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Review

Current regulatory toxicology perspectives on the development of herbal medicines to prescription drug products in the United States

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ABSTRACT

Toxicological studies constitute an essential part of the effort in developing an herbal medicine into a drug product. The US food and drug administration (FDA) published a guidance to assist academic and industry sponsors in the development of this unique group of drug products, and has recently approved an new drug application (NDA) based on green tea extract (Veregen®) for topical treatment of genital and perianal warts. In this article, current regulatory views on issues related to requirements and recommendations on various types of nonclinical toxicity studies in support of clinical trials and filing an NDA for a herbal medicine, including pharm/tox aspects of green tea extract (Veregen®) NDA, are discussed. Topics include nonclinical pharmacology/toxicology perspectives on herbal nomenclature and its identification, previous human experience and initial clinical trial proposal, regulatory aspects of acute toxicity studies, chronic toxicity studies, mutagenicity studies, reproductive toxicity studies, and carcinogenicity studies on botanicals. Certain regulatory review-related issues are also presented. It is anticipated that through a proactive two-way communication between the Agency and the sponsor, toxicological development of botanical drug product can be significantly facilitated.

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1. Introduction

Herbal medicines have a long history of use among different ethnic groups, both as a means of alternative therapies and as food supplement. Based on regulations, when an herbal is claimed to cure, treat, or prevent human disease in the US market, it will be classified as a drug and the manufacturer is required to provide scientific evidence showing that the product is safe and efficacious in humans (Ref. FDA Document 1, Wu et al., 2000). Because of the unique characteristics and status involved in the use of herbal medicines as drugs, the US Food and Drug Administration (FDA) published a guidance document to assist academic and industry sponsors to streamline development (FDA Document 1). Ever since the guidance document was being drafted, a growing trend toward systematic study of the safety and effectiveness of herbal products through the Investigative New Drug application (IND) process has been documented (Chen et al., submitted for publication; Wu et al., 2000, 2004). With respect to nonclinical toxicological aspects of herbal drug product development, inquiries from sponsors are often made on issues related to the need of various types of toxicity studies in support of filing a New Drug Application (NDA) and the product registration. This review attempts to address current perspectives towards herbal nomenclature and nonclinical toxicology issues that have emerged over the past few years.

2. Importance of herbal nomenclature for botanical drug products

Traditional ethnoherbals have complex nomenclature that is based on different culture and historical backgrounds, especially when vernacular names are employed. Correct use of an herbal name would allow identification of known toxicity and activity. This is particularly true when traditional herbal practices could vary by factors such as: (1) the selection of certain herbs might have species substitutions that are permissible under historical convention, (2) complex preparatory processes are performed in treating raw plant or plant parts into clinically dispensable herbals (e.g., slices after frying or marinating with various excipients such as wine, honey or vinegar), and (3) multiple clinically dispensable herbals are combined into a formula for specific indications during practices. These factors clearly complicate the consistency of the final product makeup when the species names were not properly controlled, as demonstrated by well-known cases of serious nephrotoxic adverse events reported in the misuse of aristolochic acid containing herbal species (FDA Document 2). In order to avoid confusion caused by the use of vernacular or common names, we believe it is important to re-emphasize the importance of using pharmaceutical names that are based on the already established binomial Latin naming system (Greuter, 2000). The pharmaceutical name designated here may differ from that of herbal commerce, and is referred to those herbals that are subjected to regulatory review with an intent for drug use. It specifies a species name (with appropriate epithet included), the plant part, and sometimes the special preparatory process performed on the herb [e.g., Radix *Rehmanniae glutinosae* (Gaertn.) Libosch. ex Fisch. et Mey. Preparata] (Wu et al., 2007). Additionally, wild or cultivated growth condition should be indicated, as certain herbals may be included in the endangered species list under Endangered Species Act or Convention on International Trade in the Endangered Species of Wild Fauna and Flora (CITES) (Wu, 2002).

3. Waiver of toxicology studies for initial clinical trial on herbal medicine intended to be used as prescription drug

3.1. Previous human experience and existing animal toxicity data

The Agency's botanical guidance document provides a unique approach to lessening requirements for animal toxicology studies prior to the launch of initial testing in humans (Wu et al., 2000). The regulatory perspective for this measure allows the sponsor to conduct a well-designed Phase I/II trial to detect initial positive signals (e.g., using surrogate marker(s) for efficacy) without prior animal studies, thus constituting a waiver of toxicological studies for an initial clinical trial. Because ethnoherbal medicines have been used historically or are readily available in the current dietary supplement market, the "Previous Human Experience" as defined under federal regulations would play an important role in providing equivalent safety evidence in support of initial Phase I/II clinical trials, in addition to existing animal data for nonclinical support. In lieu of extensive literature and database searches, as often performed by the sponsor and FDA reviewers, for existing safety information in both humans and animals, risk/benefit may be assessed by comparing the dose, duration, and patient population of the proposed human trial with historical and current market experience. Thus, "Previous Human Experience" becomes more relevant when the dose of the herbal and the duration of the proposed clinical trial fall within the domain of those in historical use or the existing animal safety database.

