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Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 4-62
5600 Fishers Lane
Rockville, MD 20857

Re: Docket No. 85N-0214-
Proposed Abbreviated New
Drug Application Regulations

Dear Sir:

Pfizer Inc. hereby submits its comments on FDA's proposed regulations to implement Title I of the Drug Price Competition and Patent Term Restoration Act of 1984. This proposal was published at 54 Fed. Reg. 28871 (July 10, 1989).

Pfizer is a research-based corporation engaged in the development, manufacture, and distribution of various products, including human drug products, and thus has an interest in the proposed regulations. These comments are organized in the order of the proposed regulations.

I. Section 314.3 - Definitions

A. Delisting of OTC Drugs

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FDA proposes to withdraw approval of and remove from the list any drug product that is the subject of a new drug application and that may now be marketed OTC pursuant to an OTC final monograph. 54 Fed. Reg. at 28876. FDA's rationale for this proposal is that such drugs are no longer "new drugs" and therefore do not require NDAs. Id. Pfizer objects to two parts of this proposal, but agrees that, if an indication for a particular active ingredient is covered by a final monograph, no ANDA should be required for a product containing that active ingredient and claiming that particular indication. First, FDA's statutory authority to withdraw an NDA simply because a final monograph has been issued is questionable. Second, even if this authority exists, FDA should not apply its proposed policy to products that have both OTC and NDA indications. Pursuant to a recent change in FDA policy, the agency will allow products containing the same active ingredients in the same strength, dosage form, and route of administration to be marketed with both prescription and OTC indications. Pfizer believes that such products must remain on the list, because otherwise the prescription version will be deprived of the patent infringement notification rights and remedies granted by the Waxman-Hatch Act whenever ANDAs that refer to it are filed. Furthermore, it should be made clear that any attempt to promote or sell drugs marketed under the monograph for indications permitted only under an NDA is a violation of both the Waxman-Hatch Act and FDA's OTC policy.

B. Listing of Drugs With Delayed Effective Dates

FDA proposes that drug products approved with delayed effective dates be considered listed drugs to which subsequent ANDAs can refer. 54 Fed. Reg. at 28877. FDA reasons that allowing such referencing "will, in some cases, conserve agency resources and reduce burdens on ANDA applicants." As an example, the agency notes that permitting ANDA applicants to refer to previously approved ANDAs that were the subject of approved ANDA suitability petitions will mean that FDA will not have to review duplicative ANDA suitability petitions. FDA also notes that it intends to respect the patent and exclusivity rights of the original listed drug and therefore the subsequent ANDA will generally share the same effective date as the first approved ANDA.

Pfizer believes that FDA should not adopt this proposed "prelisting" of drugs with delayed effective dates because it is as likely to squander FDA resources as it is to conserve them and because listing of a drug confers a benefit, the publication of patent information and rights attaching to that publication, that Congress intended to confer only upon products facing no legal bar to marketing.

There are three reasons why an ANDA may be approved with a delayed effective date: (1) a full NDA for the active

ingredient involved has Waxman-Hatch exclusivity; (2) the ANDA applicant requests that approval take effect after the expiration of a patent covering the reference drug; or (3) a patent infringement suit is brought by the pioneer drug's sponsor. In each of these situations, the delay between issuance of an approval letter and the effective date of approval will often be several years. During this period of time, the applicant may withdraw the ANDA for any number of reasons. If this ANDA was approved pursuant to a suitability petition and referenced by subsequent ANDAs, then FDA would have to determine whether or not the ANDA was withdrawn for safety and effectiveness reasons and, if it was, suspend any subsequently approved ANDAs and afford their holders an opportunity to show why their ANDAs should not be withdrawn. Proposed §§ 314.153, 314.161. This is particularly likely to occur in the following two situations:

First, it may be revealed during the course of a patent infringement suit that an ANDA with a delayed effective date has a safety or efficacy problem previously undetected by FDA. In at least one instance, this has already occurred. Such an ANDA would then have to be withdrawn. Second, the settlement of a patent infringement suit may require that the ANDA be withdrawn.

The time spent by FDA in determining the reasons for withdrawal of the first ANDA and in withdrawing subsequently

approved ANDAs that referenced it would be saved if FDA did not allow drugs with delayed effective dates to be listed drugs.

