) is reported as 72.3 million people in the United States.⁶

Even though there was a regulatory requirement to do in vivo bioavailability and bioequivalency testing for any new drug product since the mid-1970s, before the early 1990s, most topical dermatologic products had little or no direct assessment of in vivo bioavailability.^{4,5} This was understandingly due to limitations in the analytical methods that precluded the measurement of systemic blood concentrations in all but a few cases. At that time, in vivo bioavailability assessment was done through head-to-head clinical trials, often involving hundreds of subjects for a prolonged duration. From a regulatory point of view, while the science of head-to-head clinical trials were well understood, they were also recognized as the least sensitive and least reproducible method of comparison among the 4 commonly used methods listed in Title 21 of the Code of Federal Regulations.⁷ When a suitable analytical method was available, the trials that were done were plagued by methodological issues, as there was neither a “standard” trial design nor an agreement on what design factors to include in such a trial.

The Concept of Maximal Usage

While systemic side effects can be identified in safety and efficacy clinical trials, these trials, by their very nature, are focused on the “broad middle” of the patient population in terms of disease severity. Recruitment of patients, for example, at the upper end of anticipated body surface area involvement was not a primary patient recruitment driver, even though these subjects would be the ones most likely to show systemic absorption in those few trials where in vivo plasma samples were collected. In the early 1990s, the Clinical Pharmacology Review Team, in conjunction with the Medical Team at the FDA, recognized that with improved analytical methods, detection of plasma concentrations in this subset was becoming more likely and that this information could be valuable from a systemic safety standpoint by helping to establish dosing recommendations.

By considering the general determinants of dermal absorption, the concept of a study designed to provide a focused evaluation of the most severely affected patients formed the

basis of a maximal use PK trial design. The purpose of this trial was to evaluate the systemic exposure under conditions that would maximize the *potential* for drug absorption in a manner consistent with anticipated clinical use of the product. In doing so, there is a “concentrated” evaluation of that group of patients who, because of the severity of their disease, would be most likely to have higher systemic exposure through their use of higher doses and frequency. These subjects would also be most vulnerable to systemic adverse events, which could be collected during the trial and used to augment the aforementioned data from the “middle” or “average” patient participating in the other clinical development trials (phase 2 and phase 3). In addition, the collected plasma samples would be analyzed, and the resulting in vivo data could be used to estimate a safety margin based on animal toxicity studies.

FDA's Current Recommendation for a Maximal Use PK Trial

Driven by advances in analytical methods in the mid-1990s, the FDA started to request PK trials under maximal use conditions as part of systemic safety evaluation for products. The design and phrase “maximal use conditions”—also referred to as “maximal use PK trial” or “MUSt”—was included in the 2005 “Draft Guidance for Industry: Acne Vulgaris—Developing Drugs for Treatment” and presented at numerous public meetings.⁸⁻¹¹

Since its initial formulation, the core elements of maximal use have remained basically unchanged, but different versions of a standard language template have been used. The current template language itself has flexibility written into it and should be seen as a starting-off point for discussions between the sponsor and the FDA:

A maximal use pharmacokinetic (PK) trial is conducted by obtaining adequate number of PK samples following administration of your to-be-marketed formulation. This trial should be conducted in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- Frequency of dosing
- Duration of dosing
- Use of highest proposed strength
- Total involved surface area to be treated at one time
- Amount applied per square centimeter
- Method of application/site preparation
- Sensitive and validated analytical method

Steps should be taken to ensure that the target patient population (age, gender, race, etc) is properly represented in the maximal use PK trial.

Design Elements of a Maximal Use PK Trial

The elements enumerated above in the current “standard language template” were chosen to optimize the drivers of systemic availability in vivo. Their selection was based both on the current understanding of dermal drug delivery and on what the “prior art” was in dermal bioavailability trial design. This section reviews the design elements of a maximal use PK trial and provides some examples for consideration on their implementation.

