Forget Statistical Significance

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Professor

Outline

* Adverse Event Reporting and Pharmacovigilance
* Disproportionality-based data mining
* Visualization
* Future directions

Adverse Event

* Any ***serious***, undesirable experience associated with the use of a medical product in a patient.

* An adverse event is ***serious*** if it results in:
  * Death
  * Life-Threatening
  * Hospitalization (initial or prolonged)
  * Disability
  * Congenital Anomaly
  * Requires Intervention to Prevent Permanent Impairment or Damage

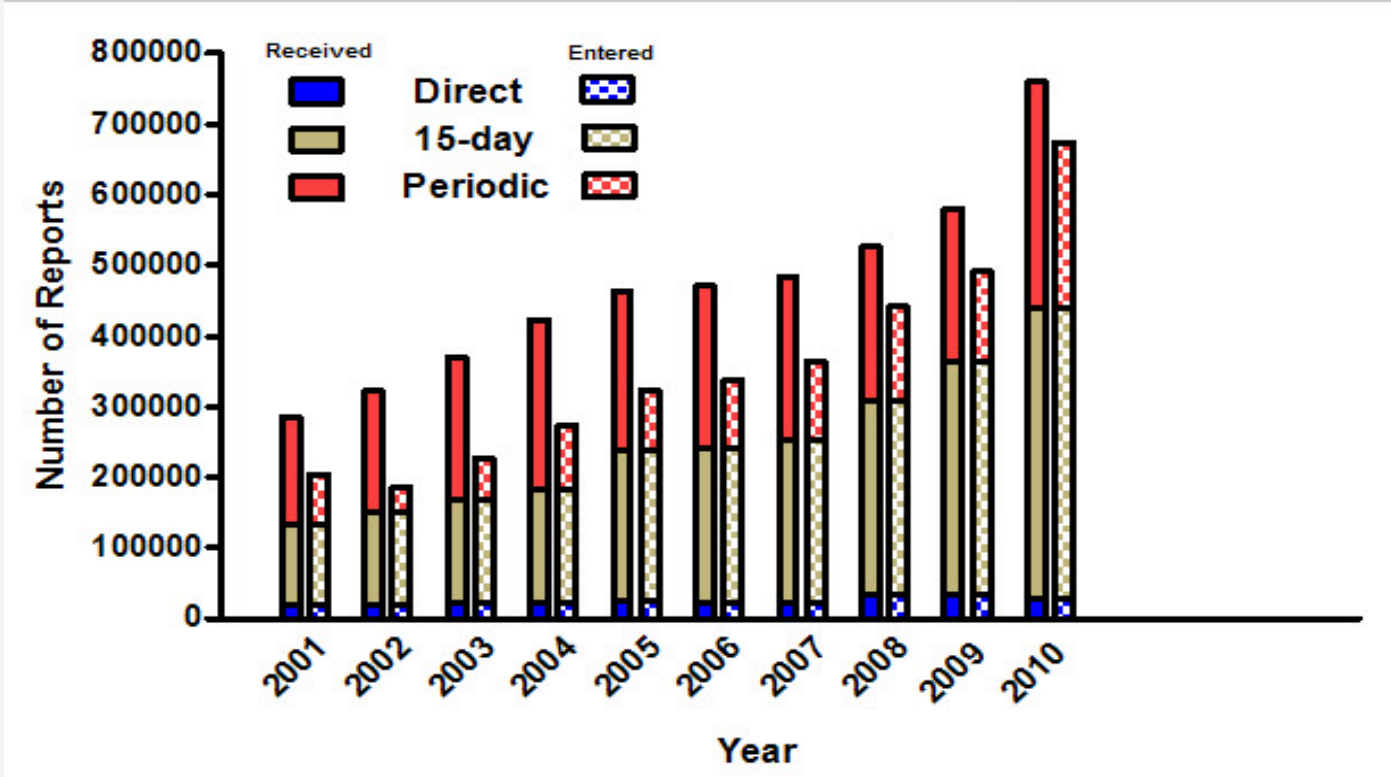
Pharmacovigilance

* Monitoring of approved medical products to identify safety concerns and take appropriate action

