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**Federal Express-Next Day**

December 17, 2002

Dockets Management Branch  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061 (HFA-305)  
Rockville, Maryland 20852

Re: Docket No. 02N-0417 – Comments of Agvar Chemicals Inc.

Gentleperson:

Agvar Chemicals Inc. submits these comments on the proposal of the Food and Drug Administration (FDA) published October 24, 2002, to revise the agency's Waxman-Hatch regulations. 67 Fed. Reg. 65448. The proposal would revise the regulations with respect to the types of patents that must be, and must not be, listed in the Orange Book, and would revise the type and amount of patent information that must be provided by an NDA holder to the FDA.

The proposal would also revise the notice requirement for paragraph IV certifications to provide that no notice to the NDA holder and patent owner is required if the ANDA applicant has already sent notice of a previous paragraph IV certification contained in the ANDA. This revision would prevent the NDA holder from obtaining an automatic 30-month stay of ANDA approval as a result of bringing a lawsuit for infringement of a subsequently issued patent listed in the Orange Book if a paragraph IV certification to a previously listed patent has been included in an ANDA, and notice of that certification had been given to the NDA holder and patent owner.

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I. The Proposed Administrative Changes Do Not Eliminate the Necessity for Legislative Changes in the Waxman-Hatch Provisions of the Statute

The Drug Price Competition and Patent Term Restoration Act (the Waxman-Hatch Act) became law in 1984. The Waxman-Hatch Act established a system for FDA approval of generic drugs that included features intended, among other things, to preserve and increase incentives for drug innovation and to provide incentives for generic drug companies to challenge patents on reference listed drugs. Experience in the 18 years since 1984 has revealed problems in the Waxman-Hatch Act that were not anticipated by Congress. This is not surprising. It is not feasible to write a complex law that will work exactly as intended and not create unforeseen problems.

The Waxman-Hatch Act has led to problems with Orange Book patent listing. It is well documented and generally accepted that brand companies use patent listings to obtain automatic 30-month stays of ANDA approval. This ability to use patents to delay ANDA approval creates an incentive for brand companies to obtain additional patents. Often the principal value of these patents is not that they protect useful inventions but that they can be used to obtain automatic stays. It has been demonstrated that some of these patents should not even be listed in the Orange Book. Some patents are inappropriately listed in the Orange Book because the FDA does not screen patent submissions, and because there is no effective mechanism for generic companies to challenge Orange Book listings.

The Waxman-Hatch Act has also led to problems with the 180-day generic drug exclusivity incentive. This incentive is awarded to the first ANDA with a paragraph IV certification. Because that ANDA blocks approval of subsequent ANDAs until the 180-day exclusivity period can be used, the right to 180-day exclusivity has formed the basis for anti-competitive arrangements between some brand and generic drug companies. The 180-day exclusivity provision can also inappropriately delay generic drug competition in other situations.

These and other problems with the 1984 law should be addressed by focused, remedial legislation. Only by fixing the statute itself can problems

created by the statute be resolved with certainty. In the last Congress, Waxman-Hatch reform legislation was passed by the Senate and introduced in the House. FDA should support the reintroduction and enactment of this legislation in the next Congress. The FDA's proposal, on which we comment below, would not resolve the problems that have developed since 1984, and would distract from necessary legislative reform that would solve the problems.

## II. Comments on Proposed Changes in FDA's Regulations

### A. Orange Book Patent Listing

#### 1. Packaging, metabolites, and intermediates.

FDA proposes to clarify its patent listing criteria. As clarified, the criteria would not permit the listing of patents on drug packaging or containers, on metabolites of active ingredients, or on chemical intermediates of active ingredients, i.e., substances that are not themselves present in finished active ingredients. 67 Fed. Reg. at 65451-52. Agvar agrees with this part of the proposal.

#### 2. Different polymorphs and waters of hydration

Agvar does not agree with that part of FDA's proposal that would permit the listing of patents on chemical variants of active ingredients, such as different polymorphs or substances with different waters of hydration. 67 Fed. Reg. at 65452-53. In fact, the agency agrees that this provision would change its current interpretation of the Waxman-Hatch Act. 67 Fed. Reg. at 65452.