Subjects—The subjects to be enrolled in a maximal use PK trial, with rare exceptions, are patients with the dermatologic disease of interest at the upper range of disease severity as per desired clinical use, rather than healthy volunteers. The reason for using patients instead of healthy volunteers is that diseased skin is physiologically different from normal skin in terms of systemic drug absorption. Normal skin is a very efficient protective barrier to the environment and most external agents. Contrast this with psoriatic plaque, where normal skin structure is disrupted with the formation of scaly plaques that, while thick, may not be as efficient as the normal skin barrier. The difference between psoriatic and normal skin was demonstrated in a PK study for tazarotene between healthy subjects and patients with psoriasis. In a review of studies looking at the systemic absorption of tazarotene gel following topical administrations, the systemic bioavailability was about 1% in healthy subjects and about 5% in patients with psoriasis.¹² Admittedly a small percentage overall, but as tazarotene is a teratogen, an adequate determination of bioavailability is necessary for proper labeling.¹³ Another example is the difference in luliconazole exposure observed following administration of luliconazole cream, 1%, in subjects with tinea cruris (3.5 g applied to the groin, thigh, and abdomen) and healthy subjects (5 g applied to the groin and 5 g to the back). Even though a lower dose was applied, the mean C_{max} (peak concentration) and AUC (area under the curve) of luliconazole in subjects with tinea cruris were approximately 3.5- and 4.5-fold, respectively, higher compared to those in healthy subjects.¹⁴ These examples clearly show that a disrupted skin barrier can markedly affect permeation and, for this reason, it is the preferred setting for evaluating dermal absorption.

When the disease state spans a wide age range to include pediatric patients, the investigator can do either a single study or separate studies. Should the single-study option be chosen, a sufficient number of subjects across the range of ages should be enrolled in both populations. For example, should the target pediatric population span the ages of 12 to 17 years, then subjects should be enrolled down to age 12, not just at age 17. By the same token, a single subject at age 12 is not sufficient to represent the entire age range. As the surface area:volume ratio changes with age, the study should be designed to capture sufficient data to allow for proper evaluation. When separate studies are contemplated, they should be initiated first in adults. The results of such trials can then be used to either refine the study in the pediatric population or support a waiver of further in vivo PK studies in the pediatric population. The approval of such a waiver is based on many factors and is ultimately an individual review issue.

The FDA does consider exceptions from the need to use patients with the disease in question when a feature of the disease presentation is an unchanged skin structure, such as pigmentation disorders (either hypo- or hyperpigmentation). In these subjects, the skin cells

themselves are normal, only lacking the proper amount of melanin; thus, normal healthy subjects could be used. When normal subjects are contemplated in a maximal use trial, the sponsor is advised to confirm the appropriateness of the population with the FDA prior to study initiation.

With regard to the other intrinsic subject factors (eg, age, race, sex), they should reflect both the distribution of the disease in the population and the demographic makeup of the United States—for example, a maximal use study in all South Asian males, even for a male-only indication (eg, male pattern baldness), would not be accepted, as it does not reflect the ethnic diversity of the US population. As to the number of subjects, the FDA's 2005 “Draft Guidance for Industry: Acne Vulgaris” provides that “an adequate number” of subjects be evaluated.¹¹ In general, the agency recommends, for any PK trial, that a sufficient number of subjects be enrolled to get estimates of the PK parameters. For orally administered drug products, this number can “usually” range from 12 to 36 subjects, depending on the observed variability. For topically applied products, where there is less information available and for which crossover designs are not feasible, a correspondingly larger number of subjects will be required. Sponsors are encouraged to discuss this element of the trial design with the FDA prior to study initiation.

Frequency of Dosing—The frequency of drug dosing in a maximal use PK trial should be consistent with the anticipated clinical use and proposed labeling. For example, if the sponsor anticipate their label to state that the topical product is to be used 2 to 3 times a day, then the maximal use PK trial should be conducted by applying the product 3 times a day instead of twice a day. Single-dose studies are not appropriate, given that the dermal absorption process is slow relative to oral dosing—unless the intended dosing regimen is for single use as, for example, certain head lice products.

Duration of Dosing—The duration of the maximal use PK trial should be chosen to allow sufficient time for drug accumulation to occur. The time required to attain maximal plasma levels is complicated in that, with the use of topical products, the affected skin can revert to healthy skin, thus improving the barrier function. As noted in this paper, once the skin barrier function is reestablished, dermal absorption is expected to change; thus, it might not be feasible to use a drug's half-life as a guide to the time required to attain steady state. In addition, the time for drug to transit the formulation into the stratum corneum and down to the viable dermis may result in a prolonged “apparent” half-life (ie, flip-flop pharmacokinetics) where the lengthened absorption phase of the topical route provides a longer half-life estimate relative to that from other routes of administration. The duration of the trial is then driven by the anticipated clinical response rate of the skin based on earlier phase 2 trials. Thus, an attempt should be made to balance the duration needed to ensure attainment of maximal blood levels before significant resolution of the lesions occurs. Sampling at several time points throughout the trial may be needed to assess attainment of steady state and aid in interpretation of the results.

