

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021018Orig1s034

Trade Name: HUMALOG Mix 50/50

Generic or Proper Name: Humalog® Mix50/50™ [50% insulin lispro protamine suspension and 50% insulin lispro 9 injection, (rDNA origin)]

Sponsor: Eli Lilly & Co.

Approval Date: September 06, 2007

Indication: Humalog Mix50/50, a mixture of 50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Based on cross-study comparisons of the pharmacodynamics of Humalog Mix50/50 and Humulin 50/50, it is likely that Humalog Mix50/50 has a more rapid onset of glucose-lowering activity compared with Humulin 50/50 while having a similar duration of action. This profile is achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro protamine suspension

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 20-563/S-075; NDA 21-017/S-040; NDA 21-018/S-034

Eli Lilly and Company
Attention: Gregory Enas, PhD
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

SUPPLEMENT APPROVAL

Dear Dr. Enas:

Please refer to your supplemental new drug applications submitted October 5, 2006, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the products described below.

NDA	Supplement	Drug Product Name
20-563	S-075	Humalog (insulin lispro injection [rDNA origin])
21-017	S-040	Humalog Mix75/25 (75% insulin lispro protamine suspension/25% insulin lispro injection [rDNA origin])
21-018	S-034	Humalog Mix50/50 (50% insulin lispro protamine suspension/50% insulin lispro injection [rDNA origin])

We acknowledge receipt of your amendments dated April 30, July 17 and 25, and August 22 and 27, 2007.

Your submissions dated April 30, 2007, received May 2, 2007, constituted a complete response to our February 11, 2007, action letter.

These supplemental new drug applications provide for the addition of disposable (prefilled) insulin injector pens: Humalog[®] KwikPen[™], Humalog Mix75/25[®] KwikPen[™], and Humalog Mix50/50[®] KwikPen[™].

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor agreed-upon, editorial revision listed below.

1. Cartons: To the back panel of each carton, add the website address "www.humalog.com" immediately following the phone number.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the

package inserts submitted August 22, 2007, text for the patient package inserts submitted August 22, 2007, and the text for the KwikPen User Manual submitted April 30, 2007). Upon receipt, we will transmit that labeling to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 20-563/S-075, NDA 21-017/S-040, NDA 21-018/S-034.**”

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the immediate container labels submitted July 17, 2007, and the carton labels submitted August 22, 2007, except with the addition of “www.humalog.com” to the back panel of the cartons as described in your August 27, 2007, submission, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 20-563/S-075 and S-064; NDA 21-017/S-040 and S-029; NDA 21-018/S-034 and S-023.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

We remind you of your July 25, 2007, agreement to review and submit to FDA incoming reports of medication errors or pharmaceutical product complaints received by Lilly for the KwikPen product line along with the new start/switch data. We request that medication error reports or pharmaceutical product complaints relating to the Global Color Differentiation System labels be submitted on a quarterly basis for one year and semi-annually thereafter.

We also wish to remind you to ensure that the established name is at least one half the size of the proprietary name on all carton and container labels.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package inserts to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letters to both the NDAs and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at 301-796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology
Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

NDA 20-563/S-075 PI
NDA 20-563/S-075 PPI
NDA 21-017/S-040 PI
NDA 21-017/S-040 PPI
NDA 21-018/S-034 PI
NDA 21-018/S-034 PPI
KwikPen User Manual

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Parks

9/6/2007 08:04:53 PM

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APPLICATION NUMBER:

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OTHER ACTION LETTERS



NDA 20-563/S-075
NDA 21-017/S-040
NDA 21-018/S-034

Lilly Research Laboratories
Attention: Belinda Schluchter, Ph.D.
Associate Manager, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Schluchter:

Please refer to your supplemental new drug applications dated October 5, 2006, received October 10, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA 20-563 Humalog (insulin lispro injection [rDNA origin])
NDA 21-017 Humalog Mix 75/25 (75% insulin lispro protamine suspension and
25% insulin lispro injection [rDNA origin])
NDA 21-018 Humalog Mix 50/50 (50% insulin lispro protamine suspension and
50% insulin lispro injection [rDNA origin])

These supplemental new drug applications provide for the addition of a new disposable insulin delivery device, (b) (4), and a (b) (4) User Manual. Also, the package inserts and patient package information have been revised to include information concerning the (b) (4).

We completed our review of these applications, and they are approvable. Before the applications may be approved, however, you must address the following deficiencies identified in reviews by two divisions in the Office of Surveillance and Epidemiology, the Division of Medication Errors and Technical Support (DMETS) and the Division of Surveillance, Research, and Communication Support (DSRCS):

DMETS

A. RECOMMENDATIONS

1. DMETS recommends that Lilly discontinue the existing disposable pen injector device ("Pen") if the proposed (b) (4) device is approved. From a medication errors perspective, the concurrent marketing of both products will undoubtedly lead to mix-ups between the products and could lead to harm.

2. DMETS does not recommend use of the modifier, (b) (4). DMETS is concerned that the use of this modifier may lead to medication errors because the modifier (b) (4) is ambiguous, and could be omitted or overlooked when prescribing, transcribing, administering, or dispensing the product.

DMETS

A. GENERAL COMMENTS

1. If the existing disposable pen injector (i.e., Humalog Pen) and the (b) (4) products are going to co-exist for any length of time in the marketplace, DMETS believes that you should include cautionary statements in the labeling to warn practitioners, patients, and caregivers that this is a new pen with different use. Specifically, the product labels and labeling include a descriptor for at least 6 months following initial marketing of the product that highlights the fact that the proposed (b) (4) is a new product to the existing Humalog line to minimize the potential for medication errors. The descriptor should highlight the fact that (b) (4) is a “new disposable pen injector” that has different instructions than the existing pen injector device and make reference to the importance of reading the User Manual prior to use. This descriptor should have adequate prominence on the primary carton label, since the information may help to avoid product selection errors resulting from overlooked modifiers. Also, in the event that the (b) (4) product is dispensed in error to a patient in place of the existing pen-injector, it could help patients to recognize the mistake and possibly avert administration of the product in error. This descriptor should have adequate prominence in the User Manual in the event that the statement on the primary carton label is overlooked or obscured by patient-specific labeling (i.e., a pharmacy label).
2. DMETS recommends that the numeric portion (i.e., 75/25) of the proprietary name be highlighted to avoid confusion within the Humalog (b) (4) product line and with Humalog Mix product line. DMETS believes it is important to highlight the numeric portion since this is the only portion of the proprietary name that differs with the Humalog (b) (4), Humalog Mix 75/25 (b) (4), and Humalog Mix 50/50 (b) (4) products. You could increase the prominence by increasing the font size of the numeric portion or use reverse color blocking (see examples below).

Humalog® Mix75/25
(b) (4)

Humalog® Mix75/25
(b) (4)

B. USER MANUAL

1. In the first instruction, “Preparing the (b) (4)” DMETS is concerned that the qualifier of part B., “For Cloudy Insulin Only,” could be confusing to some patients. DMETS asks whether it might be better to explicitly state the names of the insulins that appear cloudy (i.e., Humalog Mix 75/25, Humalog Mix 50/50) to remove ambiguity from the statement. DMETS is concerned that patient unfamiliarity with insulin appearance or that lack visual acuity may not be able to identify their insulin as “cloudy.”
2. In the “Injecting Your Dose” section, DMETS recommends the following statement be added as a bullet under the “Important Notes” subheading: “Push and hold the Dose Knob in and

count slowly for 5 seconds before removing the needle.” DMETS believes that this point should be highlighted to avoid inadvertent underdosing of insulin that could occur if patients mistakenly remove the needle before the total dose is administered from the (b) (4)

C. CARTON LABEL

1. DMETS recommends removing the (b) (4) symbol displayed on the upper portion of the primary panel. This symbol is unnecessary as you have included the “Rx Only” on the middle portion of the primary panel. DMETS is concerned that this symbol may distract attention from the proprietary name and possibly lead to confusion between the other Humalog (b) (4) products, which have similar trade dress.
2. DMETS recommends moving the statement “needles not included” (b) (4) and putting this statement before the recommended brand of insulin needles. DMETS believes this statement should be prominently displayed to avoid dispensing of the product without the needles to administer the insulin.
3. DMETS does not know what “HP-8798” indicates but recommends that it be removed from the primary carton label. If this information is necessary, DMETS recommends that it be displayed in the lower portion of the label. In the current position, DMETS believes that it could distract practitioners from other important information (i.e., proprietary name, NDC number) thus increasing the opportunity for error.
4. DMETS recommends that the middle segment of the NDC number be reassigned to reduce the likelihood of medication errors reaching the patient. DMETS is concerned that the Humalog (b) (4) could be confused with Humalog Mix 75/25 (b) (4) and Humalog Mix 50/50 (b) (4). All three products have similar nomenclature, and you have proposed to use similar packaging for each of these three products. DMETS believes that product selection errors could occur when preparing a prescription for dispensing. DMETS believes that the overlap in nomenclature (Humalog, (b) (4), package size (5 x 3 mL syringes), and trade dress diminishes the opportunity for the error to be caught prior to dispensing.

In practice, pharmacy staff often relies on NDC codes as a check to prevent dispensing errors. You have assigned the middle segment of the NDC numbers for these products sequentially (0002-8799-59, 0002-8798-59, 0002-8797-59), and thus the 10-digit codes for these products differ by one digit placed in the middle.

DMETS recognizes that it may be common practice for entities within a product line to be assigned sequential NDC codes, but DMETS believes that this eliminates a potentially important safety check that could avert product selection errors resulting from name, label, or packaging confusion among the (b) (4) product line. DMETS urges you to consider implementing this request in the interest of reducing medication errors.

5. DMETS also recommends that you give greater prominence to the middle segment of the product NDC code (i.e. 0002-**8799**-59). This portion of the NDC code is most heavily relied by pharmacy staff to distinguish products within the same product line.

6. Include a space for patients to record the date in which the pen is first used on the rear display panel of the carton. DMETS feels that this could be help to avoid errors related to use of expired pen devices.

D. PEN LABEL

DMETS is concerned that patients will have difficulty reading the label. To enhance readability of the label, DMETS recommends:

1. Enlarge the overall size of the label, if possible. DMETS recognizes that space constriction on the device itself may limit the size of the pen label.
2. Increase the font size used to display the proprietary name.
3. Remove the (b) (4) symbol next to the NDC number to decrease the cluttering on the label. This symbol is extraneous as the words “Rx Only” are already included on the label.
4. Include a space for patients to record the date in which the pen is first used if space on the label permits. DMETS feels that this could be help to avoid errors related to use of expired pen devices.

E. PACKAGE INSERT

1. DMETS recommends reformatting the “HOW SUPPLIED” section into a table. The proposed presentation is difficult to read. DMETS is concerned that a practitioner may not realize that there are two disposable pen products available for this product on the market-thus increasing the potential for confusion.
2. DMETS recommends adding a row for (b) (4) to the Table in “Storage” or specifying Pen, and (b) (4). DMETS believes that confusion could arise if the disposable pens are not specified since both products will be available in the marketplace. Similarly, the paragraph (line 424) of the “Storage” section should refer to either “Pens, and (b) (4) or generally “disposable pens.”

F. PATIENT PACKAGE INSERT

1. DSCRS recommends that you revise and rewrite the patient package insert at a 6th to 8th grade reading level because the proposed insert is written at greater than a 12th grade reading level. DMETS concurs that this reading level is not acceptable for patient materials and could potentially cause patients to be confused and lead to medication errors.
2. Within the (b) (4) section, DMETS recommends that you highlight the fact that Humalog Pen and Humalog (b) (4) have different instructions and thus it is important to read the user manual before using. DMETS is concerned that patients may not recognize that the (b) (4) is a new disposable delivery device and could use the product in error if they had previously been familiar with the Pen delivery device.

3. For the Humalog Mix 75/25 MirioPen only, the ^{(b) (4)} section (line 72) states ^{(b) (4)}
DMETS recommends revising the statement to reference the three formulations available: Humalog, Humalog Mix75/25, and Humalog Mix50/50.

DSRCS:

A. PATIENT PACKAGE INSERTS

Revise the three Humalog-product patient package inserts to meet the comprehension needs of the majority of patients with diabetes.

1. DSRCS recommends a question and answer format, such as that used for Medication Guides (see 21 CFR § 208). This format is voluntary for PPIs, but has research to support its effectiveness as a risk communication tool.
2. Use simple, short sentences to enhance readability. Avoid the use of technical terms or define them in patient-friendly terms.
3. Use cognitive accessibility principles such as “chunking” for comprehensibility. Chunking allows people to access and retrieve information more readily. (The chunking principle involves classifying items into groups to avoid information overload.)
4. Demonstrate good principles of type-size and design by using at least a 10-point font, serif type, and not using all upper case letters in the text.
5. Demonstrate good principles of page layout and design by left justifying margins, using ample white space throughout the document and using good contrast between ink and paper colors.
6. Shorten the PPI to an optimal length of 1 to 2 pages. Keep information on diabetes brief. Patient information leaflets (PPIs) are to enhance appropriate use of medications and provide important risk information. Description of an underlying medical condition should be brief or placed in a separate sheet and provided as a separate educational material for the patient.

Submit draft labeling as described above. In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes before approval of these supplemental applications.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at 301.796.1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Parks
2/11/2007 09:43:56 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021018Orig1s034

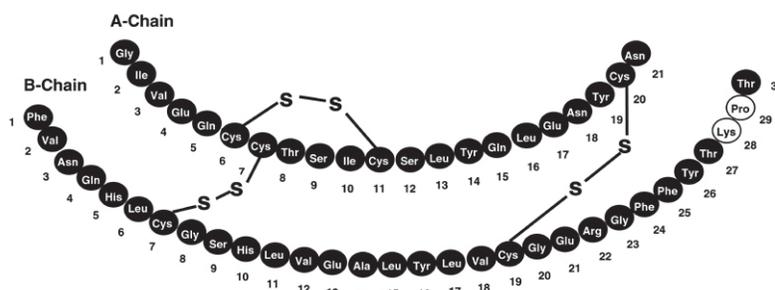
LABELING

HUMALOG[®]
INSULIN LISPRO INJECTION, USP
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

DESCRIPTION

Humalog[®] [insulin lispro injection, USP (rDNA origin)] is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. Chemically, it is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Humalog is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce insulin lispro.

Humalog has the following primary structure:



Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

The vials, cartridges, and Pens contain a sterile solution of Humalog for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid.

Each milliliter of Humalog injection contains insulin lispro 100 units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY

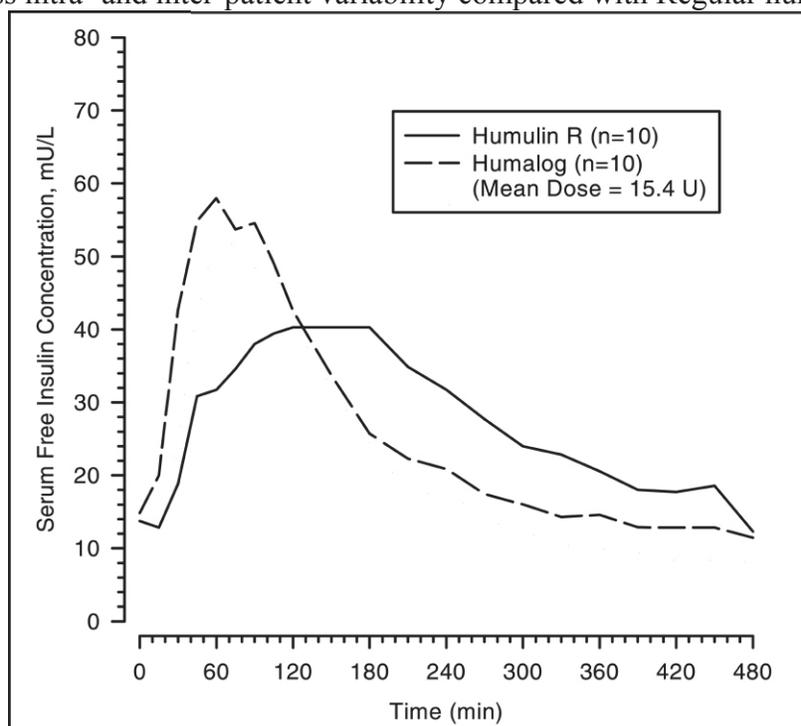
Antidiabetic Activity

The primary activity of insulin, including Humalog, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Humalog has been shown to be equipotent to human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of shorter duration. The glucose-lowering activity of Humalog and Regular human insulin is comparable when administered to nondiabetic subjects by the intravenous route.

35 Pharmacokinetics

36 *Absorption and Bioavailability* — Humalog is as bioavailable as Regular human insulin, with
 37 absolute bioavailability ranging between 55% to 77% with doses between 0.1 to 0.2 U/kg,
 38 inclusive. Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes
 39 demonstrated that Humalog is absorbed faster than Regular human insulin (U-100) (*see* Figure
 40 1). In nondiabetic subjects given subcutaneous doses of Humalog ranging from 0.1 to 0.4 U/kg,
 41 peak serum concentrations were observed 30 to 90 minutes after dosing. When nondiabetic
 42 subjects received equivalent doses of Regular human insulin, peak insulin concentrations
 43 occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type
 44 1 diabetes. The pharmacokinetic profiles of Humalog and Regular human insulin are comparable
 45 to one another when administered to nondiabetic subjects by the intravenous route. Humalog was
 46 absorbed at a consistently faster rate than Regular human insulin in healthy male volunteers
 47 given 0.2 U/kg Regular human insulin or Humalog at abdominal, deltoid, or femoral
 48 subcutaneous sites, the three sites often used by patients with diabetes. After abdominal
 49 administration of Humalog, serum drug levels are higher and the duration of action is slightly
 50 shorter than after deltoid or thigh administration (*see* DOSAGE AND ADMINISTRATION).
 51 Humalog has less intra- and inter-patient variability compared with Regular human insulin.



52 **Figure 1: Serum Humalog and Insulin Levels After Subcutaneous Injection of Regular**
 53 **Human Insulin or Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in**
 54 **10 Patients with Type 1 Diabetes.***

55 * Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.
 56

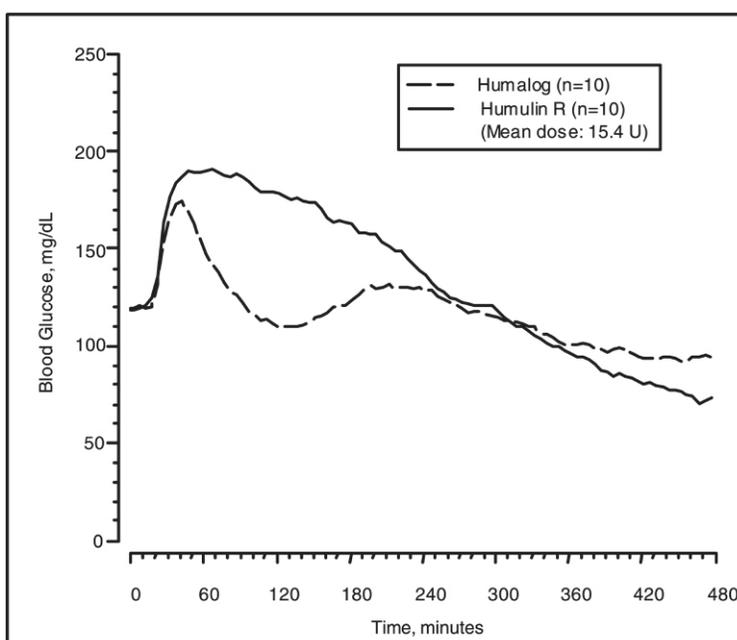
57
 58 *Distribution* — The volume of distribution following injection of Humalog is identical to that
 59 of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

60 *Metabolism* — Human metabolism studies have not been conducted. However, animal studies
 61 indicate that the metabolism of Humalog is identical to that of Regular human insulin.

62 *Elimination* — When Humalog is given subcutaneously, its $t_{1/2}$ is shorter than that of Regular
 63 human insulin (1 versus 1.5 hours, respectively). When given intravenously, Humalog and
 64 Regular human insulin show identical dose-dependent elimination, with a $t_{1/2}$ of 26 and 52
 65 minutes at 0.1 U/kg and 0.2 U/kg, respectively.

66 Pharmacodynamics

67 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
 68 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
 69 duration of glucose-lowering activity than Regular human insulin (*see* Figure 2). The earlier
 70 onset of activity of Humalog is directly related to its more rapid rate of absorption. The time
 71 course of action of insulin and insulin analogs, such as Humalog, may vary considerably in
 72 different individuals or within the same individual. The parameters of Humalog activity (time of
 73 onset, peak time, and duration) as presented in Figure 2 should be considered only as general
 74 guidelines. The rate of insulin absorption and consequently the onset of activity is known to be
 75 affected by the site of injection, exercise, and other variables (*see* General *under*
 76 PRECAUTIONS).



77
 78 **Figure 2: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or**
 79 **Humalog (0.2 U/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with**
 80 **Type 1 Diabetes.***

81 * Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

82 Special Populations

83 *Age and Gender* — Information on the effect of age and gender on the pharmacokinetics of
 84 Humalog is unavailable. However, in large clinical trials, sub-group analysis based on age and
 85 gender did not indicate any difference in postprandial glucose parameters between Humalog and
 86 Regular human insulin.

87 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
 88 Humalog has not been studied.

89 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
 90 Humalog has not been studied.

91 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and
 92 pharmacodynamics of Humalog has not been studied. In large clinical trials, which included
 93 patients with Body Mass Index up to and including 35 kg/m², no consistent differences were
 94 observed between Humalog and Humulin[®] R with respect to postprandial glucose parameters.

95 *Renal Impairment* — Some studies with human insulin have shown increased circulating levels
 96 of insulin in patients with renal failure. In a study of 25 patients with type 2 diabetes and a wide
 97 range of renal function, the pharmacokinetic differences between Humalog and Regular human
 98 insulin were generally maintained. However, the sensitivity of the patients to insulin did change,
 99 with an increased response to insulin as the renal function declined. Careful glucose monitoring
 100 and dose reductions of insulin, including Humalog, may be necessary in patients with renal
 101 dysfunction.

102 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating
 103 levels of insulin in patients with hepatic failure. In a study of 22 patients with type 2 diabetes,
 104 impaired hepatic function did not affect the subcutaneous absorption or general disposition of
 105 Humalog when compared with patients with no history of hepatic dysfunction. In that study,
 106 Humalog maintained its more rapid absorption and elimination when compared with Regular
 107 human insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog,
 108 may be necessary in patients with hepatic dysfunction.

109 CLINICAL STUDIES

110 In open-label, cross-over studies of 1008 patients with type 1 diabetes and 722 patients with
 111 type 2 (non-insulin-dependent) diabetes, Humalog reduced postprandial glucose compared with
 112 Regular human insulin (*see* Table 1). The clinical significance of improvement in postprandial
 113 hyperglycemia has not been established.

114
 115 **Table 1: Comparison of Means of Glycemic Parameters at the End of Combined**
 116 **Treatment Periods. All Randomized Patients in Cross-Over Studies (3 Months for Each**
 117 **Treatment)**

Type 1, N=1008		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^{a*}
Fasting Blood Glucose	209.5 ± 91.6	204.1 ± 89.3
1-Hour Postprandial	232.4 ± 97.7	250.0 ± 96.7
2-Hour Postprandial	200.9 ± 95.4	231.7 ± 103.9
HbA _{1c} (%)	8.2 ± 1.5	8.2 ± 1.5
Type 2, N=722		
Glycemic Parameter, (mg/dL)	Humalog ^a	Humulin R ^a
Fasting Blood Glucose	192.1 ± 67.9	183.1 ± 66.1
1-Hour Postprandial	238.1 ± 79.7	250.0 ± 75.2
2-Hour Postprandial	217.4 ± 83.2	236.5 ± 80.6
HbA _{1c} (%)	8.2 ± 1.3	8.2 ± 1.4

118 ^a Mean ± Standard Deviation.

119 * REGULAR insulin human injection, USP (rDNA origin).

120
 121 In 12-month parallel studies in patients with type 1 and type 2 diabetes, HbA_{1c} did not differ
 122 between patients treated with Regular human insulin and those treated with Humalog.

123 *Hypoglycemia* — While the overall rate of hypoglycemia did not differ between patients with
 124 type 1 and type 2 diabetes treated with Humalog compared with Regular human insulin, patients

125 with type 1 diabetes treated with Humalog had fewer hypoglycemic episodes between midnight
 126 and 6 a.m. The lower rate of hypoglycemia in the Humalog-treated group may have been related
 127 to higher nocturnal blood glucose levels, as reflected by a small increase in mean fasting blood
 128 glucose levels.

129 *Humalog in Combination with Sulfonylurea Agents* — In a two-month study in patients with
 130 fasting hyperglycemia despite maximal dosing with sulfonylureas (SU), patients were
 131 randomized to one of three treatment regimens; Humulin[®] NPH at bedtime plus SU, Humalog
 132 three times a day before meals plus SU, or Humalog three times a day before meals and Humulin
 133 NPH at bedtime. The combination of Humalog and SU resulted in an improvement in HbA_{1c}
 134 accompanied by a weight gain (*see* Table 2).

135
 136 **Table 2: Results of a Two-Month Study in Which Humalog Was Added to Sulfonylurea**
 137 **Therapy in Patients Not Adequately Controlled on Sulfonylurea Alone**

	Humulin N h.s. + SU ^a	Humalog a.c. + SU	Humalog a.c. + Humulin N h.s.
Randomized (n)	135	139	149
HbA _{1c} (%) at baseline	9.9	10.0	10.0
HbA _{1c} (%) at 2-months	8.7	8.4	8.5
HbA _{1c} (%) change from baseline	-1.2	-1.6	-1.4
Weight gain at 2-months (kg)	0.6	1.2	1.5
Hypoglycemia* (events/mo)	0.11	0.03	0.09
Number of injections	1	3	4
Total insulin dose (U/kg) at 2-months	0.23	0.33	0.52

138 ^a a.c.-three times a day before meals. h.s.-at bedtime. SU-oral sulfonylurea agent.

139 * blood glucose ≤36 mg/dL or needing assistance from third party.

140
 141 *Humalog in External Insulin Pumps* — To evaluate the administration of Humalog via external
 142 insulin pumps, two open-label cross-over design studies were performed in patients with type 1
 143 diabetes. One study involved 39 patients treated for 24 weeks with Humalog or Regular human
 144 insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.8% to 7.2% in the
 145 Humalog-treated patients and from 7.8% to 7.5% in the Regular human insulin-treated patients.
 146 Another study involved 60 patients treated for 24 weeks with either Humalog or Regular human
 147 insulin. After 12 weeks of treatment, the mean HbA_{1c} values decreased from 7.7% to 7.4% in the
 148 Humalog-treated patients and remained unchanged from 7.7% in the Regular human
 149 insulin-treated patients. Rates of hypoglycemia were comparable between treatment groups in
 150 both studies. Humalog administration in insulin pumps has not been studied in patients with type
 151 2 diabetes.

152 INDICATIONS AND USAGE

153 Humalog is an insulin analog that is indicated in the treatment of patients with diabetes
 154 mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration
 155 of action than Regular human insulin. Therefore, in patients with type 1 diabetes, Humalog
 156 should be used in regimens that include a longer-acting insulin. However, in patients with type 2
 157 diabetes, Humalog may be used without a longer-acting insulin when used in combination
 158 therapy with sulfonylurea agents.

159 Humalog may be used in an external insulin pump, but should not be diluted or mixed with any
160 other insulin when used in the pump.

161 **CONTRAINDICATIONS**

162 Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to
163 Humalog or any of its excipients.

164 **WARNINGS**

165 **This human insulin analog differs from Regular human insulin by its rapid onset of**
166 **action as well as a shorter duration of activity. When used as a meal-time insulin, the dose**
167 **of Humalog should be given within 15 minutes before or immediately after the meal.**
168 **Because of the short duration of action of Humalog, patients with type 1 diabetes also**
169 **require a longer-acting insulin to maintain glucose control (except when using an external**
170 **insulin pump). Glucose monitoring is recommended for all patients with diabetes and is**
171 **particularly important for patients using an external insulin pump.**

172 **Hypoglycemia is the most common adverse effect associated with insulins, including**
173 **Humalog. As with all insulins, the timing of hypoglycemia may differ among various**
174 **insulin formulations. Glucose monitoring is recommended for all patients with diabetes.**

175 **Any change of insulin should be made cautiously and only under medical supervision.**
176 **Changes in insulin strength, manufacturer, type (e.g., Regular, NPH, analog), species, or**
177 **method of manufacture may result in the need for a change in dosage.**

178 **External Insulin Pumps: When used in an external insulin pump, Humalog should not be**
179 **diluted or mixed with any other insulin. Patients should carefully read and follow the**
180 **external insulin pump manufacturer's instructions and the Patient Information leaflet**
181 **before using Humalog.**

182 Physicians should carefully evaluate information on external insulin pump use in this Humalog
183 physician package insert and in the external insulin pump manufacturer's instructions. If
184 unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt
185 identification and correction of the cause is necessary. The patient may require interim therapy
186 with subcutaneous insulin injections (*see PRECAUTIONS, For Patients Using External Insulin*
187 *Pumps, and DOSAGE AND ADMINISTRATION*).

188 **PRECAUTIONS**

189 **General**

190 Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated
191 with the use of all insulins. Because of differences in the action of Humalog and other insulins,
192 care should be taken in patients in whom such potential side effects might be clinically relevant
193 (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering
194 drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and
195 hypersensitivity are among other potential clinical adverse effects associated with the use of all
196 insulins.

197 As with all insulin preparations, the time course of Humalog action may vary in different
198 individuals or at different times in the same individual and is dependent on site of injection,
199 blood supply, temperature, and physical activity.

