

August 14, 2007

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Approval of Generic Versions of Pioglitazone Hydrochloride with  
Less than Complete Labeling

Dear Sir or Madam:

**CITIZEN PETITION**

We file this petition on behalf of Takeda Pharmaceuticals North America (“Takeda”). Takeda is the developer and marketer of Actos<sup>®1</sup> (pioglitazone hydrochloride). ACTOS is approved as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes. Control of Type 2 diabetes almost always requires a progression of care. While the approved labeling for ACTOS contains information on the use of ACTOS for monotherapy, it also contains extensive information on use of ACTOS for combination therapy, with a sulfonylurea, metformin, or insulin.

Takeda files this petition because the Food and Drug Administration (“FDA”) has tentatively approved, and can thus be expected to grant final approval to, Abbreviated New Drug Applications (“ANDAs”) for generic versions of ACTOS with labeling that Takeda believes is inappropriately limited to use in monotherapy. Takeda believes such labeling will provide insufficient information for doctors to prescribe the proposed generic pioglitazone, or to adequately protect patients. Takeda believes these ANDA approvals will violate section 505(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(j), and the Administrative Procedure Act, 5 U.S.C. 553, 706. In addition to the current ANDA tentative approvals for pioglitazone, Takeda believes one or more further

<sup>1</sup> Actos is a registered trademark of Takeda Chemical Industries, Ltd. and is used under license by Takeda Pharmaceuticals North America, Inc.

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pioglitazone ANDA has been filed. On the basis of information received, Takeda believes that such ANDAs also seek labeling for use only for monotherapy.<sup>2</sup>

A. Action Requested

Takeda asks FDA not to grant final approval or further tentative approvals to any generic version of pioglitazone hydrochloride that is not labeled for both monotherapy and combination therapy in the same manner as ACTOS.<sup>3</sup>

B. Statement of Grounds

Summary of Grounds: The removal of information from the label for ACTOS regarding combination therapy so as to permit a generic approval cannot be reconciled with FDA's regulation, which prohibits the removal from the labeling of a listed drug of information protected by patent or exclusivity if the differences in the labeling would affect the safety or effectiveness of the drug. The information on combination therapy in the labeling for ACTOS is essential to the safe and effective use of the drug, given that the overwhelming use of pioglitazone is in combination with other drugs for the treatment of diabetes. This information includes information necessary for appropriate prescribing decisions, as well as for patient safety.

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<sup>2</sup> We note that Takeda has prevailed at trial in its patent case with respect to the patent on the active ingredient of ACTOS. Takeda Chemical Industries, Ltd. v. Mylan Laboratories, 417 F. Supp. 2d 341 (S.D.N.Y. 2006), *aff'd sub nom. Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, --- F.3d ---, 2007 WL 1839698, 83 U.S.P.Q.2d 1169 (Fed. Cir. June 28, 2007). By order of that court, the pending ANDAs involved in that suit may not be approved for ACTOS regardless of its labeling prior to January 17, 2011, no matter how this petition is decided. Thus, consideration of this petition should not delay FDA approval of generic pioglitazone.

<sup>3</sup> In preparing this petition, Takeda has assumed that the labeling for any generic pioglitazone drug approved will have removed from it all obvious references to use of pioglitazone in combination therapy; however, the actions requested by this petition apply to any generic pioglitazone product whose labeling at the very least omits references to combination therapy in either the *Indications and Usage* or *Dosage and Administration* sections of the labeling, regardless of the content of any other labeling sections.

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Further, an approval of an ANDA with labeling that had never been approved for any listed drug would violate the statute that governs such approvals. The statute requires the conditions of use of each ANDA have been previously approved for a listed drug.

Finally, the relevant statutory and regulatory provisions on which FDA relies, and controlling judicial interpretations of those provisions, limit FDA's ability to remove information from the label of a listed drug for purposes of approving a generic of that drug to situations in which there are multiple indications for a drug, not where, as here, there is one indication and the ANDA applicants seek to remove information on use of the drug for treatment of that indication.

