EUPAS21539

NON-INTERVENTIONAL STUDY PROTOCOL
Study Information

Title	Healthcare Professional Survey to Assess the Effectiveness of Additional Risk Minimization Measures for Prescribing and Administration of Concentrated Insulin Human (Humulin® R U-500 KwikPen®)
Version identifier	Version 1
Date of last version	February 22, 2017
Active substance	Insulin Human
Medicinal product(s):	Humulin® R U-500 KwikPen®
Research question and objectives	This study aims to evaluate the impact of the Dear Health Care Provider (DHCP) Letter on prescriber understanding about the risk of hypoglycemia and educational points to be emphasized in discussion with patients.
Country of study	United States

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1 List of Abbreviations

Abbreviation	Definition
CI	Confidence interval
DHCP	Dear Health Care Provider
FDA	U.S. Food and Drug Administration
HCP	Healthcare professional
IRB	Institutional Review Board
KAB	Knowledge, attitudes, and behaviors
rDNA	Ribosomal deoxyribonucleic acid
RMiP	Risk Minimization Plan
SA	Schlesinger Associates
SD	Standard deviation
SOPs	Standard Operating Procedures
UAT	User Acceptance Testing

2 Responsible Parties

Principal Investigator of the Protocol

Name, degree(s)	Title	Affiliation	Address
Ayad Ali, PhD	Senior Pharmacoepidemiologist	Eli Lilly & Company	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285, USA

3 Milestones

Milestone	Planned date
Start of data collection	Estimated July 2017
End of data collection	Estimated October 2017

4 Rationale and Background

Humulin® R U-500 is a concentrated formulation of a polypeptide hormone structurally identical to human insulin. Developed using rDNA technology, the product has been marketed since 1996 in 20 mL vials, indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day.[1] It has proven to be of particular benefit for patients with insulin resistance because the concentrated formulation allows for delivery of a higher dose in a reasonable volume. As insulin resistance worsens, greater doses are required to meet glycemic goals and patients may face challenges in subcutaneous administration of their medicine.[2]

Although the concentrated formulation has been shown to be safe and effective when used as directed, there have been serious medication errors with Humulin® R U-500 in the past.[1,3,4] Errors have been attributed to dispensing, prescribing, and administration. The majority of instances have resulted from dosing confusion, with the most serious events occurring among patients who experience hypoglycemia from overdosing. Less frequent serious adverse events have been attributed to failures of glycemic control due to underdosing or from drug-drug interactions.

In April 2016, Eli Lilly and Company (Lilly) launched the 3 mL Humulin® R U-500 KwikPen® (prefilled pen containing 1,500 units of insulin). The new combination product uses Lilly's established KwikPen technology.

The KwikPen is anticipated to mitigate risks for dosing errors with the U-500 concentration. But changes to product labeling in July 2016 include new information healthcare professionals (HCPs) must be familiar with for informing their patients about safe use. The package insert and information disseminated to providers draws on experience with the KwikPen application to date. For example, human factors studies sponsored by Lilly showed that a small percentage of patients may choose to withdraw concentrated insulin from the pen cartridge with a syringe in cases of device malfunction. Likewise, anecdotal information suggested that patients could transfer insulin from the pen cartridge into an insulin pump.

This study is an initial evaluation of the effectiveness of a risk minimization plan (RMiP) conducted within 18-months of product launch, designed to meet a post-market commitment to the Food and Drug Administration (FDA) for the new KwikPen combination product. The study focuses on Lilly's communication with HCPs, and specifically prescribers (endocrinologists and prescribing primary care physicians, nurse practitioners, and physician's assistants). Through an online survey, the study will query knowledge of and outcomes related to the Dear Health Care Provider (DHCP) letter (Appendix I) sent to prescribers and pharmacists following the product launch. The DHCP letter is intended to alert HCPs of the risks associated with Humulin® R U-500 KwikPen®.

Early evaluation of communications constituting part of risk mitigation measures have evolved toward an emphasis on process measures. This is important because it may be difficult to detect actual impacts on relatively low-frequency medication errors across the first year or longer of an intervention. Surveys, particularly those conducted closely following implementation, focus on the extent to which the program has been executed, the intended impacts on behavior, and assessments of clinical knowledge or comprehension of risks contained in the communication. The FDA has recommended a knowledge, attitudes, and behavior survey (KAB) as a sufficient assessment tool in most cases.[5]

This KAB survey is designed to capture three of four elements appropriate to learning evaluations identified by the FDA: [6]

- *Reaction* – How satisfied are physicians with communications materials, and did they actually receive and utilize them?
- *Learning* – What knowledge about risks have they learned or had reinforced, and how comprehensible are the key messages about risks and the need to communicate those risks to patients?
- *Planned Behavior* – What changes (or intention to change) do physicians make in the areas of patient instruction and recognizing the significant potential for dosing error leading to hypoglycemia incidence?

The objectives of the fourth element *Results* (collecting concrete public health outcomes of interest such as reductions in medication dosing errors), exceed the scope of a survey of this type. Additionally, 18 months may be an insufficient period for detecting informative and compelling results on actual risk reduction.

5 Research Question and Objectives

The research questions motivating this study relate to how well the distribution of the DHCP letter has proceeded in the early post-launch period and how well that communication material conveys the most significant risks of Humulin® R U-500 KwikPen® to prescribers. The study also evaluates prescriber understanding about important patient education about those risks. As noted above, this early evaluation focuses on process measures related to reaction, learning, and planned behavior.

The primary study objective is to evaluate the impact of the DHCP letter on prescriber understanding about the risk of hypoglycemia and educational points to be emphasized in discussion with patients.

