CPG Sec. 160.900 Prescription Drug Marketing Act -- Pedigree Requirements under 21 CFR Part 203

Purpose

This document is intended to clarify for FDA personnel and the regulated industry how the agency intends to prioritize its enforcement efforts regarding the pedigree requirements in 21 U.S.C. 353(e)(1)(A) and 21 CFR Part 203 during the first year after the effective date of 21 CFR §§ 203.3(u) and 203.50.

FDA's guidance documents, including this CPG, do not establish legally enforceable rights or responsibilities. Instead, guidance documents describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidance documents means that something is suggested or recommended, but not required.

Background

The PDMA -- Overview
The Prescription Drug Marketing Act of 1987 (PDMA), as modified by the Prescription Drug Amendments of 1992, amended sections 301, 303, 503, and 801 of the Federal Food, Drug, and Cosmetic Act (the Act) to establish requirements related to the wholesale distribution of prescription drugs. A primary purpose of the PDMA was to increase safeguards to prevent the introduction and retail sale of substandard, ineffective, and counterfeit drugs in the U.S. drug supply chain.

The Pedigree Requirements
Section 503(e)(1)(A) of the Act establishes the pedigree requirement for prescription drugs. A drug pedigree is a statement of origin that identifies each prior sale, purchase, or trade of a drug, including the date of those transactions and the names and addresses of all parties to them. Under the pedigree requirement, each person who is engaged in the wholesale distribution of a prescription drug in interstate commerce, who is not the manufacturer or an authorized distributor of record for that drug, must provide to the person who receives the drug a pedigree for that drug. The PDMA states that an authorized distributor of record is a distributor that has an "ongoing relationship" with a manufacturer to distribute that manufacturer's drug products. However, the PDMA does not define "ongoing relationship."

The 1999 Final Rule
In 1999, FDA published final regulations implementing the PDMA (21 CFR Part 203). The regulations were to take effect in December 2000. After publication of the 1999 final rule, the agency received comments objecting to the provisions in §§ 203.3(u) and 203.50. Section 203.3(u) defines "ongoing relationship" to include a written agreement between manufacturer and distributor. Section 203.50 specifies the fields of information that must be included in the drug pedigree and states that the information in the pedigree should be traceable back to the first sale by the manufacturer.

Based on concerns raised by various stakeholders, the agency delayed the effective date of §§ 203.3(u) and 203.50 several times.

The Electronic Pedigree
In February 2004, FDA delayed the effective date of §§ 203.3(u) and 203.50 until December 1, 2006, in part because we were informed by stakeholders in the U.S. drug supply chain that the industry would voluntarily implement electronic track and trace technology by 2007. If widely adopted, this technology could create a de facto electronic pedigree that would document the sale of a drug product from the place of manufacture through the U.S. drug supply chain to the final dispenser. (If properly implemented, an electronic pedigree could thus meet the statutory requirement in section 503(e)(1)(A) of the Act [see above]). Although progress has been made, it appears that the use of electronic pedigree will not be widely adopted by 2007. As a result, in June 2006, FDA announced that it did not intend to delay the effective date of §§ 203.3(u) and 203.50 beyond December 1, 2006. (See insert FR cite when published.) As such, as of December 1, 2006, the provisions defining an "ongoing relationship" and setting forth certain pedigree requirements are in effect.

The Scope of this CPG
The goal of this CPG is to clarify how we intend to prioritize our pedigree-related enforcement efforts during the first year following the December 1, 2006 effective date. To that end, the CPG lists factors (below) to guide FDA's enforcement efforts. These are risk-based factors that focus our enforcement priorities on those drug products that are most vulnerable to counterfeiting and diversion or that are otherwise involved in illegal activity.

Several of the factors include examples. These examples are included only for illustrative purposes and are not meant to be inclusive of all drugs that meet these factors. FDA may, under appropriate circumstances, initiate administrative or regulatory action, including criminal prosecution, for any violation of the pedigree requirements.

The enforcement priorities described below reflect a phased-in type approach to the enforcement of the stayed pedigree provisions. By providing guidance on the types of drugs that are currently of greatest concern to FDA, we believe that wholesale distributors will have a better idea of where and how to focus their initial energies as they implement systems to come into complete compliance with 21 CFR Part 203 for all the prescription drugs that they distribute. Accordingly, this CPG expires December 31, 2012.

