Pharmacovigilance and Drug Safety Reporting Algorithms (Content and Process)

David Olaleye, SAS® Institute, Inc., Cary, NC
Michael Kilhullen, SAS® Institute, Inc., Cary, NC
Gail Kongable, University of Virginia
Tanyss Mason, SAS® Institute, Inc., Cary, NC
Eugenia Bastos, SAS® Institute, Inc., Cary, NC
Edward Helton, SAS® Institute, Inc., Cary, NC

ABSTRACT

Using SAS® software we have built out algorithms, content and processes, for pharmacovigilance or post market approval safety reporting. The processes used CDISC data standards, metadata management and data warehousing, pre or post approval spontaneous or case series standard summary safety report (ICSR or PSUR) and data exploration and signal detection. Common and more uncommon adverse events (e.g. -hypotension, kidney dysfunction, etc and pulmonary edema, respectively) were used as selected events for demonstration of these processes. nicardipine control data from two pivotal trials (published in The Journal of Neurosurgery) and the MedWatch AERS data were the pre and post approval data source. AERS (year 2000) data for both nicardipine and comparator calcium channel blockers was explored and mined using new directed signal detection algorithms and evaluated against the controlled data. The basic concepts of WHO signal detection and the FDA Pharmacovigialnce Guidance were guiding principles in the developed algorithms.

Concomitantly the use of CDISC SDTM safety domains and the ADaM requirements to unambiguously provide compliant analysis were explored. Metadata management (source code, potential imputations, flags and analysis files, etc) was also explored for standard procedures of analysis using SAS software.

INTRODUCTION

Over the past 40 years we have made numerous errors in drug safety approvals to include thalidomide, diethylstilbestrol, Xoma, Rezulin, fen/phen, Vioxx and Baycol. These drugs represent examples of compounds that contributed to untoward effects that were potentially unobserved in the controlled data and not apparent at market approval but generated a stronger signal in the post market approval period.

In 2005, primarily resulting from the Vioxx reported incidences of cardiotoxicity, the Food and Drug Administration (FDA) established two new regulatory processes for the enhanced protection of public health for FDA regulated product. The first is that the same statistical review and approval process of efficacy outcomes will now be applied to the safety data. Second, a new FDA independent Drug Safety Oversight Board (DSB) has been established to further provide an external review of safety data for marketed products. Two completely separate events, but equally important, is that the European Medicines Evaluation Agency is starting a new pharmacovigilance system in which SAS is a participant; and the FDA has initiated the process to develop a new Adverse Event Reporting System (AERS-II) to further enhance collection and analysis of drug safety data.

Adverse event (AE) reporting systems provide drug safety reviewers the opportunity to investigate a variety of drug safety questions. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. A thorough understanding of the safety profile of a marketed product requires analyzing safety data from multiple data sources not limited to pre-and post-approval safety. We demonstrate the process of performing standard safety analyses and signal detection analysis using standard processes built on a common standard metadata model (such as, CDISC-SDTM model) required as part of the regulatory requirements of pre and post approval drug safety and for pharmacovigilance regulatory reporting.

MATERIALS AND METHODS

EXPERIMENTAL DESIGN AND DATA SOURCE CONSIDERATIONS

The data from two studies, using essentially identical protocols, were performed under current GCP by the NIH Stroke Group. NICSAH 1 is placebo versus high dose and NICSAH 2 is low dose versus high dose. Both studies were randomized and double-blinded. Merging the studies gave this analysis of the controlled safety data a dose response consideration or evaluation as well.

The trials represent the intravenous treatment of subarchnoid hemorrhage (an aneurysmal bleed into the subarchnoid space) with a calcium channel blocker (nicardipine). These are sophisticated trials in a complex patient population. The results of these studies were published in the Journal of Neurosurgery and these publications and their data serve as a model for applying software technology in the compliant evaluation and reporting of drug safety and pharmacovigilance, with subsequent inquiries into signal detection and drug-drug interactions.