200 Adjustment of dosage of any insulin may be necessary if patients change their physical activity
201 or their usual meal plan. Insulin requirements may be altered during illness, emotional
202 disturbances, or other stress.

203 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated
204 with the administration of Humalog. Rapid changes in serum glucose concentrations may induce
205 symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early
206 warning symptoms of hypoglycemia may be different or less pronounced under certain
207 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as
208 beta-blockers, or intensified diabetes control.

209 **Renal Impairment** — The requirements for insulin may be reduced in patients with renal
210 impairment.

211 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or
212 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including
213 Humalog, may be necessary.

214 **Allergy** — Local Allergy — As with any insulin therapy, patients may experience redness,
215 swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to
216 a few weeks. In some instances, these reactions may be related to factors other than insulin, such
217 as irritants in the skin cleansing agent or poor injection technique.

218 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to
219 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,
220 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized
221 allergy, including anaphylactic reaction, may be life threatening. In controlled clinical trials,
222 pruritus (with or without rash) was seen in 17 patients receiving Humulin R (N=2969) and 30
223 patients receiving Humalog (N=2944) (p=0.053). Localized reactions and generalized myalgias
224 have been reported with the use of cresol as an injectable excipient.

225 Antibody Production — In large clinical trials, antibodies that cross-react with human insulin
226 and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As
227 expected, the largest increase in the antibody levels during the 12-month clinical trials was
228 observed with patients new to insulin therapy.

229 **Usage in External Insulin Pumps** — **The infusion set (reservoir syringe, tubing, and**
230 **catheter), Disetronic® D-TRON®^{2,3} or D-TRON®^{2,3}plus cartridge adapter, and Humalog**
231 **in the external insulin pump reservoir should be replaced and a new infusion site selected**
232 **every 48 hours or less. Humalog in the external insulin pump should not be exposed to**
233 **temperatures above 37°C (98.6°F).**

234 In the D-TRON®^{2,3} or D-TRON®^{2,3}plus pump, Humalog 3 mL cartridges may be used for up
235 to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and
236 a new infusion site should be selected every 48 hours or less.

237 When used in an external insulin pump, Humalog should not be diluted or mixed with any
238 other insulin (*see* INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, *For Patients*
239 *Using External Insulin Pumps, Mixing of Insulins*, DOSAGE AND ADMINISTRATION, and
240 *Storage*).

241 **Information for Patients**

242 Patients should be informed of the potential risks and advantages of Humalog and alternative
243 therapies. Patients should also be informed about the importance of proper insulin storage,
244 injection technique, timing of dosage, adherence to meal planning, regular physical activity,
245 regular blood glucose monitoring, periodic hemoglobin A_{1c} testing, recognition and management
246 of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

247 Patients should be advised to inform their physician if they are pregnant or intend to become
248 pregnant.

249 Refer patients to the Patient Information leaflet for timing of Humalog dosing (≤ 15 minutes
250 before or immediately after a meal), storing insulin, and common adverse effects.

251 *For Patients Using Insulin Pen Delivery Devices:* Before starting therapy, patients should read
252 the Patient Information leaflet that accompanies the drug product and the User Manual that
253 accompanies the delivery device and re-read them each time the prescription is renewed. Patients
254 should be instructed on how to properly use the delivery device, prime the Pen, and properly
255 dispose of needles. Patients should be advised not to share their Pens with others.

256 *For Patients Using External Insulin Pumps:* Patients using an external infusion pump should
257 be trained in intensive insulin therapy and in the function of their external insulin pump and
258 pump accessories. Humalog was tested in the MiniMed®¹ Models 506, 507, and 508 insulin
259 pumps using MiniMed®¹ Polyfin®¹ infusion sets. Humalog was also tested in Disetronic®²
260 H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and the Disetronic
261 D-TRON®^{2,3} and D-TRON®^{2,3}plus insulin pumps (with Humalog 3 mL cartridges) using
262 Disetronic Rapid®² infusion sets.

263 **The infusion set (reservoir syringe, tubing, catheter), D-TRON®^{2,3} or D-TRON®^{2,3}plus**
264 **cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced,**
265 **and a new infusion site selected every 48 hours or less. Humalog in the external pump**
266 **should not be exposed to temperatures above 37°C (98.6°F).** A Humalog 3 mL cartridge used
267 in the D-TRON®^{2,3} or D-TRON®^{2,3}plus pump should be discarded after 7 days, even if it still
268 contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported
269 to medical personnel, and a new site selected.

270 **Humalog should not be diluted or mixed with any other insulin when used in an external**
271 **insulin pump.**

272 **Laboratory Tests**

273 As with all insulins, the therapeutic response to Humalog should be monitored by periodic
274 blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
275 monitoring of long-term glycemic control.

276 **Drug Interactions**

277 Insulin requirements may be increased by medications with hyperglycemic activity such as
278 corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral
279 contraceptives, phenothiazines, and thyroid replacement therapy (*see* CLINICAL
280 PHARMACOLOGY).

281 Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity
282 or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,
283 certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme
284 inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of
285 pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the
286 symptoms of hypoglycemia in some patients.

287 **Mixing of Insulins** — Care should be taken when mixing all insulins as a change in peak
288 action may occur. The American Diabetes Association warns in its Position Statement on Insulin
289 Administration, “On mixing, physiochemical changes in the mixture may occur (either
290 immediately or over time). As a result, the physiological response to the insulin mixture may
291 differ from that of the injection of the insulins separately.” Mixing Humalog with Humulin N or
292 Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog. Given
293 alone or mixed with Humulin N, Humalog results in a more rapid absorption and
294 glucose-lowering effect compared with Regular human insulin.

295 The effects of mixing Humalog with insulins of animal source or insulin preparations produced
296 by other manufacturers have not been studied (*see* WARNINGS).

297 If Humalog is mixed with a longer-acting insulin, such as Humulin N or Humulin U, Humalog
298 should be drawn into the syringe first to prevent clouding of the Humalog by the longer-acting
299 insulin. Injection should be made immediately after mixing. Mixtures should not be administered
300 intravenously.

301 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the
302 cartridge, for the Humalog in the cartridge to be diluted or for the cartridge to be refilled with
303 insulin. Humalog should not be diluted or mixed with any other insulin when used in an external
304 insulin pump.

305 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

306 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
307 Humalog, Humalog Mix75/25, or Humalog Mix50/50. Insulin lispro was not mutagenic in a
308 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
309 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).
310 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

311 **Pregnancy**

312 *Teratogenic Effects — Pregnancy Category B* — Reproduction studies have been performed in
313 pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average
314 human dose (40 units/day) based on body surface area. The results have revealed no evidence of
315 impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and
316 well-controlled studies with Humalog, Humalog Mix75/25, or Humalog Mix50/50 in pregnant
317 women. Because animal reproduction studies are not always predictive of human response, this
318 drug should be used during pregnancy only if clearly needed.

319 Although there are limited clinical studies of the use of Humalog in pregnancy, published
320 studies with human insulins suggest that optimizing overall glycemic control, including
321 postprandial control, before conception and during pregnancy improves fetal outcome. Although
322 the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also
323 has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first
324 trimester and increase during the second and third trimesters. Careful monitoring of the patient is
325 required throughout pregnancy. During the perinatal period, careful monitoring of infants born to
326 mothers with diabetes is warranted.

327 **Nursing Mothers**

328 It is unknown whether Humalog is excreted in significant amounts in human milk. Many
329 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
330 exercised when Humalog is administered to a nursing woman. Patients with diabetes who are
331 lactating may require adjustments in Humalog dose, meal plan, or both.

332 **Pediatric Use**

333 In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3 to 11 years,
334 comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group:
335 Regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%,
336 and Humalog immediately after meals 8.5%. In an 8-month, cross-over study of adolescents
337 (n=463), aged 9 to 19 years, comparable glycemic control as measured by HbA_{1c} was achieved
338 regardless of treatment group: Regular human insulin 30 to 45 minutes before meals 8.7% and
339 Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all

340 three treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in
341 dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the
342 Humalog vial, the shelf-life may be reduced (*see* DOSAGE AND ADMINISTRATION).

343 **Geriatric Use**

344 Of the total number of subjects (n=2834) in eight clinical studies of Humalog, twelve percent
345 (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes.
346 HbA_{1c} values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic
347 studies to assess the effect of age on the onset of Humalog action have not been performed.

348 **ADVERSE REACTIONS**

349 Clinical studies comparing Humalog with Regular human insulin did not demonstrate a
350 difference in frequency of adverse events between the two treatments.

351 Adverse events commonly associated with human insulin therapy include the following:

352 **Body as a Whole** — allergic reactions (*see* PRECAUTIONS).

353 **Skin and Appendages** — injection site reaction, lipodystrophy, pruritus, rash.

354 **Other** — hypoglycemia (*see* WARNINGS and PRECAUTIONS).

355 **OVERDOSAGE**

356 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
357 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
358 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes
359 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous
360 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
361 may be necessary because hypoglycemia may recur after apparent clinical recovery.

362 **DOSAGE AND ADMINISTRATION**

363 Humalog is intended for subcutaneous administration, including use in select external insulin
364 pumps (*see* DOSAGE AND ADMINISTRATION, *External Insulin Pumps*). Dosage regimens of
365 Humalog will vary among patients and should be determined by the healthcare provider familiar
366 with the patient's metabolic needs, eating habits, and other lifestyle variables. Pharmacokinetic
367 and pharmacodynamic studies showed Humalog to be equipotent to Regular human insulin (i.e.,
368 one unit of Humalog has the same glucose-lowering effect as one unit of Regular human insulin),
369 but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the
370 more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal
371 insulin may be needed when a patient changes from other insulins to Humalog, particularly to
372 prevent pre-meal hyperglycemia.

373 When used as a meal-time insulin, Humalog should be given within 15 minutes before or
374 immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal.
375 To achieve optimal glucose control, the amount of longer-acting insulin being given may need to
376 be adjusted when using Humalog.

377 The rate of insulin absorption and consequently the onset of activity are known to be affected
378 by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently
379 faster rate than Regular human insulin in healthy male volunteers given 0.2 U/kg Regular human
380 insulin or Humalog at abdominal, deltoid, or femoral sites, the three sites often used by patients
381 with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its
382 rapid onset of action and has less variability in its onset of action among injection sites compared
383 with Regular human insulin (*see* PRECAUTIONS). After abdominal administration, Humalog
384 concentrations are higher than those following deltoid or thigh injections. Also, the duration of

385 action of Humalog is slightly shorter following abdominal injection, compared with deltoid and
 386 femoral injections. As with all insulin preparations, the time course of action of Humalog may
 387 vary considerably in different individuals or within the same individual. Patients must be
 388 educated to use proper injection techniques.

389 Humalog in a vial may be diluted with STERILE DILUENT for Humalog[®], Humulin[®] N,
 390 Humulin[®] R, Humulin[®] 70/30, and Humulin[®] R U-500 to a concentration of 1:10 (equivalent to
 391 U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when
 392 stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog
 393 contained in a cartridge or Humalog used in an external insulin pump.

394 Parenteral drug products should be inspected visually before use whenever the solution and the
 395 container permit. If the solution is cloudy, contains particulate matter, is thickened, or is
 396 discolored, the contents must not be injected. Humalog should not be used after its expiration
 397 date.

398 The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the
 399 cartridge or for the cartridge to be refilled with insulin.

400 *External Insulin Pumps* — Humalog was tested in MiniMed[®] 1 Models 506, 507, and 508
 401 insulin pumps using MiniMed[®] 1 Polyfin[®] 1 infusion sets. Humalog was also tested in the
 402 Disetronic[®] 2 H-TRONplus[®] V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the
 403 Disetronic D-TRON[®] 2,3 and D-TRON[®] 2,3 plus pumps (with Humalog 3 mL cartridges) using
 404 Disetronic Rapid[®] 2 infusion sets.

405 Humalog should not be diluted or mixed with any other insulin when used in an external
 406 insulin pump.

407 HOW SUPPLIED

408 Humalog [insulin lispro injection, USP (rDNA origin)] is available in the following package
 409 sizes: each presentation containing 100 units insulin lispro per mL (U-100).

410

10 mL vials	NDC 0002-7510-01 (VL-7510)
5 x 3 mL cartridges ³	NDC 0002-7516-59 (VL-7516)
5 x 3 mL disposable insulin delivery devices (Pen)	NDC 0002-8725-59 (HP-8725)
5 x 3 mL disposable insulin delivery devices (KwikPen [™])	NDC 0002-8799-59 (HP-8799)

411

412

413

¹ MiniMed[®] and Polyfin[®] are registered trademarks of MiniMed, Inc.

² Disetronic[®], H-TRONplus[®], D-TRON[®], and Rapid[®] are registered trademarks of Roche Diagnostics GMBH.

³ 3 mL cartridge is for use in Eli Lilly and Company's HumaPen[®] MEMOIR[™] and HumaPen[®] LUXURA[™] HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen[®] 3 mL insulin delivery device and Disetronic D-TRON[®] and D-TRON[®]plus pumps. Autopen[®] is a registered trademark of Owen Mumford, Ltd. HumaPen[®], HumaPen[®] MEMOIR[™] and HumaPen[®] LUXURA[™] HD are trademarks of Eli Lilly and Company.

Other product and company names may be the trademarks of their respective owners.

414

415 *Storage* — Unopened Humalog should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but
 416 not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated [below 30°C (86°F)]
 417 vials, cartridges, Pens, and KwikPens must be used within 28 days or be discarded, even if they
 418 still contain Humalog. Protect from direct heat and light. See table below:
 419

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Cartridge	28 days	Until expiration date	28 days, Do not refrigerate.
3 mL Pen and KwikPen (disposable)	28 days	Until expiration date	28 days, Do not refrigerate.

420
 421 *Use in an External Insulin Pump* — A Humalog 3 mL cartridge used in the D-TRON®^{2,3} or
 422 D-TRON®^{2,3}plus should be discarded after 7 days, even if it still contains Humalog. Infusion
 423 sets, D-TRON®^{2,3} and D-TRON®^{2,3}plus cartridge adapters, and Humalog in the external insulin
 424 pump reservoir should be discarded every 48 hours or less.

425 Literature issued/revised Month DD, YYYY

426 **KwikPens manufactured by**
 427 **Eli Lilly and Company, Indianapolis, IN 46285, USA**
 428 **Pens manufactured by**
 429 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 430 **Lilly France, F-67640 Fegersheim, France**
 431 **Vials manufactured by**
 432 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 433 **Hospira, Inc., Lake Forest, IL 60045, USA or**
 434 **Lilly France, F-67640 Fegersheim, France**
 435 **Cartridges manufactured by**
 436 **Lilly France, F-67640 Fegersheim, France**
 437
 438 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**

439
 440 **www.humalog.com**
 441

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Patient Information

Humalog[®] (HU-ma-log) insulin lispro injection, USP (rDNA origin)

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. Your insulin dose and the time you take your dose can change with different types of insulin.

Make sure you have the right type and strength of insulin prescribed for you.

Read the Patient Information that comes with Humalog before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider if you have questions about managing your diabetes.

What is Humalog?

Humalog is an injectable fast-acting man-made insulin. Humalog is used to control high blood sugar (glucose) in people with diabetes.

Humalog comes in:

- 10 mL vials (bottles) for use with a syringe or external insulin pump
- Prefilled pens
- 3 mL cartridges for use with a reusable pen or external insulin pump

Who should not take Humalog?

Do not take Humalog if:

- your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Humalog.
- you are allergic to anything in Humalog. See the end of this leaflet for a complete list of ingredients in Humalog.

Tell your healthcare provider:

- **about all your medical conditions.** Medical conditions can affect your insulin needs and your dose of Humalog.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. Humalog has not been studied in pregnant or nursing women.

- 33 • **about all the medicines you take, including prescription and non-prescription**
 34 **medicines, vitamins and herbal supplements.** Many medicines can affect your blood
 35 sugar levels and insulin needs. Your Humalog dose may need to change if you take other
 36 medicines.

37 Know the medicines you take. Keep a list of your medicines with you to show to all of your
 38 healthcare providers.

39

40 **How should I use Humalog?**

41 Humalog can be used with a syringe, prefilled pen, reusable pen or external insulin pump. Talk
 42 to your healthcare provider if you have any questions. Your healthcare provider will tell you the
 43 right syringes to use with Humalog vials. Your healthcare provider should show you how to
 44 inject Humalog before you start using it.

- 45 • **Read the User Manual that comes with your Humalog prefilled pen and the**
 46 **manufacturer's instructions that comes with your external insulin pump. Use**
 47 **Humalog exactly as prescribed by your healthcare provider.**
- 48 • **If you have type 1 diabetes, you need to take a longer-acting insulin in addition to**
 49 **Humalog (except when using an external insulin pump).**
- 50 • **If you have type 2 diabetes, you may be taking diabetes pills and/or a longer-acting**
 51 **insulin in addition to Humalog.**
- 52 • **Humalog starts working faster than other insulins that contain regular human**
 53 **insulin.** Inject Humalog within fifteen minutes before eating or right after eating a meal.
- 54 • **Check your blood sugar levels as told by your healthcare provider.**
- 55 • Look at your Humalog before using. Humalog should be clear, have no color and look like
 56 water. If your Humalog is cloudy, thickened, even slightly colored, or has solid particles or
 57 clumps in it, do not use. Return it to your pharmacy for new Humalog.
- 58 • Humalog can be mixed with a longer-acting human insulin, but only if you are told to do
 59 so by your healthcare provider. If you are mixing two types of insulin, always draw
 60 Humalog into the syringe first. Talk with your healthcare provider about how to properly
 61 mix Humalog with a different insulin.
- 62 • Humalog can be used in an external insulin pump either by withdrawing Humalog from a
 63 vial or using a 3 mL Humalog cartridge that is inserted into the pump.
- 64 • Humalog was tested with MiniMed®¹ Models 506, 507, and 508 insulin pumps using
 65 MiniMed Polyfin®¹ infusion sets. Humalog was also tested with the Disetronic®² H-
 66 TRONplus®² V100 insulin pump (with plastic 3.15 mL insulin reservoir), using the
 67 Disetronic Rapid®² infusion set.
- 68 • A Humalog cartridge used in the D-TRON² or D-TRONplus² pump, may be used for up to
 69 7 days. Humalog in the external insulin pump reservoir and the complete infusion set
 70 should be replaced and a new infusion site selected every 48 hours or less.
- 71 • Humalog in an external insulin pump should not be exposed to temperature above 98.6°F
 72 (37°C), such as in a sauna or hot tub, hot showers, direct sunlight, or radiant heaters.

73 • **Inject your dose of Humalog under the skin of your stomach area, upper arm, upper**
74 **leg, or buttocks. Never inject Humalog into a muscle or vein.**

75 • **Change (rotate) your injection site with each dose.**

76 • **Your insulin needs may change because of:**

77 • illness

78 • stress

79 • other medicines you take

80 • changes in eating

81 • physical activity changes

82 Follow your healthcare provider's instructions to make changes in your insulin dose.

83 • **Never dilute or mix Humalog with another insulin in the same prefilled pen, cartridge**
84 **or external insulin pump.**

85 • **Always carry a quick source of sugar to treat low blood sugar, such as glucose tablets,**
86 **hard candy, or juice.**

87 **What are the possible side effects of Humalog?**

88 **Low Blood Sugar (Hypoglycemia).** Symptoms of low blood sugar include:

89 • hunger

90 • dizziness

91 • feeling shaky or shakiness

92 • lightheadedness

93 • sweating

94 • irritability

95 • headache

96 • fast heartbeat

97 • confusion

98 Low blood sugar symptoms can happen suddenly. Symptoms of low blood sugar may be
99 different for each person and may change from time to time. Severe low blood sugar can cause
100 seizures and death. Low blood sugar may affect your ability to drive a car or use mechanical
101 equipment, risking injury to yourself or others. Know your symptoms of low blood sugar. Low
102 blood sugar can be treated by drinking juice or regular soda or eating glucose tablets, sugar, or
103 hard candy. Follow your healthcare provider's instructions for treating low blood sugar. Talk to
104 your healthcare provider if low blood sugar is a problem for you.
105

- 106 • **Serious allergic reactions** (whole body allergic reaction). Severe, life-threatening allergic
107 reactions can happen with insulin. Get medical help right away if you develop a rash over
108 your whole body, have trouble breathing, wheezing, a fast heartbeat, or sweating.
- 109 • **Reactions at the injection site** (local allergic reaction). You may get redness, swelling,
110 and itching at the injection site. If you keep having injection site reactions or they are
111 serious, you need to call your healthcare provider. Do not inject insulin into a skin area that
112 is red, swollen, or itchy.
- 113 • **Skin thickens or pits at the injection site (lipodystrophy)**. This can happen if you don't
114 change (rotate) your injection sites enough.

115 These are not all the side effects from Humalog. Ask your healthcare provider or pharmacist for
116 more information.

117

118 **How should I store Humalog?**

- 119 • **Store all unopened (unused) Humalog in the original carton in a refrigerator at 36°F**
120 **to 46°F (2°C to 8°C)**. Do not freeze.
- 121 • Do not use Humalog that has been frozen.
- 122 • Do not use after the expiration date printed on the carton and label.
- 123 • Protect Humalog from extreme heat, cold or light.

124 **After starting use (open):**

- 125 • **Vials:** Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28
126 days. Keep open vials away from direct heat or light. Throw away an opened vial 28 days
127 after first use, even if there is insulin left in the vial.
- 128 • **Cartridge and Prefilled Pens:** Do not store a cartridge or prefilled pen that you are using
129 in the refrigerator. Keep at room temperature below 86°F (30°C) for up to 28 days. Throw
130 away a cartridge or prefilled pen 28 days after first use, even if there is insulin left in the
131 cartridge or the pen.

132 **General information about Humalog**

133 Use Humalog only to treat your diabetes. Do not share it with anyone else, even if they also have
134 diabetes. It may harm them.

135

136 This leaflet summarized the most important information about Humalog. If you would like more
137 information about Humalog or diabetes, talk with your healthcare provider. You can ask your
138 healthcare provider or pharmacist for information about Humalog that is written for health
139 professionals.

140

141 For questions you may call 1-800-LillyRx (1-800-545-5979) or visit www.humalog.com.

142

143 **What are the ingredients in Humalog?**

144 **Active ingredient:** insulin lispro.

145

146 **Inactive ingredients:** glycerin, dibasic sodium phosphate, metacresol, zinc oxide (zinc ion),
 147 trace amounts of phenol and water for injection.

148

149 ¹ MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

150 ² Disetronic®, H-TRONplus®, D-TRON®, D-TRONplus and Rapid® are registered trademarks of Roche
 151 Diagnostics GMBH.

152

153 Patient Information issued/revised Month DD, YYYY

154

KwikPens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA

156

Pens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Lilly France, F-67640 Fegersheim, France

159

Vials manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA or
Hospira, Inc., Lake Forest, IL 60045, USA or
Lilly France, F-67640 Fegersheim, France

162

Cartridges manufactured by
Lilly France, F-67640 Fegersheim, France

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for Eli Lilly and Company, Indianapolis, IN 46285, USA

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www.humalog.com

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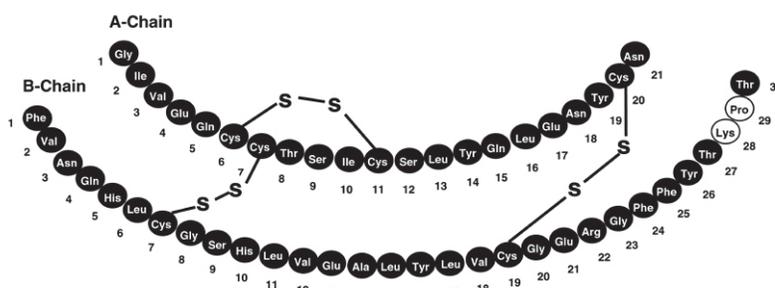
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HUMALOG[®] Mix75/25[™]
75% INSULIN LISPRO PROTAMINE SUSPENSION AND
25% INSULIN LISPRO INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

DESCRIPTION

Humalog[®] Mix75/25[™] [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce insulin lispro. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

Insulin lispro has the following primary structure:



Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

Humalog Mix75/25 vials and Pens contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

Each milliliter of Humalog Mix75/25 injection contains insulin lispro 100 units, 0.28 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg Metacresol, zinc oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and Water for Injection. Humalog Mix75/25 has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH.

CLINICAL PHARMACOLOGY

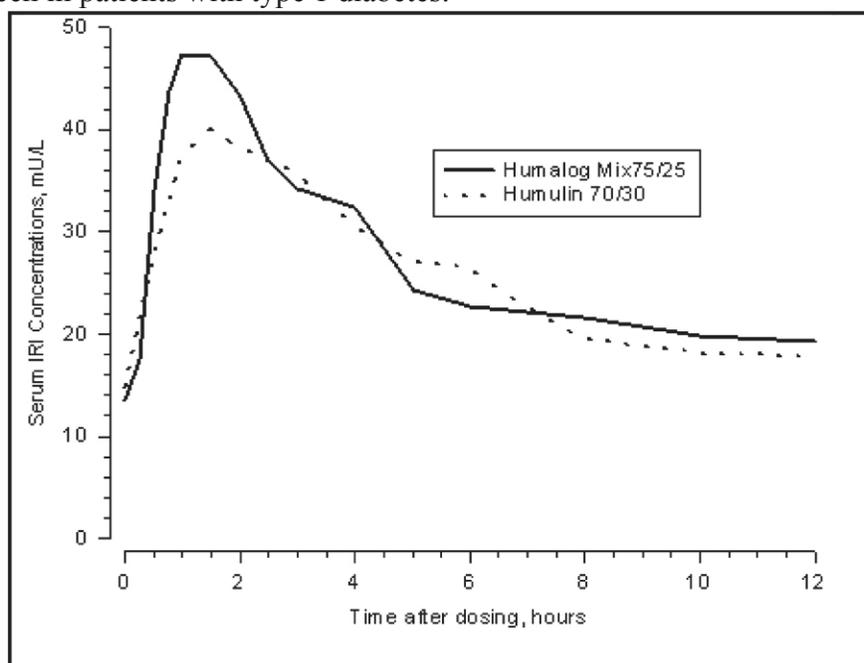
Antidiabetic Activity

The primary activity of insulin, including Humalog Mix75/25, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

36 Insulin lispro, the rapid-acting component of Humalog Mix75/25, has been shown to be
 37 equipotent to Regular human insulin on a molar basis. One unit of Humalog[®] has the same
 38 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
 39 shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared with
 40 Humulin[®] 70/30 on a unit for unit basis.

41 **Pharmacokinetics**

42 *Absorption* — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent)
 43 diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix75/25, is
 44 absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous
 45 doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to
 46 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human
 47 insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar
 48 results were seen in patients with type 1 diabetes.



49
 50 **Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous**
 51 **Injection of Humalog Mix75/25 or Humulin 70/30 in Healthy Nondiabetic Subjects.**

52 Humalog Mix75/25 has two phases of absorption. The early phase represents insulin lispro and
 53 its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin
 54 lispro protamine suspension. In 30 healthy nondiabetic subjects given subcutaneous doses
 55 (0.3 U/kg) of Humalog Mix75/25, peak serum concentrations were observed 30 to 240 minutes
 56 (median, 60 minutes) after dosing (*see* Figure 1). Identical results were found in patients with
 57 type 1 diabetes. The rapid absorption characteristics of Humalog are maintained with Humalog
 58 Mix75/25 (*see* Figure 1).

59 Figure 1 represents serum insulin concentration versus time curves of Humalog Mix75/25 and
 60 Humulin 70/30. Humalog Mix75/25 has a more rapid absorption than Humulin 70/30, which has
 61 been confirmed in patients with type 1 diabetes.

62 *Distribution* — Radiolabeled distribution studies of Humalog Mix75/25 have not been
 63 conducted. However, the volume of distribution following injection of Humalog is identical to
 64 that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

65 *Metabolism* — Human metabolism studies of Humalog Mix75/25 have not been conducted.
66 Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of
67 Humalog Mix75/25, is identical to that of Regular human insulin.

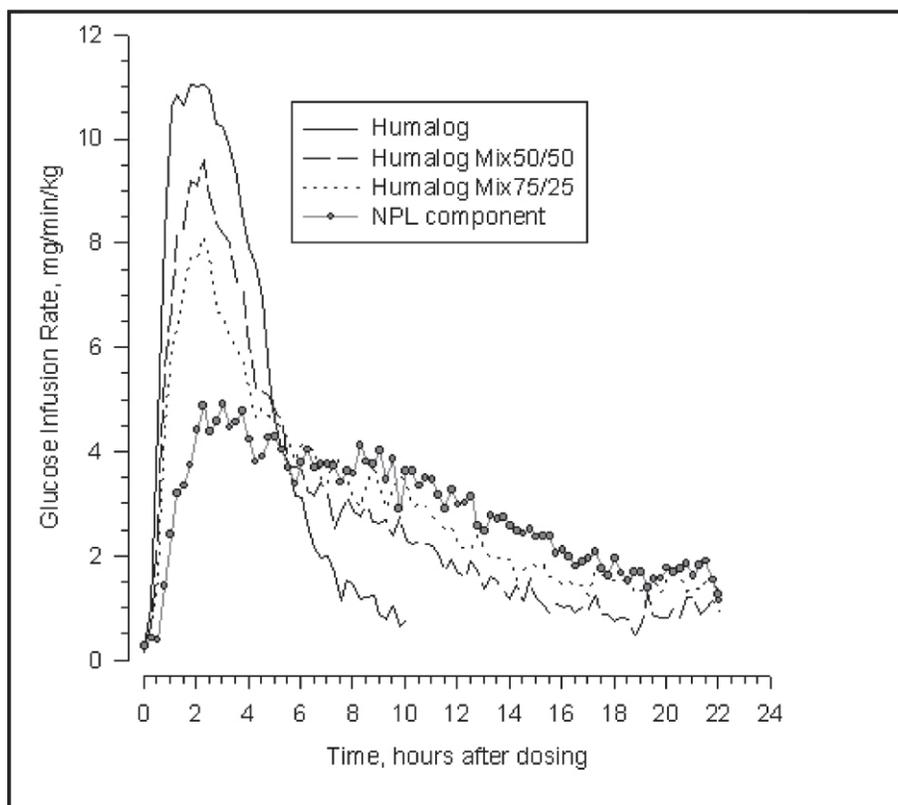
68 *Elimination* — Humalog Mix75/25 has two absorption phases, a rapid and a prolonged phase,
69 representative of the insulin lispro and insulin lispro protamine suspension components of the
70 mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot
71 be calculated after administration of Humalog Mix75/25 because of the prolonged insulin lispro
72 protamine suspension absorption.