In addition, the duration of each application in the maximal use PK trial must reflect the anticipated duration that the drug will be applied. For example, most topical treatments for head lice are applied and retained on the hair and scalp for only a brief period.^{15,16} Dermal

delivery here is clearly not desired, as the pathogenic element is the lice infestation itself. All these agents are applied with clear direction regarding method of application, duration, and whether there is a need for occlusion. In this situation, the maximal use PK trials are conducted by applying the study drug for the specified duration under the exact settings as proposed for clinical use.

Use Highest Proposed Strength—If the sponsor intends to develop a topical product with multiple strengths, the maximal use PK trial is recommended to be conducted with the highest strength. In the absence of any evidence of an active transport mechanism for an applied drug, the penetration of the drug across diseased skin is under the influence of passive diffusion. By maximizing the amount of drug on the skin, we are facilitating the concentration gradient driving force from an area of high drug concentration to one of low drug concentration. As our objective is to produce in these subjects the maximum possible exposure, it follows then that the drug strength that is recommended in the maximal use PK trial represent the highest strength proposed for clinical use. Thus, if by using this highest strength we do not raise any systemic safety concerns or if its use does not result in detectable plasma levels, then it can be inferred that lower strengths would share these characteristics. The one exception to this inference would be if the lower strengths were formulated differently. In that case, where there is a change in the excipient system, an additional trial may be required. In all such instances, the investigator is strongly encouraged to consult with the FDA before embarking on a development program for guidance on trial design.

Total Involved Surface Area to Be Treated at One Time—For topically applied products, generally, the larger the surface area of application, the larger the amount of drug absorbed. For example, when applied to a 15% body surface area in patients with fine wrinkling and mottled hyperpigmentation, tazarotene cream resulted in systemic drug exposure that was 10 times higher than that of patients who applied the drug to the face only (~3%-4% body surface area).¹⁷ It follows then that the body surface area for application in the maximal use PK trial be at or near the upper limit as anticipated in the clinical use. Unfortunately, prior to the establishment of the maximal use trial paradigm, studies were submitted to the FDA where, for example, the intended clinical use was for up to 15% to 30% body surface area, but the submitted PK trial enrolled subjects with only 5% to 10% body surface area involvement.

Surface area does, of course, represent a special case such that it can be very small, as in the treatment of individual lesions (eg, actinic keratosis), or involve almost the total body (ie, sunscreens). For the treatment of such small and discrete surface areas, there is always the possibility that a MUSt can be waived, especially when prior information regarding the pharmacokinetics of other administration routes clearly indicates that even 100% absorption would not lead to measurable levels. At the other extreme, the ubiquitous nature of sunscreens and the recommendations for their use make in vivo absorption evaluation an important part of their safety determination—given that with sunscreens, though used properly (ie, applied to all exposed skin and replenished), almost total body coverage can be

obtained. Thus, even though sunscreens are applied to intact skin, the very nature of their use defines maximal use and highlights the importance of these studies.

Amount Applied per Square Centimeter—Among patients, there is an understandable desire to induce a quick therapeutic response, especially in situations where there are cosmetic ramifications. Thus, patients—often in their attempt to “speed things along”—use higher amounts than what are recommended. Even when a patient attempts to follow the labeled instructions, there is a subjective measure to “pea-sized” or “golf ball-sized” amounts. While one cannot feasibly test all possible amounts for application, the maximal use PK trial should attempt to capture such usage by incorporating patient training, observed application procedure (at least initially and prior to the final series of plasma sample collection), the use of weighed dispensing, and other logs of application.¹⁸ The amount applied can then be compared to those captured in phase 3 safety and efficacy trials when the results of the maximal use PK trial are being evaluated. While not an ideal collection method, this type of information is instructive when developing patient instructions in “plain language” as to amounts to be used.

Application Method and Site Preparation—For most dermatologic products, site preparation consists of washing with a mild cleanser and patting the area dry prior to drug application. However, for some indications, such as diabetic foot ulcer, the application method and site preparation can alter the absorption. The removal of loose or necrotic skin, the use of topical antiseptics, and overwraps/packing can promote or retard drug absorption in unpredictable ways. The use of harsh soaps and the overuse of the ubiquitous hand sanitizer solutions can affect the absorption of a topical dermatologic product due to their ability to remove the natural oils on the surface of the skin. Therefore, the application method and site preparation used in a maximal use trial should be the same as those being used in the phase 3 clinical trials and as intended for patient use, with minimal exposure to unaffected skin.

