CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-017
21-018

ADMINISTRATIVE DOCUMENTS
### FDA CDER EES

#### ESTABLISHMENT EVALUATION REQUEST

**SUMMARY REPORT**

- **Application:** NDA 21017/000
- **Stamp:** 22-DEC-1998 Regulatory Due: 22-OCT-1999
- **Applicant:** LILLY
  LILLY CORPORATE CENTER
  INDIANAPOLIS, IN 46285

- **Priority:** 34S  
  **Org Code:** 510
- **Action Goal:**  
  **District Goal:** 23-AUG-1999
- **Brand Name:** HUMALOG MIX 25 (INSULIN LISPRO 25% INJ/1
- **Established Name:**
- **Generic Name:** INSULIN LISPRO 25% INJ/INSULIN LISPRO 75
- **Dosage Form:** INJ (INJECTION)
- **Strength:** 100 U/ML

- **FDA Contacts:**
  - **H. RHEE (HFD-510):** 301-827-6424, Project Manager
  - **S. MOORE (HFD-510):** 301-827-6430, Review Chemist
  - **Team Leader**

**Overall Recommendation:**

*ACCEPTABLE on 03-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062*

<table>
<thead>
<tr>
<th>Establishment</th>
<th>1819470</th>
<th>DMF No:</th>
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<td>AADA No:</td>
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- **Profile:** SVS
- **OAI Status:** NONE
- **Responsibilities:** FINISHED DOSAGE MANUFACTURER

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**Regulatory Due:** 22-OCT-1999  
**Priority:** 34S  
**Org Code:** 510  
**Action Goal:** District Goal: 23-AUG-1999  
**Brand Name:** HUMALOG MIX 50 (INSULIN LISPRO 50% INJ/I)  
**Established Name:**  
**Generic Name:** INSULIN LISPRO 50% INJ/INSULIN LISPRO 50  
**Dosage Form:** INJ (INJECTION)  
**Strength:** 100 U/ML  
**FDA Contacts:**  
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| Last Milestone: OC RECOMMENDATION |
| Milestone Date: 03-MAR-1999 |
| Decision: ACCEPTABLE |
| Reason: DISTRICT RECOMMENDATION |

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| Milestone Date: 03-MAR-1999 |
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*Appears this way on original*
Establishment Evaluation Request Summary Report

Application: NDA 21018/000
Applicant: LILLY LILLY CORPORATE CENTER INDIANAPOLIS, IN 46285
Brand Name: HUMALOG MIX 50 (INSULIN LYSPRO 50% INJ/I
Generic Name: INSULIN LYSPRO 50% INJ/INSULIN LYSPRO 50
Dosage Form: INJ (INJECTION)
Strength: 100 U/ML

FDA Contacts:
- H. Rhee (HFD-510) 301-827-6424, Project Manager
- W. Berlin (HFD-510) 301-827-6370, Review Chemist
- S. Moore (HFD-510) 301-827-6430, Team Leader

Overall Recommendation:
ACCEPTABLE on 03-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1819470 DMF No:
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LILLY CORP CTR/WHITE RIVER PK
INDIANAPOLIS, IN 46200

Profile: SVS OAI Status: NONE Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: OC RECOMMENDATION
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Establishment: 9610945 DMF No:
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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

Priority: 34S
Org Code: 510
Brand Name: HUMALOG MIX 25 (INSULIN LISPRO
25% INJ/I
Established Name: INSULIN LISPRO 25% INJ/INSULIN
LISPRO 75
Generic Name: INJ (INJECTION)
Dosage Form: INJ
Strength: 100 U/ML

FDA Contacts:
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W. Berlin (HFD-510)
S. Moore (HFD-510)
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301-827-6370, Review Chemist
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Milestone Date: 03-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

APPEARS THIS WAY ON ORIGINAL
CERTIFICATION

NDA Application No.: NDA 21-017

Drug Name: Humalog® Mix25

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory G. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: Gregory G. Enas, Ph. D.

Title: Director, U.S. Regulatory Affairs

Date: December 21, 1998
CERTIFICATION

NDA Application No.:  NDA 21-018

Drug Name:  Humalog® Mix50

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory G. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By:  [Signature]  
Gregory G. Enas, Ph. D.

