CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-810

PROPRIETARY NAME REVIEW(S)

ODS/DMETS comments to Novo on 1/30/06

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(WO: 22, Mailstop 4447, HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #s:**
June 27, 2005	February 28, 2006	05-0164 (NDA 21-809) and
DATE OF DOCUMENT:	**PDUFA DATE:**	05-0165 (NDA 21-810)
June 22, 2005	April 22, 2006	

TO: David Orloff, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

FROM: Charlie Hoppes, R.Ph., M.P.H., Safety Evaluator
Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Division Director
Carol Holquist, R.Ph., Director

PRODUCT NAME:	**NDA SPONSOR:**
NovoLog® Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection) and **NovoLog® Mix 50/50** (50% insulin aspart protamine suspension and 50% insulin aspart injection) **NDA#s:** 21-809 and 21-810, respectively	Novo Nordisk

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary names, NovoLog Mix 30/70 and NovoLog Mix 50/50.

2. Although DMETS continues to recommend against implementation of International Diabetes Federation color coding for insulin products, DMETS recognizes that this scheme is increasingly being implemented. In light of the proliferation of insulin products and the limited number of readily discernible colors, DMETS believes that the sponsor's color branding proposals will ultimately lead to increased confusion of products (See Section II.4. of this review). Delete color coding on labels, labeling, and on insulin delivery devices and propose a different method for differentiating the products.

3. 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.

4. Upon product launch DMETS recommends that the sponsor provide education for healthcare providers as to the availability of the new product formulations.

5. DDMAC finds the proprietary names NovoLog Mix 30/70 and NovoLog Mix 50/50 acceptable from a promotional perspective.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
(WO: 22, Mailstop 4447, HFD-420)
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 22, 2005

NDA#s 21-809 and 21-810

NAME OF DRUGS: **NovoLog® Mix 30/70**
(30% insulin aspart protamine suspension and 70% insulin aspart injection)
and
NovoLog® Mix 50/50
(50% insulin aspart protamine suspension and 50% insulin aspart injection)

NDA HOLDER: Novo Nordisk

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for assessment of the proprietary names, "NovoLog Mix 30/70 and NovoLog Mix 50/50", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and profession insert labeling, and patient information were provided for review and comment.

PRODUCT INFORMATION

Novolin and *NovoLog* are proprietary names used by Novo Nordisk for its product lines 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. There are four *Novolin* products (*Novolin R, Novolin N, Novolin L, Novolin 70/30*), and two currently marketed *NovoLog* products (*NovoLog* and *NovoLog Mix 70/30*). At present, the sponsor seeks approval of two new NovoLog Mix products, *NovoLog Mix 30/70* and *NovoLog Mix 50/50.* These products are to provide therapeutic alternatives with different long-acting/short-acting insulin balance to the existing NovoLog Mix 70/30 product.

Novolin R is a short acting human insulin analog with an onset of about 0.5 hours, 2.5 to 4 hour peak and an 8 hour duration of action. It can either be administered subcutaneously, intramuscularly or intravenously. It is usually given before meals.

Novolin N is an intermediate acting insulin with a 1.5 hour onset, 4 to 12 hour peak and 24 hour duration of action. It is administered subcutaneously.

Novolin 70/30 is a premixed combination of 70% intermediate acting insulin isophane suspension, and 30% short acting regular insulin.

Novolin insulin is also referred to as Regular (Novolin R), NPH (Novolin N), 70/30 (Novolin 70/30) and Lente (Novolin L). All formulations are available in 10 mL vials of 100 units/mL. Regular, NPH and 70/30 are also available in 3 mL (100 units/mL) *PenFill* cartridges and 3 mL (100 units/mL) disposable *Prefilled* injectable devices. A 1.5 mL NovoPen (150 units/1.5 mL) was discontinued in October 2000 and replaced by NovoPen 3 (300 units/3 mL).

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. Novolog is available in 10 mL vials of 100 units/mL and 3 mL cartridges for use with a pen device (NovoPen).

NovoLog Mix 70/30 is a premix containing 30% rapid-acting Novolog (insulin aspart) and a 70% modified long acting formulation (insulin aspart protamine suspension).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to NovoLog Mix 30/70 and NovoLog Mix 50/50 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 conducted[4]. 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 for each name, 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.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names NovoLog Mix 30/70 and NovoLog Mix 50/50. 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 NovoLog Mix 30/70 and NovoLog Mix 50/50 acceptable from a promotional perspective.

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[1] MICROMEDEX Integrated Index, 2005, 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 98-05, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

2. The Expert Panel identified one name (Novolog Mix 70/30), that was thought to have the potential for confusion with NovoLog Mix 30/70. Through independent review, two additional names (NovoLog and Novolin 70/30), were identified for review. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage. Comments from panelists almost universally expressed concern for confusion between 30/70 and 70/30. A representative comment follows, "Most insulins are stored on the nursing units – in a fast paced environment, a nurse or pharmacist may pull the wrong vial."

3. The Expert Panel also identified one proprietary name (Humalog Mix 50/50), that was thought to have the potential for confusion with NovoLog Mix 50/50. Through independent review, one additional name (NovoLog), was identified for review. These products are listed in Table 2 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for Novolog Mix 30/70

Proposed Proprietary Name	Dosage form(s), Established name	Usual adult dose	Other
NovoLog Mix 30/70	30% Insulin Aspart Protamine Suspension and 70% Insulin Aspart Injection	Inject subcutaneously before meals up to three times daily in doses determined by patient need.	
NovoLog Mix 70/30	70% Insulin Aspart Protamine Suspension and 30% Insulin Aspart Injection	Inject subcutaneously before meals up to three times daily in doses determined by patient need.	SA/LA
NovoLog	Insulin Aspart Injection, 100 units/mL	Inject subcutaneously before meals. Ordinarily used in combination with a long-acting insulin.	SA/LA
Novolin 70/30	70% NPH Human Isophane Insulin Suspension and 30% Regular Human Insulin Injection	Inject subcutaneously once or twice daily before a major meal(s) in doses determined by patient need.	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for Novolog Mix 50/50

NovoLog Mix 50/50 Proposed Proprietary Name	Dosage form(s), Established name 50% Insulin Aspart Protamine Suspension and 50% Insulin Aspart Injection	Usual adult dose Inject subcutaneously before meals up to three times daily in doses determined by patient need	Other
Humalog Mix 50/50	50% Insulin Lispro Protamine Suspension and 50% Insulin Lispro Injection	Inject subcutaneously before meals up to three times daily in doses determined by patient need.	LA
NovoLog	Insulin Aspart Injection,100 units/mL	Inject subcutaneously before meals. Ordinarily used in combination with a long-acting insulin.	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion.

All names considered to have significant phonetic or orthographic similarities to NovoLog Mix 30/70 or NovoLog Mix 50/50 were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for each of the proposed proprietary names to determine the degree of confusion of NovoLog Mix 30/70 and NovoLog Mix 50/50 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. These studies employed a total of 124 (NovoLog Mix 30/70) and 121 (NovoLog Mix 50/50) health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for NovoLog Mix 30/70 and NovoLog Mix 50/50 (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, the outpatient orders were 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.

