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June 6, 2002

Via Facsimile & Email

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

Re: Docket 02P-0191: Teva Inc. Citizen Petition re Ultram (tramadol)
Docket 01P-0495: Apotex Corp. Citizen Petition re Ultram (tramadol)

The following are the submissions of Apotex Corp. and Torpharm Inc. (collectively "Apotex") in response to the May 17, 2002 letter from Johnson & Johnson filed on Docket 02P-0191 respecting generic tramadol.

We enclose the opinion of Dr. Michael Byas-Smith dated June 6, 2002 that addresses the issue raised by Johnson and Johnson about patient safety.

Further, we briefly address below Johnson & Johnson's submission to the effect that any FDA approval of scored tablets would violate Ultram's exclusivity rights.

FDA's exclusivity is listed in the Orange Book as D-63, which is defined as "to allow a titration dosing regimen using a 25 mg dose". Notably, it is not listed as a "50 mg scored tablet" or a "25 mg dose".

The statute itself allows exclusivity for new clinical investigations submitted to FDA to support the exclusivity. In this case, the clinical studies pertain to the dosing regimen, not the scoring on the tablet. In the Exclusivity Summary for NDA 20-281 Supplement 02P-0191 at page 5, the clinical investigations submitted in the application that are essential to the approval are listed as "CAPSS-047: An Evaluation of Varying Titration Schedules (tramadol HCl) in subjects with chronic pain".

OIP-0495

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Johnson & Johnson asserts that to allow a scored tablet would eviscerate the exclusivity. This argument cannot be true as it would require FDA (in virtually all cases) to ban the manufacture of a generic alternative where any exclusivity has been granted by FDA. For example, in the case of an exclusivity pertaining to a particular use, an NDA sponsor could argue that no generic product should be approved as the product is capable of being used for the protected use. This contradicts the plain reading of the statute that permits carve-out from labeling.

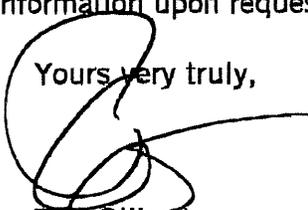
Johnson & Johnson also seeks to rely upon MAPP policy 5223.2. ("when the patent for the listed drug's scoring configuration expires, a generic firm may generally match the scoring configuration, provided there is no exclusivity on the dose obtained with that score"). Johnson & Johnson correctly points out that this section relates to patent rights, not exclusivities. However, there are no patent rights nor any exclusivities pertaining to the score of the tramadol tablets.

The exclusivity pertains to a titration dosing regimen not to a dose obtained with the score. There are many uses for a 25 mg dose that do not infringe the 16 day/25 mg titration dosing schedule. For example, using a 50 mg scored tablet, a physician could individualize patient dosing, perhaps prescribing a dose of 75 mg or 125 mg. There are many scored products on the market that do not have a dosing schedule. The scoring simply allows more flexibility in dosing, as noted in the MAPP policy, where it is stated that scoring "is useful because the score can be used to facilitate the breaking of the tablet into fractions when less than a full tablet is required for a dose."

Finally, in addition to the comments expressed by Dr. Byas-Smith respecting the lack of a safety concern, we also note that to the extent that FDA has any concern about a label that does not include a reference to 25 mg dosing, it is always open to the agency to direct that the labeling specifically advise physicians that the generic drug product should not be administered in connection with the 25 mg titration dosage regimen set forth on the label.

We would be pleased to provide further information upon request.

Yours very truly,



Tim Gilbert

TG:SM:ct
Encl.

cc. Daniel Troy
Elizabeth Dickinson

**EMORY**
UNIVERSITY
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Department of Anesthesiology

June 6, 2002

Tim Gilbert
Gilbert's Law Office
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Toronto, ON M5E 1C9
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Dear Tim:

**Re: Docket No. 02P-0191 (Petition by TEVA Pharmaceuticals USA
regarding approval of its ANDA for Tramadol Hydrochloric tablets)**

These comments are in response to the May 17, 2002 letter from Johnson & Johnson. In that document, Johnson & Johnson makes a number of statements that I do not believe are supported by the evidence I have reviewed that was filed with FDA. These are repeated in several places and I address them as follows:

Teva's proposed label

At page 4-5, Johnson & Johnson suggests that physicians will not read the proposed Teva label as limiting the indication of Teva's product to acute pain.

