

MEMORANDUM

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

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SUBJECT: Novolog[®] (insulin aspart [rDNA origin] injection, NDA 20-986)
One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review:
Drug Utilization Data
Pediatric Exclusivity Grant Date: May 24, 2005

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

EXECUTIVE SUMMARY

This consult examines the drug utilization patterns for Novolog[®] in the pediatric population (ages 0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on May 24, 2005. Novolog[®] (insulin aspart [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent.

Proprietary drug use databases licensed by FDA were used to conduct this analysis. The IMS Health, IMS National Sales Perspectives[™] was used to determine the various retail and non-retail channels of distribution. Indications for outpatient use were measured by Verispan's Physician Drug and Diagnosis Audit, while retail prescriptions, patient counts and demographics were measured by Verispan's Vector One[®]: National (VONA) and Total Patient Tracker (TPT). We examined outpatient drug use patterns for Novolog[®], as well as for the other rapid-onset insulins, insulin lispro (Humalog[®]) and insulin glulisine (Apidra[®]) for the 3 1-year periods from June 1, 2003 through May 31, 2006.

The examination of wholesale sales data indicates that 80% of Novolog[®] distribution is into retail pharmacies. Mail order pharmacies accounted for approximately 20% of the retail distribution which, at this time, are not captured by the Verispan databases which were used to measure outpatient dispensing.

The number of dispensed prescriptions for Novolog[®] increased by 39% from 1.6 million prescriptions in the pre-exclusivity period (June 2004 through May 2005) to approximately 2.2 million prescriptions in the post-exclusivity period (June 2005 through May 2006). Pediatric patients age 0-16 years accounted for approximately 13% of dispensed prescriptions in each year.

Overall, there was a 34% increase in the number of patients receiving a Novolog prescription from the pre to post-exclusivity years. During the post-exclusivity year, there were 57 thousand pediatric patients who received a Novolog prescription, and 507 thousand adult patients. The relative percent increase for adult patients was 36% while the relative increase for pediatric patients age 0-16 years was 22%.

Endocrinologists were the most frequent prescribers of Novolog and accounted for 27% of dispensed prescriptions in the post-exclusivity year. The indication for use most frequently linked to Novolog[®] for both adults and children was “Diabetes Mellitus Uncomplicated” (ICD-9 250.0).

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that Act requires the reporting of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

It is estimated that over 13,000 children are diagnosed with diabetes in the U.S. annually¹. Obesity has led to a dramatic increase in the incidence of type 2 diabetes among children and adolescents over the past two decades; however the majority of diabetic individuals in this age group have type 1 diabetes². In an analysis of data from the National Health and Nutrition Examination Survey (1999-2002), Duncan found that of those adolescents (aged 12-19) reporting diabetes; roughly 71% were categorized as having type 1 and 29% as having type 2 diabetes³. Type 1 diabetes develops when the body's immune system destroys the pancreatic beta cells which produce the hormone insulin that regulates blood glucose. In the U.S., approximately one in every 400 to 600 children and adolescents aged 20 years or younger have type 1 diabetes, corresponding to a prevalence rate of 0.16 to 0.25 percent⁴. Increases in the incidence of diabetes may be compounded by the recent changes in diagnostic criteria for diabetes⁵.

¹ Juvenile Diabetes Research Foundation International; Available at <http://www.JDRF.org>. Accessed July 27, 2006.

² Hannon TS, Rao G, Arslanian SA. Childhood obesity and type 2 diabetes mellitus. *Pediatrics*. 2005 Aug;116(2):473-80.

³ Duncan GE. Prevalence of diabetes and impaired fasting glucose levels among US adolescents: National Health and Nutrition Examination Survey, 1999-2002. *Arch Pediatr Adolesc Med*. 2006 May;160(5):523-8.

⁴ Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2003. Atlanta, Ga: US Dept of Health and Human Services, Centers for Disease Control and Prevention; 2004.

⁵ Geiss, LS, et al. “Changes in incidence of diabetes in U.S. adults, 1997- 2003. *Am J Prev Med*, 2006 May; 30(5):371-7.

Novolog[®] (insulin aspart [rDNA origin] injection, NDA 20-986) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent and is produced by recombinant DNA technology utilizing a strain of *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Novolog is indicated for the treatment of patients with diabetes mellitus, for the control of hyperglycemia. Because Novolog has a more rapid onset and a shorter duration of activity than human regular insulin, Novolog given by injection should normally be used in regimens with an intermediate or long-acting insulin. Novolog may also be infused subcutaneously by external insulin pumps. Novolog may be administered intravenously under proper medical supervision in a clinical setting for glycemic control.

