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VIA FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Dr.,
Rockville, MD 20857

Re: Caraco's Citizen's Petition And Comments To Teva's and Apotex's Related Citizen's Petitions (Docket Nos. 02P-0191 and 01P-0495)

CITIZEN'S PETITION

On behalf of Caraco Pharmaceuticals Laboratories, Ltd., the undersigned submits this petition under 21 U.S.C. § 355(j) and 21 C.F.R. §§ 10.25, 10.30 to seek immediate final approval of Caraco's ANDA No. 75-964 (tramadol hydrochloride 50 mg tablets). The petition also supports the earlier citizen's petitions filed by Teva Pharmaceuticals (Docket No. 02P-0191) and Apotex Corp. (Docket No. 01P-0495) to the extent that those companies, like Caraco, seek immediate final approval of generic tramadol.

A. Action Requested

The FDA deemed Caraco's tramadol ANDA "approvable" over four months ago on January 22, 2002, but still has not provided final approval for commercial marketing. As Caraco understands the delay, the FDA currently is considering appropriate labeling for generic tramadol. Both Teva and Apotex have proposed appropriate labels. But R.W. Johnson Pharmaceutical Research Institute and Ortho-McNeil Pharmaceutical, Inc. (hereinafter referred to jointly as "Ortho-McNeil") have objected to these proposals, arguing that they improperly delete information allegedly necessary for the safe administration of tramadol for non-protected uses.

As detailed below, while it strongly disagrees with Ortho-McNeil's objections, Caraco is now proposing a third alternative label. In an effort to clear the log jam, Caraco's proposed label resolves Ortho-McNeil's objections by including the information allegedly

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necessary for safe administration. With this proposed label – which ensures safety, protects Ortho-McNeil's exclusivity, and complies with all other labeling requirements – Caraco's ANDA is eligible for immediate final approval.

To further ensure that it is approved on the earliest possible date, Caraco agrees to use whatever label the FDA ultimately finds acceptable. Caraco believes that any one of the three proposed labels – Apotex's, Teva's or Caraco's – is appropriate to permit generic competition in the substantial market for the non-protected uses of tramadol. If the FDA nevertheless rejects all three options, Caraco respectfully asks that the FDA describe precisely what label it would find acceptable. In the end, *some* label must be appropriate because the non-patented uses of the drug are undeniably safe and effective.

B. Statement of Grounds

1. The Question Properly Before The FDA Is Not *Whether* To Approve Generic Tramadol, But Only *Which* Label Will Be Used Upon Approval.

In its recent filings with the FDA, Ortho-McNeil has attempted to frame the question as *whether* the FDA should approve any ANDA applications for generic tramadol. But that is the wrong question. Under 21 C.F.R. § 314.94(a)(8)(iv), an ANDA label may differ from the brand label when "an indication or other aspect of labeling [is] protected by patent or accorded exclusivity under [the Act]." Thus, generic companies have a right to amend their labels to avoid the dosing regimen covered by Ortho-McNeil's patent and three-year statutory exclusivity. Consequently, the only question properly before the FDA is which label is appropriate to carry out that right.

Devising an acceptable label is certainly feasible because there is a substantial and easily-defined market for tramadol outside of the narrow scope of Ortho-McNeil's patent and statutory exclusivity. Like its statutory exclusivity (coded D-63), Ortho-McNeil's patent, U.S. Patent 6,339,105 (the '105 patent), covers only a short-term titration schedule that starts with a daily dose of 25 mg and then increases at specified intervals thereafter. Thus, neither Ortho-McNeil's patent nor statutory exclusivity cover:

- Post-Titration Administration. Once the patient has been titrated with the branded product – which requires only 16 days according to the current Ultram® label – Ortho-McNeil has no protection over the subsequent and sometimes long-term administration of the drug. Thus, after titration, physicians are free to begin prescribing a lower-priced generic tramadol.

- Non-Titration Administration. As confirmed in the current Ultram® label, titration is not appropriate for some patients, including patients "for whom rapid onset of analgesic effect is required." These patients are entitled to use a lower-priced generic tramadol.

Because they do not apply to the post-titration and non-titration uses of the drug, Ortho-McNeil's patent and statutory exclusivity cannot block generic competition in these substantial segments of the tramadol market.

