CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

To all NDA and ANDA holders and applicants

OCT 31 1986

Dear Sir or Madam:

This is the fourth in a series of letters intended to provide informal notice to all affected parties of developments in policy and interpretation of the Drug Price Competition and Patent Term Restoration Act of 1984. This letter focuses on patent issues and the so-called three year exclusivity provisions of Title I of the new Act. By complying with the requests for information and certifications outlined below NDA and ANDA holders and applicants will help expedite agency actions on their NDAs and ANDAs.

PATENT ISSUES

In matters related to patents, the agency does not claim expertise. We believe that Congress intended to leave the ultimate resolution of patent issues to the U.S. Patent and Trademark Office and to the courts. Therefore, we are interpreting the statute and establishing procedures so that disputes between new drug applicants involving patents will be resolved by the notification and litigation process that is contained in the statute. The procedures we have developed to handle specific Title I patent issues are discussed below.

Filing of Patent Information by NDA Applicants:

1. Filing Errors:

Applicants submitting NDAs under Section 505(b)(1) or (2) are required to file with their applications information on all patents that claim the drug or a method of using the drug and 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. When an NDA is approved, the FDA publishes in the List of Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") the date of drug approval and the patent information supplied by the applicant; this information appears in the next monthly supplement of the Orange Book after the approval. In deciding whether 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, the agency will defer to the information submitted by the NDA applicant.

An application submitted under section 505(b)(2) or 505(j) must include a certification as to the status of any patent which, to the best of the applicant's knowledge, names the listed drug or a use for such drug for which the applicant is seeking approval. Such an application must contain a certification as to each patent on the reference listed drug published in the Orange Book. If anyone disputes the accuracy or relevance of patent information submitted by an NDA applicant and published by FDA, or believes that an NDA applicant has failed to submit required patent information, that person should first notify the agency informally, stating the grounds for the disagreement by writing to the Office of Drug Standards, HFN-200, 5600 Fishers Lane, Rockville, MD 20857. The agency

will write to the NDA holder requesting that the correctness of the filing or omission be confirmed. Unless the NDA holder withdraws or changes the patent filing, the agency will not change the patent information in the list. If the NDA holder does not change the information filed, a section 505(b)(2) or 505(j) application submitted for the drug should, despite any disagreement, contain a certification for each listed patent and any patent challenge can then be pursued through private legal action under the patent laws.

2. Information Submitted on Use Patents:

As noted above, the agency publishes information submitted by NDA applicants on patents that claim a method of using a drug (use patents). To avoid confusion about what is covered by a use patent, the agency is requesting that all NDA holders and applicants certify as to the indications or other conditions of use covered by any use patent.

Thus, for any use patent information previously filed with the agency or filed in the future, we are requesting the following certification:

> "We certify that Patent no. _____, a valid patent, covers the use of _____ for the following indications or other conditions of use:
>
> _____
>
> _____
>
> _____"

It would also be helpful to the agency if NDA applicants would state which indications or other conditions of use covered by a patent are approved for inclusion in the labeling of the products marketed in the United States. This certification as well as the certifications and information discussed below should be submitted to the NDA file and a copy should be sent to Chief, Drug Information Services Branch, HFN-84, 5600 Fishers Lane, Rockville, MD 20857. All such certifications are available under FOIA. In addition, the agency will publish the information on the indications covered by each use patent, as supplied by NDA applicants, in the Orange Book.

3. Formulation and Composition Patents:

As a reminder, for patents that claim a drug, unlike patents that claim a use, NDA applicants should only file information on those patents that refer to an approved drug product. To ensure that only appropriate formulation and composition patents are published, the Agency is reminding all holders of approved applications that for each composition or formulation patent the following statement should be submitted: "The undersigned certifies that the drug and the formulation or composition of such drug claimed by the following patents are currently approved under section 505 of the Federal Food, Drug and Cosmetic Act." The certification should be signed by the patent holder or by the person responsible for the NDA submission.

