Update on SEND

(Standard for Exchange of Nonclinical Data)

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Overview

- Current CFR requirements for data submission
- Current approaches to data submission in CDER
- Advantages of developing data standards
- SEND model and Consortium
- Ongoing pilot project with industry participants
- Software development (i.e., ToxVision)
- Next steps
- Potential issues
- Conclusions

CFR Requirements for Animal Toxicity Data

- INDs: 21 CFR 312.23(a)(8)(ii)(b)
  - A full tabulation of data suitable for detailed review...
- NDAs: 21 CFR 314.50 (d)
  - Required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment …

Current Approaches to Data Submission

- Paper Submissions
- Electronic Submissions (eNDA Guidance 1999)
  - PDF files (includes *scanned* study reports)
  - Datasets (optional):
    - SAS Transport files
    - Guidance gives examples of meta-data options
      - Ex: Animal ID, dose, duration, test name (e.g., glucose), results, units, etc.
    - Sponsors decide which variables and terminology to use as needed (i.e., flexibility to capture data generated), but only as long as terms used are consistent within each study

Current Approaches to Data Submission (cont)

- Currently, viewing and analysis of nonclinical datasets requires use of JMP/SAS software
  - Advantage: powerful program for data analysis
  - Disadvantage: difficult to use for most reviewers
- Therefore, nonclinical datasets not preferred or requested by most review divisions
- Goal should be to encourage use of datasets to enhance review process

Advantages of Developing Data Standards

- Improves communication with sponsors
- Results in more consistent data submission and storage
- Increases efficiency and reduces review time
- Allows development of *customized* software to:
  - Enable reviewers to easily replicate sponsor's tables and graphs (as both line listing and summary tables)
  - Enables reviewers to easily view and subset any data (i.e., by dose, time, test, gender, etc.)
- Having customized software is key to reviewer acceptance and use of datasets
- Does not change sponsor's study design, conduct, or data capture methods (i.e., remains flexible)

Standard for Exchange of Nonclinical Data (SEND)

- Discussions began in July 2002
- Modeled after CDISC's SDS model (v.3)
- Defines domains and variables for submitting all data generated from animal toxicity studies
- SEND Consortium consists of ~100 representatives from pharma/biotech industry, several FDA Centers, CROs, and software vendors
  - Teleconferences are held every month
  - SEND model v.1 released Aug 2003
  - Current version is 1.4 (March 2004)
- CRADA (May 1999) with PharmQuest, Inc. to develop and evaluate software tools for viewing and analyzing nonclinical data based on SEND data model

SEND Consortium

- Industry:
  - Amgen
  - AstraZeneca
  - Aventis
  - Bayer
  - Boehringer-Ingelheim
  - Eli Lilly & Co.
  - GSK
  - J&J
  - Merck
  - Novartis
  - P&G
  - Pfizer
  - Sanofi-Synthelabo
  - Schering
  - BMS
- CROs:
  - Covance
  - PPDI
  - Quintiles
- Vendors:
  - Dataceutics
  - Image Solutions
  - LifetreeTechnol.
  - Lincoln Tech.
  - Metamatrix
  - Mindspring
  - PharmQuest
  - Phonescreen
  - Webclin
  - Xybion
- FDA Centers:
  - CDER
  - CFSAN
  - CVM
  - NCTR
  - CBER
  - CDRH(?)

SEND Model (v1.4)

- Variable categories:
  - **Interventions** (dose, frequency, route, lot number, etc.)
  - **Findings** (test name, result, units, etc.)
  - No ***Events*** (considered as “Findings” in SEND)
- A list of variables are used to define specific domains:
  - Body Weights, Clinical Pathology, Microscopic Findings, etc.
- “Relates” table will be in next version:
  - For linking related observations in a particular animal
  - Ex: palpable mass observed during in-life phase > gross observation of tumor at necropsy > diagnosis of tumor-type at microscopic observation

SEND Model (cont)

- All datasets (one per domain) pre-screened by a validator tool being developed by PharmQuest, Inc.
- All study data then deposited into database repository
- Selected data accessed via a web-browser through use of specially-designed software tools
- XML format will replace SAS Transport files in future

SEND Domains (v1.4)

- Animal Characteristics
- Animal Disposition
- Body Weights
- Clinical Pathology
- Clinical Signs
- Drug/Metabolite Levels
- Exposure
- Food Consumption
- Fetal Data
- Female Fertility
- Group Characteristics
- Group Observations
- Macroscopic Findings
- Male Fertility
- Microscopic Findings
- Ophthalmoscopic Findings
- Organ Weights
- Rodent Micronucleus
- Study Summary
- Study Timing
- Tumor Analysis
- Water Consumption

Body Weights Domain (SEND)

