FDA AND THE NEW DRUG APPROVAL PROCESS

PRE-MARKETING FDA APPROVAL REQUIRED FOR NEW DRUGS

Before a company can market a "new drug," it must obtain FDA approval that such a "new drug" is both safe and effective.

A drug is any composition, compound (including inactive ingredients (excipients)) or active ingredient which:

a) is recognized as such by the FDA in the official "United States Pharmacopeia," the official "Homeopathic Pharmacopeia of the United states," or the official "National Formulary;"

b) is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals;

c) is, other than food, intended to affect the structure or any function of the body of man or other animals; and

d) is an article intended for use as a component in any of the above.

A food or dietary supplement for which a truthful and not misleading statement is made in accordance with § 403(r) of the Act is not a drug solely because the label contains such a statement. (§ 201(g) 21 USC § 321(g)).

A drug is a "new drug" if:

a) it is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof, unless it falls within one of two grandfather categories, and

b) even if so recognized, the composition is a new drug if it has not been used to a material extent or for a material time under the conditions prescribed, recommended or suggested in the labeling thereof.

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1 Basically drugs which were subject to the 1906 act and are still labeled the same, and drugs which were on commercially used or sold on October 9, 1962, which were not a "new drug" as defined under the act at that time, which are now generally recognized as effective (not a requirement prior to October 10, 1962, and which are still marketed for the same use, under the same conditions.
Thus, a known compound, composition or active ingredient is a "new drug" if it is marketed for a new intended use.

**AVOIDING PRE-MARKETING APPROVAL--THE ROLE OF OTC MONOGRAPHS**

Conversely, a drug is *not* a "new drug" and *does not* require pre-market approval by the FDA if

1. it is generally recognized as safe and effective for the intended use,
2. adequate safety and effectiveness data for the intended use is publicly available, and
3. it has been used to a material extent for a material length of time for the intended use.

There are many over-the-counter (OTC) drugs which have been on the market for many years without ever having been approved by the FDA. The FDA appointed panels of outside experts to review 26 different classes of such OTC drugs for safety and effectiveness. The FDA solicited comments and data from the industry on different drugs in each of the classes, and the panels have held extensive hearings on such information. Much of the data assembled has come from companies selling drugs in these categories.

The monographs classify drugs and indications for the drugs into one of three categories:

- **Category I.** Generally recognized as safe and effective;
- **Category II.** Not generally recognized as safe and effective and misbranded; and
- **Category III.** Insufficient data to classify.

A proposed monograph is published in the Federal Register, along with requests for comments and data. After comments are reviewed, a tentative final monograph is published in the Federal Register. Again, comments and data are solicited. Supposedly, 14 months later the monograph becomes final, and is entered in the Code of Federal Regulations (some monographs have been in limbo much longer.

If a drug and the indications (uses) for it are listed in Category I of a finally approved monograph, it can be produced and sold without premarket approval by the FDA. Many pharmaceutical companies are selling OTC drug products based on Category I listings in monographs which have *not yet been finally approved*. In essence, they are relying on data contained in the monograph as evidence that the product is generally recognized as safe and effective. There is, of course, some risk in proceeding in this manner, in that the FDA may not finally approve the monograph, and conclude that an listed drug is not generally recognized to be safe and effective.
REQUIREMENTS WHICH MUST BE MET EVEN FOR MONOGRAPHED PRODUCTS

Even if a product is monographed, there are other requirements which a company must observe in marketing a drug (21 CFR 330.1(h)):

1. The company must list the product with the FDA in accordance with section 510(j);
2. the company must observe good manufacturing practices, set forth in 21 USC 211 (they are extensive and detailed);
3. The manufacturer of the product must be registered with the FDA;
4. The product labeling must be consistent with the monograph (and with the requirements of CFR 201.66 and 330.1), and the advertising of the product must be consistent with the labeling.
5. The product must contain safe and suitable inactive ingredients which do not interfere with the effectiveness of the preparation or with tests used to determine potency and purity;
6. The product must not contain illegal color additives;
7. The product container must meet FDA requirements.
8. Specified label warnings must appear on the product label;
9. If no maximum daily dose for the active is indicated in the monograph, it must be used only at levels necessary to achieve its intended effect.

The monographs usually focus on active ingredients, and do not list excipients which may be used in the drug formulation. The US Pharmacopeia National Formulary (USP NF) contains a list of recognized inactive ingredients (excipients). The manufacturer may use, and is expected to use, such recognized excipients in formulating the drug compound, though the manufacturer should be prepared to confirm on some basis that in this specific product, the excipients do not interfere with the effectiveness of the preparation or with tests used to determine potency and purity.