As a result, the FDA also cannot block generic competition in these market segments. No statute or regulation authorizes it to do so. Ortho-McNeil has nevertheless succeeded in substantially delaying generic competition by creating issues over the language to be used in the generic label. True, a generic label must be sufficiently clear to ensure that the drug is "safe and effective" for the prescribed "nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7). But that is no obstacle here. Tramadol is indisputably safe and effective for the non-protected post-titration and non-titration uses. Ortho-McNeil's drug is safely administered for those uses everyday. Consequently, the question before the FDA is not about safety and efficacy; it is about word choice. At least *some* language must be sufficient to ensure safety and efficacy because tramadol is, in fact, safe and effective for its non-protected uses.

Under these circumstances, Ortho-McNeil cannot expect the FDA to further delay generic competition based on mere semantic issues over the language in a label. Any such result would gravely disserve the public, which has a right to the reduced prices that will follow generic competition for the non-protected uses of tramadol. It would also conflict with the very purpose of Hatch-Waxman Amendments, which were designed to bring generic drugs to the market "more cheaply and quickly." *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990).[1]

2. Caraco's Proposed Label Resolves Ortho-McNeil's Objections.

As noted, Caraco believes that both Apotex's and Teva's proposed labels are appropriate for generic tramadol. Ortho-McNeil, however, argues that these proposed labels are somehow confusing and unsafe because they delete allegedly important information. Although it disagrees with Ortho-McNeil's objections, Caraco is now proposing a label that resolves Ortho-McNeil's objections by including that allegedly important information.

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[1] Additionally, contrary to the suggestion in its most-recent filing, Ortho-McNeil has no patent protection or any other exclusivity over scored tablets. Ortho-McNeil contends that it has such exclusivity as part of its three-year exclusivity over the titration dosing regime. This is not true. There are substantial uses of 25 mg tablets outside of that exclusivity, hence, the need for scoring for non-protected uses. For instance, even in non-titration circumstances, some physicians may wish to administer 75 mg or 125 mg doses and, thus, would need scored tablets. In any event, based on the approval of the scored Ultram® tablet approved February 23, 2000, Caraco's original ANDA was filed with both an unscored tablet (completed before the innovator's approval) and a scored tablet (added after the innovator's approval) to allow the FDA to approve either tablet.

a. For Apotex's and Teva's Proposed Labels, Ortho-McNeil Contends That Certain Deleted Information Creates Confusion And, Thus, Safety Issues.

Ortho-McNeil's objections are essentially the same for both Apotex's and Teva's proposed labels. Apotex has proposed deleting any reference to the 16-day titration regimen that Ortho-McNeil added to its label after its 1998 clinical trial. Ortho-McNeil contends that the resulting "incomplete" label would be confusing and, thus, unsafe:

> If the titration regimen is deleted . . . , the resulting product would be less safe and less effective for the remaining nontitrated dosing regimen. . . . Unless the comparative benefits of the titration regimen are explained in the labeling, a physician would have no basis for assessing whether the benefits of the titrated regimen outweigh the risk of discontinuance due to adverse events.

(Ortho-McNeil Response dated 1/22/02 at page 4).

Teva similarly proposes deleting portions of the label referring to the 16-day titration regimen. Under Teva's sensible approach, the generic label would be limited to the treatment of acute pain (*i.e.*, "patients for whom rapid onset of analgesic effect is required") and would omit an indication for the treatment of chronic pain (*i.e.*, "patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect"). Ortho-McNeil objects to this proposal for precisely the same reason that it objected to Apotex's proposal:

> If the titration regimen is deleted . . . , the resulting product would be less safe and less effective for the remaining nontitrated dosing regimen. . . . Unless the comparative benefits of the titration regimen are explained in the labeling, a physician would have no basis for assessing whether the benefits of the titrated regimen outweigh the risk of discontinuance due to adverse events.

(Ortho-McNeil Response dated 5/17/02 at pages 5-6). Thus, Ortho-McNeil argues that a generic label will not be adequately safe unless it describes the benefits of the 16-day titration regimen. The absence of that information, according to Ortho-McNeil, presents a safety issue because physicians otherwise cannot intelligently choose between titration and non-titration.

b. Caraco's Proposal Label Resolves Ortho-McNeil's Objections By Including The Information Allegedly Necessary For Safety.

