In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1  YES /___/  NO /___/
Investigation #2  YES /___/  NO /___/
Investigation #3  YES /___/  NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _______  Study # ___________
NDA # _______  Study # ___________
NDA # _______  Study # ___________

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1  YES /___/  NO /___/
Investigation #2  YES /___/  NO /___/
Investigation #3  YES /___/  NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _______  Study # ___________
NDA # _______  Study # ___________
NDA # _______  Study # ___________
c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):  

Investigation #, Study # 

Investigation #, Study # 

Investigation #, Study # 

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /__/ NO /__/ Explain: ___ 

Investigation #2

IND # YES /__/ NO /__/ Explain: ___ 

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain: ______ NO /__/ Explain: ________

Page 7
Investigation #2

YES /__/ Explain _______ NO /__/ Explain _______

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /__/ 

If yes, explain: ____________________________________________

__________________________________________________________

__________________________________________________________

__________________________________________________________

/S/  5/17/99
Signature
Title: Project Manager

/S/  6/20/99
Signature of Division Director

cc: Original NDA Division File HFD-85 Mary Ann Holovac
PEDiatric PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 21-042
Supplement # ___________ Circle one: SE1 SE2 SE3 SE4 SE5 SE6
HFD-550 Trade (generic) name/dosage form: 12.5 mg + 25 mg
Action: AP AE NA
Applicant Merck Therapeutic Class

Indication(s) previously approved
Pediatric labeling of approved indication(s) is adequate inadequate

Indication in this application
(For supplements, answer the following questions in relation to the proposed indication.)

1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
   a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
   b. The applicant has committed to doing such studies as will be required.
      (1) Studies are ongoing.
      (2) Protocols were submitted and approved.
      (3) Protocols were submitted and are under review.
      (4) If no protocol has been submitted, explain the status of discussions or the back of this form.
   c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/
Signature of Preparer and Title (PM, CSO, MO, other) 5/20/99 Date

cc: Orig NDA/PLA # 21-042
HFD-550 Div File
NDA/PLA Action Package
HFD-510/Gtoendle (plus, for CDER APs and AEAs, copy of action letter and labeling)

TE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
5/95
MK-0966
Item 16 – Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.
EXCLUSIVITY SUMMARY for NDA #21-052 SUPPL # ___

Trade Name: Vioxx Suspension

Generic Name: rofecoxib 12.5 mg/mL and 25 mg/mL suspension

Applicant Name: Merck Research Laboratories  HFD-550

Approval Date __________

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
      YES /X/   NO /__/

   b) Is it an effectiveness supplement?
      YES /__/   NO /X/

      If yes, what type? (SE1, SE2, etc.) __________

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
      YES /X/   NO /__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      ___________________________________________________________________

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      ___________________________________________________________________

      ___________________________________________________________________

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac
d) Did the applicant request exclusivity?

YES /X/ NO /__/_

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 YEARS

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /__/ NO /X/

If yes, NDA # _____ Drug Name __________

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY ON ORIGINAL
PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___/    NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # ___________  ___________
NDA # ___________  ___________
NDA # ___________  ___________

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___/    NO / ___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # ___________  ___________
NDA # ___________  ___________
NDA # ___________  ___________

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.
PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__/ NO /__/  

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /__/  

APPEARS THIS WAY ON ORIGINAL
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /__/ 

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/ 

If yes, explain: ____________________________

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/ 

If yes, explain: ____________________________

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # ________________
Investigation #2, Study # ________________
Investigation #3, Study # ________________

APPEARS THIS WAY ON ORIGINAL
In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

<table>
<thead>
<tr>
<th>Investigation</th>
<th>YES</th>
<th>NO/___</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #1</td>
<td>YES</td>
<td>NO/___</td>
</tr>
<tr>
<td>Investigation #2</td>
<td>YES</td>
<td>NO/___</td>
</tr>
<tr>
<td>Investigation #3</td>
<td>YES</td>
<td>NO/___</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _______ Study # _______
NDA # _______ Study # _______
NDA # _______ Study # _______

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

<table>
<thead>
<tr>
<th>Investigation</th>
<th>YES</th>
<th>NO/___</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #1</td>
<td>YES</td>
<td>NO/___</td>
</tr>
<tr>
<td>Investigation #2</td>
<td>YES</td>
<td>NO/___</td>
</tr>
<tr>
<td>Investigation #3</td>
<td>YES</td>
<td>NO/___</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _______ Study # _______
NDA # _______ Study # _______
NDA # _______ Study # _______
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study #

Investigation #_, Study #

Investigation #_, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #___ YES /___/ NO /___/ Explain: ___

Investigation #2

IND #___ YES /___/ NO /___/ Explain: ___

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain ______ NO /___/ Explain ________
Investigation #2

YES /__/ Explain _______ NO /__/ Explain _______

________________________________________

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /__/ 

If yes, explain:

________________________________________

________________________________________

________________________________________

Signed:

Signature
Title: Project Manager

Date: 5/20/99

Signature of Division Director

Date: 7/20/99

Appears this way on original

cc: Original NDA Division File HFD-85 Mary Ann Holovac
PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA # 21-05-2  Supplement #  Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550  Trade (generic) name/dosage form: TRAMADOL HYDROCHLORIDE 100 mg/mL, 200 mg/mL
Suspension, 12 mg/mL and 25 mg/mL

Applicant: MERCK

Therapeutic Class: 10

Indication(s) previously approved _______________________________________________________

Pediatric labeling of approved indication(s) is adequate ___ inadequate ____________

Indication in this application: RELIEF OF SEVERE SYMPTOMS OF PAIN AT THE TIME AND INTENSITY TO REQUIRE AN INTRACUTANEOUS INJECTION. (For supplements, answer the following questions in relation to the proposed indication.)

1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

☐ 2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
   a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
   b. The applicant has committed to doing such studies as will be required.
      1) Studies are ongoing.
      2) Protocols were submitted and approved.
      3) Protocols were submitted and are under review.
      4) If no protocol has been submitted, explain the status of discussions on the back of this form.
   c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/---/
Signature of Preparer and Title (PM, CSO, MO, other)  5/20/97
Date

cc: Orig NDA/PLA # 21-05-2
HFD-550 Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

☐ TE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
STATISTICAL REVIEW AND EVALUATION
(Carcinogenicity Review)
ADDENDUM

NDA #: 21-042

APPLICANT: Merck Research Laboratories

NAME OF DRUG: VIOXX™ Tablets

DOCUMENTS REVIEWED: Volumes 52.28 through 52.34 of IND 46,894. Data on Floppy Diskettes supplied by the sponsor.

REVIEWING PHARMACOLOGIST: Susan D. Wilson, Ph.D. (HFD-550).

At the request of the reviewing pharmacologist, one additional tumor analysis was performed for female rats: Combined brain glioma and spinal chord glioma.

The tumor analysis results for the above analysis are displayed in the following Table.

<table>
<thead>
<tr>
<th>Organs</th>
<th>Female Rats</th>
<th>Tumor Type</th>
<th>Tumor Rates</th>
<th>Trend Test p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Spinal Chord</td>
<td>Glioma</td>
<td>Mixed</td>
<td>1 2 0 3</td>
<td>0.0914</td>
</tr>
</tbody>
</table>

No statistically significant positive linear trend was detected in the above analysis.

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)

Concur: Dr./Lin 4/7/99

cc: Archival NDA 21-042
    HFD-550/Wilson, Cook, Weir, Hyde, Division File
    HFD-725/Taneja, Lin, Huque, Division File, Chron.