#### 1. Background on ACTOS and Potential Generics

ACTOS was approved as 15 mg and 30 mg tablets on July 15, 1999. Reflecting anticipated medical use of the drug, the labeling for ACTOS contains information based on studies demonstrating safety and effectiveness when ACTOS is used both as monotherapy and in combination with other drugs used in the treatment of diabetes. The information on combination use is not limited to the indications section of the labeling, but appears pervasively throughout the various safety, clinical studies, and dosage and administration sections of the labeling. This was not a situation in which a drug was first approved, after careful review of its labeling, for one indication and later, on the basis of additional data, was approved for a second, separate indication.<sup>4</sup> Instead, there is only one indication: as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.

Moreover, the initially approved labeling fully incorporated and embraced the anticipated medical practice of using ACTOS in combination with other therapies. The Dosage and Administration section of the labeling describes the appropriate use in of ACTOS as monotherapy (including information on titration from 10 or 30 mg to 45 mg per day) and then states, "For patients not responding adequately to monotherapy, combination therapy should be considered." The

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<sup>4</sup> Additional data were submitted, in 2003, with respect to combination studies, but the combination indication had been approved at the time of the initial approval of the NDA.

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labeling then separately explains how the product should be used in combination therapy with a sulfonylurea, metformin, or insulin.

Both the monotherapy and combination therapy sections of the Dosage and Administration labeling section, therefore, anticipate the use of ACTOS as part of combination therapy. More importantly, both sections clearly reflect that ACTOS as monotherapy is intended as an uncommon or minor use. The "Monotherapy" section anticipates that patients may not respond adequately to ACTOS alone. Importantly the several "Combination Therapy" sections each anticipate specifically that administration of ACTOS will occur subsequent to, rather than prior to or commensurate with, administration of the other product that is part of the combination. In short, when used in combination, ACTOS will normally be the product added to existing monotherapy with other products, and not be preexisting monotherapy in its own right.<sup>5</sup>

This labeling approach should be understood in the context of actual clinical practice with ACTOS, where use is overwhelmingly in combination with other therapies for the treatment of diabetes, and rarely as monotherapy. As stated in the attached declaration of Silvio E. Inzucchi, M.D., due to the progressive nature of the disease, with predictable increases in blood glucose levels over time, drug therapy with combinations of drugs is usually necessary to achieve adequate glucose control. Further, ACTOS is generally administered following the administration of other drugs used to treat diabetes, mostly metformin, further emphasizing its combination use.<sup>6</sup> As a result, the number of patients using ACTOS or another drug in the same class as monotherapy ranges somewhere between 5-15 per cent, with much of this use being "off-label," that is, for patients who are pre-diabetic or for metabolic syndrome, a condition whose symptoms are thought to presage the onset of diabetes. Importantly for this

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<sup>5</sup> The labeling text in the *Dosage and Administration* section for combination therapy states, in relevant part with respect to each of the purported combinations, as follows: The current [sulfonylurea, metformin, or insulin] dose *can be continued* upon initiation of ACTOS therapy. Similarly, the *Indications and Usage* section of the labeling provides, in relevant part, "ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise *plus the single agent* does not result in adequate glycemic control" (emphasis supplied). In this case, 'single agent' refers not only to ACTOS, but to the other agents as well.

<sup>6</sup> Declaration of Silvio E. Inzucchi, M.D., ¶ 35.

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analysis, Dr. Inzucchi states that “virtually all of these cases will progress to combination therapy at some later point in time as their disease progresses.”<sup>7</sup>

In sum, therefore, labeling for pioglitazone for monotherapy use alone essentially assumes the existence of a group of patients whose only therapy is, and will remain, pioglitazone monotherapy, a patient group whose existence is arguably problematic. By definition, this class excludes the largest group of patients with Type 2 diabetes for whom pioglitazone is considered appropriate therapy: those for whom pioglitazone is added to existing therapy with a sulfonylurea, metformin, or insulin. Importantly, it also excludes those pioglitazone patients who are initially treated with pioglitazone alone, but for whom, as recognized in the labeling, monotherapy does not produce an adequate response.