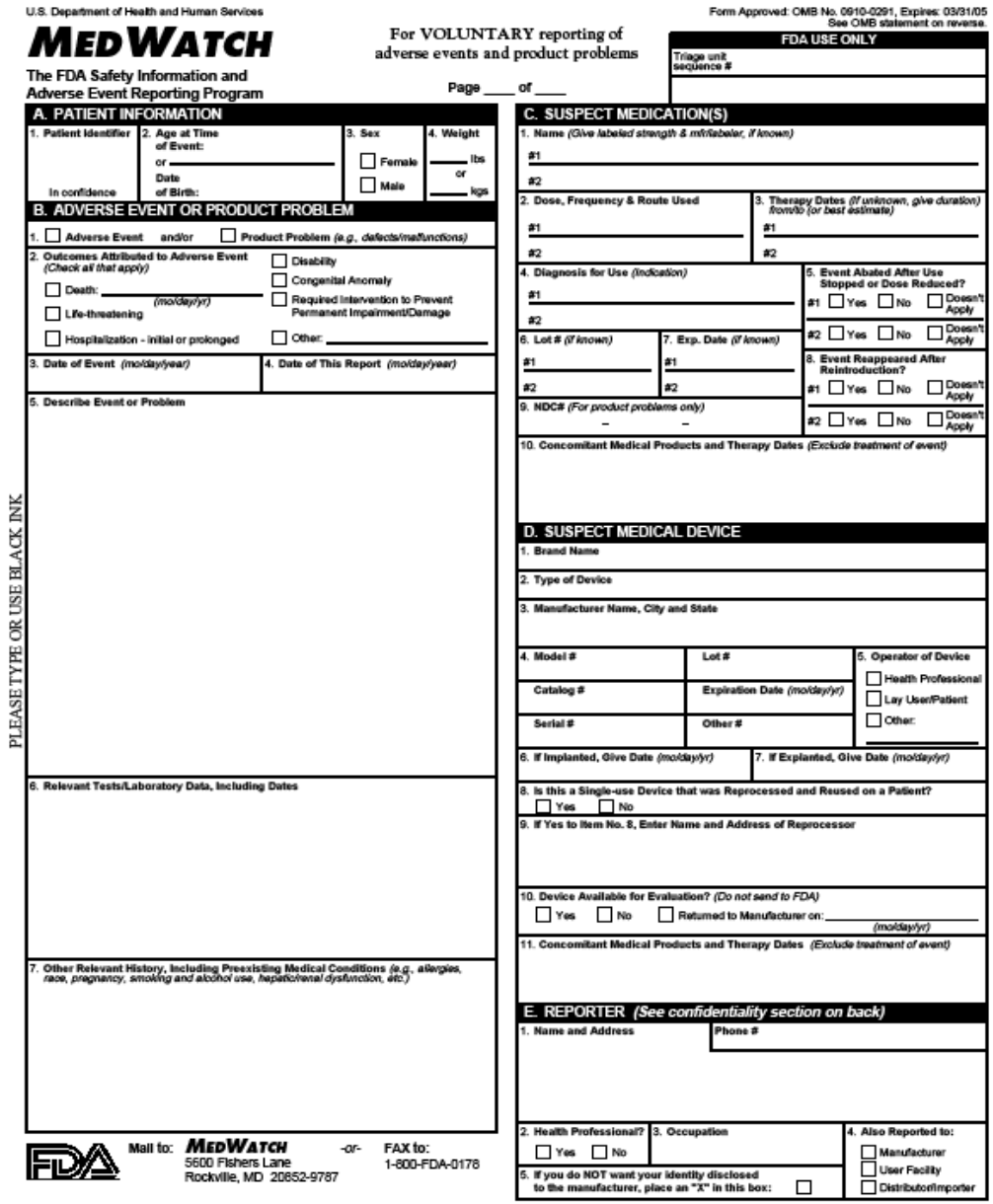
* The FDA's Adverse Event Reporting Database (AERS) is the largest repository of AE reports in the world
  * Surveillance began in 1961
  * Reports from 1969 in a searchable database
  * Approximately 3 million reports in just the past decade

Reporting of Adverse Events in the US

Figure 1. This figure illustrates the number of reports received (solid bars) and entered (checkered bars) into AERS by type of report since the year 2000 until the end of 2010.



