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

Re: Docket No. 00D-1537-- Draft Guidance for Industry on Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications

Dear Sir or Madam:

Johnson & Johnson submits these comments to the above-referenced docket, relating to the draft industry guidance on using labeling discontinued for a listed drug in an abbreviated new drug application (ANDA) for that drug.

Under the draft guidance, an ANDA applicant that cannot legally duplicate the entire labeling of the relevant reference listed drug because such labeling is protected by patent or other exclusivity rights could potentially substitute earlier, discontinued labeling of the listed drug. The draft guidance would create a mechanism by which FDA would decide whether to permit that substitution, based primarily on FDA's judgment whether the old labeling was withdrawn for safety or effectiveness reasons and whether use of the old labeling would render the product less safe or effective than the currently labeled product. Since there would have to have been a clinical study supporting the listed drug's labeling change, the new labeling would likely contain improvements in safety or effectiveness compared to the previous labeling. The draft guidance nevertheless appears to contemplate that FDA would decide whether the difference in safety and effectiveness is substantial enough to bar the generic drug's use of the old labeling. FDA would make that analysis in a potentially secret proceeding, or at best a proceeding in which the innovator could merely submit comments on a petition, and FDA would decide the degree of difference permitted in safety and effectiveness for a particular product without reference to any published standards.

The proposed policy allowing substitution of discontinued labeling is fundamentally different than the agency's current policy of permitting omission of protected indications and may produce

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an unprecedented and potentially dangerous result -- different labeling for the same drug for the same indication. Johnson & Johnson contends that this draft guidance (1) constitutes a material change to existing regulations governing labeling for the approval of generic drug products under ANDAs; (2) can only be effectuated through rulemaking provisions of the Administrative Procedure Act (APA); (3) is inconsistent with the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman amendments); and (4) for the reasons set forth below, represents a poor regulatory policy. Therefore, Johnson & Johnson requests that the agency withdraw this draft guidance.

I. The Draft Guidance Would Change Existing Law and Regulatory Requirements.

FDA contends that referencing discontinued labeling of a listed drug in an ANDA is a matter "not addressed directly" in the current regulations. Draft Guidance at lines 27-28.[1] The agency further notes that "[t]he question of whether an ANDA could refer to previously approved but subsequently altered labeling had not arisen previously." Draft Guidance at lines 176-77. The FDA is wrong that this is a novel situation. A review of the current *Orange Book* yields nearly ten instances in which exclusive terms in the listed drug's labeling replace unprotected terms because the FDA has approved a supplemental new drug application (SNDA).[2] We are aware of no instance, however, where a generic drug was approved for marketing bearing discontinued labeling while the listed drug's labeling was marketed using the protected labeling.

It is not surprising that no one has ever raised this question before because the existing regulations settle the matter -- the agency cannot approve an ANDA where the proposed labeling substitutes discontinued information for the protected terms in the currently approved labeling. In short, a basic element of the regulations is to allow for only limited omissions in ANDA labeling, which necessarily precludes the type of labeling substitutions contemplated in this draft guidance. Moreover, the regulations make clear that the generic labeling must match "currently approved" labeling for the listed drug, which again, by its terms, bars reliance on discontinued labeling. Thus the draft guidance, issued as the non-binding "current thinking" of the agency, really constitutes a change in the existing regulatory requirements.

The Federal Food, Drug, and Cosmetic Act, as amended by the Hatch-Waxman amendments, (the Act) requires that an ANDA contain:

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[1]The numbers in the draft guidance citation refer to line numbers in the PDF version of the document, in accord with the citation form requested by the agency. Draft Guidance at line 19.

[2]Examples, such as Aredia (pamidronate) and Neurontin (gabapentin), are discussed more fully below.

> information to show that the labeling proposed for the [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because . . . the [generic] drug and the listed drug are produced or distributed by different manufacturers.