Our approach was to first develop new search algorithms for analysis and reporting of untoward safety events in a public database such as AERS. Also build and demonstrate standard summary safety reports (spontaneous and case series) for the control data and to merge the studies for an integrated summary safety report as required. Our algorithms or processes were to follow standard observations and approaches

to drug safety with use of standard regulatory guidance and CDISC data models. The following information regarding nicardipine untoward effects were considered for this technology application:

1. Common un-toward effects or adverse events reported for nicardipine in the product insert/approved labeling that were selected 1) hypotension 2) renal dysfunction—reported as kidney function abnormal 3) cardiac function (tachycardia and bradycardia). A rarer event, pulmonary or lung edema was studied in the signal detection process, as well.
2. Case series and merged AEs based on demographic, medical history and laboratory variables were addressed in case summaries of safety.
3. The relationship to concomitant medications was evaluated as using data stripped and cleaned from the 2000 AERS database with SAS tools. Concomitant medication assessed: 1) vasodilators – e.g. Nitro-Dur and Isordil, 2) beta-blockers – eg. Inderal, metoproll, and Blocadren and 3) anti-coagulants – e.g. Heparin and Coumadin 4) corticosteroids and HHH therapy 5) vasopressors: dopamine, neosynephrine to oppose the vasodilation of the nicardipine calcium channel blockade.
4. Ca++ channel blocker time of exposure, dose response, diagnosis and relationship to vasospasm (– e.g. use in hypertension and stroke) and count, frequency outcome of adverse event were also addressed.

SOFTWARE, PROCESS AND TECHNOLOGY
DATA MANAGEMENT
The SAS 9 Platform and solutions provide all the tools necessary to build a manageable, scalable, and reusable warehouse environment. Leveraging a centralized metadata repository, data from our source studies could be extracted from the operational system, transformed into a standard model, and modeled into analysis ready data marts without the need for replication. The metadata repository also allows us to store the methods used in transformation and additional information about the columns, tables, and processes that can be leveraged across our organization.

The safety domains defined by the CDISC SDTM model provided a standardized data structure central to the success of the safety analysis. By using this data model, post processing steps to perform standard analyses and create specialized data marts was greatly simplified. In addition, as new analyses and reports were created, we are able to more easily integrate them into the overall process**.**

Standard embedded processes for metadata management (acquisition and filing), aggregation (domains and variables) and reporting (standard analysis datasets and standard analysis) facilitate the drug sponsor's ability to comply with the requirements for ICSR (individual case study report) or the PSUR (periodic safety update report). Standard metadata analysis and reporting/visualization within the safety reporting process are then translated to data exploration and signal detection.

STATISTICAL ALGORITHMS FOR DATA EXPLORATION AND SIGNAL DETECTION
Different methods are currently being used for signal identification and signal detection analyses. The type of method employed is driven by the signaling program objective or goal. For detection of adverse drug reactions, most statistical and signaling methods fall into two analysis domains:

1 **Intra-product (within) comparison methods** - Methods for examining spontaneous reports within the context of the index product and its user population. One example is to compare the frequency of reports for a product (drug or vaccine or device) relative to those received for the same product in previous time periods.

2 **Inter-product (between) comparison methods** - Methods for comparing spontaneous reports for the index product with those reported for the index drug class or for other products.

Signal identification methods under each analysis domain also tend to utilize any or all of these two data analysis strategies:

- Safety database querying - a systematic process whereby clinical safety databases are searched or queried for potential association between a product and adverse event that may be of regulatory or epidemiological interest. Other signaling methods can then be utilized to support and assess the strength of this signal.

- Safety database mining - a systematic process whereby large databases are searched for associations among two or more variables (say, drug product and adverse event, drug-drug interactions, etc.) that occur at a higher than expected frequency. Given an observed pattern, other signaling methods can be utilized to support and assess the strength of this signal.

Standard signal detection techniques include the Multi-Gamma Poisson Shrinker (MGPS), adopted by the FDA; the Bayesian Confidence Propagation Neural Network (BCPNN) Information Component (IC) and Relative Odds Ratio (ROR), adopted by Upsalla Monitoring Center and World Health Organization; and the Proportional Reporting Ratio (PRR), adopted by Medicines Control Agency (MCA) of EMEA. Another statistical measure recently introduced and implemented by SAS Institute in its signal detection application modules is the Adjusted Residual Score (referred to as AdjustedR). This algorithm is a statistical outlier detection measure for signaling disproportionately reported drug-adverse reaction pairs in a Drug by ADR frequency matrix table. The score serves as a statistical measure of deviation and the extent that the number of reports associated with a particular drug-ADR combination is reported to the SRS database more often than expected relative to the rest of