II. Section 314.93 - Suitability Petitions

A. Eligible Petitions

Pfizer endorses FDA's proposals to (1) accept suitability petitions only for those changes enumerated in the statute, i.e., changes in route of administration, strength, dosage form, or one ingredient in a combination product, and (2) treat a salt or ester of an active ingredient as a different active ingredient and therefore ineligible for a suitability petition. Both of these proposals are consistent with the statutory language and the intent of Congress.

B. Public Availability of Petitions

FDA specifically sought comments on its present policy of making data and information in a suitability petition publicly available. Pfizer urges FDA to continue this policy because it encourages the submission by third parties of important safety and effectiveness information about the proposed change. Such information is particularly likely to be possessed by the holder of the NDA for the reference drug, who may at one time have considered marketing the proposed altered version of the drug and therefore is in a position to make relevant comments.

III. Section 314.94(a) - Changes in the Listed Drug's Labeling

FDA has made three proposals designed to implement the statutory requirement that the ANDA drug's labeling be the same as that of the listed drug: (1) ANDA applicants must submit side-by-side comparisons of the labeling, with all differences annotated and explained (proposed § 314.94(a)(8)(iv); 54 Fed. Reg. at 28884); (2) ANDAs cannot contain significant changes in labeling, such as new warnings or precautions that are intended to address newly-introduced safety or effectiveness problems not presented by the listed drug (54 Fed. Reg. at 28884); and (3) ANDA applicants must seek approval for all of the indications previously approved for the listed drug except for those indications that are protected by patents or periods of exclusivity (proposed § 314.94(a)(4); 54 Fed. Reg. at 28881). Pfizer strongly supports adoption of these requirements.

In addition, however, Pfizer urges FDA to add one more that is in keeping with their common purpose: require the labeling of an ANDA drug to be revised to reflect changes in the labeling of a listed drug within 30 days of a change in the listed drug's labeling. As noted by the agency, "consistent labeling for duplicate versions of a drug product, insofar as possible, will avoid differences that might confuse health care professionals who prescribe or dispense prescription drug products or might create omissions of significant

information." 54 Fed. Reg. at 28881. There is little doubt that FDA would make ANDA holders revise their labeling to adopt any labeling changes made by the pioneer that are related to safety and effectiveness whether or not such a requirement is in the regulations. By codifying such a requirement, however, FDA will eliminate the need to advise ANDA holders of its requirements each time such a situation arises. This will save FDA resources and help to avoid confusion. Moreover, by requiring that such changes be made within 30 days, FDA will reduce the likelihood that a patient injury will occur as a result of a delay in labeling revision by an ANDA holder.

IV. Section 314.94(a)(12) - Patent Certification

A. Refusal to List Patents Claiming Non-Marketed Products

FDA proposes to refuse to accept and publish in the list information on patents that "claim drug products for which the applicant is not seeking or has not obtained approval." 54 Fed. Reg. at 28885. Pfizer believes that this proposal is contrary to both the language and the spirit of the Waxman-Hatch Act.

The Waxman-Hatch Act directs NDA holders and applicants to submit to FDA information concerning "any patents which claim the drug for which the applicant submitted the application."

§ 505(b)(1). As interpreted by FDA, the term "drug" usually means the active ingredient while the term "drug product" is reserved for the marketed product, i.e., the active and inactive ingredients together. See 21 C.F.R. § 314.50(d)(1)(i) & (ii). Thus, any patent that claims the active ingredient is a patent that "claims the drug for which the applicant submitted the application."

This interpretation comports with the Congressional purpose embodied in the patent filing provision of the Waxman-Hatch Act. In forging the compromise that guaranteed passage of the Act, Congress granted generic drug manufacturers a streamlined approval process and exemption from liability for patent infringement for certain testing done in support of ANDAs. In return, pioneer manufacturers received, inter alia, the benefits of notice of and information concerning possible patent infringement, and a delay in the effective date of an ANDA if a patent infringement suit is brought for a listed patent. Congress intended to "modify" the existing practice under which "FDA [did] not assist the patent holder in enforcing a patent." H.R. Rep. No. 98-857, 98th Cong., 2d Sess., Pt. 2 at 9 (1984). It specified one category of patents - process patents - that were not covered, but otherwise gave no indication that any other patents should be excluded by FDA. Id., Pt. 1 at 32.