21 U.S.C. § 355 (j)(2)(A)(v) (1999).

Based on this statutory language, FDA has promulgated detailed regulations governing the submission and consideration of ANDAs. At the outset, only those drug products that are the "same as" the listed drug are eligible for approval pursuant to an ANDA, where FDA has defined "same as" to mean

> identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent *may be omitted.*

21 C.F.R. § 314.92 (a)(1) (2000) (emphasis added). Neither the Act nor the regulations define the term "conditions of use," but FDA's position, as stated in the Preamble to the proposed rule implementing the ANDA approval process, was that "conditions of use . . . include, among other things, indications and dosage instructions." 54 Fed. Reg. 28881 (July 10, 1989). Accordingly, nothing in the current regulations contemplates that pioneer and generic products carry different instructions for use.

With respect to labeling, the regulations require that the ANDA applicant compare its proposed labeling to "currently approved" labeling for the listed drug. 21 C.F.R. § 314.94 (a)(8) (2000). The ANDA applicant must state that the labels are the same except for an enumerated list of allowable differences, the most relevant for the issues raised by the draft guidance being "*omission* of an indication or other aspect of labeling protected by patent or accorded exclusivity under [the Act]." 21 C.F.R. § 314.94 (a)(8)(iv) (2000) (emphasis added).

Thus, while it is established that generic labeling can omit a protected element of innovator drug labeling, see Bristol-Myers Squibb v. Shalala, 91 F.3rd 1493 (D.C. Cir. 1996), the agency cites no regulatory basis for substituting unprotected, but obsolete, terms into the generic label. An analogous example illustrates the regulatory shift that is proposed in this draft guidance. FDA would clearly prohibit the manufacturer of an innovator drug from marketing two versions for the same indication that are identical except for dosing instructions that differ for marketing reasons. For example, if the sponsor of a new drug application for a product to treat a cardiac condition filed for a labeling change via an SNDA to incorporate a new, patented dosing regimen and then upon approval of the supplement sought agency permission to simultaneously market the product under the same brand name to general practitioners using the old labeling and to cardiologists

using the new labeling, FDA certainly would deny that request. The supplement creates new labeling to replace the old labeling that then must be discontinued.

Yet the draft guidance, in the context of a generic product, countenances marketing akin to the example above. FDA asserts that once the unprotected information is removed, there is no "current complete labeling for the ANDA applicant to reference." Draft Guidance at lines 56-57. Thus the agency would allow the ANDA holder to reference prior complete labeling. But existing regulations contradict such a reference. The only comparator for the ANDA applicant is the currently approved labeling. If the ANDA applicant can omit the protected information, substitute the obsolete information, and prove that its drug is still as safe and effective as the listed drug, then the agency can approve the application, but such an approval would be an NDA, not an ANDA. Otherwise, the ANDA applicant must wait until the term of the exclusivity related to the particular labeling expires.

II. In Any Event, This Substantive Shift in FDA Rules Must be Made Pursuant to the APA.

Section 553 of the APA requires FDA to (1) publish notice of a proposed rulemaking in the Federal Register; (2) give interested parties an opportunity to comment on the published proposal; and (3) promulgate the final rule in the Federal Register not less than 30 days before the effective date of the rule. 5 U.S.C. § 553 (1996). General statements of policy and interpretative rules are exempt from APA notice and comment rulemaking, but substantive rules must meet those requirements. 5 U.S.C. § 553(b)(3)(A) (1996).

Although this draft guidance purports to be a non-binding statement of "current agency thinking," it constitutes a change in existing regulations. The agency has announced that it will in effect adopt some sort of sliding scale of exclusivity rights for labeling changes based on relative improvement in safety and effectiveness. Although the agency has published the guidance in the Federal Register and allowed an opportunity to comment before the guidance is "finalized," FDA's effort falls short of the APA's provisions.

Granted, FDA characterizes the draft guidance as a policy statement that "does not create or confer any rights for or on any person and does not operate to bind FDA or the public." Draft Guidance at lines 10-11. It is settled, however, that it is the substance of what the agency has purported to do that is decisive, not the label placed upon the action by the agency.[3] Indeed, the

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[3] See Columbia Broadcasting System, Inc. v. United States, 316 U.S. 407, 416 (1942); United States Chamber of Commerce v. OSHA, 636 F.2d 464, 468 (D.C. Cir.1980) ("we do not classify a rule as interpretive just because the agency says it is."); Citizens to Save Spencer Cty. v. EPA,

