



9171 02 DEC 24 19:51

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

Phone: (215) 591 3142
FAX: (215) 591 8812

December 23, 2002

Dockets Management Branch
U.S. Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852

Docket No. 02N-0417: Applications for FDA Approval to Market a New Drug: Patent 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. Comments of Teva Pharmaceuticals USA.

Teva Pharmaceuticals USA, Inc. (Teva) appreciates this opportunity to comment on the FDA's October 24, 2002 proposed rule, *Applications for FDA Approval to Market a New Drug: Patent 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*, 67 Fed. Reg. 65448, and commends FDA and the Bush Administration for its efforts to re-balance the current generic drug approval system under Hatch-Waxman. The proposed rule would amend FDA's current regulations to:

- (1) "clarify the types of patents that must and must not be listed" in FDA's publication *Approved Drug Products and Therapeutic Equivalence Evaluations* (the "Orange Book"), and revise the declaration NDA applicants must submit in order to request patents to be listed in the Orange Book; and
- (2) change the applicability and operation of the regulations governing so-called Paragraph IV Notifications such that ANDA applicants need not (or may not) submit more than one "Paragraph IV Notification" for any particular ANDA. The stated purpose of this proposal is to limit the number of 30-month approval stays per ANDA.

Teva is pleased and encouraged by FDA's recognition in the proposed rule that the current system of patent listing and 30-month stays is not operating as intended by Congress and that significant changes must be implemented to restore the crucial purpose of the Hatch-Waxman amendments to facilitate the prompt and predictable market entry of affordable generic versions of life-saving and life-enhancing therapeutic products. However, for the reasons discussed herein, Teva respectfully suggests (1) that the proposal would unlawfully expand the

02N-0417

C22

statutory provisions governing patent listing eligibility, (2) that FDA's proposal does not go as far as it could, and should, to provide for effective enforcement of the patent listing requirements, and (3) legislative changes are necessary to fully restore the balance sought by Congress. Teva urges FDA to modify the proposal in several respects, and to adopt a more proactive position in favor of new legislation immediately upon commencement of the 108th Congress.

I. CHANGES TO PATENT LISTING CRITERIA AND PROCEDURES

The listing of a patent in FDA's Orange Book is a powerful procedural mechanism that is heavily skewed in favor of brand name drug marketers because it allows them to receive early notice of a generic company's plans to launch a competing product and to unilaterally delay approval of a generic applicant's Abbreviated New Drug Application (ANDA) for 30 months or longer. Section 505(b)(1) sets forth mandatory criteria for which patents must, and must not, be submitted to FDA for listing in the Orange Book. Specifically, the statutory listing provision provides that only a "patent which claims the drug for which the applicant submitted the application" may be listed. 21 U.S.C. § 355(b)(1). Unfortunately, FDA has abdicated its obligation to enforce this provision of the statute that it is mandated by Congress to administer, and as a result inappropriate patents have been listed in the Orange Book resulting in unwarranted 30-month stays delaying ANDA approval. *See e.g., Allergan v. Alcon*, 200 F. Supp. 2d 1219, 1230, n. 9 (C.D. Cal. 2002) ("It is worth noting that the regulations issued by the FDA suggest that the '415 and '741 Patents should not have even been listed in the Orange Book. The regulations, found at 21 C.F.R. § 314.53(b) provide that 'for patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use of a pending or approved application.'"); *Andrx v. Biovail*, 175 F. Supp. 2d 1362 (S.D. Fla. 2001); *Mylan v. Thompson*, 139 F. Supp. 2d 1 (D.D.C. 2001), *rev'd. on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001); *Abbott Labs. v. Novopharm*, 104 F.3d 1305 (Fed. Cir. 1997). *See also*, Federal Trade Commission Citizen Petition, FDA Docket No. 01P-0248 (May 16, 2001); Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* at 37 (July 2002) ("most of the later-issued patents in the Orange Book raise questions about whether the FDA's patent listing requirements have been met. For example, many of the later issued patents do not appear to claim the approved drug product or an approved use of the drug.").

In recognition of these increasingly common listing violations, the proposed rule would specifically prohibit the listing of process patents, as well as patents claiming packaging, metabolites, and drug intermediates. However, it would specifically allow the listing of product-by-process patents, and would expand the definitional criteria for "drug substance" patents for purposes of Orange Book listing. Under the rule, FDA will only allow Orange Book listing of:

- Patents that claim the drug substance (as redefined in the proposed rule),
- Patents that claim the approved drug product (formulation and composition),
- Product-by-process patents, and
- Patents that claim an approved method or condition of use.

The Proposed Rule would also require NDA sponsors to submit a detailed declaration regarding each patent, that purportedly will prevent improper listings, but which, without active meaningful enforcement by FDA, will at best only deter the listing of some patents that do not meet the statutory listing criteria.