Takeda has several patents covering uses of ACTOS in combination with other diabetes medicines addressed in its labeling that extend beyond the expiration date of the patent on the active ingredient in ACTOS, pioglitazone hydrochloride. Takeda thus has a significant concern that generic companies are seeking to avoid the combination use patents by asking FDA to approve generic versions of pioglitazone hydrochloride that lack labeling information with respect to use of the drug in combination.

The labeling for ACTOS contains not only the indication for use of ACTOS with a sulfonylurea, metformin, or insulin but also information on individual clinical trials in which ACTOS was combined with each of these products separately. Potential labeling that is solely for monotherapy may lack information from any of those combination therapy trials, including effectiveness, dosing, and adverse reaction data from each of those trials. In sum, generic forms of ACTOS would not necessarily include labeling information and directions about what is by far the product’s principal use — in combination with other therapies for Type 2 diabetes — and may in fact be labeled only for a patient class whose existence is questionable.

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<sup>7</sup> Inzucchi declaration, ¶ 34. Dr. Inzucchi’s declaration describes in detail current medical practice with respect to the use of the various available drugs currently used for the treatment of Type 2 diabetes as both single agents and in combination. He notes that the extremely limited use of ACTOS in monotherapy is based on several factors, notably weight gain and fluid retention, delayed onset of action, and that the drug works best in combination with others.

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Labeling focused only on monotherapy would, moreover, presumably lack important warnings. For example, the labeling warns of cardiac effects associated with use of ACTOS in combination with insulin therapy. In addition, the labeling contains a precaution relating to hypoglycemia when ACTOS is used in combination with insulin or oral hypoglycemic agents, and advises the physician concerning the potential need to reduce the dose of the concomitant agents in combination therapy.

2. Labeling Changes Between a Listed and Generic Drug That Affect Safety or Effectiveness Are Not Permitted under FDA's regulations

As a general proposition, the Federal Food, Drug, and Cosmetic Act ("FFDCA") requires that the labeling of a drug approved under an ANDA must be the same as that of the drug that is copied, FFDCA Section 505(j)(2)(A)(v). FDA's regulations provide that it is nevertheless permitted to approve ANDAs labeled with less than all "aspects of the listed drug's labeling" if either market exclusivity or patents would prevent the generic applicant from marketing its product if the labeling contained the deleted information.<sup>8</sup>

21 C.F.R. § 314.127(a)(7).<sup>9</sup> FDA's regulations, however, permit differences in the labeling of the ANDA drug and that of the innovator resulting from patent or exclusivity protection only if "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use."<sup>10</sup> Id. FDA explained this provision in the preamble to the regulation saying:

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<sup>8</sup> As noted above, ACTOS has one indication: to improve glycemic control in type 2 diabetes patients, whether as monotherapy or as combination therapy. For purposes of the argument made in this section of the petition, however, whether Actos has one or more indications does not matter.

<sup>9</sup> As discussed below, to the extent that the FDA policy is read to permit approval of an ANDA that is labeled for a condition of use not previously approved for the innovator, that policy is at odds with the statute.

<sup>10</sup> A parallel provision allows FDA to withdraw approval of any ANDA if the labeling later becomes, after approval, different from that of the innovator. There is an exception for differences resulting from patent or market exclusivity protection on the listed drug, but again there is a caveat that FDA will not accept

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FDA cautions that it will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy.

57 Fed. Reg. 17,950, 17,968 (Apr. 28, 1992). Thus, if the differences in labeling “affect” safety or effectiveness, or make the generic drug “less” safe or effective than the innovator, approval of the generic is prohibited. There is no need for a finding that the generic drug would be unsafe or ineffective.