(continued...)

policy/interpretative rule exemption must be construed very narrowly so as not to avoid the appropriate application of the APA's general rulemaking requirements.[4]

Notwithstanding FDA's characterization, this guidance fits within the contours of a substantive rule. Courts have set out factors for making the sometimes difficult distinctions between policy statements, interpretative rules and substantive rules. A policy statement is binding on neither the public nor the agency -- "[i]t merely represents an agency position with respect to how it will treat . . . the governing legal norm." Syncor International Corp. v. Shalala, 127 F. 3d 90, 94 (D.C. Cir. 1997). This guidance, by contrast, creates a new legal norm by setting out a detailed approach to allow a practice not permitted by existing regulations.

An interpretative rule, like a policy statement, does not involve creation of new legal standards. Instead, it focuses on an agency's interpretation of existing law. Syncor, 127 F. 3d at 94-95. In fact, courts may require an agency to hew closer to APA requirements for a regulatory interpretation than a statutory interpretation because they recognize the need to limit an agency's ability to evade the APA via interpretative rule "modifications" of formally promulgated substantive rules. Id. Since the regulation setting out the requirements of generic drug labeling was issued in accordance with APA requirements, the courts will reject putative interpretations that are in reality modifications. The draft guidance here constitutes an attempt at such a modification.

The United States Court of Appeals for the District of Columbia Circuit, which has the largest APA caseload, has listed four factors, any one of which would identify a rule as substantive rather than interpretative. The factors are:

> (1) whether in the absence of the rule there would not be an adequate legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties, (2) whether the agency has published the rule in the

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[3](...continued)
600 F. 2d 844, 879 n.171 (D.C. Cir. 1979) ("The label that the particular agency puts upon its given exercise of administrative power is not, for our purposes, conclusive; rather it is what the agency does in fact.").

[4] See Orengo Caraballo v. Reich, 11 F. 3d 186, 195 (D.C. Cir. 1993) (courts "have been careful to construe section 553 (b) (A)'s exceptions to the rulemaking requirements narrowly."); United States v. Picciotto, 875 F. 2d 345, 347 (D.C. 1989) ("APA's notice and comment exemptions must be narrowly construed.").

> Code of Federal Regulations, (3) whether the agency has explicitly invoked its general legislative authority, or (4) whether the rule effectively amends a prior legislative rule.

American Mining Congress v. MSHA, 995 F. 2d 1106,1112 (D.C. Cir. 1993).

The draft guidance meets the fourth factor by effectively amending a prior legislative rule. It is a settled matter of administrative law that "[i]f a second rule . . . is irreconcilable with [a prior legislative rule], the second rule must be an amendment of the first; and, of course, an amendment to a legislative rule must itself be legislative." National Family Planning v. Sullivan, 979 F. 2d 227, 235 (D.C. Cir. 1992). FDA's current regulations allow ANDA applicants only to omit protected labeling information from the current labeling of the listed drug. The draft guidance eliminates this limitation and allows substitution of obsolete information from previous labeling. The draft guidance, therefore, is a substantive rule, as was the original regulation, and it should be subject to the full APA rulemaking requirements.

III. The Draft Guidance Is Inconsistent with ANDA Statutory Provisions.

The problems with the draft guidance go beyond compliance with the APA. It is Johnson & Johnson's position that this proposal also does not comport with the statutory provisions that authorize the ANDA process. Those provisions establish very specific parameters for the agency's consideration of an ANDA and this draft guidance falls outside those limits.

Under the proposed guidance, the Office of Generic Drugs could approve an ANDA that references discontinued labeling, if the discontinuation was not "for reasons of safety or effectiveness" and the "omission of the protected information will not render the [generic] product less safe or effective" than the listed drug. Draft Guidance at lines 106-110. See also lines 227-229. There are problems with that approach. At one level it does not go far enough, in that the standard will be whether the "omission of protected information" impacts safety or efficacy of the generic drug. The true test should be whether the substitution of obsolete information affects safety and efficacy.

