CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

ENVIRONMENTAL ASSESSMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: July 07, 2008

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Danae Christodoulou, Ph.D.
OPS/ONDQA/DPAI

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: **NDA 22-304**; Tapentadol HCl

Johnson and Johnson Pharmaceutical Research and Development, L.L.C.
920 Route 202
Raritan, NJ 08869

Background

Johnson and Johnson Pharmaceutical Research and Development, L.L.C. is requesting approval of an NDA for tapentadol hydrochloride drug substance in immediate release (IR) tablets. An EA has been submitted pursuant to 21 CFR part 25.

Discussion

The review appended below was conducted by Ruth Ganunis, Ph.D., under contract to the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (Completion date: May 19, 2008). Also attached are recommendations and an Executive Summary.

Comments and Conclusions

Based on an evaluation of the information provided in this EA and in FDA guidance, and on the scientific validity of the "no effects" conclusions of the EA, no significant adverse environmental impacts are expected from the introduction of tapentadol residues into the environment due to the use of tapentadol for the treatment of acute pain.

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT

FONSI recommended.

The maximum predicted amount of tapentadol hydrochloride drug substance manufactured for direct use in any of the next five years is [redacted] kg/year. Assuming no metabolism or environmental depletion, the firm determines the EIC to be [redacted] b(4)

Tapentadol hydrochloride is freely water soluble and has a log K_{ow} <3.5. A microbial inhibition test showed tapentadol hydrochloride to be relatively non-toxic, with an EC_{50} of 586 mg/L. The firm provided the results of 3 acute toxicity studies, including fish, invertebrate and algal species. Of these, the most sensitive species is green algae with an assessment factor of [redacted] No observed effects were seen at the MEEC. No potential adverse environmental effects resulting from the manufacture and use of tapentadol hydrochloride are identified.

REVIEW OF ENVIRONMENTAL ASSESSMENT

1. **Date:**

EA dated November 7, 2007

2. **Name of applicant/petitioner:**

Johnson and Johnson Pharmaceutical Research and Development, L.L.C.

ADEQUATE

3. **Address:**

920 Route 202
Raritan, NJ 08869

ADEQUATE

4. **Description of the proposed action:**

a. **Requested Approval:**

Johnson and Johnson Pharmaceutical Research and Development, L.L.C. is requesting approval of an NDA for tapentadol hydrochloride drug substance in immediate release (IR) tablets. An EA has been submitted pursuant to 21 CFR part 25.

ADEQUATE

b. **Need for Action:**

Tapentadol hydrochloride tablets will be used for the treatment of acute pain.

ADEQUATE

c. **Expected Locations of Use (Drug Product):**

The locations of use will typically be hospitals, clinics and/or patients in their homes.

ADEQUATE

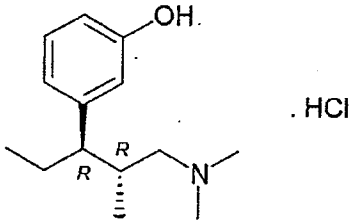
d. **Disposal Sites**

Returned product will be disposed through high temperature incineration at licensed disposal facilities. US hospitals, pharmacies, or clinics will dispose of empty or partially empty packages according to their internal handling procedures. In the home, empty or partially empty packages will be disposed by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system. Where available, disposal of unused medicines could also be through take-back programs in local community waste disposal systems or pharmacies.

ADEQUATE

5. Identification of chemicals that are the subject of the proposed action:

Nomenclature:
Established Name (USAN): Tapentadol hydrochloride
Proposed Trade Name: Not applicable
Chemical name: 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride
Chemical Abstracts Service (CAS) Registration Number: 175591-09-0
Molecular Formula: $C_{14}H_{23}NO \cdot HCl$
Molecular Weight: 257.80 (221.34 + 36.46)
Chemical Structure:



ADEQUATE

6. Environmental Issue:

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

The firm does not mention or discuss metabolites, degradants, or any other structurally related compounds that may exist in the environment. It is assumed that the subject of interest is tapentadol hydrochloride. In their calculation of the environmental concentration, they assume no metabolism or degradation.