Retention and comprehension by HCPs of the following specific key safety messages will be tested in line with this objective. Specifically, HCPs should:

- only consider prescribing Humulin® R U-500 KwikPen® to patients needing more than 200 units of insulin per day.
- specify the prescribed dose in units of insulin (5-unit increments) on the prescription.
- inform patients of their dose in units of insulin.
- educate patients that no dose conversion is needed with Humulin® R U-500 KwikPen® and that the dose window shows the number of units to be injected.
- educate patients not to withdraw Humulin® R U-500 insulin from the KwikPen® with a syringe.
- instruct patients to maintain backup Humulin® R U-500 KwikPen®.
- instruct patients in the event of a malfunction, to use their backup pen or contact a pharmacist, healthcare professional, or The Lilly Answers Center for more information at 1-800-545-5979.
- teach patients not to count clicks to determine their dose when using Humulin® R U-500 KwikPen®.

The secondary objectives include

- assessing the proportion of HCPs receiving and reading the DHCP letter and their reactions to the risk mitigation communication content.
- querying prescriber intentions regarding patient education around safe use of the Humulin® R U-500 KwikPen®.

6 Research Method

6.1 Study design

This is a cross-sectional survey to be conducted in the United States. Eligible HCPs will have received the DHCP letter in April 2016 and subsequently prescribed the Humulin® R U-500 KwikPen®. The HCPs who received the DHCP letter include endocrinology specialists, primary care physicians, advanced practice registered nurses, nurse practitioners, and physician assistants who have prescribed Humulin® U-500 (in vial dosage forms) during the 12 months prior to the Humulin® R U-500 KwikPen® product launch. A random sample of HCPs will be recruited to participate in the survey from the list of HCPs who received a DHCP letter via email. The HCP survey will be administered online.

6.2 Setting

The assessment survey will be executed and the analysis completed within approximately 18 months of the product launch.

Eligible HCPs will receive an invitation to participate via email that includes a link to the survey (Appendix II). The invitation will include an overview of the rationale for the survey, information on how to access and complete the survey online, and privacy information. The average survey is expected to take approximately 15 minutes to complete.

The invitation will also indicate that HCPs will be compensated with an incentive card having a $50 value. All those providing screening information are eligible, with the exception of HCPs who are licensed and practice in Minnesota, Vermont, Massachusetts or the District of Columbia and Advanced Practice Registered Nurses (APRNs) in Connecticut in accordance with state laws. HCPs from these states can elect to participate, although they will not be paid. HCP-identifying information will be utilized for the purposes of providing payment and will be managed by a third party vendor, Schlesinger Associates (SA).

HCPs eligible for compensation, who complete the screening questions, will be mailed their honorarium. Additionally, HCPs will be emailed a letter thanking them for their time and effort. The email will also include a link to the DHCP letter on the correct use of Humulin® R U-500 KwikPen® and a link to the correct answers to key safety message questions (Appendix III).

6.2.1 Population

The initial population in scope for selection consists of the 15,179 HCPs who were sent a DHCP letter and prescribe the Humulin® R U-500 KwikPen® within 12 months of the launch date. The sampling frame is limited to the 10,442 HCPs (69%) who have a valid email, as recruitment will be implemented via email only.

Initially 1,000 HCPs will be randomly selected in order to obtain 200 completed surveys with a target response rate of 20%. The response rate will be monitored throughout the data collection period of 3-5 months. Of the 1000 initially sent, if any are undeliverable, they will be replaced.

Follow-up via phone or email or randomly selecting additional HCPs will be assessed as options to obtain 200 completed surveys if the initial response rate is lower than 20%. If the response rate is higher than 20% then no follow-up or additional HCP sample will be required.

HCPs who complete the screener and qualify for the survey are included in the survey's analysis population. Data collected on the screener and on the survey will be available for this analysis population.

HCPs who complete the screener, but do not qualify to participate in the survey are included in the screen failures analysis. These HCPs may fail the screener because they indicate that they have not met one of the inclusion/exclusion criteria. Data collected on the screener will be available for this population.

6.2.2 Inclusion Criteria

HCPs must meet the following criteria to be eligible for inclusion in the survey:

- HCPs who received the DHCP letter.
- HCPs who prescribed the insulin product Humulin® R U-500 KwikPen®.
- HCPs must be able to read and respond to the survey in English.

6.2.3 Exclusion Criteria

HCPs meeting any of the following criteria will not be included in the survey:

- HCPs or their immediate family members are current or past employees of Lilly, Covance, SA, or the FDA.
- HCPs have participated in this Humulin® R U-500 KwikPen® survey before.

6.2.4 Survey Period

A 3-5 month data collection is estimated to recruit the HCPs and obtain approximately 200 completed surveys.

6.3 Variables

As specified in the project objectives above, the survey captures HCPs' knowledge of the key safety messages in the risk minimization communication letter as primary outcomes. While these questions contain an option for "I don't know," response will be dichotomized for analysis as correct or incorrect across seven statements. An additional multiple-choice item provides three correct options with an incorrect choice outlining an unsafe practice for dealing with KwikPen® malfunction. HCPs will also be asked about the source of their knowledge of product risks, using a single multiple choice question.

Additionally, the survey instrument has questions about the HCP's reaction to the communication. Recall of receipt of the DHCP letter is required for participation in the study. Additional reactions are queried in a series of four questions with Likert response scales for those confident about having read the material. As there are no correct answers for these appraisals of the DHCP letter, responses will be analyzed descriptively.

Finally, the HCP survey includes a question that queries planned behavior. The item asks about the prescriber's knowledge about the need for patient counseling by prescribers; it is a multiple choice question that can also be dichotomized to correct or incorrect response.

The survey also captures demographic characteristics that include age, gender, geographical location, HCP specialty, and practice information. Personal contact information about an HCP will only be collected by SA where applicable for mailing payment to study participants; this information will not be included in study datasets.

6.4 Data Sources

Responses to the HCP Survey comprised of closed-ended questions or statements with multiple response choices (i.e., questions or statements asking the HCPs to choose from a defined list of responses) and HCP information contained in the sampling frame are the source of the study data.