A. “Clarification” of Listable Patent Types

Teva strongly supports FDA’s willingness to clarify the types of patents that may be listed in the Orange Book, especially to the extent FDA reinforces the previously neglected prohibitions against listing packaging/container, metabolite, process, and drug intermediate patents. Teva also appreciates FDA’s reiteration of the requirement that patents on unapproved indications or conditions of use are prohibited from being listed. However, Teva strongly opposes the proposal to allow listing of patents claiming a different physical form of the active ingredient approved in the NDA product (including, e.g., polymorphs, hydrates, and solvates)¹, because such listing would be inconsistent with the statute, and because FDA’s stated reasoning for this position could lead to an even broader range of irrelevant patents being listed in the Orange Book.

1. The Statute Prohibits Listing of Patents Claiming Different and Unapproved Physical Forms of an Active Ingredient Even if Such Form Could Be Therapeutically Equivalent to the Approved Form.

The Proposed Rule would unlawfully expand upon the plain and limited language of the statutory patent listing criteria by allowing the listing of patents claiming different physical forms of an active ingredient, where such form has not been approved in the NDA for the Reference Listed Drug (RLD). The governing statutory listing provision provides that only a “patent which claims the drug for which the applicant submitted the application” may be listed. 21 U.S.C. § 355(b)(1) (emphasis added). However, FDA has proposed that for patent listing purposes “drug substance” will now include not only the form of the drug substance in the approved innovator product, but also “a drug substance that is the ‘same’ as the active ingredient that is the subject of the approved or pending [NDA] within the meaning of section 505(j)(2)(A)(ii) of the act.” *Proposed* 21 C.F.R. § 314.53(b). This means that patents could be listed that claim “polymorphs” of the drug substance that are different than the form approved in the NDA, but which *could potentially* be approved in an ANDA as being the “same” active ingredient as that approved in the NDA.

FDA rationalizes this approach, in part, by asserting that “if a generic drug product can be the ‘same’ as the reference listed drug, notwithstanding differences in the drug substances’ physical form, then it is consistent to interpret ‘drug substance,’ for purposes of listing patent

¹ For purposes of these comments, and for convenience, different physical forms of active ingredients will be referred to collectively as “polymorphs.”

information, as including drug substances having different physical forms.” 67 Fed. Reg. at 65452, col. 3. This reasoning misses a crucial point, however, because even where an alternative polymorph could be demonstrated to be the “same” for purposes of ANDA approval, that does not change the fact that the polymorph is not “the drug for which the [NDA] applicant submitted the application.” 21 U.S.C. § 355(b)(1). FDA admits as much when it emphasizes that a change from one polymorph to another will always require FDA approval, 67 Fed. Reg. at 65453. Because an NDA would require supplemental approval to change to a different polymorph, that new polymorph could not have been one “for which the applicant submitted the [original] application,” and therefore any patent claiming such a polymorph may not be listed under the plain language of the statute.

This distinction is essential to properly interpreting the meaning of the statutory patent listing criteria, because if the statute were intended to allow listing of patents on all forms and polymorphs of a drug regardless of their approval status, it would have been wholly unnecessary for Congress to limit Orange Book listings to patents which claim the drug substance “for which the [NDA] applicant submitted the application.” Indeed, if the statute meant what FDA proposes, it would have been superfluous for Congress to have included the limiting condition, “for which the applicant submitted the application,” because the statute could (and would) have simply stated that an NDA applicant must submit information on “any patent which claims the drug or which claims a method of using such drug....” Alternatively, if Congress had intended to permit FDA’s position, it could have provided for the listing of “any patent which claims any form of the drug for which the applicant submitted the application....” Congress did not use either of these straightforward approaches in drafting the statutory listing criteria, but rather it unambiguously limited listing eligibility to those patents that directly correspond to the drug substance and drug product specifically approved in the NDA. FDA’s attempt to re-engineer the statutory language and intent would be contrary to law, arbitrary, and capricious.³

It is axiomatic that when construing a statute, the agency and the courts must give effect to each statutory provision and should be hesitant to “adopt an interpretation of a congressional enactment which renders superfluous another portion of that same law.” *Kawaauhau v. Geiger*, 523 U.S. 57, 62 (1998), quoting *Mackey v. Lanier Collection Agency & Service, Inc.*, 486 U.S. 825, 837 (1988). See also *United States v. Generix Drug Corp.*, 460 U.S. 453, 458-59 (1983) (reversing Court of Appeals decision that rendered portion of statutory “drug” definition superfluous). Here, because FDA’s interpretation would effectively read out of the statute the term “for which the applicant submitted the application,” the proposal to allow the listing of patents on unapproved polymorphs and other unapproved forms of the active ingredient must be withdrawn.

³ In this respect, as explained in the comments of the Generic Pharmaceutical Association (GPhA), FDA also confuses the difference between what it means for a patent to “claim” a specific form of a drug substance, and for an alternative form of the substance to be bioequivalent to the form approved in the NDA for the brand name product. If Congress had intended to allow the conceptual overlap now proposed by FDA, it would have crafted very different statutory language.