The FDA gives two reasons for this proposed change. The first reason is that FDA regards some chemical variants of an active ingredient as therapeutically equivalent to the approved active ingredient, and in these cases the agency approves ANDAs that contain such variants. However, under the statute, it is the scope of the NDA as approved that determines "the drug" that must be "claimed" by a patent in order for the patent to meet the statutory listing requirement. 21 U.S.C. § 355(b)(1), (c)(2). A chemical variant of the drug that is not authorized in the NDA is not "the drug for which the applicant submitted

the application.” Therefore, under the terms of the statute, a patent on that chemical variant does not qualify for Orange Book listing.

The FDA notes that approval of an ANDA containing the chemical variant represents the agency’s conclusion that the variant is “the same” active ingredient under the ANDA approval requirements. See 21 U.S.C. § 355(j)(2)(A)(ii). As an argument that a patent on a chemical variant should be listed in the Orange Book, FDA’s reliance on the “sameness” determination as to the active ingredient in a proposed generic drug is misplaced. The ANDA approval provisions of the statute include requirements relating to “sameness,” requirements that authorize deviations from “sameness,” and requirements in which “sameness” is irrelevant. These provisions are relevant only to approval of an ANDA. They do not relate to what a brand company must submit as part of its NDA.

For this reason, injecting ANDA approval requirements into the interpretation of NDA content requirements – of which the patent listing criterion is a part – would be unjustified. It would also raise questions about listing other patents that do not claim “the drug” approved in the NDA but which might be infringed by a drug approved in an ANDA. For example, if a generic company gets a suitability petition approved for a dosage form different from the reference listed drug, the ANDA product might infringe a patent on that dosage form. Under Pfizer v. FDA, 753 F. Supp. 171 (D.Md. 1990), that patent is ineligible for Orange Book listing. But under FDA’s logic – that listing a patent on an unapproved active ingredient is justified due to “sameness” – it could be argued that listing a patent on an unapproved dosage form should be permitted due to the potential “suitability” of an ANDA for that dosage form.

Agvar recommends that FDA adhere to its current interpretation of the patent listing language of the Waxman-Hatch Act by limiting eligibility to patents that claim the active ingredient and formulation that are approved in the NDA. This interpretation will not, as the proposal suggests, disadvantage generic companies by depriving them of notice of patents that an ANDA product might infringe. Avoiding this disadvantage is the second reason FDA gives for expanding the patent listing criteria to include patents on unapproved variants of the active ingredient. Generic companies have alternate sources of patent information. If a generic company seeks approval of a chemical variant of the

active ingredient, it will know that any patents on the variant are not listed in the Orange Book. In that situation, the generic company will know that it is necessary to examine alternate sources of information to identify relevant patents.

It is not the purpose of the patent listing provision of the Waxman-Hatch Act to provide notice of all patents that an ANDA drug might arguably infringe. FDA would be ill advised to try to make Orange Book patent listing “more useful” to generic companies by blurring the listing criteria, especially at a time when there are serious problems as a result of brand companies taking advantage of vague language in FDA’s current listing regulations and FDA’s unwillingness to police the listing process.

### 3. Product by process patents

The FDA proposal would explicitly authorize the listing of product by process patents in the Orange Book. 67 Fed. Reg. at 65452. The basis for this proposal is that the claims of a product by process patent “must particularly point out and distinctly claim the product or genus of products for which patent protection is sought.” *Id.* (citing *In re Brown*, 459 F.2d 531, 535 (C.C.P.A. 1972)). However, the FDA proposal also states a concern that persons might “seek to list process patents” out of confusion about the distinction between process and product by process patents, and invites comment on ways to ensure that only appropriate product by process patents are listed. *Id.*

As we understand it, a product by process patent is necessary for a drug when the active ingredient or formulation of the drug cannot be “properly defined . . . otherwise than by reference to the process of producing” them. *In re Bridgeford*, 357 F.2d 679, 682 (C.C.P.A. 1966). We do not believe that there are likely to be many active ingredients or formulations subject to NDAs that meet this test. Most NDAs are for well-characterized, small-molecule active ingredients whose relevant attributes are described in the NDA. The same is true of the formulations of these active ingredients.