At another level, the approach goes too far in that it sets up the agency to make comparative safety and effectiveness assessments related to labeling that are outside the scope of the ANDA process. Under the mechanism in the draft guidance, an ANDA applicant will propose a generic product with labeling that differs from that of the reference listed drug, and it will argue to FDA that the proposed labeling is as safe and effective as the currently approved labeling of the listed drug, or at least close enough that it should be permitted to use the discontinued labeling. FDA will then, in the context of an ANDA, assess the safety and effectiveness of the generic drug's proposed labeling. That assessment is not permitted. The Act allows the agency to consider the

safety of inactive ingredients in the ANDA process, 21 U.S.C. § 355 (j)(4)(H) (1999), but there is no such statutory authorization with regard to labeling, where the only touchstone is sameness to the listed drug's labeling. 21 U.S.C. § 355 (j)(4)(G) (1999). If such a comparative safety and efficacy assessment is necessary for approval, then the drug in question should not be reviewed via the ANDA process. The draft guidance, therefore, would establish unlawful criteria for ANDA approvals by creating what amounts to a hybrid ANDA route to approval -- a route to approval found nowhere in the statute.

IV. The Draft Guidance Conflicts with Fundamental Statutory Policies.

In addition to the procedural and legal problems that exist, Johnson & Johnson believes this draft guidance undermines a number of the Act's basic policy principles. Those principles include the need to (1) maintain an adequate incentive to develop labeling improvements for listed drugs and (2) avoid labeling confusion that could result in negative clinical impacts on patients.

A. The Proposal Undermines Incentives for Improving the Safety and Effectiveness of Marketed Products.

The classic policy balance struck in the Hatch-Waxman amendments involves making generic drugs more widely available to the public while maintaining adequate incentives for innovation. The draft guidance gives short shrift to the innovation incentive side of the equation. One premise of the guidance is that the holder of the NDA "has obtained exclusivity or patent protection for a new aspect of product labeling." Draft Guidance at lines 52-53. By definition, therefore, this new labeling was novel enough to justify issuance of a patent or was the subject of new clinical studies that were essential to the approval of an SNDA. In return for developing this innovative aspect of labeling, the Act provides for some measure of exclusivity.

Despite these statutory provisions that establish specific exclusivity terms, the draft guidance proposes to eliminate that incentive by allowing an ANDA applicant to avoid the innovation through reference to discontinued labeling. Granted, the guidance seeks to remove the incentive only for labeling that can somehow be determined not to unduly affect safety or effectiveness, but the reality is the agency's proposed action could chill a wide range of efforts to produce better product labeling. The innovator should be able to understand and rely upon the scope of exclusivity when it undertakes the studies necessary to develop new labeling. By creating the potential to alter the effect of the exclusivity at some future date based on an unpredictable and unfettered exercise of FDA's discretion, the guidance will deter innovation.

B. The Draft Guidance Will Create Confusion for All Applicants As Well As Prescribers.

At the time this draft guidance is issued, the agency is considering a new initiative to revise the format of prescription drug labeling so as to reduce confusion and limit prescribing errors.[5] Before proposing this new format, FDA gathered evidence directly from physicians, through focus groups and surveys, to understand how physicians use and perceive current prescription drug labeling. Both the focus groups and the surveys found that the "Dosage and Administration" section of current labeling is among the most important information "needed to make a confident decision about prescribing a particular drug for a particular individual." 65 Fed. Reg. 81083 (Dec. 22, 2000).

Nonetheless, under the terms of the draft guidance, the agency will diminish a physician's ability to make confident decisions about prescribing by allowing simultaneous marketing of generic products for the same indications as the listed drug, but with labeling different than that of the listed drug, including labeling differences related to dosage and administration. This is a fundamental shift from the agency's current approach, which allows marketing of generic products with different labeling only if the difference is an omission of protected indications or other information.

In permitting different dosing instructions for versions of the same drug labeled for the same indication, the draft guidance allows differences that are much more dangerous than the omission of indications that may currently exist between innovator and generic products. The omission of a new indication from a label prevents a generic firm from promoting its product for that indication, thereby minimizing the chance that prescribers receive inconsistent promotional materials from the generic and pioneer marketers. That is not the case when there is substitution of discontinued labeling on the generic product. If the listed drug has protected labeling with a new dosing regimen, and the generic is allowed to come to market with labeling referencing the obsolete dosing, both the prescriber and the patient will be confused.