MARKETING IN THE ABSENCE OF A MONOGRAPH OR PRE-APPROVAL

Some companies have elected to sell drugs which are not listed in a monograph and have not otherwise been approved by the FDA, but which have been on the market for many years. These companies are taking the position that there is sufficient data available to establish that (1) the drug is generally recognized as safe and effective, (2) adequate safety and effectiveness data is publicly available for it, and (3) it has been used to a material extent for a material length of time. There is obviously risk associated with such a course.

THE APPROVAL PROCESS: NDA'S, ANDA'S AND THE HATCH WAXMAN STATUTORY SCHEME

If a drug is a "new drug," as that term is defined in the statute, a company must file either a New Drug Application (NDA), or an abbreviated new drug application (ANDA). The former requires original clinical data establishing that the drug is safe and effective. An ANDA can be filed base on the clinical data of a previously approved NDA, though the filer must show that its product is the same as and "bioequivalent" to the NDA approved drug.
It is important for pharmaceutical companies, both innovators and generics, to have a basic understanding of the statutory framework created by the Hatch-Waxman Act, which governs the Food and Drug Administration’s ("FDA") approval of new innovator and generic drugs. Congress's goal in passing the Act in 1984 and amending it in 2003 was to balance the competing policy interests of (1) encouraging innovator drug research and development and (2) enabling competitors to offer low-cost, generic alternatives to such drugs.5

**THE INNOVATOR'S BURDEN OF CLINICAL PROOF**

In order for the FDA to approve any new drug for sale, the applicant for approval must prove to the satisfaction of the FDA that the Drug is both "safe and effective." The innovating drug company bears the burden of proving this through expensive clinical trials, submitted to the FDA in a New Drug Application ("NDA"). 21 U.S.C. § 355(a), (b). On the other hand, the company seeking to market a generic alternative is allowed to rely on the safety and efficacy studies that supported the approval of the previously approved "listed drug." The generic drug company need only submit an Abbreviated New Drug Application ("ANDA") showing that its generic drug and the corresponding listed drug have the same active ingredients and are bioequivalent. 21 U.S.C. § 355(j)(2)(A)(ii), (iv).

**THE INNOVATOR'S REWARD FOR CLINICAL PROOF AND PATENTING**

As a reward to the innovating drug company for conducting the expensive clinical trials which support both the NDA and the generic company's ANDA, the FDA may not by law approve the generic ANDA for a period of three, five, or seven years from approval of the NDA. In addition, the innovator drug company is afforded additional Hatch-Waxman protection if it has patents covering its listed drug. During the NDA process, the innovator drug company must inform the FDA of all patents covering the drug or methods of using the drug, "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1), (c)(2). Such patents are listed electronically as "Approved Drug Products With Therapeutic Equivalence Evaluations," commonly known as the electronic "Orange Book."

In its ANDA, the generic drug company must certify:

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5 The statute refers to both innovator drugs and their generic alternatives as "new drugs," in that neither has been previously marketed.

6 Three years for a new use for a known compound, five years for a new compound, and seven years for a so called "orphan drug."

(I) that patents have not been listed for the approved drug;

(II) that any listed patent has expired;

(III) that (in essence) it does not seek approval until the date on which such patent will expire; or

(IV) that any listed patents are invalid or will not be infringed by the manufacture, use, or sale of the ANDA drug.


A generic company filing a "Paragraph IV Certification" must provide notice of their Paragraph IV Certification to both the patent owner and the NDA holder. 21 U.S.C. § 355(j)(2)(B). This notice must include a "detailed statement of the factual and legal basis for the opinion of the applicant that the patent is invalid or will not be infringed." 21 U.S.C. § 355(j)(2)(B)(iv)(II). The Hatch-Waxman Act provides that the mere act of filing a Paragraph IV ANDA constitutes an act of patent infringement. 35 U.S.C. § 271(e)(2). The patent owner and/or NDA holder then has 45-days within which to file suit for patent infringement against the Generic. If suit is filed, Hatch-Waxman prevents the FDA from approving the ANDA for another thirty months (from receipt of Notice), until there is a settlement, or until a district court decision holding the patent invalid or not infringed, whichever occurs first.

THE GENERIC’S REWARD FOR CHALLENGING DRUG PATENTS

As an incentive to ANDA filers to challenge the validity of listed patents, or to develop non-infringing products, Hatch-Waxman provides that the first ANDA applicant to file a Paragraph IV Certification shall enjoy a 180-day period of generic marketing exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv). Until that 180-day exclusivity period expires, the FDA may not approve a later-filed Paragraph IV ANDA based on the same NDA. And, the first Paragraph IV ANDA filer is entitled to its 180-days of exclusivity period whether or not it establishes that the NDA holder's patents are invalid or not infringed. 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb).