Screening questions:

- Prescribed Humulin® R U-500 KwikPen® product
- Aware of having received DHCP letter
- HCPs or their immediate family members are not current or past employees of Lilly, Covance, SA, or the FDA
- Didn't previously participate in the survey
- Agree to participate

Data on demographic characteristics:

- Age group
- Gender
- Role at facility
- Facility type
- State or territory of practice
- HCP medical specialty (e.g., General Internal Medicine, Endocrinology/Diabetology, Family Medicine, and Other)

- Number of years practicing medicine/nursing (e.g., <5 years, 5-10 years, 11-15 years, and >15 years)
- Number of Humulin® R U-500 KwikPen®-treated patients the HCPs prescribed to or managed in the 12 month period preceding the survey (self-reported). Response options are categorical in nature, e.g., 1-5 patients, 6-10 patients, 11-20 patients, and >20 patients.

Data pertaining to evaluation of the effectiveness of the risk minimization measures:

The survey includes questions/statements that will assess HCP understanding about the risks and associated behavior of the HCPs to minimize these risks. The understanding level and behaviors will be analyzed using descriptive statistics and confidence intervals (CIs) and will be used to determine the effectiveness of the risk minimization measures:

- Awareness of the DHCP letter on the correct use of Humulin® R U-500 KwikPen®
- Understanding of the key safety messages
- Self-reported practices and intentions with respect to communication of the key safety messages in clinical practice

The RMiP will be considered effective if the majority of HCPs demonstrate they are aware of the key safety messages communicated for Humulin® R U-500 KwikPen®.

6.5 Study Size

A sample size of 200 HCPs will provide a confidence interval of ±5.49 percentage points at the 95% confidence level if 80% of the HCPs answered the key risk questions correctly, as shown in Table 1.

The confidence interval for the percent correct response is calculated using the finite population correction factor as: $p \pm 1.96[\sqrt{(p(1-p))}/\sqrt{n}]*\sqrt{(N-n)/(N-1)}$ where p is the proportion of HCPs answering the survey question correctly, N is the population size, and n is sample size.

Table 1: Table of Confidence Intervals by Sample Size and % Answering the Question Correctly

-95% Confidence Level-

	Percent Answering the Question Correctly				
Sample Size	**50%**	**60%**	**70%**	**80%**	**90%**
50	±13.83	±13.55	±12.67	±11.06	±8.30
100	±9.75	±9.55	±8.94	±7.80	±5.85
150	±7.94	±7.78	±7.28	±6.35	±4.77
200	±6.86	±6.72	±6.29	±**5.49**	±4.12
250	±6.12	±6.00	±5.61	±4.90	±3.67

Note: These calculations were performed assuming a population size of 10,000. The confidence intervals are not greatly altered with varying population size assumptions.

Additional measures will assess review and understanding of the RMiP, but these measures do not drive the sample size calculation.

6.6 Data Management

All data collected during the survey will be held confidentially by SA. They will program and host the survey. The survey data will be transferred from SA to Covance via a secure method and stored on the secure SAS server within the study area. Covance's data transfer standard operating procedures (SOPs) will be followed. Only study staff who need the data to complete the analysis will be granted access. No identifiable information will be required from any HCP, but will be collected if they are eligible and wish to receive payment.

The survey is programmed to ensure the HCP cannot skip ahead and will only allow for missing data when caused by skip patterns. Skip logic as well as the ability to mark only one response or multiple responses are part of the programming for the survey administration and minimize the occurrence of data entry errors. There will be no queries to HCPs for this project. Datasets and analytic programs will be kept on the secure Covance SAS server. All statistical programs will be developed using SAS® Version 9 (or later) software.

6.7 Data Analysis

Evaluation of the effectiveness of the DHCP letter in conveying key safety information for the Humulin® R U-500 KwikPen® will be primarily descriptive in nature. Frequency distributions with 95% CIs will be calculated for responses to all questions that address the survey objectives. Responses to each question relating to the key safety messages will be categorized as "Correct response" and "Incorrect response". Additionally, "I don't know" is categorized as an incorrect response unless otherwise specified.

The following sections will be reported as part of the analysis.

6.7.1 Analysis Data Sets

The Analysis Set will consist of all eligible HCPs who undertake the survey. The Analysis Set will be used to assess all the study objectives unless otherwise stated.

The Screening Set will consist of all HCPs identified as being ineligible for reasons other than immediate refusal to participate or prior participation. Demographic information will be presented for the Screening Set.

6.7.2 Survey Administration Statistics

Survey administration statistics will be reported. This summary will include the number of:

- Survey invitations issued by and specialty
- Survey invitations returned due to incorrect email address
- HCPs who responded to the invitation to participate in the survey
- Ineligible HCPs along with the reasons for ineligibility
- HCPs eligible for participation in the survey
- Eligible HCPs who completed the survey

These values will be summarized with the counts and percentage of HCPs. The percentage will be based on the number of HCPs in previous categories which will be detailed in the table shells. For example, the percentage of ineligible and eligible HCPs will be based on the number of HCPs responding to the survey.

6.7.3 Demographic and Other Baseline Characteristics

Demographic variables will be summarized for all HCPs, the Analysis Set and the Screening Set. These will include the distribution of HCPs by:

- Age groups
- Gender
- Practice setting
- State/region
- Medical specialty
- Years in medical practice
- Number of patients treated with Humulin® R U-500 KwikPen®.

These categorical variables will be summarized with frequencies and percentages.

6.7.4 Primary Objectives and Endpoints

Frequencies and percentages, along with 95% CIs will be used to assess HCP retention and comprehension of the risks associated with the Humulin® R U-500 KwikPen®. The denominator will be the number of HCPs who complete the survey. Specifically, primary endpoints are the proportion of those correctly answering each of the following statements. Response options are either True/False or multiple choice.

- It is appropriate to prescribe Humulin® R U-500 KwikPen® to patients needing more than 200 units of insulin per day.
- It is important to clearly specify the units of insulin (5-unit increments) on the prescription when prescribing Humulin® R U-500 KwikPen®
- When prescribing Humulin® R U-500 KwikPen® it is important to inform patients of their dose in units of insulin.
- When administering the Humulin® R U-500 KwikPen®, patients do not need to convert the dose since the dose window shows the number of units to be injected.
- It is important to instruct your patients that they should always have a backup Humulin® R U-500 KwikPen® available.
- It is important to instruct your patients to not count clicks to audibly verify the correct dose.
- In the event of a Humulin® R U-500 KwikPen® malfunction, it is appropriate for patients to use a backup pen, call their healthcare provider or pharmacist, or call the Lilly Answer Center; but it is not appropriate to use a syringe to withdraw insulin from the injector.