73 **Pharmacodynamics**

74 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
75 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
76 duration of glucose-lowering activity than Regular human insulin. The early onset of activity of
77 Humalog Mix75/25 is directly related to the rapid absorption of Humalog. The time course of
78 action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix75/25), may
79 vary considerably in different individuals or within the same individual. The parameters of
80 Humalog Mix75/25 activity (time of onset, peak time, and duration) as presented in Figures 2
81 and 3 should be considered only as general guidelines. The rate of insulin absorption and
82 consequently the onset of activity is known to be affected by the site of injection, exercise, and
83 other variables (*see General under PRECAUTIONS*).

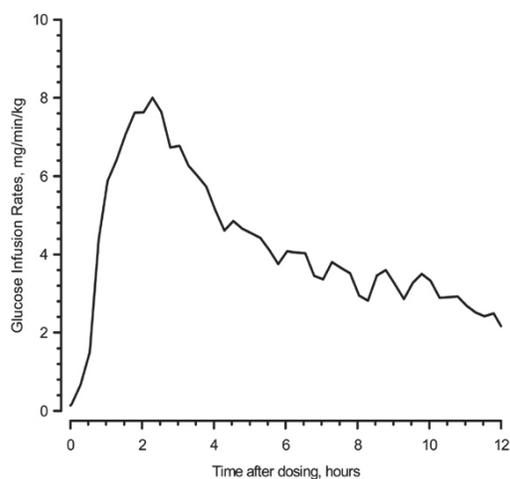
84 In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and
85 glucose-lowering activity of Humalog, Humalog[®] Mix50/50[™], Humalog Mix75/25, and insulin
86 lispro protamine suspension (NPL component) were compared (*see Figure 2*). Graphs of mean
87 glucose infusion rate versus time showed a distinct insulin activity profile for each formulation.
88 The rapid onset of glucose-lowering activity characteristic of Humalog was maintained in
89 Humalog Mix75/25.

90 In separate glucose clamp studies performed in nondiabetic subjects, pharmacodynamics of
91 Humalog Mix75/25 and Humulin 70/30 were assessed and are presented in Figure 3. Humalog
92 Mix75/25 has a duration of activity similar to that of Humulin 70/30.

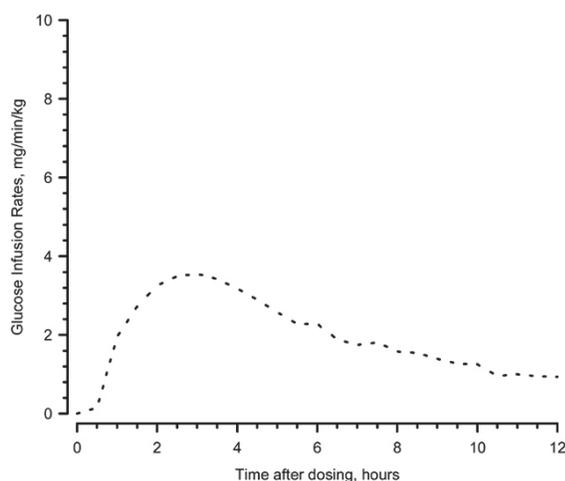


93
94 **Figure 2: Insulin Activity After Injection of Humalog, Humalog Mix50/50, Humalog**
95 **Mix75/25, or Insulin Lispro Protamine Suspension (NPL Component) in 30 Nondiabetic**
96 **Subjects.**
97

98
99 **Figure 3a**
100 **Humalog Mix75/25**



101 **Figure 3b**
102 **Humulin 70/30**



103 **Figure 3: Insulin Activity After Injection of Humalog Mix75/25 and Humulin 70/30 in**
104 **Nondiabetic Subjects.**

105 Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in
106 healthy nondiabetic subjects.

103 Figure 2 shows the time activity profiles of Humalog, Humalog Mix50/50, Humalog
104 Mix75/25, and insulin lispro protamine suspension (NPL component).

105 Figure 3 is a comparison of the time activity profiles of Humalog Mix75/25 (*see* Figure 3a) and
106 of Humulin 70/30 (*see* Figure 3b) from two different studies.

107 Special Populations

108 *Age and Gender* — Information on the effect of age on the pharmacokinetics of Humalog
109 Mix75/25 is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and
110 women administered Humalog Mix75/25 showed no gender differences. In large Humalog
111 clinical trials, sub-group analysis based on age and gender demonstrated that differences between
112 Humalog and Regular human insulin in postprandial glucose parameters are maintained across
113 sub-groups.

114 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
115 Humalog Mix75/25 has not been studied.

116 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
117 Humalog Mix75/25 has not been studied.

118 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and
119 pharmacodynamics of Humalog Mix75/25 has not been studied. In large clinical trials, which
120 included patients with Body Mass Index up to and including 35 kg/m², no consistent differences
121 were observed between Humalog and Humulin[®] R with respect to postprandial glucose
122 parameters.

123 *Renal Impairment* — The effect of renal impairment on the pharmacokinetics and
124 pharmacodynamics of Humalog Mix75/25 has not been studied. In a study of 25 patients with
125 type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between
126 Humalog and Regular human insulin were generally maintained. However, the sensitivity of the
127 patients to insulin did change, with an increased response to insulin as the renal function
128 declined. Careful glucose monitoring and dose reductions of insulin, including Humalog
129 Mix75/25, may be necessary in patients with renal dysfunction.

130 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating
131 levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the
132 pharmacokinetics and pharmacodynamics of Humalog Mix75/25 has not been studied. However,
133 in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the
134 subcutaneous absorption or general disposition of Humalog when compared with patients with
135 no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption
136 and elimination when compared with Regular human insulin. Careful glucose monitoring and
137 dose adjustments of insulin, including Humalog Mix75/25, may be necessary in patients with
138 hepatic dysfunction.

139 **INDICATIONS AND USAGE**

140 Humalog Mix75/25, a mixture of 75% insulin lispro protamine suspension and 25% insulin
141 lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for
142 the control of hyperglycemia. Humalog Mix75/25 has a more rapid onset of glucose-lowering
143 activity compared with Humulin 70/30 while having a similar duration of action. This profile is
144 achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro
145 protamine suspension.

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CONTRAINDICATIONS

Humalog Mix75/25 is contraindicated during episodes of hypoglycemia and in patients sensitive to insulin lispro or any of the excipients contained in the formulation.

WARNINGS

Humalog differs from Regular human insulin by its rapid onset of action as well as a shorter duration of activity. Therefore, the dose of Humalog Mix75/25 should be given within 15 minutes before a meal.

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog Mix75/25. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., Regular, NPH, analog), species, or method of manufacture may result in the need for a change in dosage.

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog Mix75/25 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Humalog Mix75/25 action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia — As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog Mix75/25. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment — As with other insulins, the requirements for Humalog Mix75/25 may be reduced in patients with renal impairment.

Hepatic Impairment — Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog Mix75/25, may be necessary.

Allergy — Local Allergy — As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

190 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to
191 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,
192 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized
193 allergy, including anaphylactic reaction, may be life threatening. Localized reactions and
194 generalized myalgias have been reported with the use of cresol as an injectable excipient.

195 Antibody Production — In clinical trials, antibodies that cross-react with human insulin and
196 insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures
197 treatment groups.

198 **Information for Patients**

199 Patients should be informed of the potential risks and advantages of Humalog Mix75/25 and
200 alternative therapies. Patients should not mix Humalog Mix75/25 with any other insulin. They
201 should also be informed about the importance of proper insulin storage, injection technique,
202 timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose
203 monitoring, periodic hemoglobin A_{1c} testing, recognition and management of hypo- and
204 hyperglycemia, and periodic assessment for diabetes complications.

205 Patients should be advised to inform their physician if they are pregnant or intend to become
206 pregnant.

207 Refer patients to the Patient Information leaflet for information on normal appearance, timing
208 of dosing (within 15 minutes before a meal), storing, and common adverse effects.

209 For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read
210 the Patient Information leaflet that accompanies the drug product and the User Manual that
211 accompanies the delivery device and re-read them each time the prescription is renewed. Patients
212 should be instructed on how to properly use the delivery device, prime the Pen, and properly
213 dispose of needles. Patients should be advised not to share their Pens with others.

214 **Laboratory Tests**

215 As with all insulins, the therapeutic response to Humalog Mix75/25 should be monitored by
216 periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
217 monitoring of long-term glycemic control.

218 **Drug Interactions**

219 Insulin requirements may be increased by medications with hyperglycemic activity such as
220 corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral
221 contraceptives, phenothiazines, and thyroid replacement therapy.

222 Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity
223 or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,
224 certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme
225 inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of
226 pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the
227 symptoms of hypoglycemia in some patients.

228 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

229 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
230 Humalog, Humalog Mix75/25, or Humalog Mix50/50. Insulin lispro was not mutagenic in a
231 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
232 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).
233 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

234 **Pregnancy**

235 *Teratogenic Effects — Pregnancy Category B* — Reproduction studies with insulin lispro have
 236 been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times,
 237 respectively, the average human dose (40 units/day) based on body surface area. The results have
 238 revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are,
 239 however, no adequate and well-controlled studies with Humalog, Humalog Mix75/25, or
 240 Humalog Mix50/50 in pregnant women. Because animal reproduction studies are not always
 241 predictive of human response, this drug should be used during pregnancy only if clearly needed.

242 **Nursing Mothers**

243 It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many
 244 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
 245 exercised when Humalog Mix75/25 is administered to a nursing woman. Patients with diabetes
 246 who are lactating may require adjustments in Humalog Mix75/25 dose, meal plan, or both.

247 **Pediatric Use**

248 Safety and effectiveness of Humalog Mix75/25 in patients less than 18 years of age have not
 249 been established.

250 **Geriatric Use**

251 Clinical studies of Humalog Mix75/25 did not include sufficient numbers of patients aged 65
 252 and over to determine whether they respond differently than younger patients. In general, dose
 253 selection for an elderly patient should take into consideration the greater frequency of decreased
 254 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this
 255 population.

256 **ADVERSE REACTIONS**

257 Clinical studies comparing Humalog Mix75/25 with human insulin mixtures did not
 258 demonstrate a difference in frequency of adverse events between the two treatments.

259 Adverse events commonly associated with human insulin therapy include the following:

260 **Body as a Whole** — allergic reactions (*see* PRECAUTIONS).

261 **Skin and Appendages** — injection site reaction, lipodystrophy, pruritus, rash.

262 **Other** — hypoglycemia (*see* WARNINGS and PRECAUTIONS).

263 **OVERDOSAGE**

264 Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy
 265 expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose.
 266 Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes
 267 with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous
 268 glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation
 269 may be necessary because hypoglycemia may recur after apparent clinical recovery.

270 **DOSAGE AND ADMINISTRATION**

271
 272 **Table 1* : Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-
 273 Study Comparison)**

Insulin Products	Dose, U/kg	Time of Peak Activity, Hours After Dosing	Percent of Total Activity Occurring in the First 4 Hours

Humalog	0.3	2.4 (0.8 - 4.3)	70% (49 - 89%)
Humulin R	0.32 (0.26 - 0.37)	4.4 (4.0 - 5.5)	54% (38 - 65%)
Humalog Mix75/25	0.3	2.6 (1.0 - 6.5)	35% (21 - 56%)
Humulin 70/30	0.3	4.4 (1.5 - 16)	32% (14 - 60%)
Humalog Mix50/50	0.3	2.3 (0.8 - 4.8)	45% (27 - 69%)
Humulin 50/50	0.3	3.3 (2.0 - 5.5)	44% (21 - 60%)
NPH	0.32 (0.27 - 0.40)	5.5 (3.5 - 9.5)	14% (3.0 - 48%)
NPL component	0.3	5.8 (1.3 - 18.3)	22% (6.3 - 40%)

* The information supplied in Table 1 indicates when peak insulin activity can be expected and the percent of the total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.

Humalog Mix75/25 is intended only for subcutaneous administration. Humalog Mix75/25 should not be administered intravenously. Dosage regimens of Humalog Mix75/25 will vary among patients and should be determined by the healthcare provider familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown to be equipotent to Regular human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of shorter duration. Humalog Mix75/25 has a similar glucose-lowering effect as compared with Humulin 70/30 on a unit for unit basis. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

Humalog Mix75/25 starts lowering blood glucose more quickly than Regular human insulin, allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast, mixtures containing Regular human insulin should be given 30 to 60 minutes before a meal.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. As with all insulin preparations, the time course of action of Humalog Mix75/25 may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog Mix75/25 should be inspected visually before use. Humalog Mix75/25 should be used only if it appears uniformly cloudy after mixing. Humalog Mix75/25 should not be used after its expiration date.

HOW SUPPLIED

Humalog Mix75/25 [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] is available in the following package sizes: each presentation containing 100 units insulin lispro per mL (U-100).

10 mL vials	NDC 0002-7511-01 (VL-7511)
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5 x 3 mL disposable insulin delivery devices (Pen)	NDC 0002-8794-59 (HP-8794)
5 x 3 mL disposable insulin delivery devices (KwikPen™)	NDC 0002-8797-59 (HP-8797)

302
 303 *Storage* — Humalog Mix75/25 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but
 304 not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated [below
 305 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain
 306 Humalog Mix75/25. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used
 307 within 10 days or be discarded, even if they still contain Humalog Mix75/25. Protect from direct
 308 heat and light. See table below:
 309

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (disposable)	10 days	Until expiration date	10 days. Do not refrigerate.

310
 311 Literature issued/revised Month DD, YYYY
 312 **KwikPens manufactured by**
 313 **Eli Lilly and Company, Indianapolis, IN 46285, USA**
 314 **Pens manufactured by**
 315 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 316 **Lilly France, F-67640 Fegersheim, France**
 317 **Vials manufactured by**
 318 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
 319 **Lilly France, F-67640 Fegersheim, France**
 320
 321 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**
 322
 323 **www.humalog.com**
 324

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325

Patient Information

Humalog[®] (HU-ma-log) Mix75/25[™] 75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. Your insulin dose and the time you take your dose can change with different types of insulin.

Make sure you have the right type and strength of insulin prescribed for you.

Read the Patient Information that comes with Humalog Mix75/25 before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider if you have questions about managing your diabetes.

What is Humalog Mix75/25?

Humalog Mix75/25 is a mixture of fast-acting and longer-acting man-made insulins. Humalog Mix75/25 is used to control high blood sugar (glucose) in people with diabetes.

Humalog Mix75/25 comes in:

- 10 mL vials (bottles) for use with a syringe
- Prefilled pens

Who should not take Humalog Mix75/25?

Do not take Humalog Mix75/25 if:

- your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Humalog Mix75/25.
- you are allergic to anything in Humalog Mix75/25. See the end of this leaflet for a complete list of ingredients in Humalog Mix75/25.

Tell your healthcare provider:

- **about all your medical conditions.** Medical conditions can affect your insulin needs and your dose of Humalog Mix75/25.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. Humalog Mix75/25 has not been studied in pregnant or nursing women.
- **about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.** Many medicines can affect your blood

35 sugar levels and insulin needs. Your Humalog Mix75/25 dose may need to change if you
36 take other medicines.

37 Know the medicines you take. Keep a list of your medicines with you to show to all of your
38 healthcare providers.

39

40 **How should I use Humalog Mix75/25?**

41 Talk to your healthcare provider if you have any questions. Your healthcare provider will tell
42 you the right syringes to use with Humalog Mix75/25 vials. Your healthcare provider should
43 show you how to inject Humalog Mix75/25 before you start using it. **Read the User Manual**
44 **that comes with your Humalog Mix75/25 prefilled pen.**

- 45 • **Use Humalog Mix75/25 exactly as prescribed by your healthcare provider.**
- 46 • **Humalog Mix75/25 starts working faster than other insulins that contain regular**
47 **human insulin.** Inject Humalog Mix75/25 fifteen minutes or less before a meal. If you do
48 not plan to eat within 15 minutes, delay the injection until the correct time (15 minutes
49 before eating).
- 50 • **Check your blood sugar levels as told by your healthcare provider.**
- 51 • **Mix Humalog Mix75/25 well before each use.** For Humalog Mix75/25 in a vial, carefully
52 shake or rotate the vial until completely mixed. For prefilled pens, carefully follow the
53 User Manual for instructions on mixing the pen. Humalog Mix75/25 should be cloudy or
54 milky after mixing well.
- 55 • Look at your Humalog Mix75/25 before each injection. If it is not evenly mixed or has
56 solid particles or clumps in it, do not use. Return it to your pharmacy for new Humalog
57 Mix75/25.
- 58 • **Inject your dose of Humalog Mix75/25 under the skin of your stomach area, upper**
59 **arm, upper leg, or buttocks. Never inject Humalog Mix75/25 into a muscle or vein.**
- 60 • **Change (rotate) your injection site with each dose.**
- 61 • **Your insulin needs may change because of:**
 - 62 • illness
 - 63 • stress
 - 64 • other medicines you take
 - 65 • changes in eating
 - 66 • physical activity changes

67 Follow your healthcare provider's instructions to make changes in your insulin dose.

- 68 • **Never mix Humalog Mix75/25 in the same syringe with other insulin products.**
- 69 • **Never use Humalog Mix75/25 in an insulin pump.**
- 70 • **Always carry a quick source of sugar to treat low blood sugar, such as glucose tablets,**
71 **hard candy, or juice.**

72 **What are the possible side effects of Humalog Mix75/25?**

73 **Low Blood Sugar (Hypoglycemia).** Symptoms of low blood sugar include:

- 74 • hunger
- 75 • dizziness
- 76 • feeling shaky or shakiness
- 77 • lightheadedness
- 78 • sweating
- 79 • irritability
- 80 • headache
- 81 • fast heartbeat
- 82 • confusion

83 Low blood sugar symptoms can happen suddenly. Symptoms of low blood sugar may be
84 different for each person and may change from time to time. Severe low blood sugar can cause
85 seizures and death. Low blood sugar may affect your ability to drive a car or use mechanical
86 equipment, risking injury to yourself or others. Know your symptoms of low blood sugar. Low
87 blood sugar can be treated by drinking juice or regular soda or eating glucose tablets, sugar, or
88 hard candy. Follow your healthcare provider's instructions for treating low blood sugar. Talk to
89 your healthcare provider if low blood sugar is a problem for you.

- 91 • **Serious allergic reactions** (whole body allergic reaction). Severe, life-threatening allergic
92 reactions can happen with insulin. Get medical help right away if you develop a rash over
93 your whole body, have trouble breathing, wheezing, a fast heartbeat, or sweating.
- 94 • **Reactions at the injection site** (local allergic reaction). You may get redness, swelling,
95 and itching at the injection site. If you keep having injection site reactions or they are
96 serious, you need to call your healthcare provider. Do not inject insulin into a skin area that
97 is red, swollen, or itchy.
- 98 • **Skin thickens or pits at the injection site (lipodystrophy).** This can happen if you don't
99 change (rotate) your injection sites enough.

100 These are not all the side effects from Humalog Mix75/25. Ask your healthcare provider or
101 pharmacist for more information.

102

103 **How should I store Humalog Mix75/25?**

- 104 • **Store all unopened (unused) Humalog Mix75/25 in the original carton in a**
105 **refrigerator at 36°F to 46°F (2°C to 8°C).** Do not freeze.
- 106 • Do not use Humalog Mix75/25 that has been frozen.
- 107 • Do not use after the expiration date printed on the carton and label.
- 108 • Protect Humalog Mix75/25 from extreme heat, cold or light.

109 **After starting use (open):**

- 110 • **Vials:** Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28
111 days. Keep open vials away from direct heat or light. Throw away an opened vial 28 days
112 after first use, even if there is insulin left in the vial.
- 113 • **Prefilled Pens:** Do not store a prefilled pen that you are using in the refrigerator. Keep at
114 room temperature below 86°F (30°C) for up to 10 days. Throw away a prefilled pen 10
115 days after first use, even if there is insulin left in the pen.

116 **General information about Humalog Mix75/25**

117 Use Humalog Mix75/25 only to treat your diabetes. Do not share it with anyone else, even if
118 they also have diabetes. It may harm them.

119
120 This leaflet summarized the most important information about Humalog Mix75/25. If you would
121 like more information about Humalog Mix75/25 or diabetes, talk with your healthcare provider.
122 You can ask your healthcare provider or pharmacist for information about Humalog Mix75/25
123 that is written for health professionals.

124
125 For questions you may call 1-800-LillyRx (1-800-545-5979) or visit www.humalog.com.

126
127 **What are the ingredients in Humalog Mix75/25?**

128 **Active ingredients:** insulin lispro protamine suspension and insulin lispro.

129
130 **Inactive ingredients:** protamine sulfate, glycerin, dibasic sodium phosphate, metacresol, zinc
131 oxide (zinc ion), phenol and water for injection.

132 Patient Information issued/revised Month DD, YYYY

133 **KwikPens manufactured by**

134 **Eli Lilly and Company, Indianapolis, IN 46285, USA**

135 **Pens manufactured by**

136 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**

137 **Lilly France, F-67640 Fegersheim, France**

138 **Vials manufactured by**

139 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**

140 **Lilly France, F-67640 Fegersheim, France**

141
142 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**

143 **www.humalog.com**

144
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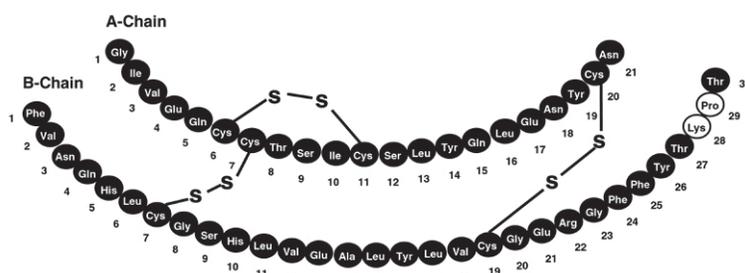
AAD_0027 NL 5542 AMP

HUMALOG[®] Mix50/50[™]
50% INSULIN LISPRO PROTAMINE SUSPENSION AND
50% INSULIN LISPRO INJECTION
(rDNA ORIGIN)
100 UNITS PER ML (U-100)

DESCRIPTION

Humalog[®] Mix50/50[™] [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce insulin lispro. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

Insulin lispro has the following primary structure:



Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

Humalog Mix50/50 vials and Pens contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

Each milliliter of Humalog Mix50/50 injection contains insulin lispro 100 units, 0.19 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg Metacresol, zinc oxide content adjusted to provide 0.0305 mg zinc ion, 0.89 mg phenol, and Water for Injection. Humalog Mix50/50 has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH.

CLINICAL PHARMACOLOGY

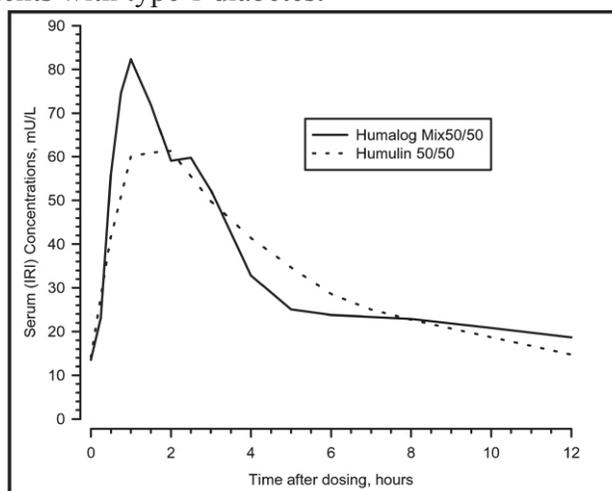
Antidiabetic Activity

The primary activity of insulin, including Humalog Mix50/50, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

36 Insulin lispro, the rapid-acting component of Humalog Mix50/50, has been shown to be
 37 equipotent to Regular human insulin on a molar basis. One unit of Humalog[®] has the same
 38 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
 39 shorter duration.

40 Pharmacokinetics

41 *Absorption* — Studies in nondiabetic subjects and patients with type 1 (insulin-dependent)
 42 diabetes demonstrated that Humalog, the rapid-acting component of Humalog Mix50/50, is
 43 absorbed faster than Regular human insulin (U-100). In nondiabetic subjects given subcutaneous
 44 doses of Humalog ranging from 0.1 to 0.4 U/kg, peak serum concentrations were observed 30 to
 45 90 minutes after dosing. When nondiabetic subjects received equivalent doses of Regular human
 46 insulin, peak insulin concentrations occurred between 50 to 120 minutes after dosing. Similar
 47 results were seen in patients with type 1 diabetes.



48
 49 **Figure 1: Serum Immunoreactive Insulin (IRI) Concentrations, After Subcutaneous**
 50 **Injection of Humalog Mix50/50 or Humulin 50/50 in Healthy Nondiabetic Subjects.**

51 Humalog Mix50/50 has two phases of absorption. The early phase represents insulin lispro and
 52 its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin
 53 lispro protamine suspension. In 30 healthy nondiabetic subjects given subcutaneous doses
 54 (0.3 U/kg) of Humalog Mix50/50, peak serum concentrations were observed 45 minutes to 13.5
 55 hours (median, 60 minutes) after dosing (*see* Figure 1). In patients with type 1 diabetes, peak
 56 serum concentrations were observed 45 minutes to 120 minutes (median, 60 minutes) after
 57 dosing. The rapid absorption characteristics of Humalog are maintained with Humalog Mix50/50
 58 (*see* Figure 1).

59 Direct comparison of Humalog Mix50/50 and Humulin 50/50 was not performed. However, a
 60 cross-study comparison shown in Figure 1 suggests that Humalog Mix50/50 has a more rapid
 61 absorption than Humulin 50/50.

62 *Distribution* — Radiolabeled distribution studies of Humalog Mix50/50 have not been
 63 conducted. However, the volume of distribution following injection of Humalog is identical to
 64 that of Regular human insulin, with a range of 0.26 to 0.36 L/kg.

65 *Metabolism* — Human metabolism studies of Humalog Mix50/50 have not been conducted.
 66 Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of
 67 Humalog Mix50/50, is identical to that of Regular human insulin.

68 *Elimination* — Humalog Mix50/50 has two absorption phases, a rapid and a prolonged phase,
 69 representative of the insulin lispro and insulin lispro protamine suspension components of the

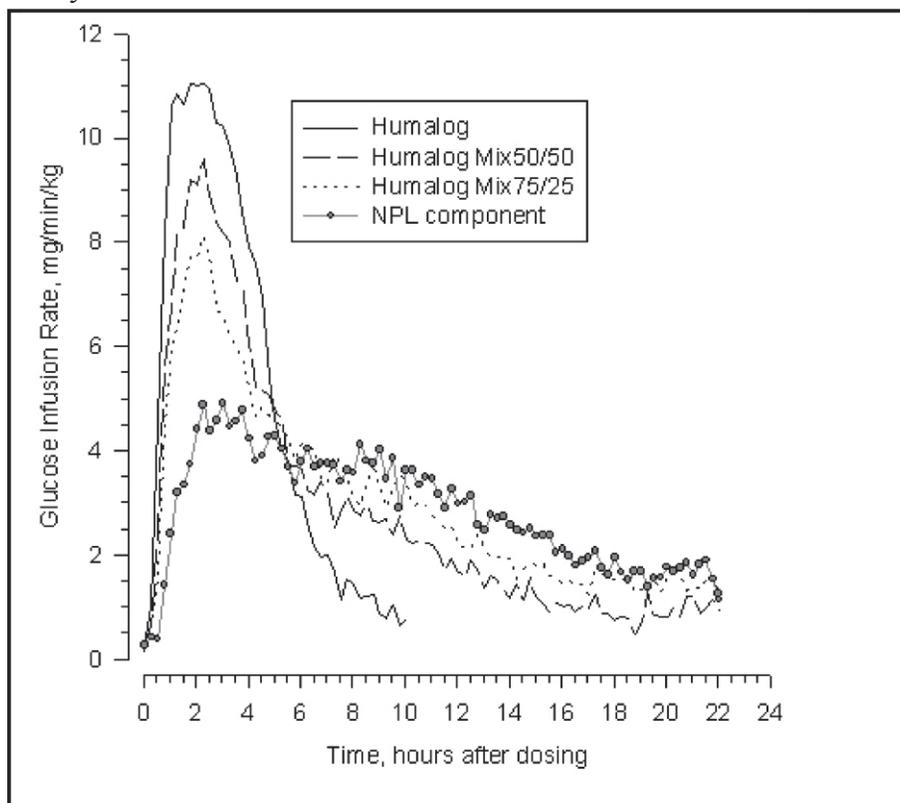
70 mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot
71 be calculated after administration of Humalog Mix50/50 because of the prolonged insulin lispro
72 protamine suspension absorption.