NovoLog Mix 30/70

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Novolog Mix 30/70 #1 WD	NovoLog Mix 30/70 1 bottle Use as directed.
Inpatient RX: Novolog Mix 30/70 insul as directed subcutaneous	

NovoLog Mix 50/50

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Novolog Mix 50/50 Disp: 1 FlexPen use as directed	NovoLog Mix 50/50 FlexPen Use as directed.
Inpatient RX: Novolog Mix 50/50 FlexPen use as directed	

2. Results:

Five respondents in the NovoLog Mix 30/70 study interpreted the proposed name as NovoLog Mix 70/30. NovoLog Mix 70/30 is a currently marketed U.S. product. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, NovoLog Mix 30/70. See Appendix A for the complete listing of interpretations from the verbal and written studies.

In the NovoLog Mix 50/50 study, none of the interpretations of the proposed name, overlap, sound similar, or look similar to any currently marketed U.S. product. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, NovoLog Mix 50/50. See Appendix B for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

Insulin errors constitute a substantial proportion of total medication errors in this country. A root cause analysis of insulin-related medication errors in the DMETS review dated March 15, 2003 (ODS 02-0037), has uncovered many risk factors for errors including, nomenclature similarities, (e.g., **NovoLog** vs. **Novolin** and Pen**Fill** vs. Pre**fill**), visual similarities and commonalities in trade dress through product lines, strength similarities, (e.g., NovoLog Mix **70/30** vs. Novolin **70/30**), and incorrect insulin administration techniques including insulin pen devices and pumps. With the March 2003 consult, DMETS made general recommendations to improve the safe use of insulin products.

More recently, in a review dated May 9, 2004 (ODS 04-0163), DMETS reviewed labeling supplements for NovoLog (NDA 20-986/S-019) and NovoLog Mix 70/30 (NDA 21-172/S-013), providing for color differentiation. DMETS recommended against approval of those supplemental applications due to concerns over the proliferation of insulin products and the limited number of distinct colors available to distinguish them. DMETS made recommendations regarding systemic application of differentiating features for insulin product labels and labeling.

1. AERS/DQRS Searches

DMETS conducted searches of the FDA Adverse Event Reporting System (AERS) and the Drug Quality Reporting System (DQRS) to determine the degree of post-marketing errors with NovoLog and NovoLog Mix 70/30. AERS was searched using the terms: MedDRA Preferred Terms (PTs), "Medication Error", "Accidental Overdose", "Overdose", "Pharmaceutical Product Complaint", and "Treatment Non-Compliance", and the drug names, "novolog%", and "novo log%". The DQRS was also searched for reports of medication errors. This search strategy uncovered 30 errors with "NovoLog" products (see Appendix C). Main sources of error included, confusion between NovoLog and Lantus (6 errors), confusion between NovoLog Mix 70/30 and NovoLog (8 errors), confusion between NovoLog Mix 70/30 and Novolin 70/30 (11 errors), NovoLog use in insulin pump (3 errors), and device malfunctions (2 errors). Issues involving errors between NovoLog and Lantus, incorrect NovoLog use in insulin pumps, and device malfunctions have been addressed in our review dated March 15, 2003 (ODS 02-0037), and will not be addressed again

in this review. Errors involving confusion between NovoLog Mix 70/30 vs. NovoLog and NovoLog Mix 70/30 vs. Novolin 70/30 have special significance in the review of the newly proposed names and are discussed further in Section D. AERS searches using the terms: MedDRA Preferred Terms (PTs), "Medication Error", "Accidental Overdose", "Overdose", "Pharmaceutical Product Complaint", and "Treatment Non-Compliance", and the drug name, "humal%", did not yield any results for confusion between NovoLog and Humalog.

2. NovoLog Mix 30/70 Name Review

In reviewing the proprietary name NovoLog Mix 30/70, the primary concerns related to look-alike and sound-alike confusion with NovoLog Mix 70/30. Through independent review, two additional drug names, Novolin 70/30 and NovoLog, were also determined to have potential for confusion with NovoLog Mix 30/70.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that NovoLog Mix 30/70 could be confused with NovoLog Mix 70/30. Two respondents from the outpatient study, two respondents from the inpatient study, and one respondent of the verbal prescription order study misinterpreted the name as NovoLog Mix 30/70 name using the "70/30" rather than "30/70". Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

a. NovoLog Mix 70/30 is identical to NovoLog Mix 30/70 except the strengths are reversed. NovoLog Mix 70/30 is the currently marketed strength of the long/short-acting proposed insulin product. NovoLog Mix 70/30 shares every product characteristics with the proposed product NovoLog Mix 30/70 except the relative amounts of long and short-acting insulin. DMETS believes that choice of the same numerals ("30" and "70") as strengths for the proposed product will result in numeric transposition, product confusion, and medication errors. In fact, five participants of verbal and written prescription studies when given the auditory or verbal cue, "30/70", transposed the numerals, and responded with "70/30". DMETS does not believe that any amount of labeling and packaging differentiation between the 70/30 and 30/70 formulations will prevent errors resulting from cognitive transposition of the product strengths and subsequent medication misfills, since these errors would be expected to occur with interpretation of the prescription rather than with product selection. DMETS believes that errors from numeric transposition could occur at many different levels including, when writing a prescription, when interpreting prescriptions, and at the point that a product is selected. In fact, these errors will likely go undetected until a patient experiences an adverse event. A patient receiving NovoLog Mix 30/70 rather than 70/30 might experience an initial hypoglycemia due to the relative increase in short acting insulin, with increased blood sugars later in the dosing cycle resulting from the reduction in long-acting insulin. Such an effect could be dangerous if the patient does not expect it, for example if the patient is driving a car and has unexpected hypoglycemia. Conversely, a patient receiving NovoLog Mix 70/30 rather than 30/70 might experience loss of blood sugar

control in the short term followed by potentially dangerous hypoglycemia later in the dosing cycle resulting from the increase proportion of long-acting insulin. Overall, DMETS believes there is potential for these products to be confused due to strong orthographic and phonetic similarities as well as shared product characteristics including numeric similarities in the strength.

b. Novolin 70/30 vs. NovoLog Mix 30/70

Novolin 70/30 was identified as a product that may be confused with NovoLog Mix 30/70 when scripted and which may sound similar when spoken. Novolin 70/30 is 70% NPH human isophane insulin suspension and 30% regular human insulin injection for once or twice daily subcutaneous injection. Novolin 70/30 has a documented history of confusion with NovoLog Mix 70/30. For that reason, and because numeric transposition of "30/70" to "70/30" was known to occur in the written and verbal prescription studies conducted, DMETS expects that errors between these names would occur with introduction of NovoLog Mix 30/70 into the marketplace.

