FDA's Final Compliance Policy Guide for Marketed Unapproved Drugs — Is Agency Enforcement at a Crossroads, or Stuck in a Traffic Circle

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AGENDA

1. Essential Concepts – What is a "Drug"? What is a "New Drug"?

2. Historical Development of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and the Different "Categories" of Drugs.

3. FDA's Compliance Policy Guide ("CPG") – What are FDA's Enforcement Policies and Priorities?

4. Examples of Recent FDA Enforcement Action.

5. What Does the Future Hold for Marketed Unapproved Drugs?

Essential Concepts – What is a "Drug;" What is a "New Drug"?

- FDC Act § 201(g)(1) defines the term "drug" as:
  - (A) articles recognized in the official United State Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and
  - (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
  - (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
  - (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)….
- Thus, whether a product is a "drug" generally depends on its "intended use." See generally 21 C.F.R. § 201.128.

Background – What is a "Drug;" What is a "New Drug"?

- FDC Act § 201(p) defines the term "new drug" so that a drug is not a "new drug" if:
  - (1) it is Generally Recognized As Safe and Effective ("GRASE") under the conditions of use for which it is labeled; and
  - (2) it has been used "to a material extent or for a material time under such conditions."

- A product that is a "new drug" may not be introduced into interstate commerce unless there is an approved marketing application (e.g., an NDA), or unless an exemption has been granted permitting the introduction of the drug into interstate commerce (e.g., an effective IND).

Historical Development of the FDC Act and the Different "Categories" of Drugs

- **The 1906 Federal Food and Drugs Act**
  - First brought drug regulation under federal law by prohibiting the sale of adulterated or misbranded drugs.
  - The statute did not require that drugs be approved by FDA in order to be marketed.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- **The 1938 FDC Act**
  - Enacted on June 25, 1938.
  - Added the requirement that "new drugs," that is, drugs not Generally Recognized As Safe ("GRAS"), be approved for safety in an NDA.
  - Drugs on the market prior to that date are exempt from "new drug" status under a "grandfather clause."
    - "Pre-1938 grandfathered drugs" are exempt from the requirement of submitting an NDA, provided the drug contains the same chemical composition, indications, and other conditions for use as the original "grandfathered drug."
  - The active ingredients in many currently marketed drugs were first introduced, at least in some form, before June 25, 1938.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- If FDA approved a drug between 1938 and 1962, FDA generally permitted Identical, Related, or Similar ("IRS") drugs to the approved drug to be marketed without independent approval.
- Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on:
  - Their own conclusion that the products were GRAS (i.e., not a "new drug"); or
  - A formal opinion from FDA that the products were not "new drugs."

Historical Development of the FDC Act and the Different "Categories" of Drugs

- **The 1962 Drug Amendments and the Drug Efficacy Study Implementation ("DESI") Program**
  - In 1962, Congress amended the FDC Act to require that a "new drug" be demonstrated to be effective, as well as safe, in order to obtain FDA approval.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- Under a "grandfather clause" included in the 1962 Drug Amendments, a drug is exempt from the effectiveness requirement if:
  - (1) Its composition and labeling has not changed since October 10, 1962 (the date on which the 1962 Drug Amendments were enacted); and
  - (2) If, on the day before the 1962 Drug Amendments became effective, the drug was:
    - Used or sold commercially in the United States;
    - Not a "new drug" as defined by the FDC Act at that time; and
    - Not covered by an effective application.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- The 1962 Drug Amendments required FDA to conduct a retrospective evaluation of the effectiveness of the drug products approved as safe between 1938 and 1962 (to which FDA added IRS drugs).
- FDA's administrative implementation of the effort was called the DESI program.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- Some currently marketed products are subject to completed DESI proceedings, but nevertheless lack approved marketing applications.
  - FDA considers all of these products to be unapproved and marketed illegally, but uses its enforcement discretion.
- Some products currently on the market are unapproved but are still undergoing DESI reviews in which a final determination regarding efficacy has not yet been made.
  - Products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- **The Prescription Drug Wrap-Up**
  - Drugs that did not have pre-1962 approvals or were not IRS to drugs with pre-1962 approvals were not subject to DESI.
  - For a period of time, FDA allowed these drugs to remain on the market and allowed new unapproved drugs that were IRS to these pre-1962 drugs to enter the market without approval.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- In 1984, FDA assessed pre-1962 non-DESI marketed drug products. The program for addressing these products became known as the "Prescription Drug Wrap-Up."
- FDA believes that drugs that were subject to the Prescription Drug Wrap-Up are all marketed illegally, unless a manufacturer of such a drug can establish that the drug is "grandfathered" or otherwise not a "new drug."