73 **Pharmacodynamics**

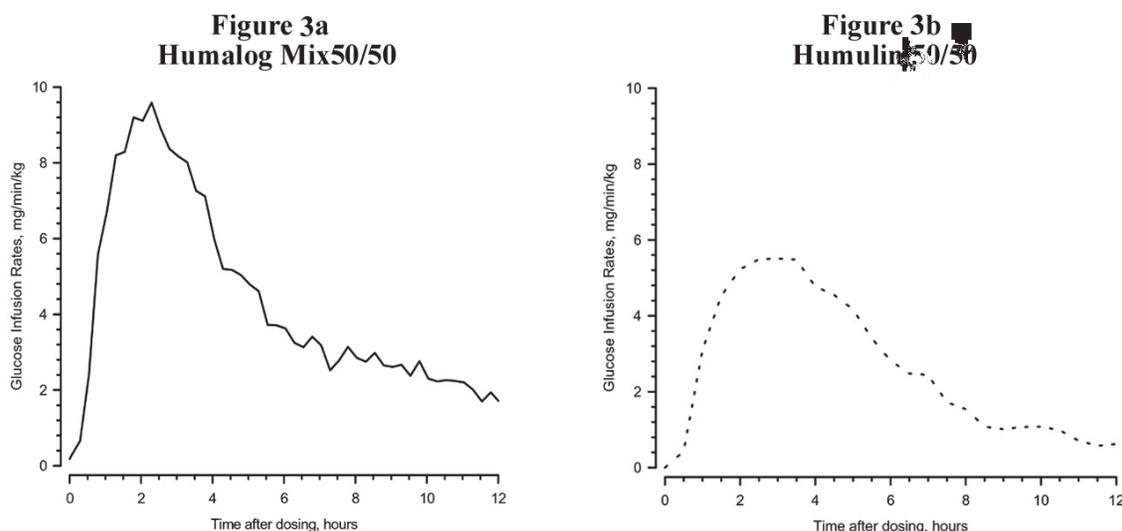
74 Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a
75 more rapid onset of glucose-lowering activity, an earlier peak for glucose-lowering, and a shorter
76 duration of glucose-lowering activity than Regular human insulin. The early onset of activity of
77 Humalog Mix50/50 is directly related to the rapid absorption of Humalog. The time course of
78 action of insulin and insulin analogs, such as Humalog (and hence Humalog Mix50/50), may
79 vary considerably in different individuals or within the same individual. The parameters of
80 Humalog Mix50/50 activity (time of onset, peak time, and duration) as presented in Figures 2
81 and 3 should be considered only as general guidelines. The rate of insulin absorption and
82 consequently the onset of activity is known to be affected by the site of injection, exercise, and
83 other variables (*see General under PRECAUTIONS*).

84 In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and
85 glucose-lowering activity of Humalog, Humalog Mix50/50, Humalog[®] Mix75/25[™], and insulin
86 lispro protamine suspension (NPL component) were compared (*see Figure 2*). Graphs of mean
87 glucose infusion rate versus time showed a distinct insulin activity profile for each formulation.
88 The rapid onset of glucose-lowering activity characteristic of Humalog was maintained in
89 Humalog Mix50/50.

90 Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed.
91 However, a cross-study comparison shown on Figure 3 suggests that Humalog Mix50/50 has a
92 duration of activity that is similar to Humulin 50/50.



94 **Figure 2: Glucose Infusion Rates (A Measure of Insulin Activity) After Injection of**
 95 **Humalog, Humalog Mix50/50, Humalog Mix75/25, or Insulin Lispro Protamine Suspension**
 96 **(NPL Component) in 30 Nondiabetic Subjects.**
 97



98 **Figure 3: Insulin Activity After Subcutaneous Injection of Humalog Mix50/50 and**
 99 **Humulin 50/50 in Nondiabetic Subjects.**
 100

101 Figures 2 and 3 represent insulin activity profiles as measured by glucose clamp studies in
 102 healthy nondiabetic subjects.

103 Figure 2 shows the time activity profiles of Humalog, Humalog Mix75/25, Humalog
 104 Mix50/50, and insulin lispro protamine suspension (NPL component).

105 Figure 3 is a comparison of the time activity profiles of Humalog Mix50/50 (*see* Figure 3a) and
 106 of Humulin 50/50 (*see* Figure 3b) from two different studies.

107 Special Populations

108 *Age and Gender* — Information on the effect of age on the pharmacokinetics of Humalog
 109 Mix50/50 is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and
 110 women administered Humalog Mix50/50 showed no gender differences. In large Humalog
 111 clinical trials, sub-group analysis based on age and gender demonstrated that differences between
 112 Humalog and Regular human insulin in postprandial glucose parameters are maintained across
 113 sub-groups.

114 *Smoking* — The effect of smoking on the pharmacokinetics and pharmacodynamics of
 115 Humalog Mix50/50 has not been studied.

116 *Pregnancy* — The effect of pregnancy on the pharmacokinetics and pharmacodynamics of
 117 Humalog Mix50/50 has not been studied.

118 *Obesity* — The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and
 119 pharmacodynamics of Humalog Mix50/50 has not been studied. In large clinical trials, which
 120 included patients with Body Mass Index up to and including 35 kg/m², no consistent differences
 121 were observed between Humalog and Humulin[®] R with respect to postprandial glucose
 122 parameters.

123 *Renal Impairment* — The effect of renal impairment on the pharmacokinetics and
 124 pharmacodynamics of Humalog Mix50/50 has not been studied. In a study of 25 patients with
 125 type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between
 126 Humalog and Regular human insulin were generally maintained. However, the sensitivity of the

127 patients to insulin did change, with an increased response to insulin as the renal function
128 declined. Careful glucose monitoring and dose reductions of insulin, including Humalog
129 Mix50/50, may be necessary in patients with renal dysfunction.

130 *Hepatic Impairment* — Some studies with human insulin have shown increased circulating
131 levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the
132 pharmacokinetics and pharmacodynamics of Humalog Mix50/50 has not been studied. However,
133 in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the
134 subcutaneous absorption or general disposition of Humalog when compared with patients with
135 no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption
136 and elimination when compared with Regular human insulin. Careful glucose monitoring and
137 dose adjustments of insulin, including Humalog Mix50/50, may be necessary in patients with
138 hepatic dysfunction.

139 **INDICATIONS AND USAGE**

140 Humalog Mix50/50, a mixture of 50% insulin lispro protamine suspension and 50% insulin
141 lispro injection, (rDNA origin), is indicated in the treatment of patients with diabetes mellitus for
142 the control of hyperglycemia. Based on cross-study comparisons of the pharmacodynamics of
143 Humalog Mix50/50 and Humulin 50/50, it is likely that Humalog Mix50/50 has a more rapid
144 onset of glucose-lowering activity compared with Humulin 50/50 while having a similar duration
145 of action. This profile is achieved by combining the rapid onset of Humalog with the
146 intermediate action of insulin lispro protamine suspension.

147 **CONTRAINDICATIONS**

148 Humalog Mix50/50 is contraindicated during episodes of hypoglycemia and in patients
149 sensitive to insulin lispro or any of the excipients contained in the formulation.

150 **WARNINGS**

151 **Humalog differs from Regular human insulin by its rapid onset of action as well as a**
152 **shorter duration of activity. Therefore, the dose of Humalog Mix50/50 should be given**
153 **within 15 minutes before a meal.**

154 **Hypoglycemia is the most common adverse effect associated with the use of insulins,**
155 **including Humalog Mix50/50. As with all insulins, the timing of hypoglycemia may differ**
156 **among various insulin formulations. Glucose monitoring is recommended for all patients**
157 **with diabetes.**

158 **Any change of insulin should be made cautiously and only under medical supervision.**
159 **Changes in insulin strength, manufacturer, type (e.g., Regular, NPH, analog), species, or**
160 **method of manufacture may result in the need for a change in dosage.**

161 **PRECAUTIONS**

162 **General**

163 Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated
164 with the use of all insulins. Because of differences in the action of Humalog Mix50/50 and other
165 insulins, care should be taken in patients in whom such potential side effects might be clinically
166 relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using
167 potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).
168 Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated
169 with the use of all insulins.

170 As with all insulin preparations, the time course of Humalog Mix50/50 action may vary in
171 different individuals or at different times in the same individual and is dependent on site of
172 injection, blood supply, temperature, and physical activity.

173 Adjustment of dosage of any insulin may be necessary if patients change their physical activity
174 or their usual meal plan. Insulin requirements may be altered during illness, emotional
175 disturbances, or other stress.

176 **Hypoglycemia** — As with all insulin preparations, hypoglycemic reactions may be associated
177 with the administration of Humalog Mix50/50. Rapid changes in serum glucose concentrations
178 may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value.
179 Early warning symptoms of hypoglycemia may be different or less pronounced under certain
180 conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as
181 beta-blockers, or intensified diabetes control.

182 **Renal Impairment** — As with other insulins, the requirements for Humalog Mix50/50 may be
183 reduced in patients with renal impairment.

184 **Hepatic Impairment** — Although impaired hepatic function does not affect the absorption or
185 disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including
186 Humalog Mix50/50, may be necessary.

187 **Allergy** — Local Allergy — As with any insulin therapy, patients may experience redness,
188 swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to
189 a few weeks. In some instances, these reactions may be related to factors other than insulin, such
190 as irritants in the skin cleansing agent or poor injection technique.

191 Systemic Allergy — Less common, but potentially more serious, is generalized allergy to
192 insulin, which may cause rash (including pruritus) over the whole body, shortness of breath,
193 wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized
194 allergy, including anaphylactic reaction, may be life threatening. Localized reactions and
195 generalized myalgias have been reported with the use of cresol as an injectable excipient.

196 Antibody Production — In clinical trials, antibodies that cross-react with human insulin and
197 insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures
198 treatment groups.

199 **Information for Patients**

200 Patients should be informed of the potential risks and advantages of Humalog Mix50/50 and
201 alternative therapies. Patients should not mix Humalog Mix50/50 with any other insulin. They
202 should also be informed about the importance of proper insulin storage, injection technique,
203 timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose
204 monitoring, periodic hemoglobin A_{1c} testing, recognition and management of hypo- and
205 hyperglycemia, and periodic assessment for diabetes complications.

206 Patients should be advised to inform their physician if they are pregnant or intend to become
207 pregnant.

208 Refer patients to the Patient Information leaflet for information on normal appearance, timing
209 of dosing (within 15 minutes before a meal), storing, and common adverse effects.

210 For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read
211 the Patient Information leaflet that accompanies the drug product and the User Manual that
212 accompanies the delivery device and re-read them each time the prescription is renewed. Patients
213 should be instructed on how to properly use the delivery device, prime the Pen, and properly
214 dispose of needles. Patients should be advised not to share their Pens with others.

215 **Laboratory Tests**

216 As with all insulins, the therapeutic response to Humalog Mix50/50 should be monitored by
217 periodic blood glucose tests. Periodic measurement of hemoglobin A_{1c} is recommended for the
218 monitoring of long-term glycemic control.

219 **Drug Interactions**

220 Insulin requirements may be increased by medications with hyperglycemic activity such as
221 corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral
222 contraceptives, phenothiazines, and thyroid replacement therapy.

223 Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity
224 or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics,
225 certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme
226 inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of
227 pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the
228 symptoms of hypoglycemia in some patients.

229 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

230 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
231 Humalog, Humalog Mix75/25, or Humalog Mix50/50. Insulin lispro was not mutagenic in a
232 battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA
233 synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test).
234 There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

235 **Pregnancy**

236 *Teratogenic Effects — Pregnancy Category B* — Reproduction studies with insulin lispro have
237 been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times,
238 respectively, the average human dose (40 units/day) based on body surface area. The results have
239 revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are,
240 however, no adequate and well-controlled studies with Humalog, Humalog Mix75/25, or
241 Humalog Mix50/50 in pregnant women. Because animal reproduction studies are not always
242 predictive of human response, this drug should be used during pregnancy only if clearly needed.

243 **Nursing Mothers**

244 It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many
245 drugs, including human insulin, are excreted in human milk. For this reason, caution should be
246 exercised when Humalog Mix50/50 is administered to a nursing woman. Patients with diabetes
247 who are lactating may require adjustments in Humalog Mix50/50 dose, meal plan, or both.

248 **Pediatric Use**

249 Safety and effectiveness of Humalog Mix50/50 in patients less than 18 years of age have not
250 been established.

251 **Geriatric Use**

252 Clinical studies of Humalog Mix50/50 did not include sufficient numbers of patients aged 65
253 and over to determine whether they respond differently than younger patients. In general, dose
254 selection for an elderly patient should take into consideration the greater frequency of decreased
255 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this
256 population.

ADVERSE REACTIONS

Clinical studies comparing Humalog Mix50/50 with human insulin mixtures did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole — allergic reactions (*see* PRECAUTIONS).

Skin and Appendages — injection site reaction, lipodystrophy, pruritus, rash.

Other — hypoglycemia (*see* WARNINGS and PRECAUTIONS).

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

Table 1* : Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-Study Comparison)

Insulin Products	Dose, U/kg	Time of Peak Activity, Hours After Dosing	Percent of Total Activity Occurring in the First 4 Hours
Humalog	0.3	2.4 (0.8 - 4.3)	70% (49 - 89%)
Humulin R	0.32 (0.26 - 0.37)	4.4 (4.0 - 5.5)	54% (38 - 65%)
Humalog Mix75/25	0.3	2.6 (1.0 - 6.5)	35% (21 - 56%)
Humulin 70/30	0.3	4.4 (1.5 - 16)	32% (14 - 60%)
Humalog Mix50/50	0.3	2.3 (0.8 - 4.8)	45% (27 - 69%)
Humulin 50/50	0.3	3.3 (2.0 - 5.5)	44% (21 - 60%)
NPH	0.32 (0.27 - 0.40)	5.5 (3.5 - 9.5)	14% (3.0 - 48%)
NPL component	0.3	5.8 (1.3 - 18.3)	22% (6.3 - 40%)

* The information supplied in Table 1 indicates when peak insulin activity can be expected and the percent of the total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.

Humalog Mix50/50 is intended only for subcutaneous administration. Humalog Mix50/50 should not be administered intravenously. Dosage regimens of Humalog Mix50/50 will vary among patients and should be determined by the healthcare provider familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown to be equipotent to Regular human insulin on a molar basis. One unit of Humalog has the same

284 glucose-lowering effect as one unit of Regular human insulin, but its effect is more rapid and of
 285 shorter duration. The quicker glucose-lowering effect of Humalog is related to the more rapid
 286 absorption rate of insulin lispro from subcutaneous tissue.

287 Direct comparison between Humalog Mix50/50 and Humulin 50/50 was not performed.
 288 However, a cross-study comparison shown in Figure 3 suggests that Humalog Mix50/50 has a
 289 duration of activity that is similar to Humulin 50/50.

290 The rate of insulin absorption and consequently the onset of activity are known to be affected
 291 by the site of injection, exercise, and other variables. As with all insulin preparations, the time
 292 course of action of Humalog Mix50/50 may vary considerably in different individuals or within
 293 the same individual. Patients must be educated to use proper injection techniques.

294 Humalog Mix50/50 should be inspected visually before use. Humalog Mix50/50 should be
 295 used only if it appears uniformly cloudy after mixing. Humalog Mix50/50 should not be used
 296 after its expiration date.

297 HOW SUPPLIED

298 Humalog Mix50/50 [50% insulin lispro protamine suspension and 50% insulin lispro injection,
 299 (rDNA origin)] is available in the following package sizes: each presentation containing 100
 300 units insulin lispro per mL (U-100).

301

10 mL vials	NDC 0002-7512-01 (VL-7512)
5 x 3 mL disposable insulin delivery devices (Pen)	NDC 0002-8793-59 (HP-8793)
5 x 3 mL disposable insulin delivery devices (KwikPen™)	NDC 0002-8798-59 (HP-8798)

302

303 *Storage* — Humalog Mix50/50 should be stored in a refrigerator [2° to 8°C (36° to 46°F)], but
 304 not in the freezer. Do not use Humalog Mix50/50 if it has been frozen. Unrefrigerated [below
 305 30°C (86°F)] vials must be used within 28 days or be discarded, even if they still contain
 306 Humalog Mix50/50. Unrefrigerated [below 30°C (86°F)] Pens, and KwikPens must be used
 307 within 10 days or be discarded, even if they still contain Humalog Mix50/50. Protect from direct
 308 heat and light. See table below:

309

	Not In-Use (Unopened) Room Temperature [Below 30°C (86°F)]	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature [Below 30°C (86°F)]
10 mL Vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL Pen and KwikPen (disposable)	10 days	Until expiration date	10 days. Do not refrigerate.

310

311 Literature issued/revised Month DD, YYYY

312

313

314

KwikPens manufactured by
Eli Lilly and Company, Indianapolis, IN 46285, USA
Pens manufactured by

315 **Eli Lilly and Company, Indianapolis, IN 46285, USA**
316 **Vials manufactured by**
317 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
318 **Lilly France, F-67640 Fegersheim, France**
319
320 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**
321
322 **www.humalog.com**
323

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324

Patient Information

Humalog[®] (HU-ma-log) Mix50/50[™] 50% insulin lispro protamine suspension and 50% insulin lispro injection (rDNA origin)

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. Your insulin dose and the time you take your dose can change with different types of insulin.

Make sure you have the right type and strength of insulin prescribed for you.

Read the Patient Information that comes with Humalog Mix50/50 before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider if you have questions about managing your diabetes.

What is Humalog Mix50/50?

Humalog Mix50/50 is a mixture of fast-acting and longer-acting man-made insulins. Humalog Mix50/50 is used to control high blood sugar (glucose) in people with diabetes.

Humalog Mix50/50 comes in:

- 10 mL vials (bottles) for use with a syringe
- Prefilled pens

Who should not take Humalog Mix50/50?

Do not take Humalog Mix50/50 if:

- your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Humalog Mix50/50.
- you are allergic to anything in Humalog Mix50/50. See the end of this leaflet for a complete list of ingredients in Humalog Mix50/50.

Tell your healthcare provider:

- **about all your medical conditions.** Medical conditions can affect your insulin needs and your dose of Humalog Mix50/50.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. Humalog Mix50/50 has not been studied in pregnant or nursing women.
- **about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.** Many medicines can affect your blood

35 sugar levels and insulin needs. Your Humalog Mix50/50 dose may need to change if you
36 take other medicines.

37 Know the medicines you take. Keep a list of your medicines with you to show to all of your
38 healthcare providers.

39

40 **How should I use Humalog Mix50/50?**

41 Talk to your healthcare provider if you have any questions. Your healthcare provider will tell
42 you the right syringes to use with Humalog Mix50/50 vials. Your healthcare provider should
43 show you how to inject Humalog Mix50/50 before you start using it. **Read the User Manual**
44 **that comes with your Humalog Mix50/50 prefilled pen.**

- 45 • **Use Humalog Mix50/50 exactly as prescribed by your healthcare provider.**
- 46 • **Humalog Mix50/50 starts working faster than other insulins that contain regular**
47 **human insulin.** Inject Humalog Mix50/50 fifteen minutes or less before a meal. If you do
48 not plan to eat within 15 minutes, delay the injection until the correct time (15 minutes
49 before eating).
- 50 • **Check your blood sugar levels as told by your healthcare provider.**
- 51 • **Mix Humalog Mix50/50 well before each use.** For Humalog Mix50/50 in a vial, carefully
52 shake or rotate the vial until completely mixed. For prefilled pens, carefully follow the
53 User Manual for instructions on mixing the pen. Humalog Mix50/50 should be cloudy or
54 milky after mixing well.
- 55 • Look at your Humalog Mix50/50 before each injection. If it is not evenly mixed or has
56 solid particles or clumps in it, do not use. Return it to your pharmacy for new Humalog
57 Mix50/50.
- 58 • **Inject your dose of Humalog Mix50/50 under the skin of your stomach area, upper**
59 **arm, upper leg, or buttocks. Never inject Humalog Mix50/50 into a muscle or vein.**
- 60 • **Change (rotate) your injection site with each dose.**
- 61 • **Your insulin needs may change because of:**
 - 62 • illness
 - 63 • stress
 - 64 • other medicines you take
 - 65 • changes in eating
 - 66 • physical activity changes

67 Follow your healthcare provider's instructions to make changes in your insulin dose.

- 68 • **Never mix Humalog Mix50/50 in the same syringe with other insulin products.**
- 69 • **Never use Humalog Mix50/50 in an insulin pump.**
- 70 • **Always carry a quick source of sugar to treat low blood sugar, such as glucose tablets,**
71 **hard candy, or juice.**

72 **What are the possible side effects of Humalog Mix50/50?**

73 **Low Blood Sugar (Hypoglycemia).** Symptoms of low blood sugar include:

- 74 • hunger
- 75 • dizziness
- 76 • feeling shaky or shakiness
- 77 • lightheadedness
- 78 • sweating
- 79 • irritability
- 80 • headache
- 81 • fast heartbeat
- 82 • confusion

83 Low blood sugar symptoms can happen suddenly. Symptoms of low blood sugar may be
84 different for each person and may change from time to time. Severe low blood sugar can cause
85 seizures and death. Low blood sugar may affect your ability to drive a car or use mechanical
86 equipment, risking injury to yourself or others. Know your symptoms of low blood sugar. Low
87 blood sugar can be treated by drinking juice or regular soda or eating glucose tablets, sugar, or
88 hard candy. Follow your healthcare provider's instructions for treating low blood sugar. Talk to
89 your healthcare provider if low blood sugar is a problem for you.

- 91 • **Serious allergic reactions** (whole body allergic reaction). Severe, life-threatening allergic
92 reactions can happen with insulin. Get medical help right away if you develop a rash over
93 your whole body, have trouble breathing, wheezing, a fast heartbeat, or sweating.
- 94 • **Reactions at the injection site** (local allergic reaction). You may get redness, swelling,
95 and itching at the injection site. If you keep having injection site reactions or they are
96 serious, you need to call your healthcare provider. Do not inject insulin into a skin area that
97 is red, swollen, or itchy.
- 98 • **Skin thickens or pits at the injection site (lipodystrophy).** This can happen if you don't
99 change (rotate) your injection sites enough.

100 These are not all the side effects from Humalog Mix50/50. Ask your healthcare provider or
101 pharmacist for more information.

102

103 **How should I store Humalog Mix50/50?**

- 104 • **Store all unopened (unused) Humalog Mix50/50 in the original carton in a**
105 **refrigerator at 36°F to 46°F (2°C to 8°C).** Do not freeze.
- 106 • Do not use Humalog Mix50/50 that has been frozen.
- 107 • Do not use after the expiration date printed on the carton and label.
- 108 • Protect Humalog Mix50/50 from extreme heat, cold or light.

109 **After starting use (open):**

- 110 • **Vials:** Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28
111 days. Keep open vials away from direct heat or light. Throw away an opened vial 28 days
112 after first use, even if there is insulin left in the vial.
- 113 • **Prefilled Pens:** Do not store a prefilled pen that you are using in the refrigerator. Keep at
114 room temperature below 86°F (30°C) for up to 10 days. Throw away a prefilled pen 10
115 days after first use, even if there is insulin left in the pen.

116 **General information about Humalog Mix50/50**

117 Use Humalog Mix50/50 only to treat your diabetes. Do not share it with anyone else, even if
118 they also have diabetes. It may harm them.

119
120 This leaflet summarized the most important information about Humalog Mix50/50. If you would
121 like more information about Humalog Mix50/50 or diabetes, talk with your healthcare provider.
122 You can ask your healthcare provider or pharmacist for information about Humalog Mix50/50
123 that is written for health professionals.

124
125 For questions you may call 1-800-LillyRx (1-800-545-5979) or visit www.humalog.com.

126
127 **What are the ingredients in Humalog Mix50/50?**

128 **Active ingredients:** insulin lispro protamine suspension and insulin lispro.

129
130 **Inactive ingredients:** protamine sulfate, glycerin, dibasic sodium phosphate, metacresol, zinc
131 oxide (zinc ion), phenol and water for injection.

132 Patient Information issued/revised Month DD, YYYY

133 **KwikPens manufactured by**
134 **Eli Lilly and Company, Indianapolis, IN 46285, USA**
135 **Pens manufactured by**
136 **Eli Lilly and Company, Indianapolis, IN 46285, USA**
137 **Vials manufactured by**
138 **Eli Lilly and Company, Indianapolis, IN 46285, USA or**
139 **Lilly France, F-67640 Fegersheim, France**
140
141 **for Eli Lilly and Company, Indianapolis, IN 46285, USA**
142
143 **www.humalog.com**
144

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Disposable Insulin Delivery Device User Manual



Introduction

The KwikPen™ is designed for ease of use. It is a disposable insulin delivery device ("insulin Pen") containing 3 mL (300 units) of U-100 insulin. You can inject from 1 to 60 units of insulin in one injection. You can dial your dose one unit at a time. If you dial too many units, you can dial backwards to correct the dose without wasting any insulin.

Before using the KwikPen, read the entire manual completely and follow the directions carefully. If you do not follow these directions completely, you may get too much or too little insulin.

DO NOT USE your KwikPen if any part appears broken or damaged. Contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or your healthcare professional for a replacement Pen. Always carry an extra Pen in case yours is lost or damaged.

This Pen is not recommended for use by the blind or visually impaired persons without the assistance of a person trained in the proper use of the product.

Preparing the KwikPen

Important Notes

- Read and follow the directions provided in the *Patient Information Sheet*.
- Check the label on your Pen before each injection for the expiration date and to make sure you are using the correct type of insulin.
- Your healthcare professional has prescribed the best type of insulin for you. **Any changes in insulin therapy should be made only under medical supervision.**
- The KwikPen is recommended for use with Becton, Dickinson and Company pen needles.
- Be sure the needle is completely attached to the Pen before use.
- Do not share your Pen or needles.
- Keep these directions for future reference.

Frequently Asked Questions about Preparing the KwikPen

- What should my insulin look like?** Some insulins are cloudy while others are clear. Be sure to refer to your *Patient Information Sheet* for the appearance of your specific insulin.
- Why should I use a new needle for each injection?** This will help ensure sterility. If needles are reused, you may get the wrong amount of insulin, a clogged needle or a jammed Pen.
- What should I do if I am not sure how much insulin remains in my cartridge?** Hold the Pen with the needle end pointing down. The scale on the clear Cartridge Holder shows an estimate of the number of units remaining. **These numbers should NOT be used for measuring an insulin dose.**

Priming the KwikPen

Important Notes

- Prime every time.** The Pen must be primed to a stream of insulin before each injection to make sure the Pen is ready to dose.
- If you do not prime, you may get too much or too little insulin.**

Frequently Asked Questions about Priming

- Why should I prime my KwikPen before each dose?**
 - Ensures that the Pen is ready to dose.
 - Confirms that a stream of insulin comes out of the tip of the needle when you push the Dose Knob in.
 - Removes air that may collect in the needle or insulin cartridge during normal use.
- What should I do if I cannot completely push in the Dose Knob when priming the KwikPen?**
 - Attach a new needle.
 - Prime the Pen.
- What should I do if I see an air bubble in the cartridge?** You need to prime the Pen. Remember, do not store the Pen with the needle attached as this may cause air bubbles to collect in the insulin cartridge. A small air bubble will not affect your dose and you can continue to take your dose as usual.

Injecting Your Dose

Important Notes

- Follow the instructions for sanitary injection technique recommended by your healthcare professional.
- Make sure you receive your complete dose by pushing and holding the dose knob in and **count to 5 slowly** before removing the needle. If insulin is leaking from the Pen you may not have held it in your skin long enough.
- The Pen will not allow you to dial more than the number of units left in the Pen.
- If your dose is greater than the number of units left in the Pen, you may either inject the amount remaining in your current Pen and then use a new Pen to complete your dose OR inject the full dose with a new Pen.
- Do not attempt to inject your insulin by **turning** the Dose Knob. You will NOT receive your insulin by turning the Dose Knob. You must **PUSH** the Dose Knob straight in for the dose to be delivered.
- Do not attempt to change the dose while injecting.
- The directions regarding needle handling are not intended to replace local, healthcare professional or institutional policies.
- Remove the needle after completing each injection.

Injecting Your Dose (continued)

Frequently Asked Questions about Injecting Your Dose

- Why is it difficult to push the Dose Knob when I try to inject?**
 - Your needle may be clogged. Try attaching a new needle. When you do this you may see insulin come out of the needle. Then prime the Pen.
 - Pressing the Dose Knob quickly may make the Dose Knob harder to push. Pressing the Dose Knob more slowly may make it easier.
 - Using a larger diameter needle will make it easier to push the Dose Knob during your injection. See your healthcare professional to determine which needle size is best for you.
 - If the Dose Knob continues to be difficult to push after following the steps above, try the steps below under "What should I do if my KwikPen is jammed?".
- What should I do if my KwikPen is jammed?** Your Pen may be jammed if it is difficult to inject a dose or dial a dose. To clear the jam:
 - Attach a new needle. When you do this you may see insulin come out of the needle.
 - Prime the Pen.
 - Dial your dose and inject.
 - If the Dose Knob is still difficult to push, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979).
- Why is insulin leaking from the needle after I finished injecting my dose?** You may have removed the needle from your skin too quickly.
 - Make sure you see a 0 in the Dose Window to confirm you received the complete dose.
 - For the next dose, push and hold the Dose Knob in and count to 5 slowly before removing the needle.
- What should I do if my dose is dialed and the Dose Knob is accidentally pushed in without a needle attached?**
 - Dial back to zero.
 - Attach a new needle. When you do this you may see insulin come out of the needle.
 - Prime the Pen.
 - Dial your dose and inject.
- What should I do if I dial a wrong dose (too high or too low)?** Turn the Dose Knob backward or forward to correct the dose before injecting.
- What should I do if I see insulin leaking from the KwikPen needle while dialing the dose or correcting the dose?** Do not inject the dose because you may not get your complete dose. Dial the Pen down to zero and prime the Pen again (see "Priming the KwikPen" steps 2 A-D). Dial your dose and inject.
- What should I do if my full dose cannot be dialed?** The Pen will not allow you to dial a dose greater than the number of insulin units remaining in the cartridge. For example, if you need 31 units and only 25 units remain in the cartridge you will not be able to dial past 25. Do not attempt to dial past this point. You may either:
 - Inject the partial dose and then inject the remaining dose using a new Pen.
 - or
 - Inject the full dose with a new Pen.
- Why can I not dial the dose to use the small amount of insulin that remains in my cartridge?** The Pen is designed to deliver at least 300 units of insulin. The Pen design prevents the cartridge from being completely emptied because the small amount of insulin that remains in the cartridge cannot be delivered.