Unlike Novo Nordisk, Lilly formulated their long/short acting analog insulin product as a 75%/25% mixture (Humalog® Mix 75/25) rather than as Humalog® Mix 70/30, which serves to differentiate it from their Humulin® 70/30 product. Even so, there have been reports in the literature of orders written for Humalog as a 70/30 mixture even though no such product exists[5]. Novo Nordisk, on the other hand, chose to formulate their long/short acting analog insulin product as a 70%/30% mixture (NovoLog® Mix 70/30). When this product entered the marketplace following its approval on November 1, 2001, healthcare providers warned about the potential for errors between NovoLog Mix 70/30 and Novolin 70/30.

Early on, the Institute for Safe Medication Practices (ISMP) predicted the possibility for confusion between Novolin 70/30 and NovoLog Mix 70/30[6], then with the passage of time, reported the occurrence of these errors[7], sometimes leading to significant hypoglycemia. DMETS identified eleven cases of medications errors resulting from confusion between NovoLog Mix 70/30 and Novolin 70/30 (see Appendix C). The following excerpt from an AERS report serves to illustrate these concerns:

> Novo Nordisk has now released Novolog 70/30. Get your error traps in early before your (sic) automatically give regular 70/30. Poor choice (in my opinion) of naming a product!! Why not Novolog 71/29??

The above report of the potential for error and others like it proved prophetic as reports of confusion between these products, often resulting in actual error began to appear as illustrated by the following excerpt:

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[5] The Insulin Challenge. *ISMP Medication Safety Alert! Nurse Advise-ERR*. 2004; 2(4): 1.

[6] Proliferation of insulin combination products increases opportunity for errors. *ISMP Medication Safety Alert!* 2002; 7(24): 2.

[7] The Insulin Challenge. *ISMP Medication Safety Alert! Nurse Advise-ERR*. 2004; 2(4): 1.

Patient received Novolin 70/30 instead of Novolog 70/30. The patient actually received the wrong insulin (probably for several days). Patient obviously experienced fluctuations in blood sugars and poor control.

An excerpt from another report follows, this time from the inpatient setting:

Patient admitted from nursing home and ordered Novolog 70/30, 40 units every morning and 15 units every evening. Nursing unit transcribed order as Novolin 70/30 and administered Novolin 70/30 from stock prior to pharmacist verification of order.

DMETS believes that errors between Novolin 70/30 and NovoLog Mix 70/30 will continue into the future and, if NovoLog Mix 30/70 is introduced into the marketplace, errors with Novolin 70/30, are likely, especially since numeric transposition between "30/70" and "70/30" is known to occur.

c. NovoLog vs. NovoLog Mix 30/70

The proposed name, NovoLog 30/70 may be confused with the marketed product NovoLog. Through post-marketing surveillance and medication safety literature, DMETS is aware of the extensive nature of medication errors resulting from the omission of a modifier from a proprietary name. In fact, searches in FDA databases identified eight reports of confusion between Novolog and NovoLog Mix 70/30. Reporters attributed errors to name similarities and similarities in the product packaging. DMETS believes that these errors could continue to occur between NovoLog and NovoLog Mix 30/70 if this product is introduced into the marketplace.

The following excerpt provides insight on why these products are being confused and offers suggestions on labeling revisions that might serve to decrease the potential for error:

The labels of Novolog and Novolog Mix 70/30 are too close in appearance to prevent errors. The product identification for NovoLog Mix 70/30 is in very small print that requires turning the bottle to read "70/30" and therefore does not stress that it is the mixture. There have been numerous near misses that I am aware of. I would suggest redesigning the label so that the 70/30 is very prominent and is in the same viewing field as the name of the product.

Another reporter states:

My son uses Novolog insulin in his pump. I receive his insulin in 3 vial increments. Two of the vials I received were the correct insulin. The third vial that was dispensed to me was a Novolog Insulin but was a 70/30 mix instead of the straight Novolog insulin. I discovered the error only when examining the insulin itself -it was cloudy as compared to clear-but I did not notice the error by looking at the box of insulin. On the boxes containing the insulin vials, the font stating "Novolog" is the same size on both types of insulin and the "70/30" is written in small font. There is very little differentiation in
packaging.

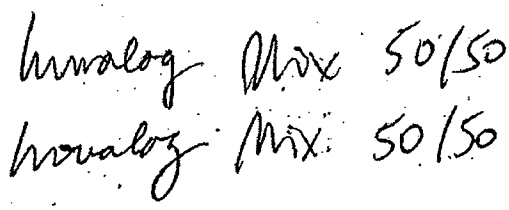
DMETS believes that errors between NovoLog and NovoLog Mix 70/30 will continue into the future and, if NovoLog Mix 30/70 is introduced into the marketplace, errors with NovoLog, are likely.

3. NovoLog Mix 50/50 Name Review

In reviewing the proprietary name NovoLog Mix 50/50, the primary concerns related to look-alike confusion with Humalog Mix 50/50 and confusion with NovoLog.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, NovoLog Mix 50/50.

a. Humalog Mix 50/50 was identified as a name with similar appearance to NovoLog Mix 50/50 when scripted. Humalog Mix 50/50 is a mixture of 50% insulin lispro protamine and 20% insulin lispro. Like NovoLog Mix products, Humalog Mix is administered subcutaneously prior to meals. The only orthographically or phonetically differentiating features involve the initial letters "Huma" vs. "Novo", which themselves may look alike, especially when scripted in lower case cursive hand. As seen in the writing sample below, the lower case "h" and "n" may look very much alike. The "o's" in "novo" may also look like the "u" in "huma" when the "o" is not completely closed at the top and the "a" in "huma" when the terminal down stroke of the "a" lacks prominence. The cursive "m" and "v" also may look similar since they are both a series of up and down strokes, which may not appear as unique letters when scripted quickly (see handwriting sample below).



Humalog Mix 50/50 and NovoLog Mix 50/50 also share many product characteristics including, route of administration (subcutaneous injection), dosage form (injection in prefilled pen device and vials), indication for use (for type I diabetes), patient population (diabetic patients), dose and dosing regimen (dosed before meals in units according to need), respectively. The products also have similar active ingredients (both are human insulin analogs). Through searches of the AERS database DMETS is not aware of reports of confusion between "Humalog" products and "Novolog" to date, however, we believe that the added commonality in the proprietary name with the introduction of "50/50" will increase the likelihood of medication errors. Overall, DMETS believes there is potential for these products to be confused due to strong orthographic similarities as well as shared product characteristics.

b. NovoLog vs. NovoLog Mix 50/50

DMETS is concerned with the potential for confusion between NovoLog and NovoLog Mix 50/50 for the reasons outlined in Section II.D.2.c. above (NovoLog vs. NovoLog Mix 30/70).

4. Color Coding and Similarities in Trade Dress for Novo Nordisk Products

As seen in the table below, labeling proposed for the new NovoLog Mix formulations employs a color stripe in shades of blue and green in the principal display panel to differentiate products. DMETS does not believe that the color stripe affords adequate differentiation of the products since the remainder of the labeling is virtually identical.