The RMiP will be considered effective if the majority of HCPs demonstrate they are aware of the key safety messages communicated for Humulin® R U-500 KwikPen® by correctly answering these statements.

6.7.5 Secondary Objectives and Endpoints

The secondary endpoints will also be assessed descriptively with frequencies and percentages. Confidence intervals for proportions will not be calculated where appraisals cannot be dichotomized to a correct or incorrect answer.

All HCPs, whether or not they have read, or recall having read the DHCP letter, will be asked a multiple choice question about the source of information (e.g. professional knowledge) or approach (e.g. guessing) that best characterized their response to the key safety questions.

Reactions to the DHCP letter based on the degree of agreement or disagreement with statements about the information will be responded to only by those HCPs affirming that they have read the DHCP letter. Specifically, statements to be evaluated include:

- The discussion of prescribing information encouraged me to better counsel my patients about the use of Humulin® R U-500 KwikPen®.
- I found the description of product features to be useful.

- I learned better how to respond to possible adverse events as a result of reading this communication.
- I found the summary of important safety information to be a useful extension of product labeling.

Planned behavior will be addressed by two questions. The first queries the HCP's understanding about the need for patient counselling with Humulin® R U-500 KwikPen® while the second directly asks the HCP about their intention to counsel patients.

6.8 Quality Control

User Acceptance Testing (UAT) will be performed on the survey using a sample of 8-10 HCPs. The UAT procedure is designed to assess comprehension among HCPs regarding the words and phrases used in select survey questions and response options. UAT will also assess the clarity of the survey questions as presented to HCPs and the interest and acceptance of the surveys among all prospective HCPs and flow and ease of completing the surveys.

Online administration allows for additional randomization of response options, offsetting potential order effects. Questions pertaining to reading and reactions to the DHCP letter are asked after the risk questions. During the course of online administration, the back-button on the survey is disabled preventing alteration of responses once reviewed and entered.

The data are also checked as part of the UAT process to make sure that all of the data collected within the online survey environment are correctly extracted from the system for use in the programming environment.

In addition to the UAT processes for the survey instrument and programming environment, several other strategies will be used to ensure data quality. The randomized sampling strategy outlined above helps ensure representativeness, avoid volunteer bias, and provides an additional means for ensuring valid data. In the analysis, demographic criteria are summarized for those who met survey inclusion criteria against those who did not meet the criteria.

All statistical programs will be developed and validated using good programming practice guidelines. This is a one-time cross-sectional survey with HCPs, there is no risk to any patients, and Institutional Review Board (IRB) approval is not required.

All analyses will be performed using SAS® Version 9 (or later) software. Covance will follow Covance's standard operating procedures in the creation and quality control of all tables, listings, figures and analyses. Lilly or its designee will review all tables, listings, and figures for accuracy.

6.9 Limitations of the Research Methods

The sample is subject to volunteer bias because HCPs decide independently whether or not to respond to the invitation to participate. There is no active follow-up to the recruitment invitation planned. To moderate the impact of self-selection, HCPs will be randomly selected from the list of HCPs who received the DHCP letter, which should be generalizable to the overall HCP population who are educated about the use of Humulin® R U-500 KwikPen®.

Additionally, the participation in the survey is reliant on the HCP's recall of whether or not the DHCP letter was received. However, it is possible that HCPs may simply not recall receiving the materials that were, in fact, received. It is also possible that they have acceptable understanding of the risks and appropriate behaviors despite not having read the DHCP letter. Lilly will explore the latter possibility with variables described in Section 6.3.

As with most survey data, information is self-reported and therefore susceptible to reporting biases. There may ultimately be discrepancies between what HCPs report about their intentions and what they ultimately do.

Lastly, this survey is administered only online. While the majority (69%) of the HCPs on the sampling frame (see Section 6.2.1) provided an email address, not everyone on the list has an email address listed. This could introduce additional selection bias.

6.10 Measures to Minimize Bias

HCPs completing the screener and meeting the Humulin® R U-500 KwikPen® survey eligibility requirements will be directed to participate in the online survey. Survey biases will be minimized through carefully constructed, non-leading survey questions, and a thorough internal validation process. Online forms will be programmed such that HCPs have access to only one survey question at a time; once a question is submitted, HCPs do not have the option of revisiting it, i.e., the back button is disabled. Lists of response options will be randomized to minimize the potential for positional bias.

Correct responses will be provided to the physicians following recording of their response, allowing for feedback on performance and reinforcing correct information and/or best clinical practice.

7 Protection of Human Subjects

7.1 Personal Information and Consent

All data collected during the survey will be held confidential by SA and used only for the purposes stated in the survey instructions. HCP names and addresses are only collected for the purposes of payment, if applicable, after the survey is completed. By answering the first question of the survey ("Do you agree to take part in this survey about Humulin® R 500 units/mL KwikPen® [Humulin® R U-500 KwikPen®]?") after reading the introductory message, HCPs are acknowledging informed consent for participation in the research study.

7.2 HCP Withdrawal

HCPs can decline to participate or stop taking the survey at any time. Only completed surveys that include all questions answered that were required to be presented for participation will be included in the analysis. HCPs will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. HCPs will be informed that their answers to the survey questions will not affect their ability to prescribe Humulin® R U-500 KwikPen®.

7.3 Central Institutional Review Board (IRB)

This protocol is exempt from IRB requirements.

8 Management and Reporting of Adverse Events/Adverse Reactions

This study does not involve data collection on clinical endpoints for patients of the individual HCPs. The online survey does not include any questions that could potentially identify a safety event, nor does it provide a free text field where study HCPs could specify information that may constitute a safety event (defined as an adverse event, product complaint, or other reports; e.g. overdose, abuse, misuse, off label use, pregnancy exposures, breast feeding exposures, lack of drug effect, medication error and suspected transmission of infectious disease). Free text fields available following completion of the survey will be used by SA only to collect contact information to provide payment of honoraria.