By proposing to not list patents that do not claim marketed products, FDA therefore is denying certain patent holders the benefits of notice, information, and delay in approval that Congress granted. The potential resulting harm to pioneers is not just a remote or theoretical possibility, for under the proposal ANDA holders can file suitability petitions and then ANDAs for products that infringe upon unlisted patents covering the active ingredients of a listed drug but that do not infringe upon the patents listed by FDA, if any. The patent holder will in most cases not be aware of the existence of the infringing ANDA prior to its approval and, even if he somehow learns of its existence and files a patent infringement suit, he will be deprived of the 30 month delay in ANDA approval granted by the Waxman-Hatch Act.

Thus, Pfizer believes that FDA should revise its proposal and accept for listing patents that claim drug products for which the applicant is not seeking or has not obtained approval.

B. Use Patents

FDA has proposed that if an ANDA "does not include any indications that are covered" by a method of use patent covering the listed drug, then the ANDA applicant can substitute for a paragraph IV noninfringement or invalidity certification a "statement" explaining why the claimed

indications are not covered by the use patent. In other words, ANDA applicants would unilaterally decide whether or not an indication is covered by a use patent.

Pfizer opposes this proposal because it is contrary to the language of the law, which provides that one of four types of certification shall be made and does not provide for the substitution of a "statement" for a certification. Patent owners will be deprived of the rights and remedies that Congress clearly intended to provide them whenever they believe that ANDAs that are infringing their patents have been submitted to FDA. Their sole recourse will be a standard patent infringement suit. Thus, FDA should require a paragraph IV certification for all method of use patents, thereby protecting a patent holder's statutory right to challenge the ANDA applicant's claim. The argument that such a requirement would encourage the filing of sham or frivolous suits is unavailing, for Rule 11 of the Federal Rules of Civil Procedure provides both a prohibition against and punishment for such a practice.

C. Amended Certifications

The proposed regulation states that "an applicant is not required to amend a submitted certification when the information on a patent on the listed drug is submitted after the abbreviated application is approved, whether or not the

approval of the abbreviated application is effective." Because the statute provides that the patent rights related to a drug product will control the effective date of the right to market a drug, Pfizer believes that any relevant patents filed with FDA before the effective date must be addressed with an appropriate certification.

V. Section 314.95 - Notice of Certification of Invalidity or Noninfringement

A. Information on Formulation and Composition Patents

Pfizer strongly opposes FDA's proposal to use a referee as a means of making information concerning the formulation or composition of an ANDA known to the patent holder. Instead, ANDA applicants should be required to provide patent holders with a list of all components of the drug product and the proportion of those components. This will allow patent holders to make a more informed decision on whether to bring an infringement suit.

B. Publication of Information Concerning Patent Holders

To facilitate notification of patent holders of possible infringement, Pfizer proposes that the name and address of the patent owner or its representative designated to receive notification under the Waxman-Hatch Act be made available by

the FDA. This could be accomplished by a requirement that the identity of such a company and/or individual along with the relevant address be included in the patent information required to be submitted in an NDA. This method would be preferable to the current proposed section 314.51(a)(1), which refers ANDA applicants to U.S. Patent and Trademark Office files, because the individual(s) identified in those files are not necessarily the individual(s) who should receive the notification. FDA could publish the name and address of the designated individuals in the Orange Book.

VI. Section 314.53 - Submission of Patent Information

A. Certification by NDA Applicants

The agency proposes to require NDA applicants to certify that (1) any formulation or composition patents submitted for listing claim the product and (2) any method of use patents submitted for listing cover the use of the product. Such certifications would be required both at the time the NDA is submitted and within 30 days of its approval. Pfizer opposes this provision because it goes beyond the explicit requirements of the Act, which simply requires NDA applicants to "file with the application, the patent number and the expiration date of any patent. . ." Furthermore, the purpose of listing such patent information is to place the ANDA applicant on notice as to all patents it may be infringing. Under the Act, therefore,

the ANDA applicant bears the responsibility to review the listed patents and determine their relevance. The proposal impermissibly shifts this task to the pioneer.