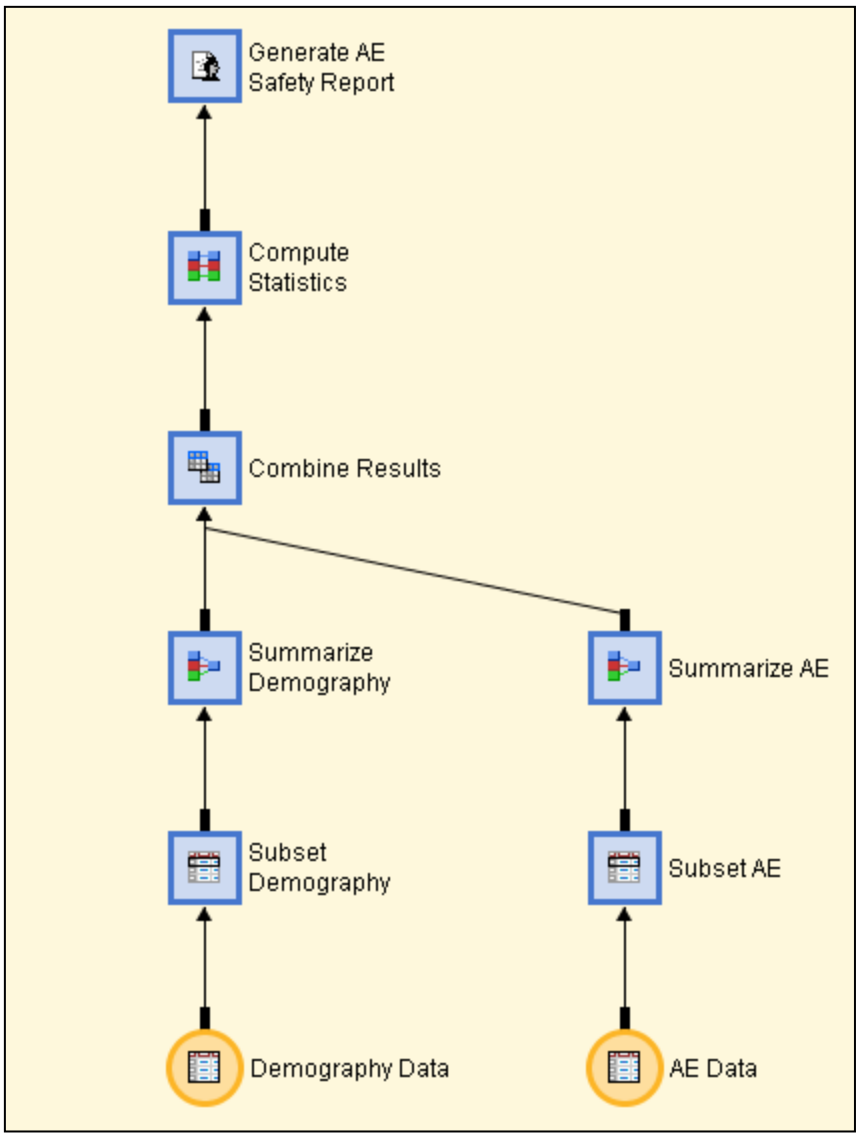
the reports in the database. Each of the three statistical algorithms attempts to quantify the disproportionality between the observed and expected values for any given Drug-AE combination to a chosen threshold.

CONTROL DATABASES METADATA MANAGEMENT AND STANDARD SUMMARY SAFETY REPORTS

Generating the control database for providing ICSR or a PSUR looks or views (or regulatory reporting) is a proprietary process performed by each regulated product sponsor for compliant reporting to the Agency. It is frequently written in SAS code and follows a common path but is not truly standardized in the industry due to individual product sponsor need and additions. The common path developed for this type of reporting with source code in the Appendix and is the path taken for individual, study and integrated reports generated from the NICSAH 1 and 2 data and the AERS data.

One of the most commonly generated tables in a clinical trial final report is a summary of the number and percent (count and frequency) of subjects experiencing one or more adverse events by treatment group. This type of report generation is a key for providing a comparison of untoward product effects before final approval. This summary table requires multiple processing steps because it requires multiple input datasets and requires additional processing to conform to the statistical procedures. The steps used to generate this report are summarized in Figure 1.

FIGURE 1: DRUG SAFETY REPORT GENERATION PROCESS



Input data are extracted from a data source and subsetted based on report requirements. Both data are summarized to provide the proper numerators and denominators. The data is then joined together and statistics such as p-values and counts are computed. The final analysis is then reported. An example of a drug safety summary report is provided in Table 1.