2. FDA's "Drug Substance" Redefinition Would Lead to Results Directly at Odds With Other Express Provisions of the Regulations

Furthermore, FDA's attempt to use the concept of "sameness" for ANDA approval purposes to modify the meaning of "drug substance" under 21 C.F.R. § 314.53, is flawed because it would impermissibly blur the definitional distinction between "drug product" and "drug substance" as applicable to the patent listing provisions. This would lead to results contrary to FDA's own stated interpretations. Specifically, as FDA emphasizes, an NDA sponsor would be required to obtain FDA approval to change the polymorph or chemical form of the active ingredient in its product, because it would be creating a new "drug product" – i.e., a product with a new "formulation and composition." Under FDA's proposed expansion of the definition of "drug substance" however, an NDA sponsor's listing of a polymorph patent would in effect be the same as listing a patent which claims an unapproved drug product. This result would be directly contrary to the express provision of the proposed rule (and prior practice) that "for patents that claim a drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application." *Proposed* 21 C.F.R. § 314.53(b) (emphasis added). This eminently correct rule simply cannot be reconciled with the proposal to allow listing of patents on unapproved polymorphs and alternative forms of an approved drug substance. FDA must amend the proposed rule to specifically prohibit the listing of patents on unapproved polymorphs and alternative forms of the approved drug substance.

3. FDA's Reasoning Would Lead to Dangerous and Unintended Consequences

FDA's underlying rationale for allowing the listing of patents on unapproved "drug substances" for which a competing generic product might be approved could undermine the balance sought by FDA by potentially allowing the listing of patents on other components or elements that are not approved in the NDA product. For example, generic parenteral, ophthalmic, otic, and topical drug products generally must contain the same active *and inactive* ingredients as the reference drug product, with the exception of preservatives, buffers, and antioxidants (for parenteral, ophthalmic, and otic products), and substances to adjust tonicity (for ophthalmic and otic products), provided that the ANDA applicant shows that the different inactive ingredient(s) do not affect safety or efficacy. *See* 21 C.F.R. §§ 314.94(a)(9)(iii)-(v). Some inactive ingredients have been the subject of patents, e.g., the preservative EDTA used in Zeneca Inc.'s Diprivan brand propofol, and currently when such a patented inactive ingredient *is actually present* in the approved drug product the patent is listable in the Orange Book, but it is not listable when it does not occur in the approved NDA product.

Using FDA's rationale – that patents may be listed if they claim an active component that might be included in a pharmaceutically and therapeutically equivalent generic product – NDA sponsors might seek to list patents on all possible buffers, antioxidants and preservatives even though they are not used in the Reference Listed Drug. This would result in even more inappropriate patents being listed, giving NDA sponsors an unwarranted advance notice of potential generic competition based on the listing of patents in which they have no legal interest or connection, and further increasing the delay potential for ANDA applicants. It is not at all

clear that FDA's reasoning, if adopted, can reasonably be limited to the "drug substance" situations identified in the proposal, and to even slightly increase the potential for such strategies would be bad public policy. FDA should clarify that to be listed in the Orange Book, a patent on a drug component (whether active or inactive) must claim a component that is actually approved in the reference NDA.

4. FDA's Stated Purpose on Proposed Listing of Unapproved Drug Substances is Unnecessary and Counterproductive.

FDA's additional justification for listing patents on unapproved forms of a drug substance – that "missing patent information could mislead potential ANDA applicants into submitting ANDAs containing" a patented polymorph or molecular form of the drug substance – is unnecessary, and underestimates the legal sophistication and scientific acuity of the modern generic drug industry. Specifically, generic drug companies today spend millions of dollars per year in patent searches and analyses, not only to identify relevant issued patents, but to track pending U.S. and foreign patent applications that may impact their product development plans. Indeed, given that other types of potentially infringed patents cannot be listed in the Orange Book (e.g., process patents), no prudent generic applicant would rely solely on the Orange Book for a determination of its freedom to pursue a particular application. For this reason as well, the expanded patent listing proposal should be withdrawn.

5. FDA Should Narrow The Scope of Listable Patents

Aside from these objections, if the proposed rule is to go forward FDA should clarify the listing criteria by identifying (but without limiting) other types of patents that are ineligible for Orange Book listing because they do not claim the drug or drug product *per se*, for example: business method patents; and patents claiming substances which may or may not be present as impurities in a drug product ("impurity patents").

B. Enhanced Patent Listing Declaration

Despite several high-profile examples of improperly listed patents, and court decisions restricting ANDA applicants' ability to independently challenge the listing of ineligible patents in the Orange Book, FDA, in its proposed rule still refuses to undertake any meaningful enforcement of the statutory Orange Book-listing criteria. Instead, the agency proposes an enhanced form of patent listing declaration to be submitted by NDA sponsors "to help ensure that only appropriate patents are listed." 67 Fed. Reg. at 65453. Teva supports FDA's proposal to strengthen the patent listing declaration, but urges the agency to adopt certain modifications to the proposed declaration system. In addition, Teva disagrees with FDA's suggestion that it lacks the *authority* to review patents for listing eligibility, and requests that the agency adopt a specific proactive mechanism for such review.

1. FDA Is Authorized to Review The Eligibility of Patents for Inclusion In The Orange Book, and Should Adopt a Mechanism for Such Review

The FDA is *the* federal agency charged by Congress with the responsibility of enforcing the provisions of the Federal Food, Drug, and Cosmetic Act. A crucially important provision of the FDCA is section 505(b)(1), which, in part, provides that an NDA applicant

[s]hall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such 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.... Upon approval of the application, the Secretary [FDA] shall publish information submitted under the two preceding sentences.