The location of the application site and its associated environmental factors are also critical, as certain sites (eg, face, scalp, axillae, groin, scrotum) may have much higher percutaneous drug absorption than the trunk and extremities.¹⁹ The impact of clothing materials and body heat can result in occlusive or semiocclusive conditions, especially in the groin and axillae areas, again increasing potential bioavailability. Where the area will be covered by clothing, subjects should be instructed about the amount of time to wait after application. In the case of tinea pedis, general care instructions—for example, to wear sandals or natural fiber socks—are to be consistent with the instructions given in the phase 3 clinical trials.

Sensitive and Validated Bioanalytical Method—As with any in vivo clinical pharmacology trial in which biological samples are collected, the need for a sensitive and properly validated bioanalytical method is a regulatory requirement. The FDA has long recognized this and has participated in workshops and publications with the scientific community focused on the validation of bioanalytical methods to include the parent drug (to establish bioavailability) and the metabolites (where indicated on the basis of toxicity). Without this confidence in the analytic methods used, one cannot have confidence in the parameter estimates derived from the collected PK samples, which calls into question the

prescribing and dosing recommendations that are based on them. The recent experience with CETERO Labs highlights the degree to which the FDA considers the integrity of analytic data to be paramount.²⁰ In the case of CETERO, the results of investigations by the FDA revealed a pattern of violations of good laboratory practices that were severe enough to call into question the results of bioavailability studies over a period of 5 years.²¹ Eventually, a phased resolution was reached wherein some studies had to be repeated while others could demonstrate analytical compliance via an FDA-developed road-map.²² The net result of this was a delay in some drug approvals that relied on CETERO data and the eventual bankruptcy of CETERO and its successor, PRACS Institute.²³ The lesson to be learned here is that a sound bioanalytical method and adherence to good laboratory practices is not an option and any deviation is done at the risk of both corporate reputation and corporate survival.

In conjunction with an appropriate bioanalytical method is the selection of a sampling paradigm sufficient to accomplish the objective. Standard PK parameters include such basic measurements as $AUC_{0-T_{last}}$ (zero to last measurable concentration), AUC_{0-inf} (zero to infinity), C_{max} , T_{max} (time to peak concentration), and k_{el} (elimination rate constant). In a multiple-dose study, the basic measurements are $AUC_{0-\tau}$ (where τ is the dosing interval), C_{max} , and T_{max} . For a topically administered drug product, the assessment of either C_{max} or T_{max} will be problematic due to the expected slow absorption phase, which will result in a generally broad, flat profile. Even so, the sampling design should take this into consideration and include sufficient samples at latter time points in an attempt to obtain these parameters.

In some cases, geometric serial sampling may be neither feasible nor appropriate (eg, in pediatrics). When a “reduced” sampling strategy is employed, the sampling times chosen for collection should be when drug concentrations are expected to occur. Ideally, the design of a sampling scheme is based on the anticipated concentration time profile for the product, according to prior experience from other populations (eg, on adult data in the case of pediatrics).

Formulation—The formulation used in the maximal use PK trial is to be identical to that used in the phase 3 clinical trial and that proposed for marketing. Drug bioavailability is highly formulation dependent for topical products, and a change in the formulation might alter the bioavailability. If the to-be-marketed formulation is different from the one evaluated under maximal use conditions, the sponsor would, in general, have to conduct a bridging study. The need for any type of bridging studies is evaluated on a case-by-case basis by the Agency—see “Guidance for Industry: Nonsterile Semisolid Dosage Forms. Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation.”²⁴ This guidance would help the sponsor determine the level of change when comparing 2 semisolid formulations and appropriate tests to demonstrate “sameness” between the 2 products.

Discussion

Normally, in conducting an experiment, the researcher holds all elements constant except for the one of interest, which is varied or excluded entirely to evaluate its impact on the system.

Here, with the maximal usage paradigm, we are turning this precept around and, instead, adjusting many factors to their maximum to elicit a response in the system (eg, absorption). As stated previously, the goal of the maximal use PK trial is not to focus on the “average” subject but rather to evaluate the population at the upper range of use that would be most likely to elicit plasma levels and systemic side effects. With our increased understanding of the mechanisms of dermal disease through an improved understanding of genetics and the microstructure of the skin, dermal drug research is undergoing a renaissance. New clinical trial designs, improved analytic techniques, and the explosion of interest in the use of biological agents have brought new interest into the realm of dermatology.