Source: FDA http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

A. PATIENT INFORMATION
1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM
1. ☐ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mo/day/yr)
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Disability
☐ Congenital Anomaly
☐ Required Intervention to Prevent Permanent Impairment/Damage
☐ Other: ____
3. Date of Event (mo/day/year)
4. Date of This Report (mo/day/year)
5. Describe Event or Problem
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. SUSPECT MEDICATION(S)
1. Name (Give labeled strength & mfr/labeler, if known)
#1
#2
2. Dose, Frequency & Route Used
3. Therapy Dates (if unknown, give duration) from/to (or best estimate)
4. Diagnosis for Use (Indication)
5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # (if known)
7. Exp. Date (if known)
8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# (For product problems only)
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE
1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device
☐ Health Professional ☐ Lay User/Patient ☐ Other: ____
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)
1. Name and Address
Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to:
☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

AERS DATA

Limited data fields on publically available dataset

Coding dictionary of adverse reactions terms has changed over time.

- New dictionary (MedDRA) adopted in late 1997
- >20,000 Preferred Terms
- Unlimited number of Preferred Terms per report

Bevacizumab (Avastin) Data Mining

Table I. Clinically novel preferred terms categorized by clinical disorder

Clinical disorder	PTs[a]	PRR	N for bevacizumab[b]
Bowel obstruction	**Duodenal obstruction**	20.88	5
	Small intestinal obstruction	15.95	143
	Obstruction gastric	14.31	16
	Gastrointestinal obstruction	8.7	9
	Intestinal obstruction	7.7	156
	Intussusception	8.6	6
	Colonic obstruction	15.2	15
	Large intestinal obstruction	13.1	5
Hepatic disorders	Hyperbilirubinaemia	3.25	30
	Hepatic atrophy	3.05	3
	Hepatic cirrhosis	2.18	32
	Hepatic ischaemia	8.9	3
	Portal hypertension	6.61	22
Cardiomyopathic disorders	Stress cardiomyopathy	3.34	4
	Cardiomyopathy	2.46	49
	Diastolic dysfunction	2.05	8
	Left ventricular dysfunction	8.16	26
	Ventricular dysfunction	2.69	25
	Ejection fraction decreased	3.2	55
	Brain natriuretic peptide increased	3.05	10
Arrythmia and conduction disorders	Nodal arrhythmia	3.25	6
	Tachyarrhythmia	2.4	9
	Arrhythmia supraventricular	7.67	17
	Sinus tachycardia	2.11	44
	Supraventricular tachycardia	3.15	41
	Electrocardiogram QRS complex abnormal	6.04	3
Vessel wall disorders	Aortic disorder	4.11	5
	Aneurysm ruptured	7.31	7
	Aortic aneurysm rupture	6.07	7
	Aortic dissection	8.25	18
Sudden cardiac death	Cardiac death	3.13	4
	Sudden cardiac death	2.68	13
	Sudden death	3.63	81
	Pulse absent	2	20

Proportional Reporting Ratio (PRR)

$$= \frac{\text{Proportion of specific AE's using the drug}}{\text{Proportion of other AE's using the drug}}$$

