Prescription Nutraceutical Clinical Evidence Requirements in the Treatment of Depression: Comparing US and EU Guidance for Phase II and III Clinical Trials

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INTRODUCTION

Nutraceuticals or medical foods are used to address a specific dietary requirement necessary to treat a disease or condition. Medical foods must be used under medical supervision but are not regulated as drugs by the US FDA or EU EMA and do not require a prescription. Medical foods have the potential to be co-packaged for concomitant use as adjunctive therapy with prescription drugs to support nutritional needs for disease management (Figure 1). Specifically in the management of Major Depressive Disorder (MDD), medical foods can be used to help regulate enzymes that support the synthesis of neurotransmitters that play an important role in regulating mood.

OBJECTIVE

Our objective was to review current guidance documents for the design of phase II and III clinical trials provided by the FDA and EMA to identify any evidence generation requirements for a medical food to enter the prescription pharmaceutical market in the US and EU as adjunctive therapy to treat MDD.

METHODS

MDD-related clinical trial phase II and III evidence requirements for safety and efficacy endpoints, study design, and study population inclusion/exclusion criteria were reviewed and summarized. FDA and EMA requirements were compared to identify key differences necessary for securing marketing authorization of a medical food as adjunctive therapy in the US and EU prescription pharmaceutical markets.

Figure 1. Types of Drug Combination Therapies Key Definitions

RESULTS

Table 1. Safety and Efficacy US-FDA Versus EU-EMA Phase II & III MDD-Specific Trials

Phase II & III MDD-Specific Trials		US-FDA	EU-EMA
	Safety	**Drug interactions**: Early pharmacokinetics and pharmacody- namics characterization should be conducted to determine dosing, dosing intervals, and drug switching strategies • Early background therapy interaction assessment highly recommended for adjunctive therapy	**Drug interactions:** Potential reactions characteristic of the class of drugs being investigated should be assessed with special efforts
		Adverse events: Any serious and unexpected adverse events should be reported to the FDA and all investigators via an IND safety report	**Adverse events:** should be characterized in relation to duration of treatment, dosage, recovery time, age, and other relevant variables • Specific AEs outlined in guidance document
	Efficacy	**Effectiveness:** must be established by independently substantial evidence from at least 2 adequate and well-controlled investigations	**Effectiveness:** must be established by at least 2 pivotal studies • Optionally an adequately weighted meta-analysis of efficacy across all clinical studies to improve precision of the estimates of clinical efficacy
		Primary endpoints: clinician-rated outcome measures: • Hamilton Depression Rating Scale (17-items) • Montgomery Asberg Depression Rating Scale • Children's Depression Rating Scale	**Primary endpoints**: rating scales • Hamilton Depression Rating Scale (17-items) • Montgomery Asberg Depression Rating Scale
		Secondary endpoints: assess other domains of symptom improvement • Clinical Global Impression (CGI-S preferred) Assessment Scale • Sheehan Disability Scale	**Secondary endpoints:** changes in global assessment or social functioning • Clinical Global Impression Assessment Scale

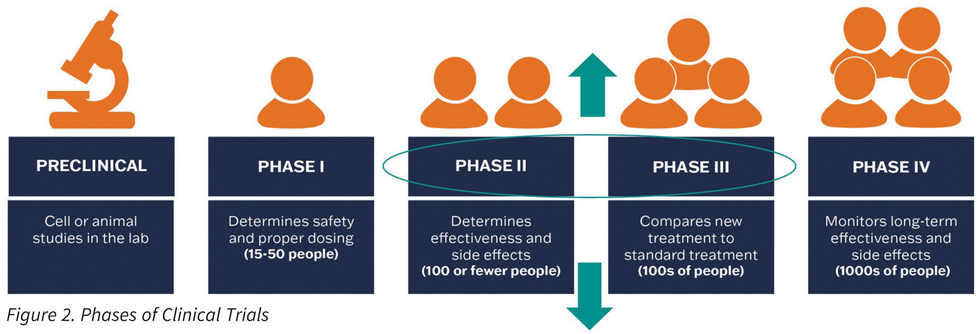

Figure 2. Phases of Clinical Trials

Table 2. Study Design and Study Population US-FDA Versus EU-EMA Phase II & III MDD-Specific Trials

Phase II & III Depression-Specific Trials		US-FDA	EU-EMA
	Study Design	**Short-term treatment trials:** 6-8 week-long randomized, double-blind, placebo-controlled designs	**Short-term treatment trials:** 6 week-long randomized double-blind comparisons versus a placebo arm and an active control arm with a fail-safe provision • Active comparator acceptable alternative
		Long-term maintenance treatment trials: FDA typically requests a post-marketing commitment to conduct a double-blind randomized withdrawal trial that's at least 6 months in duration • **Efficacy:** demonstration depends on the drug's dosing schedule, long-term safety considerations, and feasibility of long-term use	**Long-term maintenance treatment trials:** randomized double-blind with-drawal trial with suggested first phase duration of 6-12 weeks plus 6 months after re-randomization • **Efficacy:** rate of patients worsening and/or time to this event as defined in protocol typically with a clinically relevant validated rating scale
	Study Population	**MDD diagnosis:** DSM-defined MDD confirmed via semi-structured interview • Current DSM Structured Clinical Interview • MINI International Neuropsychiatric Interview	**MDD diagnosis:** confirmed using accepted diagnostic criteria, (e.g., DSM IV)
		MDD severity: Study populations should reflect a range of MDD severities	**MDD severity:** Trial recruitment focused on moderately-ill study population
		Other special populations: Recommended inclusion of other special populations and must provide rationale for restrictive inclusion and exclusion criteria • Geriatric patients • Patients with HIV/ Hep C • Patients with substance abuse history	**Other special populations:** Additional safety considerations outlined for older populations to determine a safe dose range pre-licensing

RESULTS

Endpoints:

- Safety requirements should include pharmacokinetics-informed dosing and drug switching strategies in phase II and maintenance of a safety database in phase III in the US (Table 1).
- Efficacy is established through at least 2 adequate and well-controlled investigations in both markets (Table 1, Figure 2).
- Standard primary endpoints are clinician-rated outcome measures in both markets (Table 2).
- Secondary endpoints assess other areas of symptom improvement in both markets (Table 2).

Study Design:

- Phase II trials should be randomized, double-blind, placebo controlled and last 6-8 weeks for both markets (Table 2).
- Phase III trials should be randomized double-blind withdrawal trials and last at least 6 months for both markets (Table 2).

Study Population:

- The study population should include DSM-defined MDD patients and a range of severity in the US while EU studies should focus on moderate MDD (Table 2).

CONCLUSIONS

Findings highlight the necessary evidence requirements to take a medical food to the prescription pharmaceutical market as adjunctive therapy in the treatment of MDD. Many requirement similarities exist between the US FDA and EU EMA. Minor differences are seen in safety reporting, specific endpoint measurements, and MDD severity and special population inclusion in the study.

REFERENCES

Guidance for Industry Nonclinical Safety Evaluation of Drug or Biologic Combinations; EMA Glossary; Major Depressive Disorder: Developing Drugs for Treatment Guidance for Industry; Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies; Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products; 21 CFR 312.21 Phases of an investigation; ICH guideline E8 (R1) on general considerations for clinical studies; Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev 2); Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010, Rev.3); UVA Health – Support for Phase 1 Clinical Trials (Graphic: Alex Monson) https://giving.uvahealth.com/article/support-phase-1-clinical-trials