	NovoLog Mix 30/70	NovoLog Mix 50/50	NovoLog Mix 70/30
FlexPen			
PenFill			

b(4

In a review dated May 9, 2004 (ODS 04-0163), DMETS expressed concerns regarding the sponsor's color branding proposals for new products. The proposed NovoLog colors alone could cause confusion. For example, a doctor asks which insulin a patient is using. The patient answers, "The blue one." In that case, the patient could be referring to Novolog Mix 50/50, Novolog Mix 30/70, or even Novolog Mix 70/30, which is a bluish green (see NovoLog colors at the top of page 12).

NovoLog Colors

NovoLog NovoLog Mix 70/30 NovoLog Mix 50/50 NovoLog Mix 30/70

b(4)

The patient could even be referring to their NovoLog insulin which comes in a blue FlexPen. The FlexPen color is difficult to distinguish between NovoLog Mix 50/50 color (see color bar below).

b(4)

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary names NovoLog Mix 30/70 and NovoLog Mix 50/50. In reviewing the proprietary names, the primary concerns for NovoLog Mix 30/70 related to look-alike and/or sound-alike confusion with NovoLog Mix 70/30 and Novolin 70/30, and NovoLog. The primary concerns for NovoLog Mix 50/50 related to look-alike and/or sound-alike confusion with Humalog Mix 50/50 and NovoLog. Additionally, DMETS has concerns with the colors proposed by the sponsor.

Insulin errors constitute a substantial proportion of total medication errors in this country. A root cause analysis of insulin-related medication errors in the DMETS review dated March 15, 2003 (ODS 02-0037), has uncovered many risk factors for errors including, nomenclature similarities, (e.g., **Novo**Log vs. **Novo**lin and Pen**Fill** vs. Pre**fill**), visual similarities and commonalities in trade dress through product lines, strength similarities, (e.g., NovoLog Mix **70/30** vs. Novolin **70/30**), and incorrect insulin administration techniques including insulin pen devices and pumps. With the March 2003 consult, DMETS made general recommendations to improve the safe use of insulin products.

More recently, in a review dated May 9, 2004 (ODS 04-0163), DMETS reviewed labeling supplements for NovoLog (NDA 20-986/S-019) and NovoLog Mix 70/30 (NDA 21-172/S-013), providing for color differentiation. DMETS recommended against approval of those supplemental applications due to concerns over the proliferation of insulin products and the limited number of distinct colors available to distinguish them. DMETS made recommendations regarding systemic application of differentiating features for insulin product labels and labeling.

1. NovoLog Mix 30/70 Name Review

In reviewing the proprietary name NovoLog Mix 30/70, the primary concerns related to look-alike and sound-alike confusion with NovoLog Mix 70/30. Through independent review, two

additional drug names, Novolin 70/30 and NovoLog, were also determined to have potential for confusion with NovoLog Mix 30/70.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that NovoLog Mix 30/70 could be confused with NovoLog Mix 70/30. Two respondents from the outpatient study, two respondents from the inpatient study, and one respondent of the verbal prescription order study misinterpreted the name as NovoLog Mix 30/70 name using the "70/30" rather than "30/70". Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

a. NovoLog Mix 70/30 is identical to NovoLog Mix 30/70 except the strengths are reversed. NovoLog Mix 70/30 is the currently marketed strength of the long/short-acting proposed insulin product. NovoLog Mix 70/30 shares every product characteristics with the proposed product NovoLog Mix 30/70 except the relative amounts of long and short-acting insulin. DMETS believes that choice of the same numerals ("30" and "70") as strengths for the proposed product will result in numeric transposition, product confusion, and medication errors. In fact, five participants of verbal and written prescription studies when given the auditory or verbal cue, "30/70", transposed the numerals, and responded with "70/30". DMETS does not believe that any amount of labeling and packaging differentiation between the 70/30 and 30/70 formulations will prevent errors resulting from cognitive transposition of the product strengths and subsequent medication misfills, since these errors would be expected to occur with interpretation of the prescription rather than with product selection. DMETS believes that errors from numeric transposition could occur at many different levels including, when writing a prescription, when interpreting prescriptions, and at the point that a product is selected. In fact, these errors will likely go undetected until a patient experiences an adverse event. A patient receiving NovoLog Mix 30/70 rather than 70/30 might experience an initial hypoglycemia due to the relative increase in short acting insulin, with increased blood sugars later in the dosing cycle resulting from the reduction in long-acting insulin. Such an effect could be dangerous if the patient does not expect it, for example if the patient is driving a car and has unexpected hypoglycemia. Conversely, a patient receiving NovoLog Mix 70/30 rather than 30/70 might experience loss of blood sugar control in the short term followed by potentially dangerous hypoglycemia later in the dosing cycle resulting from the increase proportion of long-acting insulin. Overall, DMETS believes there is potential for these products to be confused due to strong orthographic and phonetic similarities as well as shared product characteristics including numeric similarities in the strength.

b. Novolin 70/30 vs. NovoLog Mix 30/70

Novolin 70/30 was identified as a product that may be confused with NovoLog Mix 30/70 when scripted and which may sound similar when spoken. Novolin 70/30 is 70% NPH human isophane insulin suspension and 30% regular human insulin injection for once or twice daily subcutaneous injection. Novolin 70/30 has a documented history of confusion with NovoLog Mix 70/30. For that reason, and because numeric transposition of "30/70" to "70/30" was known to occur in the written and verbal prescription studies conducted, DMETS expects that errors between these names would occur with introduction of NovoLog Mix 30/70 into the marketplace.

Unlike Novo Nordisk, Lilly formulated their long/short acting analog insulin product as a 75%/25% mixture (Humalog® Mix 75/25) rather than as Humalog® Mix 70/30, which serves to differentiate it from their Humulin® 70/30 product. Even so, there have been reports in the literature of orders written for Humalog as a 70/30 mixture even though no such product exists[8]. Novo Nordisk, on the other hand, chose to formulate their long/short acting analog insulin product as a 70%/30% mixture (NovoLog® Mix 70/30). When this product entered the marketplace following its approval on November 1, 2001, healthcare providers warned about the potential for errors between NovoLog Mix 70/30 and Novolin 70/30.

Early on, the Institute for Safe Medication Practices (ISMP) predicted the possibility for confusion between Novolin 70/30 and NovoLog Mix 70/30[9], then with the passage of time, reported the occurrence of these errors[10], sometimes leading to significant hypoglycemia. DMETS identified eleven cases of medications errors resulting from confusion between NovoLog Mix 70/30 and Novolin 70/30.

DMETS believes that errors between Novolin 70/30 and NovoLog Mix 70/30 will continue into the future and, if NovoLog Mix 30/70 is introduced into the marketplace, errors with Novolin 70/30, are likely, especially since numeric transposition between "30/70" and "70/30" is known to occur.

c. NovoLog vs. NovoLog Mix 30/70

The proposed name, NovoLog 30/70 may be confused with the marketed product NovoLog. Through post-marketing surveillance and medication safety literature, DMETS is aware of the extensive nature of medication errors resulting from the omission of a modifier from a proprietary name. In fact, searches in FDA databases identified eight reports of confusion between Novolog and NovoLog Mix 70/30. Reporters attributed errors to name similarities and similarities in the product packaging.

