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Commentary

# Current regulatory perspectives on genotoxicity testing for botanical drug product development in the U.S.A.

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ABSTRACT

Genotoxicity testing is an important part of preclinical safety assessment of new drugs and is required prior to Phase I/II clinical trials. It is designed to detect genetic damage such as gene mutations and chromosomal aberration, which may be reflected in tumorigenic or heritable mutation potential of the drug. Botanical new drugs in the U.S. are entitled to a waiver for preclinical pharmacology/toxicology studies, including genotoxicity testing, in support of an initial clinical trial under IND, contingent on previous human experience. Recently, ethical concerns have been raised over conducting Phase I/II clinical trials of new drugs with positive genotoxicity findings in healthy volunteers. Although the relevance of this issue to patients, as opposed to healthy volunteers, depends on the drug's indication, duration of treatment, and specific findings related to the assays, the regulatory view is to avoid exposing patients to genotoxic compounds unnecessarily in clinical trials. This philosophy may impact on herbal supplement marketing and botanical drug development, in that genotoxicity data are often lacking while consumers are exposed to the herbal supplement, or healthy volunteers are tested in an initial Phase I/II clinical trial on the botanical drug. This paper presents results of a survey conducted on genotoxicity data in botanical INDs submitted to the Agency and discusses the significance of this information. The information presented indicates that the sponsors of botanical INDs have increasingly recognized the importance of genotoxicity information and may have prioritized its acquisition in their strategic drug development programs.

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## 1. Introduction

Genotoxicity studies have been traditionally used for the prediction of carcinogenicity and heritable mutation. The principles and practices of the studies employed for supporting human drug registration in the U.S. currently follow the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH)/Therapeutic Products Program Guidance (FDA ICH Guidance S2B), consisting of a battery of tests for gene mutations in bacteria, an in vitro test with cytogenetic evaluation for chromosomal damage within mammalian cells (or an in vitro mouse lymphoma tk assay), and an in vivo test for chromosomal damage using rodent hematopoietic cells. Drugs that test negative using the three-test battery strategy provide a sufficient level of safety and are considered, from a regulatory perspective, to be non-genotoxic. Drugs that test positive in the standard test battery may need to be tested more extensively, depending on their indications (FDA ICH Guidance S2A). Recently, the strategy and approach for these tests have been integrated, including a second optional battery, as proposed in the draft document (FDA ICH Guidance S2(R1)).

Botanical drug products in the U.S., like other therapeutic agents, are required to provide genotoxicity information prior to marketing approval (Wu et al., 2000, 2004; FDA Guidance for Industry, 2004; Chen et al., 2008). However, this unique category of drug products, regardless of indication, is entitled to a waiver for genotoxicity testing, along with other non-clinical pharmacology/toxicology studies, during the initial phase of drug development to support an initial clinical trial under an investigative new drug application (IND), contingent upon previous human experience (Wu et al., 2000, 2004, 2008a).

We recently conducted a survey to analyze the amount of genotoxicity data in IND and NDA submissions following publication of the Agency's botanical drug guidance document. Findings are presented and its significance discussed in the later section of this paper.

## 2. Genotoxicity information related to botanical products

Recently, ethical concerns have been raised over conducting Phase I/II clinical trials of a new drug with positive genotoxicity testing findings in healthy volunteers. A weight-of-evidence document on how to proceed with clinical studies during new drug development when genotoxicity findings are positive is available on the Agency's website (FDA Guidance for Industry and Review

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Staff, 2006). This issue may be applicable to botanical drug products and its relevancy should be considered, along with the waiver conditions provided in the botanical guidance document. Nevertheless, the risk/benefit assessment for a botanical, as for other drug products would depend on its intended use, indications, duration of treatment, and specific findings related to genotoxicity. The regulatory view is to limit unnecessary exposure of patients to genotoxic compounds in clinical trials.