Source: Shamloo et al. Drug Safety 2012

Counterfeit medications are a global problem

drug safety

More US Doctors Warned about Fake Cancer Drugs
May 2, 2012

The Food and Drug Administration has sent warning letters to more than 50 U.S. doctors and medical clinics that may have purchased counterfeit cancer injectable medication. Originally the FDA sent 19 medical practices warnings in March. The FDA warns the physicians that purchasing from foreign or unlicensed medicine suppliers puts patients at risk of exposure to potentially fake, contaminated, ineffective and dangerous medication. MORE>>>

counterfeit news

2 Sentenced for Smuggling Counterfeit Medicines Into US Via Internet
May 9, 2012

Two Israeli citizens pleaded guilty to smuggling counterfeit and misbranded drugs in the US, announced FDA-OCI. Said OCI, "Both men operated an Internet business in Israel that used multiple websites... to illegally sell large amounts of prescription drugs to U.S. purchasers...generating approximately $1,475,363 in gross proceeds." MORE>>>

press releases

Partnership for Safe Medicines Praises G8 Action to Combat Drug Counterfeiting
May 21, 2012

Washington, D.C. (May 21, 2012) – Marv Shepherd, PhD, president of the Partnership for Safe Medicines, today released the following statement regarding news that global leaders at the G8 Summit have addressed the growing threat posed by counterfeit medicines: "The... MORE>>>

Source: Partnership for Safe Medicines http://www.safemedicines.org/

Assumption:
Counterfeits may be Ineffective

Search Criteria Name: SWS-Ineffective - 1 decade Q4 2011

Search Dictionary Version: 15.00

(Drug Legend: **A**=All, **S**=Suspect, **I**=Ingredient, **N**=Drug Name) [current cases only]

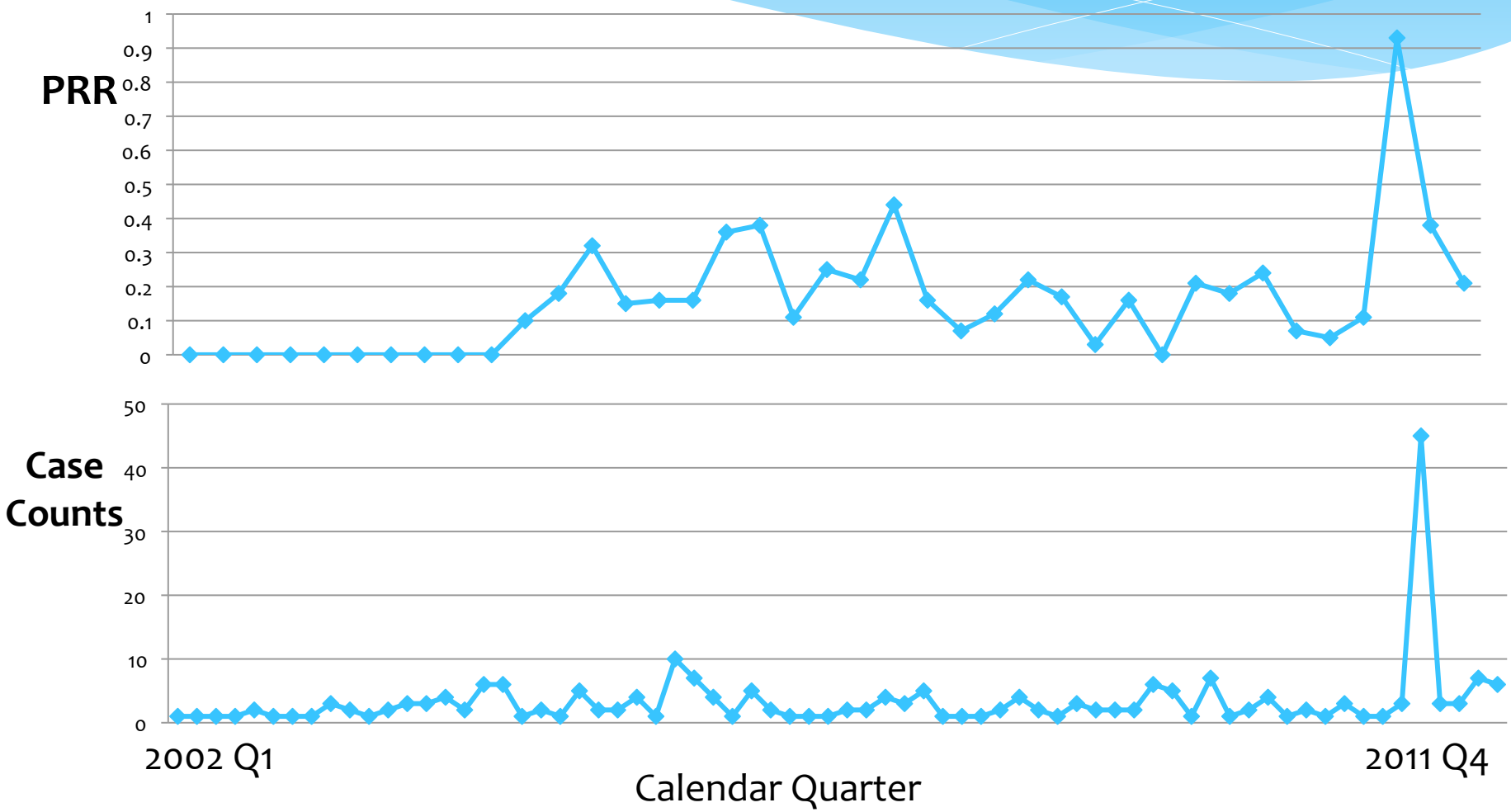
Criteria		Value
Data Source		FDA Dataset
Drugs		all
Reactions	PT(s)	no therapeutic response therapeutic product ineffective therapeutic product ineffective for unapproved indication therapeutic response decreased treatment failure drug effect decreased drug ineffective drug ineffective for unapproved indication device ineffective
Reaction boolean		[(no therapeutic response **or** therapeutic product ineffective **or** therapeutic product ineffective for unapproved indication **or** therapeutic response decreased **or** treatment failure **or** drug effect decreased **or** drug ineffective **or** drug ineffective for unapproved indication **or** device ineffective)]
Demographics		all
Report Dates		From: Jan 1, 2002 To: Dec 31, 2011
Event Dates		all
Outcomes		all