Storage and Disposal

Important Notes

- Refer to the *Patient Information Sheet* for complete insulin storage instructions.
- Pens that have not been used should be stored in a refrigerator but not in a freezer. Do not use a Pen if it has been frozen.
- Do not store the Pen with the needle attached. If the needle is remains attached, insulin may leak from the Pen, insulin may dry inside the needle causing the needle to clog, or air bubbles may form inside the cartridge.
- The Pen you are currently using should be kept at room temperature and away from heat and light.
- Keep the Pen out of the reach of children.
- Dispose of used needles in a puncture-resistant container or as directed by your healthcare professional.
- Dispose of used Pens as instructed by your healthcare professional and without the needle attached.

Use the space below to keep track of how long you should use each Pen in the carton. Once you start using a KwikPen it must be thrown out after the number of days listed in your *Patient Information Sheet*, even if there is insulin remaining in the Pen. Record the date you start using a Pen, find the number of days that the KwikPen should be used in the *Patient Information Sheet* and determine the date the Pen should be thrown out. Record the dates in the space provided below.

Pen 1 – First used on _____ DATE _____ Throw out on _____ DATE _____

Pen 2 – First used on _____ DATE _____ Throw out on _____ DATE _____

Pen 3 – First used on _____ DATE _____ Throw out on _____ DATE _____

Pen 4 – First used on _____ DATE _____ Throw out on _____ DATE _____

Pen 5 – First used on _____ DATE _____ Throw out on _____ DATE _____

Example:

Pen 1 – First used on _____ DATE _____ + Number of days you should use KwikPen (from *Patient Information Sheet*) = _____
Throw out on _____ DATE _____

If you have any questions or problems with your KwikPen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or your healthcare professional for assistance.

For more information on KwikPen and insulin, please visit our website at www.humalog.com

Manufactured by:
Eli Lilly and Company
Indianapolis, IN 46205, USA

Patents pending for KwikPen™.
Copyright © 2006, Eli Lilly and Company. All rights reserved.

The KwikPen meets the current dose accuracy and functional requirements of ISO 11606-1:2000

Getting Ready

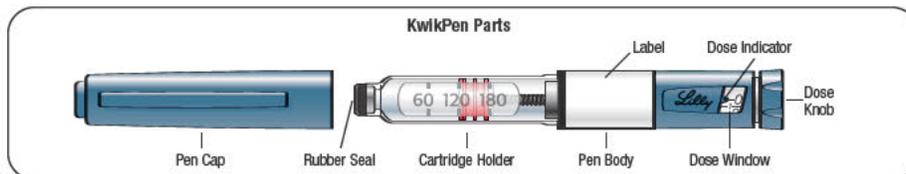
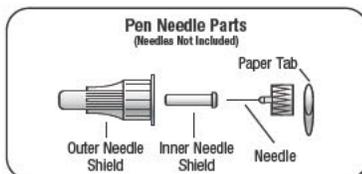
Make sure you have the following items:

KwikPen

New Pen Needle

Alcohol Swab

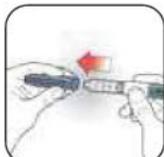
Pen Parts KwikPen, and Needle* Assembly *sold separately



Follow these instructions for each injection

1. Preparing the KwikPen

A.



Pull Pen Cap to remove. Be sure to check your insulin for:

- Type
- Expiration date
- Appearance

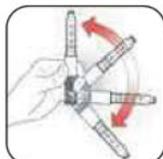
Use an alcohol swab to wipe the Rubber Seal on the end of the Cartridge Holder.

B.



For Cloudy Insulin only:

Gently roll the Pen ten times and invert the Pen ten times. The insulin should look evenly mixed.



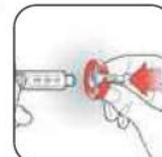
Note: Some insulins are meant to be cloudy (e.g., the insulin mixtures) while others are meant to be clear. Be sure to refer to the *Patient Information Sheet* for the appearance of your specific insulin.

C.



Remove Paper Tab from Outer Needle Shield.

D.

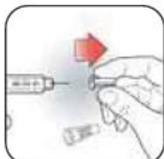


Push capped needle **straight** onto the Pen. Screw needle on until secure.

2. Priming the KwikPen

Caution: If you do not prime before each injection, you may get too much or too little insulin.

A.



Pull off Outer Needle Shield. **Do not** throw away. Pull off Inner Needle Shield and throw away.

B.



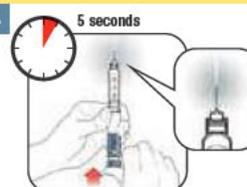
Dial 2 Units by turning the Dose Knob.

C.



Point Pen up. Tap Cartridge Holder to collect air at top.

D.



With needle pointing up, push Dose Knob in until it stops and 0 is seen in the Dose Window.

Hold Dose Knob in and **count to 5 slowly**.

Priming is complete when a stream of insulin appears from the needle tip and you have **counted to 5 slowly**.

If a stream of insulin does not appear, repeat priming steps 2B thru 2D up to four times. If the Pen still does not prime, change the needle and repeat the priming steps above.

Note: If you do not see a stream of insulin from the tip of the needle and the Dose Knob becomes hard to push, then change the needle and prime the Pen.

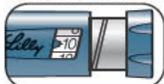
3. Injecting Your Dose

A.



Turn Dose Knob to the number of units you need to inject. If you dial too many units, you can correct the dose by dialing backwards.

Example: 10 units shown.



Example: 15 units shown.



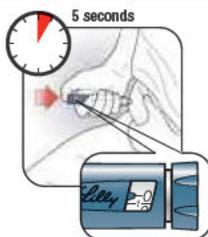
The **even** numbers are printed on the dial. The **odd** numbers, after the number one, are shown as full lines.

B.



Insert needle into skin using injection technique recommended by your healthcare professional.

Place your thumb on the Dose Knob and push firmly until the Dose Knob stops.

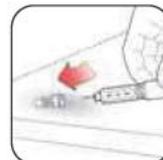


To deliver the full dose, hold Dose Knob in and **count to 5 slowly**. Remove needle from skin.

Note: Check to make sure you see 0 in the Dose Window to confirm you received the complete dose.

Note: The Pen will not allow you to dial more than the number of units left in the Pen.

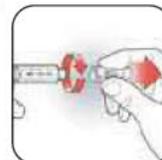
C.



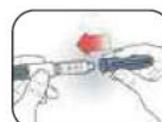
Carefully replace the Outer Needle Shield.

Note: Remove the needle after each injection to keep air out of the cartridge. Do not store the Pen with the needle attached.

D.



Unscrew the capped needle and dispose of as directed by your healthcare professional.



Replace Pen Cap.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021018Orig1s034

CHEMISTRY REVIEW(S)

NDA 20-563
NDA 21-017
NDA 21-018

DIVISION OF POST-MARKETING
Review of Chemistry, Manufacturing, and Controls

NDA 20-563/SCP-075
NDA 21-017/SCP-040
NDA 21-018/SCP-034

DATE REVIEWED: 2/5/07

REVIEW #: 1

REVIEWER: Donald N. Klein, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Prior-Approval			
(EDR and paper)	10/5/06	10/10/06	11/28/06
Consult to CDRH	11/21/06	11/21/06	<i>n/a</i>
Consult to OSE	11/26/06	11/26/06	<i>n/a</i>
Request for samples	11/28/06	<i>n/a</i>	<i>n/a</i>
Ack. Letter	11/30/06	11/30/06	<i>n/a</i>
Samples received	12/8/06	<i>n/a</i>	<i>n/a</i>
CDRH Consult	1/18/07	1/18/07	<i>n/a</i>

NAME & ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:

NDA 20-563:

Proprietary: Humalog[®]
Established (USAN)(1994): Insulin Lispro, USP.
Code: LY275585.

NDA 21-017:

Proprietary: Humalog[®] 75/25.
Established (USAN): 25% Insulin Lispro, USP, and 75% Insulin Lispro Protamine Sulfate.

NDA 21-018:

Proprietary: Humalog[®] 50/50.
Established (USAN): 50% Insulin Lispro, USP, and 50% Insulin Lispro Protamine Sulfate.

INDICATION: Hyperglycemia.

DOSAGE FORM: Injectable.

STRENGTHS:

NDA 20-563: 100 Units/mL.

NDA 21-017: 100 Units/mL.

NDA 21-018: 100 Units/mL.

ROUTE OF ADMINISTRATION: Subcutaneous.

Rx/OTC: Rx.

SPECIAL PRODUCTS: __ Yes **xx** No

SUPPORTING DOCUMENTS: None.

CONSULTS: CDRH (submitted 11/21/06; completed 1/18/07); OSE (submitted 11/26/06).

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, and MOLECULAR WEIGHT:

NDA 20-563:

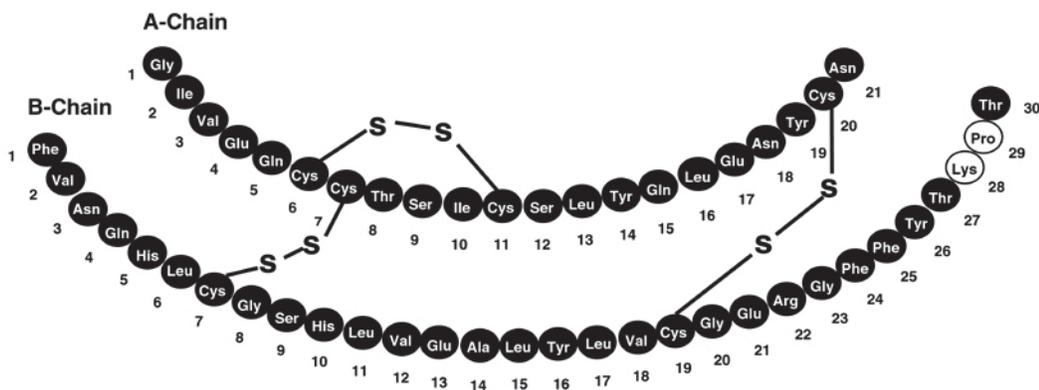
Proprietary: Humalog[®]

Chemical Name: Insulin (human), 28^B-L-lysine-29^B-L-proline-

Molecular formula: C₂₅₇H₃₈₃N₆₅O₇₇S₆.

MW: 5807.57 daltons.

CAS: 133107-64-9.



NDA 21-017:

Proprietary: Humalog[®] 75/25.

Chemical Name: 25% Insulin Lispro, USP, and 75% Insulin Lispro Protamine Sulfate.

CAS (protamine sulfate): 9009-65-8.

NDA 21-018:

Proprietary: Humalog[®] 50/50.

Chemical Name: 25% Insulin Lispro, USP, and 75% Insulin Lispro Protamine Sulfate.

CAS (protamine sulfate): 9009-65-8.

SUPPLEMENT PROVIDES FOR: An additional disposable insulin delivery device
[REDACTED]^{(b)(4)} for use with Eli Lilly's Humalog[®]
3 mL cartridges.

CONCLUSION: Recommend Approval from the CMC standpoint.

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Donald Klein
2/5/2007 12:56:02 PM
CHEMIST

Sending as requested on 12/5/07.

Jim Vidra
2/5/2007 05:30:36 PM
CHEMIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021018Orig1s034

OTHER REVIEW(S)

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE & EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)**

DATE RECEIVED: 05/07/2007 DATE OF DOCUMENT: 05/02/2008	DESIRED COMPLETION DATE: 07/06/2007	OSE Review #: 2007-1010
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TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

THROUGH: Linda Kim-Jung, Team Leader
Denise Toyer, Pharm.D., Deputy Division Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Kellie Taylor, Pharm.D., M.P.H., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:
Humalog® KwikPen™
[insulin lispro injection, (rDNA origin)]
Humalog® Mix75/25™ KwikPen™
[75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)]
Humalog® Mix50/50™ KwikPen™
[50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)]

NDA#: 20-563/S-075, 21-017/S-040, 21-018/S-034

SPONSOR: Eli Lilly

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary names, Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen with respect to potential confusion with existing drug names because of look or sound-alike similarity. DMETS is concerned that the introduction of the prefilled pen device may lead to medication errors, but believes that the future discontinuation of the currently marketed disposable Pen products and the measures described in the Sponsor's Complete Response submission should help to minimize this risk. However, DMETS notes that the modifier, KwikPen, could be construed as promotional. Although DMETS does not have reason to believe that the promotional nature of the proprietary name is likely to present a source of medication error in the usual practice setting, the concerns regarding the promotional nature of the name are described on page 11 of this review for the Division's consideration. If the name is considered by the Division to be too promotional, we encourage the Sponsor to submit a new proposed proprietary name as soon as possible.
2. DDMAC did not comment on the proprietary names Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen from a promotional perspective. CDRH did not object to the use of the name, KwikPen.
3. DMETS recommends that the Division and the Sponsor consider the comments and recommendations outlined in Section III and IV of this review in order to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communications forwarded to the Sponsor regarding this review. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-796-0080.

**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
(DMETS; White Oak 22, Mail Stop 4447)
Center for Drug Evaluation and Research**

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: June 1, 2007

NDA NUMBER: 20-563/S-075
21-017/S-040
21-018/S-034

NAME OF DRUG: **Humalog® KwikPen™**
[insulin lispro injection, (rDNA origin)]
Humalog® Mix 75/25™ KwikPen™
[75% insulin lispro protamine suspension and 25% insulin lispro injection,
(rDNA origin)]
Humalog® Mix 50/50™ KwikPen™
[50% insulin lispro protamine suspension and 50% insulin lispro injection,
(rDNA origin)]

NDA HOLDER: Eli Lilly

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for comment on the proposed labeling submitted with these supplements. These supplemental applications add a new disposable pen, KwikPen™ irreversibly integrated with approved 3 mL cartridges (100 units/mL) of Humalog, Humalog Mix75/25, and Humalog Mix50/50. The Sponsor had previously submitted (b) (4)*** as a modifier, but has since withdrawn this proposed name based on DMETS objection to the names (OSE Review 2006-900, dated February 8th, 2007).

Currently, Lilly markets disposable pens for each of the three products. The KwikPen is intended to be marketed alongside the disposable pen device, named Humalog Pen. Humalog Pen has been marketed since February 1999, and Humalog Mix 75/25 Pen has been marketed since March 2000. Humalog Mix 50/50 Pen has been marketed since February 2006.

According to the Sponsor, the proposed KwikPen incorporates design changes that are intended to make the device easier to use. In the supplemental application, the Sponsor provided a “Note to Reviewer” that claims that the KwikPen device requires “few steps to set and deliver the dose” and “less force to push the dose knob” as compared to the currently approved disposable pen-injector. Routine post-marketing surveillance of the insulin pen-injectors has identified both of these claims as an issue present with the currently-marketed disposable pen-injectors used with Lilly’s Humalog and

Humalog Mix products. Patients have reported difficulty in depressing the dose-knob of the disposable pen-injectors and, in some instances, the difficulty has led to dosage administration errors in which the patients were unable to deliver the dose of insulin.

The submission includes a new User Manual for the KwikPen™ that is used with all three Humalog products, and separate package insert, patient package insert, pen label, and carton label for each of the three products. DMETS was not provided with a model of the KwikPen device for review and comment.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

¹ MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

1. DDMAC did not comment on the proprietary names Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen from a promotional perspective. DDMAC believes that the “KwikPen” portion of the name corresponds to the disposable pen component, and that the disposable pen component represents a device even though it is irreversibly integrated to the drug cartridge. Therefore, DDMAC believes that they do not have the expertise or authority to make judgments about promotional claims for devices, even for devices that are a part of combination drug-device products. CDRH, the Center that does have authority to comment on the proprietary name of device products, did not offer any comments regarding the proprietary name.
2. DMETS representatives on the Expert Panel also noted that the modifier KwikPen could be construed as promotional. These concerns are discussed in detail on page 11.
3. The Expert Panel identified 5 proprietary names that were thought to have the potential for confusion with Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen. They are: Quixin, KwikPrep, Klonopin, Humalog product line, and the Novolog FlexPen products.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen and with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The study employed a total of 125 healthcare professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process.

Two pharmacy requisition orders were written, each consisting of a combination of marketed and unapproved drug products and prescriptions for Humalog KwikPen and Humalog Mix 50/50 KwikPen (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, a requisition order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Humalog KwikPen Study

HANDWRITTEN PHARMACY REQUISITION ORDER	VERBAL PRESCRIPTION
<p>Pharmacy Requisition Order #1:</p> <p>Humalog KwikPen #2 pens</p> <p>Humalog Mix 50/50 KwikPen #6 pens</p>	<p>Humalog KwikPen 2 Pens</p> <p>Humalog Mix 75/25 KwikPen 6 Pens</p>
<p>Pharmacy Requisition Order #2:</p> <p>Humalog KwikPen</p> <p>Humalog Mix 50/50 KwikPen</p>	

2. Results for Humalog KwikPen:

In the Humalog KwikPen and Humalog Mix 50/50 KwikPen studies, none of the interpretations of the proposed name overlap with any products currently marketed U.S. However, in the verbal prescription studies, respondents did misinterpret “Kwik-” as “Quick” and one respondent misinterpreted “Kwik” as the number “6”. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

The primary concerns of the proposed proprietary names Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen involve the use of the modifier “KwikPen” to distinguish the proposed disposable pen injector from the existing Humalog products; and the potential for the KwikPen modifier to introduce confusion with other drug products, including Quixin, Klonopin, KwikPrep, and Novolog’s FlexPen products. Table 1 on page 6 lists the product characteristics of the products identified that may be potentially confused with the proposed KwikPen products.

Additionally, there are some additional safety concerns regarding the proposed proprietary name that do not involved the potential for drug name confusion or relate directly to the potential for medication errors, but have been included for consideration.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS

Proposed Proprietary Name	Dosage form(s), Established name	Usual adult dose*	Other***
Humalog KwikPen	Insulin Lispro Injection (rDNA origin)	Inject subcutaneously 15 minutes before or immediately after meal in doses determined by patient need.	
Humalog Mix 75/25 KwikPen	75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)		
Humalog Mix 50/50 KwikPen	50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)		
Lilly's Humalog and Humulin Product Lines**	Various formulations of U-100 insulin Available in vials, cartridges, and prefilled-pen injectors	Inject subcutaneously 15 minutes before or immediately after meal in doses determined by patient need.	LA / SA
NovoLog Mix 70/30 FlexPen	70% Insulin Aspart Protamine Suspension and 30% Insulin Aspart Injection; 3 mL prefilled syringe (100 units/mL)	Inject subcutaneously before meals up to three times daily in doses determined by patient need.	LA / SA
NovoLog FlexPen	Insulin Aspart Injection, 100 units/mL; 3 mL prefilled syringe (100 units/mL)	Inject subcutaneously before meals. Ordinarily used in combination with a long-acting insulin.	
Quixin	Levofloxacin 0.5% ophthalmic solution Ophthalmic solution: Store at 15°C to 25°C (59°F to 77°F).	Treatment day 1 and day 2: Instill 1-2 drops into affected eye(s) every 2 hours while awake, up to 8 times/day Treatment day 3 through day 7: Instill 1-2 drops into affected eye(s) every 4 hours while awake, up to 4 times/day	SA
Klonopin	Clonazepam Tablet: 0.5 mg, 1 mg, 2 mg	Usual maintenance dose: 0.05-0.2 mg/kg; do not exceed 20 mg/day	LA
KwikPrep (Australia)	Oral sodium phosphate solution	Administered orally prior to bowel procedures.	LA
*Frequently used, not all-inclusive. **See Appendix B for full listing of Humalog and Humulin products *** LA (look-alike) , SA (sound-alike)			

1. Confusion with the Humalog and Humulin insulin product line

Confusion and errors within the Humalog product line are well documented in published literature and in reports obtained through FDA's Adverse Event Reporting System (AERS). Similarly, Humalog products have been confused with Humulin products. (see Appendix C for representative examples). The factors that contributed to many of these errors included the look and/or sound-alike nomenclature of the insulin products, and similar appearance of the product labeling within the manufacturer's product line.

Humalog contains insulin lispro (rDNA origin), and the Humalog product line consists of three formulations: Humalog, Humalog Mix 75/25, and Humalog Mix 50/50. Each of these three formulations are packaged as a vial, cartridge, and disposable prefilled pen. The proposed product, Humalog KwikPen, is an addition to this product line. Given the existing confusion with the Humalog product line, DMETS believes that the additional product will add to the existing name confusion problem and exponentially increase the opportunity for errors with the Humalog product line, particularly with the existing disposable pen-injector. As such, the risk of confusion with the existing Pen injector device was evaluated separately from the potential for confusion with the remainder of the product line

a.) Potential for confusion with the existing Humalog Pen product

OSE Review 2006-900 (dated February 8, 2007) of the previously proposed modifier, (b) (4)** provided extensive analysis and detail regarding the use of a modifier to differentiate the proposed disposable pen device from the existing Pen. These potential safety concerns were based on the premise that the use of a modifier may lead to medication errors because modifiers can be omitted or overlooked when prescribing, transcribing, administering, or dispensing the product. Furthermore, the medication errors that result as a consequence of the omission or oversight of the KwikPen modifier are most likely to involve mix-ups with the currently marketed disposable Pen injector device, which has minimal difference from the proposed product.

Although these same risks and safety concerns also apply to the proposed proprietary names for the KwikPen product line, the Sponsor has since informed the Agency of their intent to voluntarily discontinue the existing Pen injector device 3 years after the introduction of the proposed KwikPen product. Additionally, in the interim, the Sponsor has outlined a comprehensive Surveillance and Communication Plan to help ensure the safe usage of both products, the details of which are reviewed in Section III of this review. DMETS also noted in OSE Review# 2006-900 that the Sponsor's assessment of the comparative advantages of the proposed KwikPen product to the existing disposable pen-injection may address the causes of some medication errors identified in the post-marketing surveillance of the current disposable Pen injectors, specifically those resulting from the patient's inability to depress the dose knob and failure to properly follow the steps required to set and deliver the dose. The Sponsor has also outlined the potential risks and logistical problems involved in transitioning Humalog patients from the existing disposable Pen device to a new disposable pen device, and convinced DMETS that the marketplace would be under-prepared for a mass conversion if the existing Pen product were to be immediately discontinued. Therefore, DMETS is convinced the risks incurred by the co-existence of the two disposable pen devices in the Humalog product line are temporarily outweighed by the risks of a forced mass conversion of an under-prepared marketplace.

From a medication errors perspective, DMETS believes that the Sponsor's approach will help to minimize the overall risk of medication errors during the 3 year period. The discontinuation of the existing Pen injector device at the conclusion of the 3 year period will leave the proposed KwikPen product as the sole disposable pen injector for the Humalog product line, thus making the omission and oversight of the KwikPen modifier a less likely to source of medication error. Therefore DMETS does not object to the use of

the modifier KwikPen, to help differentiate the proposed product from the existing Pen device.

b.) Potential for confusion with other Lilly Insulin products line

The proposed KwikPen product line will deliver Humalog, Humalog Mix 75/25, and Humalog Mix 50/50, and the proposed proprietary name uses nomenclature that is similar to other Humalog products. As such, DMETS believes that there is risk that KwikPen will be confused with other Humalog products, including:

- Products within the disposable KwikPen injector product line (e.g., Humalog Mix 50/50 KwikPen being confused with Humalog Mix 75/25 KwikPen)
- Other Humalog formulations and products (e.g., Humalog KwikPen being confused with Humalog Mix 75/25 Pen)
- Humulin products (e.g., Humalog KwikPen being confused with Humulin R).
- Other disposable pen injectors (e.g., Humalog KwikPen being confused with Humulin N Pen)

All of the dosage forms share an overlapping route of administration (subcutaneous), indication of use, dosage strength (100 units/mL) and dosage form (injectable solution).

Although the packaging configuration has notable differences in some instances, there are many similarities throughout the Humalog and Humulin product lines because all of the products are manufactured by Eli Lilly. In addition, the products would be stored in the refrigerator next to each other, increasing the risk of selection and dispensing errors.

DMETS did not identify any proprietary names within the Humalog or Humulin product lines thought to have heightened risk for confusion with the proposed pen injector device that could be attributed to the use of the KwikPen modifier. Overall, DMETS believes that the risk of confusion between the Humalog KwikPen product line and the Humalog/Humulin product lines can be attributed to the similar nomenclature of the root names (Humalog) and not the proposed modifier (KwikPen). Therefore, DMETS does not object to the use of the proposed proprietary names for the Humalog KwikPen product line on the basis of name confusion with Lilly's other insulin products.

2. Confusion with the NovoLog FlexPen product line

NovoLog FlexPen and NovoLog Mix 70/30 FlexPen may look or sound similar to the proposed names, Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen. NovoLog is a proprietary name used by Novo Nordisk for a product line of recombinant human insulin analogs. The products are indicated for the treatment of adult and pediatric patients with Type-1 diabetes mellitus or adult patients with Type-2 diabetes mellitus. Currently there are two currently marketed NovoLog products: NovoLog and NovoLog Mix 70/30.

Comparable to Humalog, NovoLog (Insulin Aspart) is a faster acting insulin with a shorter duration of action than regular insulin. It is normally used together with intermediate or long acting insulin products. Because of its rapid action, NovoLog is given before a meal.

Comparable to Humalog Mix 75/25, NovoLog Mix 70/30 is a premixed insulin. It contains 30% rapid-acting NovoLog (insulin aspart) and a 70% modified long acting formulation (insulin aspart protamine suspension).

NovoLog and NovoLog Mix 70/30 are both packaged in vials, cartridges, and prefilled disposable pen injectors. The prefilled disposable pen injector used with NovoLog and NovoLog Mix 70/30 is called “FlexPen®”. Of note, FlexPen is the only disposable pen injector available for the NovoLog product line.

The proposed KwikPen and FlexPen are both disposable pen injector devices. The NovoLog and Humalog products share an overlapping route of administration (subcutaneous), indication of use, dosage strength (100 units/mL) and dosage form (injectable solution). In addition, the products would be stored in the refrigerator next to each other, increasing the risk of selection and dispensing errors. Introducing a prefix (Kwik-) to the existing modifier (Pen) increases the orthographic similarity of the modifiers and may heighten confusion with the products since NovoNordisk’s disposable pen products which use the modifier, “FlexPen”. Along with the overlap in product characteristics, the existing similarity in nomenclature (i.e. “-log,” “Mix,” “Pen”) led DMETS to consider the possibility that the introduction of the KwikPen modifier could lead to confusion between Humalog KwikPen and the NovoLog FlexPen or NovoLog Mix 70/30 FlexPen.

DMETS searched AERS and the literature to determine if any cases of confusion existed between the Humalog’s current disposable pen device and NovoLog’s FlexPen, and found none. Although DMETS does not believe this finding to be conclusive evidence that confusion between the Humalog’s KwikPen and NovoLog’s FlexPen products could not occur, DMETS believes that this finding suggests that the possibility of confusion between the proposed KwikPen products and NovoNordisk’s FlexPen products may be low. Additionally, DMETS believes that differences in the strengths (70/25, 50/50 versus 70/30), prefix of the root name (‘Huma-‘ versus ‘Novo-‘), and differences in the product packaging of the Lilly and NovoNordisk product lines may help to further minimize the risk of confusion in the marketplace.

3. Confusion with KwikPen modifier and other drug proprietary names

Three additional proprietary names that were thought to have the potential for confusion with Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen. They are: Quixin, KwikPrep, and Klonopin.

DMETS considered the possibility that prescriptions or orders for the KwikPen product line could be misinterpreted as representing two separate products (e.g., a prescription for “Humalog” and “Klonopin” written or spoken in close proximity to one another). While the drug names Quixin, Klonopin, and KwikPrep each have orthographic or phonetic similarity with the “KwikPen” modifier, DMETS does not believe that the prescribers are likely to routinely order or prescribe the product solely as “KwikPen.” KwikPen is the name of the disposable pen device, and, by itself, it does not specify which drug is to be dispensed. The KwikPen is irreversibly integrated to Humalog, Humalog Mix 75/25, and Humalog Mix 50/50 cartridges, and would not require a separate prescription or order to be issued for the pen device.

However, because the Sponsor is planning to introduce the KwikPen product line sequentially,

for some period of time there will be only one KwikPen product in the marketplace and therefore there is potential during this period of time that that prescribers could order or prescribe the product by simply referring to the products as “KwikPen”. In these circumstances, DMETS believes that the likelihood of this potential source of error is lessened for the following reasons:

- If the KwikPen portion of the name was misinterpreted as Klonopin, a practitioner would question the prescriber to clarify the strength or dose of the product. Klonopin is available in more than one strength (0.5 mg, 1 mg, 2 mg), none of which overlap with the Humalog products (75/25, or 50/50). Also, Klonopin is a tablet that is administered orally.
- If the KwikPen portion of the name was misinterpreted as Quixin, DMETS believes that the differences in route of administration (inject subcutaneously versus instill in the eye) and duration of use (chronic versus 3 to 7 days) may help to minimize the potential for error. Quixin is an ophthalmic solution marketed in one strength, which does not need be specified when ordering or dispensing the product, which does increase the potential for confusion.
- If KwikPen portion of the name was misinterpreted as KwikPrep, this product is only available in foreign marketplaces (Australia), and thus thought to present a minimal risk of confusion. It appears from internet information located online that KwikPrep is a oral sodium phosphate solution (similar to Fleets® marketed in the US).

