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FDA Perspective on Botanical Drug Development

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Disclosures

I (Dr. Hagit Marchaim) have no financial relationships to disclose concerning the content of this presentation or session.

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA.

FDA and Cannabis-Based Drugs

➢ Approved drugs:

- Marinol (Unimed Pharmaceuticals) and Syndros (Insys Therpautics) [dronabinol, a synthetic THC] are approved for anorexia associated with AIDS and nausea and vomiting associated with cancer chemotherapy.
- Cesament (Meda Pharmaceuticals) [nabilone, a synthetic compound similar to THC] is approved for nausea and vomiting caused by cancer chemotherapy

The FDA has not approved yet any product containing or derived from botanical marijuana for any indication

FDA and Cannabis-Based Drugs

Scheduling: Classification of drugs based on abuse potential; medical use; physical/psychological dependence.

➢ Controlled Substances Act (CSA) of 1970:

Marijuana is still regulated under Schedule I, defined as having:

- High potential for abuse
- No currently accepted medical use
- Lack of accepted safety for use under medical supervision

However, FDA supports **adequate and well controlled trials** which may lead to the development of **safe and effective marijuana products** to treat medical conditions

FDA and Cannabis-Based Drugs

➢ Drugs in clinical development:

- Epidiolex (GW Pharmaceuticals), a liquid formulation of pure plant-derived CBD, demonstrated Positive Phase 3 Data in Dravet Syndrome and Lennox-Gastaut Syndrome, rare pediatric epilepsy disorders. NDA submission is expected this year. FDA-authorized Expanded Access Program.

- Sativex (GW Pharmaceuticals), an oromucosal spray cannabis sativa plant extract containing THC and CBD, for the treatment of spasticity (muscle stiffness/spasm) due to MS. Approved in many countries outside the US.

FDA and Cannabis-Based Drugs

- **Source of marijuana for clinical trials:**
  - For nearly 50 years, the United States has relied on a single grower to produce marijuana used in research. This grower operates under a contract with the National Institute on Drug Abuse (NIDA).
  - Recently, DEA, in consultation with NIDA and FDA, has developed a new approach to allow additional marijuana growers to apply to become registered with DEA

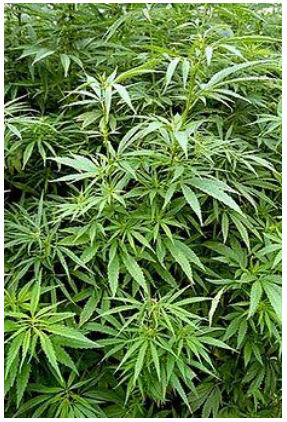
In FDA documents related to cannabis-based drugs, FDA cites its Guidance on Botanical Drug Development

FDA Guidance on Botanical Drug Development (Dec 16)

- A botanical product intended for use in diagnosing, curing, mitigating, or treating disease would meet the definition of a drug under section 201(g)(1)(B) of the FD&C Act.

- Due to the heterogeneous nature (mixtures, constituents not well defined) of a botanical drug and possible uncertainty about its active constituents, one of the critical issues for botanical drugs is therapeutic consistency.
  A totality-of-the-evidence approach:

  - Botanical raw material control
  - Quality control by chemical test(s) and manufacturing control
  - Biological assay and clinical data from multiple batches



FDA Guidance on Botanical Drug Development (Dec 16)

- The Agency will determine the relevance of prior human experience with traditional preparations to the assessment of botanical drugs' safety in clinical studies proposed under INDs on a case-by-case basis. Comparison of the IMP's identity and clinical settings with previous data should be provided.

FDA Guidance on Botanical Drug Development (Dec 16)

➢ Raw Materials

- Detailed data on the harvest location, growth conditions, stage of plant growth at harvest, harvest time/season, post-harvest processing, control of foreign matter (i.e., inorganic and organic contaminants such as soil, insects, and algae/fungi), preservation procedures, handling, transportation, and storage conditions as well tests for elemental impurities, microbial limits, tests for residual pesticides and tests for adventitious toxins (e.g., aflatoxins) will be needed in addition to other information to support raw materials control.

- For Phase 3 studies, raw materials used should be representative.

FDA Guidance on Botanical Drug Development (Dec 16)

➢ Drug Substance

- Detailed information on qualitative and quantitative aspects of the drug substance (including strength, manufacturing process, appearance, chemical identification and quantification of active constituents, mass balance, residual pesticides…)
- The composition of multi-plant drug substances, in terms of the relative ratio of the individually processed botanical drug substances or of the botanical raw materials before processing (as applicable), should be expressed.

➢ Drug Product

- Similarly, qualitative and quantitative description of the drug product will be required

FDA Guidance on Botanical Drug Development (Dec 16)

➢ Non-Clinical Data

- The amount of nonclinical information recommended to support Phase 1 and Phase 2 clinical studies with botanical products will depend on the extent of previous human use and the design of the proposed clinical studies:
  - Literature data
  - Route of administration
  - Proposed exposure in the clinical trial

- In general, requirements are similar to non-botanical drugs (ICH M3(R2)).

FDA Guidance on Botanical Drug Development (Dec 16)

➢ Clinical Studies

- If the major active constituent(s) in a botanical product is known, PK studies should be conducted. Same is for ADME, dose-response, DDI and QT studies.

- The clinical evaluation of botanical drugs in early-phase clinical studies does not differ significantly from that of synthetic drugs.

- For phase 3 studies, analyses of batch effects on clinical endpoints should be considered when drug product batches exhibit variations. Randomization of subjects to different batches in each site is highly recommended.

FDA Guidance on Botanical Drug Development (Dec 16)

Another approach to show that clinical response to a botanical drug will not be affected by variations of different batches is to demonstrate that the drug's effect is not sensitive to dose.

Thus, if a randomized, multiple-dose, parallel group design, Phase 3 study demonstrates a similar treatment effect across multiple doses, concerns about the impact of variability in chemical composition across batches may be diminished.

FDA Guidance on Botanical Drug Development (Dec 16)

➢ Conclusions

- A key challenge in botanical drug development is to ensure that different marketing batches, with their variations, will have a consistent therapeutic effect.

- Therefore, quality control of botanical drugs should include the following aspects: (1) botanical raw material control, (2) quality control by chemical tests and manufacturing control, and (3) biological assay and clinical data.

- Dose-response clinical data: If the clinical effects are not sensitive to dose (but are superior to placebo), then variations within the specifications are unlikely affect the therapeutic consistency.

- Multiple batch clinical data: Randomization of subjects to different batches can be used to assess treatment-by-batch interactions.

Thank You

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