Before issuing a final rule that specifically allows the Orange Book listing of product by process patents, the FDA should investigate the types of product by process patents that have already been listed. As part of its investigation, the

FDA should determine whether the active ingredients or formulations for which these patents have been listed are adequately characterized and described in their NDAs by the usual objective measures. If they are, the FDA should answer the question of whether these product by process patents do, in fact, claim the active ingredient or formulation, or simply a trivially specific version of the approved ingredient or formulation that is produced by a particular process.

Patents of the latter type might literally “claim” a product rather than a process. However, any “product” that is claimed is not one that is required in order to meet the terms of the NDA with respect to the active ingredient or formulation that is approved in the NDA. That is, the NDA requirements for the approved active ingredient or formulation would be satisfied by a “product” produced by alternative processes, if the NDA applicant chose to use those processes. This type of product by process patent should not be listed because it does not claim the active ingredient or formulation as defined and approved in the NDA. At a minimum, FDA should not list a product by process patent for an active ingredient or formulation if there already is an Orange Book listed patent that purportedly claims the active ingredient or formulation approved in the NDA.

#### B. Greater Patent Disclosure

The FDA proposal would require NDA sponsors, and holders of approved NDAs, to submit more detailed patent information than is currently required, and to make more specific representations about how a listed patent claim relates to the reference listed drug than is provided for in the current declaration.  
67 Fed. Reg. at 65453-54.

Agvar generally supports this part of the proposal. However, we also urge FDA to apply these more detailed disclosure provisions to all currently listed patents insofar as those provisions are a clarification of the agency’s existing requirements rather than new or different requirements. As an example, the proposal states, “[w]e note that, as is currently the case, patents that claim methods of use that are not approved for the listed drug or are not the subject of a pending application may not be submitted.” 67 Fed. Reg. at 65452.

As is generally known, the Orange Book now contains method of use patents that claim conditions of use that are not approved in the NDA for a drug. There is no justification for permitting these patents to remain listed on the basis of the currently effective, but “unclarified,” patent declaration. See 21 C.F.R. § 314.53(c)(2). The vague wording of this declaration, which can be expansively interpreted, has no doubt encouraged the listing of patents that, according to FDA, may not be listed. If, in fact, a currently listed method of use patent is eligible for Orange Book listing, the NDA holder will have no difficulty providing the information requested in the proposed regulation. If it cannot provide the information, the patent listing should be withdrawn.

Applying the new patent information provisions to existing patent listings would not be the retroactive enforcement of a new rule. The rule would not be new. It would be the old rule more clearly expressed. FDA’s position as to the rule itself – patents on unapproved uses may not be listed – has been clear since at least 1989, when the FDA stated:

With respect to a use patent, the agency proposes to require an applicant to submit a certification that identifies each patent that claims indications or conditions of use that are approved or are the subject of the application for which the applicant is seeking approval. Because all indications or conditions of use for which an applicant sought approval may not be approved, within 30 days after the date of approval of the application, if the original application submission included a certification about a method of use patent, the applicant would be required to submit an amended certification identifying the approved indications or conditions of use and the patents that claim those uses.

54 Fed. Reg. 28872, 28909 (July 10, 1989).

Similarly, NDA holders should be given the opportunity to provide information responsive to the clarified patent listing criteria for active ingredients and formulations, or else withdraw inappropriately listed patents from the Orange Book.

C. Paragraph (viii) Statements for Listed Patents  
Claiming Unapproved Uses

There is an additional issue relating to the Orange Book listing of method of use patents for conditions of use that are not approved in the NDA for the reference listed drug. The FDA proposal does not raise that issue. The issue is as follows. The Waxman-Hatch Act permits an ANDA applicant to refrain from certifying to a listed method of use patent if the ANDA applicant makes a statement that the applicant does not seek approval for a use claimed in the listed patent. This statement is known as a “paragraph (viii)” statement, after the section number of the statute that provides for it. See 21 U.S.C. § 355(j)(2)(A)(viii).

The FDA’s policy, however, is not to accept a paragraph (viii) statement for a patent that claims an unapproved use. This policy forces the ANDA applicant to submit a paragraph III or a paragraph IV patent certification. Either certification is disadvantageous to the ANDA applicant.