TABLE 1: NUMBER (%) OF SUBJECTS EXPERIENCING 1 OR MORE ADVERSE EVENTS AND TOTAL EVENTS FOR NICARDIPINE DRUG (SELECTED EVENTS WITH FREQUENCY > 3% AND SIGNIFICANT P-VALUES SHOWN)

		Description of Planned Arm										
		nicardipine .075			nicardipine .15			Placebo			P-Values	
AE Body System	AE Preferred Term	N	(%)	Total AE	N	(%)	Total AE	N	(%)	Total AE	UnAdjusted	Adjusted
	Any Adverse Events	179	98.9	1691	620	97.9	5145	444	97.2	3196	.	.
	No Adverse Experience	2	1.1	2	13	2.1	13	13	2.8	13	.	.
BLOOD	TOTAL	126	69.6	264	364	57.5	633	235	51.4	370	1.0000	1.0000
	ANEMIA	103	56.9	112	240	37.9	248	167	36.5	168	1.0000	1.0000
	COAG DIS	4	2.2	4	20	3.2	22	16	3.5	16	0.3496	1.0000
CARD	TOTAL	111	61.3	181	287	45.3	438	170	37.2	238	0.9999	1.0000
	ARRHYTHMIA VENT	1	0.6	1	1	0.2	1	1	0.2	1	0.7377	1.0000
	BRADYCARDIA	0	0.0	0	0	0.0	0	2	0.4	2	0.0326	0.8990
	TACHYCARDIA	66	36.5	72	128	20.2	132	52	11.4	52	1.0000	1.0000
GENRL	TOTAL	55	30.4	59	178	28.1	186	139	30.4	143	1.0000	1.0000
	FEVER	50	27.6	50	161	25.4	162	130	28.4	131	0.1815	1.0000
HEPAT	TOTAL	71	39.2	80	210	33.2	223	128	28.0	139	0.6762	0.9997
	LIVER FUNC ABNORM	61	33.7	62	184	29.1	185	111	24.3	112	0.9890	1.0000
INFEC	TOTAL	47	26.0	60	195	30.8	223	115	25.2	137	0.5932	0.9993
	SEPSIS	10	5.5	10	57	9.0	57	33	7.2	34	0.7723	1.0000
NERV	TOTAL	140	77.3	364	413	65.2	965	289	63.2	647	1.0000	1.0000
	INTRACRAN HYPERTENS	29	16.0	29	110	17.4	117	110	24.1	113	0.0018	0.0872
RENAL	TOTAL	40	22.1	45	134	21.2	151	60	13.1	66	1.0000	1.0000
	CREATINE PK INC	17	9.4	17	35	5.5	36	24	5.3	25	0.8269	1.0000
	KIDNEY FUNC ABNORM	24	13.3	24	101	16.0	108	33	7.2	34	1.0000	1.0000
RESP	TOTAL	86	47.5	149	331	52.3	621	194	42.5	349	0.8376	1.0000
	EDEMA LUNG	37	20.4	38	194	30.6	208	104	22.8	107	0.9882	1.0000
VASC	TOTAL	160	88.4	334	543	85.8	1209	384	84.0	820	0.7745	1.0000
	HYPERTENS(SS)(ST)	44	24.3	48	147	23.2	161	163	35.7	170	<.0001	<.0001
	HYPOTENS	51	28.2	57	215	34.0	250	80	17.5	93	1.0000	1.0000
	HYPOTENS REL	14	7.7	15	18	2.8	23	0	0.0	0	1.0000	1.0000
	VASOSPASM	109	60.2	136	356	56.2	429	314	68.7	410	<.0001	0.0008

Data Source: nicardipine Clinical Trial Studies

RESULTS

1) Building standard summary safety reports for individual or case series using SAS metadata management and data standards with merged pivotal trial control data (Figure 1 and Table 1).
2) Evaluating and exploring both post market approval data sources for directed signal detection and evaluating against pre-market/controlled data for validation of the signals, for example, kidney/renal function abnormal and lung/pulmonary edema (Table 2 and Table 3).
3) Calculate proportionate reporting rates using different signal algorithms for known untoward adverse events in the AERS database for nicardipine drug in relation to adverse events reported with the drug (Tables 2 and 3).
4) Explore signal profile likelihood of nicardipine with acute renal failure and pulmonary edema event in terms of demographic attributes and concomitant drug variables and therapies (Tables 4 and 5).