Body Weights

Findings – One record per body weight per animal

Variable Name	Variable Label	Type	Controlled Terms or Format	Origin	Role	Usage Notes
STUDYID	Study Identifier	Char			Identifier	Unique identifier for a study within the submission.
ANMLID	Animal Identifier	Char			Identifier	Animal identifier.
DOMAIN	Domain	Char	BW		Identifier	Two-character abbreviation for the domain most relevant to the observation.
BWSEQ	Sequence Number	Num			Identifier	Sequence number given to ensure uniqueness within a domain. Can be used to join related records.
BWTESTCD	Test Short Name	Char	BW		Topic	The topic variable of the domain.
BWTEST	Test Name	Char	Body Weight		Qualifier	Represents the name of the measurement.
BWORRES	Body Weight	Char			Qualifier	This field should contain all results, whether numeric or character.
BWORRESU	Units for Body Weight	Char	*		Qualifier	Unit for BWORRES (e.g., g, kg).
BWSTRESC	Character Result/Finding in Std Format	Char			Qualifier	Contains the result value for all findings, copied or derived from BWORRES or BWSTRESN in a standard format or standard units.
BWSTRESN	Numeric Result/Finding in Std Units	Num			Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from BWORRES. BWSTRESN should store all numeric test results or findings.
BWSTRESU	Standard Units	Char	*		Qualifier	Standardized unit used for BWSTRESC or BWSTRESN.
BWRESTYP	Body Weight Result Type	Char	Baseline, Intermediate, Final, Terminal		Qualifier	Indicates the type of the result. Final represents that last of a series of measurements, whereas terminal represents measurements at time of sacrifice.
BWDTC	Date/Time Animal Weighed	Char			Timing	This is the date and time of collection of the observation.
BWCMT	Comment	Char			Qualifier	Brief comment to be used when necessary, such as when certain findings or values require additional comment or explanation.

Body Weights (from Dataset)
(One observation per row)

	STUDYID	ANMLID	DOMAIN	BWTESTCD	BWTEST	BWORRES	BWORRESU	BWSTRESC	BWSTRESN	BWSTRESU	BWRESTYP	BWDTM
1	6271-259	C50080	BW	BW	Body Weight	202	g	202	202	g	Baseline	2000-01-17
2	6271-259	C50080	BW	BW	Body Weight	265	g	265	265	g	Intermediate	2000-01-24
3	6271-259	C50080	BW	BW	Body Weight	321	g	321	321	g	Intermediate	2000-01-31
4	6271-259	C50080	BW	BW	Body Weight	356	g	356	356	g	Intermediate	2000-02-07
5	6271-259	C50080	BW	BW	Body Weight	350	g	350	350	g	Final	2000-02-13
6	6271-259	C50080	BW	BW	Body Weight	349	g	349	349	g	Terminal	2000-02-14

Body Weights (from Data*base*)
(Multiple observations per row)

					BODY WEIGHT gm	
GROUP 1: CONTROL						
ANIMAL NO.\WEEK	-3	-2	-1	1	2	3
1001	125	175	250	272	307	401
1002	127	170	220	262	300	390
1003	129	194	249	313	353	420
1004	127	170	226	265	302	378
1005	122	170	200	265	353	402
1006	117	167	210	262	303	349
1007	137	192	250	311	360	406
1008	132	191	240	288	326	357
1009	128	168	200	273	345	390
1010	126	152	189	215	250	300
1011	117	192	241	294	343	382
1012	137	192	250	299	326	406
1013	132	191	240	288	300	357
MEAN	128.3	180.8	231.1	285.6	333.3	371.3
S.D.	6.7	13.0	182	21.0	15.6	18.6
N	13	13	12	12	13	12

Pilot Project
(Fed. Reg., Jan 27, 2003)

- Volunteers from industry providing sample nonclinical (i.e., animal toxicity) datasets using SEND format
- Experience from this ongoing pilot will be used to modify SEND model and associated software tools

Pilot Project (cont)