B. Submission of Information Concerning Newly-Issued Patents

Proposed Section 314.53(d)(2) would give NDA holders 30 days in which to submit information concerning newly-issued patents. Because this is not adequate time in which to compile and submit patent information, especially if the NDA holder is a licensee of the patent holder, and because a patent holder sometimes does not receive notice of the issuance of a patent from the Patent and Trademark Office within 30 days, Pfizer suggests that the period be increased to 60 days.

VII. Section 314.107(f) - Notification of Filing of a Patent Infringement Suit

A. Party Responsible for Notification

FDA proposes to require the ANDA applicant to notify FDA of the filing of a patent infringement suit within 45 days of the receipt of notification of claimed non-infringement or invalidity by the patent holder or NDA holder. The proposal, however, contains no penalty for failing to notify FDA. Also, because a failure to notify FDA would allow an ANDA applicant

to avoid the 30 month delay in effectiveness, it creates incentive for such a failure to occur. Pfizer suggests, therefore, that either (1) this provision be dropped and the duty to notify FDA be placed upon the party who brings the suit, or (2) that the ANDA applicant be required to certify that no suit has been filed and lack of such certification or false certification be made grounds for disapproving and withdrawing an ANDA.

In addition, because a suit may not be filed until the 45th day, FDA should give whichever party it places the notification duty upon a reasonable period of time after the date that the party receives notification of the suit within which to notify FDA of the suit's existence. Fifteen days seems to be a reasonable amount of time within which to notify FDA after learning of the suit.

B. Waiver of Suit

FDA proposes to allow either the patent holder or an NDA holder who also is an exclusive licensee to waive the right to bring suit within 45 days of receipt of the notice of certification. Thus, the agency treats the patent owner and the exclusive licensee as equivalent. Because the interests of these two parties may be significantly different, however, Pfizer proposes that FDA amend the proposal so that a waiver is

effective only if consented to by both the patent owner and the exclusive licensee.

VIII. Sections 314.80 and 314.98 - Post-Marketing Reports

A. Deletion of the Word "Significant" from the ADE
Definition

FDA has proposed to revise the definition of the term "adverse drug experience" by deleting the word "significant" in the phrase "any significant failure of expected pharmacological action." 54 Fed. Reg. at 28889. As a result, any adverse drug experience involving a failure of expected pharmacological action that also meets the regulation's definition of serious and unexpected will be subject to the 15 working day reporting requirement. All other failures of expected pharmacological action, i.e., those that are not both serious and unexpected, will be subject to the periodic reporting requirements. FDA states that it is proposing this change because the word significant has been a "source of confusion and ambiguity" and because it considers any report of a failure to produce the expected pharmacological action to be significant.

Pfizer strongly endorses FDA's efforts to achieve its stated intention but believes that the proposed revision will hamper rather than abet the agency's effort to do so. The revision will result in FDA being deluged by meaningless

reports and forced to expend its scarce resources separating a few grains of wheat from silos full of chaff. As discussed below, if FDA is interested in receiving information that is for the most part useful, it will retain the word "significant" in the definition of "adverse drug experience" and eliminate any existing confusion or ambiguity by explaining in more detail the meaning of the word significant. Specifically, Pfizer suggests that FDA explain that a suspected failure of pharmacological action is significant when a patient has a history of effective response to the same active ingredient, whether contained in the same proprietary product or in another manufacturer's product, or if other aspects of the case are so unusual as to make lack of pharmacological action the likely cause of the therapeutic failure.

Standard medical knowledge, common sense, and clinical experience all teach that any drug may fail to produce the desired response in some patients. Such a therapeutic failure may be pharmacological in nature, that is, the drug fails, usually at the molecular or cellular level, to act as that drug is expected to act, or non-pharmacological, that is, the drug acts as it is expected to act but, for some independent reason, the patient's disease or condition is not cured or alleviated.