9 Plans for Disseminating and Communicating Study Results

The Humulin® R U-500 KwikPen® RMiP Survey Report will include the aggregated results of approximately 200 HCP surveys.

10 References

1. Eli Lilly & Company. Information for the Physician, Humulin R Regular U-500 (Concentrated) Insulin Human Injection, USP (rDNA Origin) Description. Available at http://pi.lilly.com/us/humulin-r-u500-pi.pdf.

2. Clark A. U-500 Insulin: Not for Ordinary Use. *US Pharm.* 2010; 35(5) (Diabetes suppl):14-17. Available at http://www.uspharmacist.com/content/s/126/c/20822/

3. Eli Lilly & Company, Humulin Website, Information for Healthcare Professionals. Available at http://humulin.com/hcp-u-500.aspx?srcid=trusem_google_humulin&WT.srch=1&WT.mc_id=71700000012123956-58700000749278296-43700008340367007&&.

4. FDA. Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – March 2011. Available at http://www.fda.gov/safety/medwatch/safetyinformation/ucm250517.htm.

5. FDA. 2013. Background Materials for REMS Standardization and Evaluation Public Meeting: REMS Evaluation. Available at http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm361888.htm.

6. Framework cited above and adapted from Kirkpatrick DL, et al. 1959. Techniques for evaluating training programs. *Journal of American Society of Training Directors* 13 (3):21–26. The best known public health outcomes evaluation approach is outlined in Glasgow R, et al. 1999. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *American Journal of Public Health*. 89(9):1322-27, although this is not suited for an early stage evaluation of a health care professional communication plan.

Appendix I Dear Healthcare Provider Letter on the correct use of Humulin® R U-500 KwikPen®

Humulin® R U-500 KwikPen®
insulin human injection
500 units/mL

[**Month Year**]

IMPORTANT PRESCRIBING INFORMATION

Subject: Humulin® R U-500 KwikPen® is now available as a dedicated dosing device

Dear Healthcare Professional:

Eli Lilly and Company (Lilly) is writing to inform you of important safety information about prescribing and administration of Humulin® R U-500 insulin. Dosing and administration errors have been reported in patients using U-100 insulin syringes or volumetric (tuberculin) syringes with the Humulin R U-500 insulin vial. To reduce the potential for these errors, a Humulin R U-500 KwikPen (prefilled pen) is now available for use as a dedicated dosing device for Humulin R U-500. Humulin R U-500 is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus requiring more than 200 units of insulin per day. The safety and efficacy of Humulin R U-500 when used in combination with other insulins or when delivered by continuous subcutaneous infusion has not been determined.

Prescriber Actions

- Consider prescribing Humulin R U-500 KwikPen to those patients with diabetes mellitus who require high daily doses of insulin (that is, more than 200 units of insulin per day)
- Write prescriptions for Humulin R U-500 KwikPen in units of insulin and inform patients of their dose in units of insulin. Prescribe the dose in 5-unit increments to match the dose dial increments on the Humulin R U-500 KwikPen. No dose or volume conversion is required
  - For example, for a patient receiving 125 units of Humulin R U-500 insulin twice per day, write the prescription as "Humulin R U-500 KwikPen 125 units subcutaneously (SC) twice daily 30 minutes before breakfast and dinner"

Recommendations for Patient Counseling with the Humulin R U-500 KwikPen

- Advise your patients NOT to withdraw Humulin R U-500 insulin from the KwikPen with a syringe. This may result in incorrect dosing due to differences in syringe markings and potentially result in overdose causing severe hypoglycemia. Instruct your patients to maintain backup U-500 KwikPens. In the event of a malfunction, they should use their backup pen or contact a pharmacist, healthcare professional, or The Lilly Answers Center for more information at 1-800-545-5979
- Instruct your patients NOT to count clicks to determine their dose because they could dial the wrong dose since the Humulin R U-500 KwikPen dials in 5-unit increments

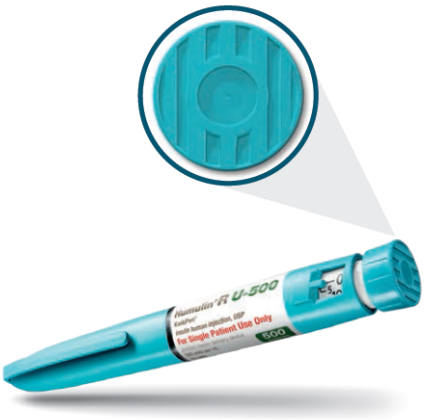
Please see Important Safety Information on last page and accompanying Full Prescribing Information.
Please see Instructions for Use included with the pen.

Lilly

Humulin® R U-500 KwikPen®
insulin human injection
500 units/mL

Features of Humulin R U-500 KwikPen

- The Humulin R U-500 KwikPen is aqua in color and has an aqua dose knob with raised ridges on the end. The pen label states "Humulin® R U-500" at the top and includes "500 units/mL" in a green highlighted box



- The Humulin R U-500 KwikPen can deliver from 5 to 300 units of insulin in a single injection
- The Humulin R U-500 KwikPen dials in 5-unit increments
- The Humulin R U-500 KwikPen is designed to dose up to a total of 1500 units per pen
- The Humulin R U-500 KwikPen cartridge holder and carton both contain the following yellow warning box:

DO NOT TRANSFER TO A SYRINGE
SEVERE OVERDOSE CAN RESULT

Reporting Adverse Events and Product Complaints

Healthcare professionals and patients are encouraged to report adverse events in patients taking Humulin R U-500 KwikPen to The Lilly Answers Center at 1-800-545-5979. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

This letter is not intended as a complete description of the benefits and risks related to the use of Humulin R U-500 KwikPen. Please refer to the enclosed Full Prescribing Information.