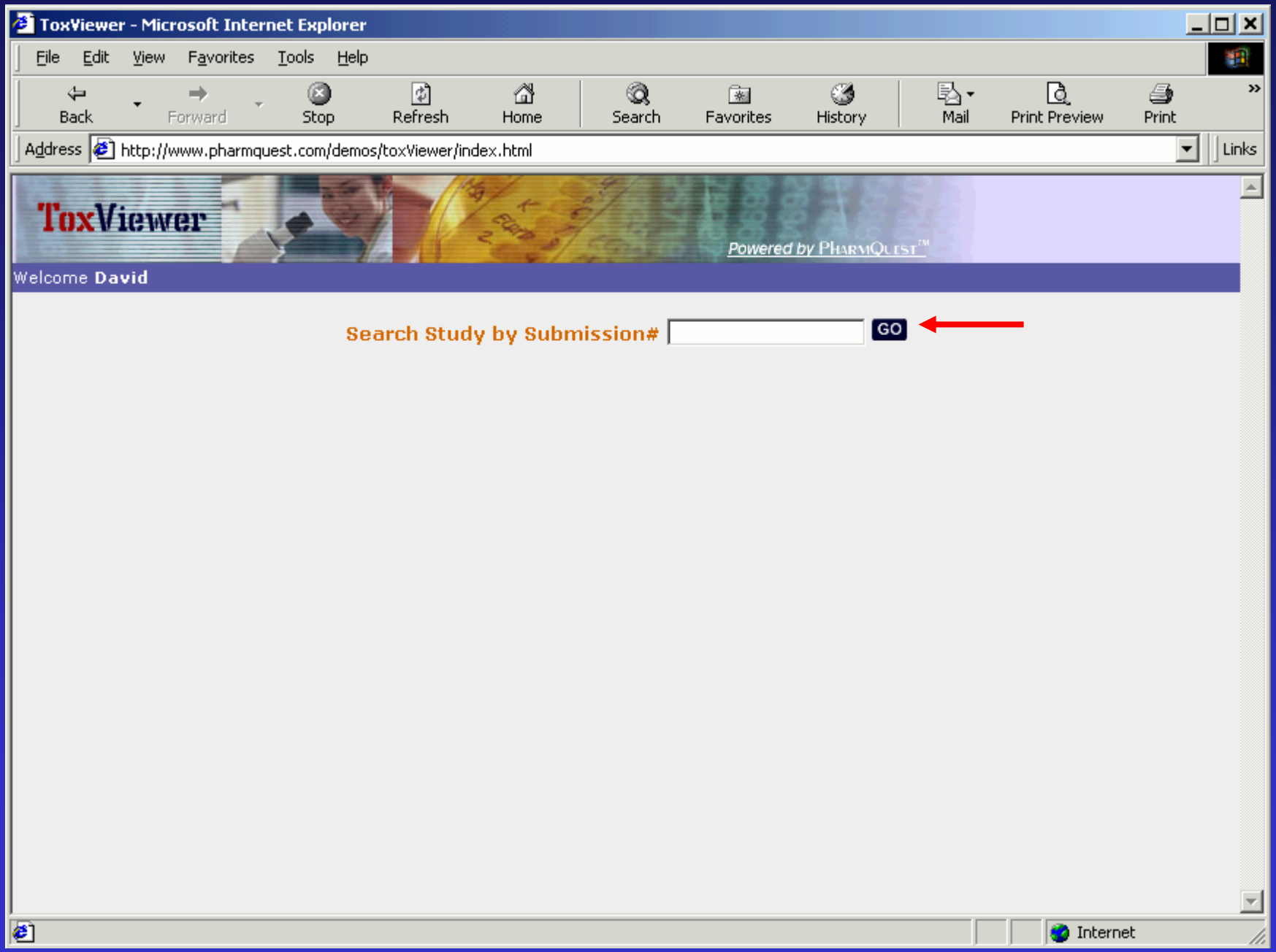
- 3-Phases (to be completed by end of 2004):
  1. Single and repeat-dose toxicity studies:
     - Datasets from 6- studies (rat and dog) received so far
  2. Carcinogenicity studies
     - Required data for statistical analysis of tumor incidences to be exported from database
  3. Reproductive toxicity studies
     - Complex issues of multi-generational design (F_0, F_1, F_2)

Pilot Participants

- Amgen
- AstraZeneca
- Bristol-Myers Squibb
- Eli Lilly & Co.
- Merck
- Novartis
- Pfizer
- Proctor & Gamble
- Sanofi-Synthelabo

ToxVision

- Software tool for viewing and analyzing nonclinical data received by the FDA in the SEND format
- Being developed through CRADA with PharmQuest, Inc.
- Enable reviewers to easily view and subset the data for further analysis or graphing
  - Data converted from single observation per row to more traditional view of multiple observations per row
- Allow reviewers to replicate most analyses, tables, graphs, and line listings from a submission with minimal or no transformation