ADEQUATE

ii. **Physical and Chemical Characterization**

Test	Endpoint
Water Solubility (at ambient temperature)	380 mg/mL
Dissociation Constants	pKa1: 9.34 pKa2: 10.45
Partition Coefficient n-Octanol/Water (log K_{ow})	2.87
Adsorption Coefficient (K_{oc}) (OECD Guideline 121)	1704
Log K_{oc}	3.23

Tapentadol hydrochloride is freely soluble in water at ambient temperature. The Partition Coefficient n-Octanol/Water (log K_{ow}) is 2.87. A value less than 3.5 indicates that the compound is not likely to bioaccumulate.

Based on the test data, tapentadol hydrochloride is expected to enter the aquatic environment.

Concern: The K_{oc} is greater than 1000, indicating that it will adsorb to biosolids and mobilize in the environment. The firm makes no comments about this high value.

iii. **Environmental Depletion Mechanisms**

No rapid, complete depletion mechanisms are known (see introductory summary; supporting data not provided).

ADEQUATE

iv. **Environmental Concentration**

The maximum predicted amount of tapentadol hydrochloride drug substance manufactured for direct use in any of the next five years is [ ]kg/year. Assuming no metabolism or environmental depletion, the firm determines the EIC to be [redacted]

b(4)

ADEQUATE

v. **Summary**

Tapentadol hydrochloride is expected to enter the aquatic environment through patient use. Based on the high water solubility and log octanol/water coefficient <3.5 (log K_{ow} 2.87) no relevant partitioning into sewage sludge is expected.

ADEQUATE

b. Environmental Effects

Test Organism (Test Method)	Condition	Result	Assessment Factor
Microbial inocula (OECD Guideline 209)	Microbial growth inhibition	NOEC = 95.9 mg/L EC_{50} = 586 mg/L	
Algae (*Pseudokirchneriella subcapitata)* (OECD Guideline 201)	Acute toxicity	NOEC = 2.4 mg/L EC_{50} = 4.5 mg/L (72 h)	—
Daphnids *(Daphnia magna)* (OECD Guideline 202)	Acute toxicity	NOEC = 4.4 mg/L EC_{50} = 25 mg (48 h)	—
Zebra fish (*Brachydanio rerio*) (OECD Guideline 203)	Acute toxicity	NOEC = 12 mg/L LC_{50} = 77 mg/L (96 h)	—

The inhibitory effect of tapentadol hydrochloride on the respiration rate of aerobic wastewater microorganisms of activated sludge was investigated in a 3-hour respiration inhibition test following OECD Guideline 209. The 3 hour EC_{50} of lacosamide in the activated sludge respiration test was — mg/L. The 3 hour NOEC was 95.9 mg/L. The microbial inhibition test showed tapentadol hydrochloride to be relatively non-toxic.

The firm conducted a 72 hour static test following OECD Guideline 201 to assess the acute toxicity of tapentadol hydrochloride to freshwater green algae. The EC_{50} for growth rate was —; the EC_{50} for yield was 4.5 mg/L. The NOEC for both endpoints, growth rate and yield was 2.4 mg/L.

The firm conducted a 48 hour static test following OECD Guideline 202 to assess the acute toxicity of tapentadol hydrochloride to the water flea (*Daphnia magna*). The 48 hour EC_{50} was estimated to be 25 mg/L. The NOEC was 4.4 mg/L.

The firm conducted a 96 hour static test following OECD Guideline 203 to assess the acute toxicity of tapentadol hydrochloride to zebra fish. The LC_{50} (Median

Lethal Concentration) was estimated to be 77 mg/L. The NOEC was determined to be 12 mg/L.

The firm provided the results of 3 acute toxicity studies. The calculated assessment factor for each is >1,000. No observed effects were seen at the MEEC.

c. Summary

The microbial inhibition test found tapentadol hydrochloride to be relatively non-toxic. The firm provided the results of 3 acute toxicity studies. The calculated assessment factor for each is >1,000. No observed effects were seen at the MEEC.

ADEQUATE

7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

ADEQUATE

8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

ADEQUATE

9. List of Preparers

Names and professional experience are provided.

ADEQUATE

10. References

References are provided.

ADEQUATE

11. Appendices

Provided.

