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Generic Competition for Withdrawn Drug Products

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When a pharmaceutical company withdraws a product from the market, the basis for the withdrawal can affect whether a competitor can commercialize a generic version of that product. A generic cannot be approved if, in the FDA's view, the product was withdrawn for "safety and effectiveness" reasons.

But how does the FDA reach that conclusion? A newly filed case may shed some light on the Agency's decision-making process.

No Generic for Products Withdrawn for "Safety and Effectiveness" Reasons

By way of background, 35 U.S.C. § 355 bars the FDA from approving an abbreviated new drug application (ANDA) for a generic version of a previously-approved drug (NDA product) if the NDA product has been withdrawn for any of the following reasons:

- Information, including new clinical evidence, shows that it is unsafe under its originally-approved conditions of use,
- New information shows a "lack of substantial evidence" that the drug will be effective under the label's conditions of use;
- Required patent information is not provided;
- If the NDA "contains any untrue statement of a material fact."

35 U.S.C. §§ 355(e), (j)(4)(I). If an ANDA filer wants to reference a withdrawn drug, it must petition for the FDA to determine whether the drug was withdrawn for reasons related to "safety and effectiveness." 21 C.F.R. § 314.122(a). The ANDA will not be approved unless the Agency determines the withdrawal was made for other reasons. *Id.* § 314.122(c).

***Somerset Pharms.*: FDA Is Not Bound by NDA Sponsor's Characterization of Withdrawal**

Prior case law provides helpful context regarding the boundaries of an appropriate FDA determination. *Somerset Pharmaceuticals, Inc. v. Shalala*. Somerset urged the FDA to expedite approval of a capsule form of the Parkinson's Disease therapeutic selegiline, noting that its then-approved selegiline tablets were susceptible to being counterfeited. After the capsule's approval, Somerset told the FDA that it would stop making the tablets because of "counterfeiting" and prescribing "mix-ups" with other drugs.

Multiple competitors countered that the selegiline tablets had been withdrawn for economic reasons, arguing that Somerset's actions were intended to delay generic competition for selegiline following the recent expiry of exclusivity for the tablet form.

The FDA determined that Somerset's tablets had not been withdrawn on "safety and effectiveness" grounds, citing several reasons: (1) the existence of counterfeit drugs did not make the tablets unsafe; (2) a preference for capsules in the target population was not a "safety issue"; and (3) confusion with other drugs would not occur for differently-named generics.

Somerset sought to enjoin generic competition on the grounds that the FDA's decision was arbitrary and capricious, but the *Somerset* court denied this effort, finding that FDA's assessment was based on "careful review" and its "conclusions appear quite reasonable in light of the available data."

***Arbor Pharms.*: What If FDA's Safety Warnings Incentivize the Withdrawal?**

Recently, Arbor Pharmaceuticals filed suit alleging that the FDA's determination concerning the withdrawal of Arbor's Nymalize product violates the Administrative Procedure Act (5 U.S.C. § 706(2)).

Nymalize (nimodipine) was approved in May 2013 for improving neurological outcomes in certain aneurysm patients. At the time, it could be administered in dose cups or through a nasogastric tube.

Arbor later reformulated Nymalize to "mitigate some of the challenges and adverse effects" and submitted a supplemental NDA on the "significantly modified" product. The new Nymalize product contained the same dose of nimodipine as the original, but more concentrated and in a prefilled syringe.

According to Arbor's complaint, although new Nymalize "offered significant advantages," it "would be hard to overstate the significance of the change" in nimodipine's concentration. Because new Nymalize would "significantly increase the risk of severe hypotension," its labeling "required critically important modifications" to prevent "potentially catastrophic results."

Arbor alleges that the FDA identified various safety concerns relating to the original Nymalize. For example:

- Upon initial review, the FDA required Arbor to "conduct a comprehensive risk analysis" in light of "identified serious safety risks" relating to potential confusion and dosing errors between the original and new Nymalize products.
- Arbor identified risks of medication error and evaluated potential solutions, which it presented to the FDA. Solutions included (among other things) discontinuing marketing the original Nymalize product.
- Despite Arbor's response, the FDA refused to approve the new Nymalize. It stated that the new concentration "is vulnerable to prescribing errors" in light of differences in the systems that physicians use to prescribe drugs.
- Per the FDA's recommendation, Arbor submitted a revised risk-mitigation plan, committing to communicating with doctors about new Nymalize, noting "New Concentration" prominently in the label, and proposing to withdraw the original Nymalize product.
- FDA then found "the residual risk to be mitigated to an acceptable level."

After competitors petitioned under § 314.122(a), the FDA found that original Nymalize had not been withdrawn for "safety and effectiveness" reasons. The FDA reasoned that although discontinuation "had been 'one' appropriate 'way to reduce the risk of confusion'" between the two drugs, it was "not necessary to discontinue marketing" the original product because "other (often-used) mitigation strategies" could be used to reduce the risk of confusion.

Arbor alleges that the FDA's determination violates the APA because:

- There is no requirement that withdrawal be "necessary" to remedy a safety risk;
- Arbor's decision to withdraw the original Nymalize product was an "objectively reasonable" way "precisely to address" the "serious safety risks that FDA itself determined were likely to result" from the product's continued marketing;

- FDA rejected Arbor's first risk-mitigation proposal, and it "beggars belief" to think that Arbor's second proposal was accepted due to the "modest" other measures proposed alongside the withdrawal;
- Similarly-situated products—with risks of serious medication errors arising from the presence of multiple concentrations on the market—have been deemed withdrawn for "safety and effectiveness" reasons.

In sum, the lawsuit filed by Arbor Pharmaceuticals raises interesting questions of statutory interpretation and the scope of FDA's powers. We will continue to monitor the case and provide updates regarding any noteworthy developments.

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