It is worth mentioning that, for non-therapeutic agents such as pesticides and insecticides, genotoxicity tests are routinely required by the Environmental Protection Agency (U.S. EPA) prior to their marketing approval (EPA Guidelines, 1986). For food additives, genotoxicity testing is part of the safety assessment required for product marketing (FDA Guidance for Industry Redbook, 2007). For dietary ingredients that existed in the market prior to the Dietary Supplement Health and Education Act (DSHEA) established in 1994, safety studies may not be required. However, there is a statutory recommendation for safety testing of new dietary ingredients that appeared after 1994, i.e., those not in the market prior to DSHEA (see reference for FDA New Dietary Ingredients in Dietary Supplements). Genotoxicity tests have been discussed in great length as part of an overall safety evaluation strategy reported by the Committee on the Framework for Evaluating the Safety of Dietary Supplements (CFESDS, 2005). Recently, the European Medicines Agency also finalized a guidance of genotoxicity tests on traditional herbal medicines (EMEA, 2008).

As a dietary supplement or a drug product, botanicals are unique in that they contain multiple chemical constituents which may be pharmacologically active, with a significant portion of these constituents remaining chemically undefined. Various botanical chemical constituents are known to have genotoxic properties (e.g., estragole, furocoumarin, methyleugenol, safrole, and aristolochic acid) (EMEA, 2008; Gold and Zeiger, 1997; NTP ROC, 2008; Wu and Farrelly, 2007). However, currently available scientific databases or studies relating to this subject focus primarily on the single chemical constituent, instead of the botanical product itself, from which the constituent is derived (see reference databases by U.S. EPA on ECOTOX; by UC Berkeley on CPDB, and by U.S. National Toxicological Program [NTP]) (Soderman, 1982; EPA Database; UC CPDB Database; NTP Database). Thus, genotoxic information obtained from studies using a whole herb or multi-component herb product is relatively lacking, compared with individual chemical constituents. This is also evidenced by the NTP's ongoing projects (Gold and Zeiger, 1997; NTP Database) in that relatively few whole botanicals were recommended to the NTP for testing (e.g., ginkgo, echinacea, and ginseng) as compared with the voluminous information available for single molecular entities, which can be either synthetic, semisynthetic or natural (Soderman, 1982). As herbalists and practitioners of alternative medicine often believe that herbal mixtures offer "combination" advantages of synergy in efficacy and mutual antagonism in toxicity, testing data on the whole botanical may become more meaningful and significant. To further corroborate this line of thinking, the Agency's Botanical Drug Products guidance document considers that additional purification, identification and characterization of active constituents existing in botanical mixtures are not necessary for the IND or NDA applications and their approval (FDA Guidance for Industry, 2004; Chen et al., 2008).

## 3. A survey of genotoxicity information provided in botanical INDs

We have conducted a survey of genotoxicity information included in botanical INDs, across all therapeutic categories within the Center for Drug Evaluation and Research (CDER) at FDA since 2001, the year that the Agency's Botanical Drug Products guidance document was released. Our objective was to evaluate, under the current regulatory environment (i.e., waiver of genotoxicity studies in support of initial clinical trial[s]), the status and trend of botanical IND submissions that provide genotoxicity information during clinical development. The survey covers the period from 2001 to 2008 and attempts to address the question of whether the sponsor proactively conducted genotoxicity studies during early phases of clinical trials on the botanical product.

## 4. Results

To the end of 2008, the total number of botanical drug products submitted to the Agency under both the pre-IND program and IND review reached over 350 (both IND and pre-IND packages). Table 1 includes only those INDs that were submitted after the release of CDER's Botanical Drug Products guidance document in 2001. During the period of 2001–2008, the number of botanical INDs totaled 215. Annual submissions remained at a steady level, ranging between 20 and 30, with the exception of 2002 (submissions <20), and 2003, 2005, and 2007 (submissions $\geqslant$30). Among these, academic/research IND submissions accounted for more than those from the commercial/industry sponsors, with indications proposed