With respect, I disagree. Tramadol has been on the market for many years and physicians who use it routinely and have a good understanding of its efficacy and side-effect profile are less likely to change their practice. If a physician does not see the need to read the Teva label, he or she is unlikely to read the J&J label also. Furthermore, there are many physicians that never treat chronic pain patients but manage acute pain routinely. If such a doctor decides to use Tramadol in this setting and he does not have experience with the drug, there is a very high probability that he will read the label or consult with a knowledgeable colleague. If J&J's label happens to be the reference they choose to determine a dosing regimen, the titration schedule for chronic use of the medication appropriately should be ignored. J&J's own product labeling targets both the category of patients suffering from acute pain and the category of patients suffering from chronic pain. There is no reason why a physician cannot use J&J's product or another company's product for acute pain. The titration method recommended for chronic pain patients would be inappropriate for acute pain management.

At page 5, Johnson & Johnson argues that the absence of titration instructions and the reference to "higher doses" makes the label "unintelligible."



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Once again I disagree. I have reviewed the proposed Teva label as set out in Teva's citizen petition and am of the opinion that physicians would be able to understand the instructions for use. In the case of Tramadol, physicians would understand the "risk of discontinuance due to adverse events associated with higher doses" to mean that tolerability of the medication is limited at higher doses. Further, physicians using the drug for acute pain management will not need to evaluate the dosing instructions for chronic pain patients.

Safety of product without inclusion of 25 mg/16 day titration labeling information

Johnson & Johnson several times overstates the results of their clinical trials. For example, they make the following statements:

- "the titration regimen was proven to result in lower incidents of dizziness/vertigo, nausea and vomiting". (page 5)
- "...the truncated labeling Teva suggests will likely result in the prescription of the non-titrated, up-to-400 mg/day regimen for patients who should be prescribed a titration regimen, and these patients will suffer a higher incidence of adverse effects and a higher discontinuance rate." (page 6)
- "...the titration regimen included in the current Ultram labeling was proven by a clinical study to reduce adverse effects compared to the original Ultram dosing regimen" (page 7)

I reviewed the reports of clinical trials submitted to FDA and to my knowledge, there is no evidence that the claim of reduced side effects is correct. In fact, these studies demonstrated only that fewer patients would discontinue tramadol. There is no data presented to show that the actual incidents of such side effects were reduced.

In addition, these trials were conducted in a subpopulation of patients, those who had previously discontinued taking tramadol and were attempting a second course of therapy. These patients do not represent the entire population of those for whom tramadol would be prescribed. In my opinion, I do not feel that results of this trial can be extrapolated to the entire patient population. For example, one might assume that the subset of patients who discontinued the medication because of side effects tolerated the second trial of the medication because they had no side effects or the symptoms were greatly attenuated. On the other hand, it could be that the patients were motivated for other reasons to stick it out the second time.

Accordingly, I cannot support the claim that the titration dosing reduces discontinuance in the general patient population, nor can I conclude that adverse effects are reduced in either the subpopulation assessed in the trial or the patient population as a whole.

Titration regimen is not "safer"

Johnson & Johnson claims that "Ortho-McNeil's clinical studies have demonstrated that the 16-day titration regimen, which starts patients at 25 mg/day is safer than the non-titrated regimen which starts patients at up to 400 mg/day".

In my view, Johnson & Johnson has not presented any evidence to support increased safety by using the 25 mg/16 day titration dosing schedule. The intensity of the side effects described by Johnson & Johnson (dizziness, vertigo, nausea and vomiting) should be categorized as nuisance side effects and do not rise to the level of safety concerns. I have reviewed U.S. patent 6,339,105, and note that the patentee agrees with this characterization. Column 2 at lines 4-6 states "...nuisance side effects such as drowsiness, vomiting and dizziness can occur during the initiation of treatment..."

There are other drugs that have nuisance side effects, yet are safe and effective for human use. Benadryl, for example, is a good OTC drug for treating pruritis. A negative side effect of the drug is that it causes sedation. At the level of sedation caused by Benadryl is not a safety concern for patients and doctors in general. Occasionally, a patient will have severe sedation and cannot function while taking Benadryl. Either another drug will be substituted or some sort of titration regimen will be used in order to obtain the benefits while reducing the side effects.

Prescription of tramadol and other analgesics can be appreciated in the same light. For patients that do not tolerate the standard dosing regimen, titration to effectiveness is the standard approach. If Johnson & Johnson has information to suggest that the symptoms in the non-titrated group are more severe than the titrated group and analgesia is more intense, this is valuable information and the clinician should have access to it. If such information truly represents a safety issue, it should be reported to FDA as an adverse event. If there is no difference within or between the groups, then Johnson & Johnson is at least overstating the data.