Novolog[®] was approved on June 7, 2000 for the control of hyperglycemia in adult patients. On September 13, 2005, the agency approved the following revision to the pediatric use subsection of the precautions section: “A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) age 6 to 18 years compared the following treatment regimens: Novolog (n = 187) or Novolin[®] R (n = 96). NPH insulin was administered as the basal insulin. Novolog achieved glycemic control comparable to Novolin R, as measured by change in HbA1c. The incidence of hypoglycemia was similar for both treatment groups. Novolog and regular human insulin have also been compared in children with type 1 diabetes (n=26) age 2 to 6 years. As measured by end-of-treatment HbA1c and fructosamine, glycemic control with Novolog was comparable to that obtained with regular human insulin. As observed in the 6 to 18 year old pediatric population, the rates of hypoglycemia were similar in both treatment groups⁶.” Also included in the October 2005 labeling revision was the removal of the reference to adult patients in the indications section. The indications section was revised to read: “Novolog is indicated for the treatment of patients with diabetes mellitus, for the control of hyperglycemia.⁷”

Novolog[®] is available in the following package sizes, each presentation containing 100 Units of insulin aspart per mL (U-100): 10 mL vials, 3 mL PenFill[®] cartridges, and 3 mL Novolog FlexPen[®] Prefilled syringes. In addition, a Novolog[®] 70/30 Mix formulation is available, consisting of 70 units of long-acting insulin aspart protamine and 30 units of rapid-acting insulin aspart per ml.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Novolog[®] (NDA 20-986) on May 24, 2005.

This review describes outpatient drug use patterns for Novolog[®] compared to the two other rapid-acting insulins, Humalog[®] and Apidra[®], during the three 1-year time periods from June 1, 2003 through May 31, 2006. Proprietary drug use databases licensed by the FDA were used to conduct this analysis.

METHODS

IMS Health, IMS National Sales PerspectivesTM data (see Appendix) were used to determine the setting in which Novolog[®] is sold. Sales of this product by number of vials/cartridges sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from May 2003 through April 2006. From these data, it was clear that this product is sold primarily to retail outlets (chain, independent, food store, mail order pharmacies, and long term care), which accounted for greater than 85% of the total number of milliliters sold in each of the 3 1-year periods in this analysis⁸. The second most common distribution channel (after chain pharmacy stores, ~40% of

⁶ Novolog[®] product labeling dated October 13, 2005.

⁷ Novolog product labeling dated October 13, 2005

⁸ IMS Health, IMS National Sales PerspectivesTM, Data extracted 7-2006, File: 0607nov2.xls

overall sales) was the mail order pharmacy channel, which accounted for 17% of the overall wholesale sales during the year of June 2005 – May 2006 and 20% of the retail specific sales.

Because the bulk of drug product sales of Novolog[®] for this time period were to retail settings, we examined the utilization patterns for Novolog[®] along with the other available rapid-acting insulin products (Humalog[®] and Apidra[®]) by focusing on the outpatient setting only.

Outpatient use and patient demographics were measured with the following data sources from Verispan, LLC: Vector One[®]: National (VONA), Total Patient Tracker (TPT) and indications for use were obtained from the Physician's Drug and Diagnosis Audit (see Appendix). Estimates of the number of drug mentions by office-based physicians, the number of dispensed prescriptions by retail pharmacies and the number of patients⁹ who received a dispensed Novolog[®] retail prescription were obtained. Unless otherwise specified, data for the drug name Novolog[®] excludes data for Novolog Mix[®] 70/30. Outpatient drug utilization patterns were examined for the 3-year period from June 1, 2003 through May 31, 2006.

RESULTS

I. Dispensed Prescriptions

There was a significant increase in the volume of prescriptions dispensed for rapid-acting insulin preparations over the 3 years of this analysis (Table 1).

During the pre-exclusivity period (June 2004 through May 2005), 7.4 million prescriptions (95% CI 7.362 – 7.374 million) were dispensed by retail pharmacies in the U.S. for these 3 rapid-acting insulin products combined. During the post-exclusivity period (June 2005 to May 2006), over 8.1 million prescriptions (95% CI 8.117 – 8.131 million) were dispensed. This represented a 10.3% increase from the pre-exclusivity period to the post-exclusivity period. Insulin Lispro (Humalog[®]) products had the highest market share among rapid-acting insulin products but their market share declined over the 3 years of this analysis from 79% in the year ending May 2004 to 59% for the year ending May 2006. Insulin glulisine (Apidra[®]) was launched in December of 2005, and accounted for approximately 8,000 (95% CI 7,800 – 8,200) prescriptions or 0.1% of the rapid-acting insulin market during the post-exclusivity period.

