Are You Protected? Are You Excluded?

Understanding Patent Certification and Exclusivity Incentives for 505(b)(2) NDAs

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The development of regulatory submission strategies that are consistent with the legal and regulatory requirements for marketing applications *and* have the potential to maximize market protection through available regulatory and patent exclusivities requires an understanding of the different types of exclusivities and how they may apply.

This article discusses the different types of exclusivities that may be applied to 505(b)(2) applications, as well as the patent certification required at the time of submission.

Patent Certification

All new drug application (NDA) and abbreviated new drug application (ANDA) candidates must certify whether their proposed products may infringe on the patents of approved drug products (known as listed drugs) referenced in their applications. This requirement was included as a provision in the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Amendments).

The 1984 amendments also required the Food and Drug Administration (FDA) to publish a comprehensive list of patents that had been submitted. This list, known as the *Orange Book*, is updated monthly. Patent certifications apply only to patents on approved drugs listed in the *Orange Book*. New regulations that went into effect on 18 June 2003 apply to patent submissions and listing requirements made on or after 18 August 2003. The final rule[1] limits a drug company to only one 30-month "stay" of a generic drug's entry into the market for resolution of a patent challenge. The final rule also limits the types of patents that can be submitted by NDA applicants, NDA holders and NDA owners to patents that claim one of the following:

- Drug substance (active ingredient).
- Drug product (formulation and composition).
- Method of use (injectable, tablet, etc.).

For both 505(b)(2) applications and ANDAs, the applicant must submit at the time of submission a statement of one of the following patent certifications for each of the listed drugs to be referenced:

- The patent information has not been filed.
- The patent has expired.
- The patent will expire on a specific date.
- The patent is invalid or will not be infringed.

If the ANDA or 505(b)(2) applicant certifies that the patent is invalid or will not be infringed (a paragraph IV certification), the applicant is required to notify the NDA holder and patent owner. The notice states that an ANDA or 505(b)(2) application containing a paragraph IV certification to a listed patent has been submitted for the NDA holder's approved drug product (known as the listed drug).

If the NDA holder brings an action for patent infringement within 45 days of this notification, then FDA will not approve the ANDA or 505(b)(2) application effective for 30 months, or such shorter or longer period as a court may order, or until the date of a court decision (known as the 30-month stay).

In addition, if a patent exists for an approved drug product that includes a specific method of use, the applicant should include a statement indicating that an approval is not sought for the same method of use.

Exclusivity

Drug development incentives, including marketing protections and patent extensions, were enacted as part of the Hatch-Waxman Amendments of 1984. A 505(b)(2) NDA may be eligible for three or five years of exclusivity as described in the following sections. The 505(b)(2) application also may be eligible for orphan drug or pediatric exclusivity.

The type of application submitted determines what marketing protections are available, as shown in **Table 1**. Details of the circumstances under which each exclusivity is granted are described in the text that follows. **Table 2** shows the time that exclusivity takes effect and whether it runs concurrently with other exclusivities.

New Chemical Entity

21 CFR Part 314.108(a) defines a new chemical entity (NCE) as "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act." Active moiety is also defined in 21 CFR Part 314.108(a) as follows:

> *...the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.*

New drug exclusivity is applicable to new chemical entities or to a significant change in an already approved chemical entity, such as a new indication. The new drug exclusivity period for an NCE is five years. A three-year exclusivity is granted to an already approved active moiety if the application contains results of clinical studies that were conducted by the sponsor and were required for approval.

Patent Exclusivity

Under the 1984 amendments, a maximum of five years of patent life can be restored for a new drug product. The determination of the time period to be restored to the patent is calculated for the regulatory review period (testing phase and approval phase) after the patent was issued. For the purpose of patent term extension, a product is defined as the active ingredient contained therein. FDA clearly states that the active ingredient does not equal active moiety (generally the molecule or ion responsible for the physiological or pharmacological action). A new ester or salt of a previously approved acid is eligible for patent extension, whereas a new acid of a previously approved salt or ester is ineligible.

Table 1. Exclusivity

Exclusivity	Application NDA	505(b)(2)	ANDA	Exclusivity Period
NCE	•	•		5 years
Approved active moiety*	•	•		3 years
Patent term extension	•	•		Up to 5 years+
Orphan drug	•	•		7 years
Pediatric	•	•		6-month extension
Generic drugs			•	180 days^

* Granted if the application contains results of clinical studies required for approval that were conducted by the sponsor.
+ Calculated from the regulatory review period.
^ First submission only.