ToxViewer - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Forward Stop Refresh Home Search Favorites History Mail Print Preview Print
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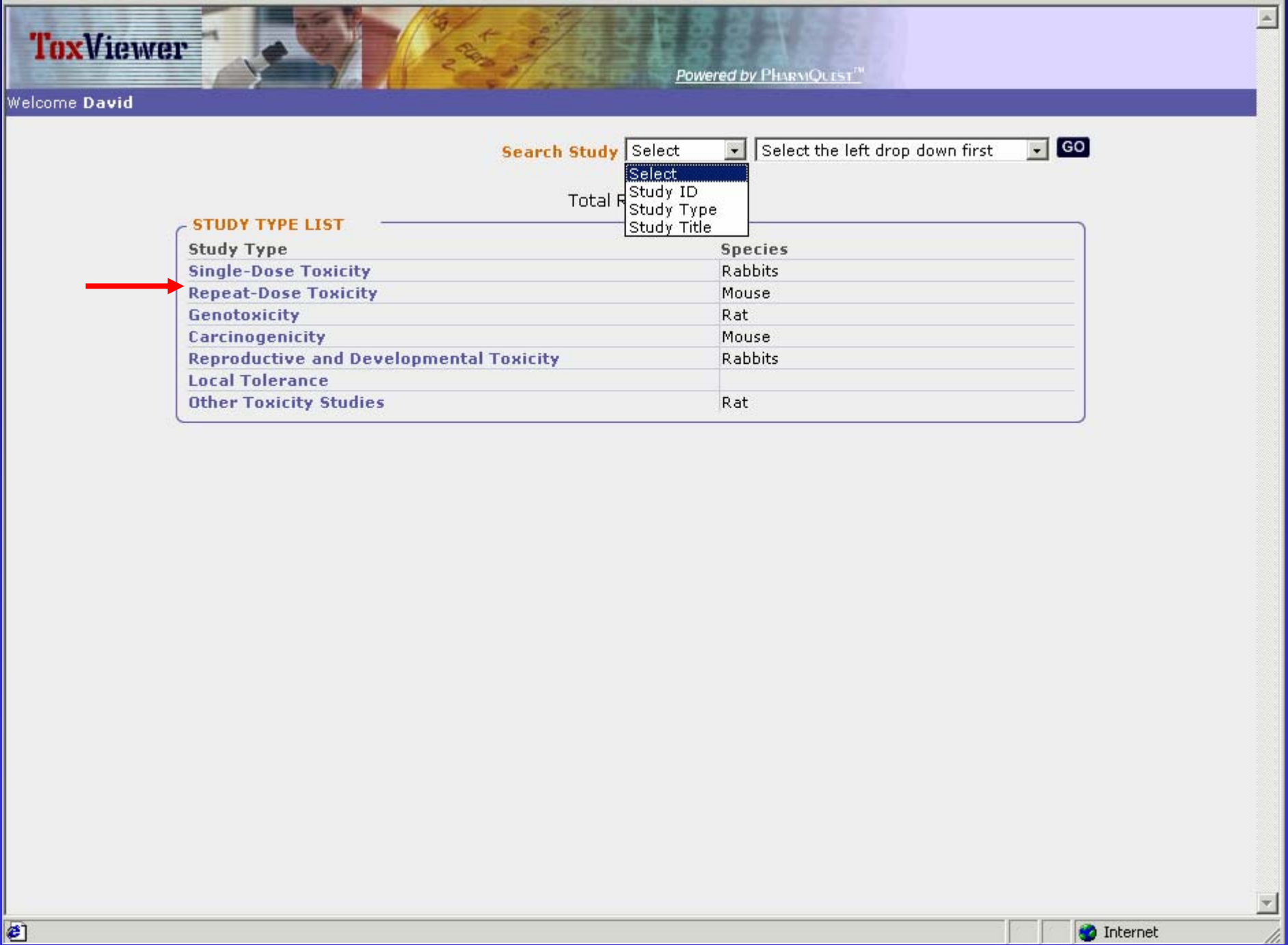
ToxViewer
Powered by PharmQuest™
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Search Study
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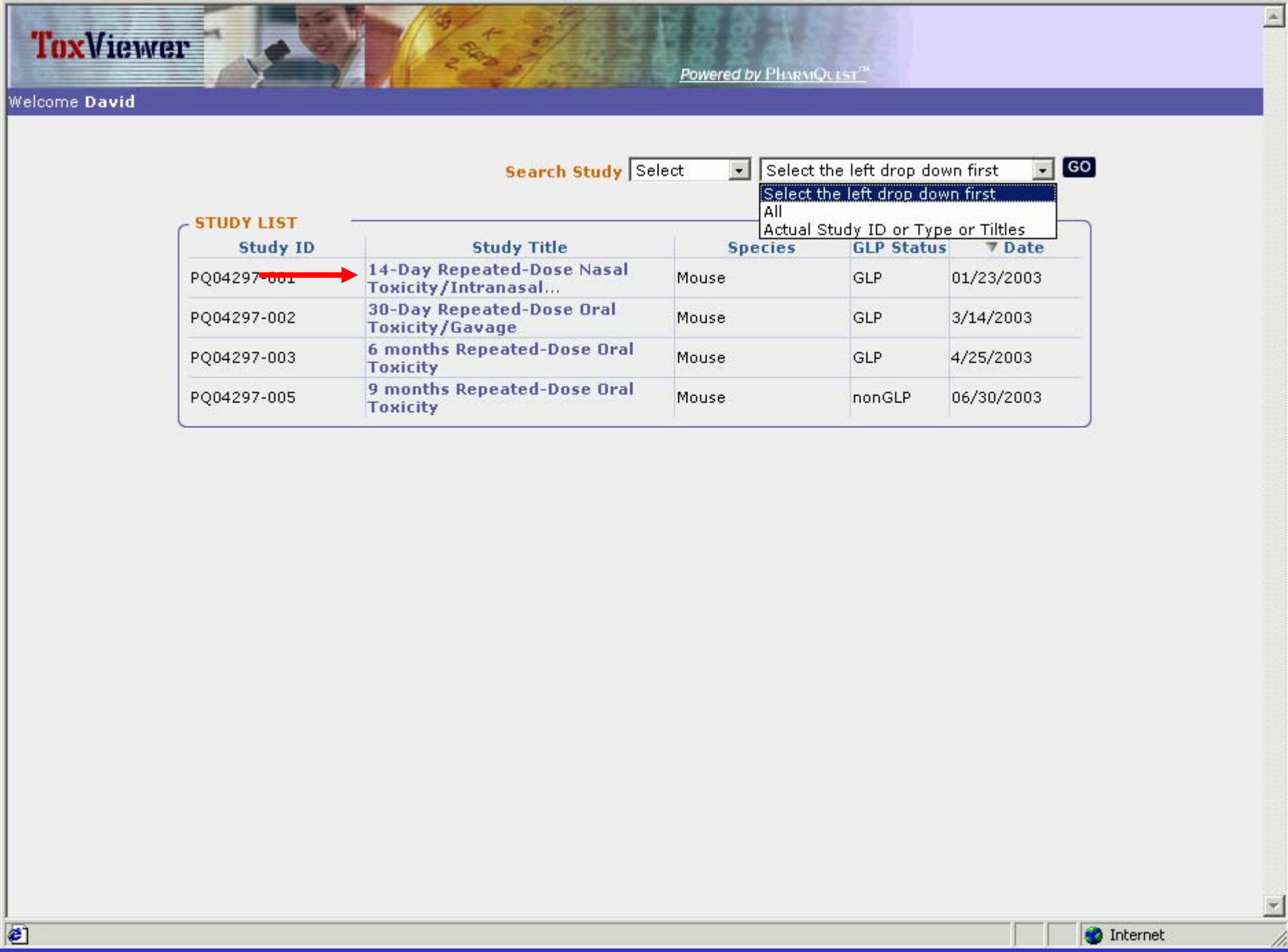
STUDY TYPE LIST
Study Type
Species
Single-Dose Toxicity
Rabbits
Repeat-Dose Toxicity
Mouse
Genotoxicity
Rat
Carcinogenicity
Mouse
Reproductive and Developmental Toxicity
Rabbits
Local Tolerance
Other Toxicity Studies
Rat
Internet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STUDY LIST
Study ID
Study Title
Species
GLP Status
Date
PQ04297-001
14-Day Repeated-Dose Nasal Toxicity/Intranasal...
Mouse
GLP
01/23/2003
PQ04297-002
30-Day Repeated-Dose Oral Toxicity/Gavage
Mouse
GLP
3/14/2003
PQ04297-003
6 months Repeated-Dose Oral Toxicity
Mouse
GLP
4/25/2003
PQ04297-005
9 months Repeated-Dose Oral Toxicity
Mouse
nonGLP
06/30/2003
Internet