Prescriptions dispensed for all insulin aspart products (Novolog, Novolog Mix) increased by 137% from June 2003 through May 2006, and increased by 39% during the pre to post-exclusivity years (Table 1).

Novolog[®] (Novolog[®], Novolog[®] Mix) was the second most commonly dispensed rapid-acting insulin product during each of the 3 1-year periods in this analysis. The total number of prescriptions for Novolog[®] rose from 1.4 million prescriptions dispensed during June 2003 – May 2004, to 2.4 million prescriptions dispensed during the pre-exclusivity period (June 2004 – May 2005), to 3.4 million prescriptions dispensed during the post-exclusivity period (June 2005 – May 2006). Novolog[®] cartridges were the most commonly dispensed dose form and accounted for nearly 50% of dispensing during the post-exclusivity year with the other dose forms (vials, syringes, 70/30 mix cartridges and vials) each accounting for 16-18% of dispensing.

⁹ Note that data concerning the total number of patients based on Verispan's Total Patient Tracker may not be summed due to aging of patients during the study period.

Table 1: Total Number of Prescriptions Dispensed (in Thousands) by Retail Pharmacies for Rapid-Acting Insulins during June 1, 2003 through May 30, 2006 (mail order pharmacies not included)

	June 1 2003 - May 31 2004		June 1 2004 - May 31 2005		June 1 2005 - May 31 2006	
	TRxs	Share	TRxs	Share	TRxs	Share
	(000)	%	(000)	%	(000)	%
Total Market	6,698	100.0%	7,368	100.0%	8,124	100.0%
Insulin Lispro	5,282	78.9%	4,949	67.2%	4,764	58.6%
Humalog Vial 100U	3,082	58.4%	3,007	60.7%	2,926	61.4%
Humalog Mix 75/25 Pn Vial 75/25U	947	17.9%	826	16.7%	765	16.1%
Humalog Cartridge 100U	682	12.9%	653	13.2%	662	13.9%
Humalog Mix 75/25 Pn Syrg	572	10.8%	464	9.4%	410	8.6%
Insulin Aspart	1,416	21.1%	2,418	32.8%	3,352	41.2%
Novolog Cartridge 100U	885	62.5%	1,297	53.6%	1,665	49.7%
Novolog Mix 70/30 Cartridge 70/30U	236	16.6%	398	16.5%	537	16.0%
Novolog Syrg 100U	163	11.5%	355	14.7%	546	16.3%
Novolog Mix 70/30 Vial 70/30U	132	9.3%	368	15.2%	604	18.0%
Insulin Glulisine	--	--	--	--	8	0.1%
Apidra Cartridge 100U	--	--	--	--	2	23.6%
Apidra Vial 100U	--	--	--	--	6	76.4%

Verispan, LLC, Vector One National (VONA) Data extracted 7-10-2006 File: A060092 7-06 VONA Novolog TRx.qry

II. Patient Demographics

Retail prescriptions for Novolog[®] dispensed to the pediatric population (ages 0 – 16 years) increased by 30%, from approximately 218 thousand prescriptions (95% CI 216,790-218,900) dispensed during the pre-exclusivity period (June 2004 - May 2005) to approximately 283 thousand prescriptions (95% CI 281,705-284,113) dispensed during the post-exclusivity period (June 2005 – May 2006) (Table 2). The percent increase for pediatrics was slightly lower than the 34% increase seen for adult patients over the same period. Novolog[®] prescriptions dispensed to the pediatric population aged 0-16 years old accounted for 12.8% of the total dispensed Novolog[®] prescriptions during the post-exclusivity period, a slight decrease from the 13.2% seen during the pre-exclusivity year .