21 U.S.C. § 355(b)(1) (emphasis added). FDA's only administrative mechanism to enforce this provision, 21 C.F.R. § 314.53(f), is in reality no enforcement mechanism at all because it leaves the determination of whether a patent remains listed in the Orange Book wholly within the discretion of the NDA sponsor. Specifically, if an ANDA applicant challenges the listability of a patent by notifying FDA pursuant to section 314.53(f), so long as the NDA sponsor does not voluntarily change or withdraw the patent information originally submitted to FDA for listing, "the agency will not change the patent information in the [Orange Book]... despite any disagreement as to the correctness of the patent information." *Id.*

FDA's assertion that it does not have the *authority* to review patents for listing eligibility, and its claim that the courts have agreed, 67 Fed. Reg. at 65453, is simply not a fair representation of the statute or the cited caselaw. First, the statutory listing provision is a mandatory, substantive requirement imposed upon NDA sponsors, and Congress has empowered FDA with at least one specific remedy for non-compliance with this provision – refusal to approve the NDA. See 21 U.S.C. § 355(d)(6) (FDA may not approve an NDA if it "failed to contain the patent information prescribed by subsection (b)."). The only patent information "prescribed by subsection (b)" is information regarding patents "which claim[] the drug for which the applicant submitted the application or which claim[] a method of using such drug...." 21 U.S.C. § 355(b)(1). FDA may only list patent "information submitted under" section 505(b), 21 U.S.C. § 355(j)(7)(A)(iii), and the only possible way to interpret this provision's use of the term "submitted under" is that it necessarily requires the patent information to have been submitted lawfully and *in compliance with* that provision. Thus, information on a patent that does not meet the statutory listing criteria cannot be deemed to be "information submitted under" section 505(b)(1) for purposes of FDA's listing obligation.⁴ 21 U.S.C. § 355(j)(7)(A)(iii). As

⁴ For example, if an NDA sponsor submitted "patent information" that consisted solely of the title of the patent, the name of the inventor, and the address of the laboratory where the invention occurred, FDA would not list the patent because the information was not "prescribed by" or "submitted under" section 505(b)(1). This is because section 505(b)(1) includes the substantive requirement that the information to be submitted must be "the patent number and the expiration date" of the patent. However, the same statutory provision also includes the substantive requirement that the patent must "claim[] the drug for which the applicant submitted the application." FDA acts

(Footnote continued)

such, not only must FDA refuse to list the patent in the Orange Book, it must also refuse to approve the NDA because it “fail[s] to contain the patent information prescribed by subsection (b).” It is untenable to suggest, as FDA does, that Congress would require FDA to deny approval to an NDA that fails to comply with the patent listing requirements, yet intend to allow the NDA applicant itself to be the ultimate arbiter of its own compliance. Yet that is exactly the system that FDA has maintained, and the unintended anticompetitive consequences have been well documented.

Moreover, the cases cited by FDA as having “concurred in [FDA’s] view that [it] lack[s] the authority to review the ‘listability’ of patents,” 67 Fed. Reg. at 65453, do not in fact hold that FDA may not substantively enforce the statutory listing provisions. Rather, the cases FDA relies on for its brand new lack-of-authority position,⁵ *American Bioscience v. Thompson, Watson Pharm. v. Henney, Mylan v. Thompson*, and *In re Buspirone Patent Litigation* all turned on FDA’s existing regulatory choice to not affirmatively enforce the statutory patent listing provisions. However, just because the courts have upheld, or commented favorably upon, FDA’s current hands-off regulatory approach does not in any way preclude the agency’s authority to adopt a different regulatory scheme in which FDA would actively enforce the statutory listing requirements. The following brief summary of the cases FDA relies upon demonstrates the errors of FDA’s analysis.

American Bioscience v. Thompson, 269 F.3d 1077 (D.C. Cir. 2001) involved the question of whether Bristol-Myers Squibb had *in fact* submitted information on another company’s patent related to the drug paclitaxel at the time of the relevant ANDA approval. The court rejected FDA’s determination that the patent information was not *actually submitted* at the time of the ANDA approval, but neither FDA nor the court addressed whether the patent met the substantive listing criteria of claiming the drug that had been approved in the NDA. Nor did the court address whether FDA would have had the statutory authority to reject the listing on such grounds. Rather, the court merely suggested that “it is not at all clear to us that the FDA, under its regulations, would be authorized to reject the obvious intent of an NDA holder even if it acted directly contrary to a court order [to de-list a patent].” *Id.* at 1085 (emphasis added). Thus, *American Bioscience* poses no barrier to FDA adopting new, substantive review and enforcement regulations for implementing the statutory patent listing requirements and restrictions.

arbitrarily and capriciously to the extent it enforces one part of section 505(b)(1), but not other parts of the same statutory provision.