This may not be an academic concern. As discussed above, a review of the *Orange Book* uncovered a number of instances where exclusive terms in the listed drug's labeling replace

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[5] See 65 Fed. Reg. 81081-81131 (Dec. 22, 2000). In the media release accompanying this proposed rule to create a new format for prescription drug labeling, the agency noted that current drug labeling contributed to medical errors that were responsible for 98,000 U.S. deaths annually because health care providers found such labeling "lengthy, complex and hard to use." HHS News Release P00-22, Physician Labeling Proposal (December 21, 2000) (available on FDA website).

unprotected terms pursuant to agency approval of an SNDA. One example involves the listed drug Aredia (pamidronate), indicated for use in hypercalcemia associated with certain conditions, including several forms of cancer. The NDA holder discontinued its 24-hour infusion dosing and replaced it with 4-hour infusion dosing. It is not at all clear, under the strict standards for product withdrawal that FDA proposes to rely on in the draft guidance, that the agency would have ordered the 24-hour infusion regimen off the market. If that is the case, then under the draft guidance, a generic product that referenced the obsolete labeling could be approved. That would result in simultaneous marketing of the same drug product for the same approved indication with different dosing regimens. A physician prescribing generic pamidronate based on obsolete labeling would require inpatient admission, whereas current labeling would call for outpatient infusion.

Similarly, the listed drug Neurontin (gabapentin), indicated to treat partial epileptic seizures, eliminated a three-day titration period and replaced it with initiation of treatment at the full, titrated dose. Whether the FDA would have ordered the withdrawal of the outdated, titrated drug is unclear, but under the terms of the draft guidance, a generic product relying on the obsolete labeling could be approved. A physician, adhering to the dosing information on the gabapentin generic label, would be relying on outdated science and would be giving the patient a suboptimal dose. Or, more likely, confusion would result from the availability in the clinical setting of both products, and their differing labels, with the likely result that the products and their appropriate dosing would be mixed up.

FDA knows that there already is too much confusion regarding prescription drug labeling. That is a key rationale for the agency's pending proposal for a new drug labeling format. The FDA should not be creating a new ground for prescriber confusion, particularly where that confusion, in the real world, can lead to negative clinical consequences or to patients receiving less than optimal therapy.

V. If FDA Finalizes this Guidance, It Should Adopt a Transparent Process.

If, notwithstanding the arguments made above, the agency decides to finalize this draft guidance, Johnson & Johnson urges FDA to ensure that the decision making process is transparent. Interested parties, including the NDA holder as well as health care providers and patients, should be allowed to participate in the process of assessing the safety and effectiveness of the discontinued labeling, as well as be able to understand and challenge the rationale for any agency assessment that emerges from that process. Under the current proposal, however, the agency indicates that it "may, on its own initiative, begin the process of determining whether labeling was discontinued for reasons of safety and effectiveness." Draft Guidance at lines 216-218.

Johnson & Johnson urges FDA to delete that provision from the draft guidance and disavow any procedures that could produce either unilateral agency action or a process that is not public. Instead, the agency should clarify that the only route for reviewing discontinued labeling is the citizen petition process, pursuant to 21 C.F.R. § 10.30 (2000). That would assure interested parties that a public docket would be created that would allow for comments on the petition. This vehicle would provide an opportunity for the NDA holder, which has marketing experience with the old labeling, to provide information that otherwise might not be available to the agency. It would also allow patients and health care providers to offer real world insights on the potential impact of such labeling. In this way, the agency will have more data to be able to consider a fuller range of safety and effectiveness issues.

VI. Conclusion

The draft guidance has fatal legal and policy flaws. We respectfully urge the agency to reconsider its position and withdraw the guidance. In any event, no action should be taken without amending the Code of Federal Regulations in accordance with the APA. If the agency nonetheless proceeds to finalize the guidance, we advocate that FDA seek input from the NDA holder and the public when the agency assesses the discontinued labeling.

Johnson & Johnson appreciates this opportunity to comment on the draft guidance and thanks the agency for its consideration of our views.

Respectfully submitted,

Helen Torelli