Table 2. Total Number of Retail Prescriptions Dispensed for Novolog[®] Vials and Pen Cartridges by Patient Age, During June 1, 2003 through May 30, 2006 (mail order pharmacies not included)

	June 1 2003 - May 31 2004		June 1 2004 - May 31 2005		June 1 2005 - May 31 2006	
	TRxs*	Share*	TRxs*	Share*	TRxs*	Share*
		%		%		%
Novolog	1,048,402	100.0%	1,652,065	100.0%	2,210,560	100.0%
0-16 Years	137,153	13.1%	217,845	13.2%	282,909	12.8%
0-1 Years	334	0.2%	452	0.2%	524	0.2%
2-11 Years	58,242	42.5%	93,310	42.8%	122,640	43.3%
12-16 Years	78,577	57.3%	124,083	57.0%	159,745	56.5%
17+ Years	906,215	86.4%	1,417,025	85.8%	1,903,419	86.1%
Unspecified	5,034	0.5%	17,195	1.0%	24,232	1.1%

Verispan, LLC, Vector One National (VONA) Data extracted 7-10-2006 File: A060092 7-06 VONA Novolog Age.qry

Data for Novolog Mix 70/30 are excluded

*Subtotals may not sum exactly, due to rounding error.

The projected number of patients of all ages who received a dispensed retail prescription for Novolog[®] during this 3-year period increased from approximately 285,429 (95% CI 284,220 – 286,639) patients from June 2003 – May 2004, 423,006 (95% CI 421,531 – 424,481) in the pre-exclusivity period (June 2004 – May 2005) and 568,498 (95% CI 566,785 – 570,210) in the post-exclusivity period (June 2005 – May 2006) (Table 3). This represented an increase of approximately 99% over 3 years and an increase of 34% from the pre to post-exclusivity periods.

The number of adult patients age 17 years and older receiving a Novolog[®] retail prescription increased by 36% from 373,254 (95% CI 371,869 – 374,638) in the pre-exclusivity period to 507,495 (95% CI 505,878 – 509,113) in the post-exclusivity period. The projected number of unique pediatric patients (aged 0 through 16 years) who received a dispensed prescription for Novolog[®] increased by 22% from 46,862 (95% CI 46,377 – 47,348) in the pre-exclusivity year to 56,989 (95% CI 56,453 - 57,525) in the post-exclusivity year.

Relative increases during the pre to post-exclusivity periods for each of the pediatric age subgroups were again lower than in adult patients, with the age 0-1 year old group rising by 1%, and the 2-11 and 12-16 year old groups increasing by 22% each. The distribution of pediatric patients by age was similar during each of the 3 1-year analysis periods.

Table 3. Total Number of Patients Receiving Prescriptions Through Retail Pharmacies for Novolog[®] Vials and Pen Cartridges by Patient Age, During June 1, 2003 through May 30, 2006* (mail order pharmacies not included)

	June 1 2003 - May 31 2004		June 1 2004 - May 31 2005		June 1 2005 - May 31 2006	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
Novolog	285,429	100.0%	423,006	100.0%	568,498	100.0%
0-16	32,401	11.4%	46,862	11.1%	56,989	10.0%
0 - 1	161	0.1%	218	0.1%	220	0.0%
2 - 11	15,588	5.5%	22,386	5.3%	27,269	4.8%
12 - 16	17,907	6.3%	26,270	6.2%	31,941	5.6%
17+	252,871	88.6%	373,254	88.2%	507,495	89.3%
Unknown	4,278	1.5%	11,732	2.8%	16,198	2.8%

Verispan, LLC, Vector One National (VONA) Data extracted 7-10-2006

Files: A060092 7-06 VONA Novolog Age.qry, A060092 7-06 VONA Novolog 0-16.qry

Data for Novolog Mix 70/30 are excluded

*Subtotals may not sum exactly, due to rounding error., Due to aging of patients during the study period (“the cohort effect”), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

III. Prescriber Specialty

Endocrinologists were the most frequent prescribers of Novolog[®] in each of the three (3) 1-year periods of observation, accounting for 29% of retail prescriptions (473 thousand, 95% CI 471,646-474,768) in the pre-exclusivity period and 27% of prescriptions (603 thousand, 95% CI 600,787-604,315) in the post-exclusivity period (Table 4). Pediatricians were the fifth most frequent prescribers during each year, with 8.4% of prescriptions (140 thousand, 95% CI 138,688-140,372) for the pre-exclusivity period and 8.9% of prescriptions (197 thousand, 95% CI 196,336-198,344) during the post-exclusivity year.