3.2. The "Initial" clinical trial

In the Agency's botanical guidance document, the initial trial refers to a phase I/II trial that involves a limited number of patients and duration of treatment. In reality, initial trials often involve much longer treatment duration than would be expected in a typical phase I/II trial. This is particularly true when intended indication requires a sufficiently long treatment duration to show effects (e.g., $\geqslant$6 month for HIV, HCV or tuberculosis trials). Further, the dose proposed by the initial trial sometimes far exceeds that recommended historically or used under dietary supplement regulations, without supporting preclinical toxicology studies to provide safety margin estimates. Finally, the sample size of the study is relatively small and dose selection is somewhat arbitrary (without prior dose-ranging studies supported). These issues related to the initial trial design (i.e., trial duration, sample size, and dosage) may compromise the study, resulting in outcomes that may inadequately address the original question as to whether the herbal is efficacious, thus produce misleading conclusions about the pharmacologic effects of the herb. The above variables and factors could be part of the reasons why most of the herbal INDs submitted to the FDA become inactive, and do not progress to the advanced phases of drug development.

In summary, the "initial" clinical trial may be viewed from the regulatory toxicology perspective as indication dependent, and its adequacy of risk assessment should be determined on a case-by-case basis, pending relevancy and quality of existing human and/or animal safety data (Wu et al., 2008a).

4. Toxicological studies on herbal medicine supporting advanced clinical trials, NDA submission and premarketing approval for its intent as drug

If the initial trial shows promising results and the sponsor plans to proceed with expanded phase II or III trials, chronic and other toxicity studies in animals become important in that they would provide information on potential target organs of toxicity and a complete toxicity profile of the herbal medicine. However, if there were existing previous human experience or animal toxicity studies that could support a longer term clinical trial, the chronic animal toxicity studies may be waived depending on the availability and quality of the existing data. This issue will be evaluated on a case-by-case basis, with complete or bridging studies requested, as discussed below.

4.1. Acute toxicology studies

It is not necessary to conduct acute, single-dose toxicity studies in animals for herbal medicines being developed under IND, because they should have sufficient previous human experience and are often granted a waiver for toxicology studies before an initial clinical trial (see above).

4.2. Chronic toxicology studies

The duration of chronic animal toxicology studies would depend on the indication of the herbal and the length of the proposed clinical trial. In general, for a herbal indicated for 14 consecutive days or less of treatment duration, data from two 2-week toxicity studies are the minimum expected, one carried out in a rodent and the other in a nonrodent mammalian species, by the route(s) of administration intended for clinical use (FDA Documents 3, 4). For herbals indicated for more than 14 and less than 90 consecutive days of treatment duration, data from two 3-month chronic toxicity studies are expected, with again, a rodent and a nonrodent species. For herbals indicated for more than 90 consecutive days of treatment duration, data from two 6-month chronic toxicity studies are expected, with the same species requirements as addressed above. This 6-month study rule may apply to herbals indicated for (1) chronic intermittent drug exposure such as bacterial infections, erectile dysfunction, and herpes and (2) life-threatening diseases such as cancer chemotherapy in advanced disease or in adjuvant use (FDA Document 5).

4.3. Nine-month nonrodent mammalian toxicity studies

For herbals indicated for conditions other than those mentioned above and that are proposed for >90 consecutive days of treatment duration or for those that have not been shown to produce any significant toxicity in the 6-month or other rat studies, a 9-month, instead of 6-month, nonrodent mammalian study should be performed (FDA Documents 3, 4). This is for the purpose of ensuring that potential target organs of toxicity are fully explored. For example, the recently approved green tea extract ointment (Veregen®) NDA indicated for external genital and perianal warts contained a completed a 9-month dermal (topical) toxicity study (conducted in minipigs) in support of its marketing approval (FDA Document 6).

For an herbal NDA submitted under accelerated approval regulations, in which clinical trials employ surrogate markers and collect limited human safety data (e.g., anti-HIV), a 1-year, instead of 9-month, nonrodent mammalian chronic toxicity study is needed before NDA submission (FDA Document 5). Although recent analyses (e.g., on pesticides and some other molecular entities) may suggest that prolonging nonrodent study to one year may not provide added value to that obtained in the shorter term studies (Parkinson et al., 1995; Box and Spielmann, 2005). However, for human pharmaceuticals, it is Agency's current policy that additional safety information obtained from animals is expected to complement the limited amount of human safety information collected for accelerated approval (e.g., currently 6-month human safety database is being used for anti-HIV drugs that are registered under accelerated approval process) (FDA Document 7). In general, all toxicology studies are expected to be carried out under the Good Laboratory Practice (GLP) provisions.

