Headline: Frestedt Inc. applauds FDA's new Draft Guidance on Drug Interaction Studies with Combined Oral Contraceptives

Subheader: Studying Drug Interactions with Combined Oral Contraceptives

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The FDA has issued a new Draft Guidance for Industry "Clinical Drug Interaction Studies With Combined Oral Contraceptives" which can be found on the FDA website at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-combined-oral-contraceptives-guidance-industry. This document discusses the need for drug-drug interaction (DDI) studies with combined oral contraceptives (COCs) containing an estrogen and a progestin when used to prevent pregnancy. The FDA reports "COCs are highly effective in preventing pregnancy when used correctly." Unfortunately, interactions between COCs and other drugs may increase pregnancy risk or compromise patient safety by changing estrogen or progestin metabolism. For example, this guidance states increased estrogen and/or progestin levels "can increase" the risk of blood clots in veins which is a "rare but serious adverse event."

Women of childbearing age often use COCs and other drugs concurrently and safely; however, DDIs between COCs and investigational new drugs have not been well studied in the past. This guidance is intended to help sponsors determine (1) when DDI studies between investigational drugs and COCs are needed, (2) how COC DDI studies should be designed and conducted and (3) what DDI data should be communicated on the drug labelling. The FDA is putting forward their "current thinking" about the types of *in vitro* (benchtop experiments) and/or clinical (human trials) assessments which will be needed for investigational new drug approval in the future. This guidance details the need to evaluate enzymes involved in progestin and estrogen metabolism including cytochrome P450 3A (CYP3A).

For new drugs the labeling must describe "clinically significant" DDI risks and should recommend not to use the new drug at the same time a woman is using estrogen/progestin-containing COCs for new drugs which increase estrogen levels or to use a back-up/alternative method of contraception for drugs which decrease progestin levels. Alternatively, when no clinically significant DDI risks are found, the drug labeling should include a statement similar to: "No clinically significant differences in [drug substance] pharmacokinetics were observed when Drug-X was used concomitantly with Drug-Y."

This guidance suggests enrolling both pre- and post-menopausal women into these COC DDI studies using a "Fixed sequence", "randomized crossover" or "parallel study design". COCs containing drospirenone with ethinyl estradiol are recommended "as a worst-case scenario for CYP3A inhibition" and the treatment "should be given at the highest proposed therapeutic dose and… duration to ensure…" maximum metabolic effects are seen during the investigational drug use.

Interested parties may submit comments on the draft guidance by February 22nd, 2021 for FDA consideration as the final guidance document is developed.

About Frestedt Inc.

Frestedt Incorporated (www.frestedt.com) is a consulting service organization founded on February 26, 2008 to provide exquisitely targeted clinical, regulatory and quality system solutions for the pharmaceutical, medical device, biotechnology and food-related industries. We provide expertise to our clients in all stages of product development from bench, preclinical, and clinical trial services to post market research and the integration of new safety, efficacy and performance data into the developing risk management portfolio. We provide design and development leadership to research centers conducting clinical trials and regulatory submissions in order to improve the quality and cost effectiveness of the research service provided. As a result of this broad-based service approach to the industry, our clients have included some of the largest and smallest manufacturers of drugs, devices and foods in the world, as well as academic centers, Clinical Research Organizations, and clinical trial sites.

About Alimentix

Alimentix (www.Alimentix.com) is a comprehensive clinical investigation center (clinical trial site) dedicated to conducting clinical trials for foods, food ingredients, dietary supplements, natural products, over the counter pharmaceuticals and non-significant risk medical device products. We have conducted trials as diverse as weight loss and osteoarthritis, for products including calcium derived from Irish seaweed, and meal replacement beverages and we have published and presented our work both privately and within public reviewed settings.

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