TABLE 2: DIFFERENT SIGNAL ALGORITHMS AS MEASURES OF DISPROPORTIONAL REPORTING OF COMBINATION PAIRS INVOLVING NICARDIPINE DRUG AND SELECTED ADVERSE EVENTS (WITH ADJUSTED/UNADJUSTED P-VALUES FOR MULTIPLICITY TESTING)

AE Preferred Term			Signal Measure Scores				P-Values**	
	Reaction Count (N)	Expected Count (E)	Adjusted Residual	PRR	IC-2SD	Chi-Sq.	Fisher (Unadjusted)	Permutation Based (Adjusted*)
HYPOTENS	307	270.705	2.295	1.140	0.010	5.267	<.0001	<.0001
PHLEB__ST_	174	124.114	4.607	1.425	0.260	21.228	<.0001	<.0001
TACHYCARDIA	204	174.231	2.329	1.179	0.019	5.426	<.0001	<.0001
HYPERGLYCEM	272	260.833	0.719	1.045	-0.121	0.517	<.0001	<.0001
HYPOTENS_REL	38	22.135	3.444	1.767	0.286	11.86	<.0001	<.0001
KIDNEY_FUNC_ABNORM	132	115.344	1.595	1.151	-0.062	2.543	<.0001	<.0001
ARRHYTHMIA_ATR	43	30.677	2.274	1.424	0.034	5.168	<.0001	0.0006
AGITATION	24	17.047	1.719	1.431	-0.112	2.955	0.0003	0.0054
HYPOXIA	31	24.792	1.274	1.263	-0.203	1.622	0.0004	0.0068
HEM_INTRAVENTRIC	22	14.959	1.858	1.499	-0.080	3.452	0.0004	0.0072
HYDROCEPHALUS	312	295.649	0.991	1.058	-0.093	0.983	0.0005	0.0084
HYPERTENS_RESIST	20	13.402	1.839	1.522	-0.091	3.383	0.0008	0.0142
HEM_CEREBR	95	85.616	1.041	1.114	-0.151	1.083	0.0013	0.0286
LEUKOCYTOSIS	56	41.574	2.288	1.366	0.034	5.235	0.0016	0.0374
HYPOCALCEM	24	20.540	0.780	1.176	-0.367	0.608	0.0022	0.0508
LIVER_FUNC_ABNORM	247	227.119	1.368	1.091	-0.070	1.871	0.0196	0.5388
EDEMA_LUNG	246	246.975	-0.064	0.996	-0.196	0.004	0.0210	0.5436
VASOSPASM	565	637.276	-3.065	0.883	-0.303	9.397	1.0000	1.0000
HYPERTENS_SS__ST_	209	271.236	-3.932	0.764	-0.580	15.457	1.0000	1.0000
Data Source: NICSAH I&II Clinical Trial Studies								

TABLE 3: DIFFERENT SIGNAL ALGORITHMS AS MEASURES OF DISPROPORTIONAL REPORTING OF COMBINATION PAIRS INVOLVING NICARDIPINE DRUG AND SELECTED ADVERSE EVENTS (WITH ADJUSTED/UNADJUSTED P-VALUES FOR MULTIPLICITY TESTING)

AE Preferred Term			Signal Measure Scores				P-Values**	
	Reaction Count (N)	Expected Count (E)	Adjusted Residual	PRR	IC-2SD	Chi-Sq.	Fisher (Unadjusted)	Permutation Based (Adjusted*)
RENAL_FAILURE_ACUTE	14	5.823	3.395	2.407	0.385	11.527	<.0001	0.0106
RENAL_FAILURE_ACUTE_ON_CHRONIC	3	0.401	4.106	7.505	0.067	16.841	<.0001	0.0106
RENAL_FAILURE_CHRONIC_AGGRAVATED	2	0.264	3.380	7.612	-0.422	11.4344	<.0001	0.1092
RENAL_IMPAIRMENT_NOS	9	5.406	1.549	1.666	-0.275	2.398	0.0007	0.2858
RENAL_FAILURE_NOS	9	6.154	1.149	1.463	-0.435	1.3209	0.0084	0.7256
HYPOTENSION	12	12.981	-0.273	0.924	-0.911	0.0746	0.1097	0.9958
TACHYCARDIA_NOS	9	8.702	0.101	1.034	-0.874	0.0102	0.1102	0.9958
PULMONARY_INFARCTION	3	0.199	6.281	15.200	0.292	39.429	<.0001	0.0106
BRADYCARDIA_NOS	18	5.100	5.722	3.535	0.970	32.742	<.0001	0.0106
HYPERTENSION_AGGRAVATED	15	3.257	6.514	4.616	1.182	42.445	<.0001	0.0106
DRUG_INTERACTION_NOS	23	8.397	5.052	2.742	0.756	25.522	<.0001	0.0106
PULMONARY_OEDEMA_NOS	5	4.589	0.192	1.090	-1.080	0.037	0.1281	0.9976
SEPSIS_NOS	6	8.555	-0.876	0.701	-1.544	0.767	0.2474	1.0000
PULMONARY_HYPERTENSION_NOS	3	2.262	0.491	1.327	-1.152	0.241	0.2681	1.0000
HEPATIC_FUNCTION_ABNORMAL_NOS	8	4.275	1.804	1.873	-0.196	3.2561	0.0012	0.3710
BLOOD_CREATININE_ABNORMAL	2	0.034	10.666	60.610	-0.133	112.99	0.0171	0.8428
Data Source: FDA-AERS 2000 Database								