ADEQUATE

Review by: Ruth Ganunis, Ph.D., May 19, 2008
Under contract to:
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

Raanan Bloom
7/7/2008 02:19:08 PM
ENV ASSESSMENT

Jon E. Clark
7/11/2008 02:25:31 PM
CHEMIST

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

Tapentadol Hydrochloride
50, 75, and 100 mg Immediate Release Tablets

NDA 22-304

Food and Drug Administration
Center for Drug Evaluation and Research

Date Completed: May 19, 2008

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-304

Tapentadol Hydrochloride
50, 75, and 100 mg Immediate Release Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant impact on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its new drug application for Tapentadol Hydrochloride Immediate Release Tablets, Johnson and Johnson Pharmaceutical Research and Development, L.L.C. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Tapentadol hydrochloride tablets will be used for the treatment of acute pain.

Tapentadol hydrochloride may enter the environment from patient use and disposal. It is expected to enter into the aquatic environment. Data indicate that the compound is unlikely to enter the terrestrial and atmospheric environments. The toxicity of tapentadol hydrochloride to aquatic organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

Empty or partially empty packages will be disposed by a community's solid waste management system that may include landfills, incineration and recycling. Minimal quantities of the unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental impacts. Adverse impacts are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY:

Ruth Ganunis, Ph.D.
under contract to
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

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Office of Pharmaceutical Science
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Office of Pharmaceutical Science
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Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment:

Environmental Assessment dated June, 2007
Appended Electronic Signature Page

TABLE OF CONTENTS

IN-TEXT TABLES

NDA Environmental Assessment for Tapentadol Hydrochloride Drug Substance in 50-, 75-, and 100-mg Immediate Release (IR) Tablets

SUMMARY

Potential environmental impacts of tapentadol hydrochloride IR tablets have been evaluated in this environmental assessment according to 21 CFR Part 25.

The calculated Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-aquatic based on use) was more than 1 part per billion (ppb, based on the fifth year projection forecast), therefore, fate and acute effects testing results were reported.

In accordance with the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications*{1}, if no rapid, complete depletion mechanisms are known, then a microbial inhibition test should be done; and if the Log K_{ow} <3.5, then an acute toxicity study should be done. If the results demonstrate that the acute EC_{50} (Median Effective Concentration) or the acute LC_{50} (Median Lethal Concentration), divided by the MEEC is ≥1,000, then no further testing should be conducted unless sublethal effects are observed at the MEEC.

For tapentadol hydrochloride, no rapid, complete depletion mechanisms are known. A microbial inhibition test showed tapentadol hydrochloride to be relatively non-toxic with an EC_{50} of 586 mg/L. The Log K_{ow} is <3.5. The calculated assessment factors for algae, daphnids, and zebra fish were each greater than 1,000 according to the calculation described above, and sublethal effects were not seen at the MEEC; therefore additional testing is not required. No potential adverse environmental effects resulting from the manufacture and use of tapentadol hydrochloride have been identified.

1. Guidance for industry-environmental assessment of human drugs and biologics applications. US FDA - Food and Drug Administration, Washington, DC, July 1998.

1. DATE

07 Nov 2007

2. NAME

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

3. ADDRESS OF APPLICANT

920 Route 202
Raritan, NJ 08869, U.S.A.

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested Approval

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., is submitting an NDA pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for tapentadol hydrochloride drug substance in IR tablets. An environmental assessment (EA) is being submitted pursuant to 21 CFR Part 25.

4.2. Need for Action

This EA supports a New Drug Application (NDA) for tapentadol hydrochloride IR tablets. This drug will be used for the treatment of acute pain.

4.3. Locations of Use

This drug will be used in hospitals and private homes across the US. It will be available by prescription only.

4.4. Disposal Sites

Disposal of prescribed product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. US hospitals, pharmacies, or clinics will dispose of empty or partially empty packages according to their internal handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system. Where available, disposal of unused medicines could also be through take-back programs in local community waste disposal systems or pharmacies.

5. IDENTIFICATION OF SUBSTANCES

5.1. Nomenclature

5.1.1. Established Name (U.S. Adopted Name-USAN)

Tapentadol hydrochloride

5.1.2. Brand/Proprietary Name/Trade Name

Not applicable

5.1.3. Chemical Name

3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride

5.2. Chemical Abstracts Service (CAS) Registration Number

175591-09-0

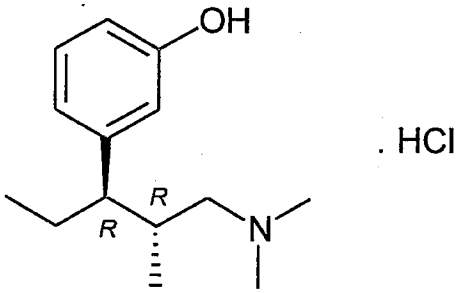
5.3. Molecular Formula

$C_{14}H_{23}NO \cdot HCl$

5.4. Molecular Weight

257.80 (221.34 + 36.46)

5.5. Structural (Graphic) Formula



6. ENVIRONMENTAL ISSUES

The manufacture and use of tapentadol hydrochloride tablets are not expected to result in significant environmental releases of the active ingredient or excipients. No potential adverse environmental effects resulting from the manufacture and use of tapentadol hydrochloride have been identified.