DMETS believes that errors between NovoLog and NovoLog Mix 70/30 will continue into the future and, if NovoLog Mix 30/70 is introduced into the marketplace, errors with NovoLog, are likely.

2. NovoLog Mix 50/50 Name Review

In reviewing the proprietary name NovoLog Mix 50/50, the primary concerns related to look-alike confusion with Humalog Mix 50/50 and confusion with NovoLog.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, NovoLog Mix 50/50.

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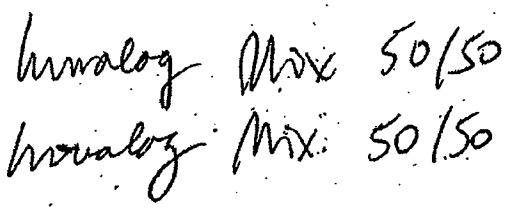
[8] The Insulin Challenge. *ISMP Medication Safety Alert! Nurse Advise-ERR*. 2004; 2(4): 1.

[9] Proliferation of insulin combination products increases opportunity for errors. *ISMP Medication Safety Alert!* 2002; 7(24): 2.

[10] The Insulin Challenge. *ISMP Medication Safety Alert! Nurse Advise-ERR*. 2004; 2(4): 1.

a. Humalog Mix 50/50 was identified as a name with similar appearance to NovoLog Mix 50/50 when scripted. Humalog Mix 50/50 is a mixture of 50% insulin lispro protamine and 20% insulin lispro. Like NovoLog Mix products, Humalog Mix is administered subcutaneously prior to meals. The only orthographically or phonetically differentiating features involve the initial letters "Huma" vs. "Novo", which themselves may look alike, especially when scripted in lower case cursive hand. As seen in the writing sample below, the lower case "h" and "n" may look very much alike. The "o's" in "novo" may also look like the "u" in "huma" when the "o" is not completely closed at the top and the "a" in "huma" when the terminal down stroke of the "a" lacks prominence. The cursive "m" and "v" also may look similar since they are both a series of up and down strokes, which may not appear as unique letters when scripted quickly (see handwriting sample below).



Humalog Mix 50/50 and NovoLog Mix 50/50 also share many product characteristics including, route of administration (subcutaneous injection), dosage form (injection in prefilled pen device and vials), indication for use (for type I diabetes), patient population (diabetic patients), dose and dosing regimen (dosed before meals in units according to need), respectively. The products also have similar active ingredients (both are human insulin analogs). Through searches of the AERS database DMETS is not aware of reports of confusion between "Humalog" products and "Novolog" to date, however, we believe that the added commonality in the proprietary name with the introduction of "50/50" will increase the likelihood of medication errors. Overall, DMETS believes there is potential for these products to be confused due to strong orthographic similarities as well as shared product characteristics.

b. NovoLog vs. NovoLog Mix 50/50

DMETS is concerned with the potential for confusion between NovoLog and NovoLog Mix 50/50 for the reasons outlined in Section 1.c. above (NovoLog vs. NovoLog Mix 30/70).

3. Color Coding and Similarities in Trade Dress for Novo Nordisk Products

As seen in the table below, labeling proposed for the new NovoLog Mix formulations employs a color stripe in shades of blue and green in the principal display panel to differentiate products. DMETS does not believe that the color stripe affords adequate differentiation of the products since the remainder of the labeling is virtually identical.

	NovoLog Mix 30/70	NovoLog Mix 50/50	NovoLog Mix 70/30
FlexPen			
PenFill			

b(4)

In a review dated May 9, 2004 (ODS 04-0163), DMETS expressed concerns regarding the sponsor's color branding proposals for new products. The proposed NovoLog colors alone could cause confusion. For example, a doctor asks which insulin a patient is using. The patient answers, "The blue one." In that case, the patient could be referring to Novolog Mix 50/50, Novolog Mix 30/70, or even Novolog Mix 70/30, which is a bluish green (see NovoLog colors below).

NovoLog Colors

NovoLog	NovoLog Mix 70/30	NovoLog Mix 50/50	NovoLog Mix 30/70

b(4)

The patient could even be referring to their NovoLog insulin which comes in a blue FlexPen. The FlexPen color is difficult to distinguish between NovoLog Mix 50/50 color (see color bar below).

b(4)

Additionally, DMETS reviewed the container labels, carton and profession insert labeling, and patient information, from a safety perspective. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Although DMETS continues to recommend against implementation of International Diabetes Federation color coding for insulin products, DMETS recognizes that this scheme is increasingly being implemented. In light of the proliferation of insulin products and the limited number of readily discernible colors, DMETS believes that the sponsor's color branding proposals will ultimately lead to increased confusion of products. Delete color coding on labels, labeling, and on insulin delivery devices and propose a different method for differentiating the products.

2. Include the route of administration on all labels and labeling where space permits and revise the statement to indicate subcutaneous use for prefilled syringe and Penfill cartridge labeling.

3. DMETS recommends that the statement, "New Product Strength" appears on product labels and labeling for a period of time not to exceed six months.

B. CONTAINER, PENFILL (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, Retail and Sample)

1. Relocate the declaration of net quantity of contents to appear as a distinct item on the carton labeling and increase its prominence.

2. Revise the expressions of strength on the principal display panel to read:

300 units per 3 mL
100 units/mL (U-100)

C. CARTON, PENFILL (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, Retail and Sample)

1. Relocate the declaration of net quantity of contents, "5 cartridges per package", to appear as a distinct item on carton labeling.

2. Revise the labeling statement [redacted] to read "300 units per 3 mL" and increase its prominence. b(4)

3. Increase the prominence of the secondary expression of strength, "100 units/mL (U-100)".

D. CARTON, FLEXPEN (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, 5 X 3 mL Retail and 1 X 3 mL Sample)

1. Relocate the declaration of net quantity of contents, "5 X 3 mL Prefilled Insulin syringes" or "1 X 3 mL Prefilled Insulin syringes", to appear as a distinct item on carton labeling.

2. Revise the expressions of strength to read as follows and increase its prominence.

300 units per 3 mL
100 units/mL (U-100)

E. CONTAINER, FLEXPEN (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, Retail and Sample)

Relocate the declaration of strength to appear beneath the statement of identity, increase its prominence, and revise as follows:

300 units per 3 mL
100 units/mL (U-100)

F. PATIENT INFORMATION

DMETS believes that Patient Information should include reference to and education about other strengths of NovoLog Mix, that there exists a NovoLog which is not a mix, and request that the patient be sure about the product that their physician intends for them to use.