Please contact Lilly at 1-800-545-5979 if you have any questions about the information in this letter or the safe and effective use of Humulin R U-500 KwikPen.

Sincerely,

Robert W. Baker, MD
Vice President, Global Patient Safety

Enclosure: Humulin R U-500 KwikPen USPI

Please see Important Safety Information on last page and accompanying Full Prescribing Information.
Please see Instructions for Use included with the pen.

Humulin® R U-500 KwikPen®
insulin human injection
500 units/mL

Important Safety Information for Humulin R U-500

Contraindications

- Humulin R U-500 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-500 or any of its excipients.

Warnings and Precautions

- **Dosing Errors: Extreme caution must be observed in measuring the dose of Humulin R U-500 because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.**

  Medication errors associated with the Humulin R U-500 vial have occurred and resulted in patients experiencing hyperglycemia, hypoglycemia, or death.

  Dispensing
  - Instruct patients to always inspect insulin vials to confirm that the correct insulin is dispensed including the correct brand and concentration.
  - The Humulin R U-500 vial, which contains 20 mL, has a band of diagonal brown stripes. "U-500" is also highlighted in red on the Humulin R U-500 vial label.

  Prescribing
  - When using a U-100 insulin syringe or tuberculin syringe, express the prescribed dose of Humulin R U-500 in units of insulin along with the appropriate corresponding markings on the syringe the patient is using.

  Administration
  - Instruct patients to always check the insulin label before each injection.
  - A majority of the medication errors with Humulin R U-500 vial occurred due to dosing confusion when the dose was prescribed in units or volume corresponding to a U-100 syringe or tuberculin syringe markings, respectively, or the prescribed dose was administered without recognizing that the markings on the syringe used do not directly correspond to the U-500 dose. Instructions for use should always be read and followed before use.
  - Instruct the patient to inform hospital or emergency department staff of the dose of Humulin R U-500 prescribed.
  - A conversion chart should always be used when administering doses from the Humulin R U-500 vial with U-100 insulin syringes or 1 mL tuberculin syringes.

  If using the Humulin R U-500 KwikPen, patients should be counseled to dial and dose the prescribed number of units of insulin (NO dose conversion is required).

  DO NOT transfer Humulin R U-500 from the Humulin R U-500 KwikPen into a syringe for administration. Overdose and severe hypoglycemia can occur.

- **Patients Should Never Share KwikPens, Needles, or Syringes with Other People,** even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.
- **Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:** Changes in insulin, manufacturer, type, or method of administration should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased.
- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction associated with insulin, including Humulin R U-500. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Severe hypoglycemia may develop as long as 18 to 24 hours after an injection of Humulin R U-500. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important, such as driving or operating other machinery.

  Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual.

  Early warning symptoms of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system, or in patients who experience recurrent hypoglycemia.

  The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of Humulin R U-500 may vary in different individuals or at different times in the same individual and depends on many conditions.

  Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

Warnings and Precautions, continued

- **Hypersensitivity and Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humulin R U-500. If hypersensitivity reactions occur, discontinue Humulin R U-500; treat per standard of care and monitor until symptoms and signs resolve.
- **Hypokalemia:** Insulin use can lead to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).
- **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

Adverse Reactions

- Adverse reactions include hypoglycemia, allergic reactions, lipodystrophy, injection site reactions, weight gain, peripheral edema, and immunogenicity.

Drug Interactions

- Some medications may alter glucose metabolism and may necessitate insulin dose adjustment. Signs of hypoglycemia may be reduced or absent in patients taking antiadrenergic drugs. Particularly close monitoring may be required.

Use in Specific Populations

- **Pregnancy Category B:** While there are no adequate and well-controlled studies in pregnant women, evidence from published literature suggests that good glycemic control in patients with diabetes during pregnancy provides significant maternal and fetal benefits.
- **Pediatric Use:** There are no well-controlled studies of use of Humulin R U-500 in children. Standard precautions as applied to use of Humulin R U-500 in adults are appropriate for use in children.
- **Geriatric Use:** There are no well-controlled studies of use of Humulin R U-500 in geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia.
- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Dosage and Administration

- Prescribe Humulin R U-500 ONLY to patients who require more than 200 units of insulin per day.
- Adhere to administration instructions to reduce the risk of dosing errors.
- Individualize dose of Humulin R U-500 based on metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Administer Humulin R U-500 subcutaneously two or three times daily approximately 30 minutes before a meal. Rotate injection sites to reduce the risk of lipodystrophy.
- Do NOT mix Humulin R U-500 with other insulins.
- Do NOT administer Humulin R U-500 intravenously or intramuscularly.
- Do NOT perform dose conversion when using the Humulin R U-500 KwikPen. The dose window of the KwikPen shows the number of units of Humulin R U-500 to be injected and NO dose conversion is required.
- Do NOT transfer Humulin R U-500 from the KwikPen into a syringe.
- CONVERT the prescribed dose of Humulin R U-500 into a "unit" or "volume" mark when using the vial and a U-100 or a tuberculin syringe device to deliver Humulin R U-500.

Storage

- Protect from heat and light. Do not freeze. Do not use Humulin R U-500 after the expiration date stamped on the label.
- **Humulin R U-500 Vials:** Unopened vials of Humulin R U-500 should be kept in a refrigerator. Opened (in-use) vials of Humulin R U-500 should be kept in the refrigerator or at room temperature and used within 40 days of opening. Throw away any opened vial after 40 days of use, even if there is insulin left in the vial.
- **Humulin R U-500 KwikPen:** Unopened Humulin R U-500 KwikPens should be kept in a refrigerator. Opened (in-use) Humulin R U-500 KwikPens should be kept at room temperature and used within 28 days of opening. Do not refrigerate opened KwikPens. Throw away any opened KwikPen after 28 days of use, even if there is insulin left in the pen.

See accompanying Full Prescribing Information.
See Instructions for Use included with the pen.