A reading that permits the regulatory test of section 314.127(a)(7) to apply to ACTOS monotherapy as distinguished from combination therapy would effectively gut the protective component of the regulation, specifically, that the labeling that remains, as stated in the regulation’s preamble, not affect product safety or efficacy. If a generic version of ACTOS labeled for use only in monotherapy is less safe and effective than such a product with labeling that explains its safe and effective use in combination (a conclusion we discuss in the next section) the regulatory test permitting removal of labeling cannot be met.<sup>11</sup>

3. Marketing of Pioglitazone Hydrochloride Without Labeling Concerning Combination Therapy Would Make That Product Less Safe and Effective than ACTOS

Because the ACTOS labeling describes how this drug should be used in the progression of treatment of patients with Type 2 diabetes, the labeling instructions and information concerning both monotherapy and combination therapy are necessary for the safe and effective use of the drug. Stated another way, under 21 CFR 314.127(a)(7), labeling of generic pioglitazone that does not contain information regarding combination use, given that such use is a pervasive part of the information in the drug’s labeling (and reflective of medical practice)

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such a difference when the differences in labeling render the ANDA product less safe or effective than the listed drug, 21 C.F.R. §314.150(b)(10).

<sup>11</sup> The potential existence of one or a small number of patients for whom pioglitazone therapy is sufficient would not justify invoking 21 CFR 314.127(a)(7). Where use of the drug is widespread in other populations, i.e. use in combination therapy, the use in those populations must be considered. See discussion of FDA’s response regarding Rapamune, *infra* at 10-11.

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and is essential for all pioglitazone patients, even those on monotherapy, can only make such a generic product both “less safe” and “less effective” than ACTOS.

In the *Indications and Usage* section, ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with diabetes. Since treatment of patients with Type 2 diabetes involves progressive therapy, and glycemic control is the principal objective of therapy, removing all information on combination use of ACTOS with other therapies, as a means of improving glycemic control, from the labeling of generic pioglitazone would significantly affect in an adverse way the safe and effective use of the drug. Indeed, this section specifically states in describing monotherapy use that combination therapy may need to be considered if glycemic control is inadequate. The *Dosage and Administration* section provides similarly.<sup>12</sup>

The *Clinical Studies* section of the ACTOS labeling, containing the basis for the drug’s approval, reflects the emphasis on combination therapy given in the development of ACTOS, showing substantially more patients studied in combination therapy (3673) compared to monotherapy (865); indeed, each individual combination therapy database, whether sulfonylurea (1262 patients), metformin (1155 patients), or insulin (1256 patients), included more patients than the monotherapy group.

In the *Information for Patients* section a special warning (risk of hypoglycemia) is included when ACTOS is used in combination with insulin or hypoglycemic patients.

As noted previously, the labeling contains *Warnings* on cardiac effects when ACTOS is used in combination with insulin, and *Precautions* related to hypoglycemia when ACTOS is used in combination with insulin or oral hypoglycemic drugs.

In the *Adverse Reactions* section, collected data from clinical trials obviously include patients on combination therapy, as the number of patients reported on exceeds significantly that of monotherapy patients studied, and the label information on the level of adverse events in combination patients (even though “similar” to patients on monotherapy) is still essential to the safe use of the product. In addition, notwithstanding the positive safety profile of

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<sup>12</sup> See footnote 5, *supra*, for the relevant text of these sections.

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pioglitazone, there are numerous examples of increased numbers and types of events on patients treated with combination therapy:

- a reported increase in edema on patients treated with insulin and ACTOS, compared to insulin alone;
- increased dyspnea, edema and weight gain in patients treated with ACTOS and insulin compared to the insulin/placebo group;
- in combination trials with either a sulfonylurea or insulin, mild to moderate increases in hypoglycemia;
- anemia reported in a greater number of patients treated with ACTOS and a combination of either sulfonylurea, insulin, or metformin than with ACTOS alone;
- edema reported in a significantly greater percentage of patients treated with combination therapy with either sulfonylurea, metformin or insulin than with ACTOS alone;
- congestive heart failure reported in a greater percentage of patients treated with combination therapy with insulin than with insulin alone.