Appendix A. Prescription Studies for NovoLog Mix 30/70

Verbal	Inpatient	Outpatient
Mevalon Mix 30/70	Novolog Mix 70/30	Novolog Mix
Novolone mix 30/70	Novolog Mix 30/70	Novolog Mix
Desnevalon mix 40/70	Novolog Mix 30/70	Novolog Mix 30/70
Novolog Mix 30/70	Novalog Mix 30/70	Novolog Mix 30/70
Novalon mix	Novolog Mix 30/70	Novolog Mix 30/70
Novolox Mix 30/70	Novolog Mix 30/70	Novolog Mix 30/70
Novolog Mix 30/70	Novolog Mix 70/30	Novolog 30/70
Novolog Mix 30/70	Novalog Mix 30/70	Novolog Mix 30/70
Nebalon Mix	Novolog Mix 30/70	Novolog Mix 30/70
Novolon Mix	Novolog Mix 30/70	Novolog Mix 30/70
Nebular Mix 30/70	Novalog Mix 30/70	Novolog Mix 30/70
Nevelormex 30/70	Novolog Mix 30/70	Novolog 70/30
Nevelon mix 70/30	Novolog Mix 30/70	Novolog Mix 30/70
Novalone mix 30/70	Novolog Mix 30/70	Novolog Mix 30/70
Levonex mix 30/70	Novolog Mix 30/70	Novolog Mix 30/70
Mevalognix 30/70	Novolog Mix 30/70	Novolog Mix 30/70
Nevalon Mix 30/70	Novolog Mix 30/70	Novolog Mix 30/70
Novalog Mix 30/70	Novalog Mix 30/70	Novolog Mix 30/70
Novolog Mix 30/70	Novoloz Mix 30/70	Novolog Mix 70/30
	Novolog Mix 30/70	Novalog Mix 30/70
	Novolog Mix 30/70	Novolog Mix 30/70
	Novolog Mix 30/70	Novolog Mix 30/70
	Novolog Mix 30/70	
	Novolog Mix 30/70	

Appendix B. Prescription Studies for NovoLog Mix 50/50

Verbal	Inpatient	Outpatient
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Nowalok Mixed 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novolog 50/50	Novolag Mix 50/50	Novolog Mix 50/50
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novalog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novalog 50/50	Novolog Mix 50/50	Novolog 50/50
Novolog 50/50	Novolog Mix 50/50	Novalog Mix 50/50
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Zolock 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Novolog Mix 50/50	Novolog Mix 50/50	Novolog Mix 50/50
Nolorox 50/50	Novolog Mix 50/50	Novolog 50/50
	Novolog Mix 50/50	NovoLog Mix 50/50
	Novolog Mix 50/50	NovoLog Mix 50/50
	Novolog Mix 50/50	Novolog Mix 50/50
	Novolog Mix 50/50	Novolog Mix 50/50
	Zolog Mix 50/50	Novolog Mix 50/50
	Novolog Mix 50/50	Novolog Mix 50/50
		Novolog Mix 50/50
		Novolog Mix 50/50
		Novolog Mix 50/50
		Novolog Mix 50/50
		Novolog Mix 50/50

Appendix C. Medication Error Reports of Confusion Involving NovoLog 70/30 (From AERS and DQRS)

(The following narrative summaries of medication error reports transcribed from AERS/DQRS data. Dates provide the time reports were received by the Agency)

AERS/ DQRS #/ DATE	TYPE OF ERROR	ABBREVIATED NARRATIVE
Confusion Between NovoLog and Lantus		
4213748-9 10/17/2003	Wrong Drug	A nurse reported that a 47-year-old woman, who was introduced to NovoLog (insulin aspart) in March for type I diabetes mellitus (since 1969), was found dead on [redacted] after injecting 30 units of NovoLog insulin in the evening of [redacted]. The nurse speculated that the woman may have mixed up her NovoLog and Lantus insulin at night, which was the amount of NovoLog insulin that was speculated to have been injected on the evening prior to her death. The woman was to receive NovoLog FlexPen insulin syringes, but had to use NovoLog vial insulin due to her health insurance coverage.
4059843-9 2/25/2003	Wrong Drug	PT, while preparing to "tapdown" a bedtime blood glucose level of 311 with Novolog (very fast acting insulin) and also take his normal bedtime dose of Langus (long-acting insulin) inadvertently picked up the wrong bottle and injected himself with 26 units of Novolog. We live 30 min. from a hospital. Fortunately, he realized what he had done, and we calculated the amount of NOVOLOG INSULIN ASPART INJECTION carbohydrate he needed. At 10g of CHO per unit, we calculated he needed 220 g of fast acting CHO to be ingested within 15 minutes w/o vomiting or passing out. 14 glucotabs, 2 cups of grape juice 1c. oatmeal with raisins & sugar & milk were used.
4068111-0 1/17/2003	Wrong Drug	MD order for Rainbow coverage with Novolog beginning at 2 units for each 20 units greater than 150. Nurses unfamiliar with Novolog (first time order for this med, Humalog is the short-acting insulin currently on formulary). Nurse researched new product in 2003 Mosby's Nursing Drug Reference. See attached pages. Page 527 lists Lantus and Novolog in the same box, leading to nursing confusion that it was the same product. Nurses wrote on computerized MAR preprinted Novolog "aka Lanus". Lantus was used for tour days for rainbow coverage of high blood sugars until the error was discovered. Compounding the error was the fact that the product ordered, Novolog, was not provided from pharmacy. Insulins are floor stocked, and the RPh receiving the order did not realize the product was new/unavailable.
4243213-4 11/28/2003	Wrong Drug	Written as "Continue home meds": nurse wrote: "Novolog 40 units q HS" no other insulin ordered – Pharmacy dispensed it (should have been Lantus).
4413147-0 8/2/2004	Wrong Drug	One of the multiple patients to MISTAKENLY ADMINISTER NOVOLOG OR HUMALOG INSTEAD OF LANTUS for evening insulin. Patient injected 20 units of Novolog instead of the proper medication –lantus- and required intensive monitoring of blood glucose as well as treatment to prevent hypoglycemia.
4429298-0 8/19/2004	Wrong Drug	Initial report 13-Aug-2004: This postmarketing spontaneous case was reported by a certified diabetes educator. This case involved an 18-year old female patient who was on Lantus (insulin glargine) 20 units at bedtime and Novolog (insulin aspart)(dose unknown). In error, she administered Novolog 20 units (the Lantus dose) and died in her sleep (NOS). No further information has been provided at this time.