Table 2. Timing of Exclusivity Periods

Type of Exclusivity	Time Exclusivity Goes Into Effect	Concurrent* or Add-on
NCE	At approval	Concurrent
Approved Active Moiety	At approval	Concurrent
Patent Term Extension	At approval	Concurrent
Orphan Drug	At approval	Concurrent
Pediatric	Upon acceptance of study reports	Attaches to end of existing exclusivity
Generic Drugs+	At time of commercial marketing or date of court decision finding the patent invalid, unenforceable or not infringed, whichever is first	NAP^,ˈ

* Exclusivities listed as concurrent may all run simultaneously from time of approval.
+ For first generic company only that submits an ANDA with a Paragraph IV certification.
^ Not applicable.
ˈ It is possible for the 180-day exclusivity period to begin prior to FDA approval.

Orphan Drug Exclusivity

The Orphan Drug Act of 1983 grants a sponsor seven years of exclusivity after approval of its orphan drug (a product that treats a rare disease affecting fewer than 200,000 Americans). In addition to marketing exclusivity, sponsors may receive tax incentives for clinical research and grant incentives to defray costs of qualified clinical testing expenses incurred during development of the orphan drug product.

Pediatric Exclusivity

The six-month pediatric exclusivity is a marketing exclusivity that is added at the end of all existing exclusivities: patent, NCE or orphan drug exclusivity. For a moiety to qualify for pediatric exclusivity, FDA must issue a written request for pediatric studies. The studies must be conducted and fully reported to FDA while the current exclusivity is in effect.

To date, according to FDA, more than 100 approved active moieties have been granted pediatric exclusivity.[2]

Generic Drugs

The 180-day exclusivity for generic drugs applies only to the first company to submit an application with a paragraph IV certification and provides an incentive for a company willing to challenge a listed patent and possibly defend a patent infringement suit. The 180-day period of exclusivity starts either on the date the company begins commercial marketing of the generic drug product or on the date of a court decision finding the patent invalid, unenforceable or not infringed, whichever is first. It is possible that the exclusivity period could begin before the company receives FDA approval of the drug.

505(b)(1) Exclusivity Barriers to a 505(b)(2)

505(b)(2) applications are subject to marketing protections of other applicants. During the period that the five-year (NCE) or three-year (new clinical trials) exclusivity is in effect for a 505(b)(1) application, FDA may not accept or approve certain applications that rely on the protected product for approval.

The only exception is if a 505(b)(2) NDA or ANDA contains a paragraph IV certification. These may be submitted to FDA after four years, although they cannot be approved until the exclusivity has expired. Likewise, a 505(b)(2) or ANDA application may not be approved by FDA during the six months of pediatric exclusivity added to the end of a patent term.

If the agency determines that approval of an application would be temporarily barred because orphan drug

exclusivity is in effect for the listed drug, the timing of the application review will be decided on a case-by-case basis by the appropriate division of FDA's Center for Biologics Evaluation and Research or Center for Drug Evaluation and Research.

Summary

A 505(b)(2) NDA for an NCE will be granted five years of exclusivity. FDA may grant three years of exclusivity to an application for an approved active moiety for which additional clinical studies were required for approval and conducted by the sponsor. Patent exclusivity may restore up to five years of patent life for a new product based on the regulatory review period (testing phase and approval phase). Also available are seven years of orphan drug exclusivity for a drug that treats a rare disease that affects fewer than 200,000 Americans, and six months of pediatric exclusivity.

Exclusivities can protect a product filed under a 505(b)(2) application; on the other hand, an applicant submitting a 505(b)(2) application that refers to a listed drug may be blocked from submission or approval if the listed drug has any remaining exclusivity. The applicant is required to show that the applicant is not infringing on any patent for an approved listed drug.

Exclusivity and patent protections need to be carefully evaluated during the development of the strategy and timing of a 505(b)(2) application to avoid delays in approval and to maximize any exclusivity associated with the 505(b)(2) NDA.

NOTES

1. Food and Drug Administration. 21 CFR Part 314. Applications for FDA approval to market a new drug: patent submission and listing requirements and application of 30-month stays on approval of abbreviated new drug applications certifying that a patent claiming a drug is invalid or will not be infringed; final rule. *Federal Register.* 18 June 2003;68(117):36675-36712.
2. Food and Drug Administration. CDER New and Generic Drug Approvals: 1998-2004. Available at: www.fda.gov /cder/approval/index.htm. Accessed 24 March 2004.

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