The physical and chemical characterizations used to evaluate potential adverse effects in the environment are presented in Table 1.

Table 1: Physical/Chemical Characterization

Property	Value	Source
Water Solubility (at ambient temperature)	380 mg/mL	Section 3.2.S.1.3{1}
Dissociation Constants	pKa1: 9.34 pKa2: 10.45	Section 3.2.S.1.3{1}
Partition Coefficient n-Octanol/Water (log K_{ow})	2.87	Section 3.2.S.1.3{1}
Adsorption Coefficient (K_{oc}) Log K_{oc}	1704 3.23	Report 13674.6123{2}

The water solubility of tapentadol hydrochloride at ambient temperature is 380 mg/mL. Tapentadol hydrochloride can be considered freely soluble in water according to current United States Pharmacopeia. {1}

The dissociation constant (pKa) indicates the tendency of an organic chemical to ionize and is related to the adsorption of the chemical into biological membranes. The pKa1 of tapentadol hydrochloride was determined to be 9.34, pKa2 was determined to be 10.45. {1}

The partition coefficient (log K_{ow}) indicates the tendency of an organic chemical to partition into lipids or fats, sorb to particulates such as soils or sediments, sorb to biomass and sludge, and distribute among the various environmental compartments. According to the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998), chemicals with log K_{ow} <3.5 do not have potential to bioaccumulate.{7} The log K_{ow} for tapentadol hydrochloride is 2.87, which is below 3.5, therefore, tapentadol does not show a potential to bioaccumulate.{1}

The adsorption coefficient (K_{oc}) indicates the tendency of an organic chemical to mobilize in the environment. The K_{oc} for tapentadol hydrochloride was evaluated in a study according to OECD Guideline 121. Based on the results of this study, the K_{oc} was 1704. {2}

Information related to the Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-Aquatic, based on use) calculation is confidential and is provided in Confidential Appendices, Section 11, APPENDIX 1.

6.1. Assessing Toxicity to Environmental Organisms

The following environmental effect studies have been conducted with tapentadol hydrochloride drug substance; the results are summarized in Table 2.

A. Microbial growth inhibition (activated sludge respiration inhibition){3}

B. Algae (*Pseudokirchneriella subcapitata)* acute toxicity{4}

C. Daphnids (*Daphnia magna*) acute toxicity{5}

D. Zebra fish (*Brachydanio rerio*) acute toxicity{6}

Table 2: Toxicity Testing of Tapentadol Hydrochloride Drug Substance with Representative Environmental Organisms

Test Organism	Conditions	Results	Source
Microbial inocula	Microbial growth inhibition	NOEC = 95.9 mg/L EC_{50} = 586 mg/L	Report 13674.6122{3}
Algae (*Pseudokirchneriella subcapitata)*	Acute toxicity	NOEC = 2.4 mg/L EC_{50} = 4.5 mg/L (72 h)	Report 13674.6119{4}
Daphnids *(Daphnia magna)*	Acute toxicity	NOEC = 4.4 mg/L EC_{50} = 25 mg (48 h)	Report 13674.6120{5}
Zebra fish (*Brachydanio rerio*)	Acute toxicity	NOEC = 12 mg/L LC_{50} = 77 mg/L (96 h)	Report 13674.6121{6}

EC_{50} = median effective concentration
NOEC = no observed effect concentration
LC_{50} = median lethal concentration

6.1.1. Microbial Inhibition Test

The influence of tapentadol hydrochloride on microorganisms was determined by measuring the respiration rate under defined conditions in a 3-hour respiration inhibition-activated sludge study according to OECD Guideline 209.