⁵ Prior to this proposal, FDA itself had never claimed a lack of authority to review patents and enforce section 505(b)(1). Rather, the agency had simply asserted that it lacked the *expertise, resources, and willingness* to do so. See 54 Fed. Reg. 28872, 28909 (July 10, 1989) (“Because FDA has no expertise in the field of patents, the agency has no basis for determining whether a use patent covers a use sought by the generic applicant.”); 59 Fed. Reg. 50343 (Oct. 3, 1994) (“FDA does not have the expertise to review patent information. The agency believes that its scarce resources would be better utilized in reviewing applications rather than reviewing patent claims.”); and *id.* at 50349 (“the agency does not have the expertise or desire to become involved in issues concerning patent law...”).

Similarly, the other cases cited by FDA did not directly present, much less resolve, the question of FDA's statutory authority, but rather turned on the agency's current regulatory scheme, and judicial deference to that regulatory scheme. In *Watson Pharmaceuticals v. Henney*, the court did not rule on the FDA's statutory authority, but rather stated that "[i]n this case, under the regulations in force now, the Court concludes with no difficulty at all that the FDA's action in listing the '365 patent was plainly not, as a matter of law, in contravention of the well-settled standards for federal agency action so as to be vulnerable to being set aside on judicial review." 194 F. Supp. 2d 442, 446 (D.Md. 2001) (emphasis added). Likewise, *Mylan v. Thompson*, 139 F. Supp. 2d 1, 10-11 (D.D.C. 2001) did not involve a direct challenge FDA's non-review of a patent listing; rather, Mylan sued Bristol-Myers Squibb ("BMS") and FDA, seeking an order directing BMS to request de-listing of its patent, and for FDA to ministerially accept such a de-listing request by BMS.⁶ The court of appeals ultimately held that there is no private authority for a generic company to seek the de-listing of a patent. Finally, *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 363 (S.D.N.Y. 2002), involved a motion to dismiss antitrust and related state law claims, which turned on whether or not FDA in fact exercises any discretion in listing patents submitted for inclusion in the Orange Book. Although the court cited to sections 505(b)(1) and (c)(2) of the act and concluded that "the FDA's actions are non-discretionary and do not reflect any decision as to the validity of the representations in an Orange Book listing," it also based this conclusion on the *American Bioscience*, *Watson*, and *Mylan* cases, each of which, as shown above, turned on the FDA's current regulatory listing scheme. Thus, *In re Buspirone* did not reach the ultimate question of whether the statute leaves room for a different regulatory scheme in which FDA would review the listability of patents.

Because the statute and caselaw do not bar, and in fact would support, a scheme of substantive FDA review of the listability of patents submitted for Orange Book listing, FDA should use this rulemaking to adopt an effective enforcement scheme for determining whether submitted patents in fact claim the drug or a method of using the drug for which the NDA was submitted. An outline of one possible scheme is discussed *infra*.

2. The Proposed Patent Listing Declaration System Should Be Strengthened

Teva supports the proposed patent listing declaration, but recommends that the system be further strengthened in several respects.

First, in order for the revised patent declaration to serve as a useful check on patent listing abuses, the declaration must be made public immediately upon approval of the NDA. This will allow those with the most at stake – potential ANDA applicants, consumers and government and private end-payers– to promptly consider whether the declaration is accurate.

⁶ See 139 F. Supp. 2d at 12 ("Mylan asks the court to declare that Bristol improperly submitted the '365 patent to the FDA for inclusion in the Orange Book because that patent did not meet 21 U.S.C. § 355(c)(2)'s requirements for such a listing. Mylan also asks that the court, upon making this determination, order Bristol to withdraw its submission of the '365 patent, and instruct the FDA to perform the "ministerial" task of de-listing the '365 patent from the Orange Book.").

Second, FDA should adopt a mechanism for reviewing the eligibility of patents for inclusion in the Orange Book, and for de-listing patents that are found to be ineligible. One possible mechanism would be to amend 21 C.F.R. § 314.53(f) such that any challenge to the appropriateness of a listed patent will be referred to an FDA Administrative Law Judge (ALJ), or other designated hearing officer, who will review the patent in conjunction with the conditions of approval of the NDA product and make an administrative recommendation to the Commissioner as to whether the patent claims the drug or an approved use of the drug.⁷ Upon a recommendation that the patent is ineligible for listing, it should be removed from the Orange Book. Upon a recommendation that the patent is eligible, the Commissioner should issue a final affirmative order that the patent be listed. An aggrieved party would then have the right to appeal the final listing or non-listing to the courts, pursuant to 21 C.F.R. § 10.45.