Accordingly, I disagree with Johnson & Johnson's conclusions that:

- "if the titration regimen is deleted from the labeling of a generic tramadol product, the resulting product would be less safe and less effective for the remaining nontitrated dosing regimen" (page 5).
- "the nontitrated regimen would be less safe and less effective than it is when presented in the context of the full and approved labeling" (page 6).

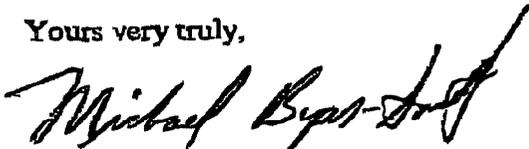
Finally, having reviewed carefully Johnson & Johnson's letter of May 17, 2002, I see no reason to change the opinion contained in my letter that

1. No safety issues are presented by the proposed generic labeling.

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2. There is no evidence to suggest that the 25 mg/16 day titration dosing schedule results in a lower incidence of side effects.
3. There is no evidence that the titration dosing improves efficacy of the drug.

Yours very truly,



Dr. Michael Byas-Smith

August 31, 2001

**EMORY UNIVERSITY SCHOOL OF MEDICINE
STANDARD CURRICULUM VITAE****Michael G. Byas-Smith, MD**

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Birth Date and Place: December 13, 1961; Union, South Carolina

Citizenship: USA

Academic Appointments:

Assistant Professor of Anesthesiology
Emory University School of Medicine
Department of Anesthesiology

Previous Academic/Professional Appointments:

Institute of Medicine (IOM), National Academy of Sciences, Committee Member 1996
Committee to Identify Strategies to Raise the Profile of Substance Abuse and
Alcoholism Research
University of Maryland School of Medicine
Department of Anesthesiology, Baltimore, Maryland
Clinical Instructor 1991-1993

Licensures/Boards: Georgia 1993
American Board of Anesthesiology, - 1992

Specialty Boards:

American Board of Anesthesiology September 1992
Subspecialty, Pain Management August 1994

M Byas-Smith

Education:

Orangeburg Wilkinson High School, Orangeburg, South Carolina	1977-1979
Morehouse College, Atlanta, Georgia, B.S. Degree in Biology	1979-1983
University of Illinois School of Medicine, Chicago, Illinois, Medical Degree	1983-1987
Cook County Hospital, Chicago, Illinois, Internship, Transitional Program	1987-1988
Emory University School of Medicine, Atlanta, Georgia, Residency, Anesthesiology	1988-1991
National Institutes of Health, Bethesda, Maryland Clinical Associate (Pain Research Fellow)	1991-1993

Military or Government Service

Public Health Service, Lieutenant Commander National Institutes of Health, Bethesda, Maryland	1991-1993
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Editorships and Editorial Boards:

Dispelling the Myths About Addiction: Strategies to Increase Understanding and Strengthen Research. National Academy Press, Washington, DC	1996
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Manuscript reviewer:

Journal of Pain 1999-present
Pain, 1995-present
Clinical Journal of Pain, 1999-present
Anesthesia and Analgesia 1999-present

Honors and Awards:

Emory University School of Medicine, Atlanta, Georgia, Chief Resident
Anesthesiology 1990-1991

Raymond Zbick Award - Outstanding performance as a medical student in anesthesiology, University of Illinois School of Medicine, Department of Anesthesiology, 1987

Society Memberships:

American Society of Anesthesiologists
International Association for the Study of Pain
American Pain Society
Society of Neuroscience
American Medical Association
American Society of Regional Anesthesia
National Medical Association

M Byas-Smith

Georgia Society of Anesthesiologists

Research focus:

My primary research interest is understanding mechanisms of opioid tolerance, pain perception and analgesia. My projects are designed to determine the effects of pain and opioid analgesic medications on brain function and identify the long-term effects of opioid administration to patients.

Patents:

Method and Compositions for Controlling Oral and Pharyngeal Pain Using Capsaicinoids.
Ref: E269/82590. Patent issued 1998.

Grant Support:**Federally funded**

Scientist Development Award (K20), NIDA, National Institutes of Health extramural award.

State funded

Advanced Technology Development Center/FRCPC Grant. Title of Proposal: A developmental program for commercialization of a capsaicin formulation designed for treatment of painful diseases involving the oral, pharyngeal and gastrointestinal mucosa.

University funded

The Effects of Opioids on Driving Ability in Patients with Chronic Pain

Formal Teaching:

Clinical Instructor

Lecturer for pain management lectureship

Instructor in departmental journal club

University Committees

Advisory Board Member, General Clinical Research Center

Affirmative Action and Equal Opportunity Committee, Emory University Department of Anesthesiology

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Lectureships, Seminar Invitations/Visiting Professorships:

Symposium, American Pain Society, Annual Scientific Meeting, Driving Under the Influence of Opioid Medications, November 2000

University of California, San Diego, California, Visiting Professor, Pharmacology of Pain Management, September 2000.