Caraco believes that Ortho-McNeil's objections rest on illusory safety concerns. Nevertheless, to facilitate immediate approval, Caraco proposes a label that would include the information Ortho-McNeil argues is necessary for safe administration. Under Caraco's proposal, the "Titration Trial" section of the generic label would be essentially identical to the Ultram®

label and, thus, would describe the benefits of the 16-day titration regimen. This, of course, would resolve Ortho-McNeil's alleged concern that the lack of such information raises safety issues.

At the same time, Caraco's proposed label would protect Ortho-McNeil's exclusivity by expressly excluding the use of the generic product for the 16-day titration regimen. To do so, Caraco proposes changing two sections of the label. First, Caraco's proposed label would add the following underlined language to the "Titration Trials" section to make clear that the 16-day titration regimen is the subject of Ortho-McNeil's exclusivity:

Ultram®	Caraco's Tramadol
Titration Trials In a randomized, blinded clinical study, with 129 to 130 patients per group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in few discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study, with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate ULTRAM therapy using slower titration rates. A 16-day titration schedule, starting with 25 mg qAM and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg q.i.d.), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg q.i.d.), resulted in few discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule. See Figure 2. Protocol CAPSS-047 Time to Discontinuation Due to Nausea/Vomiting	**Titration Trials** In a randomized, blinded clinical study, with 129 to 130 patients per group, a 10-day titration to a daily <u>tramadol hydrochloride</u> dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in few discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study, with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate <u>tramadol hydrochloride</u> tablets therapy using slower titration rates. A 16-day titration schedule, starting with 25 mg qAM and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg q.i.d.), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg q.i.d.), resulted in few discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule. <u>This titrated dosing regimen is approved for Ortho-McNeil Pharmaceutical's tramadol hydrochloride tablets. However, due to Ortho-McNeil's marketing exclusivity rights, this drug product is not labeled for use during this titrated dosing regimen.</u> See Figure 2. Protocol CAPSS-047 Time to Discontinuation Due to Nausea/Vomiting

Second, in the "Dosage and Administration" section of the label, Caraco proposes explaining clearly and directly that the generic product is intended only for the post-titration and non-titration uses of tramadol. The differences between the Ultram® label and Caraco's proposed label are indicated by underlining in the following chart:

Ultram®	Caraco's Tramadol
DOSAGE AND ADMINISTRATION Adults (17 years of age and over) For patients with moderate to moderately severe chronic paint not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily does may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day. For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.	**DOSAGE AND ADMINISTRATION** Adults (17 years of age and over) For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic affect, this drug product is intended and approved only for use after the titration regimen described above in the section of this label entitled 'Titration Trials.' Due to Ortho-McNeil's marketing exclusivity rights, this drug product is not labeled for use during the titration regimen. After titration, tramadol hydrochloride tablets 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day. For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol hydrochloride tablets 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.

The FDA adopted a similar approach in analogous circumstances in connection with metformin hydrochloride tablets, stating in the generic label that pediatric use was "approved for Bristol-Myers Squibb Company's metformin hydrochloride tablets" but that "due to Bristol-Myers Squibb's marketing exclusivity rights, this product is not labeled for pediatric use." (*See* Exhibit A at page 5).

c. Caraco's Proposed Label Resolves Ortho-McNeil's Safety Objections, Protects Ortho-McNeil's Exclusivity, And Complies With The Controlling Statute And Regulation.

Ortho-McNeil has no legitimate objection to Caraco's proposed label, which ensures safety, protects Ortho-McNeil's titration exclusivity, and complies with all other labeling requirements. Indeed, Ortho-McNeil already objected when Teva and Apotex proposed *removing* information about the 16-day titration regimen. Thus, it cannot now object when Caraco proposes *retaining* that information. Any such objection would amount to a Catch-22 – *i.e.*, whether the information is included or excluded, generic companies still lose. If it were to take that position, Ortho-McNeil effectively would be contending that its limited exclusivity over the 16-day titration regimen somehow creates exclusivity over *all* uses of tramadol. That is not a reasonable position, particularly considering that the D.C. Circuit already rejected the very same argument in *Bristol-Myers Squibb Company v. Shalala*, 91 F.3d 1493, 1499-1500 (D.C. Cir. 1996).

i. Caraco's Proposed Label Raises No Safety Concerns.