Table 4: Total Number of Retail Prescriptions Dispensed (in thousands) for Novolog[®] Vials and Pen Cartridges by Prescriber Specialty, During June 1, 2003 through May 30, 2006 (mail order pharmacies not included)

	June 1 2003 - May 31 2004		June 1 2004 - May 31 2005		June 1 2005 - May 31 2006	
	TRxs	Share [†]	TRxs	Share [†]	TRxs	Share [†]
	(000)	%	(000)	%	(000)	%
Novolog	1,048	100.0%	1,652	100.0%	2,211	100.0%
Endocrinology	334	31.9%	473	28.6%	603	27.3%
Internal Med	216	20.6%	343	20.8%	479	21.7%
General Practice*	122	11.7%	217	13.1%	344	15.6%
Unspecified	124	11.8%	229	13.9%	240	10.9%
Pediatrics	89	8.5%	140	8.4%	197	8.9%
Total Others	163	15.6%	250	15.1%	347	15.7%

*General Practice includes general practice, Family Medicine, Doctors of Osteopathy
[†]Numbers may not sum exactly, due to rounding
 Data for Novolog Mix 70/30 are excluded
 Verispan, LLC, Vector One National (VONA) Data extracted 7-10-2006
 File: A060092 7-06 VONA Novolog MD.qry

IV. Indication for Use

The most common indication for use of Novolog for both pediatric and adult patients was “Diabetes Mellitus Uncomplicated” (ICD-9 250.0), which accounted for greater than 95% of adult Novolog diagnosis mentions in both the pre and post-exclusivity periods and 100% of diagnosis mentions in pediatric patients (data not shown)¹⁰.

DISCUSSION

Based on the databases employed for this analysis, the growth in the number of adult and pediatric patients receiving Novolog was fairly constant over the three years studied. While the time periods for this study were one-year periods before and after the granting of exclusivity, the labeling for pediatric use was approved in September of 2005, 3 months into the post-exclusivity period. It is unclear whether the 9 months of post-label change data reflect any effect that the labeling change might have had on dispensing patterns.

The findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that Novolog[®] was distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives[™] and determined that Mail order pharmacies are the second most common retail distribution channel, accounting for up to 20% of wholesale sales. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

¹⁰ Verispan, LLC. Physician’s Drug and Diagnosis Audit (PDDA) Data extracted 7-2006. File: A060092 7-06 PDDA Novolog Diag-age.xls

While we conducted a comprehensive analysis of the use of this product in the outpatient settings, in which the majority of use occurred, a significant proportion of wholesale sales of Novolog[®] is to mail order pharmacies; a distribution channel not currently captured by Verispan's retail prescription audits. In addition, insulin is available over the counter and without a prescription. Although insulin preparations are typically purchased under prescription through a retail pharmacy for insurance billing purposes, an unknown amount of insulin will be purchased over the counter and is therefore unable to be captured by the prescription databases available to the Agency.

Verispan's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Verispan recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

CONCLUSION

In summary, the prescriptions dispensed for all the rapid-acting insulin products combined increased during each of the three years examined. The number of prescriptions for Novolog and the number of patients receiving a prescription for Novolog also increased during each year.

Pediatric patients accounted for approximately 13% of Novolog prescriptions. The growth in the number of patients receiving Novolog over the pre to post-exclusivity years was 36% for adults and 22% for pediatric patients age 0-16 years. In the post exclusivity year, an estimated 57,000 pediatric patients received a Novolog prescription.

Endocrinologists were the most frequent prescribers of Novolog and accounted for 27% of dispensed prescriptions in the post-exclusivity year. The indication for use most frequently linked to Novolog[®] for both adults and children was "Diabetes Mellitus Uncomplicated" (ICD-9 250.0).

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APPENDIX

IMS HEALTH

IMS National Sales Perspectives™

IMS Health IMS National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. IMS Health, IMS National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, vials, and market share. These data are based on national projections.

Data for this analysis include prescriptions dispensed for Novolog® from June 1, 2003 through May 31, 2006, inclusive.

VERISPAN, LLC

Vector One®: National (VONA)

Verispan's VONA is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims, representing over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

Data for this analysis include prescriptions dispensed for Novolog®, Humalog®, and Apidra® from June 1, 2003 through May 31, 2006, inclusive.

VERISPAN, LLC

Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, physician offices and hospitals. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Data for this analysis include patients who were dispensed a prescription for Novolog[®] from June 1, 2003 through May 31, 2006, inclusive.

VERISPAN, LLC

Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey that monitors disease states and the physician intended prescribing habits on a national-level. The survey is designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The audit is composed of approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

The term drug uses refers to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Data for this analysis include physician mentions for Novolog[®] from June 1, 2003 through May 31, 2006, inclusive.