HI U500 HCP ISI 04JAN2016

Appendix II Invitation to Participate and Healthcare Professional Survey

Email Welcome

[PROGRAMMING NOTE:]

On behalf of Eli Lilly and Company (Lilly), we would like to invite you to participate in a voluntary research survey about Humulin® R U-500 KwikPen®. The survey is part of a post-marketing commitment between Lilly and the Food and Drug Administration (FDA) to assess the effectiveness of the risk minimization tool.

This survey should take approximately 15 minutes to complete. Please consider the following important information before you start the survey. The application will time out after 15 minutes of inactivity. If your session times out, you will be able to use the original link return to the survey where you left off to complete it. If you are ready to begin the survey at this time, please click the survey link below. If not, please return to this site when it is convenient for you.

If you are eligible and complete the survey, you will be compensated in the amount of $50 for your time and participation. You are under no obligation to take this survey. Your answers to the questions in this survey will not affect your ability to prescribe Humulin® R U-500 KwikPen®.

Compensation for participation is not permitted in Vermont, the District of Columbia, Massachusetts, or Minnesota in accordance with state or federal law. Please be aware that healthcare professionals (HCPs) who are licensed and practice in these states or territories as well as Advanced Practice Registered Nurses (APRNs) in Connecticut will not be eligible for compensation for survey participation.

Your privacy will be protected. However, research survey records may be inspected by the FDA or other regulatory agencies. To the extent permitted by applicable laws and regulations, the records identifying you will not be made publicly available. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither Lilly nor its contractors will sell, transfer, or rent your information.

If you are interested in participating and to find out if you are eligible, please click on the following link below:

[SURVEY LINK]

Note: Do not use the browser's back button during this survey. You cannot change your responses once the answer is submitted.

HCP Screener

1. Do you agree to take part in this survey about Humulin® R U-500 KwikPen®?

1 ❒ Yes

2 ❒ No

[PROGRAMMING NOTE: If participant answers "2", then terminate]

2. Have you ever participated in this survey for Humulin® R U-500 KwikPen® before?

1 ❒ Yes

2 ❒ No

3 ❒ I don't know

[PROGRAMMING NOTE: If participant answers "1" or "3", then terminate]

3. Are you or were you employed, or are your immediate family members employed by Eli Lilly and Company, the marketing firm Schlesinger Associates, Covance Market Access, or the United States Food and Drug Administration?

1 ❒ Yes

2 ❒ No

3 ❒ I don't know

[PROGRAMMING NOTE: If participant answers "1" or "3", then terminate.]

4. Which state or territory are you licensed to practice in?

_____

[PROGRAMMING NOTE: Provide a drop down list of States]

[PROGRAMMING NOTE: Include logic to insert region for all locations based on selection]

5. What is your role in the management of patients with diabetes?

1 ❒ Physician

2 ❒ Advanced Practice Registered Nurse

3 ❒ Nurse Practitioner

4 ❒ Physician Assistant

5 ❒ Other

6. Please choose an option about your participation in this survey.

1 ❒ I will participate in the survey and would like to be paid.

2 ❒ I will participate in the survey but will not to be paid.

[PROGRAMMING NOTE: Compensation for participation is not permitted for HCPs in Vermont, District of Columbia, Massachusetts, or Minnesota, as well as, for Advanced Practice Registered Nurses (APRNs) in Connecticut. HCPs should be advised that they are ineligible for payment based on these restrictions, if appropriate.]

7. Are you involved in the management of patients with diabetes? This includes prescribing medications to treat diabetes or providing education to help manage diabetes.

1 ❒ Yes

2 ❒ No

[PROGRAMMING NOTE: If participant answers "2", then go to Q7 and terminate after Q14.]

8. What is your primary medical specialty?

1 ❒ General Internal Medicine
2 ❒ Endocrinology/Diabetology
3 ❒ Family Medicine
4 ❒ Other

9. How many years have you been in practice as a physician, physician assistant, or nurse practitioner since completing your medical/nursing education?

1 ❒ Less than 5 years
2 ❒ 5 – 10 years
3 ❒ 11 – 15 years
4 ❒ More than 15 years

10. In what type of facility do you work?

1 ❒ General Practice
2 ❒ Hospital
3 ❒ Other

11. Approximately, how many patients have you prescribed the Humulin® R U-500 KwikPen®?

1 ❒ 0
2 ❒ 1 – 5
3 ❒ 6 – 10
4 ❒ 11 – 20
5 ❒ More than 20

[PROGRAMMING NOTE: If participant answers "0", then terminate after Q14.]

12. Which of the following age groups best describes you?

1 ❒ Less than 30
2 ❒ 30 – 39
3 ❒ 40 – 49
4 ❒ 50 – 59
5 ❒ 60 – 69
6 ❒ 70 or older

13. What is your gender?

1 ❒ Male
2 ❒ Female

14. Are you aware that you received a Dear Health Care Provider letter from Eli Lilly and Company about the Humulin® R U-500 KwikPen® system?

1 ❒ Yes
2 ❒ No
3 ❒ I don't know

[PROGRAMMING NOTE: If participant answers "2" or "3", then terminate.]

[PROGRAMMING NOTE: End of screening questions]

[PROGRAMMING NOTE: Begin survey questions]

Survey

The following questions are about Humulin® R U-500 KwikPen®.

15. Please answer True, False, or I don't know for each of the following statements regarding Humulin® R U-500 KwikPen®.

		True	False	I don't know
a	It is appropriate to prescribe Humulin® R U-500 KwikPen® to patients needing more than 200 units of insulin per day.	o 1	o 2	o 3
b	It is important to clearly specify the units of insulin (5-unit increments) on the prescription when prescribing Humulin® R U-500 KwikPen®.	o 1	o 2	o 3
c	When prescribing Humulin® R U-500 KwikPen® it is important to inform patients of their dose in units of insulin.	o 1	o 2	o 3
d	When administering the Humulin® R U-500 KwikPen®, patients do not need to convert the dose since the dose window shows the number of units to be injected.	o 1	o 2	o 3
e	It is important to instruct your patients that they should always have a backup Humulin® R U-500 KwikPen® available.	o 1	o 2	o 3
f	It is important to instruct your patients not to count clicks to determine their dose.	o 1	o 2	o 3

[PROGRAMMING NOTE: Randomize the list above a-f.]