Caraco's proposed label raises no safety issues. The label would contain the same information as the Ultram® label. Literally no fact would be missing. Every piece of information in Ultram's label would also be included in Caraco's label, including the information that Ortho-McNeil asserts is necessary for safety, *i.e.*, the benefits of the 16-day titration regimen. Thus, if Ultram's label provides adequate safety assurances, Caraco's label necessarily also provides adequate safety assurances.

ii. Caraco's Proposed Label Raises No Exclusivity Issues.

Caraco's proposed label also protects Ortho-McNeil's titration exclusivity. In fact, the label could not be more direct. It expressly states that generic tramadol is "approved" and "intended" only for use "after" the 16-day titration regimen. Thus, Caraco's proposed label provides as much protection against unauthorized infringement as possible, even directing physicians to Ortho-McNeil's product if titration is necessary. Obviously, this provides more protection for Ortho-McNeil's exclusivity than mere silence.

Any lingering concern that Ortho-McNeil may have about its right to exclusivity is outside the FDA's jurisdiction. Ortho-McNeil may be concerned that *any* generic approval could lead to unauthorized infringement through the off-label substitution of the generic product for the patented 16-day titration regimen. But that is not an issue for the FDA. The FDA "does not regulate . . . possible substitution of a generic drug for the pioneer by doctors or pharmacists." *Bristol-Myers*, 91 F.3d at 1496.

Moreover, the D.C. Circuit already rejected the same concern about off-label substitutions in *Bristol-Myers*, where the issue was whether Bristol-Myers was entitled to exclusivity over *all* indications to protect its exclusivity over a *single* supplemental indication.

The Court held that the statute, "by its terms," provided exclusivity only for the supplemental indication, thus rejecting Bristol-Myers' contention that "economic reality" created by off-label substitution renders any such protection "illusory." *Id.* at 1500. The Court explained that Bristol-Myers' concern was "not a sufficient basis upon which to conclude that Congress intended to confer upon the manufacturer of pioneer drugs the much broader protection that [Bristol-Myers] now seeks." *Id.*

Thus, under *Bristol-Myers*, Ortho-McNeil is not entitled to broad exclusivity over *all* uses of tramadol merely to protect its limited exclusivity over the 16-day titration regimen. In an effort to distinguish the case, Ortho-McNeil argues that *Bristol-Myers* dealt only with "indications" rather than a "dosing" regimen. This is a distinction without a difference. The D.C. Circuit's reasoning applies with equal force to dosing regimens. The Court's decision rested primarily on statutory language ("different manufacturers") and a statutory provision (21 U.S.C. § 355(j)(4)(D)(iv)) that make no distinction between exclusivity over indications and exclusivity over dosing regimens.

The fact that *Bristol-Myers* dealt with only marketing exclusivity rather than patent exclusivity is equally irrelevant. The Court was construing statutory language ("different manufacturers") that make no distinction between those types of exclusivity and, thus, there is no rational basis for making such a distinction. For either kind of exclusivity, a company cannot reasonably obtain broad exclusivity over all uses of a drug simply to protect narrow exclusivity over a single use.

iii. Caraco's Proposed Label Fully Complies With The Controlling Statute And Regulation.

Finally, Caraco's proposed label fully complies with the controlling statute and regulation. In fact, the FDCA expressly authorizes Caraco's approach. The FDCA authorizes label differences "required . . . because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v).

Both the FDA and the D.C. Circuit have concluded that the reference to "different manufacturers" justifies labeling differences required to account for exclusivity, *i.e.*, an ANDA manufacturer may change its label to avoid another manufacturer's exclusivity. The D.C. Circuit reached that conclusion in *Bristol-Myers*, 91 F.3d at 1500. The FDA reached the same conclusion by enacting an implementing regulation authorizing the "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). Thus, Caraco's label complies with both the statute and the regulation by omitting an "aspect of labeling protected by patent," *i.e.*, the 16-day titration regimen.

Ortho-McNeil cannot object simply because Caraco accomplishes that "omission" by *adding* certain language to the brand label rather than simply *deleting* language as proposed by Apotex and Teva. Nothing in the controlling statute or regulation make any artificial distinction between adding language and deleting language. Although the FDA regulation refers

to the "omission of an . . . aspect of labeling," whether the "omission" is accomplished through the addition or deletion of language is irrelevant.