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Confusion Between NovoLog Mix 70/30 and NovoLog		
4148700-5 7/16/2003	Wrong Drug	My son uses Novolog insulin in his pump. I receive his insulin in 3 vial increments. Two of the vials I received were the correct insulin. The third vial that was dispensed to me was a Novolog Insulin but was a 70/30 mix instead of the straight Novolog insulin. I discovered the error only when examining the insulin itself -it was cloudy as compared to clear-but I did not notice the error by looking at the box of insulin. On the boxes containing the insulin vials, the font stating "Novolog" is the same size on both types of insulin and the "70/30" is written in small font. There is very little differentiation in packaging. This was a potentially VERY serious problem that was thankfully averted. However, I feel that the likelihood of this mistake happening to others is very high due to the similarities in packaging. I have contacted both the pharmacy that dispensed the wrong medication and the manufacturer of the insulin. When discussing the issue with the manufacturer's representative, she stated that the incident would be reported within the company but stated the incident wouldn't necessarily be reported to the FDA and in fact stated that it was possible that the FDA was responsible for their inability to modify the boxes to make it easier to distinguish the different types of insulin.
4156438-3 7/24/2003	Wrong Drug	A physician reported that a 61-year-old man, who was mistakenly introduced to NovoLog on 23 June 2003 for type II diabetes mellitus, has experienced acute arthritis and polyarthralgia since [redacted] and was subsequently hospitalized. The patient also reported that the patient developed severe hypoglycaemia. In a direct conversation with the physician, he reported the event occurred after the patient went to his pharmacy to get a refill on his NovoLog 70/30 Mix insulin prescription. The patient usually purchases three vials at a time and the pharmacist mistakenly dispense one vial of NovoLog insulin with vials of NovoLog (R) 70/30 Mix insulin. When the patient get home, he immediately started using the vial of NovoLog, not realizing that it was biven to him in error. Within four days, the patient experienced acute arthritis in both legs, feet, arms and hands. The swelling in the affected areas quickly progressed and became severe. Subsequently, the patient sustained a fever and was hospitalized from [redacted] According to the physician, the patient did not have an active infection. Etiology of the fever is unknown at this time. Information concerning treatment render to the patient while he was hospitalized and outcome of the event was not provided.
4157549-9 7/25/2003	Wrong Drug	A physician reported that a 59-year-old woman, who was mistakenly introduced to NovoLog Mix 70/30 insulin (dual acting insulin aspart) in her insulin pump (type unknown) on 09 July 2003 for type I diabetes mellitus, was hospitalized on [redacted] for elevated blood glucose levels and cerebral stroke. The event began when the woman, whose diabetes is poorly controlled as described by the reporter, was mistakenly dispensed a vial of NovoLog Mix 70/30 insulin instead of a vial of NovoLog insulin (insulin aspart) to use in her insulin pump (basal rate unknown). Not realizing that she was given the wrong insulin, the woman began using the insulin in question in her insulin pump for the next three days and her blood glucose levels decreased.

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4176670-2 8/21/2003	Wrong Drug	A nurse reported that a 24-year-old man, who was mistakenly introduced to NovoLog FlexPen prefilled insulin syringes (insulin aspart) on 05 June 2003 when his pharmacy had dispensed the product instead of his prescribed Novolin 70/30 PenFill insulin (dual-acting human insulin) due to type I diabetes mellitus, received emergency room treatment for elevated blood glucose levels and stomach pain. The patient's mother received an unknown type of insulin at the pharmacy on 3 June 2003 but she returned it as the insulin did not fit in her son's NovoPen 3 (insulin delivery device). The pharmacist then gave her a Novolin 70/30 vial until he could get her a box of the Novolin 70/30 PenFill insulin. The patient's mother used the vial of dual-acting human insulin until the pharmacist called her and told her that the requested insulin was due to arrive on 5 June 2003. Her son's blood glucose levels remained normalized while using the Novolin 70/30 vial. The patient's mother went to the pharmacy on [redacted] and the pharmacist gave her a box of NovoLog FlexPen prefilled insulin to perform her son's injections for the next 3-4 weeks. Her son became lethargic, complained of headaches and was "out of it" during that time and his blood glucose levels were continuously elevated (200 mg/dL – 400 mg/dL). She noticed that his glucose levels always became high around 3:00 p.m. However, she thought the blood glucose levels may e elevated because his right thumb and become infected. His glucose levels remained high for an unknown period of time. Patient taken to the emergency room.
4446286-9 9/7/2004	Wrong Drug	A nurse practitioner reported that an 84-year-old man, who was given NovoLog FlexPen prefilled insulin syringes instead of NovoLog Mix 70/30 FlexPen prefilled insulin syringes by a pharmacist, experienced hypoglycaemic coma which required hospitalization for [redacted]. The patient was initially introduced to NovoLog Mix 70/30 prefilled insulin syringes on 17 October 2002. The reporter stated that the patient was prescribed NovoLog Mix 70/30 FlexPen prefilled insulin syringes. He went to the pharmacy to till his prescription for NovoLog Mix 70/30 FlexPen Pen prefilled syringes and was given NovoLog FlexPen prefilled insulin syringes. The man followed the prescribed regimen for the NovoLog Mix 70/30 insulin, which was 30 units twice a day. On 20 October 2003, several days after the patient was mistakenly introduced to NovoLog FlexPen prefilled insulin syringes, he experienced his first hypoglycemic event and he became confused but did not lose consciousness. His blood glucose level was 40 mg/dL. His daughter treated the event with orange juice and he recovered. Two days later on [redacted], the patient lost consciousness while driving and was involved in a minor motor vehicle accident. He was taken to the hospital where his blood glucose level was 45 mg/dL.
4471443-5 10/6/2004	Wrong Drug	Patient to receive Novolog 70/30 instead got Novolog regular #2 bottles. Patient called pharmacy to verify and problem resolved. RPh informed patient to not use wrong insulin. Corrected problem.
4634247-6 4/13/2005	Wrong Drug	This spontaneous report..."very high blood sugars while using the wrong insulin", concerns a 82-year-old woman who was mistakenly introduced to NovoLog FlexPen (insulin aspart) instead of her prescribed NovoLog Mix 70/30 FlexPen (dual acting insulin aspart). The woman received tow boxes of NovoLog FlexPen (insulin aspart) from her physician's office in JAN-2005 (exact date unknown). While preparing her injection with the first NovoLog Flex Pen (insulin aspart) prefilled disposable pen, she noticed that the cap was orange and the insulin was clear, unlike her normally prescribed NovoLog Mix 70/30 FlexPen. She reported that even though she noticed a visible difference, she administered an injection and consequently, her blood glucose levels became elevated (300-400 mg/dL).
46235622-7 3/29/2005	Wrong Drug	The labels of Novolog and Novolog Mix 70/30 are too close in appearance to prevent errors. The product identification for NovoLog Mix 70/30 is in very small print that requires turning the bottle to read "70/30" and therefore does not stress that it is the mixture. There have been numerous near misses that I am aware of. I would suggest redesigning the label so that the 70/30 is very prominent and is in the same viewing field as the name of the product.
Confusion Between NovoLog Mix 70/30 and Novolin 70/30		
4035480-7 1/3/2003	Wrong Drug	Novo Nordisk has now released Novolog 70/30. Get your error traps in early before your automatically give regular 70/30. Poor choice (I my opinion) of naming a product!! Why not Novolog 71/29??