Therefore, DMETS believes that although each of these names have orthographic or phonetic similarity to the KwikPen modifier, the risk of medication errors in the usual practice setting is minimized due to differences in product characteristics

4. Additional concerns regarding the KwikPen Modifier

a. KwikPen modifier ambiguity

Although DDMAC was unable to comment on the use of the modifier KwikPen, the DMETS representatives of the Expert Panel noted that the modifier is phonetically identical to the word quick. This observation was supported by the verbal Prescription Study results, in which the majority of the respondents misinterpreted “Kwik-” as “Quick” in the voice prescription study (Appendix A).

DMETS recognizes that the Sponsor is attempting to convey a difference in between the proposed disposable pen injector, and the existing Pen device. The Sponsor stated in the submission that “The KwikPen modifier is unambiguous in that it reflects its’ “2-step operation, an efficient improvement over the 3 steps required for the existing Pen product line. In addition, the convenient 2-step dialing and dosing process may be more intuitive to naïve users.” Although the Sponsor claims that the KwikPen modifier has “a clear, well-understood definition that conveys to practitioners and patients the difference in use and design between the existing Pen product line and the new KwikPen product line,” the Expert Panel did comment that the KwikPen modifier may be interpreted a number of different ways including being “quicker to use,” that the product produces “lowers blood sugar more quickly,” or “requiring less steps to administer.”

Additionally, DMETS notes that the modifier “KwikPen” is not currently used in the marketplace. The July 20, 2006, Institute of Medicine (IOM) Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. FDA also participated in a meeting sponsored by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. We heard from practicing health care practitioners at this meeting to stop approving drug name modifiers that are ambiguous and error prone. The introduction of a new modifier, one that has limited potential utility for future drug products, undermines the efforts set forth for FDA by these expert safety organizations. However, in this case, since two disposable pens will co-exist in the marketplace for some period of time, it will thus be necessary to differentiate the proposed disposable pen device from the existing Pen product with a modifier, and thus does not object to the use of the KwikPen modifier in the proposed proprietary names.

b. “Kwik-” portion of the KwikPen modifier

Although DDMAC did not comment on the merits of the proposed proprietary name from a promotional perspective because DDMAC believes that they do not have the expertise or authority to make judgments about promotional claims for devices that are a part of combination drug-device products, DMETS members of the Expert Panel did note that the “KwikPen” portion of the name could be construed as promotional.

DMETS members of the Expert Panel noted that the “Kwik-” portion of the modifier is phonetically identical to the word “quick.” Although this connotation may not be a source of medication errors, the DMETS members of the Expert Panel felt that the proprietary name could be construed as promotional because the “Kwik” portion of the modifier sounds like quick. Specifically, because the name may misleadingly suggest that the pen is “quick to use” or “lowers blood sugar more quickly.” Even though fewer steps are required to set and deliver the dose, the process of setting and delivering the dose still requires a number of steps. Thus, although fewer in number, the time to complete the insulin delivery process with the Humalog KwikPen may not necessarily be reflected by the word “quick”. Additionally, the KwikPen product will deliver the same exact Humalog compositions as the existing Pen device, and thus has no unique effectiveness in lowering blood glucose more quickly.

In light of these observations, the DMETS members of the Expert Panel recommended advising the Division to consider if the promotional nature of the proposed proprietary names Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen is misleading. Although DMETS does not have reason to believe that the promotional nature of the proprietary name is likely to present a source of medication error in the usual practice setting, we would understand and concur with the Division in the event that the KwikPen portion of the name was determined to be too promotional. If the Division does have objections to the proposed names, DMETS encourages the Sponsor to submit new proposed proprietary names as soon as possible.

c. Future use of the KwikPen modifier for other drug products

A search of the USPTO website using the term “KwikPen” identified two active trademarks that incorporate this modifier: Forteo KwikPen and Humalog KwikPen. Forteo (Teriparatide [rDNA origin] injection) is used to treat osteoporosis, and is marketed by the same Sponsor, Eli Lilly (NDA 21-318).

A similar finding was noted when evaluating the previously proposed modifier (b) (4) for this product, and this potential safety issue was discussed in the March 30, 2007 teleconference. The Sponsor informed the Agency that they did not intend to share the proposed modifier with pen devices used to deliver other drug products. Although DMETS did not locate any active submissions proposing to use the KwikPen modifier**) for the Forteo drug***, DMETS wanted to express concern regarding the potential application of the KwikPen modifier to a product that delivers Forteo, since Humalog Pen and Forteo Pen confusion has been reported to FDA’s Adverse Event Reporting program (ISR 5092288-1, Event Date 08/21/2006).

DMETS has preliminary concern that the use of the KwikPen modifier for both Humalog and Forteo pen devices would unnecessarily exacerbate the existing confusion. DMETS also notes that in many of the medication errors, the identical pen device design, device color, label colors, and trade dress were noted as factors that contributed to the product confusion. DMETS therefore recommends that the Sponsor consider carefully the nomenclature and physical characteristics of the pen devices from a medication errors perspective if they do proceed with marketing Forteo KwikPen.***

III. RISK ASSESSMENT OF THE COMPLETE RESONSE ITEMS

DMETS acknowledges that the Sponsor has addressed our primary concerns from a medication errors perspective regarding the proposed proprietary name, and the risk of confusion with the existing Humalog Pen devices.

With regards to the proprietary name, the initial concerns regarding the modifier, (b) (4)*** have been addressed because the Sponsor formally withdrew this modifier and proposed KwikPen. The Safety Evaluator Risk Assessment determined that the KwikPen modifier was not likely to increase the risk of confusion with other insulin or drug products because of orthographic or phonetic similarity. The Safety Evaluator Risk Assessment did determine that the omission or oversight of the KwikPen modifier and similar nomenclature of the root names Humalog, Humalog Mix 75/25, and Humalog Mix 50/50 do present risk for confusion between the KwikPen products and other marketed insulin products. However, since two disposable Humalog pen devices will co-exist in the marketplace for some period of time, DMETS acknowledges that it is necessary to differentiate the proposed KwikPen device from the existing Pen product, and that the Sponsor has chosen to do so with the use of a modifier. Based on the overall findings of the Risk Assessment, DMETS does not object to the use of the proprietary names Humalog KwikPen, Humalog Mix 75/25 KwikPen, and Humalog Mix 50/50 KwikPen, provided that the Sponsor does not intend to use the KwikPen modifier for future disposable pen devices (i.e. Forteo KwikPen).

Additionally, DMETS believes that the Sponsor’s proposal to voluntarily discontinue the existing Pen device within 3 years, the proposed Surveillance Program (Sponsor’s Attachment 4, 11), and Comprehensive Communication Plan (Sponsor’s Attachment 11) will help to minimize the potential

for medication errors with KwikPen products. DMETS reviewed these proposed items in detail and offers the following comments:

a. Surveillance Program

DMETS recommends that as part of the Surveillance Program incoming reports of medication errors or pharmaceutical product complaints received by the Sponsor involving the KwikPen product line be reviewed and provided to the Agency along with the new start/switch data.

b. Communication Plan

DMETS notes that in the Sponsor's Attachment 11, page 175 the Sponsor states:

*“At launch we will not proactively share with HCPs and patients that the existing Pen will be discontinued. If asked we will consistently share the following verbatim: “In the best interest of good patient care, it would not be appropriate to conduct a forced conversion of the existing prefilled Pen as approximately 250, 000 patients use this pen and to our knowledge most are satisfied with it. We do encourage that you start your **new** patients on the KwikPen and that you no longer start new patients on the existing prefilled Pen unless you feel that this pen provides a unique benefit to a patient that the new KwikPen does not.”*

DMETS is not sure what information the average healthcare practitioner or patient would take away from this message, but could venture a guess that many would find their questions regarding the eventual discontinuation of the Pen product unanswered.

DMETS acknowledges that this message is attempting to promote a more guided conversion process and avoid the mass conversion of patients to the new product when the healthcare community and the Sponsor is under-prepared to meet the challenges associated with such change. From a medication safety perspective, DMETS would not like to see such a scenario arise either, but DMETS is unclear as to how this message will help to promote a guided, more natural conversion process. The only recommendation that DMETS can offer is that when the Sponsor has the necessary data to estimate the dates of voluntary discontinuation, that the message be modified to include confirmatory detail about the eventual discontinuation of the Pen product with concrete timelines.

IV. LABELING and PACKAGING:

Initial recommendations regarding the labeling and packaging of the proposed KwikPen product were provided in OSE Review # 2006-900 (dated February 8, 2007) and discussed with the Sponsor on a teleconference call (March 30th, 2007). DMETS has reviewed the labeling and packaging and found that the majority of recommendations were implemented with some minor exceptions that were discussed and agreed upon in the teleconference by the Agency and the Sponsor (see Attachments 3 and 4 of Complete Response submitted April 30, 2007 for detail). DMETS also has requested that color versions of the proposed KwikPen labels be submitted for review of Lilly's proposed Global Color Differentiation Scheme (NDA 20-563/S-064)***, and the Sponsor has agreed to submit those versions the week of July 10, 2007 for DMETS review and comment. Thus comments relating to the color versions of the labels will be deferred to OSE Review 2007-456.***

DMETS reviewed the revised User Manual for the KwikPenTM that is used with all three Humalog products, and separate carton label, pen label, package insert, and patient package insert for Humalog

KwikPen, Humalog Mix75/25 KwikPen, and Humalog Mix50/50 KwikPen, DMETS focused on safety issues relating to possible medication errors. DMETS has two comments regarding the proposed labels and packaging.

Since the existing disposable pen injector (i.e. Humalog Pen) and the KwikPen products are going to co-exist for any length of time in the marketplace, DMETS believes that the Sponsor should consider including a cautionary statement on the lower portion of the carton's primary display panel to alert practitioners, patients, and caregivers that the KwikPen is a new pen with different use. Specifically, the warning should be present for 6 months following initial marketing of each product, and highlight the fact that the proposed KwikPen is a "new disposable pen injector." If space allows the alert could also highlight the fact that the KwikPen has different instructions than the existing pen injector device, and reference to the importance of reading the User Manual prior to use. This descriptor should have adequate prominence on the primary carton label, since the information may help to avoid product selection errors resulting from overlooked modifiers. Also, in the event that the KwikPen product is dispensed in error to a patient in place of the existing pen-injector, it could help patients to recognize the mistake and possibly avert administration of the product in error. Additionally, DMETS recommends that the Sponsor consider removing the red "Important" alert from the existing Humalog Pen products, to increase the likelihood that the important alert on the KwikPen products is noticed and read.



Appendix A:

Table 1. Prescription Study Results for Humalog Mix 75/25 KwikPen (n= 42)

Pharmacy Requisition Order #1	Pharmacy Requisition Order #2	Verbal Prescription
Humalog Mix 75/25 KnikPen	Humalog mis 75/25 Kwikpen	Humalog mix 75/25 quick pen
Humalog Mix 75/25 Knikpen	Humalog Mix 75/25 Kiwkpen	Humalog mix 75/25 quick pen
Humalog Mix 75/25 Kwik Pen	Humalog Mix 75/25 Kwik Pen	Humalog mix 75/25 quick pins
Humalog Mix 75/25 Kwik Pen	Humalog mix 75/25 KwikPen	Humalog Mix 75/25 Quickpen
Humalog Mix 75/25 Kwik Pen	Humalog Mix 75/25 Kwikpen	humiloc
Humalog Mix 75/25 Kwikpen	HUMALOG MIX 75/25 KWIKPEN	Humu(o)log Meg 75/25
Humalog Mix 75/25 Kwikpen	Humalog Mix 75/25 KwikPen	
Humalog Mix 75/25 Kwikpen	Humalog mix 75/25 Kwikpen	
Humalog Mix 75/25 KwikPen	Humalog Mix 75/25 KwikPen	
Humalog Mix 75/25 Kwikpen	Humalog Mix 75/25 KwikPen	
Humalog mix 75/25 KwikPen	Humalog Mix 75/25 KwikPen	
Humalog Mix 75/25 Kwikpen	Humalog Mix 75/25 Kwikpen	
Humalog Mix 75/25 KwikPen	Humalog Mix 75/25 Kwikpen	
Humalog Mix 75/25 Kwikpens	Humalog Mix 75/25 Kwikpen	
Humalog Mix 75/26 Knikpens	Humalog Mix 75/25 Kwikpen	
	Humalog Mix 75/50 KwikPen	

Appendix B:

Table 2. Potential for errors introduced by KwikPen within Humalog product line.

Proposed KwikPen Addition:	Confusion within KwikPen Product line	If modifier is overlooked or omitted	Confusion with reusable Humalog pen injector device	Confusion within other products in the Humalog line	Confusion with other Lilly Insulin Product Products
Humalog KwikPen	Humalog Mix 5/25 KwikPen Humalog Mix 50/50 KwikPen	Humalog Pen	HumaPen Memoir (uses 3 mL cartridges of Humalog)	Humalog vials, cartridges Humalog Mix 75/25 Pen, or vials Humalog Mix 50/50 Pen, or vials	Humulin R Pen Humulin N Pen Humulin 70/30 Pen
Humalog Mix 75/25 KwikPen	Humalog KwikPen Humalog Mix 50/50 KwikPen	Humalog Mix 75/25 Pen	HumaPen Memoir (uses 3 mL cartridges of Humalog)	Humalog Pen, vials, cartridges Humalog Mix 75/25 vials Humalog Mix 50/50 Pen, or vials	Humulin 70/30 Pen Humulin Pen Humulin N Pen
Humalog Mix 50/50 KwikPen	Humalog KwikPen Humalog Mix 50/50 KwikPen	Humalog Mix 75/25 Pen	HumaPen Memoir (uses 3 mL cartridges of Humalog)	Humalog Pen vials, cartridges Humalog Mix 75/25 Pen, or vials Humalog Mix 50/50 vials	Humulin 70/30 Pen Humulin Pen Humulin N Pen

Appendix C

Representative examples of errors related to Humalog product-line name confusion

ISR 3974730-X 09/11/2002

A 48 year old female patient was prescribed Humalog Mix 75/25 Pen, but was dispensed Humalog Pen. It was reported it was likely the patient “used the Humalog [Pen] for a while” however, the patient reported “no adverse events or erratic swings of blood glucose levels.” The report indicated that the patient used a sliding scale dosage regimen, and that Hemoglobin A1C value of 10.2 following the discovery of the error.

ISR 5017175-5 05/31/2006

A patient reported to Eli Lilly that “the pharmacy had given her Humalog Pens instead of Humalog Mix 75/25 Pens. The reporter did not indicate that she had taken any of the Humalog, and further details of the error causality were not provided. However, the patient did stat that she had “noticed that the box said something different” and “that it looked different.”

ISR 3524319-1. 07/06/2000- Product Selection Errors

A 19 year old female patient reported that an outpatient pharmacy distributed wrong medication (Humalog Mix 75/25 Pen) with the correct labeling. The patient noticed the error when she was about to administer the product, but reported that “it could have been dangerous to if she took the [wrong] insulin” because “good control of my glucose levels are very important.”

ISR 4948942-2 03/17/2006

A 75 year old male patient to 42 units of Humalog in error. The patient was supposed to take 4 units of Humalog from a prefilled pen. The patient was taking Humulin N and Humalog, both via a sliding scale. The patient primed both the pens, and due to the similarity in appearance he selected the Humalog pen in error and injected the wrong dose. A short time later, he realized the mistake, and he went to the hospital with his wife. The patient was treated with IV saline and sugar, and admitted to the hospital for overnight observation. No additional adverse events were reported.

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/s/

Kellie Taylor
7/13/2007 04:25:10 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/13/2007 04:30:12 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/13/2007 04:38:40 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 7, 2007

TO: Mary Parks, M.D., Director
Division of Metabolic and Endocrine Products

VIA: Enid Galliers, Chief, Project Management Staff
Division of Metabolic and Endocrine Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review #2 of the Patient Labeling and User Manual for Humalog (insulin lispro injection [rDNA original]), sNDA 20-563/075, Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA original]), sNDA 21-017/S-040, and Humalog Mix 50/50, (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA original]), sNDA 21-018/S-034

RCM #: 2007-1010

Background/Summary

Lilly Research Laboratories submitted a Complete Response on April 30, 2007, for Humalog (insulin lispro injection [rDNA original]), sNDA 20-563/075, Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA original]), sNDA 21-017/S-040, and Humalog Mix 50/50, (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA original]), sNDA 21-018/S-034, in response to a February 20, 2007 Approvable Letter for these CMC Packaging Supplements.

DSRCS was consulted to review the revised Patient Package Insert and the “KwikPen” User Manual.

Comments and Recommendations

1. See the attached revised PPI (marked and clean) for our suggested revisions. Our revisions have shortened the document and lowered the reading grade level from 9.3. to 7.9 (Flesch-Kincaid). All patient materials should be written at or less than an 8th grade reading level. We have revised the PPI to be consistent with the Package Insert (PI). The PI is the source document for the PPI and information not contained in the PI was deleted from the PPI.
2. The draft KwikPen Disposable Insulin Delivery Device User Manual is acceptable from a patient comprehension standpoint. It has a Flesch-Kincaid Reading Level of 6.4 and was developed with

sponsor-conducted usability studies. We defer further review of this User manual to the Division of Medication Errors and Technical Support (DMETS) to comment on potential medication errors.

Comments to the review division in the attached documents are ***bolded, underlined and italicized***. Please call us if you have any questions.

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/s/

Jeanine Best
6/7/2007 08:25:33 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
6/8/2007 07:56:47 AM
DRUG SAFETY OFFICE REVIEWER

Galliers, Enid M

From: Colburn, Scott A [scott.colburn@fda.hhs.gov]
Sent: Thursday, January 18, 2007 4:50 PM
To: OC Combination Products; Milone, Joseph; Love, Patricia; Galliers, Enid M
Cc: Watson, Anthony
Subject: Consult for N 20-563/S-075
Follow Up Flag: Follow up
Due By: Friday, January 19, 2007 12:00 AM
Flag Status: Red
Attachments: Consult CDER (b)(4).pdf

Please see attached consult for the (b)(4) Insulin Pen from Eli Lilly.

Overall it appears that Eli Lilly has provided all information regarding performance, dose accuracy and labeling of their device consistent with the approaches we would expect from an insulin pen-injector. Their utilization of ISO performance standards, namely ISO 11608-1:2000 was appropriate in setting up their criteria and results.

Please feel free to contact me if there are any further questions.

Scott

Scott A. Colburn RN, BSN
Lieutenant, United States Public Health Service
Regulatory Review Officer
General Hospital Devices Branch;
Executive Secretary to the General Hospital
and Personal Use Devices Panel
FDA/CDRH/ODE/DAGID
Office: 240-276-3707
scott.colburn@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

CONSULTATION REVIEW

Date: January 18, 2007

To: CDER/DMEP

Attn: ENID GALLIERS

From: LT Scott Colburn RN, BSN - HFZ-480

Document No: N 20-563/S-075 et al.

Company Name: Eli Lilly and Company

Device/Subject of Consult Request: Pen Injector/ Dose Accuracy & and Labeling Consult

Device Information:

Proprietary Name: (b) (4)

Common Name: Pen-Injector

Classification Name: Piston Syringe

This supplement describes a disposable pen-injector (b) (4) for use with the following Lilly insulins in 3 mL cartridges:

- NDA 20-563 Humalog (b) (4) (HP-8799)
- NDA 21-017 Humalog Mix75/25 (b) (4) (HP-8797)
- NDA 21-018 Humalog Mix50/50 (b) (4) (HP-8798)

The (b) (4) device incorporates design changes intended to make the device easier to use. The (b) (4) requires fewer steps to set and deliver the dose and less force to push the dose knob down as compared to the currently approved disposable pen-injector.

The (b) (4) user manual was developed following the format established for existing Eli Lilly insulin pens.

The (b) (4) was tested according to the international standard ISO 11608-1:2000 "Pen Injectors for Medical Use - Part 1: Requirements and Test Methods".

Biocompatibility:

The plastic resins used in the (b) (4) device are commonly used in consumer products and come into contact with patient's skin only intermittently. No portion of the device comes in direct contact with the drug product. The materials were evaluated to determine compliance with the requirements of ISO 10993-1:2003." Based on this evaluation, the materials used in the device component of the (b) (4) have been deemed appropriate for this use.

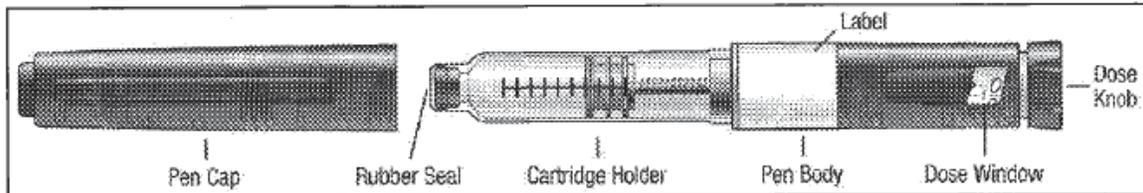
Device Description:

The (b) (4) device platform incorporates design changes intended to make the device easier to use. The (b) (4) requires fewer steps to set and deliver the dose and less force to push the dose knob down as compared to the currently approved disposable pen injector.

The system consists of two main components: the filled 3 mL cartridge and the pen injector. The device component of the (b) (4) is a disposable mechanical injection pen-injector that is designed for subcutaneous delivery of insulin.

Some of the key features of the (b) (4) are:

- Delivery of doses from 1 to 60 units as a single injection
- Dosage amounts in 1-unit increments with audible clicks while setting dose
- Ergonomic design to facilitate control and stability
- Single-step dose setting; twist-to-set dose
- Mechanical design decreases injection force.



(b) (4) is a disposable pen-injector designed for use by diabetics for the self-injection of a desired dose of insulin. The pen-injector contains a filled 3 mL cartridge of Lily insulin and is used with a detachable and disposable pen needle (supplied separately). The pen-injector allows the user to dial the desired dose from 1 to 60 Units in 1 Unit increments.

Chemical Specifications:

The components of the pen-injector do not contact the drug product. The drug product remains in the primary container closure (cartridge) when attached to the pen injector. The fluid path of the drug product into the body is through an attached, disposable, single-use sterile needle. Because there is no contact of the drug product with the device components, there are no additional stability concerns. Stability of the drug product has been established in the cartridge.

Material List from Table

Table 9.1. Materials in (b) (4)

Component	Material
(b) (4)	

Performance Requirements:

The device has been shown to meet the visual, functional and dose accuracy requirements of ISO 11608-1:2000.

Dose Accuracy:

Using a semi-automated system, each pen-injector will be expressed in combinations of two typical patient doses (8 and 28 units). Each dose will be expressed, weighed, and recorded by the system in a manner that avoids potential bias introduced by user interaction. An appropriate quality control standard will be used to determine the sample size. The system is fully documented, validated and placed in operation at the manufacturing facility. The release specification is shown below.

Dose Accuracy Release Specification

Parameters:

1. Sample Size ~ 25 pens
2. Confidence Level = 95%
3. Probability Content = 95%

Specification Limits:

1. Typical low patient dose (8 U / 1 U):
 2. Typical high patient dose (28 U / 5 %):
- Upper Specification Limit = (b) (4)
Lower Specification Limit
Upper Specification Limit
Lower Specification Limit

Recommendations to the Review Team:

Based on the information presented in the sponsors attached information, and the information requested by the CDER review team, I have the following comments regarding the dose accuracy and labeling that was provided:

1. Dose accuracy: Per ISO 11608-1:2000, the standard refers to the following dose accuracy parameters: Based on information provided by the sponsor in sections 11.1.2 to 11.1.6 and 13.4.1, the devices meet the requirements in the ISO Standard 11608-1:2000 for device delivery dose accuracy.
2. Labeling: Labeling was provided to include device and carton packaging as well as an instructions for use booklet. The sponsors labeling (pertinent to the device delivery aspects) is complete and consistent with the requirements for an insulin pen-injector. I would make a suggestion that the sponsor provided in their labeling booklet under (b) (4) that the user allow the alcohol to dry after applying it to cleans the skin. This will provide better cleansing practices and reduce any discomfort/stinging after injection from the alcohol.

If there are any questions or comments regarding the content of this consultation or if further clarification is needed on my recommendations please feel free to contact me via email (scott.colburn@fda.hhs.gov) or by phone @ 240-276-3707.

Scott A. Colburn

Scott A. Colburn, LT USPHS, RN, BSN

January 18, 2007

Date

**This is a representation of an electronic record that was signed electronically and
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/s/

Enid Galliers

2/9/2007 10:42:30 AM

CSO

Checked in on behalf of CDRH.

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE & EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)**

DATE RECEIVED: 10/10/2006 DATE OF DOCUMENT: 10/05/2006	DESIRED COMPLETION DATE: 01/12/2006 PDUFA DATE: 02/10/2007	OSE CONSULT #: 2006-900
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TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

THROUGH: Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Division Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Kellie Taylor, Pharm.D., M.P.H., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:

Humalog® (b) (4)

[insulin lispro injection, (rDNA origin)]

Humalog® Mix75/25™ (b) (4)

[75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)]

Humalog® Mix50/50™ (b) (4)

[50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)]

NDA#: 20-563/S-075
22-017/S-040
21-018/S-034

SPONSOR: Eli Lilly

RECOMMENDATIONS:

1. DMETS recommends that the Sponsor discontinue the existing disposable pen injector device ("Pen), if the proposed (b) (4) device is approved. From a medication errors perspective, the concurrent marketing of both products will undoubtedly lead to mix-ups between the products and could lead to harm.
2. DMETS does not recommend use of the modifier, (b) (4). DMETS is concerned that the use of this modifier may lead to medication errors because the modifier (b) (4) is ambiguous, and could be omitted or overlooked when prescribing, transcribing, administering, or dispensing the product.
3. DDMAC finds the proprietary names Humalog (b) (4) Humalog Mix 75/25 (b) (4), and Humalog Mix 50/50 (b) (4) acceptable from a promotional perspective.
4. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Nancy Clark, Project Manager, at 301-796-0080.

**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
(DMETS; White Oak 22, Mail Stop 4447)
Center for Drug Evaluation and Research**

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: January 5, 2007

NDA NUMBER: 20-563/S-075
22-017/S-040
21-018/S-034

NAME OF DRUG: **Humalog®** (b) (4)
[insulin lispro injection, (rDNA origin)]
Humalog® Mix 75/25™ (b) (4)
[75% insulin lispro protamine suspension and 25% insulin lispro injection,
(rDNA origin)]
Humalog® Mix 50/50™ (b) (4)
[50% insulin lispro protamine suspension and 50% insulin lispro injection,
(rDNA origin)]

NDA HOLDER: Eli Lilly

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for comment on the proposed labeling submitted with these supplements. These supplemental applications add a new disposable pen, (b) (4), for use with approved 3 mL cartridges (100 units/mL) of Humalog, Humalog Mix75/25, and Humalog Mix50/50.

Currently, Lilly markets disposable pens for each of the three products. The (b) (4) is intended to be marketed alongside the disposable pen device, named Humalog Pen. Humalog Pen has been marketed since February 1999, and Humalog Mix 75/25 Pen has been marketed since March 2000. Humalog Mix 50/50 has been marketed since February 2006.

According to the Sponsor, the proposed (b) (4) incorporates design changes that are intended to make the device easier to use. In the supplemental application, the Sponsor provided a “Note to Reviewer” that claims that the (b) (4) device requires “few steps to set and deliver the dose” and “less force to push the dose knob” as compared to the currently approved disposable pen-injector. Routine post-marketing surveillance of the insulin pen-injectors has identified both of these claims as issue present in the currently-marketed disposable pen-injectors used with Lilly’s Humalog and Humalog Mix products. Patients have reported difficulty in depressing the dose-knob of the disposable pen-injectors.

The submission includes a new User Manual for the (b) (4) that is used with all three Humalog products, and separate package insert, patient package insert, pen label, and carton label for each of the three products. DMETS was not provided with a model of the (b) (4) device for review and comment.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Humalog (b) (4), Humalog Mix 75/25 (b) (4), and Humalog Mix 50/50 (b) (4) to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a product must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Humalog (b) (4), Humalog Mix 75/25 (b) (4), and Humalog Mix 50/50 (b) (4). Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names Humalog (b) (4), Humalog Mix 75/25 (b) (4), and Humalog Mix 50/50 (b) (4) acceptable from a promotional perspective.

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

2. The Expert Panel identified 18 proprietary names that were thought to have the potential for confusion with Humalog (b)(4), Humalog Mix 75/25 (b)(4), and Humalog Mix 50/50 (b)(4). They are: Mirapex, Miradon, Mirtazapine, Minocin, Minipress, Ditropan, (b)(4), Morphine, Naropin, Mirena, Muro 128, Miraphen PE, Mupirocin, (b)(4), Histalog, Humalog product line, and Novolog FlexPen products. Additionally through independent review, two proprietary names, Humira Pen and HumaPen Memoir, were thought to have potential for confusion with Humalog (b)(4).

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Humalog (b)(4), Humalog Mix75/25 (b)(4), and Humalog Mix50/50 (b)(4), and with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The study employed a total of 125 healthcare professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process.

Two pharmacy requisition orders were written, each consisting of a combination of marketed and unapproved drug products and prescriptions for Humalog (b)(4) (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, a requisition order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Humalog (b)(4) Study

HANDWRITTEN PHARMACY REQUISITION ORDER	VERBAL PRESCRIPTION
Pharmacy Requisition Order #1: (b)(4) 	Humalog (b)(4) 6 Pens
Pharmacy Requisition Order #2: (b)(4) 	

2. Results for Humalog (b)(4)

In the Humalog (b)(4) study, none of the 41 interpretations of the proposed name overlap with any products currently marketed U.S. However, one respondent of the verbal prescription study recorded “Humalog (b)(4). (b)(4) is a foreign

trademark identified also by EPD. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Humalog (b)(4) Name Evaluation

Of the twenty names identified in EPD and independent review, the following 16 names: Mirapex, Miradon, Mirtazapine, Minocin, Minipress, Ditropan, (b)(4), Morphine, Naropin, Mirena, Muro 128, Miraphen PE, Mupirocin, (b)(4), and Histalog will not be considered further.