Patent Certifications for ANDAs or Applications Described in Section 505(b)(2):

1. In Cases Where No Patent Exists:

Sections 505(b)(2) and (j)(2)(A)(vii) require that applications submitted under 505(b)(2) and 505(j) contain certifications with respect to certain patents which claim the listed drug or which claim a use for such listed drug. Four types of certifications are specified in the statute. Questions have arisen as to what certification applicants should file if, to the best of their knowledge, no patent exists for a listed drug. In such cases, an applicant should certify that, "In the applicant's opinion and to the best of the applicant's knowledge, there are no patents which claim the listed drug referred to in this application or which claim a use for the listed drug for which [name of applicant] is seeking approval." An applicant submitting an application under section 505(b)(2) should certify that, "In the applicant's opinion and to the best of the applicant's knowledge, there are no patents which claim the drug or drugs on which studies that are relied upon in this application were performed or which claim a use for such drug or drugs."

If an ANDA or Section 505(b)(2) NDA applicant is aware of a patent that claims the drug or a method of using the drug, whether or not such patent is listed in the Orange Book, the applicant should submit one of the four certifications spelled out in sections 505(j)(2)(A)(vii) and 505(b)(2)(A).

2. Certifications Regarding Use Patents:

When a firm submits an ANDA or Section 505(b)(2) application for a listed drug for which FDA has published in the Orange Book use patent information supplied by the NDA holder, the proposed labeling may include an indication that the NDA holder has stated is covered by a use patent. When this occurs, the ANDA or Section 505(b)(2) applicant may file a certification under Section 505(j)(2)(A)(vii)(III) or 505(b)(2)(A)(iii) (that the patent will expire on a specified date) or under Section 505(j)(2)(A)(vii)(IV) or 505(b)(2)(A)(iv) (that the patent is invalid or will not be infringed by the proposed use). If a certification is submitted under subparagraph (III) or (iii), an approval of the ANDA or section 505(b)(2) application will be made effective on the date the patent expires. If a certification is submitted under subparagraph (IV) or (iv), the ANDA or section 505(b)(2) applicant must notify the patent holder and NDA holder. The patent holder and NDA holder then have 45 days in which to institute a private legal action for patent infringement. If a patent infringement action is not filed, an approval of the ANDA or section 505(b)(2) application will be made effective immediately.

If the proposed labeling does not include any indications that, according to the information supplied by the NDA holder, are covered by a use patent, the ANDA or Section 505(b)(2) applicant should provide a statement to the Agency under Section 505(j)(2)(A)(viii) or 505(b)(2)(B)

that the use patent does not claim any of the proposed indications. (As stated above, the agency is asking all NDA holders with use patent information on file to certify as to the specific indications covered by the use patents.)

General:

We want to clarify one general issue concerning patent filing and certification submissions. The Act requires an applicant submitting an application under section 505(b)(1) to file information about any patents that claim the drug, and an applicant submitting an application under section 505(j) or 502(b)(2) to make a certification and to send patent holders notice when a claim of invalidity or noninfringement of a patent is asserted. See sections 505(b)(2)(A), (b)(3) and 505(j)(2)(A)(vii), (j)(2)(B) of the Act. Questions have arisen concerning whether the various filings and certifications for section 505(b)(1), 505(b)(2) and 505(j) applications also apply to supplements to those applications. In general, what applies to section 505(b)(1), 505(b)(2) or 505(j) applications regarding patent certification also apply to supplements. If supplements to applications were not handled in the same way as the applications being supplemented, it would be possible for a 505(b)(2) or 505(j) applicant to avoid the notice requirement discussed above under the following set of circumstances.

A §505(b)(1) application is approved for indications "A" and "B". Indication "A" is protected by a use patent but indication "B" is not. A §505(b)(2) or 505(j) application is submitted for a generic version of the §505(b)(1) product for indication "B".

Because no challenge or claim of noninfringement or invalidity is alleged concerning the patent for indication "A", no notice by the generic applicant would be sent to the 505(b)(1) applicant but only a statement to the agency under 505(j)(2)(A)(viii). (Notice under 505(j)(2)(B) or 505(b)(3) occurs only when a "paragraph IV" certification is made, i.e., when the applicant certifies that a relevant patent is invalid or will not be infringed.) After the generic application is approved, a supplement to that application is submitted for indication "A". If no certification were made for this supplement, the notice requirements under section 505 would not be triggered and an important patent protection conferred by Title I would be lost.