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VIEW DATA TABLES

Click on the domain name for data views

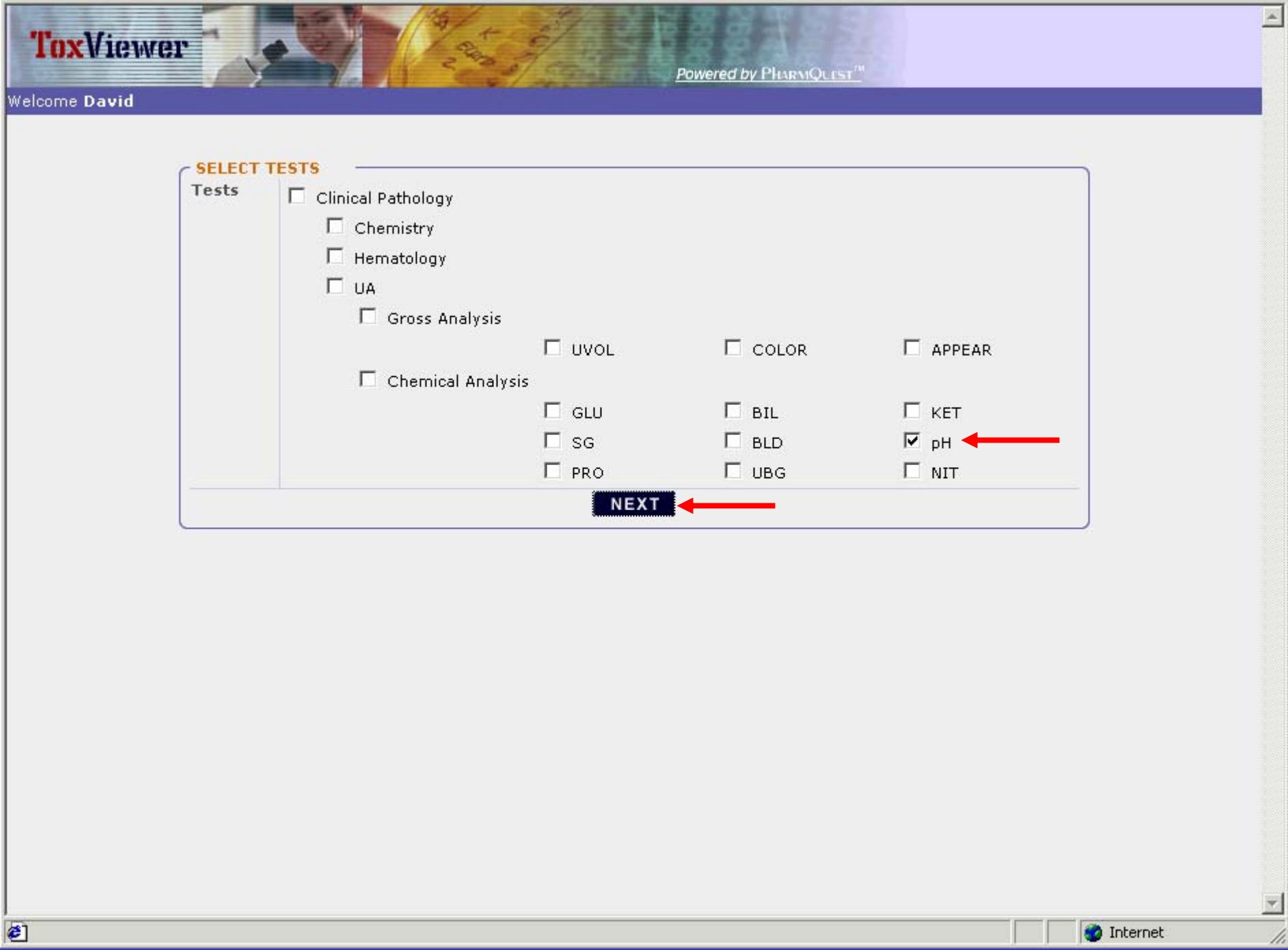
- Body Weight	- Clinical Pathology	- Clinical Signs
- Food Consumption	- Microscopic Findings	- Tumor Analysis
- Water Consumption		

