FDA Workshop on Marketed Unapproved Drugs

On January 9, 2007, FDA held a workshop on various legal and regulatory issues pertaining to marketed unapproved drugs. The purpose of the workshop was likely to promote the “voluntary” submission of marketing applications by sponsors of unapproved products. As described below, FDA also appeared to place these sponsors on notice that it planned to take more aggressive action to call for data or demand the withdrawal of these products from the marketplace.

Background

In FDA's Compliance Policy Guide (CPG) 440.100, “Marketed New Drugs Without Approved NDA or ANDAs,” issued in June 2006 (see http://www.fda.gov/cder/guidance/6911fnl.pdf), FDA explained its rationale for the workshop. Specifically, it stated that for various historical reasons, “some drugs” (estimated in the thousands) are available in the United States without required FDA approval for marketing. The manufacturers of these drugs have not received FDA approval to legally market their drugs nor are the drugs being marketed in accordance with the over-the-counter (OTC) drug review. The CPG is intended to clarify FDA's approach to prioritizing its enforcement actions and exercising enforcement discretion with regard to the universe of unapproved, illegally marketed drug products. As explained in the CPG, FDA will employ a risk-based approach which assigns enforcement priorities to:

- drugs with potential safety risks;
- drugs that lack evidence of effectiveness;
- health fraud drugs;
- drugs that present direct challenges to the new drug approval and OTC drug monograph systems;
- unapproved new drugs that are also violative in other ways; and
- drugs that are reformulated to evade FDA enforcement action.

1 It is FDA's position that few, if any, of these drugs that are currently marketed qualify as “grandfathered” or drugs that comply with the Drug Effectiveness Study Implementation (DESI). This is primarily because their formulations and/or marketing claims have deviated from the original drugs which might have claimed these transitional rights.
January 9th Meeting

The CPG is also intended to encourage companies to pursue and obtain New Drug Application (NDA) approval for drugs that other companies are marketing without approval. Following such an approval, FDA will normally allow a grace period (roughly one year) before it initiates enforcement action against marketed unapproved drugs of the same type. There may or may not be a warning before enforcement action is initiated. The shorter the grace period, the more likely it is that the first company to obtain approval will have a period of “de facto market exclusivity” before other products obtain approval.

The primary purpose of the public meeting was to explain how companies marketing unapproved drugs should pursue initial marketing approval. Accordingly, it had the tenor of a tutorial on drug regulation. The overall impact of the workshop was to educate marketers regarding the hurdles and high costs of seeking and obtaining FDA approval. It also advised them that as enforcement continues and likely accelerates, sponsors need to plan for the eventual day when their ability to market without an approval will be lost.


Compliance

- According to FDA, there is virtually no such thing as a grandfathered drug, or an old drug, or a Generally Recognized as Safe and Effective (GRASE) drug. Accordingly, all unapproved drugs will require FDA approval or strict compliance with an OTC monograph. (Regulatory law firms such as ours would be happy to review current drug marketing endeavors to render opinions concerning the legal merits of this strict FDA position.)

- Filing an NDA is neither a trigger for enforcement against others nor a shield for the filer.

- FDA always prioritizes and looks at what its remedial actions will motivate industry to do. FDA recognizes the need to accelerate enforcement, but will not commit to specific timeframes.

- Approval and enforcement proceed independently of one another.

- There is no “list” of unapproved drugs that FDA intends to remove from the market. The CPG provides the operative explanation of FDA’s risk-based approach.

- Even if a drug appears on the Drug Effectiveness Study Implementation (DESI) list, all were found to be ineffective.

- Drugs in violation of a final OTC monograph could also be targets for enforcement.
• If FDA initiates enforcement action against a company marketing multiple unapproved drugs for additional reasons regarding one product, such as good manufacturing practice (GMP) deficiencies, it will likely pursue action against all its unapproved drugs.

• FDA recognizes that the regulatory tasks are daunting and that some companies may not be able to pursue product approvals.

• FDA will be watching to determine if patients will be harmed in any manner by the removal of particular unapproved products from the market (e.g., do approved therapeutic alternatives exist).