4.4. Animal toxicokinetic and pharmacokinetic studies

Because of the complexity and diversity of chemical ingredients contained in herbal medicines, the botanical guidance document has not extensively addressed the preclinical requirements of pharmacokinetics or toxicokinetics. However, when known key chemical ingredient marker(s) are used for Chemistry Manufacturing and Control purposes, the sponsor should attempt to measure the markers whenever feasible in toxicity studies to help ensure that the animals are adequately exposed to the administered herbal. For instance, because epigallocatechin gallate (EGCg) is the known major chemical ingredient in the green tea extract, plasma levels and toxicokinetics of EGCg had been investigated in various chronic toxicity studies included in the Veregen® NDA (FDA Document 6).

Other pharmacokinetic studies that do not involve measurement of herbal chemical ingredients but could be considered useful include investigations related to (1) the inductive or inhibitory effects on P-glycoprotein drug transporters and hepatic P-450 or other drug metabolizing enzyme systems, and (2) herb–drug interactions (i.e., pharmacodynamic or pharmacokinetic synergistic, additive interactions on effects such as toxicity profile or drug levels). These investigations should be considered feasible because they relate to measurement of either drug metabolizing enzyme activities or interacted drug(s) used in combination therapy or ingested concomitantly with the herbal. The information obtained from these nonclinical studies should be helpful in predicting potential herb–drug interactions in humans.

4.5. Genotoxicity studies

Genotoxicity testing is designed to detect genetic damage such as gene mutations and chromosomal aberration, which may reflect teratogenic and tumorigenic potential of pharmaceuticals, including herbals. During the initial phase I/II studies, genotoxicity testing on herbal medicines is not required. When an herbal IND advances to phase III clinical trials, a battery of 3 tests, as described in the ICH documents (FDA Documents 4, 8–9) is required to be completed to assess genotoxic potential and fulfill final NDA requirements, regardless of indication. If one the three tests shows positive findings, alternative assays, if feasible, may be requested to determine whether those herbals intended for non-life-threatening conditions should be allowed to be studied in phase III trails. For a reference here, Ames test, in vivo rat micronucleus assay, UDS test, transgenic mouse mutation assay, and mouse lymphoma assay were completed for the Veregen® NDA (FDA Document 6).

Recently, ethical concerns have been raised over conducting Phase I/II clinical trials of new drug with positive genotoxicity findings in healthy volunteers. Although relevance of this issue depends on drug's indication, duration of treatment, and specific findings related to genotoxicity testing, the regulatory view toward it has been not to expose healthy subjects to genotoxic compounds unnecessarily in clinical trials. Thus, even though the botanical

guidance document states that genotoxicity testing is not required for an initial clinical trial, botanical drug sponsors should be encouraged to obtain this information early in product development because the testing is comparably cost-efficient (relative to animal toxicity studies) and could impact overall developmental plan (Wu et al., 2008b).

4.6. Reproductive toxicology studies

Unless there is compelling previous human experience or existing GLP data obtained on the herbal medicine, reproductive toxicity studies are needed to support advanced phase trials and the filing of an NDA. The requirements may be modified depending on the indication and patient population exposed to the herbal. For example, for herbals intended for prostate hypertrophy, teratology studies may be unnecessary. However, in regard to the recently approved green tea extract (Veregen® ointment) NDA for genital and perianal warts, reproductive toxicity studies (in rats) were performed through the intravaginal route of drug administration, in addition to several others via oral and subcutaneous, to further explore any potential reproductive risks under conditions similar to those expected in clinical practice (FDA Document 6).

In general, the assessment procedures for reproductive toxicology should follow those described in the guidance (FDA Documents 4, 10, 11), including assessment of the potential to affect fertility or early embryonic development to implantation, as well as teratology in both a rodent species and a mammalian nonrodent species, and effects on pre- and postnatal development, including maternal function.

4.7. Carcinogenicity studies

Two carcinogenicity studies should be performed for any herbal intended for use as drug for a duration that is continuous for >3 months or 6 months intermittently (FDA Documents 12–16). For shorter term treatment duration (e.g., <2 weeks in certain antibiotic therapies), carcinogenicity information is generally not needed for NDA filing. In the case of green tea extract (Veregen®) NDA, carcinogenicity study was performed because recommended treatment duration reaches 16 weeks. However, only one bioassay (via oral gavage route), instead of two, was completed for this NDA (FDA Document 6), because waiver for the second study was granted based on rationales that ample previous human experience on the drug substance exists and anticancer properties of the green tea are widely available in the literature.