Free University of Amsterdam, Seminar on neuropharmacology, Visiting Professor, Molecular Mechanisms and Targets of Analgesic Drugs, April 2000

Georgia Society of Anesthesiologists, Semiannual Meeting, Mechanisms of Pain and Analgesia

40th Anniversary, Year end seminar, Emory University School of Medicine, Department of Anesthesiology. Meeting the Demand for Better Pain Control: Are we keeping pace? 1999.

University of Pennsylvania, Department of Anesthesiology, Visiting professor. Pain mechanisms and treatment, 1999.

Georgia Society of Anesthesiologists. Regional Anesthesia Workshop. Hilton Head South Carolina, 1998.

National Medical Association. Lecture Series on Pain Management. (Future of Pain Management for the Anesthesiologist), New Orleans, Louisiana, 1998.

American Academy of Pain Medicine. Management of Neuropathic Pain San Diego, California, March, 1998.

Stanford University, Department of Anesthesiology. Visiting professor. Measuring pain using Positron Emissions Tomography. Palo Alto, California, March, 1997.

University of Kentucky, School of Oral Surgery. Update on chronic pain management. Lexington, Kentucky, April, 1996.

American Society of Anesthesiologists, Regional Refresher Course. Workshop On Chronic Pain Management. Lectures: 1. Reflex Sympathetic dystrophy: Psychiatric or Neuropathic Pain Syndrome? 2. Historical and Current Diagnostic Techniques and Clinical Management of Reflex Sympathetic Dystrophy. Milwaukee, Wisconsin, August 1995.

Michigan Center For Pain Management and Rehabilitation. Update on chronic pain management. Dearborn, Michigan September, 1995.

M Byas-Smith

Published research articles in refereed journals:

Byas-Smith M, Frolich M, Hoffman J, Votaw J: Cerebral Blood Flow During Propofol Induced Sedation and Anesthesia, *Molecular Imaging and Biology*, March/April 2002 4(2).

Byas-Smith M, Bennett G, Gracely R, Robinovic G, Max M, Dubner R: Tourniquet pain exacerbates hyperalgesia related pain induced by intradermal capsaicin injection. *Anesthesiology*, September 1999.

Iadarola MJ, Berman KF, Zeffiro TA, Byas-Smith MG, Gracely RH, Max MB, Zeffiro T, Bennett GJ: Neural activation during acute capsaicin-evoked pain and allodynia assessed with positron emission tomography. *Brain* 1998;121:931-47.

Byas-Smith MG, Max MB, Muir J, Kingman A: Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage "enriched" enrollment trial design, *Pain* 1995, 267-274.

Iadarola MJ, Max MB, Berman KF, Byas-Smith MG, Coghill RC, Gracely RH and Bennett GJ: Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain, *Pain*, 63 (1995) 55-64.

Max MB, Byas-Smith MG, Gracely RH and Bennett GJ: Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. *Clinical Neuropharmacology*, 18(1995) 360-368.

Manuscripts submitted:

Byas-Smith M, Votaw J and Hoffman J: Cerebral Blood Flow Changes During Sensory Deprivation, under revision.

Byas-Smith M, Votaw J and Hoffman J: A regional and global blood flow study of intense thermal pain and innocuous cold stimulation using 3D PET scanning, under revision.

Byas-Smith M, Votaw J and Hoffman J: Fentanyl Decreases Regional and Global Cerebral Blood Flow (CBF) and Inhibit rCBF Changes Induced By Acute Pain, under revision.

Byas-Smith M, Hoffman J, Horowitz I and Votaw J: A Study of Hypnoanesthesia in a Single Patient Using FDG and EEG Monitoring, under revision.

Byas-Smith MG, Frolich M, Votaw JR, and Hoffman JM: Cerebral blood flow (CBF) during propofol sedation in humans, Submitted *Anesthesiology*.

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Book Chapter:

Dispelling the myths about addiction: Strategies to increase understanding and strengthen research. National academy press. 1997.

Byas-Smith MG: Common Pain Syndromes Seen in Clinical Practice. In Guide to Pain Management. Springhouse Corporation, 1997.

Byas-Smith MG: Sympathetic Pain Syndromes: The Problem in Perspective. In: Tollison and Satterthwaite, editors: Sympathetic Pain Syndromes: Reflex Sympathetic Dystrophy and Causalgia, Philadelphia, 1996, Hanley & Belfus, Inc

Byas-Smith MG: Management of Acute Exacerbations of Chronic Pain Syndromes. In Sinatra, Hord, Ginsberg, Preble, editors: Acute Pain: Mechanisms and Management. St. Louis, 1992, Mosby Year Book.