The existing and proposed regulations require reporting of only the former type of failure^{*}/, which is much less common than the latter. Unfortunately, distinguishing between a pharmacological and a non-pharmacological failure in any given situation may be difficult or impossible. Often the laboratory or clinical tests needed to make such a determination have not been performed. Under the agency's admonishment that sponsors should err on the side of caution, sponsors will, because of lack of information, have to regard almost all therapeutic failures as possibly pharmacological in nature and thus reportable under the proposed revision. In reality, however, only a very small number of these failures will be due to

^{*}/ In making this assertion, Pfizer relies on the plain language of the proposed revision. However, the agency's preamble indicates that it is confused about the difference between these two types of failures, for FDA states that the "proposed revision will unambiguously require that all reports of a therapeutic failure [lack of effect] be submitted to FDA." To the contrary, the regulation revision does not employ the phrase "therapeutic failure" but instead speaks of "failure of expected pharmacological action." These phrases are not equivalent (although the latter is a subset of the former) and thus Pfizer suggests that FDA clarify the preamble language so that it corresponds to that of the regulation.

pharmacological lack of action**/.

Two examples will illustrate these points. First, increased risk of infection is found in virtually all patients with pre-existing conditions such as extreme age, debilitation, immunosuppressive disease or therapy, and chronic illnesses. Therefore, although antibiotics are given to all of these patients if an infection is suspected, failure to recover is probably more likely to be due to the underlying condition as to a failure of the antibiotic. In particular, infection is the most common immediate cause of death for patients with AIDS. Although the patient will usually have already recovered from several infectious episodes, the eventual death is not so much a failure of the antibiotic as it is a failure of the patient's overall condition. Under the existing regulation, however, such a failure would be assessed for its significance and thus may not be reportable within 15 working days. Under the proposed regulation, however, the prudent sponsor will

**/ This appears to be the reasoning used by FDA in an earlier examination of the same language at issue here. In response to comments on the proposed NDA Rewrite, FDA added the word "significant" to the phrase "any failure of expected pharmacological action" in the final version of the NDA Rewrite. 50 Fed. Reg. 7451, 7473 (Feb. 22, 1985) ("[D]rug products are not expected to be effective in all patients" and "While most instances of drug failure would be understood by physicians to represent the usual variances of biological responses, some failures of action are more important.").

report this therapeutic failure, and almost all others, to FDA.

Second, anti-anginal drugs sometimes fail to control anginal symptoms because, as is characteristic of the disease, the underlying pathology of the coronary lesions has progressed over time. As with the antibiotic example above, the drug is producing the expected pharmacological action. Because the usual reaction of the treating physician will be to switch medications without attempting to test for pharmacological action, the pharmacological or non-pharmacological cause of the failure will again not be determined. Thus, as with antibiotics all of these failures will be reportable under the proposed revision.

These examples do not exhaust the sources of adverse experiences that would be newly reportable under the proposed revision, for there are many other classes of drugs for which it will be impossible to separate the small number of pharmacological failures from the large number of non-pharmacological failures. However, when (1) a patient has been shown to respond to a drug in the past, or (2) if other aspects of the case are so unusual that it is more likely than not that there has been a pharmacological failure, then FDA will be able to derive some useful meaning from a 15 day report, that is, be able to focus on potentially important pharmacological failures. Thus, these two types of therapeutic

failures merit FDA's immediate attention and therefore Pfizer believes that they should be subject to the 15 working day reporting requirement.

The remaining reports of therapeutic failure will not be disregarded, nor will any failures of pharmacological action contained in them and missed by the system outlined above go unreported. Another proposed FDA change to the reporting requirements would require sponsors to periodically review all reports of therapeutic failures and report to FDA within 15 days any significant increase of frequency. This second new requirement will reveal any pharmacological failures of action that are otherwise impossible to separate from non-pharmacological failures of action. Moreover, coupled with retention of the word "significant," it will harness the resources of FDA and the industry in a manner designed to most efficiently process the information in which FDA is most interested.

B. Reporting Exemption for ANDAs

FDA is proposing to (1) exempt ANDAs with delayed effective dates from the postmarketing ADE requirements until the approval becomes effective and (2) not require ANDA holders to submit periodic ADE reports if no ADEs are received during the relevant period and the labeling remains the same. Because

Pfizer believes that the postmarketing requirements should apply equally to both ANDA and NDA holders, it opposes these changes.