STUDY SUMMARY

Study Title	14-Day Repeated-Dose Nasal Toxicity/Intranasal		
Study ID	PQ04297-001	**Study Type**	Repeat Dose Toxicology
Lab Name	Quintiles	**Lab Location**	Kansas City, MO 64137, USA
Species	Mouse	**Strain**	Sprague-Dawley
Study Duration	14 days	**GLP Status**	GLP
Groups	4 - Control, Low, Medium, High	**Study Design**	Parallel
Name of Treatment	PQ04297 Fine Spray	**Daily Dose**	
Route of Administration	Intranasal		
Basal Diet		**Fed/Fasted**	
Interim Sacrifice Period		**Recovery Sacrifice Period**	

GROUPS SUMMARY

	Groups			
Parameter	**Control**	**Low**	**Medium**	**High**
Name of Treatment	Vehicle	PQ04297 Fine Spray	PQ04297 Fine Spray	PQ04297 Fine Spray
Daily Dose		5 mg/Kg	7.5 mg/Kg	10 mg/Kg
Route of Administration	Intranasal	Intranasal	Intranasal	Intranasal
Number of Animals	13	6	9	7
Male	7	4	4	4
Female	6	2	5	3
Fed/Fasted	Fed	Fed	Fasted	Fasted
Caloric Restriction		Paired Feeding	Paired Feeding	Paired Feeding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Welcome David
SELECT TESTS
Tests
Clinical Pathology
Chemistry
Hematology
UA
Gross Analysis
UVOL
COLOR
APPEAR
Chemical Analysis
GLU
BIL
KET
SG
BLD
pH
PRO
UBG
NIT
NEXT
Internet

Submission #: TX89123
(PQ04297-001: 14-Day Repeated-Dose Nasal Toxicity/Intranasal)

URINALYSIS: CHEMICAL ANALYSIS

URINE pH

GROUP 1: CONTROL

ANIMAL NO.\WEEK	1	2	3	4	5	6
2001	8.0	8.5	9.0	8.5	9.5	9.5
2002	7.5	8.0	8.5	9.0	9.5	9.5
2003	6.5	7.0	8.0	7.0	7.5	7.5
2004	8.0	9.0	9.5	9.5	10	10.5
2005	5.0	5.5	6.0	6.5	7.0	7.5
2006	5.5	6.0	6.5	7.0	7.5	8.0
2007	6.0	6.5	7.0	7.5	8.0	9.0
2008	7.5	8.0	8.5	9.0	9.5	10.0
2009	7.5	7.0	7.5	8.0	8.5	9.0
2010	8.0	8.5	9.0	9.5	10.0	8.5
MEAN	6.95	7.4	7.95	8.15	8.7	8.9
S.D.	0.42	1.0	1.25	1.75	1.35	1.45
N	10	10	10	10	10	10