We believe that the issues presented by pioglitazone used in monotherapy as opposed to in combination are at least somewhat analogous to information about titration of a drug. FDA recently faced an issue concerning the approval of generic versions of Ultram® with labeling that would lack an approved titration schedule because of market exclusivity associated with that schedule. FDA's response to the assertion that exclusion of the titration schedule from the generics' labeling made the generics less safe is instructive. FDA did not say that a generic product could be approved with no titration schedule at all. In fact, FDA rejected a generic applicant's contention that it should be allowed to approve generic versions of Ultram labeled only for treatment of acute pain (a use arguably not requiring titration). Instead, it required that another titration schedule, which had been approved for Ultram previously and for which there was no blocking exclusivity, be included in the labeling. The clinical trial supporting that schedule, FDA found, "provided essential safety information that can and should

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remain in the labeling.”<sup>13</sup> If the non-protected titration scheme for Ultram was found essential to safe use of that drug, labeling that describes the appropriate treatment for diabetes patients with ACTOS in both monotherapy and combination therapy is at least as, if not more, essential to safe use of this product.

As noted above, a monotherapy-only label would exclude important information for physicians on the use of pioglitazone hydrochloride in combination with other drugs that physicians not only will inevitably use in the treatment of patients with Type 2 diabetes, i.e., sulfonylureas, metformin, and insulin, but most likely will already be using. Even in those rare cases where a physician has started a patient on pioglitazone hydrochloride monotherapy, that physician will ultimately in the normal course be expected to use that drug in combination with other diabetes therapies. To assume otherwise is to ignore the actual medical treatment of these patients.

Thus, a generic product that is labeled only for monotherapy will inevitably result in the use by physicians of a drug for combination therapy that lacks adequate label instructions and adequate label warnings for combination use. Approval of such generic products would, accordingly, directly violate FDA’s regulation, which prohibits the approval of generic products with labeling that differs from that of the innovator when the differences render the proposed drug product less safe or effective than the innovator. *See* 21 C.F.R. § 314.127(a)(7).

It is clearly not a legally sufficient response that there will be some patients for whom the drug would be prescribed only as monotherapy.<sup>14</sup> As FDA

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<sup>13</sup> Letter from Janet Woodcock, M.D. to Marcie Macdonald et al., Docket Nos. 01P-0495/CP1, 02P-0191/CP1, 02P-0252/CP1 (June 11, 2002), (“Ultram petition response”), page 8.

<sup>14</sup> The existence of such a class, even a very small one, is questionable. It clearly excludes patients taking a sulfonylurea, metformin, or insulin, whether or not such patients are then prescribed ACTOS as combination therapy. It also does not include all patients started on pioglitazone as monotherapy for, as the labeling recognizes, such patients may respond inadequately, and may subsequently require combination therapy with another agent. In reality, most if not all will. Inzucchi declaration ¶¶ 27, 34. Most other monotherapy patients, even those whose physicians are uncertain as to the need for further therapy, would by necessity also fall under the combination therapy regimen in ACTOS’ labeling, for they too are ultimately candidates for combination therapy. Rather, the only

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decided in addressing a similar issue with respect to the drug Rapamune<sup>®</sup>, FDA must take into account the fact that even patients who are at one point within a class that would be protected by limited labeling may in some cases progress to the point where the information in the full labeling becomes essential. As noted, it is absolutely clear that even the small numbers of ACTOS monotherapy patients will almost invariably progress to combination therapy.<sup>15</sup> Thus, even for patients started on pioglitazone monotherapy, the lack of information about what will be, for most of those patients, the appropriate next step would mean, as FDA concluded with respect to Rapamune, that “omission of the protected language would render the product less safe than [the innovator drug] for the remaining, non-protected conditions of use.”<sup>16</sup>

4. Approval of a Generic Pioglitazone Only for Monotherapy  
Would Compromise the Requirement for a Listed Drug and  
Create a New Drug Never Evaluated by FDA for Safety and  
Effectiveness

The first and principal requirement for the content of an ANDA is that it must contain “information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the [ANDA drug] have previously been approved for a [listed drug].” Section 505 (j)(2)(a)(i). We believe that the ANDAs seeking approval of a generic form of pioglitazone only for monotherapy fail to contain “information to show that that proposed conditions of use... has been previously approved for a listed drug,” and thus do not meet the requirements of section 505(j)(2)(a)(i).