Historical Development of the FDC Act and the Different "Categories" of Drugs

- **New Unapproved Drugs.**
  - Some unapproved drugs were first marketed, or were changed, after the 1962 Drug Amendments were enacted (i.e., drugs that were not covered in the Prescription Drug Wrap-Up).
  - Still other drugs are the subject of a formal "new drug" finding (e.g., timed-release drugs, and parenteral drugs in plastic containers).
  - FDA has taken the position that drugs in this category are all marketed illegally and are subject to enforcement action, unless covered by an approved marketing application.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- **Scope of the "Grandfather Clauses" and the GRASE Exemption.**
  - The 1938 and 1962 "grandfather clauses" have been construed very narrowly by FDA and the courts.
  - FDA believes that there are few, if any, marketed drugs that are actually entitled to "grandfather" status.
  - If a company claims that its product is "grandfathered," FDA considers it the firm's burden to prove that assertion.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- Over-the-Counter ("OTC") Drugs.
  - FDA has taken the position that OTC drugs covered by ongoing OTC monograph proceedings may remain on the market, subject to current enforcement policies.
  - FDA has extended these policies to products sold as prescription drugs with ingredients under the OTC Drug Review, deferring action until the monograph is final.
  - OTC drugs that require approval because their ingredients or claims are not within the scope of the OTC Drug Review, or are not allowed under a final monograph or another final rule, are illegally marketed unless they are the subject of an approved marketing application.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- Legally marketed drugs are those drugs:
  - Marketed in accordance with an approved NDA (and generic copies of such drugs marketed under an approved ANDA); and
  - Drugs that are exempt from the NDA requirement, which includes:
    - Pre-1938 and pre-1962 "grandfathered" drugs;
    - Drugs subject to an ongoing DESI proceeding;
    - GRASE drugs; and
    - Drugs marketed in accordance with a final or tentative OTC drug monograph.

Historical Development of the FDC Act and the Different "Categories" of Drugs

- Illegally marketed drugs subject to FDA enforcement action include:
  - Drugs marketed outside of an OTC drug final or tentative final monograph;
  - Drugs found to be effective under DESI but for which an NDA or ANDA has not been submitted;
  - Drugs subject to a completed DESI proceeding that found them to be not effective;
  - Drugs subject to the Prescription Drug Wrap-Up;
  - New unapproved drugs; and
  - Drugs that do not meet the GRASE requirements or that differ in some respect from pre-1938 or pre-1962 "grandfathered" drugs.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- Draft CPG issued in October 2003.
- Final CPG issued in June 2006 (available at http://www.fda.gov/cder/guidance/6911fnl.pdf).
  - Supersedes CPG Manual, Sec. 440.100 –Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02), as established in 1976, and subsequently amended in the 1980s and 1990s.
  - FDA revised the draft October 2003 CPG to, among other things, clarify when and how the Agency intends to exercise its enforcement discretion.
- FDA's CPG discusses the Agency's risk-based enforcement approach with regard to marketed unapproved drug products.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- FDA gives higher priority to enforcement action against unapproved drugs in the following categories:
  - (1) Drugs with potential safety risks;
  - (2) Drugs that lack evidence of effectiveness;
  - (3) Drugs that present a "health fraud;"
    - FDA defines health fraud to mean "[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate, or done without adequate knowledge or understanding of the article."

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- (4) Drugs that present direct challenges to the "new drug" approval and OTC drug monograph systems;
- (5) Unapproved "new drugs" that are also violative of the FDC Act in other ways;
  - E.g., Current Good Manufacturing Practice ("CGMP") regulation violations, misbranding, and failure to register and list; and
- (6) Drugs that are reformulated to evade an FDA enforcement action
  - E.g., when a firm, in anticipation of FDA enforcement action, changes its unapproved drug product by, for example, adding an active ingredient, in an attempt to evade such enforcement action.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- FDA evaluates whether to initiate enforcement action on a case-by-case basis, consistent with the Agency's risk-based enforcement approach.
- FDA generally does not intend to give special or advance notice that an unapproved drug may be subject to enforcement action, but may allow a grace period using the following factors:
  - (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (e.g., medically necessary drugs);
  - (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application;
  - (3) the burden on affected parties of immediately removing the products from the market;
  - (4) the Agency's available enforcement resources; and
  - (5) special circumstances relevant to the particular case under consideration (e.g., a newly approved drug).