View Chart | Export to Excel | Export to SAS

URINE pH

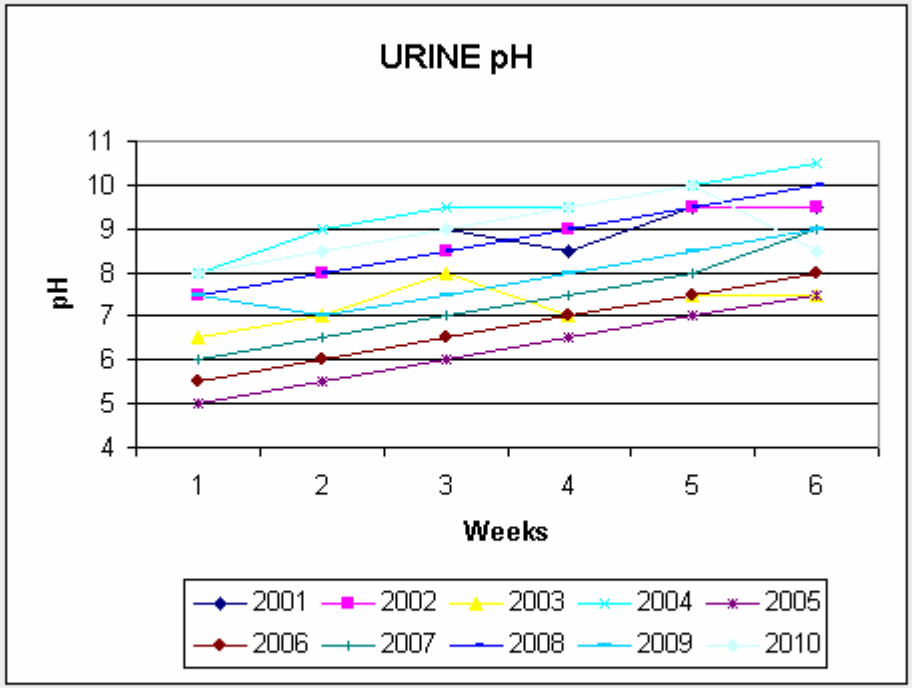
GROUP 2: LOW

ANIMAL NO.\WEEK	1	2	3	4	5	6
2001	8.0	8.5	9.0	8.5	9.5	9.5
2002	7.5	8.0	8.5	9.0	9.5	9.5
2003	6.5	7.0	8.0	7.0	7.5	7.5
2004	8.0	9.0	9.5	9.5	10	10.5
2005	5.0	5.5	6.0	6.5	7.0	7.5
2006	5.5	6.0	6.5	7.0	7.5	8.0

ToxViewer - Microsoft Internet Explorer

Submission #: TX89123
(PQ04297-001: 14-Day Repeated-Dose Nasal Toxicity/Intranasal)
GROUP 1: CONTROL

PRINT



View as Bar Chart

Close

ToxViewer

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Group Means | GO | Customize View | Change Tests

Submission #: TX89123
(PQ04297-001: 14-Day Repeated-Dose Nasal Toxicity/Intranasal)

URINALYSIS: CHEMICAL ANALYSIS

URINE pH						
GROUP NO. \WEEK	1	2	3	4	5	6
Control	7.0 ± 0.25	7.5 ± 0.3	7.5 ± 0.5	7.5 ± 0.1	7.5 ± 0.45	7.5 ± 0.55
Low	7.5 ± 0.3	8.0 ± 0.2	7.5 ± 0.4	8.0 ± 0.6	8.0 ± 0.4	8.0 ± 0.2
Medium	8.0 ± 0.2	8.5 ± 0.3	8.0 ± 0.4	8.5 ± 0.3	8.5 ± 0.2	8.5 ± 0.4
High	8.5 ± 0.5	9.0 ± 0.5	9.5 ± 0.6	9.5 ± 0.4	10 ± 0.5	10.5 ± 0.4
N	10	10	10	10	10	10

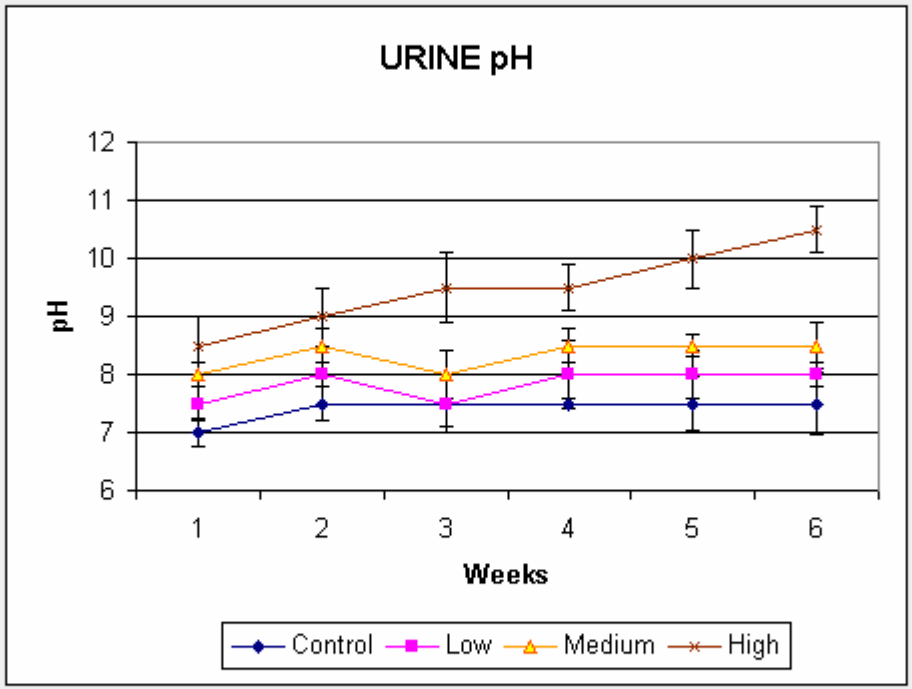
View Chart | Export to Excel | Export to SAS