Such a procedure need not and should not involve an unfettered interpretation of the scope of the patent, nor will it involve any question of patent validity or infringement. Rather the ALJ or other hearing officer would merely make a determination of whether the submission of the patent information (and its listing by FDA) complied with the governing provisions of the FDCA, i.e., section 505(b)(1). To facilitate a reasonable and expeditious determination (which should be required within 60 days of the hearing), the ALJ may allow page-limited briefing (supported as necessary by appropriate declarations) by both the NDA sponsor and the ANDA challenger, on the issue of whether and/or how the patent meets the statutory listing criteria. Contrary to the current system in which FDA's inaction amounts to a de-facto determination that a patent does meet the listing criteria, under this straightforward approach there would now be an actual substantive basis for the decision. Thus, it would solve the problem identified by Judge Huvelle in the recent case *Purepac Pharmaceutical v. Thompson*, No. 02-1657 (ESH) (D.D.C. December 16, 2002), specifically, that FDA's "self-abnegation creates the possibility for conflict between NDA holders and ANDA applicants over the proper scope" of a listed patent. *Id.* Slip Op. at 22. And the prudential advantage would be that FDA's decision would be subject to meaningful judicial review, whereas under the current system ANDA sponsors have no effective means of judicial review. In this way, patent owners and NDA sponsors would be held to the requirements of section 505(b)(1) in a way that would provide protection to ANDA applicants, while not diminishing the ultimate rights under the patent.

Third, FDA should clarify and explain what degree of oversight FDA will use in reviewing the accuracy of patent listing declarations, and what if any remedy will be available for incorrect declarations that result in a patent being improperly listed. As recent history has demonstrated, brand name drug companies are extremely aggressive and creative in their representations to FDA concerning patent listing issues. Without a meaningful FDA review of the accuracy of the enhanced declaration, and an enforcement mechanism with real teeth, NDA sponsors may continue to focus their "innovative" efforts on devising ways to manipulate and distort the proposed listing declaration process. Thus, Teva urges FDA to publicly and

⁷ FDA has broad discretion to allow a regulatory hearing with respect to "any regulatory action, including a refusal to act," and to establish the rules and procedures applicable to a particular regulatory hearing. 21 C.F.R. §§ 16.1(a), 16.60(h). The Commissioner may also delegate the authority to serve as a hearing officer to any agency employee, 21 C.F.R. § 16.42.

unequivocally commit to prosecuting false statements and other violations of the new listing mechanisms as criminal offenses, naming both the sponsor company and the responsible individuals as defendants.

Fourth, FDA should fully adopt the listing declaration questions proposed by GPhA in connection with the January 2002 Hatch-Waxman symposium hosted by FDA Chief Counsel Daniel Troy, and described more fully in GPhA's comments to this proposed rule, and in line with Teva's proposed criteria for patent listings.

Fifth, FDA should use this rulemaking to clarify and strengthen the Orange Book "use code" mechanism to prevent abusive tactics by branded companies, such as listing use codes that are so broad that they overlap with other use codes, or use codes for unapproved indications. FDA should therefore use the information in the new patent declaration to directly ascertain whether method of use claims cover uses approved by FDA for the RLD. Moreover, FDA should take the initiative to ensure that for listed method of use patents, the approved labeling elements covered by the patent are identified with specificity to allow complete and accurate use code definitions. This will allow generic applicants to promptly and accurately carve out any protected use information for which they do not seek approval.

II. THE SINGLE 30-MONTH STAY PROPOSAL

FDA's proposal would add a single provision to the Paragraph IV Notification regulations, 21 C.F.R. § 314.95, stating that "This paragraph also does not apply if the [ANDA] applicant amends its application to add a certification under § 314.94(a)(12)(i)(A)(4) [i.e., a Paragraph IV Certification] when the application already contained a [Paragraph IV] certification...to another patent." *Proposed* 21 C.F.R. § 314.95(a)(3). The requirement that is made inapplicable by the new provision is the requirement that "[f]or each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and that the applicant certifies...is invalid, unenforceable, or will not be infringed, the [ANDA] applicant shall send notice of such certification" to the NDA sponsor and each owner of the patent. 21 C.F.R. § 314.95(a) (emphasis added). According to FDA, by not requiring a Paragraph IV Notification with respect to subsequent challenged patents, the statutory 30-month stay provision will not be available for patent owners and NDA sponsors with respect to such patents.

Teva agrees with and supports the spirit of the agency's proposed rule as a positive step in the right direction, but Teva cannot support this aspect of the proposed rule as written, because it will not prevent many of the abuses that have arisen in the past. The rule would be somewhat more effective if it is implemented so that subsequent Paragraph IV Notifications and 30-month stays remain available at the option of the ANDA applicant, but even under that approach, several significant loopholes will remain unaddressed. Moreover, FDA must recognize (1) that given the aggressive and highly competitive nature of both the branded and generic segments of the pharmaceutical industry, and the dramatic change in policy embodied in the proposed rule, a judicial challenge to the rule (if finalized) is a strong possibility; and (2) that even if FDA ultimately prevails against any such challenge, the proposal does not obviate the need for a

prompt legislative solution to the many other problems inherent in the current system. Thus, even as the Agency proceeds to evaluate and respond to the submitted comments, the Administration should finally engage in the legislative process in a positive way to help enact comprehensive, and balanced, reforms to Hatch-Waxman.

A. FDA's Proposal Would Only Address One of Many Circumstances in Which Orange Book Abuse Has Previously Occurred and Would All But Foreclose Judicial Remedies Under Many Other Circumstances.