The *Indications and Usage* section of the labeling for ACTOS reads in relevant part as follows:

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class for whom such a drug would be indicated would be for patients started on pioglitazone whose physicians know to a *certainty* that that will be the only therapy they will ever use. There is no evidence that such patients even exist.

<sup>15</sup> See, e.g., Dr. Inzucchi declaration, ¶ 27: “Even when used in monotherapy, progression to treatment involving combination therapy with other agents will virtually always occur.”

<sup>16</sup> Letter from Steven K. Galson, M.D., M.P.H., to Michael S. Labson, Docket No. 2003P-0518 (Sep. 20, 2004), p. 4.

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ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

It is thus very apparent that the “conditions of use” approved by FDA for ACTOS include monotherapy only in the context of nutritional counseling, weight reduction as needed, exercise, and combination therapy as needed. When one views the ACTOS labeling in its entirety, and considers as well the underlying medical practice for achieving glycemic control in diabetic patients that it embodies, we submit that pioglitazone labeling, absent the prescribing and risk information on combination use, would not likely have been approved by the FDA review division. More importantly, for this purpose, no such label ever was approved. There was thus never a listed drug for those generic pioglitazone products either already tentatively approved without the combination drug indication, or whose review is pending. Thus at the very least the monotherapy-alone condition of use has not “been previously approved” for a listed drug that can serve as the basis for the subsequent approval of generic pioglitazone for monotherapy use alone.

FDA’s failure ever to have approved pioglitazone for monotherapy alone makes 21 CFR 314.127 inapplicable. The fact that aspects of the listed drug’s originally approved labeling may be subject to patent or other exclusivity protection does not authorize FDA to undertake a new safety and effectiveness assessment of the listed drug under the terms of 21 CFR 314.127(a)(7). Rather, we submit, the safety and effectiveness test under this regulatory section can only be applied in those situations where the generic drug under review first meets the requirement that its proposed conditions of use have been previously approved for the listed drug. Any other reading of this regulation would make it invalid

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because it would be at odds with the controlling statutory provision, i.e., Section 505(j)(2)(a)(i).<sup>17</sup>

We acknowledge that this may be an issue of first impression. The facts underlying FDA's tentative approval of pioglitazone for monotherapy are different than those involving its past implementation of these sections. We do not suggest that FDA may never delete subsequent or even one of original multiple distinct uses from a label in the approval of a generic. Here, however, FDA has only approved ACTOS for use in a course of therapy that includes both monotherapy and combination use, and has interwoven the information about monotherapy and combination therapy throughout the approved labeling for that single purpose, including clear suggestions that (1) as monotherapy, ACTOS may be insufficient therapy, and (2) when used in combination therapy, ACTOS may be added to preexisting therapy with other agents, and may not have previously been monotherapy in its own right. In this case, we submit it is impossible to remove the combination use of ACTOS from the labeling of generic pioglitazone and still adhere to the requirements of 505(j)(2)(a)(i).

5. ANDAs Can Exclude Labeling of the Listed Drug Only When the Generic Labeling Fully Copies Labeling Concerning One Indication and the Excluded Language Deals With a Separate Indication.

FDA's position that it may approve a drug with less than all of the indications approved for the innovator ("listed") drug has been upheld only with respect to situations in which there has been an initial approval of one indication, followed by approval of a second indication. See Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493 (D.C. Cir. 1996). A careful review of that decision, and of the arguments that FDA made in support of its position there, makes it clear that the statute supports approval of an ANDA **only** where FDA can point to an initial (or at best, earlier) approval of the listed drug for the indication for which the ANDA seeks approval and the excluded language covers a separate indication approved subsequently. Here, however, as noted, there was never an approval of ACTOS for monotherapy alone. Instead, monotherapy was only part of the original approved indication, which included monotherapy together with

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<sup>17</sup> We note that this provision, unlike others in FDA's ANDA regulations, is not based on any explicit statutory provision or other authority, other than that offered by general rulemaking.