Pfizer disagrees that requiring holders of ANDAs with delayed effective dates to perform literature searches and otherwise keep abreast of ADEs likely to result from use of their product is unnecessarily duplicative of work done by pioneers. Information derived from these sources is sufficiently important that all approved applicants should be required to monitor them, whether or not they are actually marketing a product.

As for the second exemption, Pfizer agrees that there is no reason to require periodic reporting in the circumstances described, but believes that this rationale applies equally well to pioneers. Thus, the exemption should apply to pioneers as well or to neither class of approved application holders.

IX. Section 314.54 - Section 505(b)(2) Applications

FDA has announced that it will treat applications for duplicates of listed drugs submitted under Section 505(b)(2) as if they had been submitted under Section 505(j). 54 Fed. Reg. at 28890. In addition, the agency sought comment as to several options for dealing with applications submitted under Section

505(b)(2) for changes of the type for which a suitability petition (and potentially a subsequent application) could be submitted under Section 505(j). Id. at 28891. Pfizer suggests that FDA adopt the option of returning the misnomered Section 505(b)(2) application to the applicant and request the submission of a suitability petition. Such applications should not be accepted or treated as Section 505(b)(2) applications because it is clear that Congress intended to create two separate, non-overlapping categories of less-than-full applications. These applications clearly fall into the ANDA category and thus must be treated as such. Moreover, FDA and the public will benefit from the notice to and comments of interested parties under the suitability petition process.

X. Section 314.107(c) - 180 Day Generic Exclusivity

FDA proposes that 180-day generic exclusivity shall be available only to applicants who (1) have been sued for patent infringement following notification to the patent owner and NDA holder of the filing of the certification of invalidity or non-infringement, and (2) have submitted a substantially complete ANDA, that is, an ANDA that contains data from required bioavailability or bioequivalence studies. The agency's rationale for the first half of this interpretation is that only applicants who spend resources litigating a patent's validity should be entitled to exclusivity. Also, FDA asserts

that, in adding the phrase "the first commercial marketing of the drug," Congress contemplated a situation in which an ANDA is in effect but a decision to keep it off the market serves the public interest. Such a situation exists, FDA states, when a patent infringement suit is pending after the expiration of the 30 month effective date delay. 54 Fed. Reg. at 28894-95.

Pfizer opposes this interpretation of the statute for several reasons. First, it is contrary to the plain language of the statute, as FDA acknowledges a Federal district court has held. Second, there is absolutely no basis in the statute or the legislative history for FDA's assertion that it knows what Congress contemplated the public interest to be. Third, FDA wrongly assumes that only applicants who are sued have made the kind of effort deserving of exclusivity. As has indeed already occurred, a generic applicant in pre-litigation defense of its position may be so convincing as to dissuade the pioneer from suing, which seems to be exactly the kind of effort Congress wished to reward. Fourth, FDA's interpretation creates an incentive to litigate and/or to prolong litigation. Such an incentive is rarely in the public interest.

XI. Section 314.108 - Exclusivity

A. Definition of "Active Moiety"

FDA proposes to interpret the five year exclusivity

provision as barring the approval of ANDAs for drugs containing the same active moiety. "Active moiety" is defined as "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 drugs substance." Pfizer believes that this definition is impermissibly restrictive, in that the statute provides for exclusivity for products for which "no active ingredient (including any salt or ester of the active ingredient) of which has been approved." The statute does not, therefore, state that five years' marketing exclusivity is unavailable for other noncovalent derivatives (such as a complex, chelate or clathrate) of the molecule. Such a further restriction on the availability of five years' marketing exclusivity is contrary to common principles of statutory construction. Moreover the development of other noncovalent derivatives of previously approved products could result in exactly the sort of innovative product that the five years' marketing exclusivity was intended to reward. Thus, Pfizer suggests that the term "active moiety" be dropped from the regulations.

Pfizer endorses FDA's proposal that active ingredients (other than esters) that require metabolic conversion to

produce an already-approved active ingredient not be barred by any five-year exclusivity of a product containing the already-approved ingredient.