Internet

ToxViewer - Microsoft Internet Explorer

Submission #: TX89123
(PQ04297-001: 14-Day Repeated-Dose Nasal Toxicity/Intranasal)

PRINT



View as Bar Chart

Close

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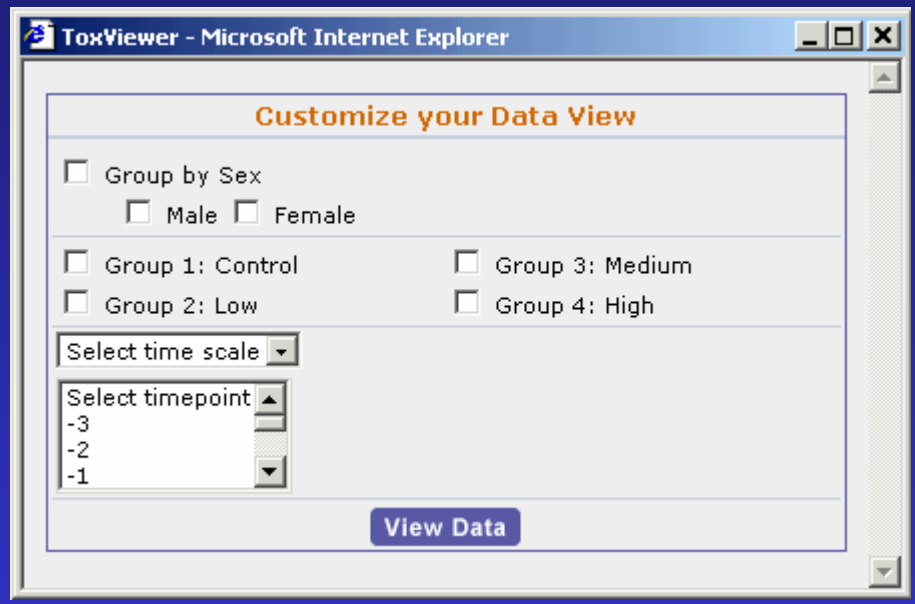
Group Means | GO | Customize View | Change Tests

Submission #: TX89123
(PQ04297-001: 14-Day Repeated-Dose Nasal Toxicity/Intranasal)

URINALYSIS: CHEMICAL ANALYSIS

URINE pH						
GROUP NO. \WEEK	1	2	3	4	5	6
Control	7.0 ± 0.25	7.5 ± 0.3	7.5 ± 0.5	7.5 ± 0.1	7.5 ± 0.45	7.5 ± 0.55
Low	7.5 ± 0.3	8.0 ± 0.2	7.5 ± 0.4	8.0 ± 0.6	8.0 ± 0.4	8.0 ± 0.2
Medium	8.0 ± 0.2	8.5 ± 0.3	8.0 ± 0.4	8.5 ± 0.3	8.5 ± 0.2	8.5 ± 0.4
High	8.5 ± 0.5	9.0 ± 0.5	9.5 ± 0.6	9.5 ± 0.4	10 ± 0.5	10.5 ± 0.4
N	10	10	10	10	10	10

View Chart | Export to Excel | Export to SAS


ToxViewer - Microsoft Internet Explorer
Customize your Data View
Group by Sex
Male
Female
Group 1: Control
Group 2: Low
Group 3: Medium
Group 4: High
Select time scale
Select timepoint
-3
-2
-1
View Data

Next Steps

- Complete pilot project (end of 2004)
- Revise SEND model accordingly
- Develop data viewing and analysis tool (ToxVision)
- Merge (harmonize) SEND with CDISC's SDS model
  - To be called Data Tabulation Model (DTM)
  - Single model for both clinical and nonclinical data with additional variables added as needed
  - Each with own Implementation Guides (to include detailed description of variables and domains with examples)
  - DTM and Implementation Guides to be posted on CDISC (and FDA?) web sites (to be used as data submission guidance for sponsors)

Potential Issues

- Ensure that DTM model for clinical and nonclinical data is truly adequate to capture and display all data generated from an animal toxicity study
  - Requires completion of the ongoing pilot and further technical and scientific discussions between CDISC, SEND, (and FDA?) representatives
- Ensure that customized software tools being developed are intuitive (i.e., manual-free) and meet the needs of *non*clinical reviewers
  - Otherwise, no better off than before with JMP
- Some additional training may be required to familiarize reviewers with software tools
  - But this should not be a major issue if the tool works the way we expect

Conclusions

- From a nonclinical perspective, development and acceptance of data standards promises to significantly improve our capability to display and analyze animal toxicity data.
- This should result in a more efficient and effective review process.
- However, importance of capturing animal toxicity data in a single Data Tabulation Model (DTM), designed primarily for clinical data, should not be underestimated, so that significant toxicities not monitorable in humans can still be detected (e.g., cancer, birth defects, and irreversible tissue damage, etc.).