The agency therefore concludes that with respect to patent certifications most supplements should be treated like full and abbreviated applications. The agency realizes, however, that not all supplements are for changes that could be patented. It appears unnecessary, for the purpose of carrying out the intent of the Act, to ask for patent certifications in supplements for such things as, for example, a change of manufacturing site, a change of equipment or a change in packaging. On the other hand some supplements may always involve changes that could be patented, e.g., supplements for new uses or other conditions of use, for these supplements certification appears to be necessary to carry out

the intent of the Act. The agency has considered various ways to ensure that patent certifications in supplements are asked for only when necessary and appropriate. The agency has concluded that supplements submitted under sections 505(b)(2) and 505(j) for the following types of change should contain an appropriate certification as specified by sections 505(b)(2)(A) and 505(j)(2)(A)(vii).

- formulation changes
- new uses or other conditions of use, e.g., route of administration
- strength changes

In addition an applicant submitting a supplement under Section 505(b) (described under either 505(b)(1) or 505(b)(2)) for one of the three changes listed above should consider whether new or existing patents claim the change requested in the supplement. If new patents or patent claims cover the changes, the applicant should file information concerning the new patents or patent claims. If existing patents for which information has already been filed cover the change, the applicant should submit a statement informing the agency of which patents cover the change. If no patents, including previously submitted patents, claim the change, the applicant should include a statement so informing the agency.

The agency welcomes comments from you on these issues. Specifically, the agency is interested in comments on whether the list of the three types of supplements for which filing and certification is requested should be expanded or contracted.

EXCLUSIVITY ISSUES

Filing of Exclusivity Information:

Under Sections 505(c)(3)(D) and 505(j)(4)(D), certain applications for drug products submitted under section 505(b) are entitled to a 3-year period of marketing exclusivity, during which the FDA is required to delay the effective date of approval of ANDA's and section 505(b)(2) applications that are submitted for the same conditions of approval. A drug product is entitled to three years of exclusivity if the application or supplement to an application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that are essential for approval. Before approving an application or supplement submitted under section 505(b), the FDA is asking for certain information in order to determine whether the drug product qualifies for three years of exclusivity. This information is not always ascertainable from a review of applications submitted in their current format. To ensure that exclusivity determinations are made as quickly and accurately as possible, we are asking that applicants who believe their 505(b) applications for drug products are entitled to exclusivity submit with their applications or supplements the information and certifications discussed below.

1. The FDA interprets the phrase "new clinical investigations" to mean investigations conducted on humans that have not been used by the agency as part of the basis for a finding of substantial evidence of effectiveness for any previously approved new drug application. The applicant should identify each investigation submitted in the application or supplement meeting these criteria. In addition, FDA requests that the applicant submit a certification that to the best of the applicant's knowledge, the investigation has not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.

2. The agency interprets "conducted or sponsored by the applicant" to mean that before or during the conduct of the investigation, the applicant or the applicant's predecessor in interest provided substantial support for the study. Ordinarily, substantial support will mean providing 50% or more of the cost of conducting the study. Therefore, FDA requests that each applicant seeking exclusivity submit a certification that the applicant sponsored or conducted any study identified in paragraph (1) above, together with information supporting the certification.

3. The FDA interprets the phrase "essential to approval" to mean that the application could not be approved by the FDA without that investigation. If an ANDA or section 505(b)(2) application could have been approved for the drug, even with a delayed effective date, or if publicly available studies, other than those conducted or sponsored by the applicant, could have supported the application, the investigation identified in paragraph (1) will not be considered essential to the approval. Therefore, FDA requests that an applicant submit a list of all published studies or publicly available reports of clinical investigations known to the applicant that are relevant to the conditions of approval sought in the application or the change sought in the supplement. In addition, FDA requests that the applicant submit a certification that (1) the applicant has thoroughly searched the scientific literature and has submitted a complete and accurate list of such published studies and publicly available reports, and (2) in the applicant's opinion, there are not sufficient published or publicly available reports of clinical investigations, other than those conducted or sponsored by the applicant, to support the approval of the application or supplement to the approved application.

The information and certifications described above are material to and will be used by the agency in determining whether a drug or change in a drug qualifies for exclusivity under the provisions of the Act. Timely submission of the requested information and certifications will help expedite agency actions on exclusivity determinations.

As with all previous letters, I encourage your comments on these policies. We will take those comments into account, if possible, when preparing the proposed regulations to implement the 1984 amendments.

Sincerely yours,

Paul Parkman

Paul D. Parkman, M.D.
Deputy Director
Center for Drugs and Biologics