The FDA’s policy is unjustified and should be changed. If the agency is not prepared to police Orange Book patent listings to screen out patents on unapproved uses, it should at least accept paragraph (viii) statements to those patents. Under its current policy, FDA not only acquiesces in impermissible Orange Book patent listings but also denies ANDA applicants the statutory choice of not certifying to those patents for the reason that, essentially, the patents do not belong in the Orange Book to begin with. This policy is doubly unfair to generic drug companies.

D. Notice of Paragraph IV Certification

The FDA proposal requests comment on whether the agency’s regulations governing the ANDA applicant’s notice of a paragraph IV patent certification could or should be amended. 67 Fed. Reg. at 65454. Agvar believes that there is statutory authority for revising the notice provision to require specific types of information. The statutory prohibition against requiring information “in addition to that required by clauses (i) through (viii)” of section 505(j)(2)(A) does not apply to information required to be included in a notice under section 505(j)(2)(B)(ii). Therefore, FDA may, by regulation, specify the content of the notice in more detail than it does at the present time. Agvar notes that the current

regulation for providing notice of a paragraph IV certification goes beyond the explicit, but general, requirements of the statute. See 21 C.F.R. § 314.95(c).

Even if the prohibition against requiring additional information applied to the ANDA applicant's notice of a paragraph IV certification, a more detailed specification of the minimum contents of a notice would not require information "in addition" to what is specifically required. Rather, it would simply define the contents of information that already is specifically required.

It is Agvar's view that the Waxman-Hatch system will work more effectively in the public interest if both brand name and generic companies carry out their statutory obligations in a way that supports the goals of Congress. In this instance, the goal of Congress was to provide brand name companies with a full explanation of an ANDA applicant's position that a listed patent is invalid or not infringed, so that the brand company could exercise its rights under the Waxman-Hatch Act. Amending the paragraph IV notice regulation to be more specific about the information the ANDA applicant must provide the NDA holder and patent owner would support that goal.

E. Automatic 30-Month Stay

The FDA proposal would interpret the Waxman-Hatch Act to limit the automatic 30-month stay to one stay per ANDA. 67 Fed. Reg. at 65454-56. The stay would be based on a paragraph IV certification to any Orange Book listed patent, no matter when the patent was issued.

In comparison, the Greater Access to Affordable Pharmaceuticals Act, S. 812, passed by the Senate on July 31, 2002, would limit the automatic stay to one stay per ANDA based on only those patents listed in the Orange Book when an NDA was initially approved. Subsequently issued and listed patents could be the basis for a court injunction against approval, but the brand name company would have to meet the accepted judicial standard for justifying such a remedy.

In general, the patents listed in the Orange Book when an NDA is initially submitted are basic patents representing the results of significant research that has led to a real pharmaceutical innovation. Later issued patents typically represent less significant scientific and technical work, and are more often of

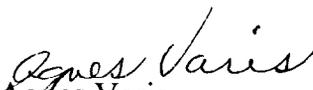
questionable validity based on the patent laws. Yet under FDA's proposal, the later issued patents would benefit from the automatic 30-month stay on a par with initially listed patents.

Agvar understands that FDA does not have unlimited legal discretion to create the most sensible approach to the multiple 30-month stay issue. The fact remains, however, that giving an automatic stay in connection with the less worthy and more questionable of the patents likely to be listed in the Orange Book is an unjustified result that perpetuates the incentive for brand companies to obtain patents that would not be worth the time and money involved if it were not for the ability to obtain the equivalent of an automatic 30-month preliminary injunction.

FDA may believe that their proposal might reduce the magnitude of the 30-month stay problem but it would not deal with the fundamental problem of weak patents being artificially strengthened by the availability of an automatic preliminary injunction. In addition, the FDA proposal relies on an interpretation of statutory language subject to second-guessing by the court system, and, therefore, is subject to the uncertainties of any potential litigation.

For the reasons explained in part I of these comments, the best way to solve the problem of multiple 30-month stays is through legislation that corrects the problem at its source, i.e., in the current statutory language. Such legislation would also address other problems, which FDA is not authorized to deal with under the current law.

Cordially yours,  
Agvar Chemicals Inc.

  
Agnes Varis  
President