Based on the results of this test, the EC_{50} (Median Effective Concentration) was calculated to be 586 mg/L. The No-Observed-Effect Concentration (NOEC, determined as the calculated 3-hour EC_{15}) was 95.9 mg/L. {3}

6.1.2. Acute Toxicity to Freshwater Green Algae

The influence of tapentadol hydrochloride on the green algal species *Pseudokirchneriella subcapitata* was investigated in a 72-hour static test, according to OECD Guideline 201.

Based on the results, the EC_{50} for growth rate was determined to be 9.8 mg/L. The EC_{50} for yield was determined to be 4.5 mg/L. The NOEC for both endpoints, growth rate and yield, was determined to be 2.4 mg/L. {4}

6.1.3. Acute Toxicity to the Water-Flea (*Daphnia magna*)

The acute toxicity of tapentadol hydrochloride to *Daphnia magna* was determined in a 48-hour static test according to OECD Guideline 202.

The 48-hour EC_{50} value was estimated to be 25 mg/L. The NOEC was determined to be 4.4 mg/L. {5}

6.1.4. Acute Toxicity to Fish

The acute toxicity of tapentadol hydrochloride to zebra fish (*Brachydanio rerio*) was determined in a 96-hour static renewal test, according to OECD Guideline 203.

Based on the results from this study, the 96-hour LC_{50} (Median Lethal Concentration) was estimated to be 77 mg/L. The NOEC was determined to be 12 mg/L. {6}

6.2. Conclusion

In accordance with the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998){7}, no further testing is required. After the microbial inhibition test found tapentadol hydrochloride to have an EC_{50} of 586 mg/L, the log K_{ow} was determined to be <3.5, after which acute ecotoxicity studies were reported. The calculated assessment factor for each of the 3 acute toxicity studies is >1,000. No observed effects were seen at the MEEC, therefore no further testing is required. The original assumption that tapentadol hydrochloride has no known environmental effects remains valid.

Information related to the tiered approach to environmental effects testing is confidential and is provided in Confidential Appendices, Section 11, APPENDIX 2.

7. MITIGATION MEASURES

Section 7 is not required when there have been no adverse environmental effects identified.

8. ALTERNATIVES TO THE PROPOSED ACTION

Section 8 is not required when there have been no adverse environmental effects identified.

9. LIST OF PREPARERS

Edward Nowak, QEP, CHMM
Director, Global Pharma R&D Environmental Health & Safety
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1000 U.S. Route 202 South
Raritan, NJ 08869-0602

More than 25 years of environmental experience; 15 years with the telecommunications research and development industry, 8 years with the United States Environmental Protection Agency, and 6 with the pharmaceutical industry.

Bachelor of Science in Civil Engineering, New Jersey Institute of Technology

Master of Science in Environmental Engineering, New Jersey Institute of Technology

Kelly Quinlan
Environmental Engineer
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1000 U.S. Route 202 South
Raritan, NJ 08869-0602

More than 2 years of environmental experience with the pharmaceutical industry.

Bachelor of Science in Environmental Science, Rutgers University

Master of Science in Environmental Science, Rutgers University (Pursuing)

10. REFERENCES

1. Section 3.2.S.1.3 of J&JPRD Drug Master File for tapentadol hydrochloride

2. Tapentadol HCl- determination of the K_{oc} coefficient following OECD Guideline 121; [redacted] OECD Guideline 121; [redacted] Report 13674.6123. (01 Nov 2007) b(4)

3. Tapentadol HCl- activated sludge respiration inhibition. [redacted] OECD Guideline 209; [redacted] Report 13674.6122. (02 Mar 2007)

4. Tapentadol HCl - acute toxicity to the freshwater green alga. [redacted] OECD Guideline 201; [redacted] Report 13674.6119. (07 Feb 2007). b(4)

5. Tapentadol HCl - acute toxicity to water fleas, (*Daphnia magna*) under static conditions, following OECD draft guideline #202. [redacted] OECD Guideline 202; [redacted] Report 1374.6120. (29 Mar 2007)

6. Tapentadol HCl – acute toxicity to zebra fish (*Brachydanio* rerio), under static-renewal conditions. [ ]OECD Guideline 203;[ ] [ ]Report 13674.6121. (30 Mar 2007)

7. Guidance for industry-environmental assessment of human drugs and biologics applications. US FDA - Food and Drug Administration, Washington, DC, Jul 1998.

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/s/

Jon E. Clark
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Moheb Nasr
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