Other publications:

Byas-Smith M, Votaw J and Hoffman J: Cerebral blood flow changes during somatosensory deprivation, Abstract, Society for Neuroscience, 1999.

Byas-Smith M, Votaw J and Hoffman J: Fentanyl Decreases Regional and Global Cerebral Blood Flow (CBF) and Inhibit rCBF Changes Induced By Acute Pain, Abstract, Society for Neuroscience, 1998.

Byas-Smith MG, Frolich M, Votaw JR, and Hoffman JM: Propofol attenuates pCO₂ mediated increase in cerebral blood flow (CBF) in normal volunteers. Abstract, Society for Neuroscience, 1996.

Byas-Smith MG, Votaw J, Alazraki N, Votaw D, Eshima D: A functional Imaging study of heat pain activation of the lower extremity using 18 F PET scan imaging techniques, Abstract, IASP 8th World Congress On Pain, August 1996.

Byas-Smith MG, Votaw JR, Hoffman JM, Votaw DB, Smith EO, and Eshima: Epidural lidocaine reduces global cerebral blood flow by 11%. Abstract, Society of Nuclear Medicine 43rd Annual Meeting, June, 1996.

Braae W, Pfeifer B, Hasenbusch S, Burchiel K, Byas-Smith M, Krames E, McGuire D, Tich N, and Luther R: Analgesia induced by SNX-111 in patients with morphine-resistant pain. Abstract, American Pain Society 15th Annual Scientific Meeting, November, 1996.

Byas-Smith MG, Umeakunne K, Wilson T, and Manatunga AK: Capsaicin relieves

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tonsillopharyngitis pain in patients with common cold symptoms. Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

Byas-Smith MG, Umeakunne K, Sebastianelli J, Bryant P and Manatunga AK: Capsaicin induced sensitization relieves pain when applied to painful conditions of the oral mucosa. Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

McKenzie-Brown A, Byas-Smith MG, Sebastianelli J, Hord AH, and Manatunga AK: The effects of altered vascular dynamics on sympathetically maintained pain: a comparison of phentolamine, sodium nitroprusside and saline. Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

Byas-Smith M, Bennett G, Robinovic G, Gracely R, Max M, Dubner R: Exacerbation and rekindling of intradermal capsaicin-evoked pain correlates temporally with loss of cutaneous capillary blood flow.
Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

Byas-Smith MG, Max MB, Gracely RH, Bennett GJ: Intravenous ketamine and alfentanil in patients with chronic causalgic pain and allodynia, Abstract, IASP 7th World Congress On Pain, August 1993.

Iadarola MJ, Berman KF, Byas-Smith MG, Gracely RH, Max MB, Zeffiro T, Bennett GJ: Positron emission tomography (PET) studies of pain and allodynia in normals and patients with chronic neuropathic pain, Society for Neuroscience, August 1993.

Gracely RH, Barcellos SA, Saltzman SJ, Byas-Smith MG, Max MB, Bennett GJ: A-beta mechano-allodynia and cold hyperalgesia following large doses of intradermal capsaicin, Abstract, Society for Neuroscience, August 1993.

Staats PS, Yearwood TL, Charapata SG, Presley RW, Wallace MS, Byas-Smith MG, Fisher R, Pallares V, Bryce DA, Mangieri EA, Luther RR, Mayo M, McGuire D and the Ziconotide Malignant Pain Study Group. Intrathecal Ziconotide in the Treatment of Refractory Malignant Pain: A Controlled Clinical Trial. New England Journal of Medicine. 2001 pending.

Byas-Smith M, Votaw J, Goodman MM, Howell L and Wilcox K. Phenylephrine increases DAT binding potential in rhesus monkey during isoflurane anesthesia. Society of Neuroscience. Abstract 2001. San Diego CA

JR Votaw, M Byas-Smith, L Martarello, LL Howell, CD Kilts, K Wilcox, MM Goodman. Interaction of Isoflurane and Sevoflurane with the Dopamine Transporter. Society of Nuclear Medicine. Abstract 2001. Toronto, Canada

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Byas-Smith MG, Frolich M, Votaw JR, and Hoffman JM: Cerebral Blood Flow During Propofol Induced Sedation, Society of Anesthesiology. Abstract. 2001. New Orleans, LA

GILBERT'S

FAX COVER PAGE

DATE: June 6, 2002

FILE NO.: 7002

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