Title:  Director, U.S. Regulatory Affairs

Date:  December 21, 1998
**PEDIATRIC PAGE**

(Complete for all original application and all efficacy supplements)

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<td>Regulatory Action:</td>
<td>AP</td>
<td>Proposed Indication:</td>
<td>Treatment of patients with diabetes mellitus for the control of hyperglycemia</td>
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ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

- NeoNates (0-30 Days)
- Children (25 Months-12 years)
- Infants (1-24 Months)
- Adolescents (13-16 Years)

Label Adequacy | Does Not Apply
Formulation Status | NO NEW FORMULATION is needed
Studies Needed | Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission?  NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIE RHEE

/S/

Date: 12-10-99

12/10/99
PEDiATRIC PAGE
(Complete for all original application and all efficacy supplements)

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ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

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- [ ] NeoNates (0-30 Days )
- [ ] Children (25 Months-12 years)
- [ ] Infants (1-24 Months )
- [ ] Adolescents (13-16 Years)

Label Adequacy: Does Not Apply
Formulation Status: NO NEW FORMULATION is needed
Studies Needed: No further STUDIES are needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIE RHEE

/S/ 12-10-99
Signature Date
RE: NDA #s 21017 and 21018 Insulin Lispro Mixtures and Pediatric Studies

The vast majority of pre-pubescent children with diabetes and many post pubescent teens with diabetes have Type 1 diabetes. The DCCT has shown that long-term complications of Type 1 diabetes can be prevented with intensive insulin therapy. (Subsequent data suggest that intensive therapy can also benefit Type 2 patients.) Fixed ratios of insulin products do not permit frequent dose adjustment and tight control—especially in those without endogenous insulin production. The use of such fixed ratio mixtures cannot be recommended in patients with Type 1 diabetes—especially children. Therefore pediatric studies have not been requested.

Elizabeth Koller, M.D.
12/17/99

CC: On NDA's 21-017 & 21-018
HFS 510/DivFiles 21-017 & 21-018
HFD-510/Koller
Exclusivity Checklist

NDA: 21-018
Trade Name: Humalog Mix 50/50
Generic Name: 50% insulin lispro protamine suspension and 50% insulin lispro (rDNA origin) injection
Applicant Name: Eli Lilly
Division: Division of Metabolic and Endocrine Drug products, HFD-510
Project Manager: Julie Rhee, 7-6424
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 | | x

  c. If yes, what type? (SE1, SE2, etc.)
     Yes | x | No

   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 of bioavailability or bioequivalence data, answer "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.

     Explanation:
     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:

     Explanation:

   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?

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

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 | x | No

   If yes, NDA #
   Drug Name:

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

3. Is this drug product or indication a DESI upgrade?
   Yes | x | No

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.
   Yes | x | No

   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.

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

Drug Product

NDA #
Drug Product

NDA #
Drug Product

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.)

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

Drug Product: Humalog

NDA # 20-563
Drug Product

NDA #
Drug Product

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

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 | x | No |

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

**Basis for conclusion:**

| 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 | x | 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 | x |

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 | |

3) 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 #: IODK
- Investigation #2, Study #: IODM
- Investigation #3, Study #: IODN

5. 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 | x |
| Investigation #2 | Yes | No | x |
| Investigation #3 | Yes | No | x |

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

- Investigation #1 -- NDA Number
- Investigation #2 -- NDA Number
- Investigation #3 -- NDA Number

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 | x |
| Investigation #2 | Yes | No | x |
| Investigation #3 | Yes | No | x |
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

| Investigation #1 -- NDA Number |  |
| Investigation #2 -- NDA Number |  |
| Investigation #3 -- NDA Number |  |

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 #1 | O P K |
| Investigation #2 | O M D |
| Investigation #3 | O D N |

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 | Yes | No | x |
| IND#: |

Explain: Study conducted outside the U.S.

| Investigation #2 | Yes | No | x |
| IND#: |

Explain: Study conducted outside U.S.

| Investigation #3 | Yes | No | x |
| IND#: |

Explain: Study conducted outside U.S.

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 | x | No |
| IND#: |

Explain:

| Investigation #2 | Yes | x | No |
| IND#: |

Explain:

| Investigation #3 | Yes | x | No |
| IND#: |

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:
Julie Rhee
Project Manager

Solomon Sobel, M.D.
Division Director

cc: OrigNDA
HFD-510/DivFile
HFD-93/Holovac

APPEARS THIS WAY ON ORIGINAL
## Exclusivity Checklist

**NDA:** 21-017  
**Trade Name:** Humalog Mix 75/25  
**Generic Name:** 75% insulin lispro protamine suspension and 25% insulin lispro (rDNA origin) injection  
**Applicant Name:** Eli Lilly  
**Division:** Division of Metabolic and Endocrine Drug products, HFD-510  
**Project Manager:** Julie Rhee (7-6424)  
**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.

