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FDA's Proposed IND Study For 'Abuse Potential' Could Close US Kratom Supplement Market

by Malcolm Spicer

> RFP states FDA "previously warned consumers about the use of Kratom (Mitragyna speciosa)" and although botanical's "use is prevalent, to date, clinical evaluations of abuse potential have not been performed."

The US Food and Drug Administration has asked for proposals to conduct an investigational new drug trial for kratom "to help characterize its abuse potential" after previously recommending scheduling ingredients from the botanical as controlled substances.

The agency's *request for proposals* states the FDA "has previously warned consumers about the use of Kratom (Mitragyna speciosa), a plant endogenous to Southeast Asia" and although the botanical's "use is prevalent, to date, clinical evaluations of abuse potential have not been performed."

The RFP, titled "Dose-Finding Study Of Kratom Alkaloids Pilot" and assigned notice identification RFPFDA21(1238584) when published on 8 July, doesn't mention the FDA's recommendation to schedule kratom constituents mitragynine and 7-hydroxymitragynine as controlled substances in response to a 2016 request for comment by the Drug Enforcement Administration.

Responses to the FDA's RFP were due by 9 August, which also was the deadline for comments the agency sought, through a 23 July notice – docket FDA-2021-N-0739, on the World Health Organization's requests for information on whether kratom – mitragynine, 7-hydroxymitragynine – should be added to the United Nations' schedule of controlled substances. (Also see "*Another Notice For Comments On Kratom: Cue Second Wave Of Support For Botanical In US?*" - HBW Insight, 22 Jul, 2021.)

The American Kratom Association industry group filed a *complaint* asking a court to order the FDA to extend to 31 August the deadline for comments responding to the WHO request.

A hearing on a *motion* for a temporary restraining order was scheduled for 9 August in the US District Court for the District of Columbia; the docket for the litigation wasn't updated with a decision from the hearing before HBW Insight posted this article.

IND Checks Box For Exclusion

The FDA's stance is that kratom isn't a dietary ingredient allowed for use in dietary supplements or food products available in the US. The agency contends kratom is excluded from being eligible for use in supplements through the new dietary ingredient notification process or in food through the generally regarded as safe process because of its abuse potential, particularly by people reportedly using it to enhance the effect of opioid drugs.

However, as sales of products containing ingredients from the botanical, available in formats including dried/crushed leaves, powder, capsules, tablets, liquids and gum/resin, continue growing in the US despite the FDA's concerns, studying kratom ingredients as an investigational new drug would strengthen the agency's argument for prohibiting their use in food and supplements. Ingredients that have been studied or approved for use as drugs are deemed unlawful for use as food additives or dietary ingredients under FDA regulations.

\The FDA states in the RFP that safety and chemical, manufacturing and control (CMC) data currently are limited to support clinical research with kratom and its alkaloids. The agency wants to "further investigate techniques and protocols with an initial Kratom HAP [human abuse potential] to help characterize its abuse potential and support future research efforts."

A pilot clinical study is needed for

Scheduling Recommendation Rescinded

The FDA previously found that kratom ingredients mitragynine and 7-hydroxymitragynine should be listed under schedule I of the Controlled Substances Act since a 2009 report on deaths in Sweden reportedly linked to the botanical. It imposed an import alert in 2014. (Also see "*FDA Turns Kratom's Future In US Dietary Supplement Market Into History*" - HBW Insight, 14 Nov, 2017.)

The agency, through the Department of Health and Human Services, submitted its findings to the DEA after it proposed scheduling extracts from kratom as controlled substances in the US in 2017. However, the HHS in 2018 changed its position and submitted correspondence to the DEA rescinding the FDA's recommendation to schedule kratom, information that was kept

"necessary data to characterize the abuse potential of botanical Kratom which may inform future clinical studies of Kratom, mitragynine, and 7-OH-MG, the primary psychoactive constituents of Kratom."

The required data sets on safety information and chemistry manufacturing and controls, which also are the "information to support an" IND, will inform dose selection, statistical analyses and primary outcome measures for future clinical studies of kratom and its alkaloids, the RFP states.

2 Steps For IND Application

The request details instructions and requirements for two-part research to prepare an investigational new drug application for kratom alkaloids.

Part one comprises generating adequate data to demonstrate the safe clinical use of botanical Kratom and support an IND application, including conducting a thorough literature review and producing appropriate safety and toxicology information to support an IND for a subsequent HAP study.

The data will steer determining the appropriate doses of botanical kratom and its preparation – in consultation with and approved by the FDA – to administer to humans which will be part of an IND application.

In part two, a clinical study will examine the abuse liability of kratom including subjective effects, with the numbers of doses of kratom and subjects determined in consultation with the FDA. The investigator also will define the inclusion/exclusion criteria for subjects, "e.g., recreational opioid users that have used botanical Kratom at least once in the past 30 days for its reinforcing effects or 'to get high'," according to the RFP.

under wraps until early 2021. (Also see "*US HHS Pulled Recommendation To Make Kratom A Controlled Substance, But Kept Mum On Change*" - HBW Insight, 28 Jan, 2021.)

Kratom is known for its mild caffeine-like effects and typically is used to relieve stress and enhance mood. In addition to reported use to enhance the effect of opioid drugs, using kratom e to offset symptoms of withdrawal from addiction to opioids and other drugs generated scrutiny by the FDA and led to the DEA's scheduling proposal.

The FDA typically has warned kratom marketers about making violative claims for their products. In May, though, it seized a Florida firm's kratom inventory through a complaint alleging the herb is a new dietary ingredient unfit for use in any supplement. (Also see "*With Seizure in Florida, FDA Targets Kratom As Unsafe For Any Use*" - HBW Insight, 24 May, 2021.)