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- Newly Approved Drugs.
  - Because FDA wants to encourage the submission of marketing applications, and because the approval of a drug that is also marketed without FDA approval is a direct challenge to the integrity of the drug approval system, "FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation."
  - In addition to the factors listed on the previous slide concerning when FDA might take enforcement action against companies marketing unapproved drugs, and how much of a grace period (if any) should generally be anticipated, FDA will also consider in the case of a newly approved drug whether the effort to obtain FDA approval was publicly disclosed.
  - FDA normally intends to allow a 1-year grace period from the date of approval before initiating enforcement action (e.g., a Warning Letter, seizure, injunction).

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- Exceptions to FDA's Enforcement Policy.
  - FDA has taken the position that OTC drugs covered by ongoing OTC monograph proceedings may remain on the market, subject to current enforcement policies. FDA has extended these policies to products sold as prescription drugs with ingredients under the OTC Drug Review, deferring action until the monograph is final.
  - Products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding.

Examples of Recent FDA Enforcement Action

- FDA's action that led to the decision in United States v. Sage Pharma., Inc., 210 F.3d 475 (5th Cir. 2000), is precedent of the Agency adding unapproved "new drug" charges after finding other FDC Act violations.
- In Sage, the United States Court of Appeals for the Fifth Circuit agreed that FDA was permitted "to address the unapproved status of a particular drug outside the established priorities in the same enforcement proceeding as other violations of the [FDC Act.]."
- Sage Pharmaceuticals' CGMP violations led to the initiation of enforcement action to which a "new drug" charge was added.
- Similar precedent in United States v. Pharmakon Laboratory, Inc. (2005).

Examples of Recent FDA Enforcement Action

- FDA's action on single-entity extended-release guaifenesin products is precedent of the Agency taking immediate enforcement action against firms marketing unapproved drugs once FDA approves an NDA for a similar product.
- In October 2002, FDA sent Warning Letters to 66 firms that marketed unapproved single-ingredient extended-release guaifenesin products claiming that the products were illegally marketed "new drugs."

Examples of Recent FDA Enforcement Action

- FDA's action was initiated after the Agency approved an NDA for MUCINEX (extended-release guaifenesin tablets) in July 2002. The approval of MUCINEX provided FDA with the impetus to immediately enforce the FDC Act. The Agency's Warning Letters noted the permissible OTC monograph use of single-ingredient immediate-release guaifenesin, and specifically cited 21 C.F.R. § 310.502(a)(14) (requiring approval of an NDA for timed-release drugs) as a basis for claiming that the firms were marketing unapproved new drugs.
  - What about FDA enforcement action with respect to MUCINEX D (guaifenesin; pseudoephedrine HCl) Extended-Release Tablets and MUCINEX DM (dextromethorphan HBr; guaifenesin) Extended-Release Tablets?
  - See FDA Warning Letter to Neil Laboratories (May 31, 2006) (available at http://www.fda.gov/foi/warning_letters/g5878d.pdf).

Examples of Recent FDA Enforcement Action

- In June 2006, FDA announced that the Agency plans to take enforcement action against companies marketing unapproved drug products containing carbinoxamine (either single-entity or combination products), because:
  - –"(1) Carbinoxamine is a drug with potential safety risks . . .; and
  - –(2) the agency has approved an application to market a carbinoxamine-containing product, and thus the continued marketing of unapproved carbinoxamine products is a direct challenge to the drug approval process."

FDA, Notice; Carbinoxamine Products; Enforcement Action Dates, 71 Fed. Reg. 33,462, 33,464 (June 9, 2006) (available at http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-9033.pdf).

Examples of Recent FDA Enforcement Action

- FDA's planned enforcement action was timed to coincide with the announcement of the availability of the final CPG, and after the Agency had approved two ANDAs in March and April 2003, submitted by Mikart, with an anticipated supplement to these applications concerning the products' use in children under two years (due to safety concerns).

What Does the Future Hold for Marketed Unapproved Drugs?

- Is FDA's issuance of the final CPG an indication that FDA will begin a wholesale enforcement initiative against companies marketing unapproved drugs . . . or will FDA enforcement be more "patchwork"?

What Does the Future Hold for Marketed Unapproved Drugs?

- What about monographs for “old” prescription drugs?
  - FDA has discussed the issue several times over the past 40 years, and most recently in 2003 when the Agency released the draft CPG.
  - Both the U.S. House of Representatives and Senate have asked FDA to examine the feasibility of such a monograph system.
  - FDA determined in August 2004 that such a system was not feasible.

What Does the Future Hold for Marketed Unapproved Drugs?

- Are there ways to decrease the risk of FDA enforcement action?
  - Seek FDA approval.
  - Ensure that your products are not violative of the FDC Act in other ways.
  - Target products that are otherwise exempted from FDA's enforcement policy.