But even if the FDA's regulation's reference to an "omission" was intended to refer to deleting language, Caraco's proposed label still would be appropriate for at least two reasons. First, the FDA's regulation does not provide an exhaustive list of the authorized differences, stating only that the generic label:

> must be the same as the labeling approved for the reference listed drug, except for changes required . . . because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences . . . *may include* . . . omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). The regulation's use of the phrase "may include" is dispositive because it is "hornbook law" that a list following the word "including" is "illustrative, not exclusive." *Puerto Rico Maritime Shipping Authority v. I.C.C.*, 645 F.2d 1102, 1112 n. 5 (D.C. Cir. 1981). Consequently, even if the word "omission" referred to *deleting* language as one "illustrative" example, generic labels still could *add* language to account for exclusivity issues arising from the fact that the drugs are made by "different manufacturers." *See also In re Mark Anthony Const., Inc.*, 886 F.2d 1101, 1106 (9th Cir. 1989) ("In construing a statute, the use of a form of the word 'include' is significant, and generally thought to imply that terms listed immediately afterwards are an inexhaustive list of examples, rather than a bounded set of applicable items."); *Cincinnati Bell Telephone Co. v. F.C.C.*, 69 F.3d 752, 762 (6th Cir. 1995) (holding that the use of the term "including" does not refer to an "exhaustive list").

Second, even if the FDA's regulation could somehow be construed as an exhaustive list of appropriate differences, the plain language of the statute takes precedence over the regulation. *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 844 (1984). Nothing in the statute's language justifies any artificial distinction between additions and deletions. It refers only to "different manufacturers." Thus, whether through the deletion or addition of language, a manufacturer is statutorily entitled to change its label to avoid another manufacturer's exclusivity. The FDA has no power to implement a regulation that creates a different rule, and certainly has no rational basis for creating an artificial distinction between adding and deleting language. *See Chevron*, 467 U.S. at 842-43 (holding that government agency has no power to implement regulations that are not based on a rational reading of the statute); *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1067 (D.C. Cir. 1998) (same); *Purepac Pharmaceutical Co. v. Friedman*, 162 F.3d 1201, 1205 (D.C. Cir. 1998) (same).

Ortho-McNeil also cannot object to the fact that Caraco's proposed label would describe the 16-day titration trials. Nothing in the statute or the FDA's regulations precludes that description. For instance, the Federal Food, Drug, and Cosmetics Act ("FDCA") delays certain

ANDA approvals after the NDA-holder obtains a supplemental approval based on clinical trials, but does not impose any restrictions on the generic label describing those trials:

> If a supplement to an application . . . contains reports of new clinical investigations . . . essential to the approval of the supplement . . . , the Secretary may not make the approval of [an ANDA] . . . for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

21 U.S.C. § 355(j)(5)(D)(iv). Thus, this provision delays approval of any ANDA for the 16-day titration regimen, which was the subject of Ortho-McNeil's supplemental application. But it does not preclude any reference to the underlying clinical trials in the generic label and, indeed, does not even address any such issue.

3. Conclusion

The FDA should not permit Ortho-McNeil to delay generic competition any longer, particularly not over a labeling issue that is not about safety and efficacy, but only about word choice. Ortho-McNeil has no legitimate objection to the language of Caraco's proposed label, which ensures safety, protects exclusivity, and complies with the law. In fact, Ortho-McNeil already objected when Apotex and Teva proposed *deleting* information about the 16-day titration regimen. It cannot now create a Catch-22 by objecting when Caraco proposes *retaining* that information.

In the end, one fundamental and indisputable fact answers all of Ortho-McNeil's arguments: Neither Ortho-McNeil's marketing exclusivity nor the '105 patent cover the post-titration and non-titration uses of tramadol. Given that fact, nothing in the FDCA or the FDA's regulations provides Ortho-McNeil with exclusivity over those uses. Thus, the FDA is obligated (indeed, duty-bound) to approve generic tramadol for those non-protected uses, which will greatly benefit the public by creating generic competition and, consequently, lower prices.

Through this citizen's petition, Caraco now joins the chorus of voices requesting immediate agency action on the many "approvable" ANDAs for tramadol. The only remaining obstacle is for the FDA to select an appropriate generic label. Caraco respectfully urges the agency to promptly make that choice and then immediately provide final approval for Caraco's ANDA No. 75-964. Caraco thanks the agency for its time and attention to this matter.

C. Environmental Impact

The actions requested by this petition are subject to categorical exclusion pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

Caraco will provide an economic impact statement at the request of the Commissioner.

E. Certification

The undersigned certifies that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

James F. Hurst

JFH/ac