The maximal usage paradigm was borne out of regulatory interest and need: interest in that there was recognition that with improving analytical techniques, what was once impossible was becoming possible; need, in a regulatory sense, that the FDA has a mission to protect the public health by approving medications that are safe and effective. In the Code of Federal Regulations (Title 21 § 320.21),⁵ there is a requirement to which all new drug applications must submit either:

1. Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or
2. Information to permit FDA to waive the submission of evidence measuring in vivo bioavailability.

The regulations go on to discuss the various types of evidence that can be used to establish this information and how a waiver can be obtained. It is important to note that dermatologic drug products are not excluded from these regulations. The absence of this information prior to the mid-1990s was a reflection of both a lack of bioanalytical tools and a lack of understanding of the drivers of dermal absorption (diseased skin, surface area, strength, etc) as presented here.

Clinical pharmacology as a science has progressed greatly in the past few decades and has helped clinicians to unravel many therapeutic puzzles over this period. In some ways, dermatology represents the last big therapeutic frontier—one in which the tools are finally getting refined enough for us to bring them to bear on the issue of drug safety. The maximal use PK trial is focused on safety and not on efficacy, where the direct observation of the clinician remains paramount. The elements selected for evaluation were chosen with our current understanding of the interplay between drug, skin, and formulation and an expectation of either a concentration or exposure response relationship for adverse events. Other elements may be added, modified, or taken away from the design as our understanding increases and as utility of the information collected from this trial expands in the future.

Beyond animal toxicity extrapolations, one can see a potential use for the maximal use PK trial design in conjunction with other dermal quantification techniques, such as microdialysis²⁵ and dermal Raman spectroscopy,²⁶ both of which measure drug penetration into the dermal tissues rather than systemic circulation. The ultimate goal would be to link local drug concentrations in the skin layers to systemic exposure, with the aim of evaluating exposure-response for local and systemic safety and efficacy. The data from diffusion cells

based on cadaver skin suffers from the use of cadaveric skin that lacks a functioning microcirculation and the need to use intact (nondiseased) skin. The diffusion cell study could be used to compare in vitro performance across formulations where that with the least (or optimal) absorption could be selected to be tested early on in a proof-of-concept trial among patients. When diffusion cells are used, cadaveric or skin from cosmetic surgery procedures (eg, “tummy tucks”) is the preferred substrate. Synthetic membranes, although available and useful for pilot formulation development, do not replicate the skin with sufficient fidelity. Its use as a stand-alone quantification of in vivo bioavailability is not possible given its limitations vis-à-vis the absorption factors discussed in this paper.

It is quite possible that other factors that are clinically meaningful (eg, age, sun exposure) could eventually be evaluated in a head-to-head manner via the maximal use paradigm once additional data become available. In the future, with improved modeling tools, we may also be able to incorporate a deeper understanding of the recovery of the skin barrier function, which contributes to the efficacy determination.

Although a deeper understanding of systemic exposure is important for an investigational product's safety profile, the new drug evaluation process is ultimately a risk-benefit assessment. For a topically applied product, the presence of systemic exposure does not mean that an investigational product is unacceptable or nonapprovable; it does require, however, a thoughtful evaluation of its implications with regard to safety. From a clinical pharmacology perspective, then, the maximal use PK trial is a tool that can open the door to a better therapeutic understanding for safety and, potentially, efficacy. The time will come when we can resolve intradermal-intralesional levels and combine those data with improved biomarkers that are predictive of response. To that end, sponsors are strongly encouraged to discuss their development plans with regulatory authorities to appropriately design their maximal use PK trial to obtain the maximum regulatory benefit. Ultimately, the best tool in the world is useless without an understanding of its use and, most important, its limitations.

Summary of Factors

The maximal use PK trial contains in its design those factors that are expected to have the greatest impact on bioavailability. They were chosen on the basis of our understanding of the impact of disease on the skin's inherent barrier properties and on clinical pharmacology principles of drug absorption/formulation effects. It is designed as a flexible structure to allow for assessment of the maximum exposure of a topical investigational agent in an appropriate patient population. The trial is predicated such that maximum exposure generates the highest systemic concentration, which provides an objective assessment of systemic absorption. The systemic absorption of a topical investigational agent may cause systemic side effects, including drug-drug interactions, which can affect the safety profile. Beyond direct effects, the information generated by this trial design provides a link to animal toxicology results and allows one to do risk assessment that otherwise would not be possible. No matter how well designed a trial is, early and open communication with the FDA is the key to optimal implementation of a maximal use PK trial design and is strongly encouraged.

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