DMETS also considered the possibility that prescriptions or orders for the (b)(4) product line could be misinterpreted as representing two separate products (e.g., a prescription for “Humalog” and (b)(4) written in close proximity to one another).

While each of the aforementioned names has orthographic or phonetic similarity with the (b)(4),” modifier, DMETS does not believe that the prescribers are likely to order or prescribe the product solely as (b)(4),” (b)(4) is the name of the disposable pen device, and, by itself, it does not specify which drug is to be dispensed. The (b)(4) is irreversibly integrated to Humalog, Humalog Mix 75/25, and Humalog Mix 50/50 cartridges, and would not require a separate prescription or order to be issued for the pen device.

DMETS believes that the likelihood of this potential source of error is low for the following reasons:

- If the (b)(4) portion of the name was misinterpreted as Mirapex, Miradon, Mirtazapine, Minocin, Minipress, Miraphen PE, Miraphen PSE, Ditropan, (b)(4), Naropine, and Morphine a practitioner would question the prescriber to clarify the strength or dose of these products. With the exception of (b)(4) each of these products are available in more than one strength, none of which overlap with the Humalog products (75/25, or 50/50). Additionally, none of these products are dosed in units, or used subcutaneously. Overall, DMETS believes these characteristics help to minimize the potential for the (b)(4) to be misinterpreted as a separate product on a prescription or medication order.
- If the (b)(4) portion of the name was misinterpreted as Mirena, Muro 128, Mupirocin, DMETS believes that the differences in indications of use, dosage form, and route of administration will help to minimize the potential for error. Mirena (levonorgestrel intra-uterine device), Muro 128 (normal saline ophthalmic ointment), and Mupirocin (topical cream, ointment) are each marketed in just one strength, which does not need be specified when ordering or dispensing the products.
- If (b)(4) portion of the name was misinterpreted as (b)(4) and (b)(4), these products are only available in foreign marketplaces (Korea and Korea/Japan). Although one participant in the verbal prescription studies, recorded “Humalog (b)(4),” as their response, DMETS does not believe that these names represent a substantial risk for confusion with products marketed in the United States.

- The name Histalog will not be reviewed further because although the name Histalog shares orthographic and phonetic similarity to the root name “Humalog,” DMETS does not believe that the introduction of the (b) (4) device to the product line will lead to confusion between these products. Histalog (Betazole Hydrochloride) is an injectable product used to evaluate gastric function, and an AERS search of Histalog and Humalog medication errors did not identify any reports of product confusion. Furthermore, the product appears to be discontinued.⁷

Therefore, only 3 names (Humira Pen, the Humalog product line, and NovoLog FlexPen products) will be discussed further. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage. A detailed evaluation of each name listed will follow the table.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS

Proposed Proprietary Name	Dosage form(s), Established name	Usual adult dose*	Other**
Humalog (b) (4)	Insulin Lispro Injection (rDNA origin)	Inject subcutaneously 15 minutes before or immediately after meal in doses determined by patient need.	
Humalog Mix 75/25 (b) (4)	75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)		
Humalog Mix 50/50 (b) (4)	50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)		
Humalog Product Line	Various formulations of U-100 insulin Available in vials, cartridges, and prefilled-pen injectors	Inject subcutaneously 15 minutes before or immediately after meal in doses determined by patient need.	LASA
Humira Pen	Adalimumab injection 40 mg/0.8 mL	For rheumatoid or psoriatic arthritis administer 40 mg subcutaneously every other week.	LASA
NovoLog Mix 70/30 FlexPen	70% Insulin Aspart Protamine Suspension and 30% Insulin Aspart Injection; 3 mL prefilled syringe (100 units/mL)	Inject subcutaneously before meals up to three times daily in doses determined by patient need.	LASA
NovoLog FlexPen	Insulin Aspart Injection, 100 units/mL; 3 mL prefilled syringe (100 units/mL)	Inject subcutaneously before meals. Ordinarily used in combination with a long-acting insulin.	
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

a. Potential for confusion within the Humalog product line

Humalog is the active ingredient in Humalog (b) (4). Humalog contains insulin lispro (rDNA origin) and is also available as a vial, cartridge, or disposable pen. Humalog (b) (4) is an addition to this product line. The Humalog product line currently consists of three formulations (Humalog, Humalog Mix 75/25, Humalog Mix 50/50) available in a variety of containers (cartridges, prefilled syringes, and vials).

Confusion and errors within the Humalog product line are well documented in published literature and in reports obtained through FDA’s Adverse Event Reporting System

⁷ Drugs@fda website accessed 1/12/2007

(AERS). Similarly, Humalog products have been confused with Humulin products. (see Appendix A and attached articles for examples). The root cause analysis for many of the errors is the look and/or sound alike nomenclature of the insulin products, along with similarity in labeling within a manufacturer's product line.

Unfortunately, DMETS believes that the additional product will add to the existing name confusion problem and *exponentially* increase the opportunity for errors with the Humalog product line, particularly if the Sponsor continues to market the existing disposable pen-injector (see Table 2 below).

Table 2. Potential for errors introduced by (b) (4) within Humalog product line.

Proposed (b) (4) Addition:	Confusion within (b) (4) Product line	If modifier is overlooked or omitted	Confusion with reusable Humalog pen injector device	Confusion within other products in the Humalog line	Confusion with other Lilly Insulin Product Products
Humalog (b) (4)	Humalog Mix 5/25 (b) (4) Humalog Mix 50/50 (b) (4)	Humalog Pen	HumaPen Memoir (uses 3 mL cartridges of Humalog)	Humalog vials, cartridges Humalog Mix 75/25 Pen, or vials Humalog Mix 50/50 Pen, or vials	Humulin R Pen Humulin N Pen Humulin 70/30 Pen
Humalog Mix 75/25 (b) (4)	Humalog (b) (4) Humalog Mix 50/50 (b) (4)	Humalog Mix 75/25 Pen	HumaPen Memoir (uses 3 mL cartridges of Humalog)	Humalog Pen, vials, cartridges Humalog Mix 75/25 vials Humalog Mix 50/50 Pen, or vials	Humulin 70/30 Pen Humulin Pen Humulin N Pen
Humalog Mix 50/50 (b) (4)	Humalog (b) (4) Humalog Mix 50/50 (b) (4)	Humalog Mix 75/25 Pen	HumaPen Memoir (uses 3 mL cartridges of Humalog)	Humalog Pen vials, cartridges Humalog Mix 75/25 Pen, or vials Humalog Mix 50/50 vials	Humulin 70/30 Pen Humulin Pen Humulin N Pen

As outlined in Table 2 (above), the proposed (b) (4) product line uses very similar nomenclature. Because of this, DMETS believes that (b) (4) will be confused with:

- Products within the disposable (b) (4) injector product line (i.e. Humalog Mix 50/50 (b) (4) being confused with Humalog Mix 75/25 (b) (4))
- Other disposable pen injectors (e.g., Humalog (b) (4) being confused with Humalog Pen)
- HumaPen Memoir, a reusable pen injector device used with Humalog cartridges
- Other Humalog formulations and products (e.g., Humalog (b) (4) being confused with Humalog Mix 75/25 Pen)
- Humulin products (e.g., Humalog (b) (4) being confused with Humulin N Pen).

All of the dosage forms share an overlapping route of administration (subcutaneous), indication of use, dosage strength (100 units/mL) and dosage form (injectable solution). Although the packaging configuration has notable differences in some instances, there are many similarities throughout the Humalog and Humulin product lines because all of the products are manufactured by Eli Lilly. In addition, the products would be stored in the refrigerator next to each other, increasing the risk of selection and dispensing errors.

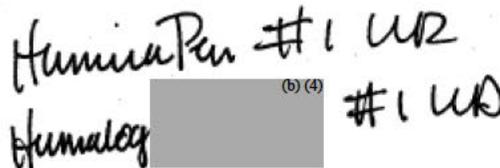
b. Similarity to Humira Pen

Humira Pen may look and sound similar to Humalog (b) (4). Humira (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Humira is indicated for reducing signs and symptoms, inducing major clinical

response, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. The recommended dose of Humira for adult patients with rheumatoid arthritis or psoriatic arthritis is 40 mg administered every other week as a subcutaneous injection.

An AERS search examined the potential for confusion between the Humalog Pen products with Humira Pen did not identify any cases of regarding confusion with the products. However, DMETS is concerned that the introduction of the modifier (b) (4) to the word Pen increases the potential for confusion with (b) (4) Pen since the (b) (4) (b) (4). Humalog (b) (4) and Humira Pen owe their look and sound-alike similarities to the likeness of their root names (“Hu”) and the identical descriptor, “Pen”.

Like Humalog (b) (4), Humira Pen is a prefilled pen injector for subcutaneous administration that is stored in the refrigerator. Both products may also be ordered without specification of quantity (e.g. 1 box) or directions (e.g. take as directed) (See example below).



The image shows two lines of handwritten text. The first line reads "Humira Pen #1 UR" and the second line reads "Humalog (b) (4) #1 UR". The (b) (4) is written in a small font size.

However, the “log” portion of the Humalog root name helps to differentiate the name when spoken or written. In the writing sample above it is apparent that Humalog (b) (4) is lengthier than Humira Pen, and the letter ‘g’ of Humalog introduces a downstroke that is not present in Humira Pen. Additionally the products do have some notably different product characteristics, including indications of use (rheumatoid or psoriatic arthritis versus diabetes), and dosage frequency (every other week versus several times daily), which if included on the prescription or medication order, would help to further differentiate the products in practice.

c. Similarity to the NovoLog FlexPen product line

NovoLog FlexPen and NovoLog Mix 70/30 FlexPen may look or sound similar to the proposed names, Humalog (b) (4), Humalog Mix 75/25 (b) (4), and Humalog Mix 50/50 (b) (4). NovoLog is a proprietary name used by Novo Nordisk for a product line of recombinant human insulin analogs. The products are indicated for the treatment of adult and pediatric patients with Type-1 diabetes mellitus or adult patients with Type-2 diabetes mellitus. Currently there are two currently marketed NovoLog products: NovoLog and NovoLog Mix 70/30.

Comparable to Humalog, NovoLog (Insulin Aspart) is a faster acting insulin with a shorter duration of action than regular insulin. It is normally used together with intermediate or long acting insulin products. Because of its rapid action, NovoLog is given before a meal.

Comparable to Humalog Mix 75/25, *NovoLog Mix 70/30* is a premixed insulin. It contains 30% rapid-acting NovoLog (insulin aspart) and a 70% modified long acting formulation (insulin aspart protamine suspension).

NovoLog and NovoLog Mix 70/30 are both packaged in vials, cartridges, and prefilled disposable pen injectors. The prefilled disposable pen injector used with NovoLog and NovoLog Mix 70/30 is called “FlexPen®”. Of note, FlexPen is the only disposable pen injector available for the NovoLog product line.

The proposed (b) (4) and FlexPen are both disposable pen injector devices. The NovoLog and Humalog products share an overlapping route of administration (subcutaneous), indication of use, dosage strength (100 units/mL) and dosage form (injectable solution). In addition, the products would be stored in the refrigerator next to each other, increasing the risk of selection and dispensing errors. Introducing a prefix (b) (4) to the existing modifier (Pen), may heighten confusion with the products since NovoNordisk’s uses a modifier, “Flex-“, for their disposable pen device. Along with the overlap in product characteristics, the similarity in nomenclature (i.e. “-log,” “Mix,” “Pen”) lead DMETS to consider the possibility that the introduction of the (b) (4) device could lead to confusion with NovoLog FlexPen or NovoLog Mix 70/30 FlexPen.

DMETS searched AERS and the literature to determine if any cases of confusion existed between the Humalog’s current disposable pen device and NovoLog’s FlexPen, and found none. Although DMETS does not believe this finding to be conclusive evidence that confusion between the Humalog’s (b) (4) and NovoLog’s FlexPen products could not occur, DMETS believes that this finding suggests that the possibility of confusion between the proposed (b) (4) products and NovoNordisk’s FlexPen products may be low. Additionally, DMETS believes that differences in the strengths (70/25, 50/50 versus 70/30), prefix of the root name (‘Huma-‘ versus ‘Novo-‘), and differences in the product packaging of the Lilly and NovoNordisk product lines may help to further minimize the risk of confusion in the marketplace.

2. (b) (4) Modifier Issues

DMETS has concerns regarding the use of the modifier, (b) (4). DMETS is primarily concerned that the use of this modifier may lead to medication errors because the modifier (b) (4) is ambiguous, and could be omitted or overlooked when prescribing, transcribing, administering, or dispensing the product. Therefore, DMETS does not recommend use of the modifier, (b) (4).

a. Ambiguity of the modifier

With respect to the use of the modifier (b) (4) DMETS is concerned that the modifier is ambiguous. We recognize that the accepted practice to convey differences in product formulations is to include an appropriate modifier. However, the modifier (b) (4) is not currently used in the marketplace, and several members of the Expert Panel questioned the meaning of the prefix (b) (4). DMETS could not relate the prefix (b) (4) to any terms or words defined in the English language. Because the modifier does not have a clear definition, DMETS believes that the modifier (b) (4) may not convey to practitioners or patients the differences in design between the existing disposable pen injector and proposed (b) (4) device.

Additionally, the July 20, 2006, Institute of Medicine (IOM) Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize

abbreviations, acronyms, and terms to the extent possible. DMETS believes that the introduction of a new modifier that is ambiguous undermines this effort.

FDA also participated in a meeting sponsored by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. We heard from practicing health care practitioners at this meeting to stop approving drug name modifiers that are ambiguous and error prone.

DMETS contends that the modifier “(b)(4)” is ambiguous, and contradicts the goals set forth by healthcare practitioners, the IOM, and NCC MERP and should not be approved for use in the US Marketplace.

b. Omission and oversight of modifiers

DMETS conducted prescription studies to simulate the prescription ordering process for Humalog (b)(4). In this case, there was confirmation that the proposed name could be confused with Humalog. In the verbal prescription study, 4 of the 9 respondents specified “Humalog” only instead of “Humalog (b)(4),” attesting to the fact that the modifier can be overlooked when interpreting verbal prescriptions or orders.

Modifiers can be omitted from prescriptions.⁸ Prescribers can simply forget to specify the modifier when prescribing or ordering the medication. Prescribers may also not be aware that two disposable pens are available for the Humalog product line, and chose to specify “Pen” or “disposable pens” in place of “(b)(4).” It is also conceivable that Pharmacists or Nurses may not be universally aware of the co-existence of both disposable pen injectors, and thus not question the order or prescription.

In addition, modifiers can be overlooked by practitioners. The only difference in the nomenclature of the two disposable pen-injectors is the (b)(4) portion of the modifier. In the context of a medication order or prescription, DMETS believes that this difference could be overlooked in some instances.

The omission or oversight of the modifier on a prescription or medication order for (b)(4) would likely result in confusion with the existing pen-injector. The confusion could occur at any point in the medication use process: prescribing, transcribing, dispensing or administering the drug. Although these errors could conceivably result in the patient receiving the same active drug, administration errors and harm could result if the patient or caregiver is unaware of the product differences. Specifically, the disposable pens have different steps which must be taken to prime and set the dosage. The labeling of both products note that failure to follow the instructions for priming and setting the pen to deliver the dose could result in the patient receiving “too much or too little insulin.”

Therefore, DMETS recommends that the currently marketed disposable pen be discontinued. With the discontinuance of the existing disposable ‘pen’ then the proposed pen device can be marketed without the use the modifier.

⁸ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

3. Concurrent availability of (b) (4) and “Pen” injectors

One of DMETS’ primary concerns is that the Sponsor intends to market the proposed (b) (4) alongside the current disposable pen injector device (“Pen”) which is also used with Humalog, Humalog Mix 50/50, and Humalog Mix 75/25. From a medication errors perspective, the concurrent marketing of both products will undoubtedly lead to mix-ups between the products and could lead to harm. DMETS believes that if the (b) (4) device is approved, the Sponsor should be asked to voluntarily discontinue the existing disposable pen-injector for the following reasons:

a. Potential reduction in medication error occurrences related to device design

The Sponsor states that the proposed (b) (4) injector incorporates design changes that are intended to make the device easier to use. In the supplemental application, the Sponsor provided a “Note to Reviewer” document that states that the (b) (4) device requires “fewer steps to set and deliver the dose” and “less force to push the dose knob” as compared to the currently approved disposable pen-injector. Routine post-marketing surveillance of the insulin pen-injectors has confirmed that both of these issues have been implicated in medication error reports involving the currently-marketed disposable pen-injectors used for Lilly’s Humalog and Humalog Mix products (See Appendix B). Patients have reported difficulty in depressing the dose-knob of the disposable pen-injectors. For example:

ISR 4980979-X, 04/18/2006

74 year old female with right eye blindness and right eye macular degeneration, experienced “difficulty pressing in the dosing knob” of the Humalog Mix 75/25 Pen. The patient also reported that “no insulin would come out event though a ‘2’ appeared in the window. The full dose was then administered from a new pen, and the defective pen was returned to the company. No follow up analysis on the returned pen was included with the report. The patient also reported that she “cannot read the dose on the pen because of her eyes.”. The patient stated that she had used the device for 1 year.

Some reports have indicated in their analysis that the route cause of the medication error was the failure of the patient to properly follow the steps required to set and deliver the dose:

ISR 5032594-X 07/20/2006

A 71 year old patient who had used Humalog Pen for “years” contacted Eli Lilly stating there was “always a small bubble in every pen.” The bubble was estimated to be the size of a “small pin head”. The patient used 15 units of Humalog before meals, and reported that he had “recently” been experiencing blood sugars ranging from 184 mg/dL to 216 mg/dL despite increasing his Humalog dosage to 23 units and reducing carbohydrate intake. According to the report the patient stored the Pens in the refrigerator prior to use and at room temperature while in use. The Pen was not stored with needle attached. The patient denied shaking or agitating the pen. However, the report indicated that the patient was not priming the pen in accordance with the User Manual instructions. Specifically, the patient:

- Primed the pen in horizontal position.
- Patient did not count to five after pressing on the injection button.
- Patient did not look for a centered diamond in the dose window after the injection and priming of the device.

Patient did no reset the pen to the arrow after the dose.

Given the Sponsor’s assessment of the comparative advantages of the new product to the existing disposable pen-injection, it seems to DMETS that the discontinuation of

the existing pen-injector could remedy some of the issues identified in the post-marketing surveillance of the disposable pen injectors.

b. Differences in Design that can lead to potential confusion

With the concurrent marketing of two pen devices with different directions for use can lead to medication errors. One could argue that confusion between “(b) (4)” and the disposable “Pen” is likely to result in the patient receiving the same active drug; however, DMETS believes that administration errors and harm could result if the patient is unaware of the product differences. Specifically, the existing disposable pen injector and proposed (b) (4) device have different steps which must be taken to prime and set the dosage.

- i. The existing disposable “Pen” injector has several priming steps in priming and setting the dose related to centering the (◆) or (→) is shown in the dose window. These icons are not used for (b) (4), thus eliminating several steps and decreasing the complexity of these tasks.
- ii. The existing disposable “Pen” injector also uses (◆) or (→) icons in the dose window as visual cues to indicate that the total dose is injected. The user manual specifically advises patients to continue depressing the dose knob even if a “0” appears in the Dose Window. In the (b) (4) device, the appearance if a “0” in the Dose Window indicates that the patient has received the full dose.
- iii. In addition, the Pen user manual indicates that the Dose Knob is pulled outwards to allow dialing of the insulin dose; whereas the (b) (4) Dose Knob does not require this action to manipulate the device. DMETS is concerned that patients familiar with the functionality of the existing Pen device who are dispensed the (b) (4) in error, could inadvertently break the (b) (4) device while attempting to pull the Dose Knob outwards.

DMETS believes that these differences could be overlooked by a patient or caregiver, which could result in administration errors. DMETS believes that these differences could be particularly problematic if patients or caregivers, who are familiar with using one of the disposable pen devices, is inadvertently dispensed the other. In several instances throughout the product’s labeling of the (b) (4) and disposable pen-injector device, the Sponsor warns:

“if you do not follow these directions completely, you may get too much or too little insulin.”

“Before each injection, you should prime the pen, a necessary steps to make sure the pen is ready to dose....If you do not Prime, you may receive too much or too little insulin.”

c. User competency with pen devices

DMETS is also concerned that the concurrent availability of two disposable pen injector designs within the same product line makes it difficult for consumers and healthcare practitioners, particularly nurses, to learn how to use the disposable pens and maintain competence. The Institute for Safe Medication Practices (ISMP) has voiced this concern about the wide variety of pen injector designs used in the

marketplace (Article attached for further detail).⁹ DMETS believes that the concurrent availability of two designs for disposable pen injectors used for the same product line needlessly exacerbates the risk for medication errors that could result from healthcare practitioners or consumer failure to use the pen injector properly.

Therefore, for these reasons, DMETS believes that if the (b) (4) device is approved, the Sponsor should be asked to voluntarily discontinue the existing disposable pen-injector.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the new User Manual for the (b) (4) that is used with all three Humalog products, and separate carton label, pen label, package insert, and patient package insert for Humalog, Humalog Mix75/25, and Humalog Mix50/50, DMETS focused on safety issues relating to possible medication errors. DMETS identified the following areas of improvement, in order to minimize potential user error.

A. GENERAL COMMENTS

1. If the existing disposable pen injector (i.e. Humalog Pen) and the (b) (4) products are going to co-exist for any length of time in the marketplace, DMETS believes that the Sponsor should include cautionary statements in the labeling to warn practitioners, patients, and caregivers that this is a new pen with different use. Specifically, the product labels and labeling include a descriptor for at least 6 months following initial marketing of the product that highlights the fact that the proposed (b) (4) is a new product to the existing Humalog line to minimize the potential for medication errors. The descriptor should highlight the fact that (b) (4) is a “new disposable pen injector” that has different instructions than the existing pen injector device, and make reference to the importance of reading the User Manual prior to use. This descriptor should have adequate prominence on the primary carton label, since the information may help to avoid product selection errors resulting from overlooked modifiers. Also, in the event that the (b) (4) product is dispensed in error to a patient in place of the existing pen-injector, it could help patients to recognize the mistake and possibly avert administration of the product in error. This descriptor should have adequate prominence in the User Manual, in the event that the statement on the primary carton label is overlooked or obscured by patient-specific labeling (i.e. a pharmacy label).
2. DMETS recommends that the numeric portion (i.e. 75/25) of the proprietary name be highlighted to avoid confusion within the Humalog (b) (4) product line and with Humalog Mix product line. DMETS believes it is important to highlight the numeric portion since this is the only portion of the proprietary name that differs with the Humalog (b) (4), Humalog Mix 75/25 (b) (4), and Humalog Mix 50/50 (b) (4) products. The Sponsor could increase the prominence by increasing the font size of the numeric portion or use reverse color blocking (see examples below).

Humalog® Mix75/25

(b) (4)

Humalog® Mix75/25

(b) (4)

⁹ ISMP Medication Safety Alert! Acute Care Edition, Vol 11, Issue 24. November 30 2006.

B. USER MANUAL

1. In the first instruction, “Preparing the (b) (4)” DMETS is concerned that the qualifier of part B., “For Cloudy Insulin Only,” could be confusing to some patients. DMETS wonders whether it might be better to explicitly state the names of the insulins that appear cloudy (i.e. Humalog Mix 75/25, Humalog Mix 50/50), to remove ambiguity from the statement. DMETS is concerned that patient unfamiliarity with insulin appearance, or that lack visual acuity, may not be able to identify their insulin as “cloudy”.
2. In the “Injecting Your Dose” section, DMETS recommends the following statement be added as a bullet under the “Important Notes” subheading: “Push and hold the Dose Knob in and count slowly for 5 seconds before removing the needle.” DMETS believes that this point should be highlighted to avoid inadvertent underdosing of insulin that could occur if patients mistakenly remove the needle before the total dose is administered from the (b) (4).

C. CARTON LABEL

1. DMETS recommends removing the (b) (4) symbol displayed on the upper portion of the primary panel. This symbol is unnecessary as the Sponsor has included the “Rx Only” on the middle portion of the primary panel. DMETS is concerned that this symbol may distract attention from the proprietary name, and possibly lead to confusion between the other Humalog (b) (4) products which have similar trade dress.
2. DMETS recommends moving the statement “needles not included” (b) (4) and putting this statement before the recommended brand of insulin needles. DMETS believes this statement should be prominently displayed to avoid dispensing of the product without the needles to administer the insulin.
3. DMETS does not know what “HP-8798” indicates, but recommends that it be removed from the primary carton label. If this information is necessary, DMETS recommends that it be displayed in the lower portion of the label. In the current position, DMETS believes that it could distract practitioners from other important information (i.e. Proprietary name, NDC number) thus increasing the opportunity for error.
4. DMETS recommends that the middle segment of the NDC number be reassigned to reduce the likelihood of medication errors reaching the patient. DMETS is concerned that the Humalog (b) (4) could be confused with Humalog Mix 75/25 (b) (4) and Humalog Mix 50/50 (b) (4). All three products have similar nomenclature, and Lilly has proposed to use similar packaging for each of these three products. DMETS believes that product selection errors could occur when preparing a prescription for dispensing. DMETS believes that the overlap in nomenclature (Humalog (b) (4) package size (5 x 3 mL syringes), and trade dress, diminishes the opportunity for the error to be caught prior to dispensing.

In practice, pharmacy staff often relies on NDC codes as a check to prevent dispensing errors. Lilly has chosen to assign the middle segment of the NDC numbers for these products sequentially (0002-8799-59, 0002-8798-59, 0002-8797-59), and thus the 10-digit codes for these products differ by one digit placed in the middle.

DMETS recognizes that it may be common practice for entities within a product line to be assigned sequential NDC codes, but DMETS believes that this eliminates a potentially

important safety check that could avert product selection errors resulting from name, label, or packaging confusion among the (b) (4) product line. DMETS urges the Sponsor to consider implementing this request in the interest of reducing medication errors.

5. DMETS also recommends that the Sponsor give greater prominence to the middle segment of the product NDC code (i.e. 0002-**8799**-59). This portion of the NDC code is most heavily relied by pharmacy staff to distinguish products within the same product line.
6. Include a space for patients to record the date in which the pen is first used on the rear display panel of the carton. DMETS feels that this could be help to avoid errors related to use of expired pen devices.

D. PEN LABEL

DMETS is concerned that patients will have difficulty reading the label. To enhance readability of the label and recommends:

1. Enlarge the overall size of the label, if possible. DMETS recognizes that space constriction on the device itself may limit the size of the pen label.
2. Increase the font size used to display the proprietary name.
3. Remove the (b) (4) symbol next to the NDC number to decrease the cluttering on the label. This symbol is extraneous as the words “Rx Only” are already included on the label.
4. Include a space for patients to record the date in which the pen is first used if space on the label permits. DMETS feels that this could be help to avoid errors related to use of expired pen devices.

E. PACKAGE INSERT

1. DMETS recommends reformatting the “HOW SUPPLIED” section into a table. The proposed presentation is difficult to read. DMETS is concerned that a practitioner may not realize that there are two disposable pen products available for this product on the market- thus increasing the potential for confusion.
2. DMETS recommends adding a row for (b) (4)” to the Table in “Storage” or specifying Pen, and (b) (4). DMETS believes that confusion could arise if the disposable pens are not specified since both products will be available in the marketplace. Similarly, the paragraph (line 424) of the “Storage” section should refer to either “Pens, and (b) (4) or generally “disposable pens.”

F. PATIENT PACKAGE INSERT

1. DSCRS sent a memo to DMEP that states that the sponsor should revise and rewrite the patient package insert at a 6th to 8th grade reading level because the proposed insert is written at greater than a 12th grade reading level. DMETS concurs that this reading level is not acceptable for patient materials, and could potential cause patients to be confused and lead to medication errors.

2. Within the [REDACTED] (b)(4) section, DMETS recommends that the Sponsor highlight the fact that Humalog Pen and Humalog [REDACTED] (b)(4) have different instructions and thus it is important to read the user manual before using. DMETS is concerned that patients may not recognize that the [REDACTED] (b)(4) is a new disposable delivery device, and could use the product in error if they had previously been familiar with the Pen delivery device.
3. For the Humalog Mix 75/25 [REDACTED] (b)(4) only, the [REDACTED] (b)(4) section (line 72) states [REDACTED] (b)(4). DMETS recommends revising the statement to reference the *three* formulations available: Humalog, Humalog Mix75/25, and Humalog Mix50/50.

Appendix A: Prescription Study Results (n=41)

Pharmacy Requisition Order #1	Pharmacy Requisition Order #2	Verbal Prescription
Humalog (b) (4)	Humalog (b) (4)	Humalog
Humalog	Humalog	Humalog (b) (4)
Humalog	Humalog	Humalog
Humalog	Humalog	
	Humalog	

Appendix B: Selected examples of errors related to Humalog product-line name confusion

ISR 3974730-X 09/11/2002

A 48 year old female patient was prescribed Humalog Mix 75/25 Pen, but was dispensed Humalog Pen. It was reported it was likely the patient “used the Humalog [Pen] for a while” however, the patient reported “no adverse events or erratic swings of blood glucose levels.” The report indicated that the patient used a sliding scale dosage regimen, and that Hemoglobin A1C value of 10.2 following the discovery of the error.