An important element of the Hatch-Waxman patent challenge scheme is the mechanism to allow pre-approval litigation of potential future infringement by a generic product. The 30-month stay aspect of this mechanism, which is procedurally intertwined with the Paragraph IV Notification procedure, protects generics from the risk of ruinous damages for infringement of the patent if necessary. It does so by allowing a judicial determination of invalidity and/or non-infringement prior to marketing, but as highlighted by the FTC Report, it has also led to abuses. Although the proposed rule would reduce some such abuses by limiting the availability of 30-month stays, it would provide greater protection if it is implemented to allow optional notifications on subsequent patents, with corresponding additional stays. It is not clear from the proposed regulation or the preamble exactly how FDA intends to implement the 30-month stay limitation with respect to these issues, but the answer is vitally important because in some circumstances an ANDA applicant may wish to seek the certainty of a court decision on a subsequently challenged patent before marketing.

If finalized as written, and implemented so as to prohibit more than one Paragraph IV Notification, the proposed rule would only reduce the risk of improper delay associated with trivial/ineligible patents that are inappropriately listed after another patent has been challenged by a Paragraph IV Certification and Notice. Under these limited circumstances, the proposed rule would relieve an ANDA applicant of the need to provide notification with respect to such a patent and would thereby avoid an additional 30-month stay. However, there are several other common scenarios in which this narrow interpretation of the proposed rule would provide no protection, and in fact could make things even worse.

First, the proposed rule does not provide a mechanism for ANDA applicants to pre-litigate patents that are not the first to be listed and challenged for a particular drug. For example, in the uncommon but not unheard of circumstance where an ANDA contained a Paragraph IV Certification on filing as to one patent, and a subsequently listed patent raised significant questions of validity and/or infringement, the applicant may not be able to resolve those issues as to the second patent before marketing of its product and before subjecting itself to potentially ruinous damages. This shortcoming would be remedied in large part if FDA were to implement the proposal in a way that allows ANDA applicants the option to provide multiple Paragraph IV Notifications and voluntarily open themselves up to subsequent 30-month stays. This is because NDA and patent holders would have a greater incentive to litigate the subsequent patents prior to ANDA approval.

Second, where the initial or only patent(s) are improperly listed, there is no mechanism to challenge their listing, and ANDA sponsors will be unnecessarily forced to file a Paragraph IV Certification and Notification and potentially face an improper 30-month stay.

Third, where the initial patent is properly listed, valid, and dominating (e.g., a valid patent claiming the approved form of the drug substance), such that ANDA applicants must submit a Paragraph III Certification, the NDA sponsor would retain a free hand to improperly delay generic approval. Specifically, the NDA holder could subsequently list (perhaps on the eve of the first patent's expiration) a patent that is weak or narrow (not dominating, e.g., a formulation patent) and thereby subject ANDA applicants to an inappropriate 30-month stay because it would be the first challenged patent. FDA's proposal provides no relief in these circumstances because it will still put the ANDA sponsor at risk of a 30-month stay based on an improper patent.

Because so much of the proposed scheme would depend on serendipity and/or patent timing issues that may be subject to manipulation by patent holders, it does not provide for the predictability and timeliness of generic approvals that are an essential part of the intended balance of Hatch-Waxman.

B. If Finalized, The Proposed Regulations Should Be Interpreted To Encompass Optional Subsequent Paragraph IV Notifications

The FDA's position should be restated to make clear that while an NDA holder is only entitled to a single paragraph IV notification and 30 month stay for any ANDA, generic applicants are allowed to voluntarily provide optional Paragraph IV Notifications for a second (or subsequent) listed patent, which may result in additional 30-month stay or stays. The answer to whether voluntary subsequent notifications and 30-month stays will be permitted may well determine whether Teva supports or opposes this change.

In considering whether an ANDA applicant would be absolutely limited to providing a single Paragraph IV Notification, or whether an applicant could *voluntarily* provide a Paragraph IV Notification for a second (or subsequent) listed patent, and if so whether an additional 30-month stay would be available, FDA should recognize that the proposal could be interpreted to allow such voluntary subsequent notifications. This is because the regulatory notification provision of subsection 314.95(a)(1) is currently mandatory for all Paragraph IV Certifications (“the applicant shall send notice of such certification...”), but by making this provision “inapplicable” for subsequent Paragraph IV Certifications, it arguably just makes the mandatory nature of the notification inapplicable and leaves open the option of a voluntary second (or third) notification. Although FDA's discussion of the rule states that “only one 30-month stay in the ANDA's approval date is possible,” 67 Fed. Reg. at 65455, it also seems to suggest that it is only removing the obligation to submit a subsequent notification. *See id* (“the addition of a second Paragraph IV Certification ... would not trigger an *obligation* to provide a second notice...”) (emphasis added). Thus, FDA should clarify that the statement that “only one 30-month stay in the ANDA's approval date is possible,” 67 Fed. Reg. at 65455, refers to what is possible for the NDA holder to expect, rather than what is possible for an ANDA applicant to obtain. Such optional notification (and the 30 month stays which would ensue if the patentee brought an

action on the optional notification) would be good for the patentee, and good for the ANDA applicant.