FORFEITURE OF THE 180-DAYS EXCLUSIVITY

The "Medicare Modernization Act" or "MMA" enacted on December 8, 2003 provided six circumstances under which the first filer forfeits its 180-day generic exclusivity (21 U.S.C. § 355(j)(5)(D)(i)(I-VI)):

I. The first filer fails to market by the later of either:

   (1) the earlier of 30 months after filing the ANDA or 75-days after final approval, or

   (2) 75-days after at least one of the following has happened as to each of the Paragraph IV certified patents:

      a) final court decision of invalidity or no infringement,\(^7\)

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\(^7\) Prior to the enactment of the "Medicare Modernization Act" or "MMA" on December 8, 2003, a first filer's 180 days of exclusivity began upon entry of any court decision holding the patent invalid or not infringed, or upon market introduction, whichever occurred first. 21 U.S.C. 355(j)(5)(B)(iv) 2000.
b) settlement or consent judgment that all patents are invalid or not infringed, or
c) delisting of the patents.

II. The first filer withdraws its ANDA or the Secretary considers it withdrawn for failure to meet the requirements for approval.

III. The first filer amends or withdraws its Paragraph IV certificate for all patents certified.

IV. The first filer fails to obtain tentative approval within 30 months of filing the ANDA.

V. The first filer enters into an agreement which is found, in an action filed by the Attorney General or the FTC, to violate the antitrust laws.

VI. All the patents certified expire.

The MMA forfeiture amendments do not apply to Paragraph IV ANDAs filed before the December 8, 2003 enactment of the MMA.

**USING THE FIRST ANDA FILER'S EXCLUSIVITY TO BLOCK GENERIC COMPETITION**

Because the FDA cannot approve any subsequently filed ANDA until after the first filer's 180-days of exclusivity have expired, it is possible for the first filer to delay the market entry of any generic alternative to an NDA approved drug, by simply delaying its own entry. If for any reason a first filer is delaying market entry, only a final court decision holding the patent invalid or not infringed will end the delay (absent one of the other less likely grounds for forfeiture), by forcing the first filer to market within 75-days or forfeit its 180-days of exclusivity altogether. Thus a court decision adverse to the NDA holder's patent at least assures the subsequent filers of approval within 255-days of the court decision.

Subsequent filers have a strong incentive to certify invalidity or non-infringement of the NDA patent under Paragraph IV, in an attempt to provoke litigation which will lead to a court decision. The NDA holders, on the other hand, have strong incentive to avoid litigation that would trigger the first ANDA filer's exclusivity period. This, of course, blocks any generic competition until the first ANDA filer markets, or until expiration of the NDA holder's patents on the drug.

**DECLARATORY JUDGMENT TO REMOVE THE FIRST ANDA FILER OBSTACLE**

Hatch-Waxman's "civil action to obtain patent certainty" (21 U.S.C. § 355(j)(5)(C)) affords the subsequent ANDA filer a vehicle for hastening removal of this first filer roadblock. Under this provision, if the NDA holder fails to sue a Paragraph IV ANDA filer within 45-days, the ANDA filer can sue the NDA holder to obtain a declaratory judgment that the Orange-Book-listed patents are invalid or not infringed.

In *Caraco Pharmaceutical Laboratories, LTD. v. Forest Laboratories, Inc. (Fed. Cir. 2008)*, the Federal Circuit Court of Appeals held that an NDA holder could not avoid such a declaratory judgment action merely by granting the declaratory judgment plaintiff a "covenant not to sue." In support of its decision, the Court quoted the following excerpt from the Congressional Record:
When generic applicants are blocked by a first generic applicant's 180-day exclusivity, the brand drug company could choose not to sue those other generic applicants so as to delay a final court decision that could trigger the "failure to market" provision and force the first generic to market. In . . . these . . . circumstances, generic applicants must be able to seek a resolution of disputes involving all patents listed in the Orange Book with respect to the drug immediately upon the expiration of the 45-day period. We believe there can be a case or controversy sufficient for courts to hear these cases merely because the patents at issue have been listed in the FDA Orange Book, and because the statutory scheme of the Hatch-Waxman Act relies on early resolution of patent disputes. The declaratory judgment provisions in this bill are intended to encourage such early resolution of patent disputes.


CONCLUSION

We at Varnum have experience in assisting pharmaceutical companies navigate the intricacies of the statutory scheme governing FDA approval of innovator drugs and their generic alternatives. We have experience in litigating patents certified under Hatch-Waxman's "Paragraph IV." We look forward to opportunities to assist you.

James A. Mitchell
Kathrin E. Richards