B. Meaning of the Phrase "Conducted or Sponsored By the Applicant"

Pfizer believes that FDA's proposed 50% of the cost rule is unduly restrictive. Rather, the phrase should be interpreted in accordance with the every day meaning of its words, e.g., to sponsor is to assume responsibility for.

Also, Pfizer disagrees with FDA's statement that an applicant who purchases a study cannot be considered a sponsor because he has taken no financial risk. 54 Fed. Reg. at 28899. This is erroneous because purchasing a study does entail a financial risk, in that FDA may find the study insufficient to support the proposed innovation. More importantly, the rule is inconsistent with FDA's interpretation that the buyer of an NDA receives any exclusivity attaching to that NDA. There are no grounds for distinguishing post-approval sales from pre-approval sales, and thus the rule is illogical.

C. Meaning of the Phrase "Essential to Approval"

Pfizer urges FDA to develop a pre-submission mechanism for

informing sponsors whether a particular study may be considered "essential for approval".

D. Definitions of "Clinical Investigation" and "New Clinical Investigation."

FDA proposes definitions of the terms "clinical investigation" and "new clinical investigation" in proposed Section 314.108(a) yet, in proposed Section 314.50(j)(4)(i), refers to "the definitions of "new" and "clinical investigations" set forth in §314.108(a)." These inconsistencies should be eliminated.

XIII. Determination That A Listed Drug Was Withdrawn For Safety Or Effectiveness Reasons

In order to implement the statutory requirement that ANDAs cannot refer to drugs that manufacturers voluntarily withdrawn for safety and effectiveness reasons, FDA proposes to adopt the following rebuttable presumption: "If a drug manufacturer withdraws a drug from the market which accounted for significant sales to that manufacturer, and there is no evidence to the contrary, it will be presumed that the withdrawal was for safety or effectiveness reasons." Furthermore, the agency specifically seeks comments on a sales figure or other methodology that will be appropriate to establish this presumption. 54 Fed. Reg. at 28907.

Pfizer strongly urges that FDA not adopt this proposal. First, it is inconsistent with the Act, which provides that a drug is considered listed until the Secretary determines otherwise, language that contemplates that the presumption be that withdrawal was not for safety and effectiveness reasons. Second, it is erroneous to presume that manufacturers do not withdraw products for business reasons. Merrell Dow's product Bendectin is a good example of a drug withdrawn for business reasons i.e., product liability concerns. Third, the existence of the presumption could be used against manufacturers in product liability suits. Because the proposal permits any person to petition FDA for a determination of whether a listed drug has been voluntarily withdrawn for safety or efficacy reasons, FDA may find itself being petitioned by private litigants fairly regularly, a less than ideal use of agency resources.

If FDA does adopt the proposed presumption, however, Pfizer suggests that it does not use a sales figure as a means to establish this presumption because this would unfairly skew the presumption against larger companies. For example, if FDA were to use \$3 million in annual sales of a drug as the threshold for establishing the presumption, such a product would represent 1/1000 of the sales of a \$3 billion company and 10% of the sales of a \$30 million company. Withdrawal of such

a product is likely to be inconsequential to the former company and therefore is likely to be for business reasons, while to the second company withdrawal would be a serious or even disastrous event and therefore more likely to occur only if there are safety or effectiveness concerns about the product.

XIII. Section 320 - Bioequivalence

FDA has proposed substantial revisions to the bioavailability and bioequivalence requirements contained in 21 C.F.R. Part 320. In essence, however, these proposals simply codify the existing system used by the agency. The agency has failed to add substance to the requirements for demonstrating in vivo bioavailability or bioequivalence or to expand upon the types of evidence that can establish bioavailability or bioequivalence. As the unfolding generic drug scandal has already amply demonstrated, however, the current system is woefully inadequate at establishing the bioequivalence of ANDAs to listed drugs. Pfizer, therefore, submits that the regulations be amended to include the following:

- (1) A single dose comparison between the ANDA and the listed drug; and
- (2) A multiple dose in vivo comparison between the ANDA drug and the listed drug in a therapeutic setting, i.e., testing in patients with the disease or condition that the drug is intended to treat; and

(3) In vivo testing of two consecutive production size lots.

These requirements are necessary to establish the bioequivalence of an ANDA to a listed drug through in vivo testing.

Sincerely,


James C. Shehan