16. In the event of a Humulin® R U-500 KwikPen® malfunction, what would you instruct patients to do? (please select all that apply)

1 ❒ Use a backup pen
2 ❒ Use a syringe to withdraw the insulin from the KwikPen®
3 ❒ Contact a pharmacist or healthcare professional
4 ❒ Contact the Lilly Answer Center for more information at 1-800-545-5979

17. My answers to the true/false statements earlier about the Humulin® R U-500 KwikPen® were based on…(choose all that apply)

1 ❒ Professional knowledge about the use of human insulin products.
2 ❒ Previous experience with KwikPen® technology in other Lilly products such as Humalog
3 ❒ Familiarity with the Humulin® R U-500 KwikPen® package insert.
4 ❒ Knowledge gained from interaction with Lilly's sale representative.
5 ❒ Knowledge gained from the Humulin Dear Health Care Provider letter.
6 ❒ Guessing
7 ❒ Online information

[PROGRAMMING NOTE: Randomize the response options above 1-7.]

18. Did you read the Dear Health Care Provider letter provided to you by Eli Lilly and Company on "Important Prescribing Information" for the Humulin® R U-500 KwikPen® (insulin human)?

1 ❒ Yes
2 ❒ No
3 ❒ I don't recall

[PROGRAMMING NOTE: If participant answers "1" then go to following items based on agreement scales. If participant answers "2" or "3" skip the following series of 4 items identified under 19 and go to the following question.]

19. Based on your reading of the Dear Health Care Provider letter provided to you by Lilly, please evaluate your reaction to the material you received by indicating the level of your agreement or disagreement with the following statements:

a. The discussion of prescribing information encouraged me to better counsel my patients about the use of Humulin® R U-500 KwikPen®.
   1 ❒ Strongly disagree
   2 ❒ Disagree
   3 ❒ Neutral
   4 ❒ Agree
   5 ❒ Strongly Agree

b. I found the description of product features to be useful.
   1 ❒ Strongly disagree
   2 ❒ Disagree
   3 ❒ Neutral
   4 ❒ Agree
   5 ❒ Strongly Agree

c. I learned better how to respond to possible adverse events as a result of reading this communication.
   1 ❒ Strongly disagree
   2 ❒ Disagree
   3 ❒ Neutral
   4 ❒ Agree
   5 ❒ Strongly Agree

d. I found the summary of important safety information to be a useful extension of product labeling.

1 ❒ Strongly disagree
2 ❒ Disagree
3 ❒ Neutral
4 ❒ Agree
5 ❒ Strongly Agree

20. Do you or another healthcare professional at your practice discuss the safe use of the Humulin® R U-500 KwikPen® with patients receiving their initial prescription?

1 ❒ Yes, I directly counsel my patients.
2 ❒ Patient counseling about the use of medicines or new products is the responsibility of a nurse or diabetes educator in my practice setting.
3 ❒ No, counseling is generally not provided for patients about the use of prescription insulin.

21. Given what you know about Humulin® R U-500 KwikPen®, mark the best answer:

1 ❒ The product's ease of use and advanced safety features make counseling by prescribers unnecessary.
2 ❒ Prescribers should counsel their patients about the safe use of this product.
3 ❒ Any potential medication error is likely to result from dispensing and counseling is best left to pharmacists in their interactions with patients.
4 ❒ Humulin® R U-500 KwikPen® is not fundamentally different from any other human insulin product and patients with experience in self-administration can use the product safely based on product instructions.

22. Based on my knowledge about Humulin® R U-500 KwikPen®, I intend to counsel patients on its use.

1 ❒ Yes
2 ❒ No

[PROGRAMMING NOTE: End of Survey Questions]

Closing

[PROGRAMMING NOTE: Display the following when complete or screen failed]

[PROGRAMMING NOTE: Ask respondent for their contact information so payment can be mailed]

Thank you for providing your participation. Your survey is considered complete.

Appendix III Thank - You Letter and Correct Survey Responses

Dear [FIRST NAME] [LAST NAME]:

On behalf of Eli Lilly and Company, the maker of Humulin® R U-500 KwikPen®, we want to thank you for taking part in the Humulin® R U-500 KwikPen® Survey.

Additionally, to ensure that survey participants have accurate information about the risks of Humulin® R U-500 KwikPen®, we have provided links to the following two documents:

- A copy of the correct answers to the survey questions about the Humulin® R U-500 KwikPen® key safety messages
- A copy of the Humulin® R U-500 KwikPen® Dear Health Care Provider (DHCP) letter.

<Insert the correct answers to the survey questions link>

<Insert DHCP letter link>

Sincerely,
The Humulin® R U-500 KwikPen® Survey Team

Correct Survey Responses to Humulin® R U-500 KwikPen®

15. Please answer True, False, or I don't know for each of the following statements regarding Humulin® R U-500 KwikPen®.

		True	False	I don't know
a	It is appropriate to prescribe Humulin® R U-500 KwikPen® to patients needing more than 200 units of insulin per day.	■	o	o
b	It is important to clearly specify the units of insulin (5-unit increments) on the prescription when prescribing Humulin® R U-500 KwikPen®.	■	o	o
c	When prescribing Humulin® R U-500 KwikPen® it is important to inform patients of their dose in units of insulin.	■	o	o
d	When administering the Humulin® R U-500 KwikPen®, patients do not need to convert the dose since the dose window shows the number of units to be injected.	■	o	o
e	It is important to instruct your patients that they should always have a backup Humulin® R U-500 KwikPen® available.	■	o	o
f	It is important to instruct your patients to not count clicks to determine their dose.	■	o	o

16. In the event of a Humulin® R U-500 KwikPen® malfunction, what would you instruct patients to do? (please select all that apply)

- ■ Use a backup pen
- ❒ Use a syringe to withdraw the insulin from the KwikPen®
- ■ Contact a pharmacist or healthcare professional
- ■ Contact The Lilly Answer Center for more information at 1-800-545-5979