TABLE 4: SIGNAL LIKELIHOOD PROFILE FOR NICARDIPINE-RENAL_FAILURE_ACUTE PAIR BY DEMOGRAPHIC FACTORS, CONCOMITANT MEDICATIONS AND THERAPIES

Strata				Signal Measure Scores			
	Strata Attribute	Reaction Count (N)	Expected Count (E)	Adjusted Residual	PRR	IC-2SD	Chi-Sq.

Gender	**FEMALE**	0	2.610	.	.	.	2.6182
	MALE	17	3.586	**7.091***	**4.753***	**2.140***	50.4186*
	UNKNOWN	0	0.157	.	.	.	0.1575
Age Group	**20-39**	0	0.533	.	.	.	0.5352
	40-59	6	0.755	**6.039***	**7.971***	**1.396***	36.5595*
	<=19	0	0.213	.	.	.	0.2139
	>=60	11	4.946	**2.725***	2.226	**1.140***	7.4486*
	UNKNOWN	0	0.450	.	.	.	0.4511
Report Profile	**DRUG_EVENT_ONLY**	0	0.008	.	.	.	0.0078
	MULTI_DRUGS_SINGLE_EVENT	4	0.162	**9.537***	**24.786***	**0.857***	91.0921*
	MULTI_EVENTS_SINGLE_DRUG	0	0.127	.	.	.	0.1274
	MULT_DRUGS_MULTI_EVENTS	13	5.917	**2.917***	2.199	**0.370***	8.5107*
Cumulative Trend	**2000Q1 TO 2000Q1**	7	1.839	**3.814***	**3.814***	**0.457***	14.5452*
	2000Q1 TO 2000Q2	9	3.265	**3.181***	2.760	**0.306***	10.1194*
	2000Q1 TO 2000Q3	12	5.112	**3.053***	2.350	**0.281***	9.3194*
	2000Q1 TO 2000Q4	17	6.224	**4.328***	2.734	**0.630***	18.7302*
Drug-Drug Interactions							
CILAZAPRIL	**NO**	14	6.119	**3.192***	2.290	**0.324***	10.1905*
	YES	3	0.511	**3.482***	**6.508***	**0.370***	12.6006*
FUROSEMIDE	**NO**	8	4.413	1.710	1.814	-0.040	2.9248!
	YES	9	1.833	**5.297***	**4.924***	**2.018***	28.2241*
HYPERIUM	**NO**	14	6.069	**3.226***	2.309	**0.336***	10.4060*
	YES	3	0.533	**3.379***	**5.848***	**0.415***	11.6656*
LEVOTHYROXINE	**NO**	14	6.068	**3.226***	2.309	**0.465***	10.4123*
	YES	3	0.209	**6.106***	**14.431***	**0.450***	37.4844*
Concomitant Therapies and Events							
PROTEIN_TOTAL_DECRE	**NO**	14	6.127	**3.187***	2.287	**0.325***	10.1559*
	YES	3	0.118	**8.390***	**27.594***	**0.370***	70.7824*
HAEMATEMESIS	**NO**	14	6.168	**3.160***	2.271	**0.333***	9.9828*
	YES	3	0.055	**12.558***	**56.147***	**0.381***	157.2448*
HEPATIC_FUNCTION_AB	**NO**	13	6.046	**2.834***	2.152	**0.242***	8.0310*
	YES	4	0.171	**9.260***	**23.826***	**0.924***	85.9753*
LEUCOCYTOSIS_NOS	**NO**	14	5.806	**3.407***	2.414	**0.438***	11.6111*
	YES	3	0.438	**3.872***	**6.888***	**0.484***	15.0577*
Data Source: FDA-AERS 2000 Database							