ISR 5017175-5 05/31/2006

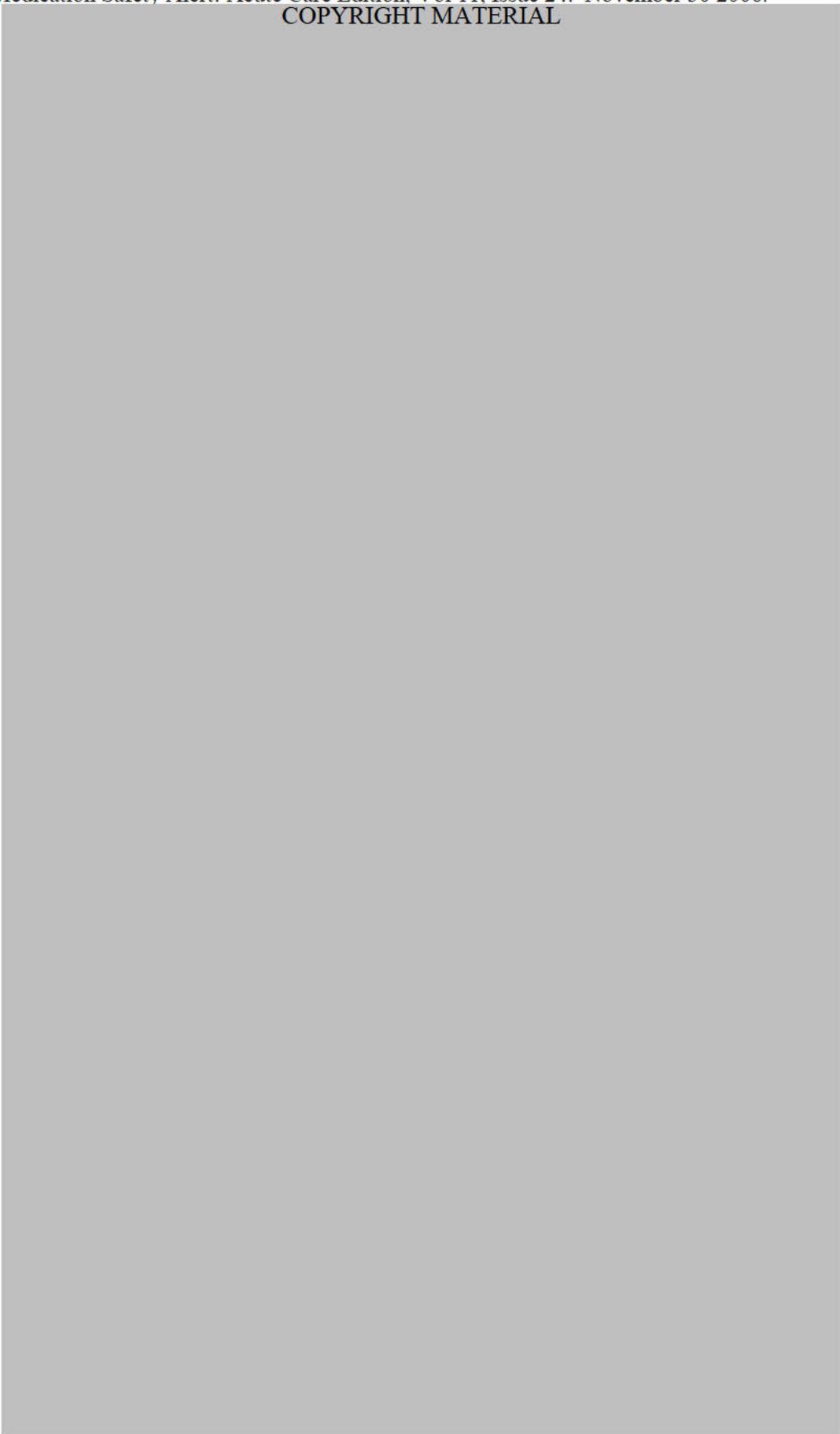
A patient reported to Eli Lilly that “the pharmacy had given her Humalog Pens instead of Humalog Mix 75/25 Pens. The reporter did not indicate that she had taken any of the Humalog, and further details of the error causality were not provided. However, the patient did state that she had “noticed that the box said something different” and “that it looked different.”

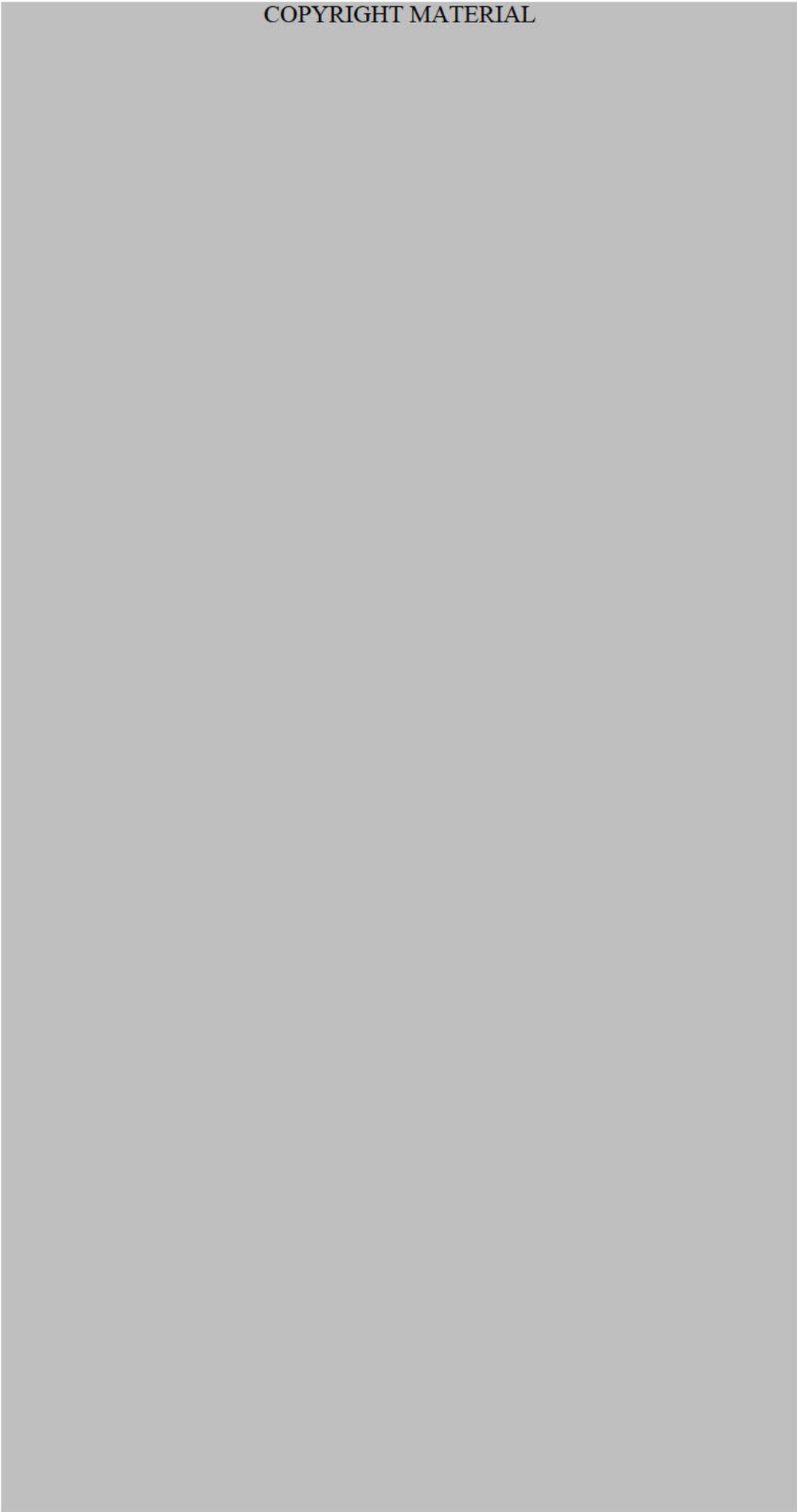
ISR 3524319-1. 07/06/2000- Product Selection Errors

A 19 year old female patient reported that an outpatient pharmacy distributed wrong medication (Humalog Mix 75/25 Pen) with the correct labeling. The patient noticed the error when she was about to administer the product, but reported that “it could have been dangerous to if she took the [wrong] insulin” because “good control of my glucose levels are very important.”

ISR 4948942-2 03/17/2006

A 75 year old male patient took 42 units of Humalog in error. The patient was supposed to take 4 units of Humalog from a prefilled pen. The patient was taking Humulin N and Humalog, both via a sliding scale. The patient primed both the pens, and due to the similarity in appearance he selected the Humalog pen in error and injected the wrong dose. A short time later, he realized the mistake, and he went to the hospital with his wife. The patient was treated with IV saline and sugar, and admitted to the hospital for overnight observation. No additional adverse events were reported.





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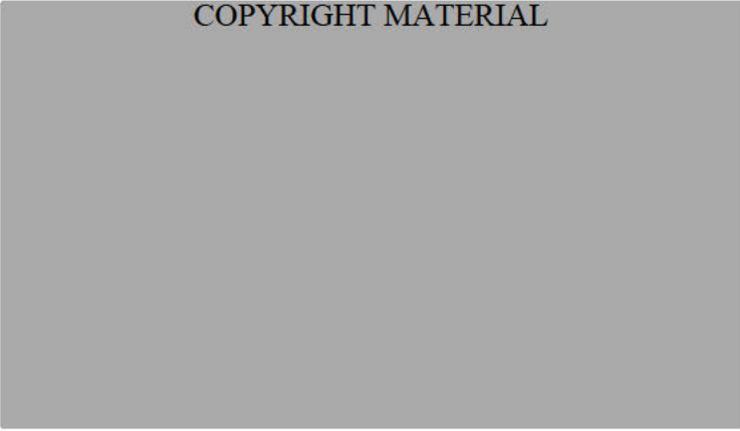
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/s/

Kellie Taylor
2/8/2007 04:13:52 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
2/8/2007 04:21:19 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 9, 2007

TO: Mary Parks, M.D., Director
Division of Metabolic and Endocrine Products

VIA: Enid Galliers, Chief, Project Management Staff
Division of Metabolic and Endocrine Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCs Review of the Patient Labeling and User Manual for Humalog (insulin lispro injection [rDNA original]), sNDA 20-563/075, Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA original]), sNDA 21-017/S-040, and Humalog Mix 50/50, (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA original]), sNDA 21-018/S-034

Background/Summary

Lilly research Laboratories submitted Prior Approval Supplements (SCP-packaging changes) for an additional disposable insulin delivery device (b)(4) on October 10, 2006, for Humalog (insulin lispro injection [rDNA original]), sNDA 20-563/075, Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA original]), sNDA 21-017/S-040, and Humalog Mix 50/50, (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA original]), sNDA 21-018/S-034. Revised labeling, including prescribing information (PI) and patient information (PPI) to include information on the (b)(4), along with a (b)(4) Disposable Insulin Deliver Device User Manual were submitted for review.

Comments

Diabetes is a chronic medical condition in which patients are expected to perform complex self-management activities in order to avoid death and disability. Health-related materials including diabetes materials are often written at levels that far exceed many people's reading abilities.¹ An insufficient ability to comprehend health-related information can lead people to feel overwhelmed and unable to develop and integrate the necessary skills and knowledge for self-care of their condition.¹ Research^{2,3} has shown that inadequate health literacy in diabetics is associated with worse glycemic control and higher rates of retinopathy and may contribute to more diabetes-related problems.

Approximately one half of U.S., English-speaking adults read and comprehend materials only when written at less than an 8th grade reading level. Approximately one third of adults in the U.S. cannot read and understand basic materials.¹ Health literacy is usually lower than general literacy because of the

unfamiliarity with health-related and medical terminology.⁴ The association between educational attainment and health literacy skills is poor.¹ It is difficult to identify people with low general or health literacy because they come from all walks of life. Patients with low literacy are often ashamed of the condition and are quite successful at hiding the limitation.

1. The submitted PPIs have a Flesch-Kincaid Reading Levels ranging from 11.9 to 12.3 (approximating a 12th grade reading level) and a Flesch Reading Ease ranging from 37.9 to 39.7%. These PPIs along with other approved insulin product PPIs fail to address the health literacy needs for the majority of diabetic adults in the U.S. To enhance comprehension across a broad patient population, patient materials should be written at a 5th to 8th grade reading level and have a reading ease of at least 60% (60% corresponds to an 8th grade reading level).
2. The draft (b)(4) Disposable Insulin Deliver Device User Manual has a Flesch-Kincaid Reading Level of 6.5 and a Flesch Reading Ease of 70.6%. The reading level and reading ease are both acceptable for patient information. This manual was developed with sponsor-conducted usability studies.

Recommendations

1. Have the sponsor revise the three Humalog-product PPIs to meet the comprehension needs of the majority of patients with diabetes.
 - We recommend a question and answer format, such as that used for Medication Guides (see 21 CFR § 208). This format is voluntary for PPIs, but has research to support its effectiveness as a risk communication tool.
 - Use simple, short sentences to enhance readability. Avoid the use of technical terms or define them in patient-friendly terms.
 - Use cognitive accessibility principles such as “chunking” for comprehensibility. Chunking⁵ allows people to access and retrieve information more readily. (The chunking principle involves classifying items into groups to avoid information overload.)
 - Demonstrate good principles of type-size and design by using at least a 10-point font, serif type, and not using all upper case letters in the text.
 - Demonstrate good principles of page layout and design by left justifying margins, using ample white space throughout the document and using good contrast between ink and paper colors.
 - Shorten the PPI to an optimal length of 1 to 2 pages. Keep information on diabetes brief. Patient information leaflets (PPIs) are to enhance appropriate use of medications and provide important risk information. Description of an underlying medical condition should be brief or placed in a separate sheet and provided as a separate educational material for the patient.
2. We again suggest consideration for insulin class language to include in product-specific patient labeling to ensure consistency and comprehension across the Class of products.

Please let us know if you have any questions. We will be happy to review a revised, patient-friendly PPI.

¹Chew, LD. The impact of low health literacy on diabetes outcomes, *Diabetes Voice* 2004; 49: 30-32

²Williams MV, Baker DW, Parker RM, Nurss JR. Relationship of functional health literacy to patients' knowledge of their chronic disease. A study of patients with hypertension and diabetes. *Arch Intern Med* 1998; 158: 166-72

³Schillinger D, Grumbach K, Piette J, Wang F, Osmond D, Daher C, Palacios J, Sullivan GD, Bindman AB. Association of health literacy with diabetes outcomes, *JAMA* 2002; 288: 475-82

⁴The National Academy of Sciences. Health Literacy: A Prescription to End Confusion, 2004

⁵Gobet, F, Lane PC, Croker S, Cheng PC, Jones G, Oliver I, & Pine JM. Chunking mechanisms in human learning. *Trends in Cognitive Sciences* 2001; 5(6): 236-243

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/s/

Jeanine Best
1/9/2007 09:45:53 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/9/2007 01:22:13 PM
DRUG SAFETY OFFICE REVIEWER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021018Orig1s034

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 020563/S-075
NDA 021017/S-040
NDA 021018/S-034

GENERAL ADVICE

Eli Lilly and Company
Attention: Christopher L. Jordan
Manager, Global Regulatory Affairs – U.S.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Jordan:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA/Supplement	Drug Product Name
020563/S-075	Humalog (insulin lispro injection [rDNA origin])
021017/S-040	Humalog Mix 75/25 (75% insulin lispro protamine suspension/25% insulin lispro injection [rDNA origin])
021018/S-034	Humalog Mix 50/50 (50% insulin lispro protamine suspension/50% insulin lispro injection [rDNA origin])

We also refer to our Supplement Approval correspondence dated September 6, 2007, which describes your agreement to submit to FDA reports of medication errors or pharmaceutical product complaints and start/switch data for the KwikPen product line on a quarterly basis for one year and semi-annually thereafter. This surveillance reporting was based on concerns for medication errors between the prefilled KwikPen injector pens and your existing disposable pen line.

We also refer to your January 7, 2011, submissions containing requests to discontinue the above-described surveillance reporting for KwikPen.

We have reviewed your requests. We agree that this surveillance reporting for KwikPen can be discontinued because you have discontinued manufacturing of the original disposable pen line and the existing supply of the original disposable pen line was exhausted in 2010. Therefore, this potential source of medication error is no longer possible and continued surveillance of this risk is no longer warranted.

NDA 020563/S-075
NDA 021017/S-040
NDA 021018/S-034
Page 2

If you have questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
09/21/2011

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/s/

Enid Galliers

5/7/2007 08:16:30 PM

A desk copy of the complete response + consult
form was delivered to Samuel Chan on 5-4-7.

COMIS did not show these submissions on 5-4-7

so this consult could not be checked into

DFS until 5-7-7. The electrolabeling became available in
the EDR on 5-7-7.

SIGNATURE OF REQUESTER Enid Galliers	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DFS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Enid Galliers

5/7/2007 09:15:40 PM

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, November 09, 2010 2:31 PM
To: Christopher L Jordan
Subject: RE: Request to Discontinue Kwikpen Reporting

Hello Chris,

The Division of Medication Error Prevention and Analysis has the following requests:

- 1) Please submit two working samples of the proposed Humalog Mix 50/50 Kwikpen with the [REDACTED] (b) (4) (NDA 021018).
- 2) We note that your human factors study submitted February 26, 2009, compared Humalog Mix 75/25 and Humalog Mix 50/50 KwikPens. Do you intend for the Humalog Mix 75/25 KwikPen to also have a [REDACTED] (b) (4). Are you intending to submit a prior approval labeling supplement for the Humalog Mix 75/25 KwikPen?
- 3) Please refer to the communication sent on July 28, 2009. Due to concern about the potential confusion between the similar colored Humalog (maroon) and Humalog Mix 50/50 (red) KwikPens, we requested that you compare these two pens to ensure the proposal to [REDACTED] (b) (4) will not increase the risk of confusion between them. Please submit the protocol and results from any comparison study that was done for these two products. Are you intending to submit a prior approval labeling supplement for the Humalog KwikPen?
- 4) We received a CBE-0 on May 14, 2010 notifying the FDA that Lilly intended to discontinue the original prefilled insulin delivery device for NDA 020563, NDA 021017, and NDA 021018. DMEPA would like clarification on whether patients and health care providers have been informed, and whether your supply of the original prefilled pens has been exhausted. When was production discontinued for the Humalog, Humalog Mix 75/25, and Humalog Mix 50/50 original prefilled pens? If the supply has not been exhausted, when do you project the supply to run out?
- 5) When was the GCDS system introduced to the market?

Please provide an expected response timeframe.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
11/09/2010

Galliers, Enid M

From: Galliers, Enid M
Sent: Friday, August 17, 2007 8:21 PM
To: 'William L Current'; 'Jason T Johnson'
Cc: Galliers, Enid M
Subject: Follow-up to my 5:41 PM phone message to JTJ today regarding the Mother supplement

Attachments: marked-up changes.Mother.doc

Eli Lilly & Co.

Attention: William Current, PhD, and Jason T. Johnson

RE: NDA 18-780/ NDA 18-781/ NDA 19-717/ NDA 20-100
NDA 20-563/ NDA 21-017/ NDA 21-018

Dear Bill & Jason:

After reviewing the ACE & ARB CBE labeling submissions dated June 4 and 5, 2007, we recommend that the following changes be made to package inserts (PIs) and patient package inserts (PPIs) in other pending supplements that contain labeling to more accurately reflect the mechanisms by which interaction of insulins with these drugs reduces insulin requirements. The labeling changes are shown in marked-up, highlighted format in the attached MS Word document.



marked-up
anges.Mother.doc (

For the pending six supplements submitted October 28, 2005, and one submitted December 7, 2006, this change can be accomplished with your official agreement to incorporate these changes, and we can describe these revisions in approval letters that will have the August 10, 2007, (i.e., uncorrected) labeling attached.

For the three KwikPen supplements, the changes should be made to the revised PPIs you plan to submit during the week of August 20, 2007. Revised PIs should also be submitted.

Fortunately, the carton and container labels for the seven GCDS supplements are not affected by this request.

Please feel free to discuss alternate plans to achieve our goals.

Best regards,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

1 page of Draft Labeling has been Withheld in Full as b 4 (CCI/TS) immediately following this page.

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/s/

Enid Galliers
8/19/2007 12:54:19 PM
CSO

Galliers, Enid M

From: Galliers, Enid M
Sent: Sunday, July 22, 2007 9:29 PM
To: 'William L Current'
Cc: 'Belinda J Schluchter'; 'Jason T Johnson'; [REDACTED] (b) (6)
Subject: RE: KwikPen GCDS

To: Eli Lilly & Co.
William L. Current, Senior Regulatory Advisor, US Regulatory Affairs

RE: Humalog, Humalog Mix 70/30, Humalog Mix 50/50 KwikPens

Dear Bill:

DMEP has additional clarifications and modifications to the recommendations previously forwarded to you on labeling for the KwikPens.

For the KwikPen carton labeling:

DMEP concurs with DMETS's suggestion to include statement like "new disposable pen injector" on the KwikPen cartons that will alert patients to the fact that the KwikPen is new or different. DMEP adds a suggestion to highlight this statement on KwikPen cartons with a different color and/or shape than the red oval alert (to remind patients to read the instructions every time) used on the Humalog Pen carton.

For the revised Patient Package Insert (PPI) [based on the Humalog Mix 70/30 PPI that was marked-up by DSRCS]:

A. Line 30 - *Do not take Humalog if your blood sugar is too low*

- DMEP thinks this is an oversimplification. It is usually bad advice to omit an insulin dose because of hypoglycemia. It only sets things up for hyperglycemia a few hours later. The label already states that Humalog should not be taken without a meal within 15 minutes. If the patient has a low glucose, but is not symptomatic, the best course would be to delay the insulin until the meal is served. If symptomatic, the hypoglycemia should be treated before the insulin is given. These conditions are captured better in the original language than in the revised language.
- For the hypoglycemia comment, DMEP favors language along the lines of what was originally used: Line 30 (on the clean, revised copy) could instead read: "your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your healthcare provider's instructions on the use of Humalog Mix75/25."

B. Line 115 - [REDACTED] (b) (4)

Hypokalemia can be a serious consequence when ketoacidosis is treated with insulin. However, there is rarely, if ever clinically important hypokalemia when insulin is used by patients in the standard outpatient setting. Few patients will know what [REDACTED] (b) (4) really means. DMETS believes that putting this statement in will add confusion.

C. Additional minor changes:

- Line 82 on the clean copy: "Never inject [REDACTED] (b) (4) into a muscle or vein" - I would replace the word [REDACTED] (b) (4) with "Humalog Mix75/25"
- DSRCS removed the following wording "Low blood sugar may affect your ability to drive a car or use mechanical equipment, risking injury to yourself or others" - DMEP thinks this should be added back starting after the word "death" in Line 98 of the clean copy.
- Line 104: "Severe, life-threatening allergic reactions can happen with [REDACTED] (b) (4) insulin" should instead read "...can happen

with insulin"

4. Line 109, "(b) (4)" should instead read "... (b) (4)"

5. Line 113, "(b) (4)" should instead read "...your injection sites enough"

6. In some places there is a space between Mix and 75/25 and in other places there is no space. It is not readily apparent whether this inconsistency was introduced during FDA's editing process.

Best regards,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

7/22/2007

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/s/

Enid Galliers

7/22/2007 09:34:06 PM

CSO

Galliers, Enid M

From: Galliers, Enid M
Sent: Wednesday, July 18, 2007 4:12 PM
To: 'William L Current' (b) (6)
Cc: 'Belinda J Schluchter'; 'Jason T Johnson';
Subject: KwikPen issues

Dear Bill,

TO SPONSOR: Eli Lilly & Co.

RE:

- NDA 20-563/S-075 - Humalog KwikPen (insulin lispro [rDNA origin] injection)
- NDA 21-017/S-040 - Humalog Mix75/25 KwikPen (75% insulin lispro protamine suspension and 25% insulin lispro injection, [rDNA origin])
- NDA 21-018/S-034 - Humalog Mix50/50 KwikPen (50% insulin lispro protamine suspension and 50% insulin lispro injection, [rDNA origin])

DMETS' Comments and Recommendations regarding KwikPen response:

TRADE NAMES:

1. DMETS and DMEP have no objection to the use of the proprietary names Humalog KwikPen, Humalog Mix 70/30 KwikPen, and Humalog Mix 50/50 KwikPen.

SURVEILLANCE PROGRAM:

2. DMETS recommends that as part of the Surveillance Program incoming reports of medication errors or pharmaceutical product complaints received by the Sponsor involving the KwikPen product line be reviewed and provided to the Agency along with the new start/switch data. DMEP concurs with this recommendation.

LABELING AND PACKAGING

DMETS reviewed the revised User Manual for the KwikPen that is used with all three Humalog products, and separate carton label, pen label, package insert, and patient package insert for Humalog KwikPen, Humalog Mix75/25 KwikPen, and Humalog Mix50/50 KwikPen. DMETS focused on safety issues relating to possible medication errors. DMETS and DMEP have the following comments regarding the proposed labels and packaging.

3. Since the existing disposable pen injector (i.e., Humalog Pen) and the KwikPen products are going to co-exist for any length of time in the marketplace, DMETS believes that the Sponsor should **consider including a cautionary statement on the lower portion of the carton's primary display panel to alert practitioners, patients, and caregivers that the KwikPen is a new pen with different use. Specifically, the warning should be present for 6 months following initial marketing of each product, and highlight the fact that the proposed KwikPen is a "new disposable pen injector."** If space allows the alert could also highlight the fact that the KwikPen has different instructions than the existing pen injector device, and reference to the importance of reading the User Manual prior to use. **This descriptor should have adequate prominence on the primary carton label**, since the information may help to avoid product selection errors resulting from overlooked modifiers. Also, in the event that the KwikPen product is dispensed in error to a patient in place of the existing pen-injector, it could help patients to recognize the

mistake and possibly avert administration of the product in error.

DMEP requests that Lilly provide a response to items 2 and 3.

DMEP is essentially in concurrence with DSRC's recommendations regarding the revisions to the PPI. However, the division will send specific comments on items that may be negotiable or not necessary within a few days - possibly by July 20.

Best regards,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

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/s/

Enid Galliers
7/18/2007 04:37:41 PM
CSO



NDA 21-018/S-034

PRIOR APPROVAL SUPPLEMENT

Eli Lilly and Company
Attention: William L. Current, Ph.D.
Senior Associate Director
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Current:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Humalog Mix 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA origin])
NDA Number:	21-018
Supplement number:	S-034
Date of supplement:	October 05, 2006
Date of receipt:	October 12, 2006

This supplemental application proposes to add an additional disposable insulin delivery device, ^{(b) (4)} for use with Lilly's Humalog Mix 50/50 3mL cartridges.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 11, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 12, 2007.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Regulatory Project Management Staff
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers

11/30/2006 01:10:57 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Enid Galliers, CPMS, DMEP (HFD-510) WO, B. 22, Rm 3356; Phone 30-796-1211		
DATE 11/26/06	IND NO.	NDA NO. N 20-563/S-075 N 21-017/S-040 N 21-018/S-034	TYPE OF DOCUMENT SCP packaging supplement Adds a new disposable pen for injecting insulin	DATE OF DOCUMENT 05-OCT-2006 DATE RECEIVED 10-OCT-2006
NAME OF DRUG Humalog (insulin lispro [rDNA origin]) injection Humalog Mix 75/25 Humalog Mix 50/50		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE January 12, 2007
NAME OF FIRM: Eli Lilly & Co.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: These supplements add a new disposable pen, (b) (4), for use with approved 3 mL cartridges of Humalog, Humalog Mix 75/25, and Humalog Mix 50/50. The submission includes a new USER MANUAL for the (b) (4) (used for all three Humalog products), and separate PI, PPI, pen label, and carton label for each of the three products. All the labeling is available in the EDR. The usability study was submitted in paper, but it has been scanned and can be provided if requested. (All these materials have been consulted to CDRH also.) Please comment on the labeling submitted for these supplements. To allow time for labeling discussions, please complete your reviews by Jan 12, 2007. UF goal = 10-FEB-2007				
SIGNATURE OF REQUESTER Enid Galliers		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DFS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Enid Galliers

11/26/2006 04:40:40 PM

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH

Division: DAGID/GHDB

Mail Code: HF Z-480

Consulting Reviewer Name: ANTHONY WATSON

Building/Room #: CORP/RM 340D, 9200 CORP BLVD

Phone #: 240-276-3700

Fax #:

Email Address: ANTHONY.WATSON@FDA.HHS.GOV

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: DMEP

Mail Code: HFD-510

Requesting Reviewer Name: ENID GALLIERS

Building/Room #: WO B.22, RM 3356

Phone #: 301-796-1211

Fax #: 301-796-9712

Email Address: ENID.GALLIERS@FDA.HHS.GOV

RPM/CSO Name and Mail Code: ENID GALLIERS

Requesting Reviewer's Concurring

Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 11-21-2006

Requested Completion Date: 1-15-2007

Submission/Application Number: N 20-563/S-075 et al.
(Not Barcode Number)

Submission Type: sNDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 10-10-06

Official Submission Due Date: 2-10-2007

Name of Product: (b) (4) for Humalog, Humalog Mix 75/25 and Humalog Mix 50/50

Name of Firm: Eli Lilly & Co.

Intended Use: (b) (4) is a disposable insulin injection device.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

The following materials are being sent via email: [scanned images] (b) (4) device information is submitted in 510(k) format with a Piston Syringe Review Checklist. System Assembly and Lot Release of the complete (b) (4) is included. [electronic documents] Package inserts & patient package inserts, pen and carton labels for the (b) (4) filled with each of the three Humalog products, one (b) (4) User Manual (pdf & Word) which will be used for all three insulin products. Cover letter and Reviewer Note.

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Please review the reliability and dose delivery accuracy of the (b) (4) edit the User Manual; and comment on the other labeling pieces if necessary.
The complete submission is being sent via email. If any necessary information is missing, we will need to request it from the applicant.

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/s/

Enid Galliers

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