**New Drug Applications (NDAs)**

• 505(b)(1) and 505(b)(2) NDAs require the same standard for approval – substantial evidence of safety and effectiveness – but have different sources of data.

• While the standard of approval is not high, the required way of showing it – adequate and well-controlled studies – makes it a high standard.

• The Food and Drug Administration Modernization Act (FDAMA) allows for a single trial and confirmatory evidence. For symptomatic conditions, it will be unusual to approve a drug based on a single study.

• Studies need to be well-controlled, convincing and statistically significant (2-sided, p value of <0.05).

• There are five kinds of controls:
  - placebo;
  - no treatment;
  - dose response;
  - active (superiority or non-inferiority); and
  - historical.

• Active controls are now in some dispute, because effective drugs do not necessarily show efficacy in all trials (e.g. antidepressants).

• Unapproved drugs marketed for a long time will still require substantial evidence. A long marketing history tells FDA little about effectiveness, but may say something about safety.

• An Investigational New Drug (IND) application is required even for a small pilot study, and even if there is a marketing history of safe use.
• For unapproved marketed drugs, there is:
  - a lack of adverse reaction data to examine;
  - a lack of controlled or even uncontrolled systemic safety evaluation; and
  - often a lack of preclinical (animal) characterization.

• For unapproved marketed drugs, it is useful to look at:
  - what is known and proven;
  - whether the drug moiety has been approved;
  - and, if so, whether it has been approved for a similar indication;
  - foreign experience; and
  - published literature.

• If a drug cannot be lawfully marketed in conformance with a final monograph, it may be possible to utilize FDA’s finding of safety and efficacy for an ingredient in that monograph to support a 505(b)(2) NDA. Such a “monograph deviation” approach would require providing data to support the differences between the monograph and the test drug.

• Pre-IND meetings are encouraged.

• There is now an Unapproved Drugs Coordinator, Sally Loewke, M.D. She should be invited to pre-IND meetings. While she cannot attend all, she will at least try to attend the internal pre-meetings.

Abbreviated New Drug Applications (ANDAs)

• To submit an ANDA, there must almost always be a Reference Listed Drug (RLD). An exception is the applicability of a suitability petition.

• Labeling must generally be the same as brand name labeling. Portions protected by patents or exclusivity may be deleted. There may also be differences with respect to excipients; pharmacokinetic (PK) data.

• Stability data – three months. One demonstration batch – this must be the source of bioequivalence (BE) data and stability data.

• To show BE, FDA will use PK data where possible, and alternatively will use pharmacodynamic (PD) data.
• BE parameters:
  - Area under curve (AUC) and maximum concentration (CMax).
  - Must show 90 percent confidence interval which fits between 80 and 125 percent, measuring variability between the test drug and the reference drug.

• Topicals will usually require some kind of clinical data. FDA encourages sponsors to request specifics on BE data for topicals, but cautions that there is a backlog of up to one year in responding to such requests.

**Preclinical/Nonclinical**

• General discussion of types of data – pharmacology, safety pharmacology, general toxicity, genetic toxicity, PK, absorption and distribution of metabolic elimination (ADME), reproductive toxicity and carcinogenicity studies.

• Purpose – to determine whether it is safe for use in humans, what is a safe starting dose and whether there are dose-limiting toxicities.

• While waivers are possible, there are certain toxicities which are difficult to detect (e.g. genetic damage, fertility, birth defects).

• Published literature may help.

• A carcinogenicity study is likely necessary if intended for continuous use for six months or more, or if used intermittently for chronic or recurrent conditions, or if there are genetox concerns.

**User Fees**

• These are daunting. For FY 2007, application fees for NDAs containing clinical data are $896,200 and for NDAs without clinical data, $448,100.

• There are no user fees for:
  - ANDAs
  - INDs
  - Monographs
  - Drug Master Files

• There are also product fees ($49,750) and establishment fees ($313,100).

• All fees, including establishment fees, are the responsibility of the sponsor.
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