**Table 1**
Botanical INDs and related genotoxicity information submitted to CDER FDA during 2001-2008.

| Year | Total INDs | Inclusion of genotoxicity information (either literature information or studies, or both) | Inclusion of genotoxicity studies performed |
|---|---|---|---|
| 2001 | 21 | 4 | 3 |
| Commercial/industry | 6 | 2 | 2 |
| Academic/research | 15 | 2 | 1 |
| 2002 | 16 | 3 | 1 |
| Commercial/industry | 5 | 1 | 0 |
| Academic/research | 11 | 2 | 1 |
| 2003 | 31 | 6 | 1 |
| Commercial/industry | 5 | 1 | 1 |
| Academic/research | 26 | 5 | 0 |
| 2004 | 22 | 4 | 1 |
| Commercial/industry | 3 | 1 | 1 |
| Academic/research | 19 | 3 | 0 |
| 2005 | 38 | 9 | 3 |
| Commercial/industry | 8 | 4 | 3 |
| Academic/research | 30 | 7 | 0 |
| 2006 | 22 | 3 | 1 |
| Commercial/industry | 6 | 0 | 0 |
| Academic/research | 16 | 3 | 1 |
| 2007 | 38 | 12 | 7 |
| Commercial/industry | 14 | 7 | 7 |
| Academic/research | 24 | 5 | 0 |
| 2008 | 27 | 11 | 4 |
| Commercial/industry | 4 | 4 | 3 |
| Academic/research | 23 | 7 | 1 |
| Sum | 215 | 54 | 21 |

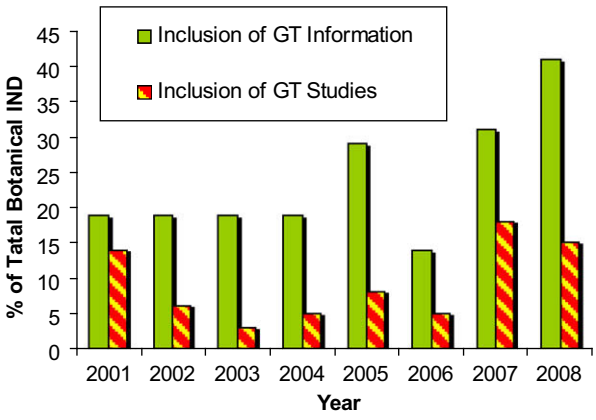


**Fig. 1.** Percentage of botanical IND submissions (2001–2008) that included genotoxicity information or studies (green bar: inclusion of GT Information refers to those that contain either studies performed or literature information, or both; shaded bar: inclusion of GT Studies refers to those that contain actual studies performed.). (For interpretation of the references to colours in this figure legend, the reader is referred to the web version of this paper.)

and investigations focused primarily in areas of unmet medical need, such as oncological, dermatological, cardiovascular and antiviral therapies. The submission profile is, in general, similar to earlier surveys conducted and published previously (Wu et al., 2000; Chen et al., 2008).

In regard to genotoxicity, a modest trend toward increasing inclusion of information (either from the literature or from studies performed by the sponsor) on genotoxicity appeared in the IND packages over the last 8 years, peaking in the last 2 years (32–41%), suggesting significant awareness of the impact of genotoxicity in the overall safety evaluation of the botanical product. Further, there seems to be a sporadic trend toward early conduct of genotoxicity studies as a proactive approach adopted by sponsors in recent years, even though the studies can be waived during the initial trial period. Factors contributing to the increases could include various reasons ranging from relative cost-effectiveness of the assays to the availability of more regulatory guidance documents, post-market safety concerns with dietary supplements, changes in internal regulatory practices (requesting this information on a case-by-case basis), or greater reliance on the predictive performance of genotoxicity assays (Fig. 1).

## 5. Summary

In summary, our data indicate that the sponsors of botanical INDs have increasingly recognized the importance of genotoxicity information and may have prioritized its acquisition in their strategic drug development programs. Considering that genotoxicity studies are comparably cost-effective (relative to animal toxicity studies), are highly reproducible, and have high statistical power, botanical drug sponsors should be encouraged to obtain this information early in their product development.

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