For indications in which the life expectancy in the indicated population is expected to be short (e.g., <2–3 years in some patients with cancer), long-term carcinogenicity studies are usually not necessary. Thus, "anticancer" herbals with chemotherapeutic potential for treatment of advanced systemic disease do not generally need carcinogenicity studies. However, when treatment with a chemotherapeutic herbal becomes successful and life is significantly prolonged, there may be late concerns regarding the emergence of secondary cancers. When an herbal is intended for adjuvant therapy (such as antioxidant, free radical scavengers, or as immunity enhancers) in patients with cancer or for prolonged use in nonmalignant indications, carcinogenicity studies are also usually needed. In regard to those herbals proposed to be used frequently, in an intermittent manner in the treatment of chronic or recurrent conditions (such as flu prevention, allergic rhinitis), carcinogenicity studies are generally needed.

In addition to the waiver provided for the green tea extract (Veregen®) NDA (see above), other conditions that may be suited for a waiver of carcinogenicity studies are as follows: herbals that have (1) very limited systemic exposure without accumulation based on nonclinical and clinical pharmacokinetic data or (2) negative histopathology data from chronic toxicology studies at the maximal feasible dose, without any preneoplastic lesions and other toxicological effects, including genotoxicity, or (3) noncarcinogenic knowledge of other compounds in the same phytochemical class. When an alternative method (ie, CB6F1-TgHras2, p53 transgenic mouse, and the neonatal mouse model) to replace one of the 2-year bioassays is considered, a model sensitive to nongenotoxic carcinogenic events should be used when the herbal product is shown to be nongenotoxic, and an appropriate model should be chosen when a genotoxic herbal is to be evaluated. For example, carcinogenicity study included in the green tea extract (Veregen®) NDA was performed using a 26-week p53 transgenic mouse model, primarily due to positive mouse lymphoma mutation results (see Veregen® product labeling). The p53 mouse model is considered useful for identifying mutagenic carcinogens, and negative results from this bioassay may suggest the genotoxic herbal does not present a carcinogenic potential to humans through a p53-mediated mechanism (FDA Document 17).

In summary, the Review Division should be consulted if an alternative model is considered. It is especially helpful for the sponsor to request that the executive carcinogenicity assessment committee (EXEC CAC) review the protocol for such a study. Further, any waiver request for a carcinogenicity study or proposal for an alternative model may be submitted with its protocol, rationale, and justification to the Review Division and EXEC CAC for evaluation and discussion.

5. Regulatory toxicology review issues related to herbal medicine IND and NDA applications

5.1. Dosing and duration of the proposed initial clinical trial exceed those recommended traditionally/historically

As discussed earlier, some botanical IND sponsors proposed an excessively higher dose or longer duration of treatment than that used historically and traditionally. This generated safety concerns for the product because the usefulness and relevancy of previous human experience with the herbal to the proposed human protocol were diminished and resulted in requests for modification of the sponsor's clinical protocol by the Agency.

5.2. Claims of "nontoxicity", lack of information on target organ of toxicity, and unaddressed equivalency to daily amount of raw herbs used in traditional practice

When the herbal formulation is prepared through modern extraction methods, it is helpful to have information on equivalency of the proposed product to that used traditionally or historically in terms of the daily amount and dose recommended. This information would help alleviate concerns for the safety of human patients. It is also important to note that phrases such as "[the herbal] is virtually nontoxic" are often used in the presentation of INDs. Granting that toxicity is only a relative term, a sufficiently high dose and long duration of treatment would no doubt produce definitive toxic or side effects. Realistically, a clear toxicity profile and identified definitive target organs of toxicity in animals are most helpful for risk assessment and prediction of adverse events as the herbal is rigorously tested in humans.

5.3. Use of animal products and endangered species

In many traditional herbological practices, animal and mineral products are part of formulas dispensed. The regulatory approach to these products, although nonherbal, has been similar (FDA Document 1). They both share the same regulatory philosophy in

regard to concerns of safety and efficacy of the product. In recent years, animal parts obtained from the cow have appeared in botanical INDs, and concerns over bovine spongiform encephalopathy (BSE) have been raised. For these concerns, the sponsor has been required to provide assurance that the products are derived from BSE-free locations or the species that is endangered is obtained from cultivated sources.

6. Summary

In summary, the need for toxicology data in support of advanced human trials on herbal medicines under IND or NDA submissions requires adherence to the Agency's and ICH guidances for each respective toxicology study. However, it is advisable to consult the Review Division for examination of experimental designs and dose selection of the studies to be conducted. When compelling previous human experience or animal data relevant to the type of toxicity exist, a waiver of the related toxicology studies or bridging studies may be considered by the FDA on a case-by-case basis. In such circumstances, consultation with the Review Division are recommended to facilitate product development.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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