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4127232-4 6/11/2003	Wrong Drug	Maybe I didn't submit this correctly a few minutes ago. Significant problems regarding availability of Novolin 70/30 and Novolog Mix 70/30. Staff has identified tremendous potential for med error with similar nomenclature and same strength.
4144369-4 7/9/2003	Wrong Drug	Significant concern regarding Novolin 70/30, Novolog mix 70/30. Pharmacists see this as a med error waiting to happen.
4217562-X 10/24/2003	Wrong Drug	patient ordered Novolog 70/30. Order entered, verified and administer as Novolin 70/30. When error communicated to MD, MD insisted on Novolog 70/30 'as at home' Since Novolog 70/30 not stocked DUE TO ERROR POTENTIAL, Patient asked to bring in own Novolog 70/30. PATIENT BROUGHT IN NOVOLIN 70/30 from home.
4243149-9 11/28/2003	Wrong Drug	Physician order written: Insulin 70/30 MIX, 80 units bid, 50 units @hs sliding scale novolog at noon. Pharmacist dispensed Novolog 70/30 mix for scheduled and sliding scale insulin. Physician intended patient to receive Novolin 70/30 MIX for scheduled and novolog 70/30 MIX for sliding scale.
4409969-2 7/28/2004	Wrong Drug	We recently had a medication error involving Novolin 70/30 in our hospital. Neither the RPh who received the order, not the nurse who administered the insulin was aware that there is a Novolin 70/30 and a novolog 70/30. The Novolog 70/30 was entered in the pharmacy computer, dispensed and given. The order was for Novolin 70/30. I suspect this will result in several errors as many healthcare professionals are not aware both of these products exist.
4443740-0 9/7/2004	Wrong Drug	Patient received Novolin 70/30 instead of Novolog 70/30. The patient actually received the wrong insulin (probably for several days). Patient obviously experienced fluctuations in blood sugars and poor control.
4444737-7 9/7/2004	Wrong Drug	Patient admitted from nursing home and ordered Novolog 70/30, 40 units every morning and 15 units every evening. Nursing unit transcribed order as Novolin 70/30 and administered Novolin 70/30 from stock prior to pharmacist verification of order.
4631519-6 4/5/2005	Wrong Drug	The 70/30 NPH/ Novolog was mistaken for the 70/30 NPH/Regular for a few doses. No apparent effect noted when finally caught by pharmacist. These were both non-formulary and not stocked due to earlier error potential review of insulin product. The ironic thing was that we thought we addressed it by communicating with Endocrine MDs and deciding not to carry the mixes and make them non-formulary.
4658671-0 5/11/2005	Wrong Drug	This spontaneous report, reported by a pharmacist, received from the United States reported as "pharmacy dispensing error and seizures" concerns a 14-year-old male patient treated with NovoLog Mix (dual-acting insulin aspart) vial from 22 March 2005 to 29 April 2005 instead of his prescribed NovoLog (insulin aspart) vial for use in his insulin pump for type I diabetes mellitus. The pharmacist reported that a dispensing error occurred on 22 March 2005 and that the boy's mother reported to them that she took her son to the Emergency Room on '————after he began having seizures at home. On 29 April 2005, the mother realized that the pharmacy had dispensed the wrong insulin to her son and she subsequently notified them.
4715410-2 7/14/2005	Wrong Drug	Insulin ordered Novolog 70/30 Pharmacy sent Novolin 70/30 Error discovered before given to client. Vial and box incorrectly labeled as Novolog with CT's name.
NovoLog Use in Insulin Pump		
D 139945 5/12/04	Wrong Route	Reporter purchased a carton of NovoLog insulin for use in an insulin pump. The carton was sealed and the cap on the vial was intact. Immediately before use, the consumer noticed that the insulin was cloudy in appearance. After inspecting the insulin vial, the consumer learned that the insulin was the NPH 70/30 mix which cannot be used with the insulin pump. In addition, the expiration date on the bottle is 5/04. However, the expiration date on the carton is 5/05. The lot number on the bottles is NW50125. The lot number on the carton is NW52089. Of note, the vial of insulin had only one punctured hole where the consumer inserted the needle. The reporter contacted the manufacturer who stated this incident could not have possibly occurred since the NovoLog insulin and the NPH 70/30 insulin are made at two different times. Of note, the reporter has additional cartons of insulin with lot number NW52089 (lot number on sealed carton) and those bottles of insulin are Novolog Insulin with the 5/05 expiration date. The reporter also reported this incidence to the pharmacist.

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M 137437 8/11/2003	Wrong Route	In an effort to convert me, and thus influence my choice of analog insulin for my patient recommendations, the Novolog rep gave me 2 bottles of Novolog to try in my pump. I started with a new cartridge and infusion set for the Novolog, and began using it on Friday, 8/1/03. By the next day, I was seeing higher BG values -going from BG values being within target before starting the Novolog-. Thinking I was coming down with a virus, I adjusted for the elevated BG's. Tuesday, 8/5/03, morning's fasting BG was 400mg/dl and upon reviewing my daily totals history, I found that I have been using at least twice as much insulin on the Novolog as what I use taking Humalog. Again, I thought I was coming down with a virus, keeping in mind the rep's assurance that Novolog was equipotent to Humalog and that he had kept the insulin "cool". This AM's fasting BG was 500 mg/dl and I am positive for blood ketones. Upon determining this, I immediately DC'd the Novolog, injected the appropriate dose of Humalog, changed out all my pump infusion supplies and notified both the Novolog rep and the Endocrinologist I work with. He recommended I report his adverse event to the FDA.
M142129 3/3/2005	Wrong Route	The patient is a 6 yo male using vovolog insulin via the Paradigm insulin pump for almost 2 years. On 12/28/04, the parents of the child filled his insulin set with Novolog. Over the next few days, the child's glucose level shot up to the high 200s. Normal for him is in the 100s. Attempts to correct these highs with additional insulin were of little help. Changing to another lot # of Novolog & another insulin set. His glucose levels immediately normalized.
	Device Malfunction	
4026936-1 12/16/2002	Device Malfunction	A women reported that her 19-year-old daughter, who was introducted to NovoLog PenFill insulin with the Innovo insulin delivery device for type 1 diabetes mellitus in December 2001, experienced elevated blood glucose levels with ketones and a bacterial infection for which she was hospitalized or [redacted] The woman reported that for several months without incident, her daughter was relying on the clicks for dose selection when the dose indicator window of the Innovo insulin delivery device was showing blank. The event began in early morning on [redacted] when her daughter was feeling nauseated and ill with vomiting.
4492189-3 11/1/2004	Device Malfunction	A 70-year-old woman, who was introduced to NovoLog Mix 70/30 FlexPen prefilled insulin syringes in 2003 for type 2 diabetes, reported that she experienced elevated blood glucose levels from 11 April 2004 to May 2004 and blurred vision since 11 April 2004. The woman also reported that three or four of her NovoLog Mix 70/30 FlexPen prefilled insulin syringes had push buttons that were hard to depress. She stated that she believed she did not receive the correct dosages of insulin while using these particular FlexPen syringes, and that she experienced elevated blood glucose levels and blurred vision as a result.

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/s/

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12/23/2005 10:25:21 AM
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