Factors to Consider for Enforcement Focus

Consistent with our risk-based approach to the regulation of pharmaceuticals, during the first year after the December 1, 2006 effective date, FDA intends to give higher priority to enforcement efforts regarding the pedigree requirements in 21 U.S.C. § 353(e)(1)(A) and 21 CFR Part 203 for prescription drugs that fall in the following categories:

FACTOR 1: High Value in the U.S. Market

FDA experience demonstrates that drug products that have a high market value, that are high-priced, or have high sales volume are more frequently subject to counterfeiting and diversion. Questions to consider for this factor include:

Does the drug product have a high sales volume or price in the U.S.?
There are several resources available that rank sales volume and sales in the U.S., including

Drug Topics. In the context of counterfeiting and diversion, brand name drugs are more likely to fall within this category. Examples of drug products in the U.S. that had a high sales volume and/or price in 2005 include: Lipitor, Nexium, Risperdal, Plavix

Is the drug product a "high priced/specialty" product used for a serious or life-threatening disease?
Drugs that are used to treat patients with HIV/AIDS, cancer, or other serious or life-threatening diseases are often higher priced drugs that may be more susceptible to counterfeiting or diversion. Counterfeit versions of these drugs, or those that are illicitly obtained through drug diversion and stored or handled improperly, could result in serious adverse consequences for these patients by depriving them of effective treatments for serious or life-threatening diseases. Examples of these products include:
Procrit, Epovir, Combivir, immune globulin (IGIV), Gamimune, Gammagard, Epogen, Serostim

Is the drug in high demand?
Drugs that are in high demand are vulnerable to counterfeiting and diversion because buyers may be desperate to stock the product, and criminals capitalize on the situation. For example, a drug such as Tamiflu is in high demand due to fears of a possible influenza pandemic. Another example of a drug that is in high demand is:
Oxycontin

Is there a shortage of the drug?
A drug may be in high demand if there is a shortage. This could occur if there are manufacturing concerns that limit the ability to manufacture the product. FDA maintains a list of drugs that are currently in short supply at http://www.fda.gov/cder/drug/shortages/default.htm . Current examples of drugs in short supply include:
certain metered dose inhalers, reserpine tablets

FACTOR 2: Prior Indicators

Are there prior cases of the drug being counterfeited or diverted in the U.S.? Is there a history of false pedigrees associated with the product?
FDA frequently sees the same drugs as targets for counterfeiting and diversion. In most of these instances, pedigrees are falsified or no pedigrees are provided in order to cover up the true illicit source of the drugs. Based on FDA experience, some examples of drugs that have been counterfeited or diverted are listed below. We note that these examples are based on publicly available information and do not include all drugs that have a prior confirmed case of being counterfeited or diverted. Furthermore, inclusion on this list of examples is not meant to imply that the drug is currently counterfeited or diverted or that its safety has been compromised.
Examples: Viagra, Procrit, Zyprexa, Serostim, Tamiflu, Combivir, Epovir, Sustiva, Trizivir, Zerit, Diflucan, Lamisil

FACTOR 3: Reasonable Probability (for newly-approved drugs)

This factor is intended to identify those drugs that may not fall within the other factors because there is insufficient marketing history (i.e., this factor "looks forward" for drug products that are new to the market.)

Is there a reasonable probability that the drug may be counterfeited or diverted based on Factors 1 and 2?

Does the drug have priority review status?
This information is available when a drug is approved and can be found http://www.fda.gov/cder/rdmt/default.htm.

Based on drug products that are in a similar drug class, is the drug predicted to have a high potential market size and value?

Other Violations of Law

The preceding factors notwithstanding, the agency intends to enforce the requirements of 21 U.S.C. § 353(e)(1)(A) and 21 CFR Part 203 (including sections §§ 203.3(u) and 203.50) against wholesale distributors and others who are engaged in conduct related to the manufacture or distribution of counterfeit drugs, or engaged in the manufacture or distribution of prescription drugs that otherwise violate the Act or other laws. This is true regardless of the type of drug at issue or whether it falls into one of the risk-based factors listed above.

This CPG expires: December 31, 2012

Revised 12/23/2010 to include date extension to 12/31/2012.