The FDA's observation that under its proposal patent holders can still enforce their subsequently listed patents and seek damages and injunctive relief under 35 U.S.C. §§ 283 and 284, 67 Fed. Reg. 65455 points out the advantage to the patent holder of early resolution of patent disputes, even without the advantage of the thirty month period. Optional notification would simply give the patent holders the possibility of obtaining an additional thirty month period or periods – and would add an incentive to list all appropriate patents. Although FDA notes that patent owners do not need notification to sue on subsequent patents for which no notification was received, without the possibility of a 30-month stay, patent owners may instead choose to wait until generic marketing and seek potentially ruinous damages.

Moreover, if the proposed rule did not allow optional notifications, ANDA sponsors might not be able to bring declaratory judgment actions to seek a pre-approval judicial decision in those cases in which the patent holder does not sue, because the statute restricts the courts' jurisdiction to decide declaratory judgment actions brought under an ANDA until 45 days after service of a Paragraph IV Notification. If no notification is received, arguably no declaratory action could be brought, thus removing a powerful tool to speed the entry of generic drugs on to the market. *See generally, Teva Pharmaceuticals v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999).

Without an option to serve additional Paragraph IV Notifications, FDA's proposal could severely undermine the ability of ANDA sponsors to seek pre-approval judicial resolution of validity and infringement issues in many of the circumstances in which previous Orange Book abuses have occurred.

III. LEGISLATION IS STILL NEEDED TO RESTORE THE INTENDED BALANCE AND CLOSE REMAINING LOOPHOLES

Even if FDA finalizes the proposed rule in any form, there will remain numerous problems and loopholes in the Hatch-Waxman scheme that can only be addressed by new legislation, including but not limited to the following.

First, it should be emphasized that a simpler and more effective means of avoiding multiple 30-month stays would be to eliminate the stay altogether and replace it with a specialized preliminary injunction standard that would allow NDA sponsors to seek protection of their patents pending resolution of the Paragraph IV patent litigation, but that would not *automatically* give a 30-month windfall exclusivity for even the weakest of listed patents. Alternatively, FDA should support legislation that would allow a 30-month stay only for patents listed within 30 days of initial NDA approval, and that would bar future enforcement of a patent against an ANDA applicant if the patent owner does not promptly list the patent in the Orange Book and bring a Paragraph IV infringement action within 45 days of an ANDA applicant's Paragraph IV Notification.

Moreover, even with the FDA's proposed curbs on inappropriate patent listings and limited 30-month stays, the 180-day exclusivity period for first Paragraph IV ANDA filers still creates the possibility of extended blockage of approval for subsequent ANDA filers. Thus,

FDA should support legislative changes that would establish 180-day exclusivity period forfeiture provisions to prevent exclusivity holders from unduly delaying another generic product's launch (e.g., where the applicant fails to market within 60 days of a final approval or a final appellate court decision (whichever is later), or fails to obtain at least tentative approval within 30 months, or fails to challenge subsequently listed patents). Such a forfeiture provision would eliminate the problem of FDA's current "shared" patent-by-patent exclusivity approach by allowing the first Paragraph IV applicant a grace period of 60-days to challenge a subsequently listed patent and if no such challenge is brought the exclusivity is forfeited.

In the event FDA does not implement a regulatory mechanism for the substantive review of patents submitted by NDA holders, including an effective means for de-listing ineligible patents, FDA should support legislation that would provide for meaningful enforcement of the listing requirements. A private cause of action whereby ANDA applicants can seek a judicial determination of the listability of patents would be one such legislative alternative.

In addition, FDA should support legislation to confirm and codify the agency's longstanding bioequivalence regulations, in order to reduce the likelihood of legal challenges to FDA's scientific decisions regarding approval of certain types of generic drugs.

Finally, misuse of the supplemental 3-year exclusivity provision of Hatch-Waxman, 21 U.S.C. § 355(j)(5)(D)(iv) to delay generic competition is rapidly becoming a major problem, as brand name companies make creative, but minor, labeling changes (often related to minor safety issues) in such a way as to make "carving out" the protected labeling aspects while maintaining a complete and grammatically coherent generic label difficult or impossible. Recent labeling changes to the Ultram (tramadol) labeling is just one example of such tactics, and FDA should either establish a regulatory solution, or support legislation that would reform the supplemental exclusivity system (i.e. mandate preservation of appropriate verbiage in reference drug labeling to permit a carve out of protected information), and/or specifically codify FDA's longstanding policy that exclusivity is unavailable for safety related labeling changes. *See* 54 Fed. Reg. 28872, 28899 (Proposed Rule, July 10, 1989), 59 Fed. Reg. 50338, 50356-57 (Final Rule, October 3, 1994).

CONCLUSION

Teva appreciates and supports much of FDA's proposal and its intentions, but as discussed herein, there remain numerous open questions that need to be clarified before any final rule is promulgated. In addition, administrative tweaking of the current regulations can in no way achieve the broad reforms that are necessary to restore the intended balance of Hatch-Waxman. Teva urges the FDA and the Administration to work with the generic industry to achieve prompt, effective, and balanced legislative changes beginning immediately.

Respectfully submitted,