TABLE 5: SIGNAL LIKELIHOOD PROFILE FOR NICARDIPINE-PULMONARY (OR LUNG) EDEMA PAIR BY DEMOGRAPHIC FACTORS

Strata	Strata Attribute	Reaction Count (N)	Expected Count (E)	Signal Measure Scores			
				Adjusted Residual	PRR	IC-2SD	Chi-Sq.
Gender	**FEMALE**	4	2.370	1.060	1.688	-0.195	0.4712
	MALE	1	2.126	-0.773	0.470	-1.974	1.1244
	UNKNOWN	0	0.085	.	.	.	0.5982
Age Group	**20-39**	1	0.483	0.744	2.072	-1.145	0.5554
	40-59	1	0.581	0.550	1.721	-1.288	0.3022
	<=19	0	0.158	.	.	.	0.1580
	>=60	2	3.521	-0.811	0.568	-1.379	0.6599
	UNKNOWN	1	0.280	1.361	**3.578**	-1.111	1.8579
Report Profile	**DRUG_EVENT_ONLY**	0	0.004	.	.	.	0.0036
	MULTI_DRUGS_SINGLE_EVENT	0	0.060	.	.	.	0.0604
	MULTI_EVENTS_SINGLE_DRUG	2	0.147	**4.833**	**13.724**	-0.160	23.4911*
	MULT_DRUGS_MULTI_EVENTS	3	4.445	-0.686	0.675	-1.767	0.4712
Cumulative Trend	**2000Q1 TO 2000Q1**	0	1.270	.	.	.	1.2744
	2000Q1 TO 2000Q2	1	2.452	-0.929	0.408	-2.834	0.8629
	2000Q1 TO 2000Q3	4	3.970	0.015	1.008	-1.287	0.0002
	2000Q1 TO 2000Q4	5	4.589	0.192	1.090	-1.080	0.0368
Data Source: FDA-AERS 2000 Database							

DISCUSSION

We have attempted to follow the new FDA Guidance on Pharmacovigilance Practices and Pharmacoepidemiological Assessment as outlined below.

A. Good Reporting Practice
B. Characteristics of a Good Case Report
C. Developing a Case Series and Assessing Causality of Individual Case Reports
D. Summary Descriptive Analysis of a Case Series
E. Use of Data Mining to Identify Product-Event Combinations
F. Safety Signals That May Warrant Further Investigation
G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

Using SAS 9 and SDD for algorithms of pharmacovigilance, these required build processes were applied to controlled trial data and year 2000 AERS. We applied good reporting practice procedures and data standards to the ICSRs and case series analysis to the required build of a database needed for directed signal detection. Using SAS analytics in data exploration, we applied acquired knowledge for evaluating the rate and incidence of more uncommon untoward effects in the MedWatch data for nicardipine and other products in this pharmacological class.

Contact Information

David Olaleye
SAS Institute, Inc
Ste 201
1400 Morris Dr
Wayne PA 19087-5512
Work Phone 610-640-0940
Fax 610-640-1488
david.olaleye@sas.com
www.sas.com

Michael Kilhullen
SAS Institute, Inc
Ste 200
1430 US Highway 206
Bedminster NJ 07921
Work Phone 908-470-0080
Fax 908-470-0081
michael.kilhullen@sas.com
www.sas.com

Tanyss Mason
SAS Institute, Inc
100 SAS Campus Dr
Cary, NC 27513
Work Phone 919-531-7162
Fax 919-677-4444
tanyss.mason@sas.com
www.sas.com

Edward Helton
SAS Institute, Inc
100 SAS Campus Dr
Cary, NC 27513
Work Phone 919-531-4062
Fax 919-531-9445
ed.helton@sas.com
www.sas.com

Eugenia Bastos
SAS Institute Inc
Post-Montgomery Bldg Ste 3400
1 Montgomery St
San Francisco CA 94104-5534
Work Phone 415-421-2227
Fax 415-421-1213

Gail Kongable
gkongable@epsilongroup.com