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<td>a. Is it an original NDA?</td>
<td>x</td>
<td>No</td>
<td></td>
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<tr>
<td>b. Is it an effectiveness supplement?</td>
<td>Yes</td>
<td>No</td>
<td>x</td>
</tr>
<tr>
<td>c. If yes, what type? (SE1, SE2, etc.)</td>
<td>Yes</td>
<td>x</td>
<td>No</td>
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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.")

# Explain:

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.

**Explanation:**

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:

**Explanation:**

d. Did the applicant request exclusivity? | Yes | No | x |

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

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

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 |

**Drug Name:**

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.**

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** (even if a study was required for the upgrade).

### PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

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<tr>
<td>1. Single active ingredient product.</td>
<td>Yes</td>
<td>No</td>
<td>x</td>
</tr>
</tbody>
</table>

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 esterates) 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 | Yes | No | x |
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.

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>NDA #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>NDA #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.)

<table>
<thead>
<tr>
<th>Yes</th>
<th>x</th>
<th>No</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Drug Product:</th>
<th>NDA #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humalog</td>
<td>20-563</td>
</tr>
</tbody>
</table>

If the answer to Question 1 or 2 under Part II is "NO," go directly to the signature blocks. 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.

<table>
<thead>
<tr>
<th>Yes</th>
<th>x</th>
<th>No</th>
</tr>
</thead>
</table>

If "NO." go directly to the signature blocks.

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?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>x</th>
<th>No</th>
</tr>
</thead>
</table>

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

Basis for conclusion:

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?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>x</th>
<th>No</th>
</tr>
</thead>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>x</th>
</tr>
</thead>
</table>

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?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

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 #: IODK
Investigation #2, Study #: IODM
Investigation #3, Study #: IODN

3. 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 reestablish 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></th>
<th>Yes</th>
<th>No</th>
<th>x</th>
</tr>
</thead>
</table>

Investigation #1
Investigation #2
Investigation #3

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

Investigation #1 -- NDA Number
Investigation #2 -- NDA Number
Investigation #3 -- NDA Number

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></th>
<th>Yes</th>
<th>No</th>
<th>x</th>
</tr>
</thead>
</table>

Investigation #1
Investigation #2
Investigation #3
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

<table>
<thead>
<tr>
<th>Investigation #1 - NDA Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2 - NDA Number</td>
</tr>
<tr>
<td>Investigation #3 - NDA Number</td>
</tr>
</tbody>
</table>

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"):

<table>
<thead>
<tr>
<th>Investigation #1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
</tr>
<tr>
<td>Investigation #3</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Investigation #1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
</tr>
<tr>
<td>Explain: Study conducted outside the U.S.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
</tr>
<tr>
<td>Explain: Study conducted outside the U.S.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
</tr>
<tr>
<td>Explain: Study conducted outside the U.S.</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Investigation #1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
</tr>
<tr>
<td>Explain:</td>
</tr>
</tbody>
</table>

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Explain:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND#:</td>
</tr>
<tr>
<td>Explain:</td>
</tr>
</tbody>
</table>

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 | x |

If yes, explain:
PATENT INFORMATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Humalog® Mix50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (r-DNA origin)], as indicated. This product is the subject of this application for which approval is being sought:

<table>
<thead>
<tr>
<th>Patent No.</th>
<th>Expiration Date</th>
<th>Claim Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,461,031</td>
<td>June 16, 2014</td>
<td>formulation, method of use</td>
</tr>
<tr>
<td>5,474,978</td>
<td>June 16, 2014</td>
<td>formulation</td>
</tr>
<tr>
<td>5,514,646</td>
<td>May 7, 2013</td>
<td>formulation, composition, method of use</td>
</tr>
<tr>
<td>5,747,642</td>
<td>June 16, 2014</td>
<td>formulation</td>
</tr>
</tbody>
</table>

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

EXCLUSIVITY

Eli Lilly and Company (Lilly) does not claim the three-year period of exclusivity for the use of Humalog® Mix50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (r-DNA origin)] in the treatment of Diabetes Mellitus provided by 21 C.F.R. 314.108 (b)(5).

[Signature]

Date: December 21, 1998

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs
Eli Lilly and Company
PATENT INFORMATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Humalog® Mix25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (r-DNA origin)], as indicated. This product is the subject of this application for which approval is being sought:

<table>
<thead>
<tr>
<th>Patent No</th>
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<tr>
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The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

EXCLUSIVITY

Eli Lilly and Company (Lilly) does not claim the three-year period of exclusivity for the use of Humalog® Mix25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (r-DNA origin)] in the treatment of Diabetes Mellitus provided by 21 C.F.R. 314.108 (b)(5).

[Signature]

Date: December 21, 1998

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs
Eli Lilly and Company

APPEARS THIS WAY ON ORIGINAL