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combination therapy as part of a labeled continuum of use for achieving glycemic control in diabetic patients.

The FDA's position that it is proper to approve ANDAs that lack protected labeling information was justified in *Bristol-Myers* on three grounds, none of which apply when the labeling sought to be excluded by the ANDA applicant is not a separate indication. First, FDA argued that the three-year exclusivity granted by the statute in certain circumstances for new indications of a previously approved drug was designed to protect only that new indication, not to prevent approval of any generic version of the listed drug. That is, of course, not an issue when the patents in question cover an aspect of the only indication, improving glycemic control in patients with Type 2 diabetes, that was initially approved for the drug.

Second, FDA pointed to the provision of FFDCA Section 505(j)(4)(B) that says that FDA shall refuse to approve an ANDA if "(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application." The *Bristol-Myers* court explained that this provision meant that Congress intended that the **indication** in the generic label have been previously approved, though it did not matter if the label lacked other **indications** found in the innovator's label.<sup>18</sup>

Third, FDA pointed to certain legislative history of the Hatch-Waxman Act. The legislative history also, however, only contemplates approval of generics that lack protected "indications," not generics for which full information cannot be provided about the drug's single indication, the case here, because part of that

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<sup>18</sup> The provision, the court said,

Expresses the legislature's concern that the new generic be safe and effective of each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference.

91 F. 3d 1500. The court's conclusion echoed FDA's own position in its brief to the court that in this provision "Congress foresaw and accommodated both the labeling and approval of a generic drug where the ANDA seeks approval for **less than all of the indications** of the pioneer drug." Brief for the Appellees at 29 (emphasis added).

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information is protected. Thus, the House Report of this legislation, upon which FDA has relied, states that:

[T]he bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved as explained below.

\* \* \*

The applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval of only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d Sess. at 21. *See also id.* at 22:

For example, the listed drug may be approved for two indications. If the applicant is seeking approval only for indication No. 1, and not indication No. 2 because it is protected by a use patent, then the applicant must make the appropriate certification and a statement explaining that it is not seeking approval for indication No. 2.

Similarly, FDA's regulation stating that an ANDA applicant can avoid certification to certain patents by deleting covered information from the ANDA label refers to deletion of "indications." 21 C.F.R. § 314.94(a)(12)(iii).<sup>19</sup>

The fact that there is only one approved indication for ACTOS, *i.e.*, improvement of glycemic control in patients with Type 2 diabetes, makes it inappropriate, both under the statute and FDA's regulations, to permit deletion of information, particularly safety and effectiveness information, about that sole approved indication.

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<sup>19</sup>We recognize that FDA, in the context of the Ultram petition discussed above, concluded that, based on preambles to its regulations, it could permit deletion of information about methods of use as opposed to indications, Ultram petition response, page 6 n.6. With all due respect, for the reasons stated in the text we believe that conclusion was in error. FDA cannot ignore either the terms of its regulations or the statutory intent.

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6. Conclusion

For all the foregoing reasons, we believe it would be inappropriate under the law and FDA's regulations, would provide physicians inadequate information to prescribe, and would put patients at risk, for FDA to approve a generic version of ACTOS that did not include all approved labeling describing the use of that product in combination therapy.

C. Environmental Impact

The relief requested by this petition would result in the refusal to approve ANDAs (thus not changing the status quo) or the clarification of requirements for such approvals. Because the grant of the petition would not have an effect on the environment, no environmental assessment is required. 21 C.F.R. 25.31(a).

D. Economic Impact

Information on the economic impact of the action requested by this petition will be submitted if requested by the Commissioner.

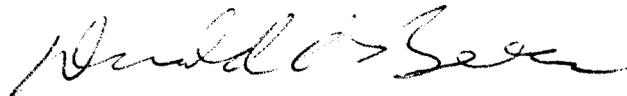
E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition

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relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



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