Results
10,558 ingredients x 40 quarters (and n statistics)

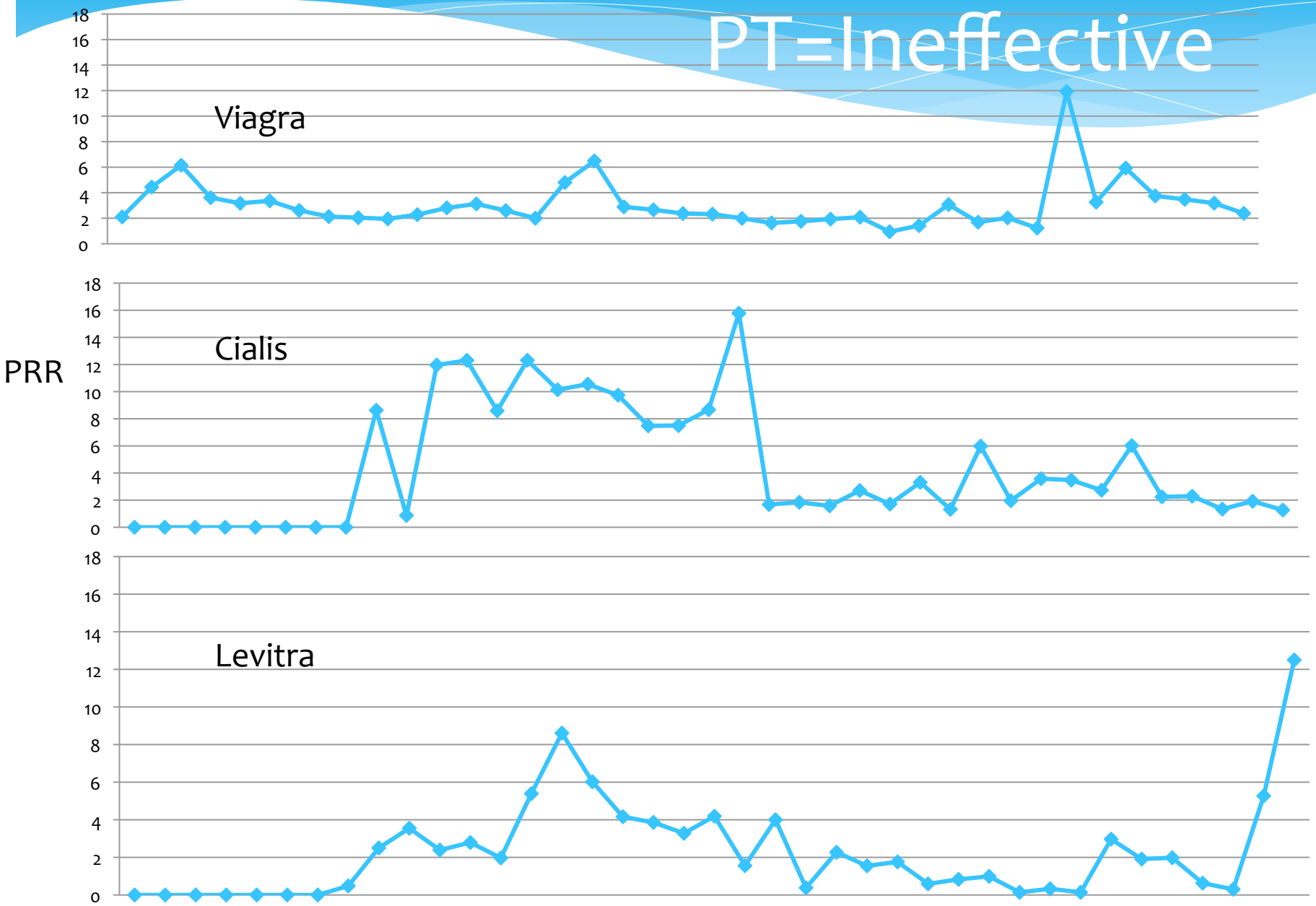
ABACAVIR	0	0	0	0	0	0	0	0	0	0	0	0	0	0.5	0.49	0
ABACAVIR SUCCINATE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABACAVIR SULFATE	0.38	0.76	0.48	0	0.35	0.48	0	0.76	0.3	0.83	0.56	0.62	0.43	0.62	0.59	1.24
ABARELIX	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABARELIX, INJECTABLE SUSPENSION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABATACEPT	0	0	0	0	0	0	0	0	0	0	0	2.74	0	0	0	6.56
ABCIXIMAB	0	0.5	0	0	0.51	0.43	0	2.68	0.28	0	0	0.18	0.49	0.35	0	0
ABF 656 , STUDY DRUG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABI-007 (PACLITAXEL PROTEIN-BOUND), STUDY DRUG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABILAX TBD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABIRATERONE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABIRATERONE ACETATE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABOBOTULINUMTOXINA (BOTULINUM TOXIN TYPE A)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABOBOTULINUMTOXINA (BOTULINUM TOXIN TYPE A) (CLOSTRIDIUM BOTULINUM TOXIN TYPE A)	0	0	0	0	0	0	0	0	0Inf		0	0	0	0	0	0
ABOCOAT, TBD CREAM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABSORBABLE GELATIN POWDER	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABSORBABLE GELATIN SPONGE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABSORBABLE GELATIN SPONGE, NON DRUG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABSORBASE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABT-450, STUDY DRUG, HCV PROTEASE INHIBITOR (ABT-450/R, BOOSTED WITH RITONAVIR)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ABX-EGF, MONOCLONAL ANTIBODY, HUMAN	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Avastin (Bevacizumab)

Feb 22, 2012 FDA issues warning of counterfeit Avastin



PT=Ineffective



Future Directions

* Threshold-based data mining is unnecessarily restrictive
  * Subject matter, expert driven mining is the goal
* Criteria to best identify counterfeits (e.g. Preferred Terms) needs to be developed
  * It will vary by the drug, its dosage form, and the ingredients in the counterfeit product.
* Geographic data on reporting and lot numbers will increase the value of AERS data
  * Priorities - high cost biologics and high value medical devices
* National surveillance for the emergence of counterfeits and other safety concerns should be carried out across agencies and databases